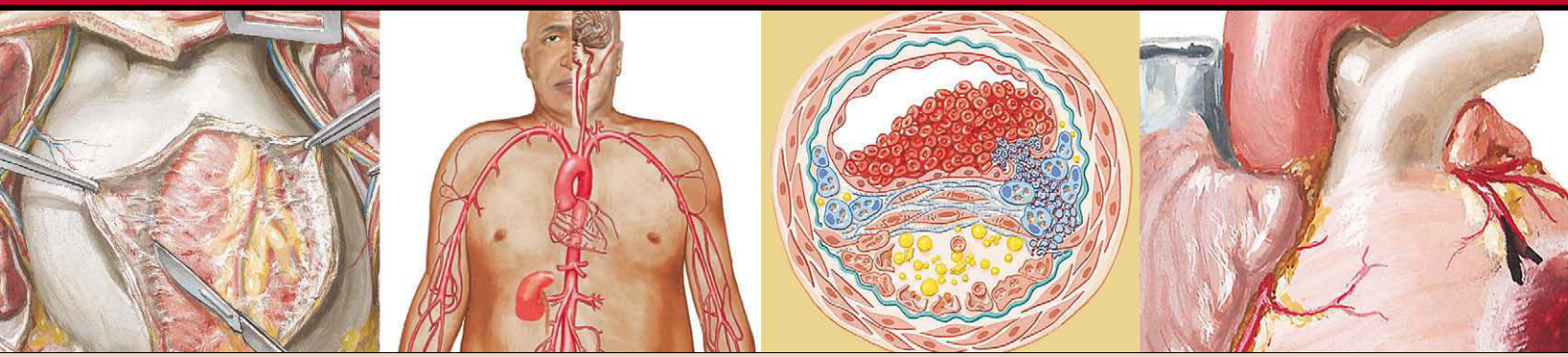
Netter's Cardiology

2nd edition



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About the Editors

Marschall S. Runge, MD, PhD, was born in Austin, Texas, and was graduated from Vanderbilt University with a BA in General Biology and a PhD in Molecular Biology. He received his medical degree from the Johns Hopkins School of Medicine and trained in internal medicine at Johns Hopkins Hospital. He was a cardiology fellow and junior faculty member at Massachusetts General Hospital. Dr. Runge's next position was at Emory University, where he directed the Cardiology Fellowship Training Program. He then moved to the University of Texas Medical Branch in Galveston, where he was Chief of Cardiology and Director of the Sealy Center for Molecular Cardiology. He came to the University of North Carolina (UNC) in 2000 as Chair of the Department of Medicine. He is currently the Charles Addison and Elizabeth Ann Sanders Distinguished Professor of Medicine and Chair of the Department of Medicine. In addition, in 2004, Dr. Runge was appointed President of UNC Physicians and Vice Dean for Clinical Affairs. Dr. Runge is board-certified in internal medicine and cardiovascular diseases and has spoken and published widely on topics in clinical cardiology and vascular medicine. He maintains an active clinical practice in cardiovascular diseases and medicine in addition to his teaching and administrative activities in the Department of Medicine and the UNC School of Medicine.

George A. Stouffer, MD, was born in Indiana, Pennsylvania, and was graduated from Bucknell University and the University of Maryland School of Medicine. He completed his internal medicine residency, cardiology fellowship, and interventional cardiology fellowship at the University of Virginia. During his cardiology fellowship, he completed a 2-year National Institutes of Health research fellowship in the laboratory of Gary Owens at the University of Virginia. He was on the faculty at the University of Texas Medical Branch from 1995 to 2000, where he became an associate professor and served as Co-Director of Clinical Trials in the Cardiology Division and as Associate Director of the Cardiac Catheterization Laboratory. He joined the faculty at the University of North Carolina in 2000 and currently serves as the Henry A. Foscue Distinguished Professor of Medicine and Director of the Cardiac Catheterization Laboratory. Dr. Stouffer's main focus is clinical cardiology with an emphasis on interventional cardiology, but he is also involved in clinical and basic science research. His basic science research is in the areas of regulation of smooth muscle cell growth, the role of the smooth muscle cytoskeleton in regulating signaling pathways, thrombin generation, and renal artery stenosis.

Cam Patterson, MD, MBA, was born in Mobile, Alabama. He was a Harold Sterling Vanderbilt Scholar and studied Psychology and English at Vanderbilt University, graduating summa cum laude. He participated in the Honors Research Program at Vanderbilt and conducted research in behavioral pharmacology during that time. Dr. Patterson attended Emory University School of Medicine, graduating with induction in the Alpha Omega Alpha Honor Society, and completed his residency in Internal Medicine at Emory University Hospitals. He became the youngest-ever Chief Resident at Grady Memorial Hospital at Emory University in 1992, supervising over 200 house officers in four hospitals. He completed 3 years of research fellowship under the guidance of Edgar Haber at the Harvard School of Public Health, developing an independent research program in vascular biology and angiogenesis that was supported by a National Institutes of Health fellowship. In 1996, he accepted his first faculty position at the University of Texas Medical Branch, and in 2000, Dr. Patterson was recruited to the University of North Carolina at Chapel Hill to become the founding director of the UNC McAllister Heart Institute. In 2005, he also became Chief of the Division of Cardiology at UNC. Dr. Patterson is the Ernest and Hazel Craige Distinguished Professor of Cardiovascular Medicine, and he has been recognized at UNC with the Ruth and Phillip Hettleman Prize for Artistic and Scholarly Achievement. He is an Established Investigator of the American Heart Association and a Burroughs Wellcome Fund Clinical Scientist in Translational Research. He is a member of several editorial boards, including *Circulation* and *Journal of Clinical Investigation*, and is an elected member of the American Society of Clinical Investigation and the Association of University Cardiologists. Dr. Patterson maintains active research programs in the areas of angiogenesis and vascular development, cardiac hypertrophy, protein quality control, and translational genomics and metabolomics. He is also the director of the Cardiac Genetics Clinic. He received his MBA from the UNC Kenan-Flagler School of Business in 2008.

Preface

The first edition of *Netter's Cardiology* was an effort to present to clinicians the ever-increasing amount of medical information on cardiovascular diseases in a concise and highly visual format. The challenge that clinicians face in "keeping up" with the medical literature has continued to grow in the 5 years since the first edition of *Netter's Cardiology*. This need to process the ever-expanding medical information base and apply new findings to the optimal care of patients is acute in all areas of medicine, but perhaps it is most challenging in disciplines that require practitioners to understand a broad spectrum of evidence-based medicine, such as the field of cardiovascular diseases. The explosion of medical knowledge is also a very real educational issue for learners at all levels—students, residents, practicing physicians—who must rapidly determine what is and is not important, organize the key information, and then apply these principles effectively in clinical settings.

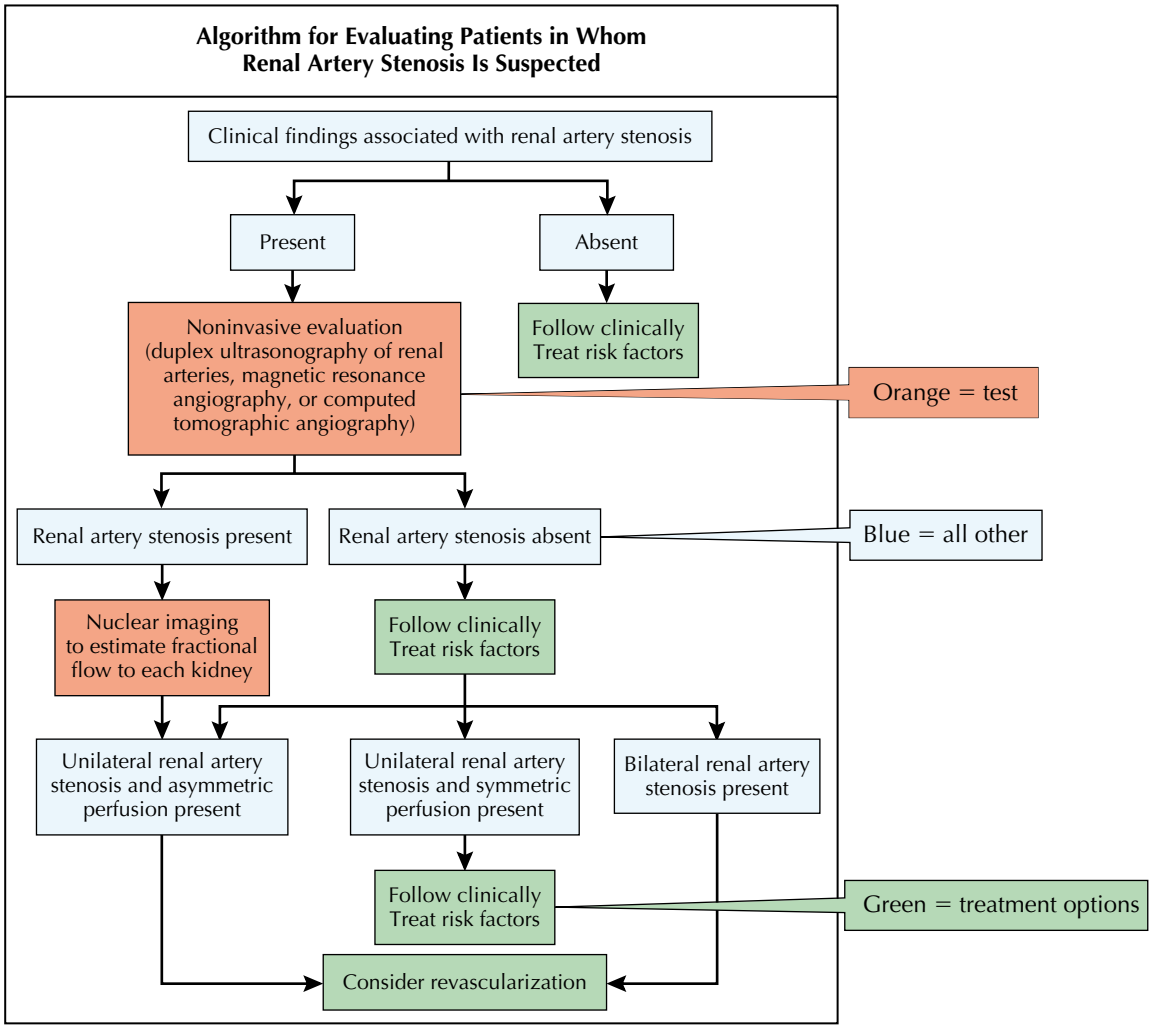
For the second edition of *Netter's Cardiology*, our goal was to produce an improved text that keeps these issues in clear focus and also addresses important clinical areas that were not well covered in the first edition or in many other cardiology texts. To accomplish this expansion while maintaining a concise text that could be used as a ready reference, we again avoided exhaustive treatment of topics. We also have made every effort to present the essential information in a reader-friendly format that increases the reader's ability to learn the key facts without getting lost in details that can obfuscate the learning process.

After a careful review of reader comments about the first edition, we made some substantial changes to achieve our educational goals. Chapters were added and topics expanded to address reader concerns about the lack of coverage of a number of important topics commonly encountered in clinical practice. Examples include these new chapters: Chest Radiography, Echocardiography, Stress Testing and Nuclear Imaging, Cardiac Computed Tomography and Magnetic Resonance Imaging, Left and Right Heart Catheterization, Identifying the Patient at High Risk for Acute Coronary Syndrome: Plaque Rupture and "Immediate Risk," Cardiogenic Shock after Myocardial Infarction, Stress-Induced Cardiomyopathy, Supraventricular Tachycardia, Sleep Disorders and the Cardiovascular System, Cardiovascular Toxicity of Noncardiac Medications, and Sudden Cardiac Death in Athletes. The chapter subheadings of "Optimum Treatment" and "Avoiding Treatment Errors" are new additions that address concerns about therapeutic errors that can lead to patient harm. We also added boxes and algorithms that provide in an easy-to-read format quick overviews of critical diagnostic and therapeutic information covered in the text. (See the sample algorithm on the following page.) References are annotated in the second edition of *Netter's Cardiology* to guide the reader to a more in-depth review, if considered necessary. As in the first edition, the contributing authors have taken advantage of the genius of Frank Netter by carefully selecting the best of his artwork to illustrate the most important clinical concepts covered in each chapter. When Netter artwork was unavailable or difficult to apply to illustrate modern clinical concepts, we again utilized the great artistic talents of Carlos A. G. Machado, MD, to create new artwork or to skillfully edit and update some of Frank Netter's drawings. The combination of Dr. Machado's outstanding skills as a medical artist and his knowledge of the medical concepts being illustrated was an invaluable asset.

As in the first edition, we chose to use authors from the University of North Carolina School of Medicine at Chapel Hill or those with close ties to the university. This allowed us to select authors who are clinical authorities, many of whom are also well known for their national and international contributions. All have active clinical practices that require daily use of the information covered in their chapters, and all are well aware of the approach to patient management utilized by their peers at other institutions and in other practice settings. Many of the contributing authors of the first edition have continued on as second-edition authors and have provided updates. Each author, whether a previous contributor or not, was given clearly defined guidelines that emphasized the need to distill the large amount of complex information in his or her field and to present it concisely in a carefully prescribed format maintained across all chapters. The result is a text that is truly clinically useful and less of a compendium than is commonly the case in many medical texts.

We believe that the changes we have made in the second edition substantially improve *Netter's Cardiology* and ensure that it will continue to be a highly useful resource for all physicians, both generalists and subspecialists, who need to remain current in cardiology—from trainees to experienced practitioners. Whether we have succeeded will obviously be determined by our readers. Based on our experience with the revision of the first edition, we welcome the comments, suggestions, and criticisms of readers that will help us improve future editions of this work.

Algorithms have been color coded for quick reference.



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About the Artists

Frank H. Netter, MD

Frank H. Netter was born in 1906 in New York City. He studied art at the Art Student's League and the National Academy of Design before entering medical school at New York University, where he received his MD degree in 1931. During his student years, Dr. Netter's notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

In 2005, Elsevier Inc. purchased the Netter Collection and all publications from Icon Learning Systems. Now over 50 publications featuring the art of Dr. Netter are available through Elsevier Inc. (in the United States: www.us.elsevierhealth.com/Netter; outside the United States: www.elsevierhealth.com).

Dr. Netter's works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book *Netter Collection of Medical Illustrations*, which includes the greater part of the more than 20,000 paintings created by Dr. Netter, has become one of the most famous medical works ever published. *The Netter Atlas of Human Anatomy*, first published in 1989, presents the anatomic paintings from the Netter Collection. Now translated into 16 languages, it is the anatomy atlas of choice among medical and health professions students the world over.

The Netter illustrations are appreciated not only for their aesthetic qualities but, more importantly, for their intellectual content. As Dr. Netter wrote in 1949, "clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a *medical illustration* if it does not serve to make clear some medical point." Dr. Netter's planning, conception, point of view, and approach are what inform his paintings and what makes them so intellectually valuable.

Frank H. Netter, MD, physician and artist, died in 1991.

Learn more about the physician–artist whose work has inspired the Netter Reference Collection: www.netterimages.com/artist/netter.htm.

Carlos A. G. Machado, MD

Carlos A. G. Machado was chosen by Novartis to be Dr. Netter's successor. He continues to be the main artist who contributes to the *Netter Collection of Medical Illustrations*.

Self-taught in medical illustration, cardiologist Carlos A. G. Machado has contributed meticulous updates to some of Dr. Netter's original plates and has created many paintings of his own in the style of Netter as an extension of the Netter Collection. Dr. Machado's photorealistic expertise and his keen insight into the physician–patient relationship inform his vivid and unforgettable visual style. His dedication to researching each topic and subject he paints places him among the premier medical illustrators at work today.

Learn more about his background and see more of his art at: www.netterimages.com/artist/machado.htm.

Acknowledgments

This second edition of *Netter's Cardiology* benefited enormously from the hard work and talent of many dedicated individuals.

First, we thank the contributing authors. All are current or former faculty members at the University of North Carolina School of Medicine, Chapel Hill, or have close ties to the institution. Without their intellect, dedication, and drive for excellence, *Netter's Cardiology*, 2nd edition, could not have been published. We had a solid foundation on which to build the second edition, thanks to the hard work of the first-edition contributing authors, many of whom we were fortunate to have continue on to this edition. We are also grateful for the invaluable editorial contribution that Dr. E. Magnus Ohman made to the first edition.

Special recognition goes to John A. Craig, MD, and Carlos A. G. Machado, MD. They are uniquely talented physician–artists who, through their work, brought to life important concepts in medicine in the new and updated figures included in this text. Anne Lenehan, Elyse O'Grady, Marybeth Thiel, and Julie Goolsby at Elsevier were instrumental in helping us make a very good first edition more comprehensive and more focused in its second edition.

We are also indebted to Ms. Angela Clotfelter-Rego, whose superb organizational skills helped make this text a reality. Special thanks go to Carolyn Kruse for excellent editing and Dr. Deborah Montague for invaluable reviewing and updating of the pharmacologic information.

We would especially like to acknowledge our families: our wives—Susan Runge, Meg Stouffer, and Kristine Patterson—whose constant support, encouragement, and understanding made completion of this text possible; our children—Thomas, Elizabeth, William, John, and Mason Runge; Mark, Jeanie, Joy, and Anna Stouffer; and Celia, Anna Alyse, and Graham Patterson—who inspire us and remind us that there is life beyond the computer; and, finally, our parents—whose persistence, commitment, and work ethic got us started on this road many, many years ago.

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The History and Physical Examination

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The ability to determine whether disease is present or absent—and how that patient should be treated—is the ultimate goal for clinicians evaluating patients with suspected heart disease. Despite the number of diagnostic tests available, never has the importance of a careful history and physical examination been greater. Opportunities for error in judgment are abundant, and screening patients for coronary risk using a broad and unfocused panel of laboratory and noninvasive tests can lead to incorrect diagnoses and unnecessary testing. Selection of the most appropriate test and therapeutic approach for each patient is based on a skillfully performed history and physical examination. Furthermore, interpretation of any test results is based on the prior probability of disease, which again is based on the history and physical. While entire texts have been written on cardiac history and physical examination, this chapter specifically focuses on features of the cardiac history and the cardiovascular physical examination that help discern the presence or absence of heart disease.

THE CONCEPT OF PRIOR PROBABILITY

The history and physical examination should allow the clinician to establish the prior probability of heart disease—that is, the likelihood that the symptoms reported by the patient result from heart disease. A reasonable goal is to establish a patient's risk of heart disease as "low," "intermediate," or "high." One demonstration of this principle in clinical medicine is the assessment of patients with chest pain, in which the power of exercise stress testing to accurately diagnose coronary heart disease (CHD) depends on the prior probability of disease. In patients with a very low risk of CHD based on clinical findings, exercise stress testing resulted in a large number of false-positive test results. Because up to 15% of exercise stress tests produce positive results in individuals without CHD, use of this test in a low-risk population can result in an adverse ratio of false-positive to true-positive test results and unnecessary cardiac catheterizations. Conversely, in patients with a very high risk of CHD based on clinical findings, exercise stress testing can result in false-negative test results—an equally undesirable outcome, because patients with significant coronary artery disease (CAD) and their physicians may be falsely reassured that no further evaluation or treatment is necessary.

Emphasis is increasing on quantifying prior probability to an even greater degree using various mathematical models. This is a useful approach in teaching and may be clinically feasible in some diseases. However, for the majority of patients with suspected heart disease, categorizing risk as low, intermediate, and high is appropriate, reproducible, and feasible in a busy clinical practice. Therefore, obtaining the history and physical examination represents a key step before any testing, to minimize use of inappropriate diagnostic procedures.

THE HISTORY

A wealth of information is available to clinicians who carefully assess the patient's history. Key components are assessment of the chief complaint; careful questioning for related, often subtle symptoms that may further define the chief complaint; and determination of other factors that help categorize the likelihood of disease. Major symptoms of heart patients include chest discomfort, dyspnea, palpitations, and syncope or presyncope.

Chest Discomfort

Determining whether chest discomfort results from a cardiac cause is often a challenge. The most common cause of chest discomfort is myocardial ischemia, which produces angina pectoris. Many causes of angina exist, and the differential diagnosis for chest discomfort is extensive (Box 1-1). Angina that is reproducible and constant in frequency and severity is often referred to as *stable angina*. For the purposes of this chapter, stable angina is a condition that occurs when CAD is present and coronary blood flow cannot be increased to accommodate for increased myocardial demand. However, as discussed in Chapters 12 through 14, there are many causes of myocardial ischemia, including fixed coronary artery stenoses and endothelial dysfunction, which leads to reduced vasodilatory capacity.

A description of chest discomfort can help establish whether the pain is angina or of another origin. First, characterization of the quality and location of the discomfort is essential (Fig. 1-1). Chest discomfort because of myocardial ischemia may be described as pain, a tightness, a heaviness, or simply an uncomfortable and difficult-to-describe feeling. The discomfort can be localized to the mid-chest or epigastric area or may be characterized as pain in related areas, including the left arm, both arms, the jaw, or the back. The radiation of chest discomfort to any of these areas increases the likelihood of the discomfort being angina. Second, the duration of discomfort is important, because chest discomfort due to cardiac causes generally lasts minutes. Therefore, pain of very short duration ("seconds" or "moments"), regardless of how typical it may be of angina, is less likely to be of cardiac origin. Likewise, pain that lasts for hours, on many occasions, in the absence of objective evidence of myocardial infarction (MI), is not likely to be of coronary origin. Third, the presence of accompanying symptoms should be considered. Chest discomfort may be accompanied by other symptoms (including dyspnea, diaphoresis, or nausea), any of which increase the likelihood that the pain is cardiac in origin. However, the presence of accompanying symptoms is not needed to define the discomfort as angina. Fourth, factors that precipitate or relieve the discomfort should be evaluated. Angina typically occurs during physical exertion, during emotional stress, or in

Box 1-1 Differential Diagnosis of Chest Discomfort

Cardiovascular

Ischemic

- Hyperthyroidism
- Tachycardia (e.g., atrial fibrillation)
- Coronary spasm
- Coronary atherosclerosis (angina pectoris)
- Acute coronary syndrome
- Aortic stenosis
- Hypertrophic cardiomyopathy
- Aortic regurgitation
- Mitral regurgitation
- Severe systemic hypertension
- Severe right ventricular/pulmonary hypertension
- Severe anemia/hypoxia

Nonischemic

- Aortic dissection
- Pericarditis
- Mitral valve prolapse syndrome: autonomic dysfunction

Gastrointestinal

- Gastroesophageal reflux disease
- Esophageal spasm
- Esophageal rupture
- Hiatal hernia
- Cholecystitis

Pulmonary

- Pulmonary embolus
- Pneumothorax
- Pneumonia
- Chronic obstructive pulmonary disease
- Pleurisy

Neuromusculoskeletal

- Thoracic outlet syndrome
- Degenerative joint disease of the cervical or thoracic spine
- Costochondritis
- Herpes zoster

Psychogenic

- Anxiety
- Depression
- Cardiac psychosis
- Self-gain

other circumstances of increased myocardial oxygen demand. When exercise precipitates chest discomfort, relief after cessation of exercise substantiates the diagnosis of angina. Sublingual nitroglycerin also relieves angina, generally over a period of minutes. Instant relief or relief after longer periods lessens the likelihood that the chest discomfort was angina.

Although the presence of symptoms during exertion is important in assessing CHD risk, individuals, especially sedentary ones, may have angina-like symptoms that are not related to exertion. These include postprandial and nocturnal angina or angina that occurs while the individual is at rest. As described herein, "rest-induced angina," or the new onset of angina, connotes a pathophysiology different from effort-induced angina. Angina can also occur in persons with fixed CAD and increased myocardial oxygen demand due to anemia, hyperthyroidism, or similar conditions (Box 1-2). Angina occurring at rest, or with minimal exertion, may denote a different pathophysiology, one involving platelet aggregation and clinically termed "unstable angina" or "acute coronary syndrome" (see Chapters 13 and 14).

Patients with heart disease need not present with chest pain at all. Anginal equivalents include dyspnea during exertion, abdominal discomfort, fatigue, or decreased exercise tolerance. Clinicians must be alert to and specifically ask about these symptoms. Often, a patient's family member or spouse notices subtle changes in endurance in the patient or that the individual no longer performs functions that require substantial physical effort. Sometimes patients may be unable to exert themselves due to comorbidities. For instance, the symptoms of myocardial ischemia may be absent in patients with severe peripheral vascular disease who have limiting claudication. One should also be attuned to subtle or absent symptoms in individuals with diabetes mellitus (including type 1 and type 2 diabetes), a "coronary risk equivalent" as defined by the Framingham Risk Calculator.

When considering the likelihood that CHD accounts for a patient presenting with chest discomfort or any of the aforementioned variants, assessment of the cardiac risk factor profile is important. The Framingham Study first codified the concept of cardiac risk factors, and over time, quantification of risk using these factors has become an increasingly useful tool in clinical medicine. Cardiac risk factors determined by the Framingham Study include a history of cigarette smoking, diabetes mellitus, hypertension, or hypercholesterolemia; a family history of CHD (including MI, sudden cardiac death, and first-degree relatives having undergone coronary revascularization); age; and sex (male). Although an attempt has been made to rank these risk factors, all are important, with a history of diabetes mellitus being perhaps the single most important factor. Subsequently, a much longer list of potential predictors of cardiac risk has been made (Box 1-3). An excellent, easy-to-use model for predicting risk is the Framingham Risk Calculator, as described in the Adult Treatment Panel III guidelines from the National Heart, Lung and Blood Institute (see "Evidence" section).

Symptoms suggestive of vascular disease require special attention. Peripheral vascular disease may mask CHD, because the individual may not be able to exercise sufficiently to provoke angina. A history of stroke, transient ischemic attack, or atheroembolism in any vascular distribution is usually evidence of significant vascular disease. Sexual dysfunction in men is not an uncommon presentation of peripheral vascular disease. The presence of Raynaud's-type symptoms should also be elicited, because such symptoms suggest abnormal vascular tone and function, and increase the risk that CHD is present.

Determining whether the patient has stable or unstable angina is as important as making the diagnosis of angina. Stable angina is important to evaluate and treat, but does not necessitate emergent intervention. Unstable angina, or acute coronary syndrome, however, carries a significant risk of MI or death in the immediate future. The types of symptoms reported by patients with stable and unstable angina differ little, and the risk factors for both are identical. Indeed, the severity of symptoms is not necessarily greater in patients with unstable angina, just as a lack of chest discomfort does not rule out significant CHD. The important distinction between stable and unstable coronary syndromes rests in whether the onset is new or recent and/or progressive (e.g., occurring more frequently or with less

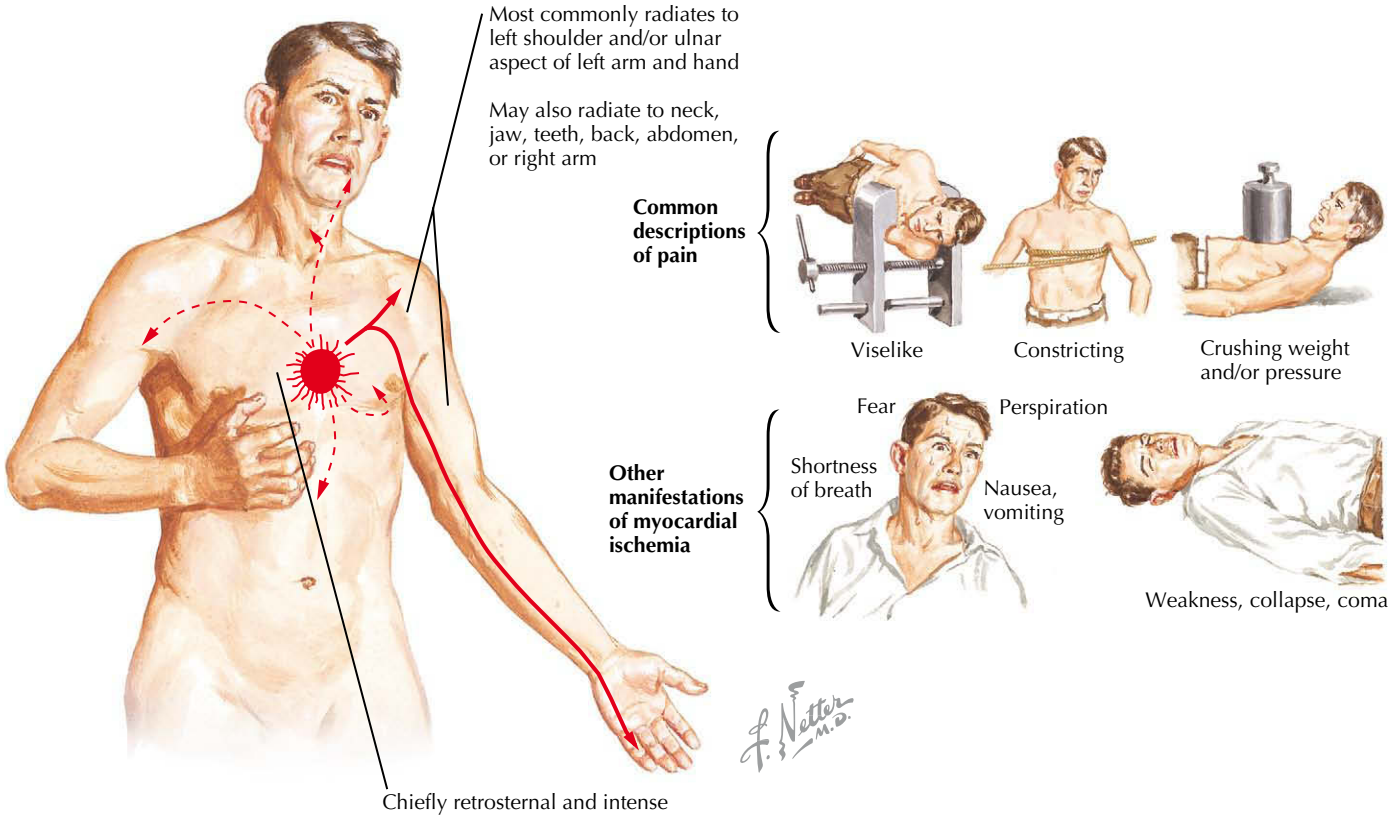


Figure 1-1 *Pain of myocardial ischemia.*

exertion). The initial presentation of angina is, by definition, unstable angina; although for a high percentage of individuals this may merely represent the first recognizable episode of angina. For those with unstable angina, the risk of MI in the near future is markedly increased. Likewise, when the patient experiences angina in response to decreased levels of exertion or when exertional angina has begun to occur at rest, these urgent circumstances require immediate therapy. The treatment of stable angina and acute coronary syndrome is discussed in Chapters 12, 13, and 14. The Canadian Cardiovascular Society Functional Classification of Angina Pectoris is a useful guide for everyday patient assessment (Box 1-4). Categorizing patients according to their class of symptoms is rapid and precise and can be used in follow-up. Class IV describes the typical patient with acute coronary syndrome.

Box 1-2 Conditions that Cause Increased Myocardial Oxygen Demand

- Hyperthyroidism
- Tachycardia of various etiologies
- Hypertension
- Pulmonary embolism
- Pregnancy
- Psychogenic
- Central nervous system stimulants
- Exercise
- Psychological stress
- Fever

Finally, it is important to distinguish those patients who have noncoronary causes of chest discomfort from those with CHD. Patients with gastroesophageal reflux disease (GERD) often present with symptoms that are impossible to distinguish from angina. In numerous studies, GERD is the most common diagnosis in patients who undergo diagnostic testing for angina and are found not to have CHD. The characteristics of the pain can be identical. Because exercise can increase intra-abdominal pressure, GERD may be exacerbated with exercise, especially after meals. Symptoms from GERD can also be relieved with use of sublingual nitroglycerin. GERD can also result in

Box 1-3 Cardiac Risk Factors

- Diabetes
- Smoking
- Hypertension
- High cholesterol
- Hyperlipidemia
- Sedentary lifestyle
- High-fat diet
- Stress
- "Metabolic syndrome"
- Family history of CHD (including history of MI, sudden cardiac death, and first-degree relatives who underwent coronary revascularization)
- Age
- Male sex
- Obesity

CHD, coronary heart disease; MI, myocardial infarction.

Box 1-4 Canadian Cardiovascular Society Classification of Angina Pectoris

- **I** Ordinary physical activity, for example, walking or climbing stairs, does not cause angina; angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
- **II** Slight limitation of ordinary activity; for example, angina occurs when walking or stair climbing after meals, in cold, in wind, under emotional stress, or only during the few hours after awakening, when walking more than two blocks on the level, or when climbing more than one flight of ordinary stairs at a normal pace and during normal conditions.
- **III** Marked limitation of ordinary activity; for example, angina occurs when walking one or two blocks on the level or when climbing one flight of stairs during normal conditions and at a normal pace.
- **IV** Inability to carry on any physical activity without discomfort; angina syndrome may be present at rest.

From Campeau L. Grading of angina pectoris [letter]. *Circulation.* 1976;54:522–523.

early-morning awakening (as can unstable angina) but tends to awaken individuals 2 to 4 hours after going to sleep, rather than 1 to 2 hours before arising, as is the case with unstable angina. Other causes (see Box 1-1) of angina-like pain can be benign, or suggestive of other high-risk syndromes, such as aortic dissection or pulmonary embolus. Many of these "coronary mimics" can be ruled out by patient history, but others, such as valvular aortic stenosis, can be confirmed or excluded by physical examination. The goal of taking the history is to alert the clinician to entities that can be confirmed or excluded by physical examination, or that necessitate further diagnostic testing.

Dyspnea, Edema, and Ascites

Dyspnea can accompany angina pectoris or it can be an anginal equivalent. Dyspnea can also reflect congestive heart failure (CHF) or occur because of noncardiac causes. The key to understanding the etiology of dyspnea is a clear patient history, which is then confirmed by a targeted physical examination.

Dyspnea during exertion that quickly resolves at rest or with use of nitroglycerin may be a result of myocardial ischemia. It is important to establish the amount of activity necessary to provoke dyspnea, the reproducibility of these symptoms, and the duration of recovery. As with angina, dyspnea as an anginal equivalent or an accompanying symptom tends to occur at a given workload or stress level; dyspnea occurring one day at low levels of exertion but not prompted by vigorous exertion on another day is less likely to be an anginal equivalent.

In patients with CHF, dyspnea generally reflects increased left ventricular (LV) filling pressures (Fig. 1-2). Although most commonly LV systolic dysfunction is the cause of the dyspnea, dyspnea also occurs in individuals with preserved LV systolic function and severe diastolic dysfunction. These two entities present differently, however, and physical examination can

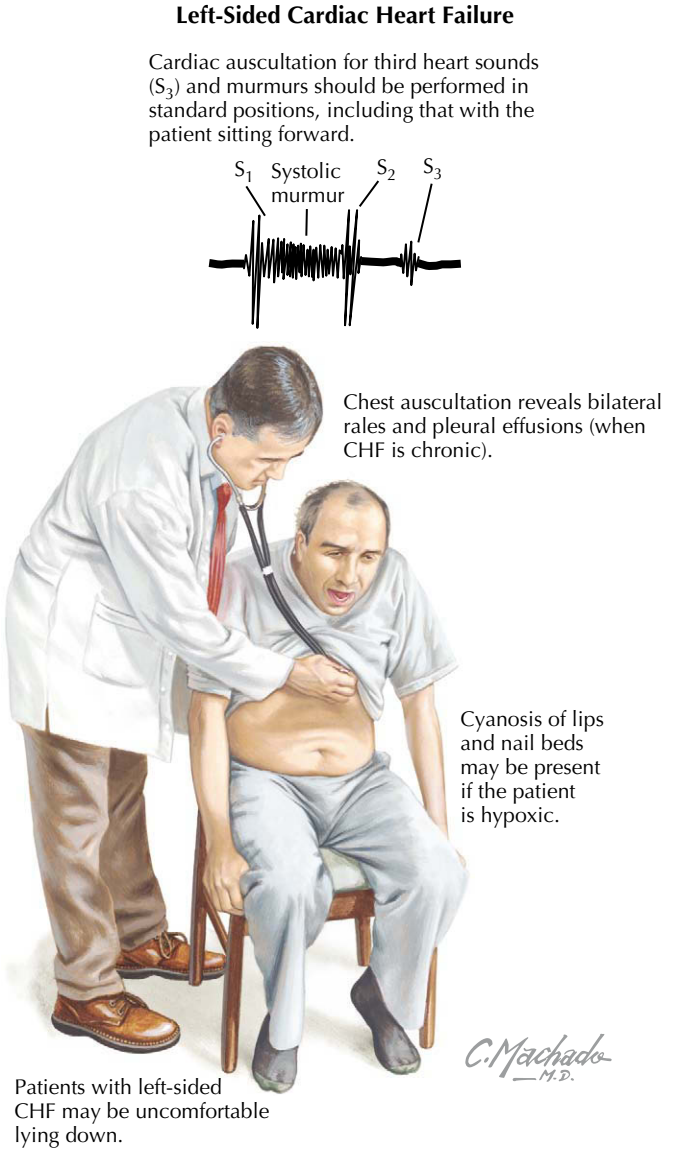


Figure 1-2 *Physical examination.* CHF, congestive heart failure.

distinguish them. With LV systolic dysfunction, dyspnea tends to gradually worsen, and its exacerbation is more variable than that of exertional dyspnea resulting from myocardial ischemia, although both are due to fluctuations in pulmonary arterial volume and left atrial filling pressures. Typically, patients with LV systolic dysfunction do not recover immediately after exercise cessation or use of sublingual nitroglycerin, and the dyspnea may linger for longer periods. Orthopnea, the occurrence of dyspnea when recumbent, or paroxysmal nocturnal edema provides further support for a presumptive diagnosis of LV systolic dysfunction. Patients with LV diastolic dysfunction tend to present abruptly with severe dyspnea that resolves more rapidly in response to diuretic therapy than does dyspnea caused by LV systolic dysfunction. The New York Heart Association (NYHA) Classification for CHF (Table 1-1) is extremely useful in following patients with CHF and provides a simple and rapid means for longitudinal assessment. The NYHA Classification

Table 1-1 Comparison of the ACC/AHA and the NYHA Classifications of Heart Failure

ACC/AHA Stage		*NYHA Functional Class*	
Stage	**Description**	**Class**	**Description**
A	Patients without structural heart disease and without symptoms of heart failure but who are at high risk for the development of heart failure	No comparable functional class	
B	Patients with structural heart disease that is strongly associated with the development of heart failure but who have never shown signs or symptoms of heart failure	I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
C	Patients who have current or prior symptoms of heart failure and underlying structural heart disease	II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
		III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
D	Patients with advanced structural heart disease and symptoms of heart failure at rest despite maximal medical therapy	IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

ACC/AHA, American College of Cardiology/American Heart Association; NYHA, New York Heart Association. NYHA data from the Criteria Committee of the New York Heart Association. *Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis*. Boston: Brown; 1964. ACC/AHA data from ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult. *Circulation.* 2005:112:e154–e235.

also correlates well with prognosis. Patients who are NYHA class I have a low risk of death or hospital admission within the following year. In contrast, the annual mortality rate of those with NYHA class IV symptoms exceeds 30%.

As with chest discomfort, the differential diagnosis of dyspnea is broad, encompassing many cardiac and noncardiac causes (Box 1-5). Congenital heart disease, with or without pulmonary hypertension, can cause exertional dyspnea. Patients with significant intra- or extracardiac shunts and irreversible pulmonary hypertension (Eisenmenger's syndrome) are dyspneic during minimal exertion and often at rest. It is also possible to have dyspnea because of acquired valvular heart disease, usually from aortic or mitral valve stenosis or regurgitation. All of these causes should be easily distinguished from CHD or CHF by physical examination. Primary pulmonary causes of dyspnea must be considered, with chronic obstructive pulmonary disease (COPD) and reactive airways disease (asthma) being most common. Again, a careful history for risk factors (e.g., cigarette smoking, industrial exposure, allergens) associated with these entities and an accurate physical examination should distinguish primary pulmonary causes from dyspnea due to CHD or CHF.

Peripheral edema and ascites are physical examination findings consistent with pulmonary hypertension and/or right ventricular (RV) failure. These findings are included in the history because they may be part of the presentation. Although patients often comment on peripheral edema, with careful questioning they may also identify increasing abdominal girth consistent with ascites. Important questions on lower extremity edema include determination of whether the edema is symmetric (unilateral edema suggests alternate diagnoses) and whether the edema improves or resolves with elevation of the lower extremities. The finding of "no resolution overnight" argues against RV failure as an etiology. In addition, for peripheral edema and ascites, it is important to ask questions directed toward determining the presence of anemia, hypoproteinemia, or other

Box 1-5 Differential Diagnosis of Dyspnea

Pulmonary
- Reactive airways disease (asthma)
- Chronic obstructive pulmonary disease
- Emphysema
- Pulmonary edema
- Pulmonary hypertension
- Lung transplant rejection
- Infection
- Interstitial lung disease
- Pleural disease
- Pulmonary embolism
- Respiratory muscle failure
- Exercise intolerance

Cardiac
- Ischemic heart disease/angina pectoris
- Right-sided heart failure
- Aortic stenosis or regurgitation
- Arrhythmias
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Congestive heart failure
- Mitral regurgitation or stenosis
- Mediastinal abnormalities
- Pericardial tuberculosis
- Transposition of the great arteries

Other
- Blood transfusion reaction
- Measles

causes. The differential diagnosis of edema is broad and beyond the scope of this chapter.

Palpitations and Syncope

It is normal to be aware of the sensation of the heart beating, particularly during or immediately after exertion or emotional stress. *Palpitations* refer to an increased awareness of the heart beating. Patients use many different descriptions, including a "pounding or racing of the heart," the feeling that their heart is "jumping" or "thumping" in their chest, the feeling that the heart "skips beats" or "races," or countless other descriptions. A history showing that palpitations have begun to occur during or immediately after exertion, and not at other times, raises the concern that these sensations reflect ventricular ectopy associated with myocardial ischemia. It is more difficult to assess the significance of palpitations occurring at other times. Supraventricular and ventricular ectopy may occur at any time and may be benign or morbid. As discussed in Chapters 29, 30, and 31, ventricular ectopy is worrisome in patients with a history of MI or cardiomyopathy. Lacking this information, clinicians should be most concerned if lightheadedness or presyncope accompanies palpitations.

Syncope generally indicates an increased risk for sudden cardiac death and is usually a result of cardiovascular disease and arrhythmias. If a syncopal episode is a presenting complaint, the patient should be admitted for further assessment. In approximately 85% of patients, the cause of syncope is cardiovascular. In patients with syncope, one must assess for CHD, cardiomyopathy, and congenital or valvular heart disease. In addition, neurocardiogenic causes represent a relatively common and important possible etiology for syncope. Box 1-6 shows the differential diagnosis for syncope. It is critical to determine whether syncope really occurred. A witness to the episode and documentation of an intervening period are very helpful. In addition, with true syncope, injuries related to the sudden loss of consciousness are common. However, an individual who reports recurrent syncope (witnessed or unwitnessed) but has never injured himself or herself may not be experiencing syncope. This is not to lessen the concern that a serious underlying medical condition exists but instead to reaffirm that the symptoms fall short of syncope, with its need for immediate evaluation.

Box 1-6 Differential Diagnosis for Syncope

Cardiogenic

- Mechanical
  - Outflow tract obstruction
  - Pulmonary hypertension
  - Congenital heart disease
  - Myocardial disease: low-output states
- Electrical
  - Bradyarrhythmias
  - Tachyarrhythmias
- Neurocardiogenic
  - Vasovagal (vasodepression)
  - Orthostatic hypotension

Other

- Peripheral neuropathy
- Medications
- Primary autonomic insufficiency
- Intravascular volume depletion
- Reflex
- Cough
- Micturition
- Acute pain states
- Carotid sinus hypersensitivity

THE PHYSICAL EXAMINATION

There are several advantages to obtaining a patient's history before the physical examination. First, the information gained in the history directs the clinician to pay special attention to aspects of the physical examination. For instance, a history consistent with CHD necessitates careful inspection for signs of vascular disease; a history suggestive of CHF should make the clinician pay particular attention to the presence of a third heart sound. Second, the history allows the clinician to establish a rapport with patients, to assure patients that he or she is interested in their well-being, and that the physical examination is an important part of a complete evaluation. In this light, the therapeutic value of the physical examination to the patient should not be underestimated. Despite the emphasis on technology today, even the most sophisticated patients expect to be examined, to have their hearts listened to, and to be told whether worrisome findings exist or the examination results were normal.

General Inspection and Vital Signs

Much useful information can be gained by an initial "head-to-toe" inspection and assessment of vital signs. For instance, truncal obesity may signal the presence of type 2 diabetes or the metabolic syndrome. Cyanosis of the lips and nail beds may indicate underlying cyanotic heart disease. Hairless, dry-skinned lower extremities or distal ulceration may indicate peripheral vascular disease. Other findings are more specific (Fig. 1-3). Abnormalities of the digits are found in atrial septal defect; typical findings of Down's syndrome indicate an increased incidence of ventricular septal defect or more complex congenital heart disease; hyperextensible skin and lax joints are suggestive of Ehlers-Danlos syndrome; and tall individuals with arachnodactyly, lax joints, pectus excavatum, and an increased arm length-to-height ratio may have Marfan's syndrome. These represent some of the more common morphologic phenotypes in individuals with heart disease. Vital signs can also be helpful. Although normal vital signs do not rule out CHD, marked hypertension may signal cardiac risk, whereas tachycardia, tachypnea, and/or hypotension at rest suggest CHF.

Important Components of the Cardiovascular Examination

The clinician should focus efforts on those sites that offer a window into the heart and vasculature. Palpation and careful inspection of the skin for secondary changes because of vascular disease or diabetes is important. Lips, nail beds, and fingertips

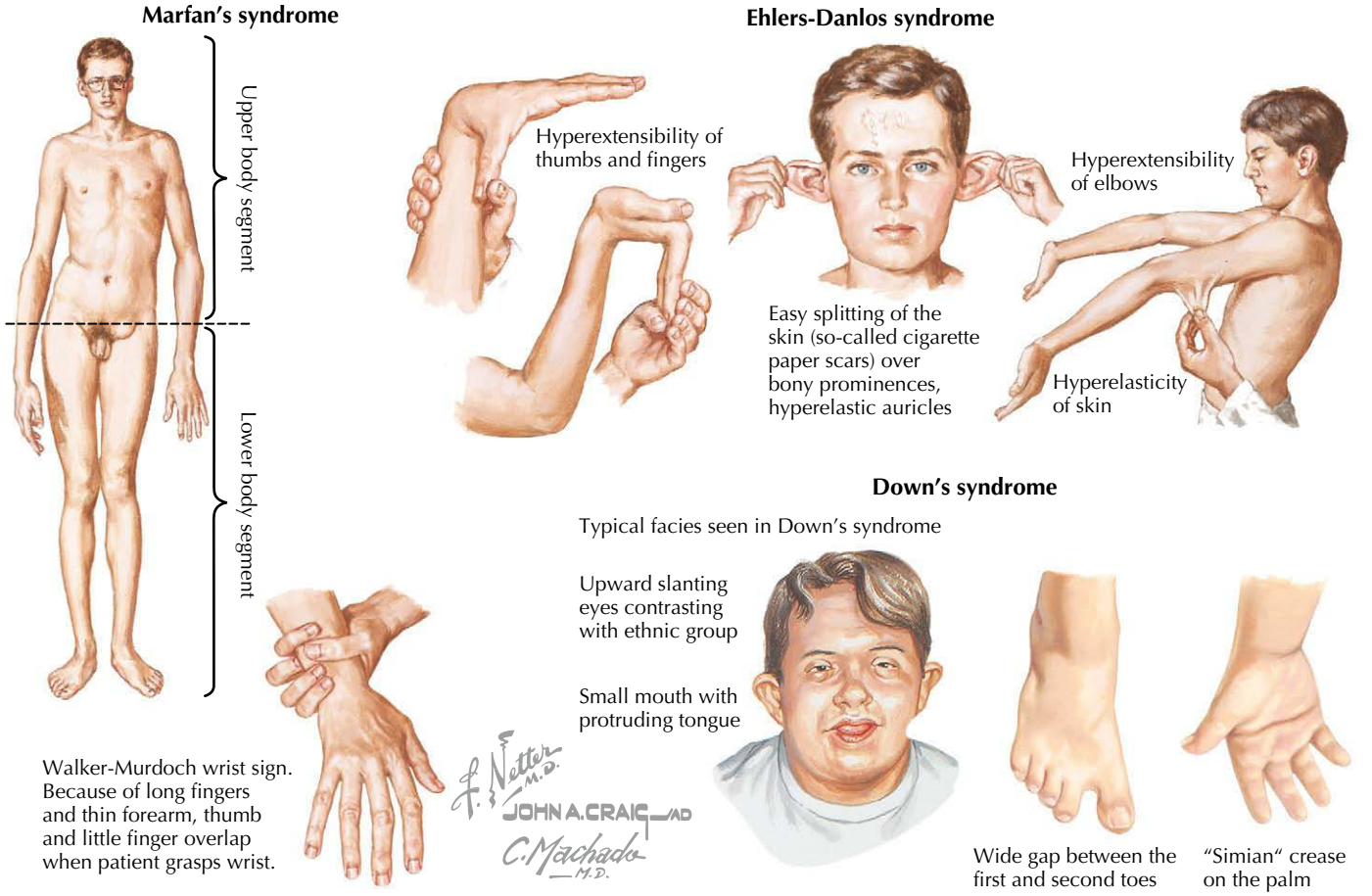


Figure 1-3 *Physical examination: general inspection.*

should be examined for cyanosis (including clubbing of the fingernails) and, when indicated, for signs of embolism. Examination of the retina using an ophthalmoscope can reveal evidence of long-standing hypertension, diabetes, or atheroembolism, denoting underlying vascular disease. Careful examination of the chest, including auscultation, can help to differentiate causes of dyspnea. The presence of dependent rales is consistent with left-sided heart failure. Pleural effusions can result from long-standing LV dysfunction or noncardiac causes and can be present with predominantly right-sided heart failure, representing transudation of ascites into the pleural space. Hyperexpansion with or without wheezing suggests a primary pulmonary cause of dyspnea, such as COPD or reactive airways disease. The presence of wheezing rather than rales does not rule out left-sided heart failure. It is not uncommon to hear wheezing with left-sided CHF. Most commonly, wheezing from left-sided CHF is primarily expiratory. Inspiratory and expiratory wheezing, particularly with a prolonged inspiratory-to-expiratory ratio, is more likely to be caused by intrinsic lung disease.

The vascular examination is an important component of a complete evaluation. The quality of the pulses, in particular the carotid and the femoral pulses, can identify underlying disease (Fig. 1-4). Diminished or absent distal pulses indicate peripheral vascular disease. The examiner should also auscultate for bruits over both carotids, over the femoral arteries, and in the abdomen. Abdominal auscultation should be performed, carefully listening for aortic or renal bruits, in the mid-abdominal area before abdominal palpation, which can stimulate increased bowel sounds. Distinguishing bruits from transmitted murmurs in the carotid and abdominal areas can be challenging. When this is a concern, carefully marching out from the heart using the stethoscope can be helpful. If the intensity of the murmur or bruit continually diminishes farther from the heart, it becomes more likely that this sound originates from the heart, rather than from a stenosis in the peripheral vasculature. Much information is available about the peripheral vascular examination, but by following the simple steps outlined herein, the examiner can gather the majority of the accessible clinical information.

Examination of the jugular venous pulsations is a commonly forgotten step. Jugular venous pressure, which correlates with right atrial pressure and RV diastolic pressure, should be estimated initially with the patient lying with the upper trunk elevated 30 degrees. In this position, at normal jugular venous pressure, no pulsations are visible. This correlates roughly to a jugular venous pressure less than 6 to 10 cm. The absence of jugular vein pulsations with the patient in this position can be confirmed by occluding venous return by placing a fingertip parallel to the clavicle in the area of the sternocleidomastoid muscle. The internal and external jugular veins should partially

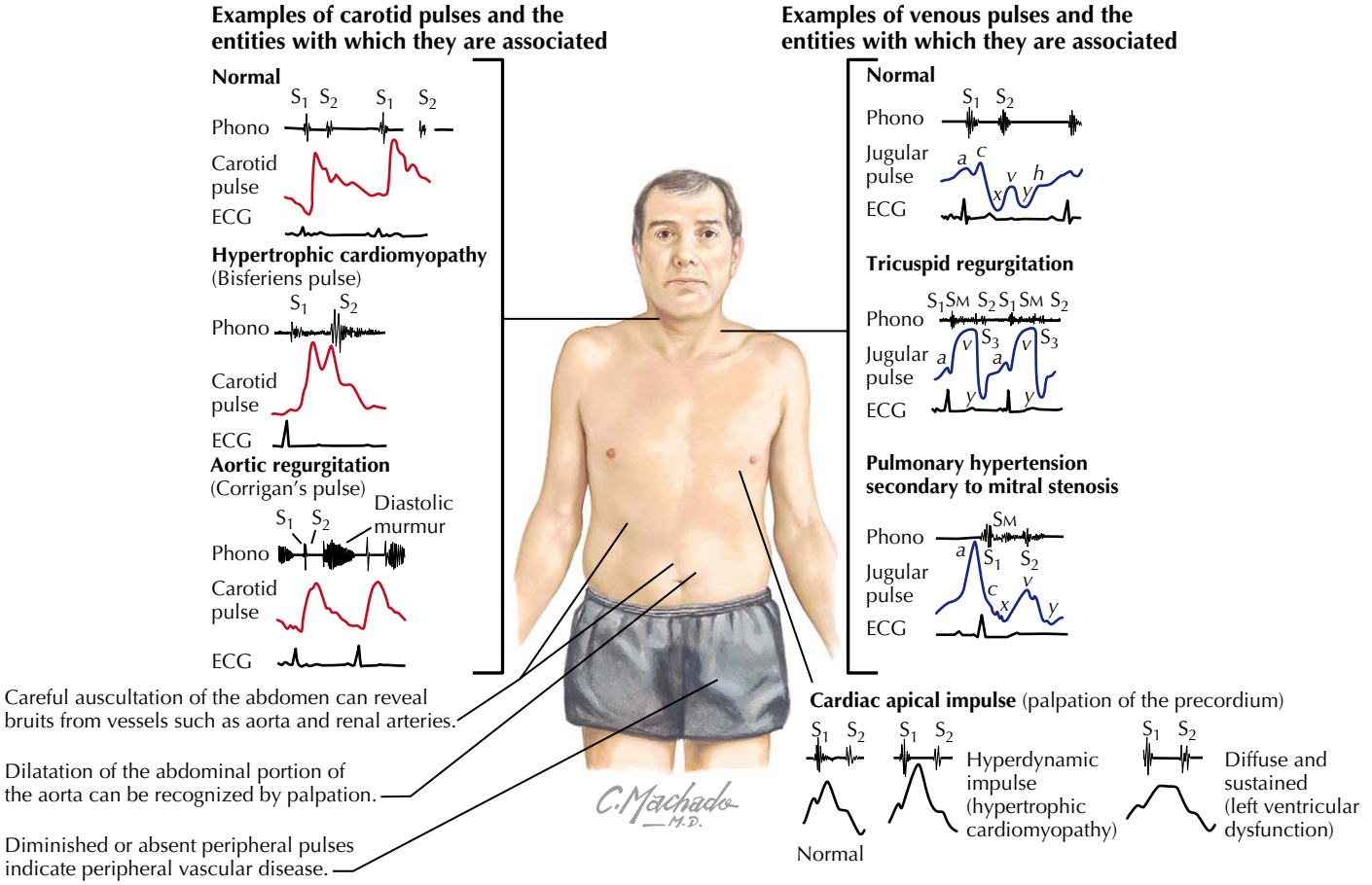


Figure 1-4 *Important components of cardiac examination.* ECG, electrocardiogram.

fill. Although with normal jugular venous pressure examination of the waveforms is less important, the head of the examination table can be lowered until the jugular venous pulsations are evident. When the jugular venous pulsations are visible at 30 degrees, the examiner should note the waveforms. It is possible to observe and time the *a* and *v* waves by simultaneously timing the cardiac apical impulse or the carotid impulse on the contralateral side. An exaggerated *a* wave is consistent with increased atrial filling pressures because of tricuspid valve stenosis or increased RV diastolic pressure. A large *v* wave generally indicates tricuspid valve regurgitation, a finding easily confirmed by auscultation.

Finally, before cardiac auscultation it is important to palpate the precordium. This is the easiest way to identify dextrocardia. Characteristics of the cardiac impulse can also yield important clues about underlying disease. Palpation of the precordium is best performed from the patient's right side with the patient lying flat. The cardiac apical impulse is normally located in the fifth intercostal space along the midclavicular line. Most examiners use the fingertips to palpate the apical impulse. It is often possible to palpate motion corresponding to a third or fourth heart sound. Use of the fingertips offers fine detail on the size and character of the apical impulse. A diffuse and sustained apical impulse is consistent with LV systolic dysfunction. Patients with hypertrophic cardiomyopathy, in contrast, often have a hyperdynamic apical impulse. Thrills, palpable vibrations from loud murmurs or bruits, can also be palpated.

The RV impulse, if identifiable, is located along the left sternal border. Many clinicians prefer to palpate the RV impulse with the base of the hand, lifting the fingertips off the chest wall. In RV hypertrophy, a sustained impulse can be palpated, and the fingertips then can be placed at the LV impulse to confirm that the two are distinct. In patients with a sustained RV impulse, the examiner should again look for prominent *a* and *v* waves in the jugular venous pulsations.

Cardiac Auscultation

Hearing and accurately describing heart sounds is arguably the most difficult part of the physical examination. For this reason and because of the commonplace use of echocardiography, many clinicians perform a cursory examination. The strongest arguments for performing cardiac auscultation carefully are to determine whether further diagnostic testing is necessary; to correlate findings of echocardiography with the clinical examination so that, in longitudinal follow-up, the clinician can determine progression of disease without repeating echocardiography at each visit; and because the more a clinician makes these correlations, the better his or her skills in auscultation will become and the better his or her patients will be served. It should also

be noted that, with normal general cardiac physical examination results, the absence of abnormal heart sounds, and a normal electrocardiogram, the use of echocardiography for evaluation of valvular or congenital heart disease is not indicated. Furthermore, if there are no symptoms of CHF or evidence of hemodynamic compromise, echocardiography is not indicated for assessment of LV function. Practice guidelines from cardiologists and generalists agree on this point, as do third-party insurers. It is neither appropriate nor feasible to replace a careful cardiovascular examination using auscultation with more expensive testing.

The major impact of echocardiography has been in quantitative assessment of cardiovascular hemodynamics—that is, the severity of valvular and congenital heart disease. No longer is it necessary for the clinician to make an absolute judgment on whether an invasive assessment (cardiac catheterization) is needed to further define hemodynamic status or whether the condition is too advanced to allow surgical intervention based on history and physical examination. But instead of diminishing the role of cardiac auscultation, the advent of echocardiography has redefined it. Auscultation remains important as a screening technique for significant hemodynamic abnormalities, as an independent technique to focus and verify the echocardiographic study, and an important means by which the physician can longitudinally follow patients with known disease.

There are several keys to excellence in auscultation. Foremost is the ability to perform a complete general cardiac physical examination, as described. The findings help the examiner focus on certain auscultatory features. Second, it is important to use a high-quality stethoscope. Largely dictated by individual preference, clinicians should select a stethoscope that has bell and diaphragm capacity both (for optimal appreciation of low- and high-frequency sounds, respectively) and that fits the ears comfortably and is well insulated so that external sounds are minimized. Third, it is important to perform auscultation in a quiet environment. Particularly as skills in auscultation are developing, trying to hone these in the hall of a busy emergency department or on rounds while others are speaking is time spent poorly. Additionally, taking the time to return to see a patient with interesting findings detected during auscultation, and repetition, are keys to becoming competent in auscultation.

The patient should be examined while he or she is in several positions: while recumbent, while in the left lateral decubitus position, and while sitting forward. Every patient is different and, using all three positions, the examiner can optimize the chance that soft heart sounds can be heard. Likewise, it is important to listen carefully at the standard four positions on the chest wall (Fig. 1-5), as well as over the apical impulse and RV impulse (if present). It is also best to isolate different parts of the examination in time. Regardless of the intensity of various sounds, it is best always to perform the examination steps in the same chronologic order, so that the presence of a loud murmur, for instance, does not result in failure to listen to the other heart sounds.

Listen for S_1 (the first heart sound) first. As with jugular venous pulsations, the heart sounds can be timed by simultaneously palpating the cardiac apical impulse or the carotid upstroke. Even the most experienced clinician occasionally needs to time the heart sounds. Is a single sound present, or is the first heart sound split? Is a sound heard before S_1, indicating an S_4? Next, listen to the second heart sound. Normally the first component (A_2, the aortic valve closing sound) is louder than the second component (P_2, the pulmonic valve closing sound). A louder second component may indicate increased pulmonary pressure. A more subtle finding is a reversal of A_2 and P_2 timing that occurs with left bundle branch block and in some other circumstances. Additionally, it is important to assess whether A_2 and P_2 are normally split or whether they are widely split with no respiratory variation—a finding suggestive of an atrial septal defect. The examiner should then listen carefully for a third heart sound. An S_3 is often best heard over the tricuspid or mitral areas and is a low-frequency sound. It is heard best with the bell and is often not heard with the diaphragm.

After characterizing these heart sounds, it is time to listen carefully for murmurs. Murmurs are classified according to their intensity, their duration, their location, and their auscultatory characteristics: crescendo, decrescendo, blowing, among others. It is also important to note the site where the murmur is loudest and whether the murmur radiates to another area of the precordium or to the carotids. All of these features contribute to determining the origin of the murmur, the likelihood that it represents an acute or chronic process, and how it affects the diagnostic and therapeutic approaches. Most importantly, it is necessary for clinicians to judge whether a murmur represents cardiac disease or is innocent. Innocent murmurs, also termed "flow murmurs," are common in children. More than 60% of children have innocent murmurs. Innocent murmurs become less common in adults; however, an innocent murmur can still be found into the fourth decade of life. Alterations in hemodynamics induced by pregnancy, anemia, fever, hyperthyroidism, or any state of increased cardiac output can produce an innocent murmur. These murmurs are generally midsystolic, heard over the tricuspid or pulmonic areas, and do not radiate extensively. They are often loudest in thin individuals. Innocent murmurs do not cause alterations in the carotid pulse and do not coexist with abnormal cardiac impulses or with other abnormalities, such as extra heart sounds (S_3 and S_4), in adults. In elderly individuals a common finding is a systolic murmur that shares auditory characteristics with the murmur of aortic stenosis; however, carotid upstrokes are normal. This finding, aortic sclerosis, may necessitate confirmation by echocardiography. It represents sclerosis of the aortic leaflets but without significant hemodynamic consequence.

The characteristics of the most common and hemodynamically important murmurs are shown in Figure 1-5. As noted, the murmur is defined not only by its auditory characteristics but also by the company it keeps. Often the key to excellence in auscultation is being thorough in all aspects of the cardiovascular examination.

Maneuvers

No discussion of cardiac auscultation would be complete without the use of maneuvers to accentuate auscultatory findings. As shown in Figure 1-6, patient positioning can alter peripheral vascular resistance or venous return, accentuating murmurs that are modulated by these changes. Murmurs associated with fixed

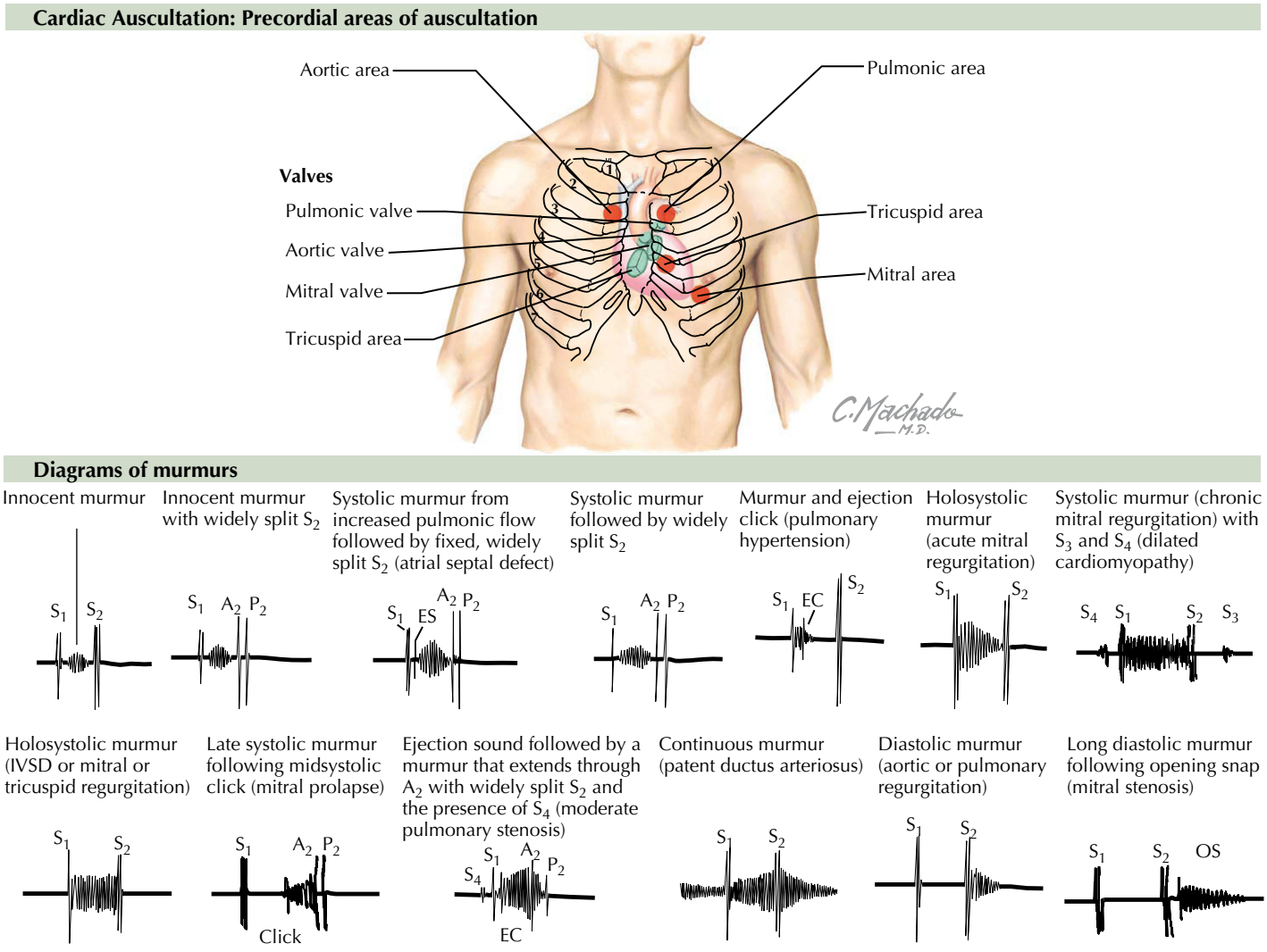


Figure 1-5 *Cardiac auscultation: Correlation of murmurs and other adventitious sounds with underlying pathophysiology.*

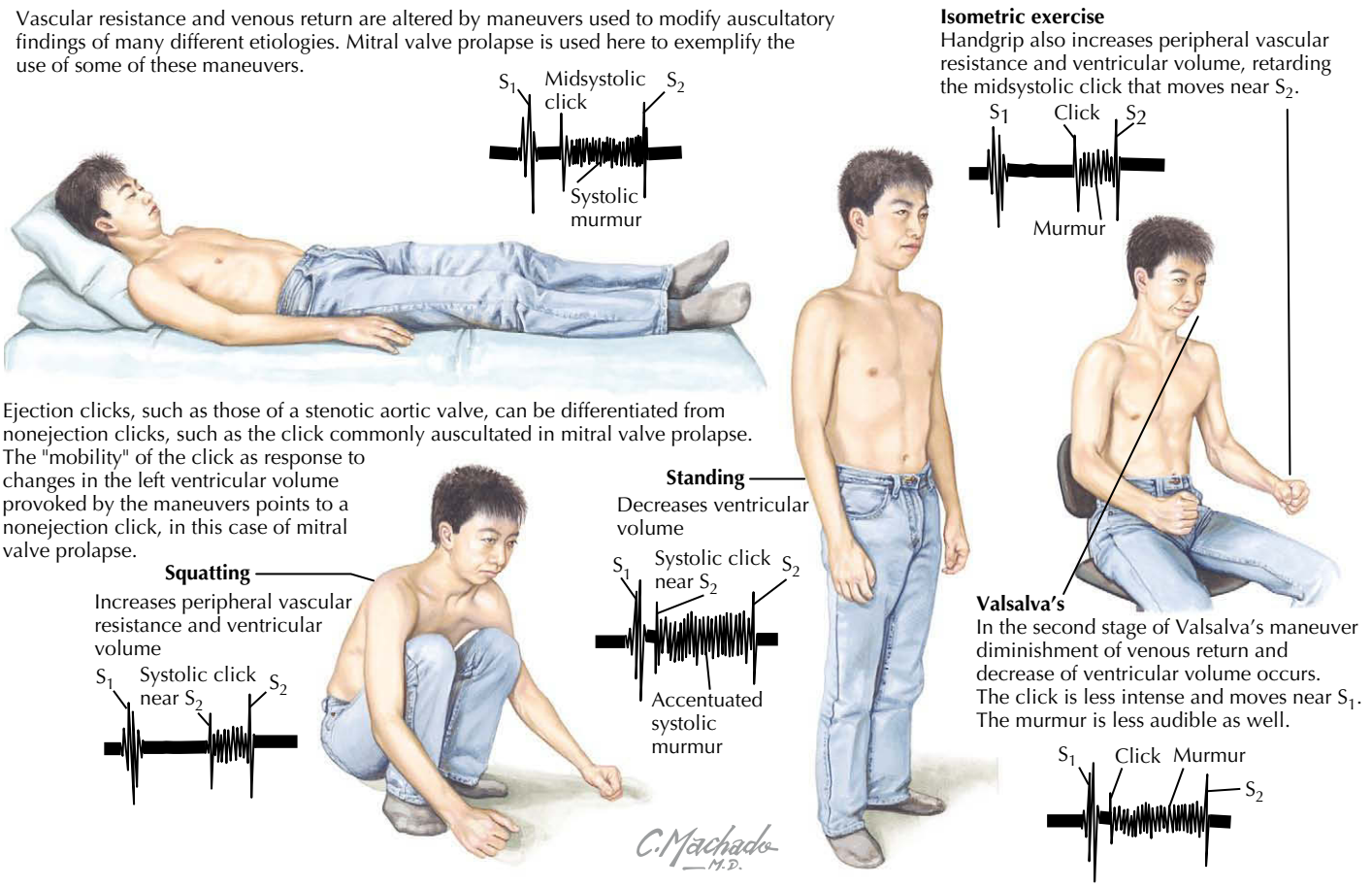


Figure 1-6 *Maneuvers.*

valvular lesions change little with changes in position or the maneuvers illustrated in Figure 1-6. Thus, these maneuvers are most useful for diagnosing entities in which hemodynamic status affects murmurs. The two classic examples are the click and murmur of mitral valve prolapse, as shown, and the aortic outflow murmur of hypertrophic cardiomyopathy (not shown).

FUTURE DIRECTIONS

Handheld echocardiography machines can be carried on the shoulder and have a small transducer that can obtain echocardiographic images of sufficient quality to quantify murmurs and assess LV dysfunction. Although these portable echocardiographic machines have advantages and have been incorporated in medical school curricula at many institutions, they have not yet replaced the stethoscope, nor are they likely to do so.

The roles of cardiac history and physical examination have changed. Before the noninvasive testing of today, astute clinicians were the arbiters of whether invasive diagnostic testing was needed, based largely on examination findings alone. Today it is believed that the role of the clinician is to use physical examination findings to establish the prior probability of cardiovascular disease, whether CHD, valvular heart disease, or congenital heart disease, thereby determining the need for further testing. In the continual quest for improved noninvasive testing, it is likely that a clinician's skill will continue to evolve as the interplay between history taking, physical examination, and diagnostic testing further develops.

ADDITIONAL RESOURCES

ACC/AHA Joint Guidelines. <http://www.americanheart.org/presenter.jhtml?identifier=3004542>; Accessed 22.02.10.

Guidelines outlining the current opinion of experts from the American College of Cardiology and the American Heart Association for managing cardiovascular diseases.

American Heart Association. Heart Profilers. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3000416>; Accessed 22.02.10.

Provides individual specific information based on your risk profile.

National Heart, Lung and Blood Institute. National Cholesterol Education Program. Available at: <http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof>; Accessed 22.02.10.

A website where you can enter patient-specific data to calculate the 10-year risk of a cardiac event based on Framingham data (Framingham Risk Calculator).

EVIDENCE

Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med.* 1979; 300:1350–1358.

A classic discussion of the importance of pre-test and post-test probabilities in interpreting any diagnostic testing.

Harvey WP. *Cardiac Pearls [video recording].* Atlanta: Emory Medical Television Network; 1981.

This video recording is a timeless example of Dr. Harvey—a master clinician—and his approach to the evaluation of patients with cardiovascular disease.

Hurst JW, Morris DC. *Chest Pain.* Armonk, NY: Futura Publishing; 2001.

Drs. Hurst and Morris provide a sophisticated summary on the evaluation of patients with chest pain.

National Heart, Lung and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) and *ATP III Update 2004: Implications of Recent Clinical Trials for the ATP III Guidelines*. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol>; Accessed 10.11.09.

An overview of the current recommendations regarding treatment of elevated lipids.

Coronary Atherosclerosis

Cam Patterson and Marschall S. Runge

2

Cardiovascular diseases (CVDs)—coronary artery disease (CAD), hypertension, congestive heart failure, and stroke—are the leading cause of death and disability in elderly individuals in the Western world. In the United States, the CVD death toll is nearly 1 million each year, and the estimated cost of CVD treatment was over $400 billion for 2006, with the likelihood that the incidence of CVD will continue to increase as the population ages and because of the marked increases in diabetes and obesity that are occurring today. The U.S. Census Bureau projects that nearly one in four individuals will be 65 years of age or older by 2035, and adults older than 65 years are two and a half times more likely to have hypertension and four times more likely to have coronary heart disease than are those in the 40- to 49-year age group. Additionally, throughout all age groups, the incidence of obesity and diabetes has increased dramatically across the United States.

Although the prevalence of atherosclerotic disease continues to increase in developed countries, death rates from CVDs in the United States have decreased by more than a third in the past 2 decades. This effect is due to primary and secondary prevention strategies and to improvements in care and rehabilitation of patients with atherosclerotic diseases.

Despite this encouraging news, atherosclerotic diseases remain an enormous challenge for the clinician, for several reasons. Many preventive strategies involve lifestyle changes that test the compliance of even the most devoted patients. The disease itself progresses silently for decades before symptoms develop, and the initial clinical presentation of atherosclerotic disease is often a catastrophic event, such as myocardial infarction (MI), stroke, or sudden cardiac death (SCD). The diagnosis of atherosclerotic disease, particularly through noninvasive methods, is imperfect, and clinical manifestations of atherosclerotic diseases are often subtle and easily mistaken for causes that are more benign. Therefore, although the diagnosis and treatment of atherosclerotic diseases remain of paramount importance, the promise of future advances rests in a more detailed understanding of atherosclerosis, leading to earlier diagnosis and prevention that is ultimately more effective.

ETIOLOGY AND PATHOGENESIS

Atherosclerotic plaques lead to clinical events (angina, MI) by two mechanisms. First, with gradual enlargement, plaques may obstruct blood flow within epicardial vessels, resulting in ischemia to the myocardial tissue dependent on the affected vessel's blood supply. Alternatively, plaques may become symptomatic because of acute rupture or thrombosis, resulting in catastrophic acute occlusion of a vessel, the hallmark of MI. Indeed, the two mechanisms are apt to be linked, because less catastrophic (and subclinical) episodes of plaque rupture are probably one of the mechanisms by which nonocclusive plaques enlarge to become symptomatic.

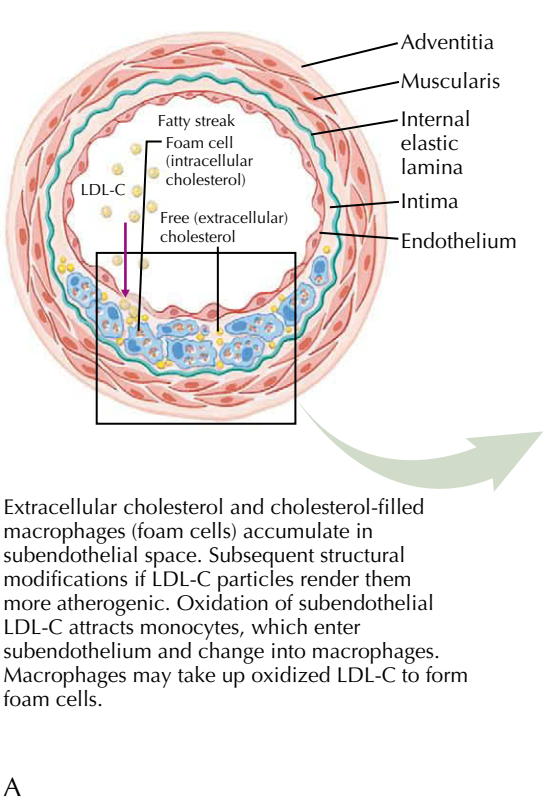
The concept that endothelial injury is an inciting event in atherosclerosis is common to most theories of pathogenesis. Endothelial injury is a component of the earliest stages of atherosclerosis, the formation of lesions that can be detected only at autopsy, the fatty streak (Fig. 2-1A). Most of the well-characterized risk factors for atherosclerosis (hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, advanced age, elevated plasma homocysteine concentrations) injure the endothelium, initiating a chain of events, all attributes of atherosclerosis: smooth muscle cell (SMC) proliferation, inflammatory cell recruitment, and lipid deposition within the blood vessel (Fig. 2-1B). Though still early in development, potential diagnostic and/or therapeutic approaches based upon inflammatory signaling pathways now known to be important in atherogenesis hold promise.

Endothelial injury and the subsequent events that occur in the vessel wall initiate the progression from stable to unstable atherosclerotic plaques, ultimately leading to the rupture of unstable plaques, thrombosis of the vessel, and, in many cases, MI (Fig. 2-2). Lesion development in the medium and small vessels of cerebral vessels leads to stroke, and in renal and mesenteric vasculature contributes to diabetic complications.

An abundance of evidence suggests that atherosclerotic lesions, at least in part, result from an excessive inflammatory response. For example, although elevated low-density lipoprotein cholesterol (LDL-C) is a risk factor for premature atherosclerosis, the LDL-C must undergo oxidative modification to cause damage to the arterial wall. Cytokines, growth factors, and oxidative stress may also contribute to atherosclerosis by mechanisms that are independent of LDL-C oxidation. Any of these mediators can rapidly react with and inactivate nitric oxide, enhancing proatherogenic mechanisms such as leukocyte adhesion to endothelium, impaired vasorelaxation, and platelet aggregation (Fig. 2-3).

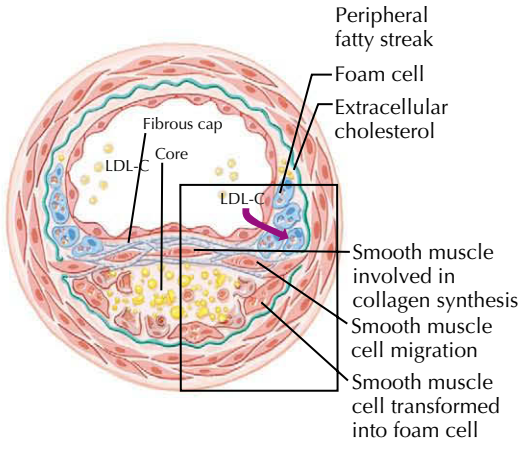
Numerous adaptive changes in vascular structure occur with aging in healthy individuals. These changes include increases in arterial stiffening, aortic root size, and aortic wall thickness (which resembles the increased intimal medial thickness during early atherogenesis) and measurable abnormalities in vascular function, such as enhanced arterial systolic and pulse pressure. Collagen content is increased, but elastin content is decreased.

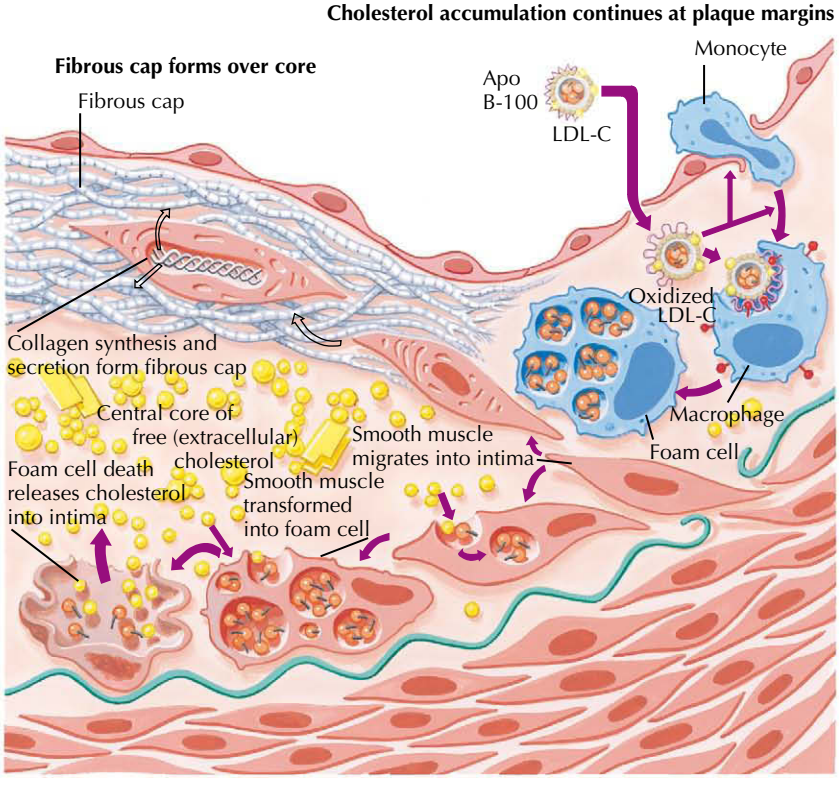
Throughout the spectrum of atherogenesis, SMCs play a pivotal role. SMCs are not terminally differentiated and can undergo phenotypic modulation, reverting to cells capable of proliferation, migration, and secretion of mediators involved in these processes. These modulated SMC phenotypes have potentially opposing functions because they can repair vascular damage but can also contribute to vascular disease such as hypertension and atherosclerosis. In arteries prone to develop atherosclerosis, and in the sites of plaque destabilization and rupture, the terminal events in lesion progression—the number of SMCs—is often decreased. Because SMCs are



Extracellular cholesterol and cholesterol-filled macrophages (foam cells) accumulate in subendothelial space. Subsequent structural modifications if LDL-C particles render them more atherogenic. Oxidation of subendothelial LDL-C attracts monocytes, which enter subendothelium and change into macrophages. Macrophages may take up oxidized LDL-C to form foam cells.

A





Fibrous plaque larger than fatty streak and occupies more of arterial lumen. Thickened cap synthesized by modified smooth muscle cells. Central core consists of extracellular cholesterol. Foam cells surrounding core derived primarily from smooth muscle cells. Fatty streaks may continue to form at periphery of plaque.

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B

Figure 2-1 *Atherogenesis:* (**A**) Fatty streak formation. (**B**) Fibrous plaque formation. LDL-C, low-density lipoprotein cholesterol.

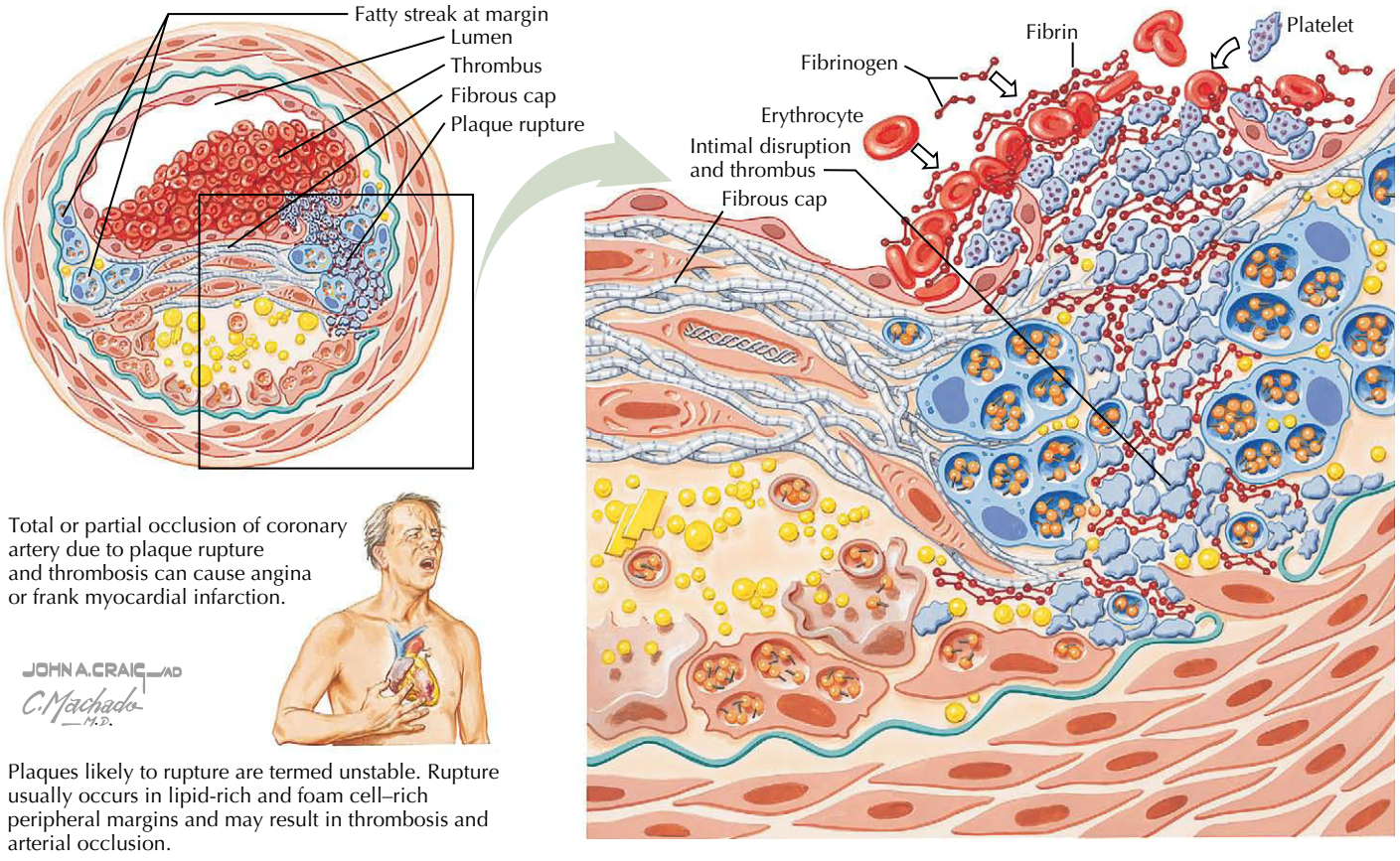


Figure 2-2 *Atherogenesis: Unstable plaque formation.*

important in maintaining plaque stability (most of the interstitial collagen fiber deposition important for tensile strength of the fibrous cap is secreted by SMCs), the paucity of SMCs increases the likelihood of plaque rupture. Therefore, it is likely that SMC proliferation is deleterious in the early stages of atherosclerotic lesion formation, whereas loss of SMCs (and decreased capacity for proliferation) in later stages increases the likelihood of plaque destabilization and clinical outcomes such as MI and stroke.

A large body of data now implicates both circulating and resident stem cells in the pathogenesis of and protection against atherosclerosis. Although the biology and contribution of stem cells to progression and regression of atherosclerosis remains incompletely understood, some data suggest that depletion of stem cells during the process of aging serves as a trigger for progression of atherosclerotic lesions.

Advances in molecular biologic and genetic approaches promise a more detailed understanding of atherosclerosis and improved diagnostic and therapeutic methods. In the past 2 decades, an explosion of information based on identification of genes and proteins involved in experimental atherosclerosis has resulted in better understanding of the biology of atherosclerosis. Unfortunately, these advances have generally not translated into better diagnostic testing. In addition, because with rare exceptions atherosclerosis is a multigenic disease, gene therapy and other similar approaches are less likely to offer therapeutic effectiveness (see Chapter 72).

CLINICAL PRESENTATION

Understanding the symptoms of myocardial ischemia is essential in the context of atherosclerosis, and the brief descriptions provided represent an overview. These topics are discussed in more detail in Chapters 1, 12, 13, and 14. There are three classic clinical presentations of coronary atherosclerosis. The first is angina pectoris, the characteristic ischemia-induced chest pain. The chest pain of angina is typically retrosternal, with radiation to the arms and neck, and is often accompanied by dyspnea (Fig. 2-4). Angina may occur predictably with exertion (stable angina) or, more ominously, at rest or in an accelerating pattern (unstable angina). The symptoms of stable angina are often subtle and difficult to distinguish from other causes of chest discomfort. This is particularly true in women, in whom the typical symptoms described herein are less commonly present.

If not treated promptly, unstable angina may be a harbinger of MI, the second classic presentation of atherosclerosis. Patients with MI frequently, but not exclusively, present with chest pain; however, unlike anginal pain, the pain of MI is typically unremitting and more severe and may be accompanied by autonomic symptoms, such as nausea and vomiting. Arrhythmias may ensue

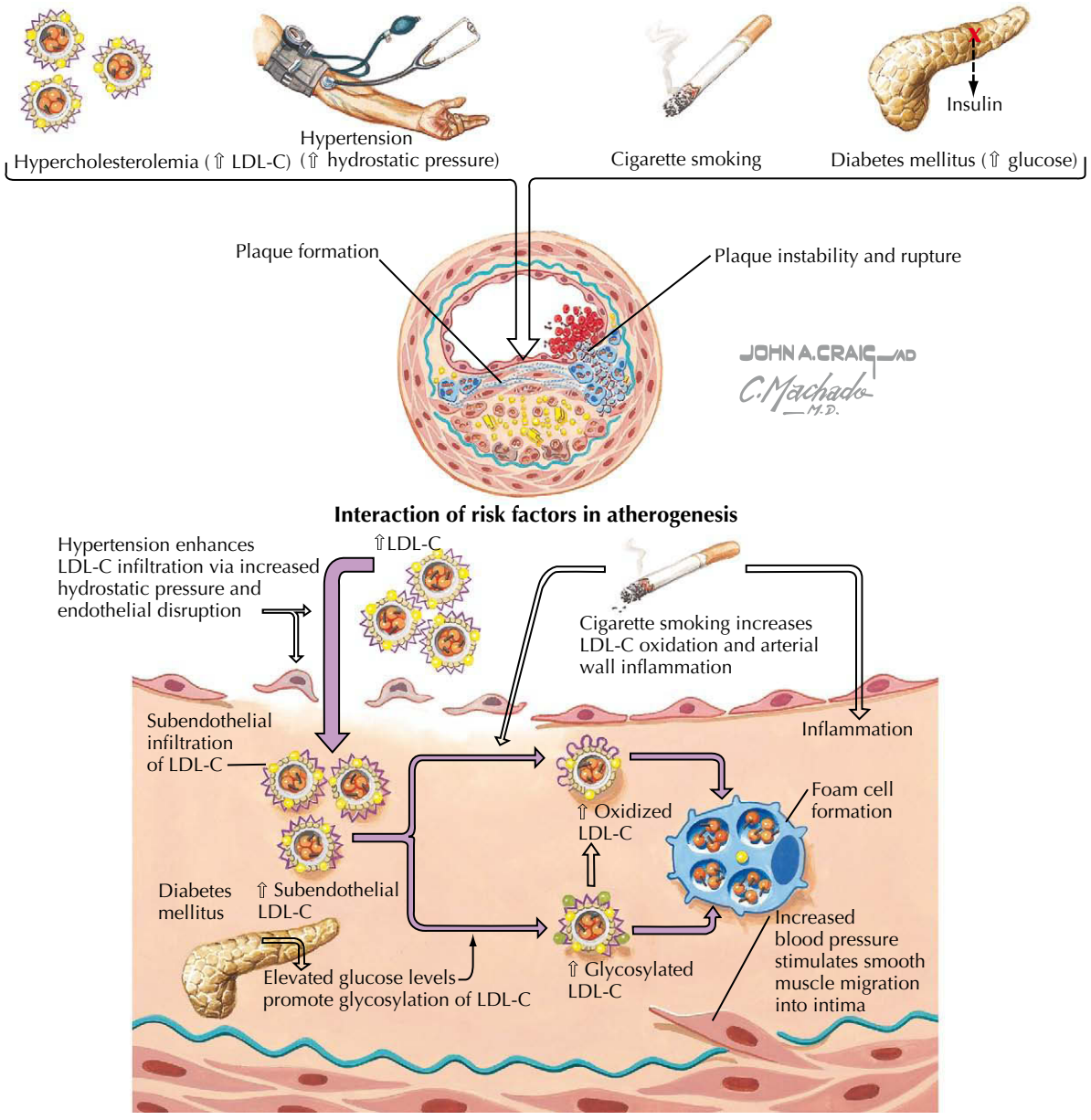
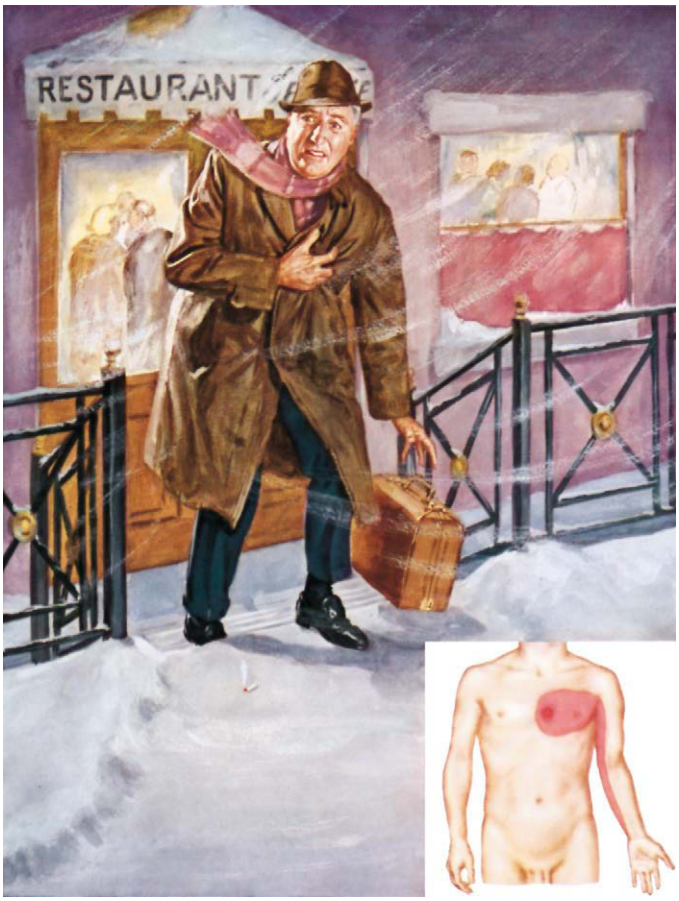


Figure 2-3 *Classical risk factors in coronary artery disease: Relationship to excessive inflammatory responses.* LDL-C, low-density lipoprotein cholesterol.

from ischemia-induced electrical instability of the myocardium. In severe cases, symptoms of heart failure because of acute left or right ventricular dysfunction may also be present. Ventricular dysfunction is an ominous sign in patients with MI and merits prompt attention.

The third presentation of atherosclerosis is SCD due to ventricular fibrillation, which is the first clinical manifestation of coronary atherosclerosis in about 25% of patients with the disease (see Chapter 30). The only hope of survival for patients who present with SCD is prompt administration of cardiopulmonary resuscitation and ventricular defibrillation. Several studies have demonstrated that community-based efforts to train the public in resuscitation techniques, to provide access to automatic external defibrillation devices, and to improve emergency medical access improve survival in out-of-hospital SCD. Resuscitation after SCD is more effective in patients admitted to the hospital, largely because of continuous electrocardiographic monitoring and the development of coronary care units that provide advanced care for patients who experienced MI.

It should be noted that more than 50% of patients with myocardial ischemia present with atypical symptoms ranging from "anginal equivalents" to nonspecific symptoms in the setting of acute MI. For this reason, a high index of clinical suspicion should endorse further diagnostic testing in individuals with atypical symptoms.



Common precipitating factors in angina pectoris: Heavy meal, exertion, cold, smoking

Characteristic distribution of pain in angina pectoris

F. Netter M.D.

Figure 2-4 *Angina pectoris.*

Typical anginal pain is frequently exertional and subsides predictably within a few minutes of rest. The pain may also be exacerbated by emotional stress and drug use, including tobacco and cocaine. It is often described as aching, pressure, heaviness, or squeezing. The diagnosis is further complicated by the number of other causes of chest discomfort, many of which are also medical emergencies. Other CVDs, including aortic dissection and acute pericarditis, may produce chest pain. More common cardiac, noncoronary causes of ischemic chest pain are systemic hypertension and endothelial dysfunction or syndrome X. Individuals with marked hypertension may experience exertional chest pain as a result of subendocardial ischemia, which often occurs in the absence of angiographically significant coronary stenosis. Similarly, patients with syndrome X experience effort-induced chest pain, probably due to subendocardial ischemia from the inability of the coronary arteries to undergo vasodilation normally. Based on the biology of atherosclerosis, as discussed above, it is no surprise that considerable overlap exists between patients with hypertension and/or endothelial dysfunction and those with significant atherosclerotic lesions. Pulmonary causes of chest pain include pulmonary embolism and pulmonary hypertension, the latter of which may be exertional and difficult to distinguish from myocardial ischemia based on symptoms alone. Gastrointestinal diseases are very common and frequently difficult to distinguish from angina pectoris based on medical history; gastroesophageal reflux and esophageal spasm frequently cause chest discomfort similar to angina, as can gastritis and peptic ulcer disease. Musculoskeletal conditions, such as muscle strains and arthritis, may produce angina-like symptoms. Finally, the distribution of herpes zoster pain may suggest angina pectoris to the clinician, particularly if the typical herpes zoster rash has not yet appeared. Thus, the nonspecific nature of angina pectoris symptoms, plus the broad overlap with other common disorders, contributes to the difficulties in the diagnosis of CAD based on signs and symptoms alone.

DIFFERENTIAL DIAGNOSIS

Identification of patients with coronary atherosclerosis is one of the classic dilemmas in clinical decision making for three reasons. First, as much as 70% luminal obstruction by an atherosclerotic lesion is necessary to cause hemodynamically significant obstruction that results in myocardial ischemia and the symptoms of angina. Second, many lesions that rupture or undergo thrombosis and lead to MI are nonobstructive, and neither the identification of suspect lesions by angiography or the early warning symptoms of angina necessarily forewarn of dramatic clinical presentations such as unstable angina or MI. Third, the symptoms of angina pectoris, and even MI, can be especially subtle and difficult to distinguish from other causes of chest discomfort, even for an experienced clinician. Moreover, often cardiac symptoms are not recognized by the patient before an acute presentation. The failure to identify the symptoms of myocardial ischemia is one of the most common, and the most costly, clinical errors. For all these reasons, there is much interest in advanced diagnostic testing for cardiovascular risk, as discussed in detail in Chapters 3 to 10.

DIAGNOSTIC APPROACH

The suspicion of coronary atherosclerosis is raised by a careful history and physical examination—in particular, the solicitation of symptoms of angina pectoris and the consideration of potential risk factors for the development of atherosclerosis. Lacking definitive noninvasive diagnostic testing for coronary atherosclerosis, the importance of the history and physical examination cannot be overstated.

A host of diagnostic methods are available for the clinician evaluating a patient for CAD. The first step in the evaluation of patients suspected of having coronary atherosclerosis is 12-lead electrocardiography. In patients with MI the characteristic abnormality detected is ST-segment elevation, whereas patients with angina may have evidence of prior myocardial injury (Q waves) or ST-segment depression, or a normal ECG. Other abnormalities may also occur, and ST-segment changes may disappear when ischemic symptoms resolve. Electrocardiography is a relatively specific but not highly sensitive indicator of CAD, and a normal ECG never excludes coronary disease under any circumstances. When MI is suspected, cardiac markers

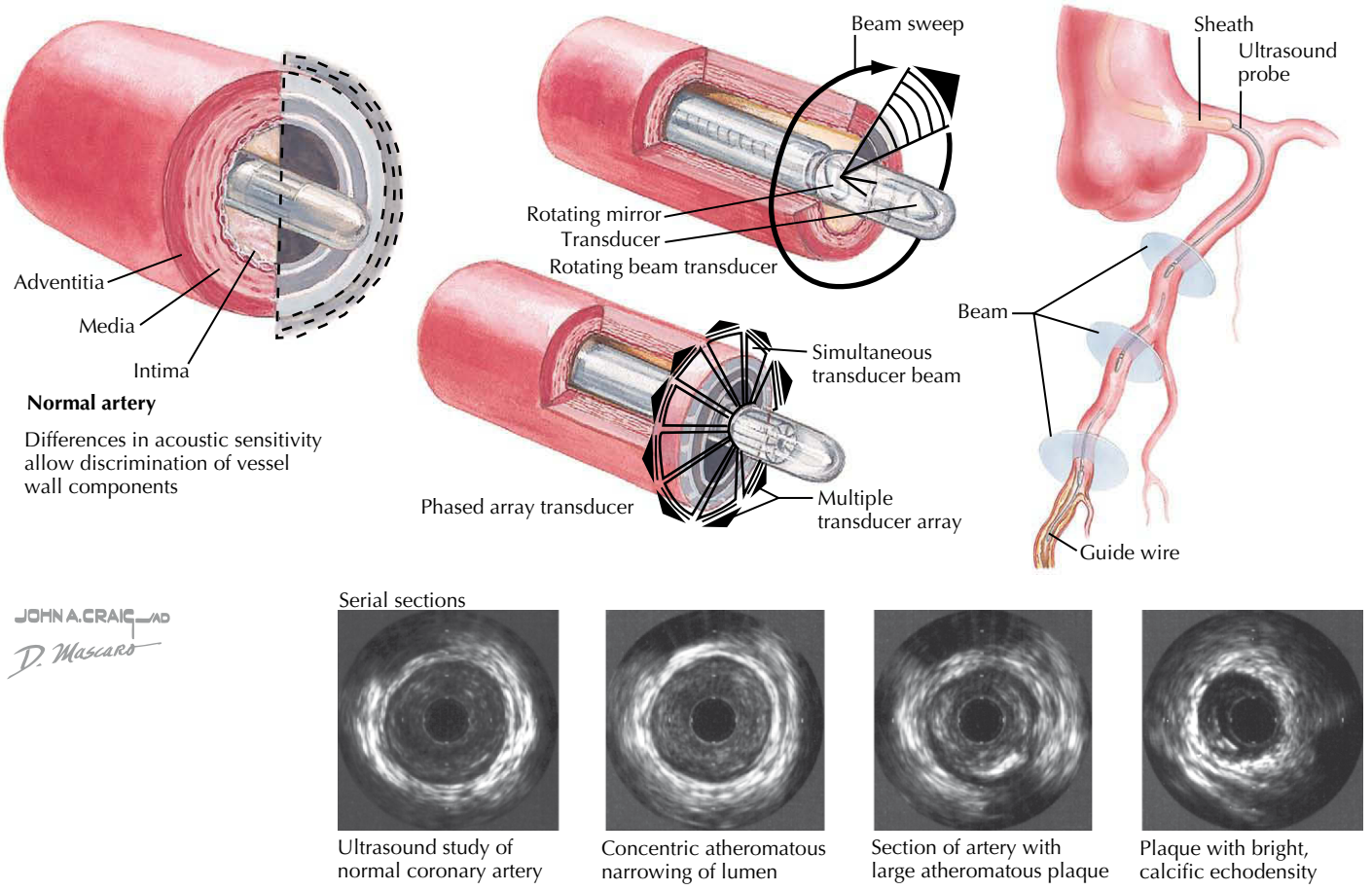


Figure 2-5 *Intravascular ultrasonography.*

(creatine kinase-MB and troponin T or I) should be monitored for evidence of myocardial injury.

Additional studies to test for atherosclerosis fall in two groups: functional studies and anatomic studies. Among the functional studies, the most straightforward is the exercise treadmill test, which detects ST depression during exercise as a marker for obstructive CAD. Though simple to perform and relatively specific, the sensitivity of exercise treadmill tests falls in the 70% to 80% range at best. The sensitivity of provocative studies such as the treadmill test can be greatly enhanced by adding radionuclide scintigraphy, echocardiography, or PET (particularly when knowledge of myocardial viability is important). Functional studies have the advantage of being noninvasive and, although their sensitivities in detection of significant CAD are improving, they do not equal the sensitivity of coronary angiography. Typically, the predictive accuracy of any noninvasive test is best with severe multivessel CAD; the predictive accuracy of these tests in single-vessel CAD is in the range of 65% to 75%. Therefore, if clinical suspicion is high and a definitive diagnosis is needed, anatomic evaluation (coronary angiography) should be considered even in individuals with negative noninvasive evaluation results.

The definitive anatomic test for CAD is coronary arteriography, which is the gold standard for diagnosis of coronary atherosclerosis. It is also the most invasive diagnostic procedure for atherosclerosis and, although the risks of angiography in otherwise healthy patients are very low, postprocedure complications occur in a small percentage of patients. Coronary arteriography provides detailed information about the size and extent of atherosclerotic lesions. Further definition of lesion characteristics can be performed using intravascular ultrasound (Fig. 2-5) or other imaging methods; however, these additional studies are more commonly used for research than for clinical purposes. In addition to its invasive nature, the other disadvantage of coronary arteriography is that functional information regarding the extent of ischemia from a given lesion is not provided; this may not matter in the case of severe stenoses, but in moderate stenoses (50% to 70%), it can be important. Recent advances in imaging have led to the expanded utilization of noninvasive CT angiography; best employed for the detection of proximal coronary artery stenosis, this technology may ultimately obviate the need for routine coronary angiography in many circumstances.

MANAGEMENT AND THERAPY

Optimum Treatment

The management of patients with coronary atherosclerosis depends on the initial presentation of the disease. For patients

presenting with acute MI, thrombolysis or acute percutaneous revascularization should be considered, if appropriate, combined with pharmacologic therapies, as described in detail in Chapters 13 and 14. Patients with stable angina pectoris are generally treated with aspirin, β-blocker therapy, and nitrates as needed for symptoms (Chapter 12). Percutaneous coronary intervention is an increasingly important therapy, even in stable coronary syndromes (Chapters 12 and 15). Coronary artery bypass surgery may be needed for patients with refractory angina or those with extensive coronary disease that is not amenable to percutaneous revascularization (Chapter 16). In selected subsets—multivessel CAD in diabetic persons or in individuals with impaired left ventricular systolic function—coronary artery bypass surgery is effective.

Although well-validated therapies for the consequences of coronary atherosclerotic disease exist, specific therapies aimed at treating or preventing atherosclerosis itself are lacking. Risk factor modification largely prevents progression of atherosclerotic lesions that have formed (and lessens the formation of new lesions), but there is scant evidence that lesions can substantially regress, even with aggressive risk factor modification. Lipid-lowering agents—statins in particular—are thought to stabilize lesions through various mechanisms, ultimately decreasing the likelihood of plaque rupture, acute coronary syndrome, or cardiac death. Numerous studies have demonstrated risk reduction in individuals treated with statins. Similarly, aspirin therapy may prevent complications related to atherosclerosis by inhibiting platelet function, but aspirin probably has little effect on atherosclerotic lesions.

Avoiding Treatment Errors

The database of clinical trials in individuals at risk for acute cardiac events is growing exponentially. Guidelines are frequently updated from the major international cardiovascular societies, and practitioners are encouraged to consult them regularly as treatment recommendations evolve. Of course, the most common treatment error in patients with coronary atherosclerosis is undertreatment. It is crucial that neither patients nor their health care providers underestimate cardiovascular risk, a significant proportion of which is modifiable.

FUTURE DIRECTIONS

For the immediate future, investigators of the pathogenesis of coronary atherosclerosis will probably focus on the interplay between genetic and environmental factors. Current approaches include (1) identifying families of genes (using DNA gene chip or microarray technologies), proteins, or metabolic factors that may predispose individuals to atherosclerosis development; (2) defining genetic-environmental interactions that accelerate atherosclerosis; and (3) elucidating key cellular events in atherogenesis using genetic approaches, from initiation of gene expression to how vascular and myocardial cells deal with degraded proteins and other cellular components.

Several new approaches are under consideration as therapeutic methods for patients with atherosclerosis. Gene therapy approaches, particularly those designed to inhibit cell cycle events in SMCs within lesions, have been in development for several years, but little progress has been made in clinical application. Antioxidant strategies are under consideration to arrest or reverse atherosclerotic lesions, given the pleiotropic effects of oxidants on cellular events that accelerate the atherosclerotic process. Although the use of antioxidant vitamins has not been beneficial, more effective antioxidant strategies may be necessary to reverse or prevent the progression of lesion formation and may optimally be targeted to patients with markers of high levels of oxidative stress as detected noninvasively. Similarly, there is significant interest in therapies that diminish inflammation, but prospective randomized studies have yet to be completed.

Until the latter part of the 1950s, only palliative therapies were widely available to patients with atherosclerosis and its complications. Although huge strides have been taken in the approach to this disease, much progress remains to be made. First, specific serum markers of atherosclerosis would be hugely beneficial, not only for diagnosis, but as a screening tool for testing large populations at risk for atherosclerosis. The use of inflammatory markers, such as C-reactive protein levels, is an important step in this direction, but more sensitive and specific tests are needed. Second, improvements in the ability to analyze coronary artery anatomy noninvasively are needed; recent improvements in CT and MRI technologies are especially promising. Finally, development of specific therapies that can reverse or prevent atherosclerotic lesion development remains a hope for the future. Gene therapy remains promising if appropriate targets can be identified and safety issues resolved. However, newer studies documenting the involvement of many redundant signaling pathways in atherogenesis, along with improvements in targeted pharmacologic therapies, probably indicate that pharmaceutical approaches will dominate future therapies.

ADDITIONAL RESOURCES

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Use of Diagnostic Testing

Thomas Burchell, Anthony Mathur, and Peter Mills

3

The physician confronted with a patient with suspected cardiovascular disease has a multitude of tests available to provide diagnostic and prognostic information. Chapters 4 through 10 describe the various modalities for diagnosing cardiovascular diseases. This chapter focuses on the selection of the most appropriate tests for individual patients.

Generally, the available cardiovascular diagnostic tests can be divided into two categories: Tests that assess anatomy and tests that assess function. These categories are merging, as tests once used solely for anatomic purposes are modified to also assess function. The choice of test depends not only on the question being asked but also on the cost-effectiveness and predictive value of the test and the relative value of anatomic versus functional information. An anatomic assessment (using a test validated by comparison with coronary angiography) may be useful in some settings, but it does not eliminate the need for a functional assessment, which may be even more predictive of a patient's prognosis and need for further intervention.

New imaging techniques must be carefully evaluated for accuracy, ability to provide the needed information, and cost-effectiveness compared with existing methods of obtaining similar information. It should be noted that the initial description of the sensitivity and specificity of a diagnostic test may overestimate what can be achieved in practice. Initial publications usually describe the assessment of a diagnostic test under rigorous conditions by experienced operators in a highly selected population. The true measure of a test is its ability to produce reliable information in a typical clinical environment.

This chapter reviews the available tests that most frequently provide diagnostic and prognostic information in the evaluation of patients with suspected cardiovascular disease. As with all diagnostic tests, the pre-test probability of disease must be considered carefully, both in choosing the most appropriate test and in its interpretation.

DIAGNOSTIC TESTS

Electrocardiography

The resting ECG is the most frequently performed investigation in evaluating patients with cardiovascular disease (see Chapter 4). Electrocardiography is a highly versatile diagnostic test, providing information on a broad spectrum of clinical conditions, ranging from metabolic disturbances (e.g., hypo- and hyperkalemia) and pharmacologic toxicity to ischemic heart disease (e.g., acute myocardial infarction [MI], unstable angina), arrhythmia, and pericardial disease (see Chapter 4). With such versatility, this simple-to-perform test is cost effective.

In the investigation of suspected or known arrhythmias, Holter electrocardiographic monitoring augments the resting ECG by allowing correlation of patient symptoms to the rhythm disturbance and the subsequent monitoring of the patient's response to treatment. This can be in the form of a continuous 24- to 72-hour monitor, a patient-activated event monitor worn for 1 to 4 weeks, or a subcutaneous Reveal device (up to 2 years). Continuous ST-segment monitoring also collects prognostic data on patients who have had a coronary event.

Exercise ECG is a relatively inexpensive investigation used in the diagnosis and management of coronary artery disease (CAD). However, with a sensitivity of approximately 67% and a specificity of 84% for the detection of significant CAD in an optimal setting (and much lower accuracy reported in other settings), the main value of exercise ECG lies in excluding CAD in patients who have a moderate or low pre-test probability of significant coronary stenoses. The risk of false-negative results in patients with a high pre-test probability of CAD is relatively high; these patients should be referred for a more sensitive test such as coronary angiography.

Biochemical Markers

Serum troponin T and I are highly sensitive and specific markers for myocardial injury that are widely accepted as the standard biomarkers for the diagnosis of MI. Elevated troponin levels predict mortality in acute coronary syndromes as well as other diseases, including heart failure, renal failure, and sepsis. In acute MI, serum troponin levels rise after 2 to 3 hours, become detectable in the bloodstream at 6 to 12 hours, and remain elevated for up to 14 days. Caution interpreting positive troponin results should be used, however, because of the wide range of nonischemic cardiac and noncardiac conditions that can cause elevated serum concentrations. These conditions are numerous and include tachyarrythmia, myocarditis, direct current cardioversion, renal failure, sepsis, pulmonary embolism, and stroke. The other main caution in interpretation is an understanding of the details of the test used locally; the many commercially available assays have different upper limits of normal.

Brain natriuretic peptide and its co-secreted N-terminal fragment are useful in the diagnosis of acute heart failure in an emergency department and management of chronic heart failure in a primary care setting. They may be useful to establish prognosis in heart failure, in that both markers are typically higher in patients with worse outcomes. Although they are highly sensitive and therefore have very few false-negative results, they unfortunately lack the specificity needed to exclude false-positive results and are often therefore used as a "rule out" test for heart failure. Serum levels are elevated in patients with renal failure, because both peptides are renally excreted. Results should be interpreted in the clinical context, and positive results should invariably be followed by functional imaging such as an echocardiogram to formally assess cardiac function.

Echocardiography

Echocardiography provides a versatile and cost-effective method for assessing cardiac anatomy and function (see Chapter 6). The

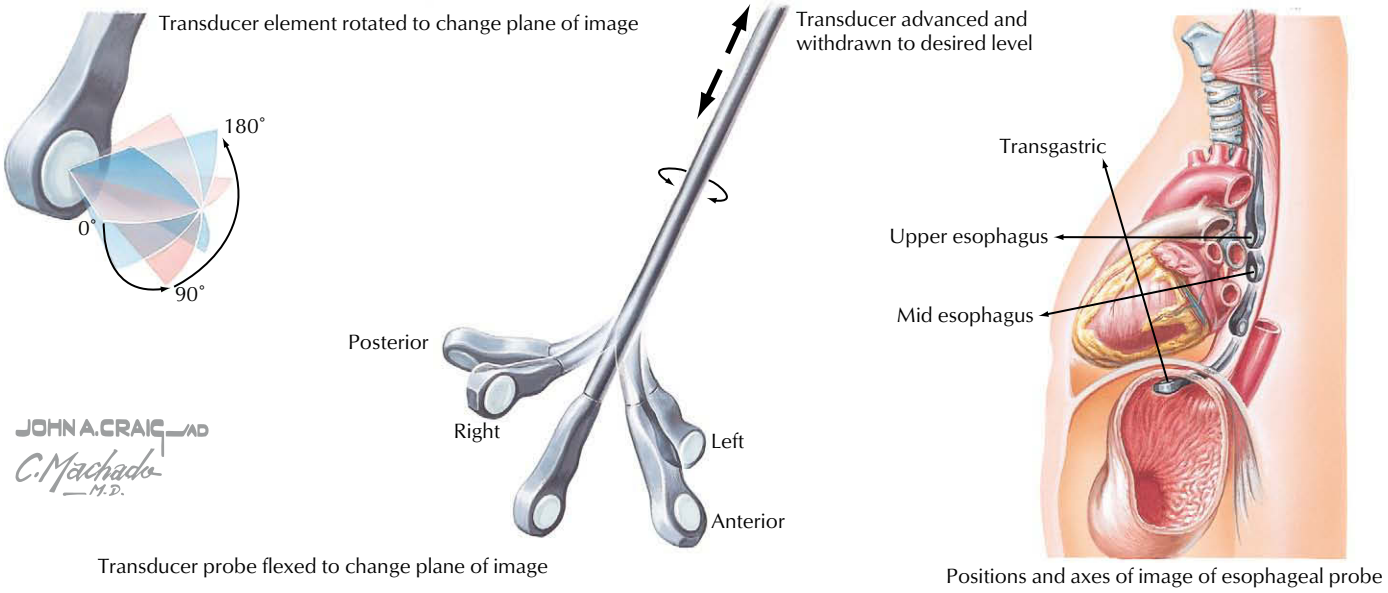


Figure 3-1 *Transesophageal echocardiography.*

greatest values of echocardiography are the capacity for simultaneous assessment of valvular, pericardial, myocardial, and extracardiac abnormalities. Because complex image processing is not needed, the results of the study are immediately available to the experienced echocardiographer. In addition, it is possible to perform echocardiography on critically ill patients who cannot be moved, or in other circumstances when a portable test is preferable. For these reasons, echocardiography is the preferred screening imaging test for further assessing suspected myocardial dysfunction. Moreover, the use of Doppler echocardiography (Doppler) to measure flow allows the measurement of peak velocity across valves, the mapping of regurgitant jets, the estimation of pulmonary artery pressures, and the detection of shunts (e.g., ventricular and atrial septal defects). The severity of valvular heart disease and its contribution to the clinical presentation can be determined immediately. For patients with chest pain, congestive heart failure, or arrhythmias, echocardiography provides a rapid means of determining underlying cardiovascular function.

Transesophageal echocardiography adds to the sensitivity of transthoracic echocardiography, because views of the heart are not impeded by artifact related to the lungs or chest wall (Figs. 3-1 and 3-2). In addition, transesophageal echocardiography allows visualization of structures that are usually not well seen by transthoracic echocardiography (e.g., the left atrial appendage). The development of transesophageal echocardiography has also been an important advance in the management of patients who are undergoing cardiothoracic surgery, providing information on left ventricular (LV) function and the success of valvular repair. In addition, transesophageal echocardiography may allow a more accurate determination of valvular dysfunction and assessment for bacterial endocarditis, intracardiac thromboses, or both.

In addition to its usefulness in assessing valvular heart disease, echocardiography provides information on regional wall motion abnormalities suggestive of myocardial ischemia or necrosis in patients with CAD. The addition of pharmacologic or exercise-induced stress to detect inducible ischemia provides increased sensitivity and specificity compared with ECG exercise testing (Fig. 3-3, upper panel). In 21 studies, the sensitivity of exercise stress echocardiography averaged 84% (range 71% to 97%) and the specificity averaged 86% (range 64% to 100%). The use of echocardiography can be limited by technical considerations, including an inability to obtain diagnostic images in some patients (an estimated 15%). Stress echocardiography is indicated for individuals who have an intermediate prior probability of CAD and for individuals with abnormal ECGs or who are prescribed medications that can cause ECG abnormalities with stress (such as digoxin). In either of these cases the predictive value of exercise ECG is substantially reduced, justifying the use of an imaging technique during stress.

CONTRAST ECHOCARDIOGRAPHY

Injection into the circulation of contrast agents that reflect ultrasound (either agitated saline or microspheres) helps demonstrate intracardiac shunts, improves resolution of cardiac structures, and enhances spectral Doppler signals of flow-through heart valves (see Fig. 3-3, lower panel). Although contrast echocardiography is not indicated for all patients, it can allow quantification of the severity of an intracardiac shunt, thereby indicating whether invasive testing (cardiac catheterization) or surgery is needed. It can also improve border detection within the left ventricle allowing more accurate assessment of LV function.

TISSUE DOPPLER

The processing of Doppler signals reflected by the myocardium gives two-dimensional directional information that allows better visualization of the endocardium and assessment of ventricular

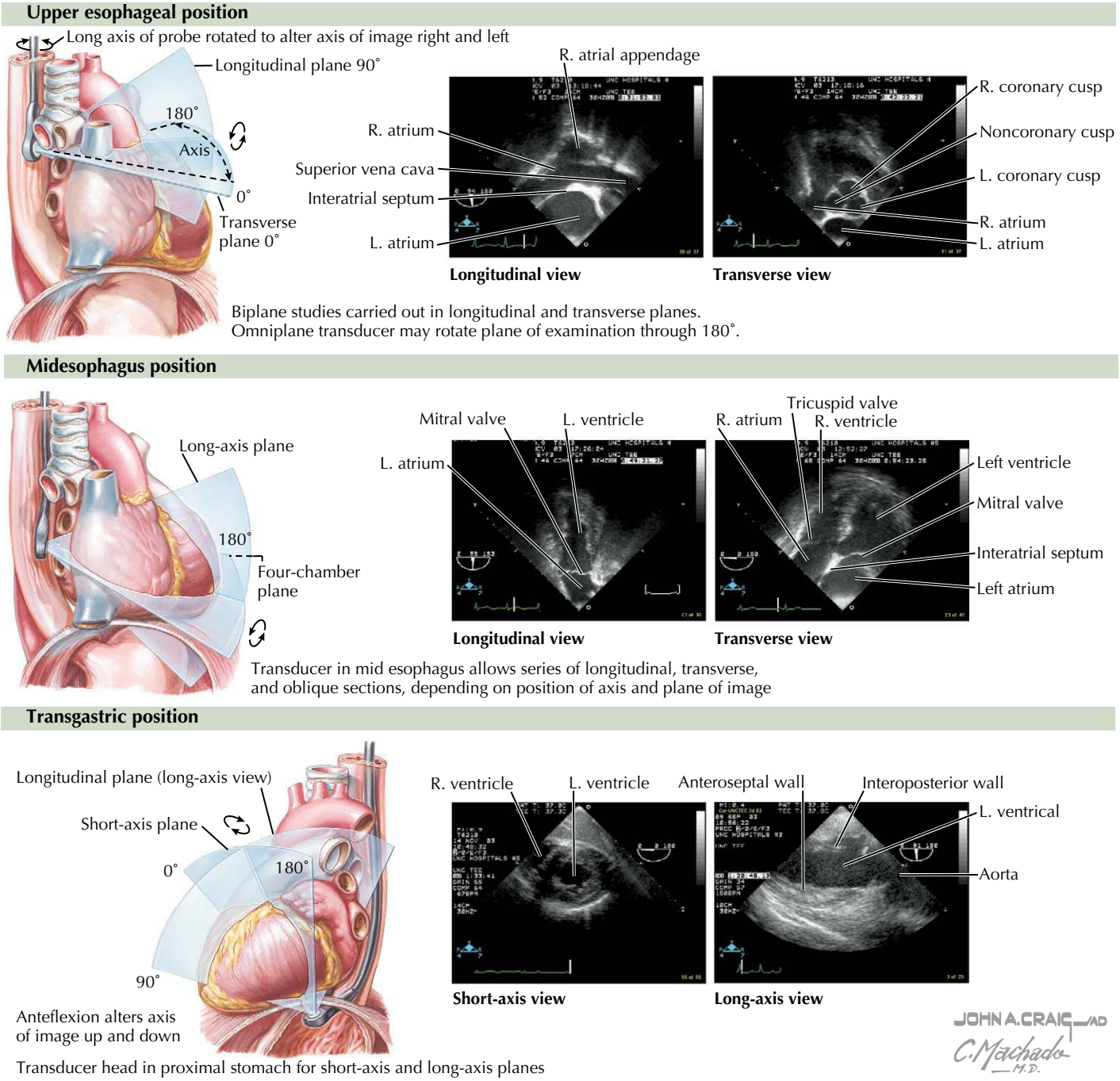


Figure 3-2 *Transesophageal echocardiography: Positions.*

wall motion. Tissue Doppler is helpful for the assessment of regional wall abnormalities at rest or with stress as well as being a useful adjunct in assessing diastolic dysfunction. Though not needed in every study, tissue Doppler can be extremely useful in difficult-to-image individuals.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

This relatively new extension to echocardiography technology allows the visualization of cardiac structures in three dimensions over time. Three-dimensional echocardiography (3D echo) can be performed using either modified transthoracic or transesophageal probes. It can provide high-quality images of structural abnormalities, valves, and shunts that can be especially useful in congenital abnormalities. It is technically difficult to perform and is mainly used in specialist centers for LV function analysis and preoperative visualization of the mitral valve.

Radionuclide Testing

Radionuclide imaging assesses LV function and detects inducible ischemia secondary to CAD. As described in Chapter 7,

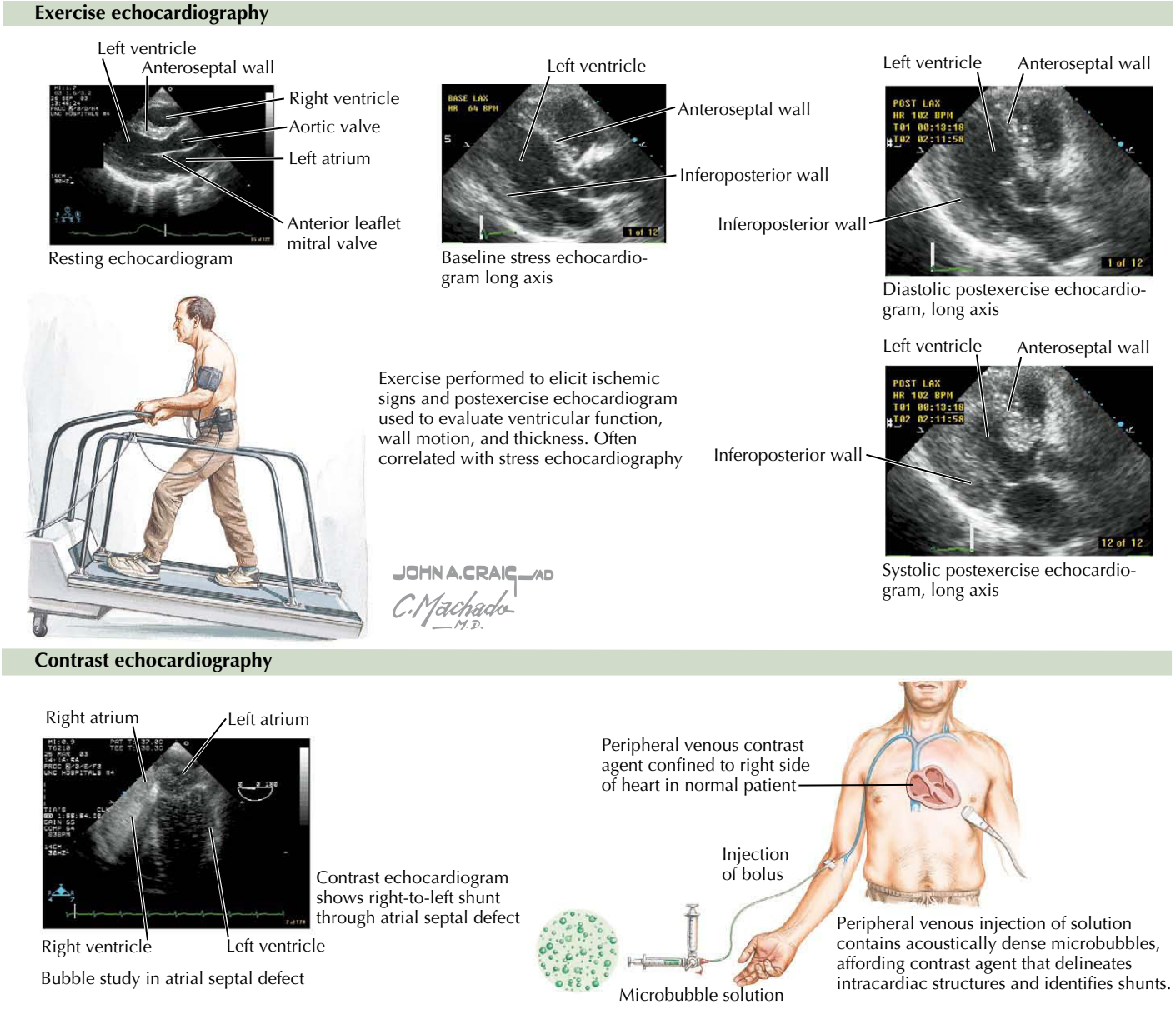
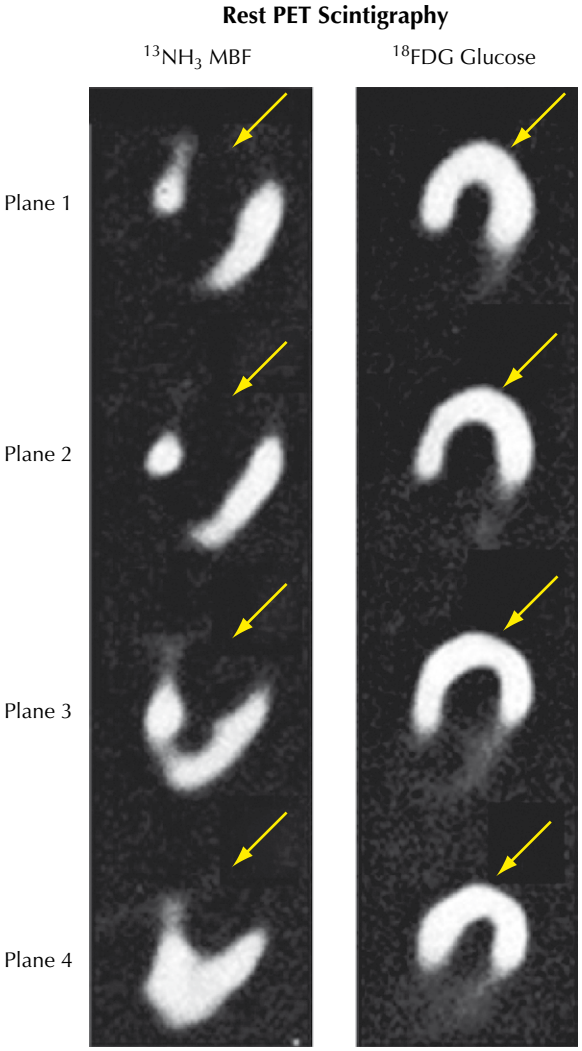


Figure 3-3 *Exercise and contrast echocardiography.*

quantitative assessment of right and left ventricular ejection fractions (EFs) is highly accurate with this technique and can be related to long-term prognosis.

Stress (exercise or pharmacologic) radionuclide myocardial perfusion imaging (MPI) in patients with suspected CAD yields a sensitivity of approximately 85% to 90%. When gated SPECT is used, the specificity for excluding CAD is approximately 90%. Thus, radionuclide imaging is more specific and sensitive in detecting significant CAD than is exercise ECG testing and (like exercise echocardiography) has particular value when the resting ECG is abnormal and when patients are unable to achieve more than 85% of their maximum predicted heart rate because of locomotor or other reasons. The accuracy for diagnosing CAD is probably similar to the accuracy of stress echocardiography, and the choice often depends on study availability and frequency of use at a given center. One advantage of stress MPI is that the number of patients for whom this imaging technique cannot be used is small. In addition, stress radionuclide MPI has a proven role in predicting future cardiac events and, importantly, is able to predict a low mortality and subsequent infarction rate in patients with a totally normal scan. The use of certain radioactive tracers (such as thallium) leads to a high false-positive rate; therefore, technical considerations are paramount when performing and interpreting such scans. In general, the indications for stress MPI are similar to those for stress echocardiography: an intermediate prior probability of disease, an abnormal baseline ECG, or both. Both tests are also useful for patients who cannot exercise adequately, because pharmacologic agents can be used to induce stress.

PET, on its own or in combination with cardiac CT (PET-CT), is still used mainly as a research technique. It



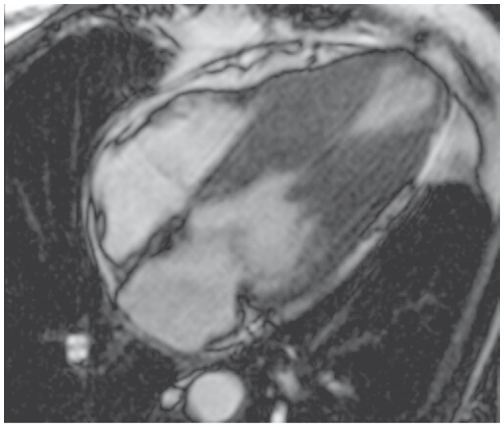
This is an example of a mismatch pattern on PET. The pattern was found in a patient who had a significant anterior perfusion abnormality on $^{13}NH_3$ imaging for assessment of MBF, but who demonstrated significant uptake of ^{18}FDG in the anterior wall. This pattern is indicative of hypoperfused but metabolically active hibernating myocardium.

Image courtesy of Heinrich R. Schelbert, MD, PhD, FACC.

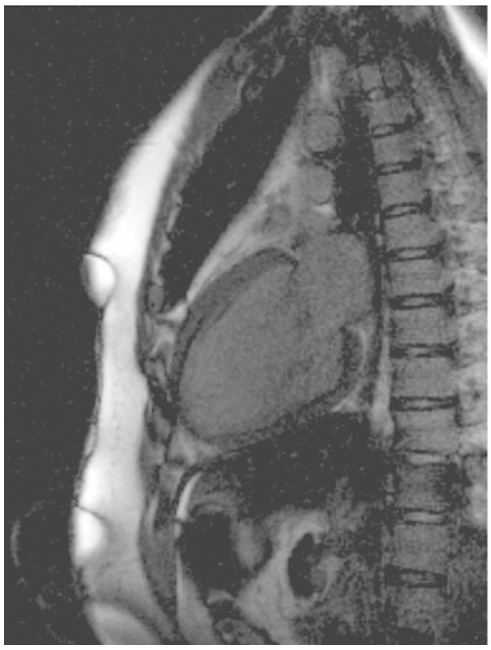
Figure 3-4 *Cardiac positron emission tomography (PET).* ^{18}FDG, 18-fluorine labeled 2-deoxy-2-fluoro-D-glucose; MBF, myocardial blood flow.

does, however, have validated clinical applications; quantitative assessment of perfusion using rubidium-82 or $^{13}NH_3$ has a sensitivity of 92% and a specificity of 90% for the detection of significant proximal CAD. The other main clinical use is the assessment of myocardial viability before planned revascularization, using 18-fluorine labeled 2-deoxy-2-fluoro-D-glucose (^{18}FDG; Fig. 3-4). Mainstream clinical use of PET is limited by availability, technical complexity, and high cost.

Radionuclide imaging carries a relatively high radiation burden and in many centers is being replaced with either stress echocardiography or stress cardiac MRI, which do not use ionizing radiation (see below).



Cardiac MRI in the four-chamber long-axis view demonstrating midventricular variant of hypertrophic cardiomyopathy

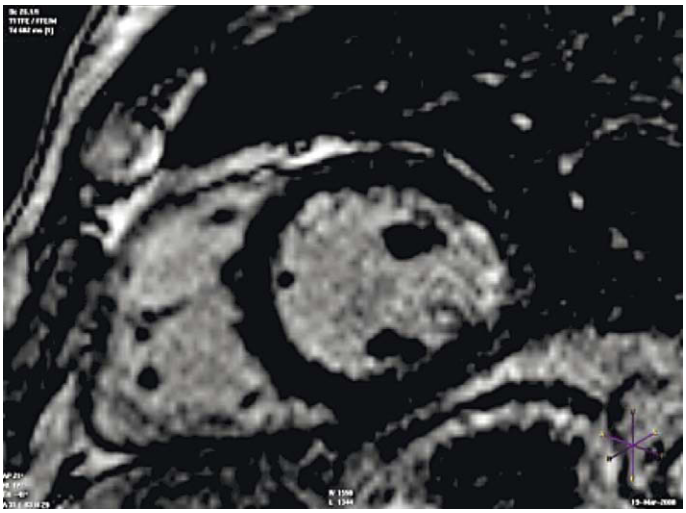


Hyperenhanced cardiac MRI used to detect myocardial viability in a patient with subtotally occluded left anterior descending and RCA and an ejection fraction of 30%. Myocardial scarring shows up as bright contrast in this technique, and this study shows normal myocardial viability despite the presence of multivessel coronary artery disease and left ventricular dysfunction.

Figure 3-5 *Cardiac magnetic resonance imaging (MRI).* RCA, right coronary artery.

Magnetic Resonance Imaging

MRI is a relatively safe and extremely sensitive imaging modality that is superior to other noninvasive investigations in diagnosing congenital heart disease, diseases of the aorta, anomalous coronary arteries, and right ventricular dysplasia (Fig. 3-5). It is also now the accepted gold standard test for assessing left and right ventricular volumes, regional and global function as measured by EF, with a reproducibility of ±2.5% under experimental conditions. The role of MRI has been further extended to evaluation of myocardial perfusion both at rest and



This is a short-axis late gadolinium enhanced cardiac magnetic resonance image taken at the level of the mid ventricle. It shows an area of increased signal intensity in the lateral wall, indicating a previous subendocardial myocardial infarction.

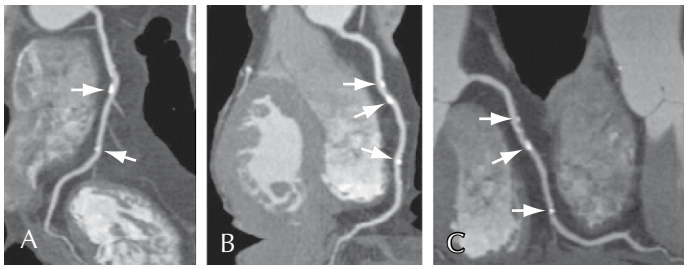
Image courtesy of Dr. Mark A. Westwood and Dr. L. Geri Davies, the London Chest Hospital, UK.

Figure 3-6 *Magnetic resonance viability imaging.*

under pharmacologic stress using gadolinium-based contrast agents. MRI can be useful in assessing myocardial viability before planned revascularization, because it can accurately visualize wall thickness throughout the left ventricle, allowing an assessment of whether normal wall thickening occurs with systole. It is now also possible to assess viability in areas of previous infarction using late gadolinium enhancement (Fig. 3-6), which accurately delineates scar from normal myocardium, even in areas of the left ventricle where the wall is thinned.

Advances in MRI contrast agents and imaging technology have led to the development of "coronary magnetic resonance angiography" capable of imaging the major coronary arteries; however, this is unlikely to outperform either standard coronary angiography or CT coronary angiography because of the physical limitations in temporal resolution. The use of MRI is limited because of the cost and availability of scanners capable of gating the image to the ECG (which is necessary to resolve cardiac structure) and because an increasing number of patients have permanent pacemakers or implantable defibrillators that are currently absolute contraindications for MRI.

Thus, for obtaining anatomic information, most cardiologists advocate transthoracic echocardiography as a first step, followed by either transesophageal echocardiography or MRI if better definition of the cardiac structures is needed. For assessment of CAD, stress ECG would be used as a screening test only in individuals with a low pre-test probability of disease and a normal baseline ECG. Perfusion MRI, CT coronary angiography, stress echocardiography, or MPI should be used for individuals who have an intermediate prior probability of disease, an abnormal baseline ECG, or both, or who are taking medications that could nonspecifically alter the ECG during exercise. Patients who are unable to exercise are also well suited for pharmacologic stress testing with echocardiographic, MRI, or nuclear imaging. For most individuals with a high pre-test probability of CAD, coronary angiography should be considered as an initial diagnostic step.



This is a multiplanar reconstruction (MPR) of a 64-slice cardiac CT scan showing the right coronary artery projected in **(A)** axial, **(B)** coronal, and **(C)** saggital views. It shows multiple calcified plaques (*arrows*) but the lumen of the artery is unobstructed.

Figure 3-7 *Computed tomography (CT) coronary angiography.*

Computed Tomography

With the advent of multislice and dual-source CT scanners, the improvement in both spatial and temporal resolution has allowed this imaging modality to effectively visualize the heart, significantly reducing the movement artifacts seen previously. This specifically allows imaging of the coronary arteries (Fig. 3-7) and significant stenoses within them and can be used in certain circumstances instead of coronary angiography. The positive and negative predictive values of CT angiography are approximately 82% and 93%, respectively, as compared with coronary angiography. It is therefore a useful test to rule out significant CAD in patients with low or intermediate pre-test probability, who have a contraindication to conventional coronary angiography. The relatively large radiation dose (approximately 10 to 15 mSv), though decreasing with technologic advances, does however mean some clinicians would prefer to use alternative tests such as stress echocardiography or stress MRI, which do not use ionizing radiation.

Cardiac Catheterization

Cardiac catheterization, considered the gold standard investigation for patients with CAD, allows the assessment of both coronary artery anatomy and LV function with very high spatial and temporal resolution (Fig. 3-8). Historically, cardiac catheterization provided the only means of measuring hemodynamic parameters (e.g., pressure and oxygen saturation) within various heart chambers to assess cardiac anatomy and physiology. Most of these techniques have been superseded by noninvasive tests already described. There are difficult situations, such as the assessment of some valvular lesions or the differentiation of pericardial constriction from myocardial restriction (see Chapters 10, 20, and 43), that still often require cardiac catheterization.

Today, the most common use of cardiac catheterization is in conjunction with coronary angiography for anatomic delineation of CAD and LV function in anticipation of revascularization (Chapters 9 and 10). Because of its invasive nature, coronary

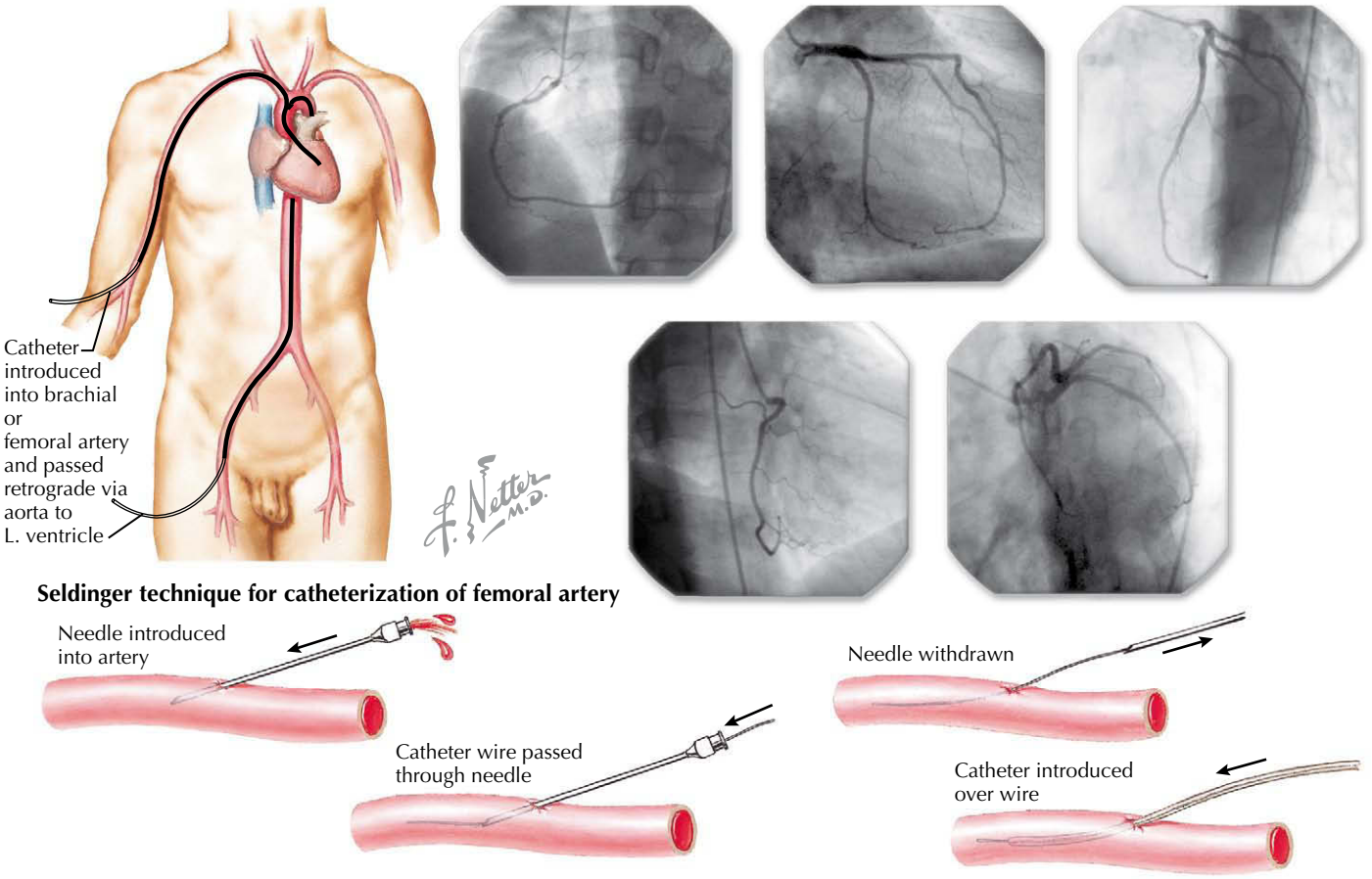


Figure 3-8 *Left-sided heart catheterization.*

angiography carries a 0.1% risk of a major adverse cardiovascular event in most laboratories; for this reason, it is often performed after a positive or equivocal noninvasive test. However, the sensitivities and specificities of stress echocardiography, MPI, and stress cardiac MRI are such that a patient with a high pre-test probability of CAD would be at risk for a false-negative noninvasive test. For these individuals, coronary angiography should be the initial diagnostic test. Coronary angiography is required before revascularization, by either percutaneous approaches or bypass surgery.

Based on the direct access to the coronary arteries provided by coronary angiography, new techniques have been developed to provide increased accuracy in the diagnosis of coronary heart disease. Intravascular ultrasound provides high-resolution images of the coronary arterial wall and has greater sensitivity in identifying the extent of coronary atheroma than does coronary angiography alone (see Chapter 9). In particular, intravascular ultrasound emphasizes the importance of the "burden" of plaque that extends toward the adventitia rather than encroaching on the lumen. Functional information about the physiologic impact of a coronary stenosis is obtainable through measurements of blood flow and pressure drop across these lesions with miniaturized pressure and Doppler transducers on the ends of guide wires. These measurements correlate with long-term prognosis and thus provide a means of targeting therapy on physiologic as well as anatomic grounds. Thus, in an individual with compelling symptoms, a noninvasive test diagnostic of myocardial ischemia, or both, but with only moderate stenoses by coronary angiography, intravascular ultrasound and/or Doppler flow measurements may be indicated to ascertain whether a moderate stenosis by angiography is functionally important and a candidate lesion for revascularization.

Electrophysiology Studies

Although resting ECG and Holter monitoring often provide diagnostic information on the conditions of patients presenting with palpitations or syncope, electrophysiology studies have a role in diagnosing the conditions of patients in which a cardiac etiology is unclear. Invasive stimulation studies are used to diagnose both ventricular and supraventricular arrhythmias and to test the integrity of the conduction system in patients with syncopal episodes (see Chapter 33).

AVOIDING DIAGNOSTIC TESTING ERRORS

Whichever test(s) you use in your diagnostic workup, it is not uncommon to get unexpected or surprising results. This can cause confusion, especially if the result does not fit the clinical

picture. There is obviously the possibility that the result is incorrect, being either false positive or false negative, as discussed. There is also the possibility of detecting bystander disease that may be unrelated to the disease process being investigated (e.g., features of hypertrophic cardiomyopathy being identified on a viability/perfusion cardiac MRI scan for coronary disease). It may, however, still not explain the findings, in which case it is essential to revisit the history and clinical examination, because these can provide a wealth of useful information. It must be remembered that tests are always an adjunct to clinical history and examination, and sometimes the addition of more complex cardiac investigations does not lead to an improvement in diagnostic capability.

FUTURE DIRECTIONS

The near future in cardiac testing lies with improvements in current technology, allowing safer, more accurate tests to guide the physician in patient care. Cardiac CT, with more sources and slices, will allow increases in temporal and spatial resolution, respectively, while reducing the overall radiation dose. This should improve the accuracy of assessing coronary disease and potentially allow plaque characterization. Cardiac MRI will become more widespread as the number of scanners increases and the body of evidence builds further. This modality will more than likely replace the common use of radionuclide imaging for assessment of LV function and myocardial perfusion. The potential for coronary visualization exists and will undoubtedly continue to be refined for clinical use. There is further promising work in MRI spectroscopy coils, allowing the assessment of metabolic function as well as perfusion and viability. Pacemakers and implantable cardiac defibrillators will probably be made MRI "safe," allowing the scanning of this important patient group.

With the advent of more powerful computers, real-time 3D echo will become widely available; the exact indications for its use, however, are yet to be determined, since it lacks large validation studies. New testing modalities will undoubtedly appear, but the reader is cautioned to wait until these are validated for the clinical question being asked before being tempted to adopt them into clinical practice.

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Comprehensive review and comment about recent advances in all aspects of cardiac imaging.

Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol.* 2002;40(8):1531–1540.

EVIDENCE

Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation.* 2000;101:1465–1478.

Review article describing nuclear techniques in assessing myocardial ischemia.

Camici PG. Positron emission tomography and myocardial imaging. *Heart.* 2000;83:475–480.

Review article describing the advantages of and uses for myocardial PET imaging.

Jerosch-Herold M, Muehling O. Stress perfusion magnetic resonance imaging of the heart. *Top Magn Reson Imaging.* 2008;19:33–42.

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Meijboom WB, van Mieghem CA, Mollet NR, et al. 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. *J Am Coll Cardiol.* 2007;50:1469–1475.

Study assessing the usefulness of 64-slice CT coronary angiography to detect or rule out coronary artery disease (CAD) in patients with various estimated pre-test probabilities of CAD compared to the gold standard of invasive coronary angiography.

Sekhri N, Feder GS, Junghans C, et al. Incremental prognostic value of the exercise electrocardiogram in the initial assessment of patients with suspected angina: cohort study. *BMJ.* 2008;13;337:a2240.

Multicenter cohort study assessing the relative and prognostic benefits of performing an exercise ECG in addition to a clinical history and resting ECG in patients attending the Rapid Access Chest Pain Clinic in the United Kingdom. Concluded that the addition of an exercise ECG added little prognostic value above clinical history and resting ECG.

Electrocardiography

Leonard S. Gettes

4

It is now more than 100 years since the Dutch physiologist Willem Einthoven recorded the first ECG from humans. Although the number of recording leads has increased from 3 to at least 12 and the recording instruments have evolved into sophisticated automated digital recorders capable of recording, measuring, and interpreting the electrocardiographic waveform, the basic principles underlying the ECG are unchanged. The electrocardiograph is basically a voltmeter that records, from the body surface, the uncanceled voltage gradients created as myocardial cells sequentially depolarize and repolarize.

The ECG is the most commonly used technique to detect and diagnose heart disease and to monitor therapies that influence the heart's electrical activity. It is noninvasive, virtually risk free, and relatively inexpensive. Since its introduction, a large database has been assembled correlating the ECG waveform recorded from the body surface to the underlying electrical activity of individual cardiac cells on the one hand, and to the clinical presentation of the patient on the other, thereby providing insight into the electrical behavior of the heart and its modification by physiologic, pharmacologic, and pathologic events.

LEADS

Twelve leads are routinely used to record the body surface ECG: three bipolar limb leads labeled I, II, and III; three augmented limb leads labeled aVR, aVL, and aVF; and six unipolar chest leads labeled V_1 through V_6 (Fig. 4-1). In the bipolar limb leads, the negative pole for each of the leads is different, whereas in the unipolar chest leads, the negative pole is constant and created by the three limb leads. This is referred to as *Wilson's central terminal.* The positive chest lead is, in effect, an exploring lead that can be placed anywhere. In children, the routine ECG often includes leads placed on the right side of the chest in positions referred to as V_3R and V_4R. Similar right-sided chest leads are often used in adults to diagnose right ventricular infarction, and one or more leads placed on the back are sometimes used to diagnose posterior wall infarction.

The chest leads are relatively close to the heart and are influenced by the electrical activity directly under the recording electrode. This is in contrast to the limb leads in which the electrodes are placed outside of the body torso. Changes in the position of an individual chest lead or the relationship between the chest leads and the heart may cause significant changes in the ECG pattern. For instance, if the patient is in a sitting rather than a supine position, the relationship of the various chest leads to the heart will change and the ECG waveform recorded by the chest leads may be altered. Similarly, if a chest lead is placed an interspace too high or too low, the ECG waveform recorded by that lead will change. For this reason, when serial ECGs are recorded, it is important that lead placement be consistent and reproducible. In contrast, limb leads may be placed anywhere on the various limbs with little significant alteration of the ECG waveform. However, when they are placed within the body torso, as is the case during exercise testing and when patients are monitored in critical care areas, the waveform recorded by the limb leads will be affected.

ELECTROCARDIOGRAPHIC WAVEFORM

The ECG waveform consists of a P wave, a PR interval, the QRS complex, an ST segment, and T and U waves. The relationship of these waveform components to the underlying action potentials of the various cardiac tissues is shown in Figure 4-2A, as is an example of a normal 12-lead ECG in Figure 4-2B. The P wave reflects depolarization of the atria, the QRS complex reflects depolarization of the ventricles, and the ST segment and T wave reflect repolarization of the ventricles. The U wave occurs after the T wave and is thought to be an electromechanical event coupled to ventricular relaxation.

Depolarization of the sinus node occurs before the onset of the P wave, but its voltage signal is too small to be recorded on the body surface by clinically used electrocardiographic machines and the event is electrocardiographically silent. Similarly, the electrical activity of the atrioventricular (AV) junction and the His-Purkinje system, which occur during the PR interval, is electrocardiographically silent.

P Wave

The P wave is caused by the voltage gradients created as the atrial cells sequentially depolarize. The shape and duration of the P wave are determined by the sequence of atrial depolarization and the time required to depolarize the cells of both atria. The sinus node is located at the junction of the superior vena cava and the right atrium, and the direction of atrial depolarization, from right to left, from superior to inferior, and from anterior to posterior reflects this geography. This results in a P wave that is characteristically upright or positive in leads I, II, V_5, and V_6 and inverted or negative in lead aVR. In lead V_1, the P wave may be upright, biphasic, or inverted. The amplitude and duration of the normal sinus P wave may be affected by atrial hypertrophy and dilation and by slowing of interatrial and intra-atrial conduction.

Impulses arising from an ectopic atrial focus are associated with P waves whose shape depends on the location of the focus. If the abnormal focus is in close proximity to the sinus node, the sequence of atrial activation will be normal or nearly normal, and the P wave will resemble the normal sinus P wave. The more distant the ectopic focus is from the sinus node, the more abnormal will be the sequence of atrial activation and the P-wave configuration. For instance, impulses originating in the inferior portion of the atrium or within the AV node will depolarize the atria in a retrograde, superiorly oriented direction and will be associated with the P waves that are inverted in leads II, III, and aVF and upright in lead aVR (Fig. 4-3).

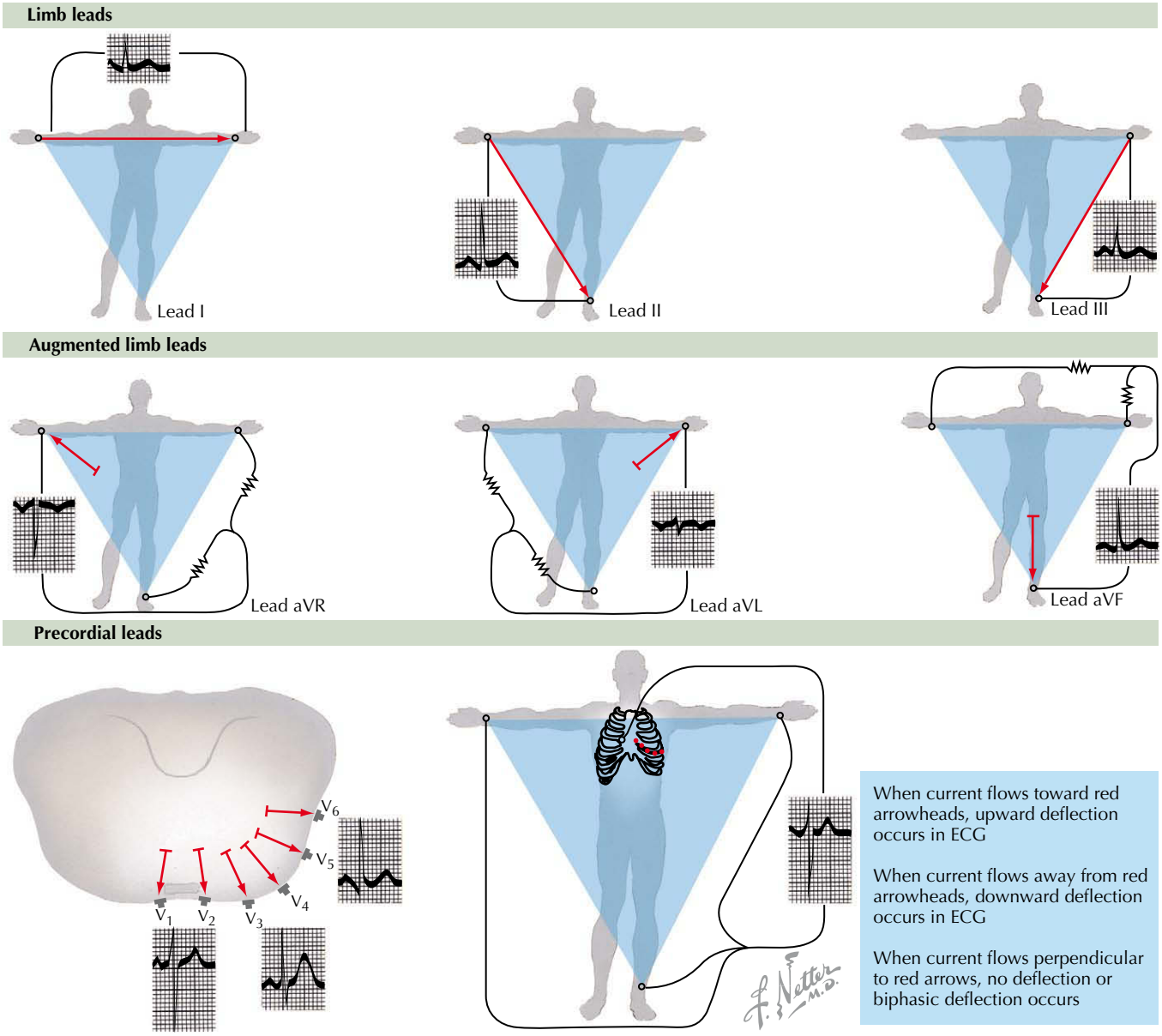


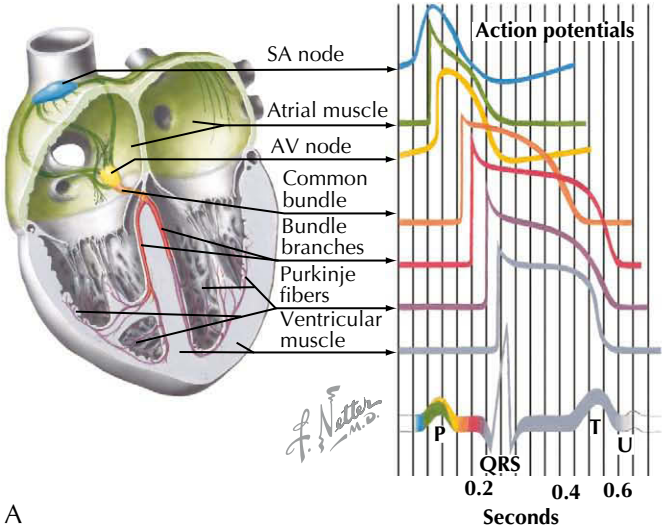
Figure 4-1 *Electrocardiographic leads and reference lines.* ECG, electrocardiogram.

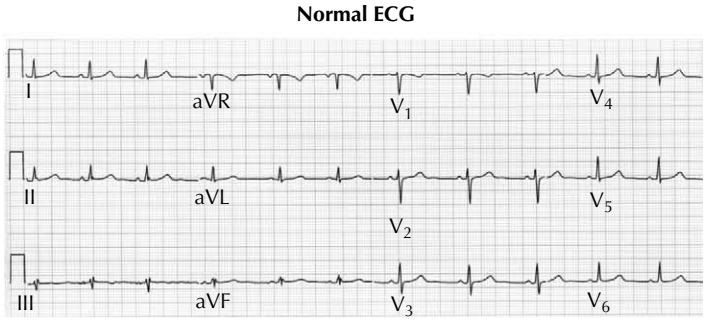
PR Interval

The PR interval extends from the onset of the P wave to the onset of the QRS complex and includes the P wave and the PR segment (the segment from the end of the P wave to the onset of the QRS), which consists of atrial repolarization and depolarization of the AV node and His-Purkinje system. The PR interval is prolonged by factors that slow AV nodal conduction, such as a decrease in sympathetic tone or an increase in vagal tone, by drugs that have these effects such as digitalis and the β-adrenergic blocking agents, and by a variety of inflammatory, infiltrative, and degenerative diseases that affect the AV junction. The PR interval is shortened when impulses bypass the AV node and reach the ventricles via an AV nodal bypass tract to cause ventricular preexcitation (Wolff-Parkinson-White syndrome).

QRS Complex

The QRS complex reflects ventricular depolarization. The interventricular septum is the first portion of the ventricle to be depolarized. Thereafter, the impulse spreads through the His-Purkinje system and then depolarizes the ventricles simultaneously, from apex to base and from endocardium to epicardium. Because the left ventricle is three times the size of the right, its depolarization overshadows and largely obscures right ventricular depolarization. The QRS complex reflects this left ventricular dominance, and for this reason, the QRS complex is usually upright or positive in leads I, V_5, and V_6, the left-sided and more posterior leads, and negative or inverted in aVR and V_1, the right-sided and more anterior leads. It is only in situations such as right bundle branch block and significant right ventricular hypertrophy that the electrical activity





Example of a normal ECG recorded from a 24-year-old woman. Note that the P wave is upright in leads I and II and inverted in aVR. The QRS complex gradually changes from negative to V_1 to positive V_6. Note that the polarity of the T wave is similar to that of the QRS complex.

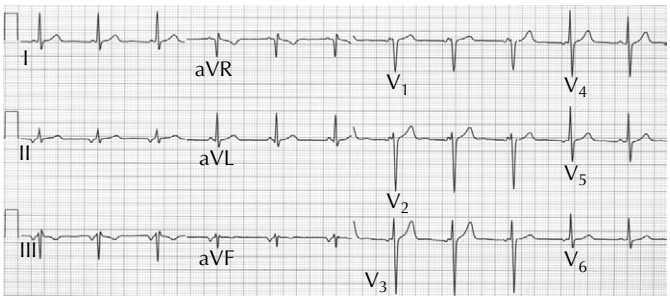
Figure 4-2 (**A**) Relation of action potential from the various cardiac regions to the body surface electrocardiogram (ECG). (**B**) Normal ECG.

associated with right ventricular depolarization is identified on the ECG.

The QRS complex is altered in both shape and duration by abnormalities in the sequence of ventricular activation. These include the bundle branch blocks (Fig. 4-4A), the fascicular blocks, ventricular preexcitation (Fig. 4-4B), nonspecific intraventricular conduction disturbances, and ectopic ventricular beats (Fig. 4-4C). The increase in QRS duration may range from a few milliseconds, as in the case of fascicular blocks, to more than 40 milliseconds, as with bundle branch blocks. The fascicular blocks reflect conduction slowing in one fascicle of the left bundle and are characterized by a shift in electrical axis and subtle changes in the initial portion of the QRS complex. The bundle branch blocks are caused by conduction slowing or block in the right or left bundle branch, usually caused by fibrosis, calcification, or congenital abnormalities involving the conducting system. They are associated with more pronounced abnormalities in the sequence of ventricular activation than are the fascicular blocks and thus with more significant changes in the QRS configuration. Intraventricular conduction abnormalities may also occur without a change in QRS configuration and reflect slow conduction without a change in the sequence of activation. Such slowing may be caused by cardioactive drugs, an increase in extracellular potassium concentration, and diffuse fibrosis or scarring as may occur in patients with severe cardiomyopathies.

The electrocardiographic criteria for the diagnosis of intraventricular conduction disturbances have been published. Important features include the following:

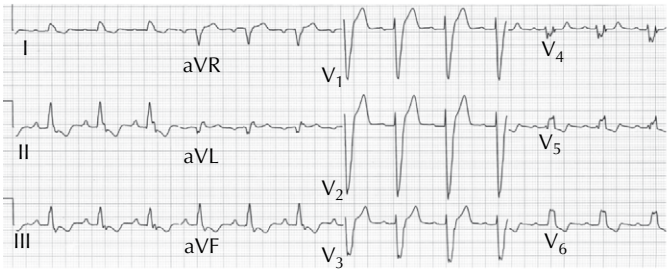
1. The fascicular blocks, by altering the initial portion of the QRS complex as well as the electrical axis in the frontal plane, may obscure the diagnosis of a prior myocardial infarction (MI) while causing other changes that can simulate an infarction.
2. Right bundle branch block does not affect the initial portion of the QRS complex, because activation of the interventricular septum and the left ventricle are unaffected. Thus, the electrocardiographic changes of a prior MI or left ventricular hypertrophy can still be appreciated.
3. Left bundle branch block and ventricular preexcitation do affect the initial portion of the QRS complex. Thus, the ECG changes associated with a prior MI and hypertrophy can be obscured or, as frequently occurs with ventricular preexcitation, can be mimicked.
4. Abnormalities in the sequence of depolarization are always associated with abnormalities in the sequence of repolarization. This results in secondary changes in the ST segment and T wave. This is particularly prominent in the setting of left bundle branch block and ventricular preexcitation (see Figs. 4-4A and B).
5. Changes in intraventricular conduction may be rate dependent and present only when the rate is above a critical level or after an early atrial premature beat. In this situation it is referred to as *rate-dependent aberrant ventricular conduction*.
6. The shape and duration of the QRS complex of ectopic ventricular beats will be influenced by the site of the ectopic focus just as the shape and duration of atrial ectopic beats are influenced by their site of origin.



Electrocardiogram showing an ectopic atrial rhythm. It was recorded from a 59-year-old man. The polarity of the P wave is abnormal. It is inverted in leads II, III, and aVF and upright in lead aVR.

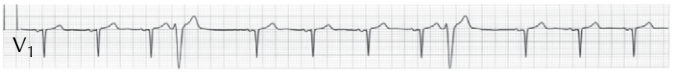
Figure 4-3 *Ectopic atrial rhythm.*

Left bundle branch block



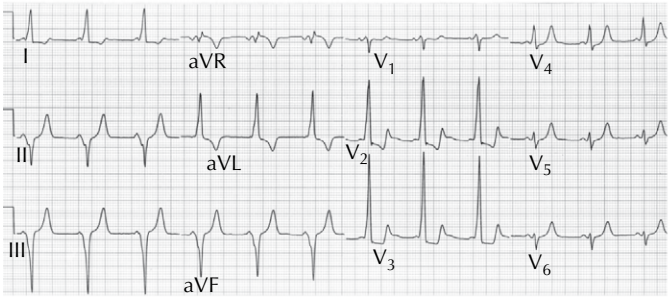
(**A**) Electrocardiogram showing left bundle branch block. It was recorded from a 73-year-old man. Note that the QRS complex is diffusely widened and is notched in leads V_3, V_4, V_5, and V_6. Note also that the T wave is directed opposite to the QRS complex. This is an example of a secondary T-wave change.

Ventricular premature beats



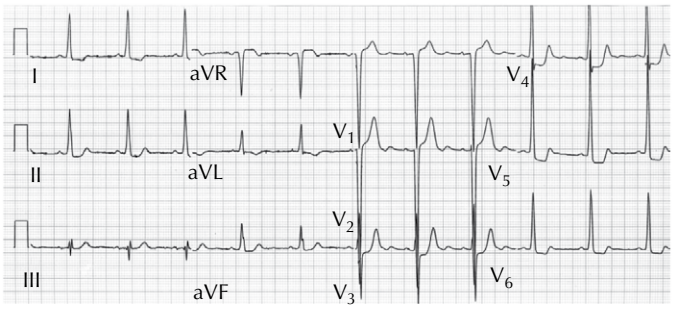
(**C**) Ventricular premature beats recorded from a 30-year-old man with no known heart disease.

Ventricular preexcitation



(**B**) ECG showing ventricular preexcitation. It is recorded from a 28-year-old woman. Note the short PR interval (0.9 seconds) and the widened QRS complex (0.134 seconds). The initial portion of the QRS complex appears slurred. This is referred to as a *delta wave*. This combination of short PR interval and widened QRS complex with a delta wave is characteristic of ventricular preexcitation. Note also that the T wave is abnormal, another example of a secondary T-wave change.

ECG changes of LV hypertrophy



(**D**) Example of the ECG changes of LV hypertrophy. It is recorded from an 83-year-old woman with aortic stenosis and insufficiency. Note the increase in QRS amplitude, the slight increase in QRS duration to 100 ms, and the ST-segment and T-wave changes.

Figure 4-4 (**A**) Left bundle branch block. (**B**) Ventricular preexcitation. (**C**) Ventricular premature beats. (**D**) Electrocardiogram (ECG) changes of left ventricular (LV) hypertrophy.

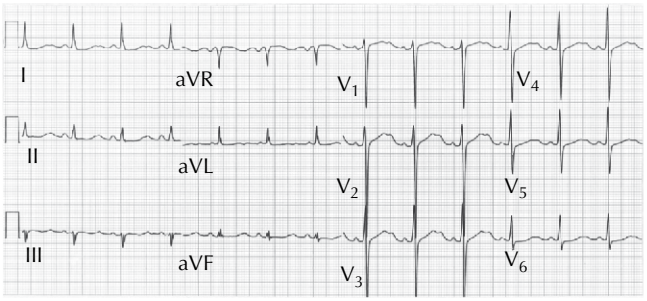
The amplitude of the QRS complex is subject to a variety of factors including the thickness of the left ventricular and right ventricular walls, the presence of pleural or pericardial fluid, or an increased tissue mass. QRS amplitude is also affected by age, sex, and race. For instance, younger individuals have greater QRS voltages than older individuals, and men have greater QRS voltages than women. In left ventricular hypertrophy, the R wave in the left-sided leads (V_5 and V_6) and the S wave in the right-sided chest leads (V_1 and V_2) are increased. QRS duration may increase, reflecting the increased thickness of the left ventricle and there may be changes in repolarization causing changes in the ST segment and T wave (Fig. 4-4D). Right ventricular hypertrophy is more difficult to diagnose electrocardiographically. Initially it causes cancellation of left ventricular forces, resulting in a decrease in S-wave amplitude in the right-sided leads V_1 and V_2 and a decrease in R-wave amplitude in the left-sided lead V_5 and V_6. With more advanced right ventricular hypertrophy, an increased R wave occurs in the right-sided leads, and a deeper S wave is seen in the left-sided leads. Pericardial and pleural effusions decrease QRS voltage in all leads, as may infiltrative diseases such as amyloidosis.

ST Segment and T Wave

The ST segment and T wave reflect ventricular repolarization. During the ST segment, the ventricular action potentials are at their plateau voltage and only minimal voltage gradients are generated. Therefore, the ST segment is at the same voltage level as (i.e., is isoelectric with) the TP and PR segments, during which time there are also no voltage gradients created because the action potentials are at their resting levels. The T wave is caused by the voltage gradients created as the ventricular cells rapidly and sequentially repolarize. If the sequence of repolarization were the same as the sequence of depolarization, the T wave would be opposite in direction to the QRS complex. However, the sequence of repolarization is reversed relative to the sequence of depolarization. As a result, the normal T wave is generally upright or positive in leads with an upright or positive QRS complex (leads I, V_5, and V_6) and inverted or negative in leads with an inverted QRS complex (aVR and V_1) (see Fig. 4-2B).

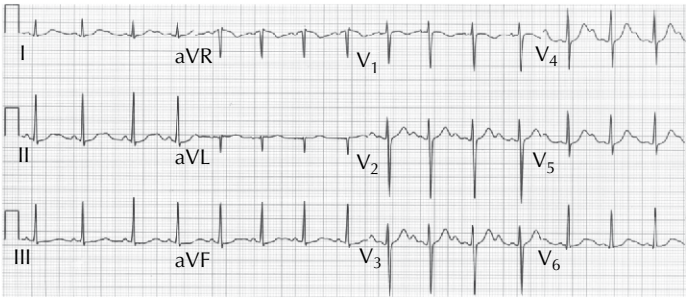
Abnormalities in repolarization are manifest by elevation or depression of the ST segment and changes in polarity of the T wave. As mentioned, such changes may be secondary to intraventricular conduction disturbances, or they may be due to

Changes associated with hypokalemia



(**A**) Example of the changes associated with hypokalemia. It is recorded from a 44-year-old man who was receiving long-term thiazide therapy. The QT interval is prolonged due to the presence of a U wave, which interrupts the descending limb of the T wave and is of equal amplitude to the T wave. In this patient, the serum potassium concentration was 2.7 mM.

Congenital long QT syndrome



(**B**) Recorded from a 16-year-old girl with syncopal episodes that were documented to be due to rapid ventricular tachycardia. It is an example of long QT syndrome. The T wave is notched and prolonged in much the same way as was shown in the patient with hypokalemia. However, in this patient, the serum potassium concentration was normal.

Figure 4-5 (**A**) Electrocardiogram (ECG) changes associated with hypokalemia. (**B**) Congenital long QT syndrome.

primary changes in repolarization, occurring as the result of electrolyte abnormalities or cardioactive drugs, or as the manifestation of diseases such as hypertrophy, ischemia, or myocarditis. Changes in T-wave polarity occurring in the absence of QRS and ST-segment changes are among the most difficult ECG abnormalities to interpret because they are nonspecific and may result from a variety of nonpathologic as well as pathologic causes. The following guidelines have served as an approach to interpreting T-wave abnormalities:

1. In general, T-wave amplitude should be equal to or greater than 10% of the QRS amplitude.
2. Inverted T waves in lead I are always abnormal and usually indicative of underlying cardiac pathology.
3. Minor T-wave changes such as T-wave flattening or slightly inverted T waves, particularly when they occur in the absence of known cardiac abnormalities or in populations at low risk for cardiac disease, are more likely to be nonspecific and nonpathologic than more marked T-wave changes or T-wave changes occurring in the presence of cardiac disease.
4. Flat or inverted T waves often occur in association with rapid ventricular rates and in the absence of other ECG changes. These changes are nonspecific and not indicative of underlying cardiac disease.

Elevation or depression of the ST segment indicates the presence of voltage gradients during the plateau and/or resting phases of the ventricular action potential and are most often a manifestation of cardiac disease. Among the most common causes of ST-segment elevation are acute transmural ischemia and pericarditis. High serum potassium and acute myocarditis may also cause ST-segment elevation and simulate ischemia, although this is rare. A normal variant referred to as *early repolarization* is a fairly common cause of ST elevation, particularly in young males. These changes characteristically occur in the V leads, involve elevation of the junction of the ST segment with the end of the QRS complex, and may simulate acute ischemia or pericarditis.

Left ventricular hypertrophy, cardioactive drugs, low serum potassium, and acute nontransmural or subendocardial ischemia are the most common causes of ST-segment depression.

U Wave

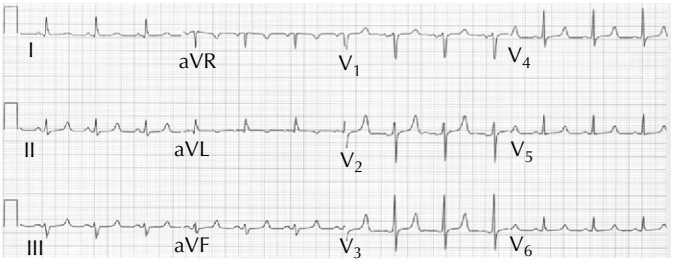
The U wave follows the T wave or may arise within the terminal portion of the T wave and be difficult to distinguish from a notched T wave. It is most easily seen in leads V_2 to V_4. An increase in U-wave amplitude is frequently associated with hypokalemia (Fig. 4-5A) and with some direct-acting cardiac drugs. Notching of the T wave resembling an increase in the U-wave amplitude and lengthening of the QT-U interval also often occurs in patients with congenital long QT syndrome (Fig. 4-5B).

QT ABNORMALITIES

The QT interval is measured from the onset of the Q wave to the end of the T wave and is slightly longer in females than in males. Changes in the duration of the QRS complex, the ST segment, and/or the T wave alter the QT interval. The QT interval is rate dependent, reflecting the rate-dependent changes in the duration of the action potential. It shortens at faster heart rates and lengthens at slower rates. To accommodate this rate dependency, several correction factors have been applied to the measured QT interval and used to generate the corrected QT interval (QTc). The QT interval is also influenced by a variety of other factors including (but not limited to) temperature, drugs, electrolyte abnormalities, neurogenic factors, and ischemia.

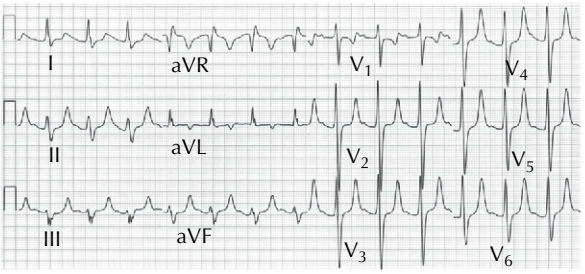
There is an extensive and ever-increasing list of drugs that lengthen the QT interval by prolonging the ST segment or the T wave, and it is often necessary to monitor the ECG when drugs recognized as having the potential for lengthening the QT interval are initiated. This is clinically important because lengthening of the QT interval following administration of these drugs may be a harbinger of a specific type of ventricular

ST-segment and QT-interval changes associated with hypocalcemia



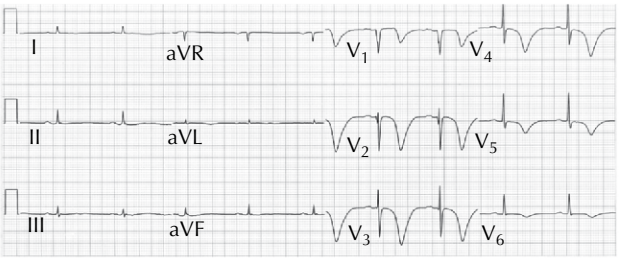
(**A**) ST-segment and QT-interval changes associated with hypocalcemia. It is recorded from a 53-year-old man with chronic renal disease. The ST segment is prolonged, but the T wave is normal. The QT interval reflects ST-segment lengthening and is prolonged.

Changes associated with hyperkalemia



(**B**) Example of the ECG changes associated with hyperkalemia. It is recorded from a 29-year-old woman with chronic renal disease. The P wave is broad and difficult to identify in some leads. The QRS is diffusely widened (0.188 seconds) and the T wave is peaked and symmetrical. These changes are characteristic of severe hyperkalemia and, in this patient, the serum potassium concentration was 8.2 mM.

T-wave changes induced by a recent ischemic event



(**C**) T-wave changes induced by a recent ischemic event, recorded from a 70-year-old man. The QT interval is prolonged and the T waves are markedly inverted in the precordial leads (V_1 through V_6). These changes gradually evolved over several days, and coronary angiography recorded the day this tracing was taken revealed a subtotal occlusion of the left anterior descending coronary artery.

Figure 4-6 (**A**) Hypocalcemia. (**B**) Electrocardiogram (ECG) changes associated with hyperkalemia. (**C**) T-wave changes induced by a recent ischemic event.

tachycardia, torsades de pointes, which may progress to ventricular fibrillation.

Low serum potassium and low serum calcium are both associated with prolongation of the QT interval. However, their electrocardiographic patterns are different and distinctive. As mentioned, low potassium causes ST-segment depression T-wave changes, a prominent U wave, and prolongation of the QT-U interval (Fig. 4-6A), whereas low calcium lengthens the ST segment, usually without causing significant T-wave changes (Fig. 4-6A). Marked elevations in serum potassium (usually above 6.5 mM) may cause prolongation of the QRS complex. Increases in serum potassium and in serum calcium shorten the QT interval by shortening the ST segment. High potassium also shortens the duration of the T wave and makes it more symmetrical, giving it a tented or peaked appearance (Fig. 4-6B).

Abnormalities in one or more of the several genes that regulate the repolarizing currents are responsible for causing congenital long QT syndrome, a significant cause of ventricular arrhythmias that often lead to sudden cardiac death. The ECG changes associated with congenital long QT syndrome (see Fig. 4-5B) are often difficult to distinguish from those caused by low potassium (see Fig. 4-5A) and low calcium (see Fig. 4-6A).

Marked QT prolongation and deeply inverted T waves occur frequently within the first several days following an acute MI, particularly when the infarction is due to occlusion of the left anterior descending coronary artery (Fig. 4-6C). This QT prolongation usually resolves within a day or two, although the T-wave inversion may persist for longer periods of time. Similar T-wave and QT-interval changes may occur in the chest leads following an acute ischemic event but in the absence of an infarction. This particular ECG pattern usually indicates a severely but not totally obstructed proximal portion of the left anterior descending coronary artery.

Some neurologic events, particularly intracranial hemorrhage and an increase in intracranial pressure, may cause T-wave inversion and dramatic lengthening of the QT interval, similar to that shown in Figure 4-6C. When it occurs in this clinical setting, it is called the *cerebrovascular accident pattern* and is thought to represent an imbalance of sympathetic stimulation. These ECG changes generally resolve within a few days.

ACUTE ISCHEMIA AND INFARCTION

Acute myocardial ischemia and infarction cause a series of metabolic, ionic, and pathologic changes in the region supplied by the occluded coronary artery that cause characteristic changes in the ST segment, QRS complex, and T wave (Fig.

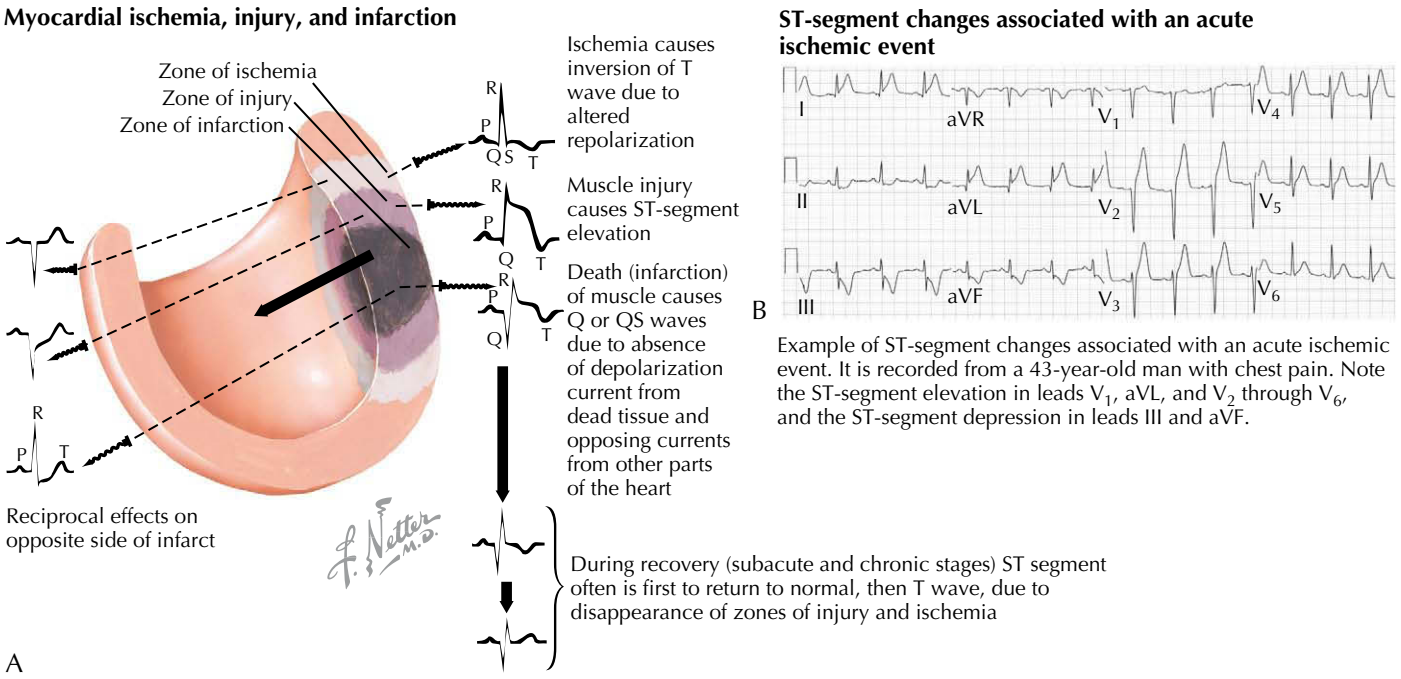


Figure 4-7 (**A**) Myocardial ischemia, injury, and infarction. (**B**) ST and T wave segment changes associated with acute ischemic event.

4-7A). The recognition of these changes permits the early diagnosis and prompt treatment—either thrombolytic therapy or percutaneous coronary revascularization—that can reverse ischemia and prevent the loss of myocardial cells and its sequelae.

The sequence of ECG changes associated with acute ischemia and infarction is as follows:

1. Peaking of the T wave
2. ST-segment elevation and/or depression
3. Development of abnormal Q waves
4. T-wave inversion

Peaking of the T waves in leads overlying the ischemic region is the earliest ECG manifestation of acute transmural ischemia and is transient. It is only rarely observed because the ECG is usually not recorded early enough to permit its detection unless the patient is in a hospital setting when ischemia first begins. ST elevation and depression are the most frequently observed early changes and develop within minutes of the onset of the acute event. The ST changes are caused by voltage gradients across the border between the ischemic and nonischemic regions that result in an electrical current, referred to as an *injury current*, flowing across the ischemic border. Whether these injury currents cause ST elevation or depression depends on the extent and location of the ischemic zone and the relationship of the ECG electrodes to the ischemic zone. In general, electrodes directly overlying a region of transmural ischemia will record ST elevation, whereas all other electrodes will record ST depression or no change in the ST segment (Fig. 4-7B).

Subendocardial ischemia, such as that associated with subtotal coronary occlusion and that which is often brought on by exercise in patients with flow-limiting coronary artery obstruction, does not extend to the epicardium. Thus, none of the body surface leads directly overlie the ischemic region, and ST depression, rather than ST elevation, is recorded.

The development of abnormal Q waves indicates slowed or absent conduction through the ischemic region and may last indefinitely. Abnormal Q waves that mimic those associated with infarction may also occur in other settings, particularly hypertrophy of the interventricular septum and intraventricular conduction disturbances, most notably ventricular preexcitation.

The various ECG changes in the setting of an acute ischemic event permit localization and an estimation of the extent of the ischemic or infarcted region and, by inference, identification of the occluded vessel.

ARRHYTHMIAS

The ECG is indispensable for the diagnosis of cardiac arrhythmias. For instance, abnormally rapid heart rates (>100 bpm) may have multiple causes, including sinus tachycardia, atrial and AV nodal re-entrant tachycardia (Fig. 4-8A), atrial flutter, atrial fibrillation (Fig. 4-8B), and ventricular tachycardia (Fig. 4-8C). The correct diagnosis is made by analysis of the rate and configuration of the P wave, its relation to the QRS complexes, and the shape and duration of the QRS complex. Abnormally slow heart rates (<50 bpm) may also be caused by several entities, including sinus bradycardia or sinoatrial or AV block (Fig. 4-8D). Again the diagnosis can be established by noting the rate, regularity, and configuration of the P wave and QRS complexes, the relation of the P wave to the QRS complexes, and the PR interval.

Irregular rhythms may be due to atrial and ventricular premature beats (Figs. 4-8E and 4-4C), atrial fibrillation with a slow ventricular response, and incomplete (second-degree) sinoatrial or AV block (Fig. 4-8F).

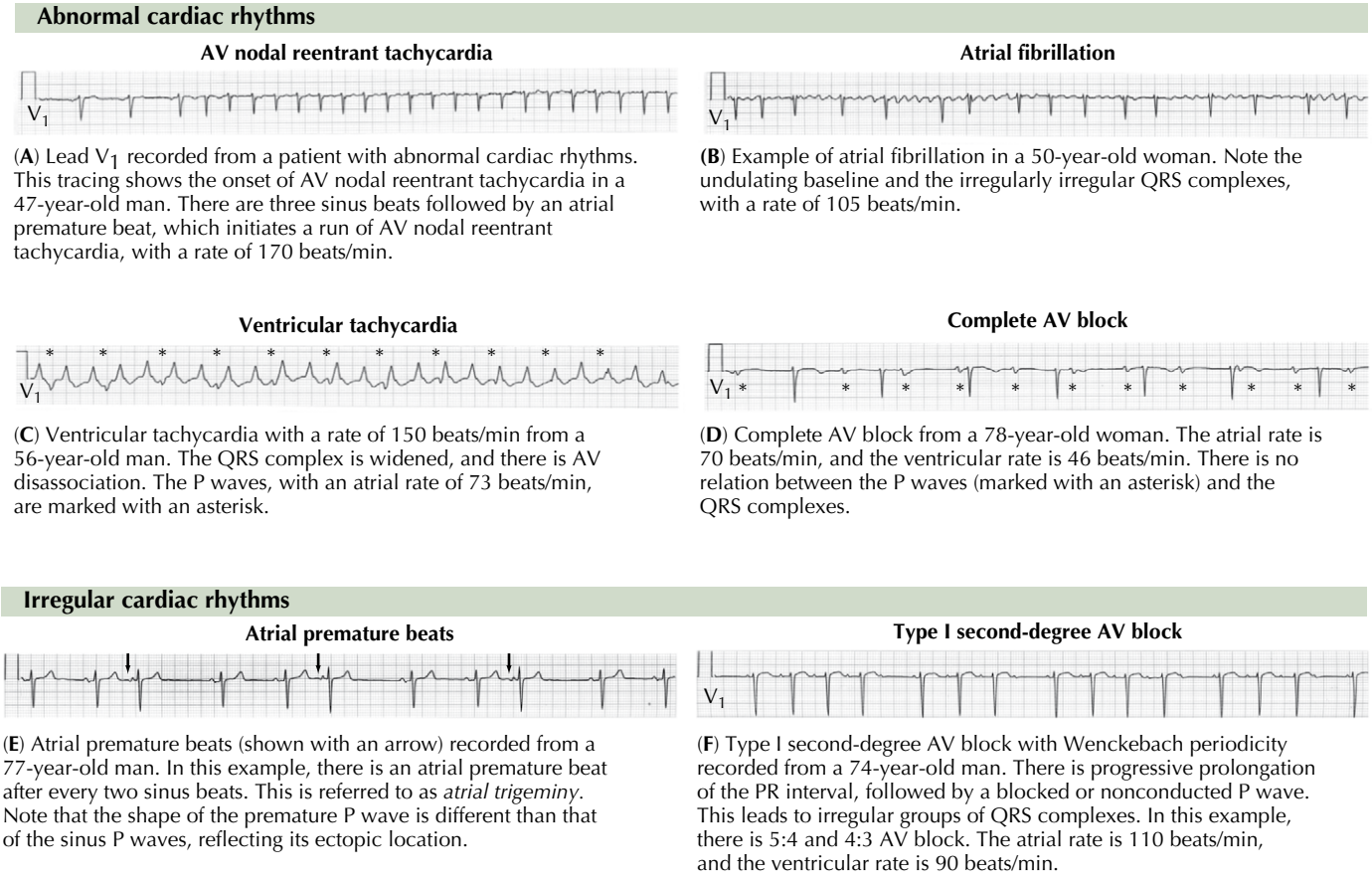


Figure 4-8 (**A**) Atrioventricular (AV) nodal re-entrant tachycardia. (**B**) Atrial fibrillation. (**C**) Ventricular tachycardia. (**D**) Complete AV block. (**E**) Atrial premature beats. (**F**) Second-degree AV block (type I).

FUTURE DIRECTIONS

The ECG provides a window into the electrophysiologic properties of the heart and their modification by physiologic, pharmacologic, and pathologic factors. When correctly interpreted, it provides diagnostic and prognostic information that is of inestimable help in the diagnosis and treatment of patients with a wide variety of cardiac diseases. It is of particular importance in the diagnosis of myocardial ischemia and arrhythmias and in the evaluation of patients with chest pain, heart murmurs, palpitations, shortness of breath, and syncope. The use of the ECG recorded during daily activities and during stress further adds to its capabilities. The value of the ECG is greatly enhanced when pertinent patient information, such as symptoms, drug usage, and important laboratory findings, is provided to the reader. It is reasonable to anticipate that in the future, additional leads such as V_3R, V_4R, and $V_{7–9}$ may be recorded and/or provided by computer reconstruction; that new analytic measurements, particularly those dealing with the QRS complex and the T wave, will be developed; and that the library of diagnostic and prognostic statements will be expanded. However, it is important to stress that the automated interpretations provided by computerized ECG systems now and in the future may be incomplete or inaccurate, particularly when the tracing is abnormal. For that reason, over-reading, by qualified personnel is essential.

ADDITIONAL RESOURCES

American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. Recommendations for the standardization and interpretation of the electrocardiogram.

This scientific statement is a six-part series of reports designed to update ECG standards and interpretation. The articles were published simultaneously in Circulation, Journal of the American College of Cardiology, and Heart Rhythm.

Part I. Kligfield P, Gettes LS, Bailey JJ, et al. The electrocardiogram and its technology. *Circulation.* 2007;115:1306–1324, *J Am Coll Cardiol.* 2007;49:1109–1127, *Heart Rhythm.* 2007;4:394–412.

Focusing on the computerized, automated technology currently employed, this article emphasizes areas that have clinical relevance.

Part II. Mason JW, Hancock EW, Gettes LS. Electrocardiography diagnostic statement list. *Circulation.* 2007;115:1325–1332, *J Am Coll Cardiol.* 2007;49:1128–1135, *Heart Rhythm.* 2007;4:412–419.

Provides a set of diagnostic statements that are more concise and streamlined than the existing diagnostic statements and should eliminate differences in the various systems currently in use.

Part III. Surawicz B, Childers R, Deal BJ, Gettes LS. Intraventricular conduction disturbances. *J Am Coll Cardiol.* 2009;53:976–981, *Circulation.* 2009;119(10):e235–e240.

This article reviews and updates standards for adults and children.

Part IV. Rautaharju PM, Surawicz B, Gettes LS. ST segment, T and U waves and the QT interval. *J Am Coll Cardiol.* 2009;53:982–991, *Circulation.* 2009;119(10):e241–e250.

Focuses on the various components of repolarization, their electrophysiologic basis, and electrocardiographic features.

Part V. Hancock EW, Deal BJ, Mirvis DM, et al. Electrocardiogram changes associated with cardiac chamber hypertrophy. *J Am Coll Cardiol.* 2009;53:992–1002, *Circulation.* 2009;119(10):e251–e261.

Reviews the various electrocardiographic criteria employed to diagnose chamber hypertrophy in children and adults and recommends changes to clarify statements currently in use.

Part VI. Wagner GS, MacFarlane P, Wellens H, et al. Acute ischemia/infarction. *J Am Coll Cardiol.* 2009;53:1003–1011, *Circulation.* 2009;119(10):e262–e270.

This final article in the series reviews the electrocardiographic manifestations of acute ischemia/infarction and suggests changes to permit identification of culprit lesion locations.

EVIDENCE

Chou TC. In: Surawicz B, Knilans TK, eds. *Chou's Electrocardiography in Clinical Practice.* 6th ed. Philadelphia: WB Saunders; 2008.

A complete text with excellent figures and extensive, up-to-date references.

Gettes LS. *ECG tutor (CD-ROM).* Armonk, NY: Future Publishing; 2000.

This animated graphic CD-ROM illustrates the electrophysiologic basis for the ECG and the interpretive approach.

Surawicz B. *Electrophysiologic Basis of ECG and Cardiac Arrhythmias.* Baltimore: Williams & Wilkins; 1995.

Provides an in-depth correlation of basic electrophysiologic phenomena to the waveform of the normal and abnormal body surface ECG.

Wellens HJJ, Gorgels PM, Doevendans PA. *The ECG in Acute Myocardial Infarction and Unstable Angina: Diagnosis and Risk Stratification.* Norwell, MA: Kluwer Academic Publishers; 2004.

An in-depth review and analysis of the electrocardiographic changes of acute ischemia/infarction and their use to predict the infarct-related artery, the size of the jeopardized myocardium, and the potential for reversibility.

Chest Radiography

Andrew O. Zurick III and Park W. Willis IV

5

Imaging techniques are central to the evaluation and management of patients with known or suspected heart disease. While technological advances in recent years have produced a broad spectrum of diagnostic imaging studies, each with advantages and appropriate clinical applications, it is necessary for clinicians treating patients with cardiovascular diseases to understand the applications and limitations of the available methodologies and use them effectively, but efficiently. This chapter focuses on technological aspects of cardiac and more specifically chest radiography and how this common imaging modality can still provide very useful information in the evaluation of patients with cardiovascular diseases.

TECHNICAL ASPECTS

Roentgenology is the science of both ionizing and nonionizing radiation modalities for the diagnosis and treatment of disease. Wilhelm Conrad Roentgen, a German physics professor who initially discovered x-rays in 1895, discovered that he could film his thumb and forefinger and their bones on a screen through the use of cathode rays. X-rays form part of the continuum of electromagnetic radiation, exhibiting both electrical and magnetic forces. They are typically generated by passing a current across a diode resulting in the generation of electrons, which are subsequently aimed at a metal anode that then gives off x-rays. The remarkable property of x-rays is their differential ability to penetrate through different types of matter, many of which are otherwise opaque to visible light.

X-ray beam projection determines resolution and magnification. As x-rays emerge from the x-ray tube, divergence occurs. When x-rays are captured by film, geometric distortion results as a function of the distance of the x-ray beam from the midline and the distance of the object from the film. The farther an object from the x-ray source, the less geometric distortion occurs; however, this greater distance also necessitates added energy to penetrate the object and expose the film. Ideally, the farther an object is from the x-ray tube, the more parallel the x-rays are that penetrate it. However, an object closer to the x-ray source will require greater x-ray divergence to cover the area of interest. Overall, resolution is improved by increasing the distance between the object and x-ray source at the expense of increased patient radiation exposure. Standard chest x-ray (CXR) examinations are obtained with a source-to-image distance of 6 feet.

An x-ray image of an object will only occur if there is a difference in the transmission of x-rays between the surrounding medium and the object of interest. Shades of gray or "contrast" result from different amounts of x-ray absorption between the surrounding medium and object of interest. The differential density of myocardium, blood, vascular tissue, and the surrounding air-filled lung allows distinction of these structures in CXRs. Thus, the CXR provides a means to assess the heart, the great vessels and the pulmonary veins, the lung fields, and the mediastinum. CXRs can be difficult to interpret, since imaging technique, body size, age, and other factors can all impact image quality.

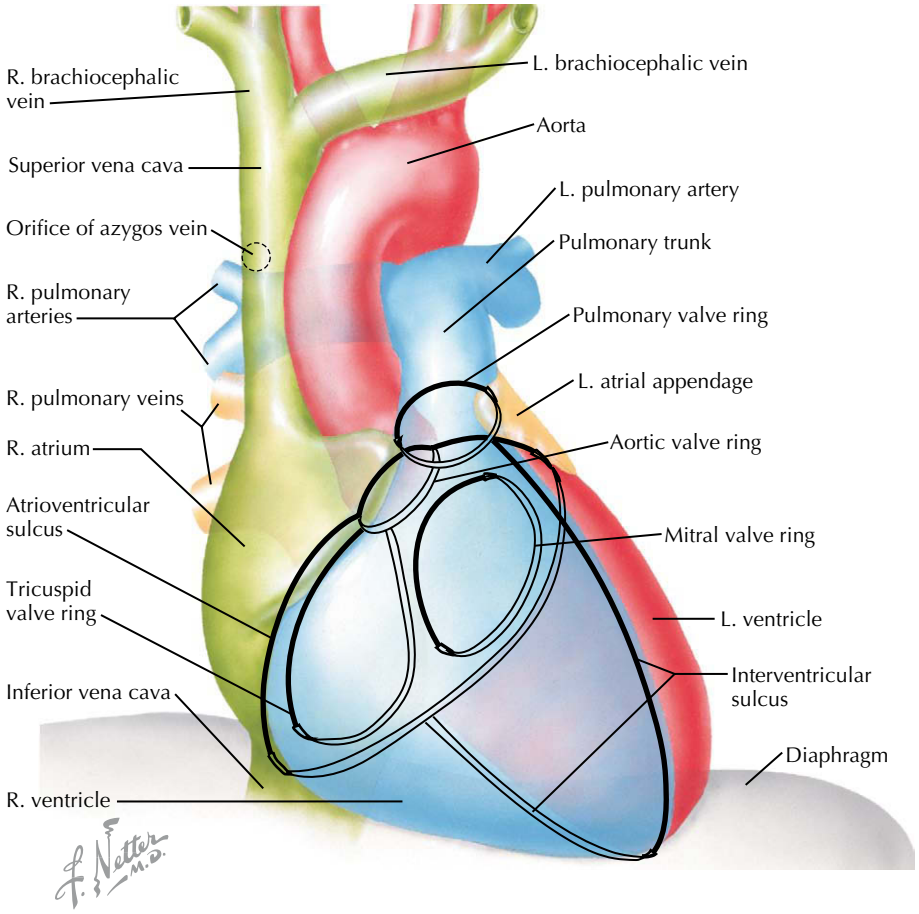
Safety Considerations

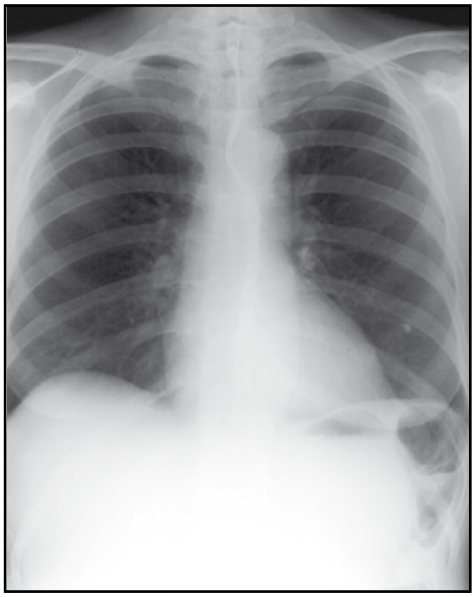
The risks of a single CXR are minimal. However, it is important to understand that even low-level, environmental radiation exposure (to sunlight) has effects on biologic systems, including resultant cell death by apoptosis. Because ionizing radiation has a dose-dependent effect, it is important to minimize unnecessary radiation exposure. The risks of medical radiation exposure include development of malignancy and/or genetic alteration. Lifetime cancer risk has been estimated to increase 0.5% to 1.4%, based on lifetime risk estimates for a general population, following 10 rad of x-ray or gamma radiation received by the whole body.

Chest Radiology—Normal Anatomy

The CXR can be very useful in detecting abnormalities in the structure of the heart and great vessels. To do so requires an understanding of the cardiac and vascular structures normally seen in a CXR. In the standard posteroanterior projection (Fig. 5-1), the right mediastinal border of the heart is formed by the right atrium (the lower portion of the mediastinal border) and the superior vena cava, which appears above the right atrial border as a slight bulge or straightening. The right atrium is not visible on the lateral view. Superimposed on the superior vena cava is the ascending aortic arch, a short convexity along the upper right mediastinum. The right pulmonary artery courses under the ascending aorta and is visualized as a faint shadow with numerous fading branches. The azygos vein arches over the right primary mainstem bronchus and connects to the superior vena cava. The upper left mediastinal border is composed of a prominence due to the aortic arch (the "aortic knob"), which tapers toward the mediastinum to a less-prominent main pulmonary trunk. The left pulmonary artery projects laterally from the trunk and forms smaller branches. Below the pulmonary trunk, the superior left heart border is formed by the left atrial appendage, and the lateral border of the left ventricle forms a convex or straight structure tapering to the left diaphragmatic border.

In the lateral projection, the lower third of the anterior border of the cardiac silhouette is formed by the apex and the outflow tract of the right ventricle, abutting in the lower quarter or third of the sternum and the anterior chest wall (Fig. 5-2). The upper two thirds is composed of the outflow portion of the right ventricle and the ascending aorta. The posterior wall of the left atrium forms most of the posterior border of the heart. Inferiorly, small portions of the right atrium and the inferior vena cava are profiled just above the diaphragm. With posteroanterior and lateral CXRs, the clinician can detect abnormalities





Interpretation of normal posteroanterior radiogram of heart

Figure 5-1 *Radiology and angiocardiography.*

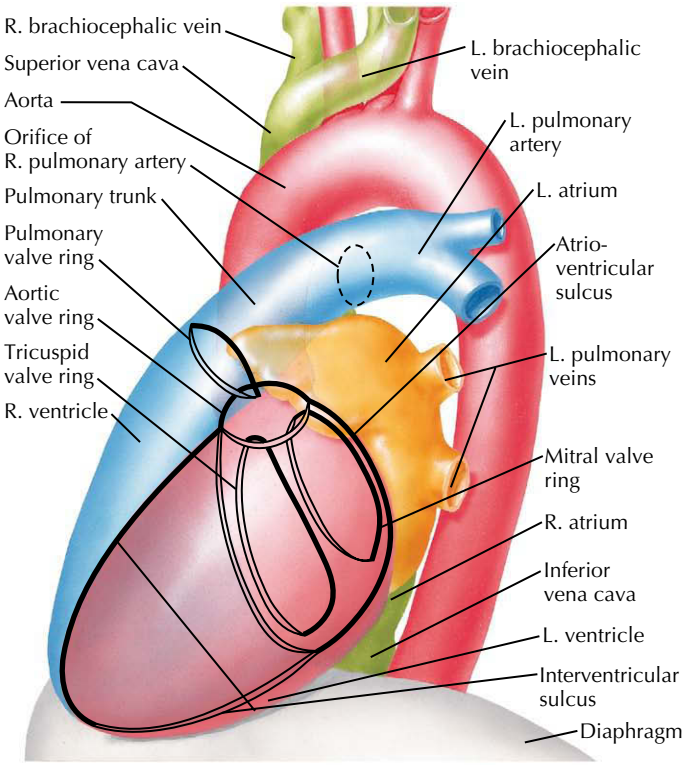
directly and infer valvular or structural heart disease and abnormalities in the great vessels and the lungs.

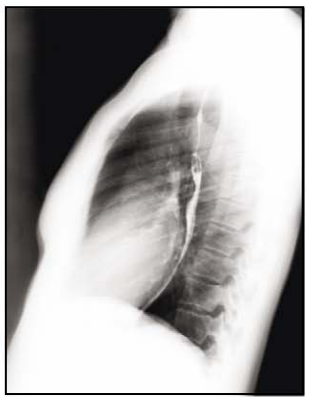
CLINICAL APPLICATIONS

Patients with heart disease may have any number of CXR abnormalities. The CXR is usually normal in uncomplicated coronary artery disease (CAD). However abnormalities in the aorta or lungs can be helpful in the evaluation of patients with chest pain. Additionally, structural abnormalities due to advanced coronary heart disease are often seen on screening CXRs. When calcification of one or more of the coronary arteries is seen on a screening CXR, this finding correlates with advanced coronary heart disease. CXRs detect only very advanced coronary artery calcification. Electron beam CT is much more sensitive for detecting coronary artery calcification. The CXR can be abnormal when CAD is complicated by heart failure or a ventricular aneurysm. In patients with long-standing systemic arterial hypertension, secondary left ventricular hypertrophy can manifest as elongation of the cardiac silhouette along the left hemidiaphragm and a plump, or downwardly displaced, apex. There may be associated dilation of the aortic root and the left atrium.

The CXR can also help confirm a diagnosis of valvular heart disease. For instance, in aortic stenosis, radiographic abnormalities include valvular calcification, poststenotic dilation of the aortic root, and left ventricular hypertrophy. Chronic moderate to severe aortic regurgitation causes left ventricular dilation. Long-standing mitral stenosis is often also accompanied by radiographic evidence of valvular calcification, but surrounding soft-tissue densities make visualization difficult. A deliberately overpenetrated CXR can be useful in visualizing mitral valve calcification. Because echocardiography is widely available and more sensitive in detecting valvular abnormalities, an overpenetrated CXR is rarely ordered today. More commonly, hemodynamically significant mitral stenosis can present to noncardiologists as left atrial enlargement seen on CXR. A left atrial enlargement can be seen as upward displacement of the left atrial border on the posteroanterior CXR and/or a double-density shadow that reflects a small amount of pulmonary parenchyma separating the left and right atrial borders. When associated pulmonary hypertension is present, mitral stenosis also causes pulmonary artery dilation. Chronic mitral regurgitation causes left atrial dilation and, when severe, left ventricular dilation.

The lateral CXR is the best view for distinguishing aortic and mitral valve calcification, and it is also useful for evaluating right ventricular and left atrial chamber dilation. Increased left ventricular size can be detected when the left ventricle extends posteriorly beyond the right atrium, forming the lower posterior heart border.





Interpretation of normal left lateral radiogram of heart

Figure 5-2 *Structural relationships between cardiac and vascular structures (lateral projection).*

Coarctation of the aorta is commonly associated with radiographic signs of hypertension. The classic finding of "notching of ribs" 3 to 9 from dilated collateral internal mammary arteries is often also present. Tetralogy of Fallot commonly manifests as a "boot-shaped" heart, reflecting right ventricular hypertrophy; the aortic arch is right-sided in 25% of cases.

Because the pulmonary vessels are surrounded by lung, even minor changes in size and distribution (reflecting alterations in flow or pressure) are easily identified. The primary radiographic manifestation of left heart failure is pulmonary vasculature prominence, reflecting elevated left atrial filling pressure and pulmonary venous congestion. The lower lobe peripheral vessels become less well defined and relatively small, while the upper lobe vessels remain well defined and increase in size. These changes become detectable when mean pulmonary venous pressure exceeds 15 mm Hg. As pressures rise to 20 mm Hg and above, fluid in the interlobular septa first appears at the lung bases, causing peripheral linear opacities perpendicular to the lateral pleural surface, the so-called Kerley's B lines. Pulmonary edema occurs when mean pulmonary venous pressure rises to 25 to 30 mm Hg and is typically a central, symmetric fluffy-appearing infiltrate with a butterfly appearance. Depending on etiology, generalized cardiomegaly or specific chamber enlargement can also occur.

LIMITATIONS

The CXR is limited because only the perimeter of the heart is visualized; because this technique does not differentiate among myocardium, valves, or blood pool; and because other methodologies are more accurate in assessing myocardial and valvular function.

FUTURE DIRECTIONS

The role of cardiac imaging in the evaluation of cardiac disease will continue to expand. Imaging techniques are generally safe and increasingly provide valuable decision-making information. The advantage of chest radiology is that it is inexpensive and widely available and can provide vital patient information useful in diagnosis and treatment of disease.

Newer imaging modalities are likely to continue to complement information derived from chest radiography. Positron emission tomography scanning currently is utilized to assess for ischemic heart disease, providing improved sensitivity and specificity over traditional single-photon emission CT and additionally can assess for myocardial viability with radiolabeled glucose after infarction. New multidetector CT scanners can effectively evaluate the heart and the vasculature, including coronary artery imaging. Finally, MRI is expected to make a significant impact in clinical use, with the potential to detect coronary stenosis, ischemia during stress, and myocardial viability in addition to providing valvular and functional information with a single imaging modality.

ADDITIONAL RESOURCES

Baron MG. The cardiac silhouette. *J Thorac Imaging.* 2000;15:230–242.

An excellent review of CXR utility in evaluating the cardiac silhouette, detailing information that can be obtained regarding the presence, nature, and severity of the disease as well as prognosis.

Dinsmore RE, Goodman DJ, Sanders CA. Some pitfalls in the valuation of cardiac chamber enlargement on chest roentgenograms. *Radiology.* 1966;87:267–273.

A clinically useful review documenting difficulties in the interpretation of CXRs and how to avoid common missteps.

Libby P, Braunwald E. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 8th ed. Philadelphia: Saunders/Elsevier; 2008.

A comprehensive, analytic review of the utility of CXR in the evaluation of cardiovascular diseases.

Webb S. *The Physics of Medical Imaging.* Bristol, UK: Institute of Physics Publishing; 2000.

This book provides a thorough review of the physics of medical imaging. Intended for those who desire an intensive review of the physics underlying medical imaging.

Echocardiography

Andrew O. Zurick III and Park W. Willis IV

6

Echocardiography is a highly reproducible, safe, and widely available noninvasive imaging technique integral to the practice of modern clinical cardiology. Utilizing high-frequency ultrasound to image cardiac and great vessel structure and blood flow, this method provides definitive anatomic and hemodynamic information crucial in the initial diagnosis and management of patients with a wide range of cardiac and vascular conditions. Though often considered a mature imaging technique, echocardiographic technology continues to improve. New clinical applications are continuously evolving, and diagnostic cardiovascular ultrasound is now being utilized in almost all fields of cardiology. Echocardiography is the most commonly used imaging technology for patients with known or suspected cardiovascular disease.

IMAGING METHODS AND CLINICAL APPLICATIONS

Transthoracic Echocardiography

A comprehensive transthoracic echocardiographic examination (TTE) includes the acquisition of standard two-dimensional (2D) and M-mode views of the intrathoracic structures complemented by continuous- and pulsed-wave spectral Doppler data and color flow Doppler imaging. Commercial echocardiographic imaging systems also have tissue harmonic imaging capability, and this technique is now routinely applied in most laboratories to enhance endocardial definition in patients with technically difficult TTE examinations. In addition, many laboratories routinely utilize tissue Doppler imaging (TDI) as part of standard TTE examination protocol. TDI, analogous to pulsed-wave Doppler assessment of blood flow velocity, is used to measure longitudinal myocardial motion. When combined with a comprehensive TTE examination, TDI can yield clinically useful information regarding diastolic ventricular function and cardiac filling pressures. Small, lightweight, and highly portable ultrasound systems are also available for bedside TTE imaging. Commonly referred to as "handheld" TTE devices, these instruments possess limited capability as compared with standard echocardiographic equipment, but advances have made this technology easier to use while simultaneously incorporating a wider range of imaging features; some of these models can perform many functions of a larger system.

Transthoracic 2D echocardiography is the foundation of the clinical echocardiographic examination. Tomographic images from multiple locations on the chest wall, defined by the transducer position and image plane (Fig. 6-1), provide a reliable, portable, and reproducible evaluation of cardiac chamber sizes, myocardial thickness, ventricular contractile performance, valvular structure and function, the pericardium, and great vessels. Doppler echocardiographic assessment of the direction and velocity of blood flow within the heart and great vessels is valuable in the detection and quantification of obstructive lesions and valvular regurgitation (Fig. 6-2). Transthoracic 2D directed M-mode echocardiography is especially valuable in the evaluation of mitral and aortic valve motion in dynamic and fixed left ventricular outflow obstruction, in the timing of mitral valve closure in aortic regurgitation, and in the assessment of pericardial disease. This technique also provides a precise measurement of cardiac chamber sizes and wall thickness throughout the cardiac cycle allowing accurate estimates of overall left ventricular contractile performance and ejection fraction, provided there are no segmental wall motion abnormalities.

Although coronary arteries cannot be reliably imaged by TTE, the method is nevertheless valuable in the assessment of known or suspected coronary artery disease (CAD). Echocardiographic evidence of segmental ventricular contractile dysfunction can be used to screen for acute or chronic ischemic myocardial injury or infarction, secondary to CAD. However, the diagnosis of CAD is not absolute, because segmental wall motion abnormalities can also be caused by cardiac trauma, myocarditis, and infiltrative myocardial diseases. In addition, multivessel CAD can cause globally decreased ventricular contraction without segmental wall motion abnormalities, a circumstance generally necessitating further evaluation.

TTE is the most reliable and reproducible clinical laboratory method for the initial diagnostic evaluation and follow-up of patients with congenital and valvular heart disease, including the evaluation of right ventricular systolic pressure and pulmonary arterial hypertension. Anatomic information about the nature of a congenital defect and its hemodynamic consequences, including the direction and magnitude of intracardiac shunts and estimation of pulmonary and systemic blood flow, can be estimated by 2D and Doppler techniques.

In stenotic valvular lesions, M-mode techniques can be useful in assessing valvular thickness and motion, ventricular chamber sizes, ventricular wall thickness, and atrial chamber dimensions. This information is valuable in estimating the hemodynamic effects of a stenotic valve abnormality. Transthoracic 2D echocardiography shows a more complete picture of the valvular, subvalvular, and annular structures, and when 2D echocardiography is combined with Doppler ultrasound techniques, obstructive gradients can be accurately measured and cross-sectional valve area can be estimated. Regurgitant valvular lesions can be accurately quantified by color flow Doppler imaging. Clinical decisions regarding medical therapy and operative intervention for patients with valvular disease are usually based on TTE 2D and Doppler echocardiographic data, supplemented by information from cardiac catheterization.

TTE is the primary tool for evaluating the presence and hemodynamic consequences of pericardial effusion. 2D imaging and a comprehensive Doppler examination can reliably identify patients with pericardial effusion and tamponade pathophysiology. TTE-guided pericardiocentesis, either at the bedside or in the cardiac catheterization laboratory, can reduce procedural complications and improve therapeutic results. A

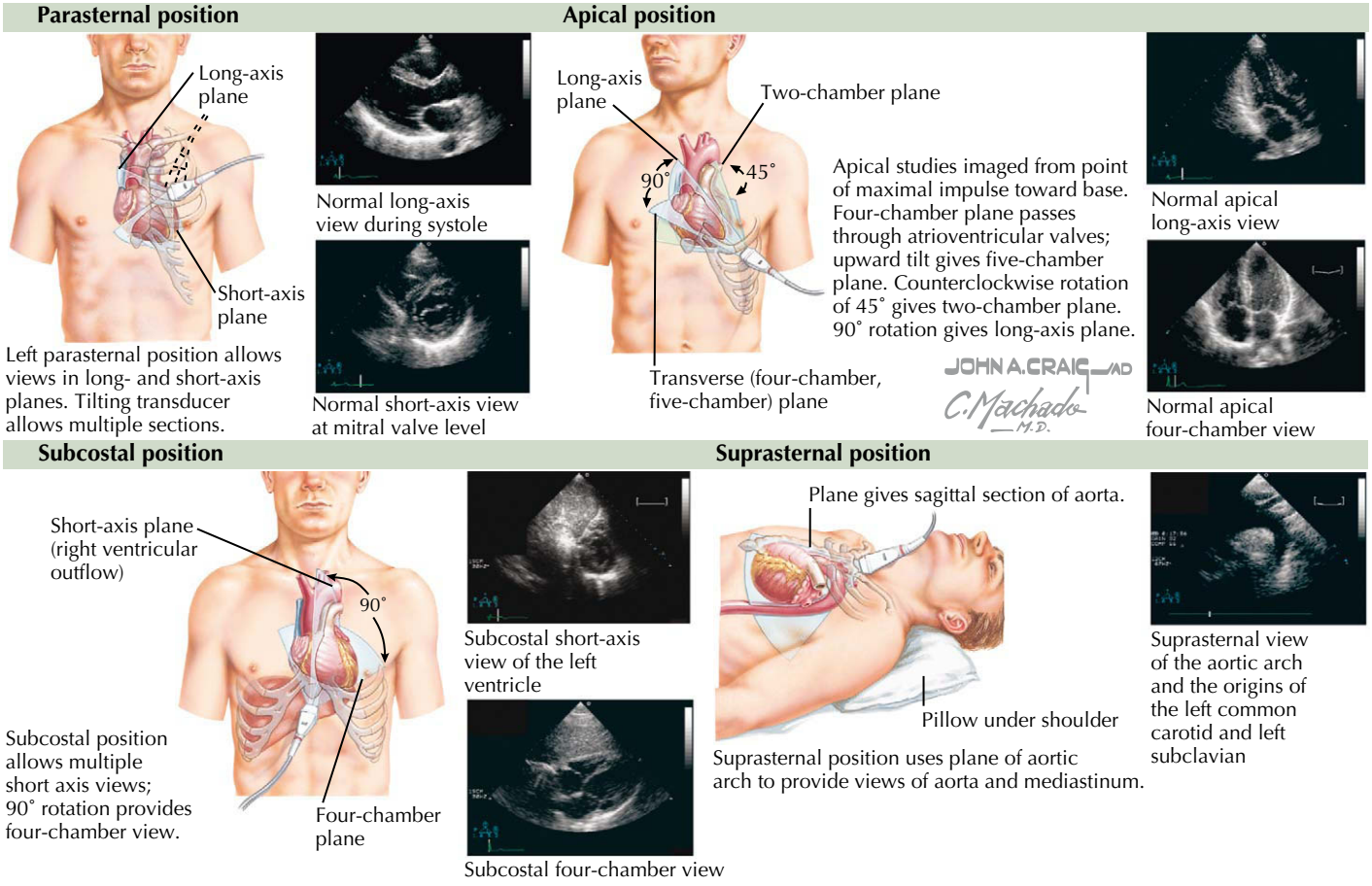


Figure 6-1 *Transducer positions in echocardiographic examination.*

thickened pericardium and typical hemodynamic alterations can alert the clinician to the diagnosis of pericardial constriction, but magnetic resonance imaging and catheterization are usually needed for full evaluation. Analysis of Doppler-measured ventricular inflow velocities and TDI can be useful in differentiating between pericardial constriction and infiltrative cardiomyopathy.

"Handheld" ultrasound imaging devices are most widely utilized for the rapid triage of patients in emergency department and intensive care unit settings. This technology can provide accurate assessment for pericardial effusion, left and right ventricular contractile performance, and segmental wall motion abnormalities. Although these devices can also detect valve disease, dilation of the aorta, and structural defects in patients with congenital heart disease, comprehensive echocardiographic evaluation of patients with these conditions and complete assessment of diastolic ventricular function usually require a standard TTE imaging system.

Transesophageal Echocardiography

A transesophageal echocardiographic examination (TEE) requires that an ultrasound probe be passed into the esophagus, posterior to the heart. Because of decreased distance between the transducer and the heart, as well as the absence of interference from bone and lung tissue, the signal-to-noise ratio is more favorable than with TTE, and higher-frequency transducers can be used to improve resolution. Therefore, TEE image quality is generally superior to that of TTE, particularly for posterior structures including the pulmonary veins, left atrium, interatrial septum, and mitral valve.

TEE is most commonly applied in the evaluation for clinically suspected patent foramen ovale (PFO), atrial septal defects (ASDs), valvular vegetations, left atrial or atrial appendage thrombus, and aortic disease. TEE can provide important complementary information when standard transthoracic images are insufficient to resolve a clinical differential diagnosis, especially in the specific conditions noted above. TEE is being utilized with increasing frequency as a complementary diagnostic method in clinical cardiac electrophysiology before elective cardioversion and invasive procedures including ablative therapy for atrial fibrillation. TEE is also useful in the cardiac catheterization laboratory to assist with transseptal puncture and for optimal percutaneous placement of closure devices in patients with PFO or ASD. Intraoperative TEE, initially utilized primarily to monitor operative results of mitral valve repair, is now being used for a broader range of indications.

Stress Echocardiography

Exercise and pharmacologic stress echocardiography are now standard procedures in most echocardiography laboratories.

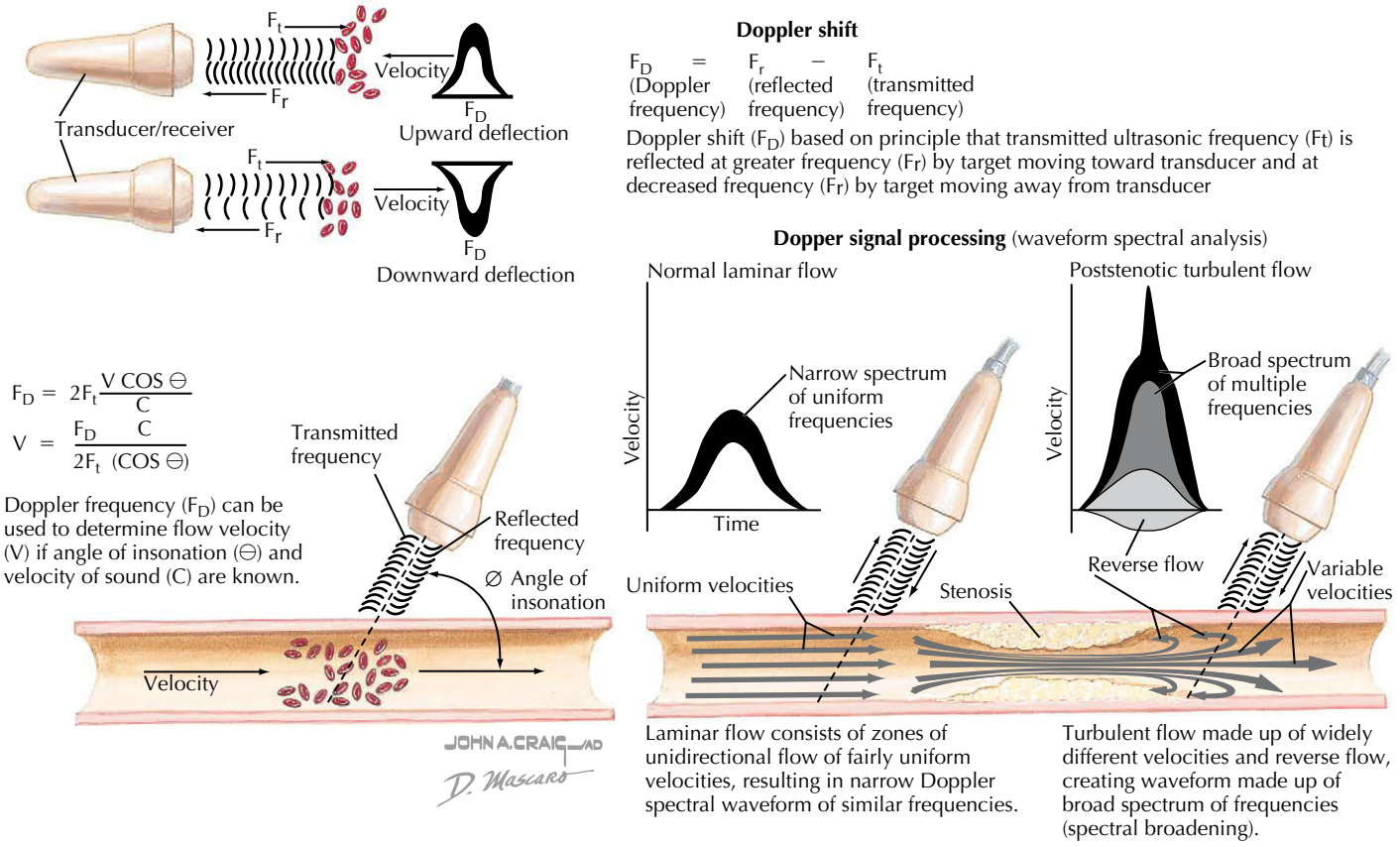


Figure 6-2 *Principles of Doppler echocardiography.*

The clinical utility of stress echocardiography depends on acquisition of high-quality TTE images of the left ventricle, in multiple planes, at maximal cardiac workload. With exercise stress, patients must be highly motivated not only to reach, but ideally exceed, target heart rate, because cardiac workload falls rapidly with cessation of exercise. Repositioning of the subject and immediate post-stress image acquisition usually requires 30 to 60 seconds, and test sensitivity falls when echocardiographic data are recorded at less than maximal workload. For these reasons, equivocal test results are fairly common with exercise stress. This is rarely a problem with pharmacologic stress, because patient repositioning is not necessary and maximal cardiac workload can be maintained while image acquisition is completed. Pharmacologic stress also has a technical advantage in that patients are not moving during the study; sequential images can be recorded as cardiac workload is gradually increased, and respiratory interference at peak stress is not a limiting factor.

TTE combined with the use of pharmacologic agents (usually dobutamine) is an accurate, noninvasive approach to determining CAD's presence and/or severity. A stress-induced segmental wall motion abnormality usually indicates flow-limiting CAD. This technique is more accurate than routine treadmill testing across a wide spectrum of patients, including those with single or multivessel CAD and those with normal or abnormal ECGs at rest. In addition to providing a useful approach for detecting obstructive CAD, stress echocardiography can be used to assess an area of myocardium at risk, for detection of myocardial viability, in risk stratification after myocardial infarction, and for evaluation of the results of coronary revascularization. Stress echocardiography is especially useful in detecting CAD in patients after heart transplantation, in those being considered for renal transplantation, and for preoperative evaluation of individuals undergoing vascular surgery. With advances in ultrasound imaging, and because the technique is readily available and does not require handling of radionuclides, the use of stress echocardiography has expanded dramatically.

Contrast Echocardiography

In clinical cardiology, contrast echocardiography is now widely used to detect intracardiac and intrapulmonary shunts, augment Doppler velocity signals, and enhance endocardial border definition. Intravenous injection of agitated normal saline is most often used for opacification of the right heart, shunt detection, and augmentation of tricuspid regurgitant jets so as to allow more accurate estimation of right ventricular systolic pressure. Commercially available contrast agents, termed *microbubbles*, are made of a high-molecular-weight gas encapsulated in a shell of phospholipid or protein. Modifications of the microbubble shell and gas properties have resulted in improved stability of these agents as they pass through the pulmonary circulation following intravenous injection, and high-quality imaging of the left heart chambers can be reliably obtained. Microbubbles are also small enough to pass through the microcirculation and thus can be utilized to assess myocardial perfusion. Gas-filled microbubbles

are used principally for left ventricular opacification during rest or stress echocardiography in patients with technically suboptimal TTE images. Myocardial perfusion imaging with contrast echocardiography is not routinely used for clinical purposes.

Intravascular Ultrasound and Intracardiac Echocardiography

The development of intravascular ultrasound (IVUS) and intracardiac echocardiography (ICE) techniques has extended the application of echocardiography and bridged traditional boundaries between noninvasive and invasive imaging methods. IVUS utilizes a miniaturized transducer on the end of a flexible, steerable catheter that is inserted into arteries allowing in vivo ultrasound imaging of vascular anatomy from the inside out. ICE relies upon a catheter-like ultrasound probe that can be advanced to the right heart chambers via the femoral vein and inferior vena cava; in certain circumstances, these probes can also cross the interatrial septum. ICE probe technology has evolved rapidly and is capable of high-resolution 2D echocardiography and a full complement of Doppler imaging modalities.

Intracoronary IVUS is commonly utilized in cardiac catheterization laboratories to delineate atherosclerotic plaque morphology, lesion length, and obstruction severity when standard coronary angiographic and pressure data are ambiguous. Intracoronary IVUS can help guide percutaneous coronary intervention and stent implantation and aid in the diagnosis of in-stent restenosis. ICE is a valuable tool to monitor noncoronary interventional procedures in interventional electrophysiology and cardiac catheterization laboratories. Invasive procedures in these laboratories are lengthy, and conventional monitoring methods including fluoroscopy, TTE, and TEE are therefore less practical; in addition, these methods have inherent technical limitations, especially with respect to delineation of posterior structures, when the patient is supine. ICE has proven useful for direct visualization of the pulmonary veins and left atrial appendage during invasive ablation procedures for atrial fibrillation. Additionally, ICE is now used to assist with guidance of radiofrequency catheter ablation of atrial arrhythmias in the right side of the heart. ICE augments fluoroscopy through improving visualization of landmarks, ensuring endocardial contact, and assisting with transseptal puncture. This technique is also useful in the prompt detection of procedural complications including intracardiac thrombus formation, pericardial effusion, and pulmonary vein obstruction. In the cardiac catheterization laboratory, ICE has demonstrated clinical utility in guiding percutaneous closure of ASD and PFO. ICE can assist in delineating the details of defect size and location, identifying important adjacent structures, and in optimal positioning of the closure device. Following device deployment, ICE is useful in confirming position, and Doppler methods can be used to detect residual shunt. ICE is also useful in monitoring percutaneous left atrial appendage closure and balloon mitral valvuloplasty.

Three-dimensional Echocardiography

Three-dimensional (3D) echocardiography, via either a transthoracic or transesophageal approach, can provide improved definition of spatial relationships between normal and abnormal cardiac structures. Because 3D echocardiography has the capability to display cardiac structural relationships with improved accuracy and images can be viewed from different orientations after acquisition, anatomy is more intuitively and quickly appreciated. High-resolution 3D methods can help eliminate the need for cognitive reconstruction of image planes currently required for high-quality interpretation of standard 2D images.

3D echocardiography has the potential to provide more accurate and reliable measurements of cardiac chamber dimensions and function. This is especially true and probably most important when dealing with complex shapes such as the right ventricle or aneurysmal left ventricle, when quantification by 2D methods, which rely on geometric assumptions about shape, are less accurate. Significant advances in ultrasound, electronic, and computer technology have made real-time–rendered 3D images more practical and potentially valuable in clinical practice. There is evidence to support the use of 3D echocardiography for quantification of left ventricular mass, volume, and ejection fraction, as well as in the measurement of the mitral valve area in patients with mitral stenosis. This technique is commonly used for intraoperative evaluation of the mitral valvular apparatus during repair.

LIMITATIONS

Although modern echocardiography imaging systems are sophisticated multimodality devices, echocardiography remains an operator-dependent technique. The demands of routine patient care require thoughtful, yet streamlined examinations through the selective use of appropriate methods according to clinical circumstances. High-quality echocardiographic imaging requires a solid foundation of training in cardiac anatomy, cardiovascular physiology, and pathophysiology. A working knowledge of ultrasound physics, as well as considerable technical skill, expertise, and patience of the physician or technician obtaining images, are essential. Even in trained hands, image acquisition is limited by obesity, chronic obstructive pulmonary disease, and patient discomfort; chest wall injuries or recent surgery can make a TTE particularly challenging. Suboptimal images may be seen in up to 10% to 15% of all patients undergoing echocardiography. Because of this difficulty, contrast media have been used more widely to enhance endocardial definition. However, because of reported serious cardiopulmonary complications, the U.S. Food and Drug Administration has issued a black-box warning against the use of commercially available contrast agents in acutely ill patients. Responsible use of handheld echocardiographic devices requires appropriate training and experience in cardiac ultrasound. A major limitation of these instruments is misdiagnosis and inappropriate treatment resulting from use by inexperienced operators and/or suboptimal image quality.

TEE is limited in many clinical circumstances. Patients must be physically able, well-oriented, and sufficiently cooperative to follow simple commands, so as to successfully swallow the ultrasound probe. Structural limitations prevent complete visualization of the left ventricle. Although generally well tolerated, TEE carries risk related to sedation and esophageal intubation; complications include esophageal perforation and aspiration of gastric contents.

FUTURE DIRECTIONS

Evolving technological improvements, increasing availability, and new clinical applications will fuel continued growth in the use of echocardiographic imaging. The ongoing explosion of new echocardiographic modalities will present the echocardiographer with constantly challenging questions regarding appropriate application of these methods to standard examination protocols. As novel cardiovascular applications of ultrasound, currently utilized principally as research tools, are refined, these methods will reach the clinical horizon and become feasible for everyday use. Myocardial contrast echocardiography, used principally in research settings for years, is being applied clinically in some centers to evaluate integrity of the coronary microcirculation following myocardial infarction. 3D echocardiography, long envisioned to hold tremendous potential as an advanced imaging modality, will continue to evolve. Significant advances have moved this technology forward by simplifying data acquisition and improving image quality. As 3D methods become more practical and less time-consuming, clinical applications will increase in the daily practice of clinical cardiology. Echocardiographic analysis of strain and strain rate deformation, utilizing a combination of TDI and speckle tracking methods, are now being used in clinical research protocols to define myocardial deformation of whole left ventricular segments. This work suggests that strain and strain rate provide a more accurate assessment of segmental dysfunction after acute myocardial infarction than tissue velocities alone. Strain and strain rate have also been proposed as an alternative means to evaluate ventricular myocardial mechanical dyssynchrony for the purpose of predicting benefits from cardiac resynchronization therapy.

ADDITIONAL RESOURCES

Chu E, Kalman JM, Kwasman MA, et al. Intracardiac echocardiography during radiofrequency catheter ablation of cardiac arrhythmias in humans. *J Am Coll Cardiol.* 1994;24:1351–1357.

Prospective cohort study evaluating preliminary experience using ICE as an adjunct to fluoroscopy for guiding radiofrequency catheter ablation of right-sided atrial arrhythmias.

Hernández F, García-Tejada J, Velázquez M, et al. Intracardiac echocardiography and percutaneous closure of atrial septal defects in adults. *Rev Esp Cardiol.* 2008;61:465–470.

Retrospective study reviewing 52 adult patients with ASD who underwent transcatheter closure using an Amplatzer occluder device under ICE monitoring. The authors concluded that ICE can be safely and effectively utilized in this setting.

Jamal F, Kukulski T, Sutherland GR, et al. Can changes in systolic longitudinal deformation quantify regional myocardial function after an acute infarction? An ultrasonic strain rate and strain study. *J Am Soc Echoardiogr.* 2002;15:723–730.

This longitudinal, case-controlled study of 40 patients was conducted to investigate the additional value of strain rate and strain versus myocardial velocity alone in the identification and quantification of regional asynergy following myocardial infarction. The authors conclude that strain rate and strain provide a better assessment of segmental dysfunction severity than myocardial velocities alone after myocardial infarction.

Lang RM, Mor-Avi V, Sugeng L, et al. Three-dimensional echocardiography. The benefits of the additional dimension. *J Am Coll Cardiol.* 2006;48:2053–2069.

Well-written review article describing the utility of 3D echocardiography in clinical practice and advantages of the technique; includes discussion of available literature.

Lester SJ, Tajik AJ, Nishimura RA, et al. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. *J Am Coll Cardiol.* 2008;51:679–689.

A thorough and exceptionally well-written update on 2D echocardiographic and Doppler assessment of diastolic function.

Olszewski R, Timperley J, Szmigielski C, et al. The clinical applications of contrast echocardiography. *Eur J Echocardiogr.* 2007;8:S13–S23.

An excellent review of the literature with in-depth discussion of the clinical applications of contrast echocardiography.

EVIDENCE

Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA guidelines for the clinical application of echocardiography. *Circulation.* 1997;95:1686–1744.

Comprehensive document detailing evidence-based guidelines for appropriate application of echocardiography in a wide range of clinical circumstances.

Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography. *Circulation.* 2003;108:1146–1162.

An update of original evidence-based guidelines for the use of echocardiography published in 1997. A relatively brief and concise document, it is best appreciated in the context of the original publication, cited above.

Douglas PS, Khandheria B, Stainback RF, et al. ACCF/ASE/ACEP/ASNC/SCAI/SCCT/SCMR 2007 appropriateness criteria for transthoracic and transesophageal echocardiography. *J Am Coll Cardiol.* 2007;50:187–204.

Detailed review of the risks and benefits of TTE and/or TEE for several indications and in a wide range of clinical scenarios. Most data are presented in table format, making it a readily accessible and useful reference.

Douglas PS, Khandheria B, Stainback RF, et al. ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography. *Circulation.* 2008;117:1478–1497.

This expert panel rated indications for stress echocardiography by the appropriateness method, combining expert clinical judgment with the scientific literature to evaluate risk and benefit. Covers the majority of clinical situations faced by practicing physicians; consensus recommendations are presented in a concise table format.

Stress Testing and Nuclear Imaging

7

Arif Sheikh and Luis A. Tamara

Stress electrocardiography and stress imaging studies are widely used noninvasive procedures that provide important information on cardiac function and the presence of hemodynamically significant coronary artery disease (CAD). The correct use of stress testing is critically important in the cost-effective management of patients with known or suspected CAD. When the most appropriate procedure is performed, it provides important diagnostic and prognostic information that determines the optimal management strategy to be undertaken for that individual. Stress testing is also used in patients with known CAD so as to determine exercise "prescriptions" before cardiac rehabilitation (Fig. 7-1).

EXERCISE STRESS TESTING

Exercise stress testing involves subjecting a patient to increasing levels of exercise with continuous electrocardiographic monitoring for myocardial ischemia and arrhythmias. Although the sensitivity and specificity of stress electrocardiography in the detection of CAD are low (in the range of 55% to 75%) compared with more advanced testing (including the use of imaging), stress electrocardiography is widely available, relatively inexpensive, and can provide important prognostic information about the patient. Generally, diagnostic treadmill stress testing is done on patients with a low pre-test likelihood of having CAD. However, exercise stress testing can also be used in patients with known CAD to evaluate the effectiveness of current therapies, to ascertain overall functional capacity, and to determine general prognosis. In children with congenital heart disease, treadmill stress testing can be used to quantify functional capacity.

The sensitivity of exercise stress testing for detecting CAD is proportional to the heart rate (HR) achieved during exercise. Thus, in preparation for the study, patients are usually asked to transiently discontinue medications that affect HR response (e.g., β-blockers or calcium channel blockers). Patients should fast for at least 4 hours before the test. Exercise is done on a treadmill or, alternatively, using a bicycle ergometer. In special circumstances, arm ergometry and isometric hand exercises can be used. There are several different protocols for treadmill stress testing. All of them start exercise at a given rate and incline angle and then gradually increase one or both parameters until an adequate HR and exercise endurance are achieved. Generally, exercise is continued until the patient reaches a target HR of at least 85% of the maximum predicted HR (MPHR) for the patient's age (220 bpm – age in years ± 10 to 12 bpm). Studies that have correlated ECG changes with CAD generally involve reaching this target HR. Once a patient reaches the target HR, he or she should continue to exercise until fatigued or until signs or symptoms develop. If a patient exceeds a double product (HR × systolic blood pressure) of 25,000 as a secondary target, the test may be considered adequate. If the patient does not attain an exercise level at least equivalent to 5 metabolic equivalents, the study may be considered inadequate. Hemodynamic instability, gross ECG changes, or severe patient symptoms are also indications to terminate the procedure.

At the end of exercise testing, the patient slowly reduces the intensity of exercise. Vigorous exercise results in increased blood flow and pooling in the extremities, and a "step-down" phase (low-level exercise) allows the patient to re-equilibrate before ceasing exercise. After exercise termination, patients are monitored in a supine position until they are no longer tachycardiac (i.e., HR < 100 bpm) if not back to baseline HR. Importantly, if there were any ECG changes or symptoms experienced by the patient during the study, post-test monitoring should be continued with any necessary treatments until these have resolved, even if hemodynamics (HR and blood pressure) have returned to acceptable levels. The post-test monitoring serves to reveal any arrhythmias or ST-segment changes that may develop and be late signs of ischemic disease (Fig. 7-2).

The ECG must be interpreted with certain caveats. Although the standard 12-lead configuration can be used, in many instances a modified 12-lead configuration is substituted. This involves placing limb leads more proximally than is done for a standard ECG (electrodes are placed on the shoulders rather than arms for instance). This change results in ST-segment changes being accentuated and more easily detected during stress. This may also result in a baseline "stress" ECG that differs from a supine ECG done with standard lead placement.

The presence of myocardial ischemia during the test is suggested if previously normal ST segments show flattened or down-sloping depression more than 1 mm below the baseline in three consecutive beats. An important issue concerns ST-segment changes that can occur in some individuals simply because of the increased respiratory rate that accompanies exercise. A pre- or post-stress ECG performed with hyperventilation should be done to allow comparison of ECG changes associated with increased respiratory rate.

The prognostic information obtained from a treadmill stress test is often very useful for deciding on the next diagnostic or therapeutic step for a given patient. Of the several methods used for prognosis following treadmill stress testing, the most widely used is the Duke Treadmill Score. The time of exercise, the presence (or absence) of ST-segment changes during the study, and patient symptoms are used to determine a "score" that correlates with event-free survival.

Bicycle-based studies use a comparable approach to provide similar information. The patient maintains a steady—or, rarely, increasing—pedaling rate over a period of time with regular increases in the intensity required for pedaling. At comparable HRs, a higher level of physiologic stress (reflected by metabolic equivalents) is present in individuals walking on a treadmill than individuals pedaling a bicycle. The data available for comparing these two forms of exercise are quite limited, however. Caution should be used in translating clinical information between forms of exercise.

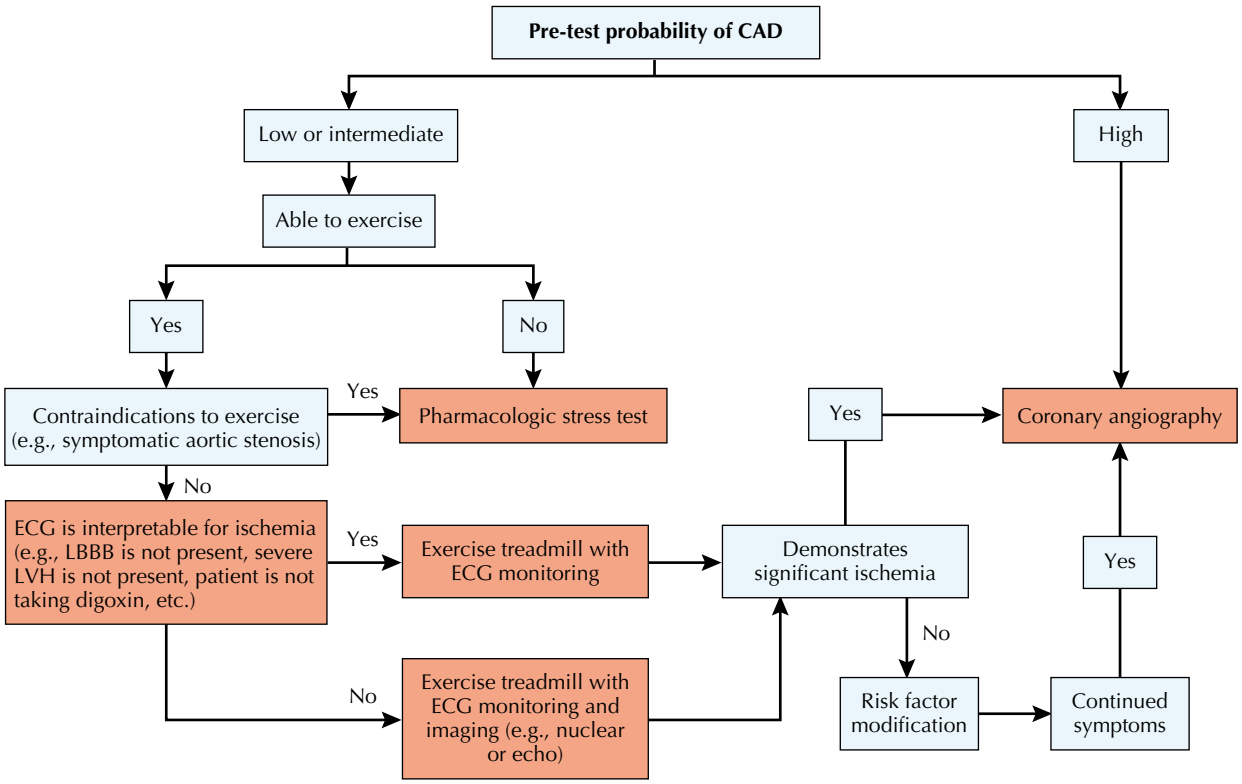


Figure 7-1 *Evaluation for hemodynamically significant coronary artery disease (CAD) in clinically stable patients.* LBBB, left bundle branch block; LVH, left ventricular hypertrophy.

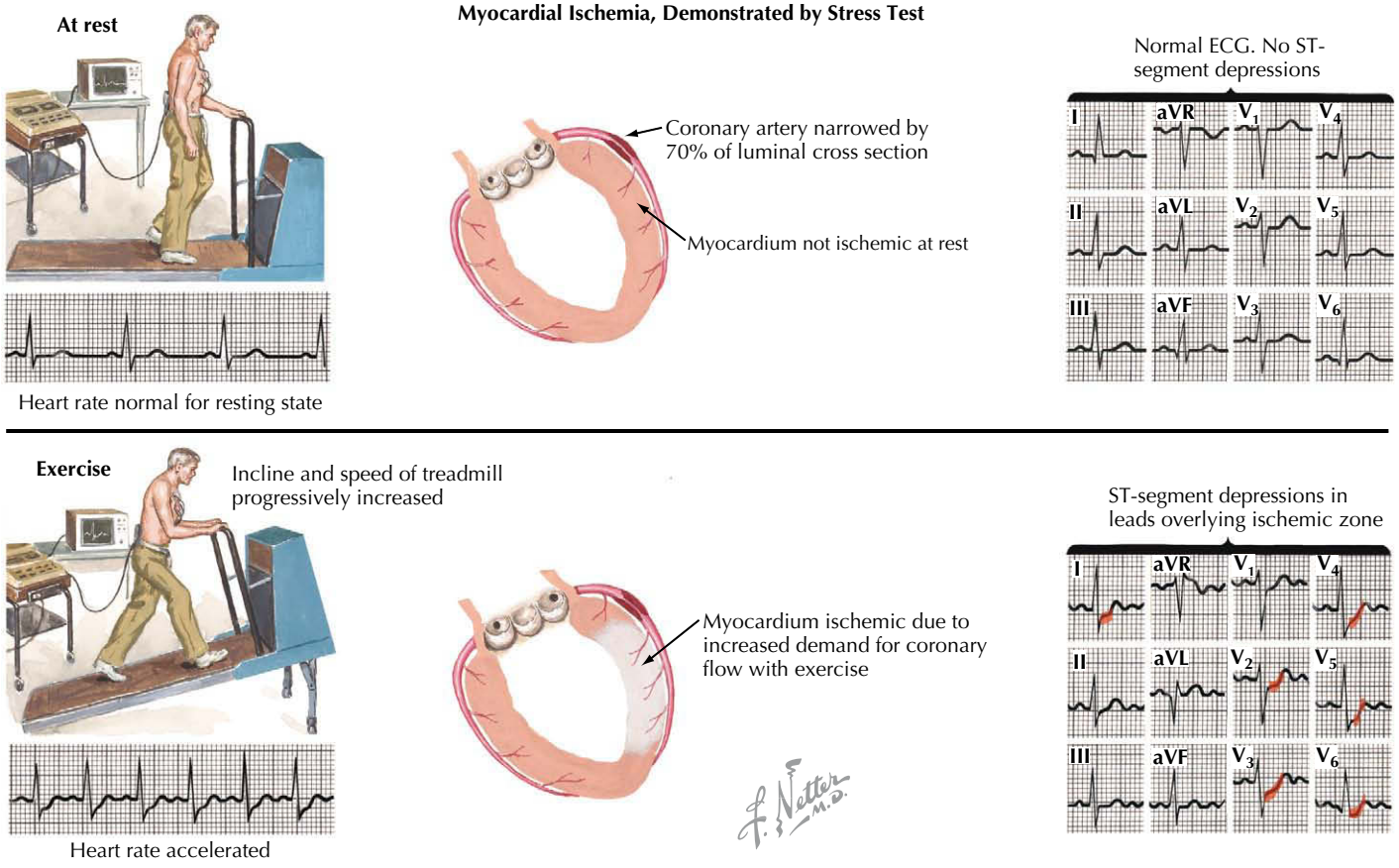


Figure 7-2 *Testing to detect myocardial ischemia.*

Contraindications to exercise include unstable coronary syndrome, decompensated heart failure, severe obstructive valvular and hypertrophic cardiomyopathic disease, untreated life-threatening arrhythmias, and advanced atrioventricular block. (Under certain circumstances, exercise testing under rigorously controlled conditions is performed on patients with aortic stenosis to determine their suitability for aortic valve replacement surgery.) Severe baseline hypertension (>220/120 mm Hg) or presence of large arterial aneurysms are also contraindications, as are systemic illnesses such as acute pulmonary embolus and aortic dissection. Exercise studies should be used cautiously in individuals with an implantable cardiac defibrillator, particularly if their underlying ECG shows a prolonged QRS interval (due to an underlying bundle branch block or paced rhythm), because in this circumstance, the defibrillator may "recognize" the rapid HR induced by exercise as ventricular tachycardia. Individuals with an abnormal baseline ECG, particularly with ST-segment abnormalities, should be referred for a stress imaging study, because ECG changes in the setting of an abnormal baseline ECG are far less specific for CAD. Patients with significant left ventricular hypertrophy on their baseline ECG or those taking digoxin have similar limitations for interpretation of ischemia with exercise. Arrhythmias such as uncontrolled atrial fibrillation may also make interpretation of exercise stress ECGs difficult or impossible, and patients with these arrhythmias should be considered for a stress-imaging study.

CARDIAC STRESS IMAGING

Stress-imaging studies combine either treadmill stress testing or an infusion of either dobutamine or a coronary vasodilator (most commonly dipyridamole or adenosine) with imaging of the heart. Imaging can be accomplished by a variety of modalities; those most commonly used are echocardiography or nuclear imaging. MRI has also been used and CT is being studied as a modality for stress imaging. Stress imaging is preferred over treadmill stress testing in several settings: (1) when the ECG is uninterpretable for myocardial ischemia (e.g., left bundle branch block, digoxin effect); (2) when a patient is unable to exercise (but can undergo a pharmacologic stress-imaging study); or (3) when a treadmill stress test is positive for ischemia in a low-risk patient, and correlation by imaging is preferred to cardiac catheterization. Many physicians also prefer stress imaging as a primary approach, rather than ECG-only stress testing, for all patients because of the higher sensitivity and specificity of stress imaging. Even with rapid advances in other modalities, stress imaging remains a highly effective and available modality to evaluate ischemia and function at present, and it is likely that this will be the case in coming years.

Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI) involves injection of a radiopharmaceutical that distributes throughout the myocardium in a manner dependent upon coronary blood flow. Images are obtained at peak stress and at rest. Changes in the distribution of the radiopharmaceutical can reflect comparable blood flow at rest and stress, diminished blood flow with stress compared to rest (reflecting stress-induced ischemia), or diminished blood flow both with stress and at rest—correlating with prior myocardial infarction (MI). Left ventricular function and ejection fraction (EF) and left ventricular size at rest and with stress can also be measured with this technique. The sensitivity of stress-nuclear imaging for detection of hemodynamically significant CAD is 85% to 90%. The prognostic value of a negative stress-nuclear imaging study is also excellent in otherwise low- to intermediate-risk patients.

Imaging can be done with single-photon emission CT (SPECT), with Anger gamma cameras, or with positron emission tomography (PET). These systems offer different spatial resolution and use different tracers; however, the basic theory of stress perfusion and the functional images obtained are essentially the same.

Radiotracers

Thallium-201 (^{201}Tl) thallous chloride, a radioactive analogue of potassium, was the most commonly used tracer for myocardial perfusion for several decades. Although its use has declined with the advent of technetium-99m (^{99m}Tc)–based agents, ^{201}Tl continues to be useful as part of dual-isotope protocols and in viability imaging. Its relatively low energy results in images that lack resolution. However, the higher myocardial extraction fraction of ^{201}Tl compared with ^{99m}Tc-based agents has resulted in its continued use.

The two most commonly used ^{99m}Tc-based MPI agents are ^{99m}Tc-sestamibi (MIBI) and ^{99m}Tc-tetrofosmin. Images obtained with the two agents are comparable and have higher resolution than images obtained using ^{201}Tl for cardiac imaging. MIBI demonstrates a slightly higher extraction fraction than tetrofosmin and is therefore more commonly used, although the use of MIBI results in a slightly higher radiation dose to the patient compared with tetrofosmin. A previously used ^{99m}Tc-based agent, teboroxime, demonstrated a substantially higher extraction fraction than the aforementioned agents, but its rapid washout from the myocardium limited its clinical utility. Teboroxime is no longer marketed in the United States.

PET radiopharmaceuticals utilize positron-emitting radionuclides to create images. Rubidium-82 (^{82}Rb) chloride is a positron-emitting potassium analogue. It has the lowest extraction fraction of the available PET radiopharmaceuticals (~60%). This extraction fraction is still higher than that of either sestamibi or tetrofosmin. The half-life of ^{82}Rb is very short—approximately 75 seconds. There are benefits and limitations for the use of ^{82}Rb given its very short half-life. The short half-life essentially precludes use of ^{82}Rb for exercise stress imaging. However, it facilitates obtaining images when the patient is truly at the peak of performance induced by pharmacologic stress. For this reason, ^{82}Rb images can be used to accurately assess cardiac reserve—as defined as the difference between left ventricular ejection fraction (EF) at rest and at peak stress. The short half-life of ^{82}Rb also facilitates obtaining pharmacologic stress and resting images in a relatively short period of time.

^{82}Rb has a lower intrinsic spatial resolution than the other PET agents but is still far better than the SPECT tracers. Although a cyclotron is not necessary to generate ^{82}Rb, the generator system used is quite expensive and, for this reason, ^{82}Rb PET imaging is only available at some centers.

Other tracers are used for PET imaging, but none are used for cardiac imaging as commonly as ^{82}Rb. Nitrogen-13 ammonia ($[^{13}N]NH_3$) has a high extraction fraction (approximately 83%) and a 10-minute half-life. It can be used for exercise-nuclear imaging. Oxygen-15 ($[^{15}O]H_2O$) water is short-lived (half-life of 2 minutes) and possesses a very high extraction fraction of approximately 95%. However, its freely diffusible nature means that ^{15}O is distributed into tissues adjacent to the myocardium, including the lungs and cardiac blood pool. For this reason, imaging is complicated, requiring sophisticated background subtraction techniques. Although both ^{13}N and ^{15}O have higher intrinsic spatial resolution than ^{82}Rb, they require generation in a cyclotron. Their short half-lives mean that these isotopes can only be used in facilities with an on-site cyclotron. For most institutions performing PET-myocardial imaging studies, ^{82}Rb is preferred for this logistic reason.

Newer fluorine-18 (^{18}F)–labeled perfusion tracers that would allow exercise imaging and do not require an on-site cyclotron are being developed and studied. The ^{18}F tracers have a very high extraction fraction, making them physiologically attractive in the assessment of CAD.

Stress with Myocardial Perfusion Imaging

In stress with MPI, the radiopharmaceutical is injected when the patient is at the maximum level of stress. Exercise stress is preferred for MPI because of the added prognostic information obtained based on exercise and functional tolerance. Exercise improves imaging characteristics of the tracers, leading to less artifact and improved sensitivity and specificity.

The same contraindications noted above for treadmill stress testing apply for patients undergoing exercise-MPI. Many of the limitations inherent in ECG-only exercise testing (e.g., left bundle branch block, pacing, atrial fibrillation, left ventricular hypertrophy, and baseline ST and T-wave changes) can largely be overcome when using MPI. In general, the sensitivity and specificity of MPI for detection of CAD are better when coupled with exercise than when coupled with pharmacologic stress. For this reason, if a patient is able to exercise, exercise-MPI is preferred.

When patients are unable to exercise due to poor functional capacity, orthopedic, or other factors, MPI can be performed using pharmacologic stress. Two general approaches are used in pharmacologic stress testing. Dobutamine (discussed below and more often used for stress echocardiography than for stress-MPI) is similar to exercise in that it increases HR and myocardial contraction. Dipyridamole and adenosine (which work by similar mechanisms) cause coronary vasodilation.

Dipyridamole causes vasodilation by blocking endogenous adenosine breakdown and raising its levels. Coronary blood flow is increased except in areas where hemodynamically significant stenoses are present, precluding dipyridamole-induced increased flow. A relative decrease in the intensity of the MPI signal indicates an inability to increase flow to that area of the myocardium and, it can be deduced, the presence of flow-limiting CAD in the coronary artery supplying that area. Comparison of images obtained at stress with images obtained at rest makes it possible to determine if there is a relative decrease in flow with stress. This "reversible" myocardial perfusion defect correlates with viable tissue in the distribution of a coronary artery with a significant stenosis. If a portion of the myocardium has limited perfusion at stress and at rest, this indicates that the myocardium in that area is probably not viable. Most commonly a "nonreversible" defect indicates the presence of infarcted myocardium.

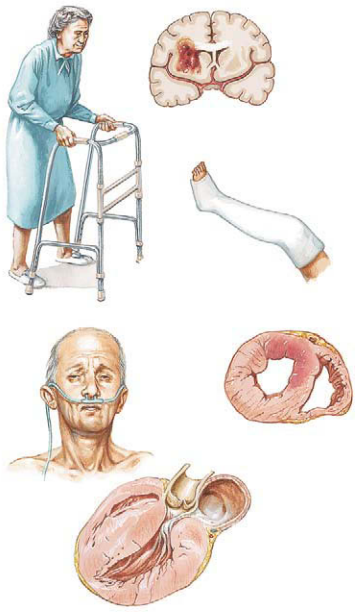
Adenosine can also be directly infused and is preferred in many centers over dipyridamole. Adenosine infusion results in a more consistent serum adenosine level (and more consistent coronary vasodilatation) than does the infusion of dipyridamole. Adenosine infusion is associated with more symptoms than dipyridamole infusion, but these symptoms are very short-lived because adenosine has a very short half-life.

The use of dipyridamole or adenosine is contraindicated in patients with active bronchospastic disease and in those with advanced heart block or sick sinus syndrome without a pacemaker. Additionally, patients taking aminophylline or theophylline must discontinue the use of these drugs before vasodilator pharmacologic stress testing, since these drugs counteract the effects of adenosine. Similarly, stress-MPI should be postponed for anyone who has had caffeine (which also blocks the effects of dipyridamole and adenosine) within the previous 12 hours.

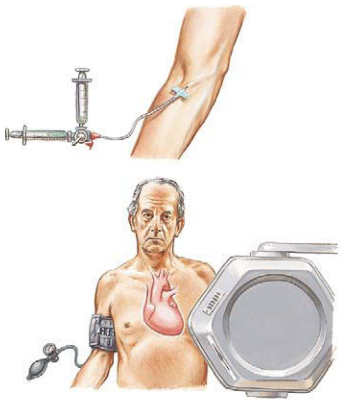
If a patient receiving dipyridamole or adenosine does have either bronchospasm or another side effect with drug infusion, these side effects can be mitigated by infusion of aminophylline or theophylline. It is rare that reversal of the effects of adenosine is required because of its short half-life.

If patients are able to perform submaximal exercise, a combination of a vasodilator (dipyridamole or adenosine) with exercise can be performed. This protocol, sometimes called adenosine-exercise or "adenowalk," among other names, has the advantages of decreasing adenosine's side effects as well as improving image quality by decreasing splanchnic tracer accumulation. Vasodilator-exercise protocols allow limited exercising of patients who are not able to attain target HRs. However, patients with contraindications to either exercise or dipyridamole/adenosine (see above) should not be considered for a combined stress study. Additionally, vasodilator-exercise stress testing should not be performed in patients with a history of cerebrovascular and/or carotid disease, especially if walking is the exercise mode. Rapid loss of consciousness and collapse on the treadmill have been reported, due to cerebrovascular perfusion steal, resulting from pharmacologic vasodilation coupled with exercise (Fig. 7-3).

If patients have contraindications to vasodilator stress and are also unable to exercise, dobutamine pharmacologic stress can be performed. Dobutamine is administered as an incremental infusion, starting at low doses (5–10 μg/kg/min) and gradually increasing the dosage to as much as 40 to 50 μg/kg/min until the patient's MPHR is reached. Atropine can be used for HR augmentation if the target HR is not reached with maximal dobutamine doses. Stress targets are similar to those for exercise with a goal of reaching a target HR of 85% of the patient's MPHR. It is important to note that because systolic blood pressure remains constant or falls with dobutamine, whereas it rises with exercise, the double product (and thus level of stress) associated with a given HR is less during dobutamine testing than with exercise testing. Clinical variables such as fatigue, which is



Patients unable to or contraindicated for exercise



Tracer injection at peak vasodilation, then imaging after completion

Myocardial perfusion at rest and peak vasodilation

Vasodilator test: non-stress test

Figure 7-3 *Pharmacologic stress nuclear testing.*

useful in treadmill stress testing, are generally not useful with dobutamine administration.

The major contraindications to dobutamine/atropine stress-MPI are the presence of narrow-angle glaucoma and a history of prostatic enlargement and urinary obstruction. In addition, a relative contraindication to dobutamine/atropine stress-MPI is a propensity for inducible arrhythmias.

Recently, pharmacologic stress agents that are more selective for the adenosine receptor present in coronary vasculature (A2a) have been developed. These agents have a lower affinity for noncoronary adenosine receptors, and there should thus be a lower risk of common side effects such as bronchospasm, atrioventricular nodal blockade, and flushing. Thus far, this is unproven. Only one of these agents, regadenoson, is approved by the U.S. Food and Drug Administration for clinical use. Two other agents, binodenoson and apadenoson, are being evaluated.

Finally, less conventional stress methods such as cold pressor testing and mental stress are described in the literature. There are no head-to-head comparisons of these methods for inducing stress and the pharmacologic approaches described above.

Imaging Protocols

^{99m}Tc-MIBI and tetrofosmin are the most commonly used SPECT radiopharmaceuticals. Several imaging protocols utilizing these agents have been developed. A commonly used protocol is the 1-day rest-stress, wherein a low dosage of approximately 261 to 370 MBq is administered to the patient at rest. After a 30-minute equilibration period, imaging is carried out. The second step in this protocol is to stress the patient (exercise or pharmacologic stress), administering approximately three times the resting dosage of radiotracer at peak stress, and then again performing imaging after at least 15 minutes.

A variation of this protocol used in some nuclear laboratories for low-risk patients is the 1-day stress-rest study. In this case, stress images are obtained first. Resting images can be omitted if the stress images are completely normal. The disadvantage of this approach is that stress images are obtained at lower doses of radiotracer and thus may be of lower quality.

A 2-day protocol obtains stress and rest images on 2 separate days after administration of relatively high dosages of radiopharmaceutical (1110 MBq). This protocol allows for better image quality, especially in obese patients in whom high-quality images cannot otherwise be attained. If the stress images are obtained on day 1 and are normal, rest images are not necessary in an otherwise low-risk patient. The limitations of this study protocol are the higher radiation doses and the inconvenience of having the patient return on a subsequent day.

A dual-isotope protocol uses ^{201}Tl for the resting images followed by post-stress images obtained with a ^{99m}Tc-based tracer. However, differences in spatial resolution between ^{201}Tl and ^{99m}Tc can sometimes complicate the interpretation of subtle findings. This approach is less commonly recommended.

Imaging can also be performed using ^{201}Tl only. Given the limitations of ^{201}Tl, the only feasible approach is to perform a stress-rest study. The entire study can be performed with a single injection of tracer, and one can obtain additional

physiologic and prognostic information (such as lung uptake) and an assessment of myocardial viability. However, these studies are not done frequently in most laboratories, since they require higher radiation doses, are more time-consuming, and provide images that are of lower resolution.

PET tracers utilize protocols based on SPECT imaging. Given its exceedingly short half-life, ^{82}Rb protocols can be either rest-stress (more common) or stress-rest. An entire ^{82}Rb study can be completed within 30 minutes. An advantage of PET tracers is that despite higher γ-emission energies, their radiation doses are comparably lower while delivering better images than the SPECT tracers.

Image Interpretation

SPECT nuclear images are analyzed in three ways. The "raw" rotating-image interpretation is a critical step that allows the reader to assess whether patient motion, attenuation artifacts (breast overlap, diaphragmatic interference, or other factors) must be considered in interpretation of the study. Occasionally the presence of significant extracardiac findings such as breast or lung masses, thyroid or parathyroid nodules, and lymphadenopathy is seen on these raw images. The second step is to examine reconstructed images that are presented as "slices" of the myocardium. Using this set of images it is possible to visualize myocardial perfusion from apex to base, anterior to inferior wall, and interventricular septum to lateral wall, and assess flow-limiting CAD (Fig. 7-4; Table 7-1). The amount of ischemic or infarct burden can be quantified. By dividing the ventricle into segments (usually 17 or 20) and then deriving scores based on extent and severity of segments affected by pathology, a quantitative assessment can be made that strongly correlates with patient outcomes. The summation of these data, the "sum score," can be compared for the rest and stress studies. Third, gated images can also be obtained and reviewed in a looped-cine method. These images allow determination of wall motion abnormalities, ventricular volumes, and left ventricular EF. Analysis of wall motion also provides an independent means to assess apparent perfusion defects and confirm infarction, ischemia, or the presence of an artifactual perfusion abnormality.

The approach to interpretation of PET imaging is similar to that described above for SPECT imaging. Reconstructed perfusion and gated images are approached the same way, but no "raw" images are displayed because of the manner in which PET images are acquired. An important step to consider in PET is that of alignment of the emission and transmission (the latter being CT in PET-CT units) scans. By default, PET has an attenuation correction built in for the reconstruction of its final images. A misalignment between the two portions of the scan can result in serious artifact, which can be misread if not recognized and/or corrected. Although this can be frequently corrected by manual realignment of the images, occasionally the relevant scan has to be repeated to obtain the correct data.

With the variety of techniques available, it is important to choose the optimal imaging modality (SPECT vs. SPECT-CT vs. PET), tracer, stress modality, and imaging protocol, tailoring each for the specific patient situation so as to maximize the information obtained. For example, the overall prognosis of a normal stress-MPI study is better in patients who exercised than in those who were evaluated with a vasodilator study, so careful attention should be paid to understand the meaning of the results in the context of the patient's history and how the study was performed. That being said, in most institutions the default study is stress-MPI, and the other studies described above are used for special indications.

Table 7-1 Myocardial Perfusion Patterns

Scan Finding	Interpretation
No perfusion defect on either stress or rest study	Normal
Perfusion defect at stress that is normal at rest	Ischemia
Perfusion defect both at stress and rest	Myocardial scar
Perfusion defect at rest but normal at stress	Probable artifact, consider subendocardial infarction (reverse redistribution)

SPECT-CT, PET-CT, and Hybrid Imaging

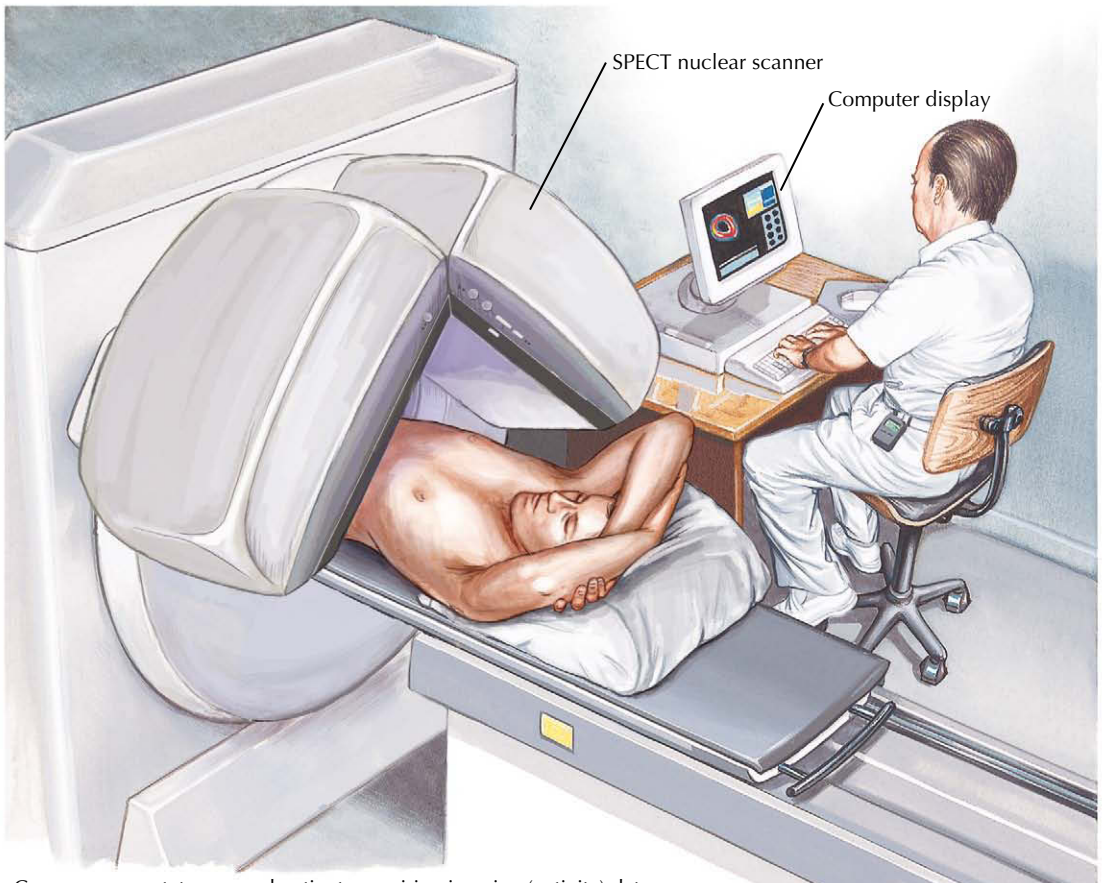
The addition of CT to both SPECT and PET imaging can be useful for anatomic localization of perfusion defects and for attenuation correction (important for PET perfusion studies, particularly in obese patients). Due to the higher isotope energies involved with PET imaging, its inherent attenuation correction, and the superior tracer characteristics of PET radiopharmaceuticals compared with the current ^{99m}Tc-based SPECT agents, PET images are of far superior quality and utility in the diagnosis of CAD in obese patients.

PET imaging also makes possible quantification of myocardial blood flow and coronary flow reserve. PET may also be useful for detection of endothelial dysfunction and assessment of multivessel ischemia, which can produce apparently normal stress imaging by SPECT if ischemia is global and balanced.

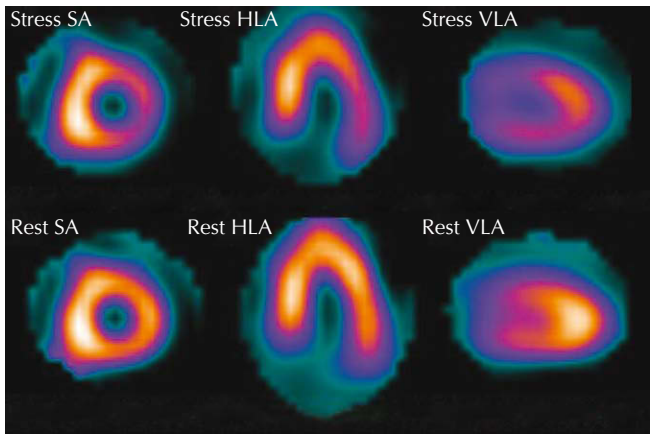
The advent of cardiac CT angiography (CTA) has allowed the development of hybrid imaging techniques wherein perfusion/metabolic information provided by SPECT or PET is fused with structural information provided by CTA. This approach offers the potential advantage of evaluating both the extent and severity of atherosclerotic vascular disease and its effect on myocardial perfusion.

EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY (MUGA SCAN)

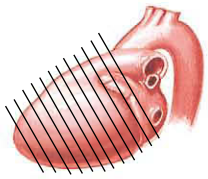
Multiple-gated acquisition (MUGA) scanning is an approach used to quantify both left and right ventricular function, based on images generated following the injection of ^{99m}Tc-labeled erythrocytes. The labeling procedure can be performed in vitro using a commercially available kit (UltraTag; Mallinckrodt, St. Paul, MN), in vivo, or semi–in vitro. The in vitro method provides the highest labeling efficiency and best images but is the most laborious, time-consuming, and expensive technique.



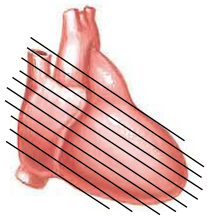
Camera array rotates around patient, acquiring imaging (activity) data.



Computer reconstructs acquired image data into a series of tomographic slices displayed in three standard views: short axis, horizontal long axis, and vertical long axis.



Short axis



Horizontal long axis

Vertical long axis

Figure 7-4 *Stress nuclear imaging by single-photon emission CT (SPECT).* HLA, horizontal long axis; SA, short axis; VLA, vertical long axis.

Once the circulating blood pool has been appropriately labeled, determination of wall motion abnormalities, left ventricular volumes, and EF can be made. These measures are accurate and reproducible, and are often used for serial follow-up of EF in patients receiving cardiotoxic drugs—particularly chemotherapeutic agents.

An advantage of MUGA is the ability to do first-pass imaging, which allows evaluation of the right ventricle, as well as quantitative shunt analysis. Whereas the latter procedure is now predominantly done via echocardiography, the former is still sometimes used in select patient populations, and in some cases, combined with standard myocardial perfusion scans as an approach to evaluating right ventricular function.

Stress-MUGA scanning can be performed either with dobutamine or with an exercise ergometer bicycle that is attached to a seat or the bed on which the patient lies. It offers the ability to provide real-time EF imaging, as well as imaging of any wall motion abnormalities that develop during the study

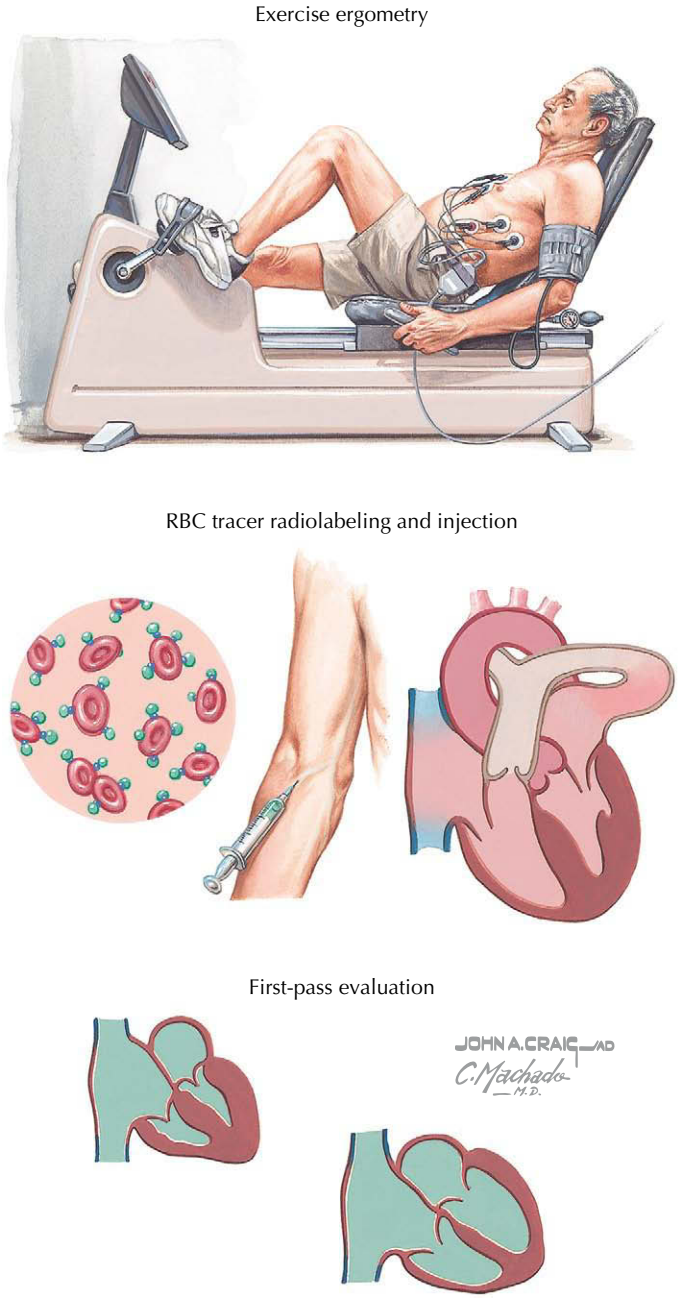


Figure 7-5 *MUGA and stress-MUGA scanning.*

(Fig. 7-5). MUGA scanning is feasible in extremely obese patients as well.

OTHER USES OF CARDIAC NUCLEAR MEDICINE

Shunt Analysis

Using first-pass techniques, MUGA scans have been used to calculate shunt fractions in various pathologies, especially congenital heart disease in the pediatric population. Because of advances in echocardiography and its use today as the first-line noninvasive approach to intracardiac shunt assessment, MUGA scanning is rarely used for this indication.

Viability

Since more patients survive myocardial infarctions (MIs) as a result of advances in cardiology, detection of myocardial viability has become increasingly important. Identifying a hibernating myocardium that is still viable but chronically hypoperfused and ischemic is important for decision making with respect to revascularization. Because ^{201}Tl is a potassium analogue, its exchange across a membrane is a hallmark of a viable myocyte. Viability protocols make use of ^{201}Tl's ability to undergo redistribution and involve imaging at baseline, following redistribution, and often following repeat injection of an extra dosage. Viable myocytes will take up ^{201}Tl for as long as 24 hours after injection. A newer approach has been to use administration of nitrates to increase perfusion and enhance ^{201}Tl uptake. In theory this approach causes vasodilation in areas that are otherwise hypoperfused at baseline, causing increased flow to those regions, and resulting in improved uptake. The specificity of this procedure can be improved by obtaining gated images with sequentially low- and higher-dose dobutamine infusion during imaging.

Unlike ^{201}Tl that is utilized as a perfusion marker, ^{18}F, 2-deoxyglucose (FDG) is a marker of myocardial glucose metabolism. Myocardial uptake of FDG is facilitated by prior administration of glucose, often coupled with intravenous insulin administration to drive glucose utilization by viable cardiomyocytes. In conjunction with perfusion imaging, FDG imaging can provide useful information for the assessment of myocardial viability.

Although revascularization has been shown to improve morbidity and mortality in patients with salvageable myocardium, not all viable myocardium is salvageable. For this reason, the detection of viable myocardium must be taken in context of the overall clinical picture and the coronary anatomy.

Sarcoidosis

Cardiac sarcoid causes focal granulomatous inflammation at various locations in the myocardium, which can result in electrical or functional cardiac disturbances. In patients with cardiac sarcoid, ^{201}Tl imaging shows patchy defects that presumably correspond to areas of scarring and/or inflammation. Because of the low resolution of ^{201}Tl images, small defects can be missed. Other techniques have utilized tracers such as ^{67}Ga-citrate or ^{111}In-octreotide that can detect areas of active inflammation in conjunction with a perfusion tracer. More recent uses of fasting FDG-PET have also been successful in detecting inflammatory lesions that have increased tracer uptake as well as detecting areas of scarring that have no uptake. Although detection of such pathology might seem more logically done with MRI given its much higher resolution, nuclear imaging offers the possibility of detecting lesions with active inflammation.

Chest Pain

An imaging protocol for acute chest pain involves administration of a radiopharmaceutical while the patient is having a chest pain syndrome. In a low- to intermediate-risk patient, a normal scan has a very high negative predictive value for the absence of an acute coronary syndrome. This protocol has been used in

emergency room settings in low- to intermediate-risk patients with otherwise undifferentiated chest pain and allows for safe discharge with outpatient follow-up.

COMPARISON TO OTHER CARDIAC IMAGING MODALITIES

It is useful to consider nuclear imaging techniques (SPECT and PET) with newer cardiac imaging technologies such as cardiac MRI (CMRI) and cardiac CTA, because their use has increased dramatically within the last few years and there are advantages and disadvantages for each. CMRI is capable of generating exquisite images of cardiac structures with a resolution far superior to nuclear techniques and without the need for ionizing radiation. This technology is also useful for viability assessment. Cardiac CTA provides high-resolution images of coronary and other cardiac anatomy and pathology that are not possible with current nuclear techniques, with radiation doses somewhat comparable to SPECT imaging but higher than PET. While its negative predictive value for the detection of CAD is excellent, its positive predictive value in determining disease severity is considerably lower. It is anticipated that as technology advances, cardiac CTA characterization of coronary anatomy will improve. It is also possible that CT technology will be able to provide a combined scan that includes stress testing, viability assessment, and coronary anatomy, all in a reasonable time frame and with an acceptable radiation dose. There are, however, limitations of these newer technologies. For patients with renal insufficiency who have a higher risk of allergic or nephropathic complications, nuclear tracers are preferred over studies that require intravenous contrast (either CT or MRI). MRI studies are generally contraindicated in patients with implanted cardiac rhythm devices (pacemakers and implantable cardiac defibrillators [ICDs]; coronary stents are not a contraindication for MRI imaging). At present, CMRI and cardiac CTA are less widely available than nuclear studies.

Ultimately, it may be the combination of imaging modalities that provides the greatest information for cardiac patients. Imaging that combines anatomic information from CT or MRI with physiologic information from PET or SPECT is already the state of the art for evaluation of obese patients.

FUTURE DIRECTIONS AND CARDIAC MOLECULAR IMAGING

New Technology

There have been numerous important innovations in nuclear cardiology over the past 10 years. Important imaging advances include the development of upright cameras that improve patient comfort and image resolution by allowing close contact between the patient and detector and the development of high-efficiency, solid-state detectors and "cardiocentric" collimators that allow the acquisition of high-count images in a relatively short period of time. Improvements to older nuclear cameras, including multi-pinhole SPECT and fan-beam collimators, reflect cost-effective approaches to improving image quality without the purchase of entirely new imaging systems. Similarly, there have been major advances in image analysis. Iterative reconstruction utilizing resolution-recovery algorithms reduces artifactual distortion and allows reduced image acquisition times without sacrificing image quality. These improvements have also renewed interest in imaging agents more suited for rapid image acquisition.

Combined-modality imaging (PET-MRI and SPECT-MRI) has proven to be useful for detection and prognostication in cancer patients. The idea of combining high-resolution images with physiologic/functional measures is equally attractive for the assessment of CAD, and studies on combined-modality imaging are currently in progress.

Ventricular Dyssynchrony Assessment

Biventricular pacing has been shown to reduce symptoms in some patients with advanced heart failure, presumably by improving dyssynchronous left ventricular contraction. However, not all patients improve. It has been hypothesized that the patients who obtain maximal benefit are those who have the greatest restoration of synchronous contraction of the left ventricle. This has stimulated research focused on using nuclear imaging (SPECT-MPI or other modalities) to assess the effect of placing pacemaker leads in specific locations in the right and left ventricles. Comparison of synchrony at baseline and with pacing could facilitate optimization of lead placement and outcomes from biventricular pacing in this setting.

Fatty Acid Imaging

Fatty acid (FA) imaging has been proposed as a sensitive and specific method to determine whether a patient presenting with a recent history of ischemic symptoms did indeed have an ischemic event. Although cardiac biomarkers such as creatinine kinase and cardiac troponins are sensitive indicators of myocardial necrosis, there is no current test to confirm if a recent event represented ischemia at a level insufficient to result in measurable levels of these cardiac biomarkers.

Under fasting, ischemic, or hypoxic conditions, FA metabolism is suppressed and glucose oxidation becomes increasingly important for myocardial energy production. This finding has led to the notion that alterations in FA metabolism could function as a sensitive marker for myocardial ischemia. Radiopharmaceuticals such as iodine-123 15-(*p*-iodo-phenyl)-3-*R*,*S*-methylpentadecanoic acid ([^{123}I]BMIPP)—a FA analogue—is being studied as an imaging agent. Because metabolic abnormalities usually persist long after the ischemic event has resolved, this type of radiotracer could be used to identify areas of hypoperfused myocardium long after the patient's symptoms of angina have abated and flow has been restored. Carbon-11 palmitate is a PET tracer that can also be utilized for imaging myocardial FA metabolism but is restricted to locations with cyclotrons. FDG is another agent potentially capable of detecting recent ischemia.

Cardiac Neurotransmission Imaging

Radioiodine-labeled meta-iodobenzylguanidine (MIBG) has been recently studied as an imaging agent based on the notion that cardiac receptors for neurotransmitters may be altered in certain disease states. Alterations in MIBG uptake may identify

myocardium that is mechanically functional but highly sensitive to catecholamine stimulation and arrhythmogenic on that basis. MIBG has been studied in patients with idiopathic ventricular tachycardia/fibrillation, arrhythmogenic right ventricular dysplasia, and cardiac dysautonomias including diabetic neuropathy and drug-induced cardiotoxicity. In conjunction with EF, brain natriuretic peptide, or some other variables, MIBG scanning has been reported to accurately predict patients who will benefit from ICD placement. Given our current inability to distinguish between patients with low EF who require defibrillation for ventricular tachycardia/fibrillation within 5 years of ICD placement and those who will not—and the high cost of ICD implantation—more precision in determining patients at high risk and low risk, beyond assessment of left ventricular function, is a very attractive concept.

Myocyte Death Imaging

^{99m}Tc-pyrophosphate imaging was initially developed for assessment of MI. This approach is rarely used now because of the accuracy of other imaging modalities, including MRI. Newer tracers such as ^{99m}Tc-glucarate are being studied to determine whether it is possible to detect myocyte death at the earliest stages of MI. This information could be useful in the development of interventional strategies.

An entirely different question is whether it would be possible to detect cardiomyocyte apoptosis, which is an early event in cardiac transplant rejection. Radiolabeled annexin V is being studied as an approach to imaging cardiomyocyte apoptosis with the hope that a sensitive imaging study could replace the need for frequent screening endomyocardial biopsies, given the morbidity associated with this invasive approach.

Atherosclerotic Plaque Imaging

One of the challenges of cardiovascular imaging in general has been the detection and evaluation of vulnerable plaque. FDG has been proposed as an imaging agent in this regard as has annexin V. Challenges to these approaches include spatial resolution, detection limits, and biologic correlation of positive images with vulnerable plaques. Although research in this area is at an early stage, the goal of being able to detect vulnerable plaques by any means is of great importance given the large number of individuals who die each year as a result of acute MI.

Nuclear cardiology procedures remain accurate, cost-effective, and relevant tools in management of the cardiac patient. Nuclear imaging also offers the promise of providing highly specific information that can guide clinical decision making for a variety of cardiovascular pathologies.

ADDITIONAL RESOURCES

Academy of Molecular Imaging (AMI). Available at: <http://www.ami-imaging.org>; Accessed 22.02.10.

Resources similar to those of SNM and ASNC (below).

American Society of Nuclear Cardiology (ASNC). Available at: <http://www.asnc.org>; Accessed 22.02.10.

Guidelines for the use of nuclear cardiology procedures, protocols, and so forth. Also discusses appropriateness criteria.

Gambhir SS. *Nuclear Medicine in Clinical Diagnosis and Treatment.* Philadelphia: Elsevier; 2004.

Overview of nuclear medicine techniques, including cardiac nuclear medicine.

Libby P, Bonow RO, Mann DL, Zipes DP. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 8th ed. Philadelphia: Elsevier; 2008.

Basic overview of stress testing and cardiac nuclear medicine.

Society of Nuclear Medicine (SNM). Available at: <http://www.snm.org>; Accessed 22.02.10.

Resources similar to ASNC, but also additional information about molecular imaging.

Zaret B, Beller G. *Clinical Nuclear Cardiology: State of the Art and Future Directions.* 3rd ed. Philadelphia: Elsevier; 2005.

In-depth overview of cardiac nuclear medicine, including protocols, indications, and future directions.

EVIDENCE

Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: Comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol.* 2006;13(1):24–33.

Diagnostic superiority of PET vs. SPECT MPI.

Brindis RG, Douglas PS, Hendel RC, et al. American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group; American Society of Nuclear Cardiology; American Heart Association. ACCF/ASNC Appropriateness Criteria for Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging (SPECT MPI): A Report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology endorsed by the American Heart Association. *J Am Coll Cardiol.* 2005;46(8):1587–1605.

Presents appropriateness criteria for MPI utilization.

Nichols K, Saouaf R, Ababneh AA, et al. Validation of SPECT equilibrium radionuclide angiographic right ventricular parameters by cardiac magnetic resonance imaging. *J Nucl Cardiol.* 2002;9(2):153–160.

Discusses the development and validation of SPECT-MUGA.

Cardiac Computed Tomography and Magnetic Resonance Imaging

8

Andrew O. Zurick III and J. Larry Klein

The past decade has seen rapid development in cardiovascular imaging technologies coupled with novel clinical applications. Noninvasive imaging technologies now allow for assessment of cardiac morphology, function, perfusion, and metabolism. The explosion in imaging has led to increasing financial expenditures. From 1999 to 2003, diagnostic imaging services reimbursed under the U.S. Medicare physician fee schedule grew more rapidly than any other type of physician service. Both cardiac computed tomography (CCT) and cardiac magnetic resonance imaging (CMR) have interesting and unique advantages compared with alternate imaging modalities. Understanding the applications and limitations of these modalities will permit optimal and efficient use in the future.

CARDIAC COMPUTED TOMOGRAPHY

Chest pain is a common clinical problem and one of the most common complaints of individuals presenting for urgent medical evaluation. One of the most important, life-threatening causes of chest pain is coronary artery disease (CAD). Although cardiac catheterization is the best method to assess for the presence of hemodynamically significant CAD available today, it is impractical as a screening test. It is invasive and costly, can be especially dangerous in some subsets of patients, and when used broadly as a screening tool is performed on a substantial number of patients who have no significant CAD and/or whose chest pain is unrelated to cardiac causes.

For decades, investigators have sought to develop new technologies that would allow rapid noninvasive imaging of the coronary arteries and other cardiac structures. One such technology that has evolved rapidly is CCT. Although not yet as accurate as cardiac catheterization, CCT now permits visualization of the coronary arteries and coronary lumen as well as assessment of cardiac function, the pericardium, left atrial anatomy, congenital heart disease, pulmonary arterial and venous anatomies, and diseases of the aorta.

Technology of CCT

Imaging the heart and coronary arteries with CT is challenging for several reasons and requires more sophisticated imaging and analysis approaches than are required for other body regions. Major difficulties arise because coronary arteries are relatively small structures with branches of interest in the range of 2 to 4 mm in diameter, and they are moving structures. The coronary arteries show rapid cyclic motion throughout the cardiac cycle—essentially moving in three dimensions with each heartbeat. Furthermore, when the subject breathes, the heart and vessels move within the chest. However, several major advances in recent years have dramatically improved the resolution of coronary artery images. These include acquiring more data/images at one time, decreasing the time patients must hold their breath; development of smaller CT x-ray detectors, increasing spatial resolution to visualize smaller structures; the development of scanners with increased rotational speed resulting in increased temporal resolution so that moving objects such as the arteries can be "frozen"; and the ability to gate the CT acquisition to the patient's ECG, allowing visual reconstruction of the heart and arteries during different phases of the cardiac cycle. Typically, the coronary arteries have less motion in diastole when the heart is filling compared with systole when the heart is contracting. Temporal resolution is directly related to x-ray tube gantry rotation time. A standard single source (one x-ray tube) allows for a temporal resolution of 167 ms. Newer scanners from some vendors afford dual-source CT technology (two x-ray tubes in the gantry), resulting in an effective scan time of 83 ms independent of heart rate. The small size of cardiac structures requires excellent spatial resolution, which is on the order of 0.4 to 0.75 mm with current technology. Respiratory motion artifact is minimized by asking the patient to hold his or her breath during image acquisition. Even with these advances, CCT lacks the resolution attained in the cardiac catheterization laboratory where images can be obtained at 30 frames per second, yielding temporal resolutions that can be greater than 33 ms with spatial resolution less than 0.1 mm.

Several different CT technologies have been used for cardiac imaging. Electron beam CT (EBCT), initially introduced in the mid-1970s, utilizes an electron source reflected onto a stationary tungsten target to generate x-rays, allowing for very rapid scan times. EBCT is well suited for cardiac imaging because of its high temporal resolution (50–100 ms) with an estimated slice thickness of 1.5 to 3 mm and the ability to scan the heart in a single breath hold. This technology was initially used to quantify coronary arterial vessel wall calcium volume and density—generating a patient-specific score—and it remains the primary use of EBCT. Coronary calcium scores are independent of other traditional cardiac risk factors in the prediction of cardiac events and, as such, can be considered an excellent biomarker for the presence of CAD and the risk of future cardiac events. Efforts to use EBCT technology to visualize the lumen of the coronary artery with the administration of intravenous contrast agents have thus far proven to be limited, in large part as a result of the very limited spatial resolution.

EBCT has been largely supplanted by newer, multidetector CT (MDCT) technology, which involves a mechanically rotated x-ray source and offers increasing spatial resolution. New generations of scanners permit the simultaneous acquisition of more data ("slices"). These advances have allowed for markedly increased spatial resolution and for complete acquisition of data during one breath hold. Coronary calcium scoring can also be performed using MDCT with results that are comparable to those obtained by EBCT. What MDCT offers, however,

is sufficient spatial resolution to make coronary CT angiography (CTA) feasible. Proof-of-concept studies were initially performed using MDCT machines capable of obtaining four to eight slices per scan.

As technology has advanced, 64-slice (and higher) scanners are now available and allow acquisition of higher resolution images without the requirement for long breath holds or extremely slow heart rates. It is currently recommended that CTA be performed using a minimum of a 64-slice scanner. These scanners are now commonly available in many hospitals. With this type of scanner, 64 simultaneous anatomic slices are acquired, allowing a complete cardiac study to be performed with one breath hold, typically in 10 to 15 seconds. Because of the limited temporal resolution, a successful diagnostic scan on a conventional 64-slice scanner requires that the heart rate be steady and usually less than 60 to 65 bpm. Newer prototypes allow up to 320 anatomic slices to be simultaneously acquired. With a minimal slice thickness of 0.75 mm, an entire heart can be imaged in a single heartbeat. Even with 320-slice scanners, temporal resolution does not reach what can be obtained routinely in a cardiac catheterization laboratory, and images are better in patients with relatively low heart rates. To overcome the necessity of a slow heart rate, one vendor has placed two x-ray sources in the scanner (so-called dual source). This technology offers an improved temporal resolution even with heart rates approaching 100 bpm and greater.

Data Acquisition Techniques

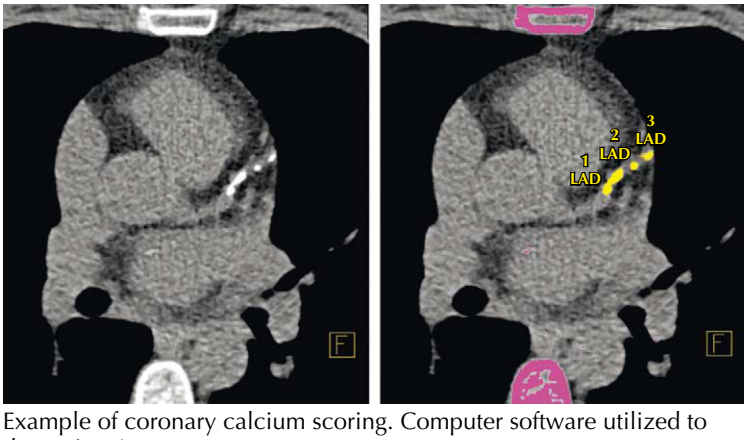
For CTA using a single-source scanner, it is necessary to image with heart rates less than 65 bpm. Most commonly, an oral or intravenous β-blocker is given to slow the heart rate. In some settings, sublingual nitrates may be administered to dilate the coronary arteries and allow them to be more easily imaged. Coronary CTA requires intravenous administration of a contrast agent to opacify the lumen of the coronary arteries. The intravenous contrast agents used for CTA carry the same dose-dependent risks in patients with renal dysfunction as contrast agents used for cardiac catheterization, as well as the risk of an allergic reaction to iodine. Respiratory motion is minimized by patient breath hold from 6 to 20 seconds, depending on scanner generation and cardiac dimension. Data acquisition varies somewhat based on scanner type. The most common data acquisition protocol utilizes a spiral mode involving continuous data acquisition during constant rotation of the x-ray tube while the patient is simultaneously continually advanced on the table through the x-ray gantry. To minimize radiation exposure, data acquisitions can be performed in sequential mode (step and shoot). This involves acquisition of single transaxial slices sequentially as a patient is advanced stepwise through the scanner.

Excessive cardiac motion can lead to blurring of the contours of the coronary vessels. For this reason, a regular heart rate is necessary for optimal imaging of the coronary arteries. Relative contraindications to performing CTA include the presence of frequent ectopic beats or atrial fibrillation. Coordinating data acquisition and analysis to the cardiac cycle involves either prospective triggering or retrospective gating. In prospective triggering, data are acquired in late diastole, based on simultaneous ECG recordings. In retrospective gating, data are collected during the entire cardiac cycle. Post-processing then allows only data from specific periods of the cardiac cycle to be used for image reconstruction.

Clinical Indications

CORONARY ARTERY CALCIUM SCORE

Coronary artery calcium (CAC) is recognized as a marker of subclinical atherosclerosis. CAC scoring utilizes no contrast and readily detects calcium because of its high x-ray attenuation coefficient (or CT number) measured in Hounsfield units (HU) (Fig. 8-1). The Agatston scoring system assigns a calcium score based on maximal CT number and the area of calcium deposits. Initially promoted as part of a screening paradigm, CAC was originally made available for patient-initiated evaluation of coronary risk on a fee-for-service basis. More recently, analysis of several large clinical datasets has confirmed that the "coronary calcium score" is a predictor of coronary events, independent of



Example of coronary calcium scoring. Computer software utilized to determine Agatston score.

Artery	No. of lesions (1)	Volume [mm³] (3)	Equiv. mass [mg/cm³ CaHA] (4)	Score (2)
LM	0	0.0	0.00	0.0
LAD	3	181.9	43.32	247.6
LCX	0	0.0	0.00	0.0
RCA	0	0.0	0.00	0.0
Total	3	181.9	43.32	247.6

(1) Lesion is volume based
(2) Agatston score
(3) Isotropic interpolated volume
(4) Calibration factor 0.787

Figure 8-1 *Coronary calcium scoring.* LAD, left anterior descending; LCX, left circumflex; LM, left main; RCA, right coronary artery.

traditional risk factors. In at least one study, calcium score was more predictive than C-reactive protein and standard risk factors for predicting CAD events.

The coronary calcium score is derived by identifying coronary arterial tree segments that have attenuation characteristics (HU) greater than 130 that correlate with the attenuation due to calcium. These calcified lesions are scored by size and density with a weighting factor for increasing density. Technically, the score reflects analysis of contiguous pixels in the x, y, and z directions that are calcium-positive. Discrete lesions are scored separately, and the density of calcium within each lesion is graded from 1 to 4 according to the HU. The sums of all the lesions are totaled to arrive at a single coronary calcium score. In general, the higher the score, the greater the amount of calcified plaque within the arterial tree. There is a positive correlation of cardiac events with this score. Many individuals younger than 50 years have no coronary artery calcification and thus have a calcium score of 0.

The Multiethnic Study of Atherosclerosis (MESA) Group published a series of articles suggesting that the calcium score is an independent risk factor for cardiac events. Also, MESA's website has the capacity to allow comparison of an individual patient's calcium score against their large database. This score takes into account age, sex, and race, and generates a percentile compared to the database studies. The 2007 American College of Cardiology (ACC)/American Heart Association (AHA) Clinical Expert Consensus Document on CAC scoring states that in patients with intermediate coronary heart disease risk (10%–20% 10-year risk of estimated coronary events), it may be reasonable to consider use of CAC measurement based on evidence that it demonstrates incremental risk prediction such that patients might be reclassified to a higher risk status and subsequently initiated on pharmacotherapy, particularly for cholesterol lowering. The presence of a high calcium score may prompt clinicians to use more aggressive therapy as if they were reclassified in a higher risk group, or to convince patients who are reluctant to take drugs such as statins to take their disease more seriously.

CTA utilizes intravenous contrast to differentiate vessel lumen from vessel wall. In 2006, the ACC and many other societies with interests in cardiac imaging put together recommendations of "appropriateness criteria" for utilization of cardiac CTA that include appropriate (Box 8-1) and inappropriate uses of this technology. The most common appropriate utilization is diagnostic study of patients presenting with chest pain who do not have significant ECG changes or elevated cardiac biomarkers but have an intermediate probability of CAD. At experienced centers with careful data acquisition, sensitivities range from 83% to 99% and specificities from 93% to 98% with remarkably high estimated negative predictive value (95%–100%), indicating that CCT may be used to reliably rule out the presence of significant flow-limiting coronary atherosclerotic disease. It should be pointed out that CCT would be inappropriate for patients at high risk for or with other indications of cardiac ischemia such as elevated biomarkers or significant ECG changes. Those patients should be referred immediately for invasive imaging.

Bypass graft imaging is more easily accomplished than coronary artery imaging because of the larger size of bypass grafts (particularly saphenous vein grafts) and less rapid movement of bypass grafts as compared with native coronary arteries. The patency or occlusion of grafts can be determined by the presence or absence of distal target vessel contrast enhancement (Fig. 8-2). Imaging internal mammary grafts is often more difficult because of artifacts caused by metallic clips near the grafts. Imaging of coronary artery stents is challenging because of artifacts caused by metal that can obscure visualization of the coronary artery lumen. Studies evaluating CCT to assess in-stent restenosis have been somewhat disappointing, yielding sensitivities of 54% to 83%. Stents less than 3.0 mm in diameter are much more likely to be nonevaluable. An additional important application of CCT is in patients with congenital abnormalities of their coronary arteries, including anomalous coronary arteries and the presence of intramyocardial bridges (coronary arteries that, for a portion of their course, are not epicardial but rather covered by a layer of myocardial tissue).

Box 8-1 Appropriate Indications for CCT

Detection of CAD (Symptomatic)

- Intermediate pre-test probability of CAD
- ECG uninterpretable or unable to exercise
- Evaluation of suspected coronary anomalies
- Uninterpretable or equivocal stress test (exercise, perfusion, or stress echo)

Structure and Function

- Assessment of complex congenital heart disease including anomalies of coronary circulation, great vessels, and cardiac chambers and valves
- Evaluation of coronary arteries in patients with new-onset heart failure to assess etiology
- Evaluation of cardiac masses
- Patients with technically limited images from transthoracic echocardiogram, MRI, or transesophageal echocardiogram
- Evaluation of pericardial conditions
- Evaluation of pulmonary vein anatomy before invasive radiofrequency ablation for atrial fibrillation
- Noninvasive coronary vein mapping before placement of biventricular pacemaker
- Noninvasive coronary arterial mapping, including internal mammary artery before repeat cardiac surgical revascularization
- Evaluation of suspected aortic dissection or thoracic aortic aneurysm
- Evaluation for suspected pulmonary embolism

CAD, coronary artery disease; CCT, cardiac computed tomography; ECG, electrocardiogram.

CARDIAC CHAMBER AND VALVULAR EVALUATION

Through appropriate timing of chamber contrast enhancement, extensive cardiac morphologic and functional information can be obtained by CCT. Myocardial mass and ventricular function can be estimated with high accuracy. CCT can also provide a detailed morphologic picture of left atrial anatomy—information that can be very useful before planned catheter (radiofrequency) ablation for atrial fibrillation. Three-dimensional anatomic data obtained by CCT can be fused with electrical mapping data acquired in the electrophysiology lab

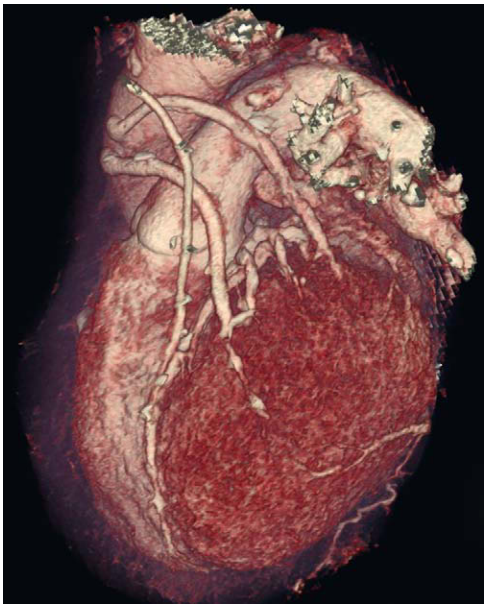


Figure 8-2 *3D cardiac computed tomography volume rendering showing patent bypass grafts.*

and greatly facilitates the procedure. Characterization of native and prosthetic heart valves by CCT is not recommended in the current ACC/AHA guidelines. CCT may indeed become useful in assessing valve structure and function, but additional research is needed.

CONGENITAL HEART DISEASE

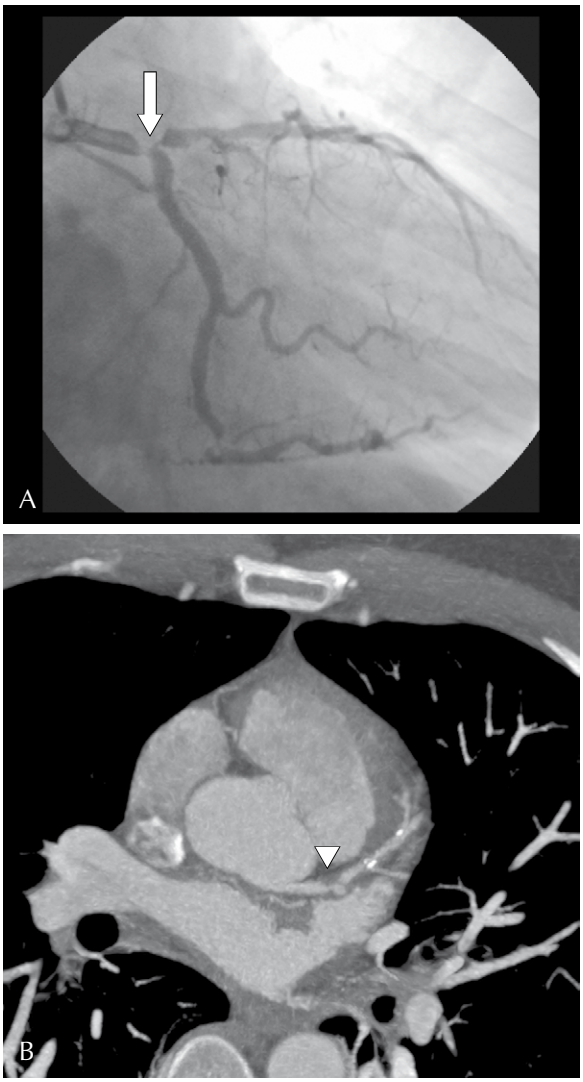
Assessment of complex congenital heart disease including anomalous coronary circulation, great vessels, cardiac chambers, and valves are all appropriate indications for CCT. Specific indications include shunt detection, aortic geometry in coarctation or Marfan's syndrome, partial or total anomalous pulmonary venous return, and pulmonary artery visualization in patients with cyanotic heart disease.

EVALUATION OF INTRACARDIAC AND EXTRACARDIAC STRUCTURES

In patients with technically limited images from echocardiogram or MRI, CCT can be utilized to evaluate for cardiac mass (i.e., tumor or thrombus). Pericardial diseases can also be evaluated using CCT looking specifically for a pericardial mass, constrictive pericarditis, or complications of cardiac surgery. Contrast enhancement of the pericardium or thickening of the pericardium (normal thickness is <2 mm) suggests an inflammatory process.

EVALUATION OF AORTIC AND PULMONARY DISEASE

In patients with suspected pulmonary embolism, CCT has both high sensitivity and specificity (>90%) for the diagnosis of proximal pulmonary embolism. Emboli can be visualized in the main pulmonary artery and as far distally as the segmental pulmonary



(**A**) Conventional coronary angiogram showing severe left main coronary artery disease (*arrow*) and (**B**) complementary coronary CT angiogram showing same left main lesion (*arrowhead*) with mixed calcified and noncalcified plaques.

Figure 8-3 *Conventional diagnostic coronary angiogram and coronary computed tomography (CT) angiogram.*

artery branches. Evaluation of the pulmonary venous anatomy is useful before (and after) atrial fibrillation ablation to assess for pulmonary vein stenosis. CCT assessment of the aorta typically requires contrast enhancement. Three-dimensional reconstruction can be useful diagnostically and also before planned endovascular repair. Typical indications for CCT in assessment of the aorta include aneurysm, communicating dissection, and noncommunicating dissecting intramural hematoma.

CCT Clinical Examples

Evaluation of patients with chest pain can be a very difficult task. Many patients do not present with typical symptoms, and given the likelihood of significant CAD in young patients, consideration of CCT as part of the evaluation of individuals with typical or atypical chest pain is appropriate (Fig. 8-3A and B).

Coronary CT Angiography in Asymptomatic Individuals (Screening)

Currently there is no indication for performing CTA in asymptomatic patients. Indeed, the appropriateness criteria definitively recommend against the use of CCT in the asymptomatic population until further evidence suggests that it would positively affect outcomes.

CCT Limitations

CCT involves exposure to radiation and the potential for radiation-related risk (particularly related to the risk of cancer induction). Radiation exposure (effective dose) is quantified in millisieverts (mSv). Patient radiation doses are dependent upon tube current (milliamperes) and tube voltage (kiloelectron volts), as well as duration of radiation exposure, and are estimated to be 3 to 15 mSv. For comparison purposes, typical gated cardiac single-photon emission tomography carries a similar radiation dose (effective dose = 10–15 mSv), while conventional coronary angiography carries a lower radiation dose (effective dose = 6 mSv) compared with CCT. ECG-correlated tube current modulation (reduction of tube current in systole) can reduce radiation exposure by 30% to 50%. Studies have estimated that CCT yields a lifetime risk of 0.07% of inducing a fatal cancer in the general population. Although this risk is low, it does mean that CCT is not well suited for use as a screening test on a regular and repeated basis.

A typical CCT requires 80 to 130 mL of nonionic contrast medium containing 300 to 350 mg of iodine per milliliter. Allergic contrast reactions are reported in 0.2% to 0.7% of patients receiving nonionic contrast materials. In the absence of preexisting renal disease, the risk of renal dysfunction due to contrast administration is low.

Future Directions

It is estimated that nearly 60 million CT scans were performed in the United States in 2001, with utilization growth estimated at 9% per year in the coming decade. Current CCT use has not constituted a broad replacement for conventional coronary angiography, but in appropriately selected patients, it may serve as a useful alternative. Dual-source CCT has improved temporal resolution, and 320-detector row coronary CTA now allows imaging of the entire heart in a single heartbeat. Combination cardiac PET/CT promises to provide additional information regarding cardiac morphology, perfusion, and metabolism. At present, CCT is not covered by many insurance carriers. Based on the results of ongoing clinical studies—demonstration of both efficacy and cost-effectiveness of CCT as a diagnostic modality—there may well be expanded coverage of CCT by insurers.

CARDIAC MAGNETIC RESONANCE IMAGING

CMR is less advanced as a noninvasive diagnostic imaging technique for the evaluation of cardiovascular disease, both clinically and in research applications. Nonetheless, improvements in image quality, speed of data acquisition, and reliability are increasing the usefulness of CMR for clinical applications. CMR is similar to echocardiography in that neither utilizes ionizing radiation to acquire high-resolution images. However, CMR offers considerably more detailed cardiac morphology than either echocardiography or CCT. In addition, the versatility of CMR permits imaging of a large field of view in nearly any plane. CMR has been demonstrated to be very useful for assessment of valvular heart disease, complex congenital heart disease, intracardiac and extracardiac masses, and pericardial disease, as well as for measurement of blood flow velocity, tissue characterization via perfusion imaging, and noninvasive angiography.

Technology of CMR

MRI (including CMR) is based upon the following general principles. Water is a major component of all tissues in the body. Each water molecule contains two hydrogen nuclei (or protons). Protons can be aligned by application of a powerful magnetic field. A second radiofrequency electromagnetic field can then be briefly applied and then turned off. As protons return to their original alignment after the electromagnetic field is turned off ("relaxation"), they generate a net magnetization that decays to its former position with energy loss in the form of a radio signal that can be detected with a radiofrequency antenna and quantified. Image tissue contrast depends on differences in the decay of net magnetization in the longitudinal plane (T_1) and transverse plane (T_2). Through the application of additional electromagnetic fields (gradient fields), radio waves coming from the body can be detected, allowing spatial localization within an imaging plane.

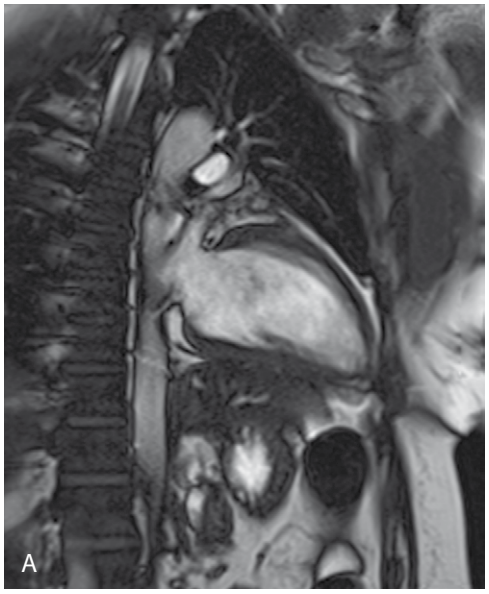
Data Acquisition Sequences and Techniques

CMR utilizes two basic imaging sequences: *spin echo* ("dark blood") and *gradient echo* ("bright blood"). Spin-echo sequences are commonly used for multislice anatomic imaging, providing clear delineation of the mediastinum, cardiac chambers and great vessels. Alternatively, gradient echo sequences are used more for physiologic assessment of function through cine acquisitions. Because of higher possible imaging speeds, gradient echo is more appropriately used for coronary artery imaging, ventricular and myocardial perfusion assessment, valvular assessment, and aortic flow quantification. *Phase velocity mapping* (PVM) entails application of a bipolar velocity-encoding gradient to provide quantitative flow velocity and volume flow. All cardiac and most vascular CMR sequences require cardiac gating. Through acquisition of multiple segments at different phases of the cardiac cycle, a cine image loop can be created tracking cardiac motion. Perfusion imaging, through the use of intravenous contrast agents, permits cardiac tissue characterization. Currently, only gadolinium-based contrast agents, chelated to other nontoxic molecules for clinical use, are utilized for imaging the cardiovascular system.

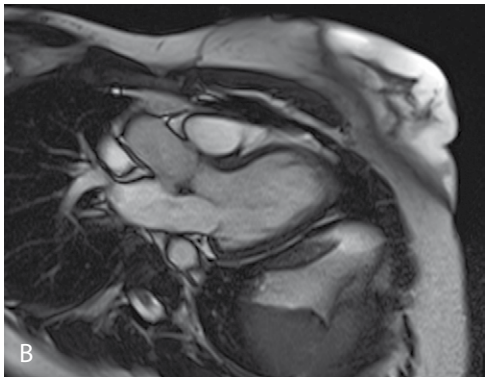
Clinical Indications

VENTRICULAR FUNCTION

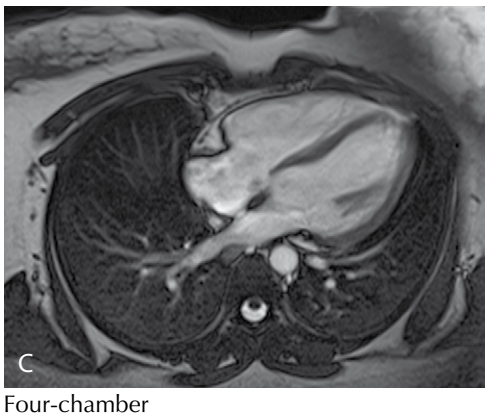
CMR is highly accurate and reproducible, providing clinically useful measurements of cardiac wall thickness and chamber



Two-chamber

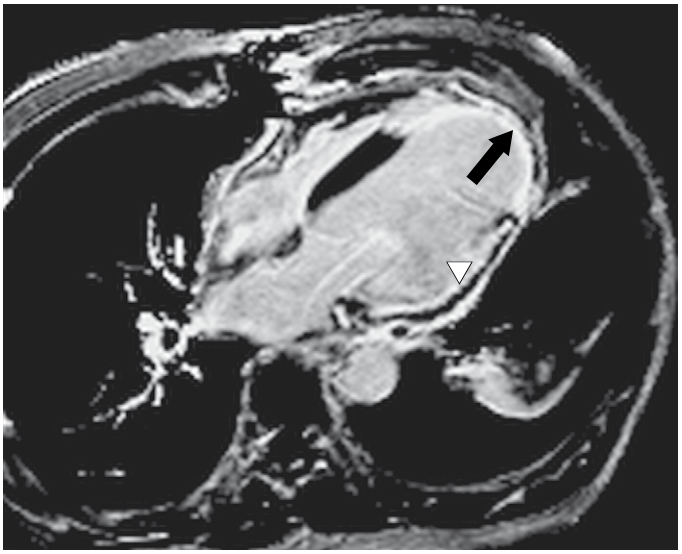


Three-chamber—LVOT view



Four-chamber

Figure 8-4 *Magnetic resonance imaging can generate images of the heart in arbitrary orientation.*



Example of a patient that has sustained a myocardial infarction and demonstrates an area of transmural scar at the apex (*arrow*) and nontransmural scar involving the lateral wall (*arrowhead*).

Figure 8-5 *Cardiac magnetic resonance imaging—transmural and nontransmural scars.*

volumes (Fig. 8-4). Increasingly, CMR is becoming recognized as the "gold standard" for assessment of left and right ventricular function. Left ventricular ejection fraction, left ventricular end-diastolic volume, left ventricular end-systolic volume, stroke volume, and left ventricular mass can all be reliably quantified. Left ventricular diastolic function can also be reliably interrogated using PVM, which, unlike echocardiography, is not limited to a one-dimensional approach and thus allows more complete, and thereby accurate, evaluation of myocardial relaxation.

AORTIC DISEASE

CMR has rapidly evolved into a clinically reliable, reproducible modality to evaluate the aorta and its primary branch vessels. Gadolinium-enhanced three-dimensional CMR angiography is an extremely rapid technique that can accurately depict aortic aneurysms, dissections, and thrombus. Stent-graft planning, now a common use of CMR, is often used before stent-graft placement in aortic disease, allowing selection (and when necessary custom design) of stent-grafts to be used. Aortic branch vessels, including carotid, renal, and mesenteric vessels, can also be very accurately evaluated with MRI.

ISCHEMIC HEART DISEASE

CMR can be used to assess myocardial viability and the extent of myocardial infarction. It is the imaging modality of choice for patients in whom there is a question about whether the distribution of a targeted revascularization is viable or not (Fig. 8-5). For this application, compared with nuclear imaging, CMR is much more sensitive in detecting subendocardial viability (and lack of viability) and, obviously, CMR does not require injection of radionuclides. Gadolinium is excluded from myocardial cells with intact membranes and thus is very useful in defining areas of infarction. Correlation with anatomic specimens suggests a sensitivity and specificity above 95%. Delayed hyperenhancement (DHE) protocols are based on the high-intensity ("bright") signal that characterizes first-pass perfusion

images of infarcted myocardium. First-pass perfusion images that appear hypointense are probably a combination of ischemic and infarcted tissues. An inverse relationship between hyperenhancement and viability is related to the extent of transmural infarction. The highest likelihood of recovery exists when the transmural infarction extent, as assessed by DHE, is less than 50%.

CARDIOMYOPATHIES

CMR is becoming an important tool in the evaluation of dilated cardiomyopathy, hypertrophic cardiomyopathy, and infiltrative disorders. It provides accurate assessment of ventricular function in patients with dilated cardiomyopathies. DHE CMR has a niche role in helping to differentiate heart failure related to dilated cardiomyopathy from CAD. Even so, the distinction is not perfect. More than 10% of patients with dilated nonischemic cardiomyopathy have gadolinium enhancement that is identical in appearance to that seen in patients with CAD.

CMR is equally useful in assessment of patients with cardiomyopathy. In hypertrophic cardiomyopathy, CMR can localize hypertrophy, particularly when echocardiography data are equivocal. Cine images can also demonstrate systolic anterior motion of the anterior mitral valve leaflet and dynamic outflow tract obstruction, useful measures in selecting an optimal therapeutic approach. CMR also has a role in the evaluation of patients with suspected infiltrative cardiomyopathies. Sarcoidosis is an infiltrative granulomatous disease pathologically known to nonuniformly involve the myocardium. This patchy distribution tends to result in a moderate to high number of false-negative cardiac biopsy results. When an initial biopsy result is negative in patients with suspected cardiac sarcoidosis, one must consider the benefits of repeated biopsy procedures, given the risks inherent in this procedure. CMR late hyperenhancement using gadolinium can depict areas of interstitial changes and granulomatous disease (Fig. 8-6). In patients with a high pre-test probability for cardiac sarcoid, CMR can potentially serve as a reliable screening tool obviating the need for biopsy, particularly if the diagnosis of sarcoidosis has been confirmed by biopsy of noncardiac tissue. Amyloid infiltration in the myocardium may show increased signal with DHE imaging sequences. Additionally, the combination of ventricular hypertrophy without ECG concordance, atrial wall thickening, valve thickening, and restrictive diastolic filling pattern can collectively raise the clinical suspicion for infiltrative cardiac amyloidosis. CMR is also capable of confirming the diagnosis of arrhythmogenic right ventricular dysplasia, a diagnosis that historically is based upon meeting several major and minor criteria. Use of contrast agents and DHE imaging may permit detection of fibro-fatty right ventricular free wall infiltration, an observation that increases specificity for this otherwise difficult diagnosis.

Patchy, nontransmural delayed hyperenhancement involving mid-septum and inferoseptum in a patient with cardiac sarcoidosis (*arrow*).

Figure 8-6 *Sarcoidosis: CMR phase-sensitive inversion recovery.*

PERICARDIAL DISEASES

Normal pericardium thickness on CMR is 1 to 4 mm. Functional and structural abnormalities of the pericardium are typically evaluated with CMR only when echocardiography or CCT provides equivocal information. CMR has been reported to provide 93% accuracy for the detection of constrictive pericarditis, given the appropriate clinical presentation. Findings include thickened pericardium, ascites, atrial enlargement, hepatomegaly, and systemic and pulmonary vein enlargement. Tissue tagging is a clinically applicable technique in the evaluation of constrictive pericarditis. Failure to see slippage between the visceral and parietal pericardia suggests fibrosis, scarring, or connections between these two normally separate tissue layers. CMR has also proven useful in the evaluation of pericardial cysts.

VALVULAR HEART DISEASE

Due to high temporal and spatial resolution, CMR has become a valuable complementary technique for evaluating the severity of valvular heart disease. Through a combination of steady-state free precession and PVM, CMR can provide a comprehensive valvular assessment. Although echocardiography is capable of superior temporal resolution, is more accessible, and is less labor-intensive, CMR is user-independent, capable of imaging flow in three dimensions (x, y, and z planes), more accurate for measuring absolute flow volumes and velocities, and feasible in patients whose body habitus precludes obtaining optimal echocardiographic images. In valvular regurgitant lesions, PVM

can provide exact quantifications of regurgitant volume and regurgitant fraction. In patients with aortic stenosis, planimetry of the aortic valve provides accurate measurements rather than geometric estimations available via echocardiography and catheterization techniques. Additionally, CMR provides accurate measurement of peak transstenotic jet velocities that are orthogonal to the valve, not merely across it.

CARDIAC MASSES

CMR is the imaging modality of choice for evaluation of cardiac masses because of its ability to characterize tissue. Spin-echo imaging provides excellent images for evaluation of the presence, extent, attachment site, and secondary effects of cardiac mass lesions. CMR has a proven role in the identification of intracardiac thrombi, primary and secondary cardiac tumors, and pericardial cysts (Fig. 8-7). A unique feature of benign cardiac tumors on CMR is that they generally exhibit an isointense signal with respect to the myocardium in both T_1- and T_2-weighted imaging sequences. Contrast uptake is most often an ominous sign suggestive of malignant lesions.

CONGENITAL HEART DISEASE

CMR is an ideal imaging modality for the assessment of congenital heart disease, providing superior anatomic imaging coupled with functional interrogation and reproducibility. In the evaluation of great vessel abnormalities, CMR is the gold standard for assessment of aortic coarctation. Through velocity mapping of the coarctation jet, a pressure gradient can be determined. Tetralogy of Fallot, including overriding aorta, membranous ventricular septal defect, right ventricular hypertrophy, and infundibular or pulmonary stenosis, can be completely characterized before and after correction. CMR is also capable of reliably depicting anomalous coronary arteries and their relation to other cardiac structures and the great vessels.

PULMONARY VASCULAR DISEASE

CMR is well suited for the evaluation of pulmonary artery aneurysms and dissection. Evaluation of pulmonary vein stenosis is becoming increasingly important with the increased use of radiofrequency catheter ablation for supraventricular arrhythmias and atrial fibrillation. CMR is capable of evaluating pulmonary venous stenosis. In addition, CMR can noninvasively confirm anomalous pulmonary venous drainage associated with an atrial septal defect—an important consideration before corrective surgery.

CORONARY ARTERY BYPASS GRAFT IMAGING

Although coronary angiography remains the "gold standard" for evaluating coronary atherosclerotic disease, CMR will probably be used in the future for noninvasive assessment of the coronary arteries. CMR imaging of coronary artery bypass grafts (for assessment of patency) is already quite accurate. The main limitations to CMR coronary angiography include limited spatial resolution, respiratory motion, rapid coronary motion (up to 20 cm/s in certain phases), and inability to easily assess distal runoff. Quantification (and sometimes even detection) of coronary luminal stenoses remains challenging. At present this is an area of significant research. Coronary flow velocities can be estimated by CMR, and some centers are now using adenosine infusion with CMR to measure coronary flow as a diagnostic test for functionally important CAD. Anomalous coronary arteries can be identified through the use of CMR. In particular, CMR is well suited to demonstrate the relationship of anomalous coronary arteries to other vascular structures (the aorta and main pulmonary artery) and thus to make decisions on the need and timing of surgery.

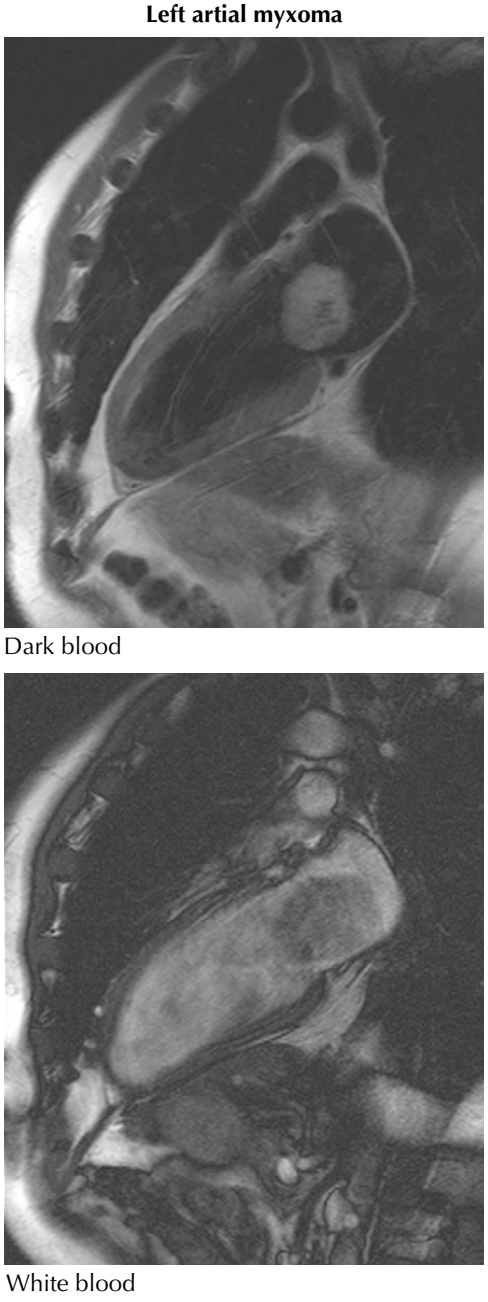


Figure 8-7 *Blood sequences showing left atrial myxoma.*

Safety, Risks, and Contraindications

Because of the physical nature of CMR, magnetic field generation poses a risk to patients of moving metallic, ferromagnetic projectiles while physically inside the scanner. Care must be taken to ensure protocols are in place to minimize this risk. Most prosthetic heart valves, vascular stents including coronary artery stents, and orthopedic implants are safe to be imaged using CMR, but at present CMR is generally contraindicated for patients with metallic implants and implantable pacemakers and defibrillators. A major concern in this regard has been that the programming of these devices would be deleteriously altered. In vitro and in vivo experiments have suggested that certain devices may be MRI-safe; however, there remains a risk-benefit assessment on a case-by-case basis. Some patients with previous neurologic procedures remain at increased risk from MR technology. Neurologic consultation is essential under these circumstances.

Future Directions

CMR has advanced rapidly in the past decade, and the clinical applications for its use continue to evolve. Ultrafast imaging through improved magnet design will continue to improve the logistic constraints associated with CMR. CMR holds promise for further assessment and characterization of atherosclerotic plaque burden and composition, and research is active in this area.

ADDITIONAL RESOURCES

Achenbach S. Computed tomography coronary angiography. *J Am Coll Cardiol.* 2006;48:1919–1928.

Thorough review of various issues concerning CT scanner technology, image acquisition and reconstruction, image interpretation, and potential clinical applications.

Finn PJ, Kambiz N, Vibhas D, et al. Cardiac MR imaging: state of the technology. *Radiology.* 2006;241:338–354.

Review covering some of the major milestones in cardiac MR; discusses some of its technical and diagnostic clinical uses.

Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCCT/SCMR/NASCI/SCAI 2006 Appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions and Society of Interventional Radiology. *J Am Coll Cardiol.* 2006;48:1475–1497.

This article critically and systematically creates, reviews, and categorizes appropriateness criteria for cardiovascular CT and MRI.

The Multi-Ethnic Study of Atherosclerosis (MESA). Available at: <http://www.mesa-nhlbi.org>; Accessed 22.02.10.

A medical and scientific forum sponsored by the National Heart, Lung and Blood Institute of the National Institutes of Health sharing clinical information regarding the study of the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinical overt cardiovascular disease or progression of subclinical disease. The website incorporates links to coronary artery calcium tools, publications, ancillary studies, and power calculations.

EVIDENCE

Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15:827–832.

Landmark cohort study that demonstrated the utility of ultrafast CT to detect and quantify CAC levels.

Arad Y, Goodman KJ, Roth M, et al. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: The St. Francis Heart Study. *J Am Coll Cardiol.* 2005;46:158–165.

Prospective, population-based study that demonstrated that electron beam CT coronary calcium score predicts CAD events independent of standard risk factors more accurately than standard risk factors and C-reactive protein, and redefines Framingham risk stratification.

Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med.* 2007;357:2277–2284.

Review article describing the use of CT and the associated radiation doses and subsequent biologic effects of ionizing radiation.

Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008;358:1336–1345.

Landmark study evaluating large population-based sample consisting of men and women from multiple racial and ethnic groups using CT methods for measurement of CAC. Established that the coronary calcium score is a strong predictor of incident coronary heart disease and provides predictive information in addition to standard atherosclerotic risk factors.

Di Carli MF, Dorbala S, Meserve J, et al. Clinical myocardial perfusion PET/CT. *J Nucl Med.* 2007;48:783–793.

Thorough review article discussing myocardial perfusion PET/CT.

Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med.* 2000;342:1077–1084.

Retrospective study evaluating outcomes in 1230 cardiomyopathy patients of multiple etiologies. With a mean follow-up of greater than 4 years, the underlying cause of heart failure was determined to have prognostic value with peripartum cardiomyopathy having better long-term outcomes.

Feuchtner GM, Schachner T, Bonatti J, et al. Diagnostic performance of 64-slice computed tomography in evaluation of coronary artery bypass grafts. *AJR Am J Roentgenol.* 2007;189:574–580.

Retrospective study evaluating patient cohort with prior coronary artery bypass graft surgery, comparing 64-slice CT and conventional coronary angiography. The 64-slice CT was found to be accurate at excluding greater than 50% graft stenosis, but was subject to possible stenosis severity overestimation and had limited ability in detecting distal anastomosis stenosis.

Giorgi B, Mollet NRA, Dymarkowski S, et al. Clinically suspected constrictive pericarditis: MR imaging assessment of ventricular septal motion and configuration in patients and healthy subjects. *Radiology.* 2003;228:417–424.

Prospective study evaluating ventricular septal motion in patients suspected of having constrictive pericarditis. Determined that abnormal diastolic ventricular septal motion is frequent among patients with constrictive pericarditis and may be useful in distinguishing constrictive pericarditis from restrictive cardiomyopathy.

Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 Clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert

Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2007;49:378–402.

Clinical expert consensus document providing a current perspective on the role of CAC scanning by fast CT in clinical practice.

Hajime S. Magnetic resonance imaging for ischemic heart disease. *J Magn Reson Imaging.* 2007;26:3–13.

Extensive, thorough review article discussing the use of MRI in patients with ischemic heart disease.

Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med.* 2007;357:2153–2165.

Excellent review on sarcoidosis discussing epidemiology, search for environmental causes, genetic features, immunopathogenesis, clinical features, diagnosis, organ involvement, therapy, and future directions.

Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med.* 2000;343:1445–1453.

Prospective cohort study evaluating contrast-enhanced MRI in patients with ventricular dysfunction before revascularization. Concluded that reversible myocardial dysfunction can be identified by contrast-enhanced MRI before revascularization. Of regions with greater than 50% hyperenhancement before revascularization, 90% failed to improve after revascularization was completed.

Krombach GA, Hahn C, Tomars M, et al. Cardiac amyloidosis: MR imaging findings and T1 quantification, comparison with control subjects. *J Magn Reson Imaging.* 2007;25:1283–1287.

Comparison study that looked specifically at the T_1 time of the myocardium in a patient with known amyloidosis compared with other individuals without known myocardial disease. Concluded that T_1 quantification may increase diagnostic confidence in patients with amyloidosis.

Oncel D, Oncel G, Tastan A, Tamci B. Evaluation of coronary stent patency and in-stent restenosis with dual-source CT coronary angiography without heart rate control. *AJR Am J Roentgenol.* 2008;191:56–63.

Prospective study evaluating in-stent restenosis and occlusion in a small patient cohort with known clinical CAD having all undergone prior coronary artery stent placement with dual-source CT. The accuracy of dual-source CT in the detection of in-stent restenosis and occlusion was reported at 96%.

Stein PD, Fowler SE, Goodman LR, et al. The PIOPED II investigators. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med.* 2006;354:2317–2327.

Prospective, multicenter investigation of the accuracy of multidetector CTA alone and combined with venous phase imaging for the diagnosis of acute pulmonary embolism. In patients with suspected pulmonary embolism, multidetector CTA with venous phase imaging was found to have higher diagnostic accuracy compared with CTA alone.

Stein PD, Yaekoub AY, Matta F, Sostman HD. 64-slice CT for diagnosis of coronary artery disease: a systematic review. *Am J Med.* 2008;121:715–725.

Systematic review of all published trials that used 64-slice CT to diagnose CAD. Concluded that a negative 64-slice CT reliably excludes significant CAD with a reported negative predictive value of 96% to 100%.

Tandri H, Saranathan M, Rodriguez ER, et al. Noninvasive detection of myocardial fibrosis in arrhythmogenic right ventricular cardiomyopathy using delayed-enhancement magnetic resonance imaging. *J Am Coll Cardiol.* 2005;45:98–103.

Prospective study evaluating 30 consecutive patients with known arrhythmogenic right ventricular disease using myocardial delayed-enhancement MRI. Concluded that noninvasive detection of right ventricular myocardial fibro-fatty changes in arrhythmogenic right ventricular disease is possible with myocardial delayed-enhancement MRI and correlated well with histopathology and predicted inducible ventricular tachycardia on programmed electrical stimulation.

Diagnostic Coronary Angiography

George A. Stouffer

9

The ability to directly visualize coronary arteries was a seminal advance in the history of modern medicine and led directly to the development of the concept of transluminal angioplasty (first performed in 1964), coronary artery bypass grafting (first performed in 1967), percutaneous transluminal peripheral balloon angioplasty (first performed in 1974), and percutaneous transluminal coronary balloon angioplasty (first performed in 1977). With the high prevalence of coronary artery disease (CAD) in industrialized countries, coronary angiography remains an important diagnostic modality. This chapter focuses on coronary anatomy and the technique of coronary angiography and its clinical uses.

CORONARY ANATOMY AND ANOMALIES

The right coronary artery (RCA) arises from the right coronary sinus and runs in the right atrioventricular groove (Fig. 9-1). Generally, the conus artery and the sinoatrial artery arise from the RCA. In approximately 85% of individuals, the posterior descending coronary artery arises from the RCA (defined as a right dominant coronary circulation). The left main coronary artery arises from the left coronary sinus. Within a few centimeters of its origin, it divides into the left anterior descending (LAD) coronary artery (in the anterior interventricular groove), the left circumflex coronary artery (in the atrioventricular groove), and, in a minority of cases, a ramus intermedius artery.

Coronary artery anomalies are found in 1% to 1.5% of individuals (Fig. 9-2), and most of these anomalies are benign. The most common coronary artery anomaly is the presence of separate origins of the LAD and left circumflex arteries from the aorta (i.e., absence of a left main coronary artery), which occurs in 0.4% to 1% of individuals and is occasionally associated with a bicuspid aortic valve. Clinically significant anomalies include origin of a coronary artery from the opposite coronary sinus (e.g., left main artery originating from the right coronary sinus), presence of a single coronary ostium (and hence a single coronary artery), and origin of a coronary artery from the pulmonary artery.

DESCRIPTION OF TECHNIQUE

Coronary angiography delineates the course and size of the coronary arteries, identifies coronary anomalies, and provides information on the location and degree of any obstruction (Box 9-1). Coronary angiography is performed by injecting radiopaque contrast dye directly into the ostium of the left and right coronary arteries. Access to the aorta is usually gained via percutaneous puncture of the femoral artery; however, brachial, radial, and axillary arteries can also be used for arterial access. Specific preformed catheters are passed over a guide wire into the aortic root. Selection of the catheter to be used depends on the access site, the coronary artery being investigated, and operator preference. The wire is removed, and the coronary artery is cannulated with fluoroscopic guidance. Contrast dye is injected during cineradiography, while blood pressure and ECG are continually monitored and sequential frames are recorded.

Complete evaluation of coronary arteries involves angiography in multiple projections (Figs. 9-3 and 9-4). This is necessary in order to appreciate the three-dimensional aspects of the coronary arteries with this two-dimensional imaging technique. These views are obtained by rotating the imaging system to different positions around the patient, who lies supine on a radiolucent table. Views from the left or right of the patient can be obtained by varying the degrees of the angle. The imaging system can also be rotated from head (cranial) to toe (caudal) positions. Although almost limitless combinations of potential imaging positions exist, several standard views are utilized that in most cases allow full visualization of the coronary arteries. In all cases, multiple views help to delineate vessel tortuosity and avoid potential misinterpretations as a result of either foreshortening of specific areas or overlapping coronary artery branches.

The most commonly used views for left coronary angiography include right anterior oblique (RAO) with cranial and caudal angulation, left anterior oblique (LAO) with cranial and caudal angulation, and anteroposterior with cranial and caudal angulation. Views most commonly used for RCA angiography include RAO and LAO projections with or without cranial angulation. Individual variation in coronary anatomy or location of stenoses often necessitates customization of projections. Standard nomenclature to define coronary segments has been developed by several groups, including investigators in the Coronary Artery Surgery Study and the Bypass Angioplasty Revascularization Investigation.

The usual method of analyzing angiograms in clinical practice is visual identification of areas of relative narrowing, with quantification by comparing the minimal diameter of the narrowed coronary segment with that of an adjacent, normal-appearing reference segment. Although experienced observers may estimate the degree of stenosis visually, stenoses can be quantified using calipers or quantitative computer angiography. Because atherosclerotic plaques are often eccentric, orthogonal views are needed to accurately determine the degree of obstruction.

Flow in coronary arteries can be estimated at the time of coronary angiography with a scale developed by the Thrombolysis in Myocardial Infarction (TIMI) investigators. Flow defined as TIMI 0 indicates a completely occluded artery. TIMI 1 flow describes a severe lesion in which dye passes the area of narrowing but does not extend to the vessel's distal portion. With TIMI 2 flow the distal vessel is opacified but not as rapidly as would be expected or as rapidly as nonobstructed vessels. TIMI 3 flow is "normal." The TIMI flow index has shown significant prognostic value. TIMI "frame counts," the number of frames necessary for dye to reach the vessel's distal portion, are used as a quantitative index of flow.

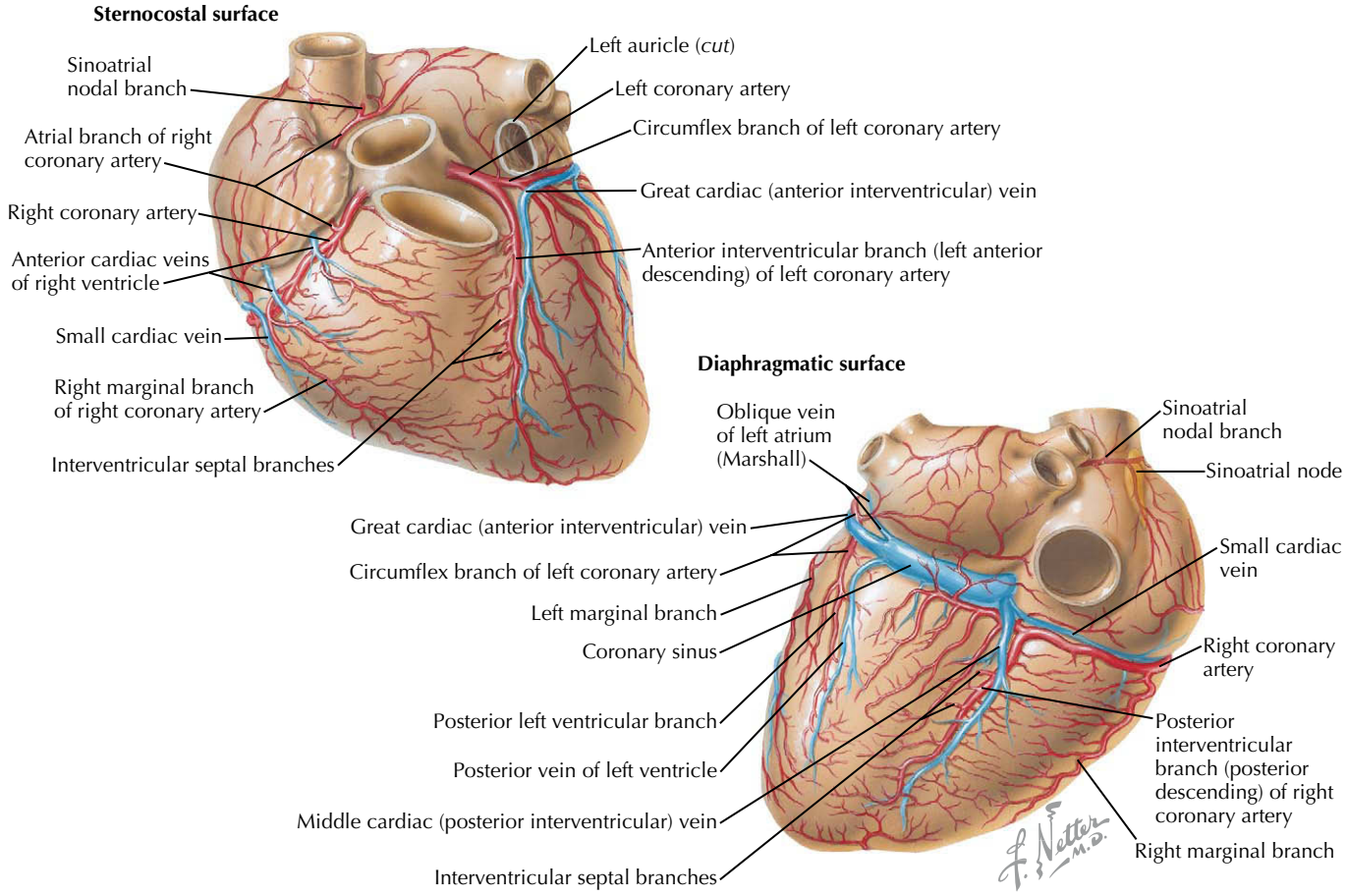
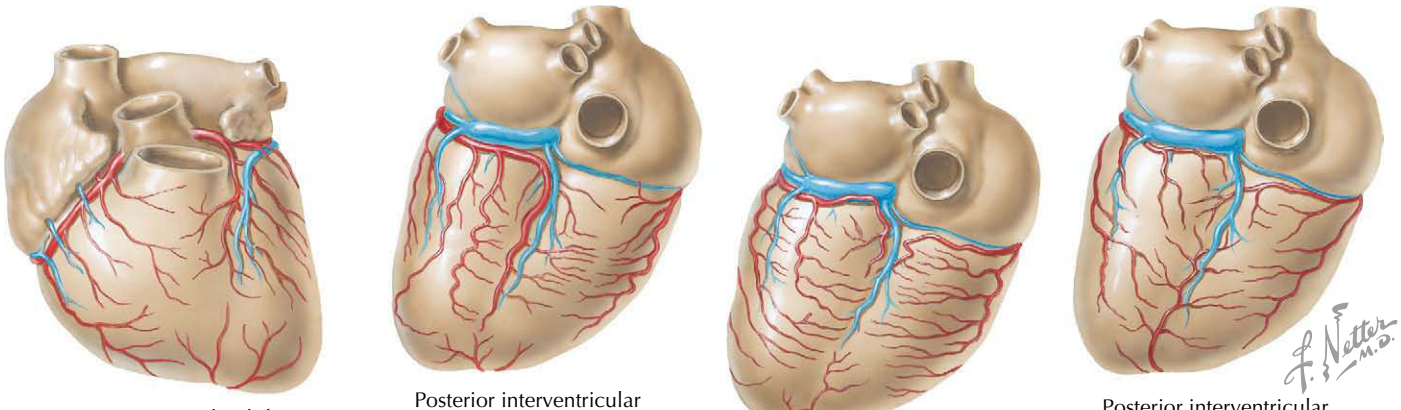


Figure 9-1 *Coronary arteries and cardiac veins.*



Anterior interventricular (left anterior descending) branch of left coronary artery very short. Apical part of anterior (sternocostal) surface supplied by branches from posterior interventricular (posterior descending) branch of right coronary artery curving around apex.

Posterior interventricular (posterior descending) branch derived from circumflex branch of left coronary artery instead of from right coronary artery.

Posterior interventricular (posterior descending) branch absent. Area supplied chiefly by small branches from circumflex branch of left coronary artery and from right coronary artery.

Posterior interventricular (posterior descending) branch absent. Area supplied chiefly by elongated anterior interventricular (left anterior descending) branch curving around apex.

Figure 9-2 *Coronary arteries and cardiac veins: variations.*

Box 9-1 Information Provided by Selective Coronary Angiography

- Origin of major coronary arteries
- Size of coronary arteries
- Course of coronary arteries
- Branches originating from large and medium coronary arteries
- Degree and location of lumen irregularities
- Presence of fistulas
- Presence of collaterals
- Presence of bridging
- Presence of large thrombus
- Aneurysms
- Spasm and response to nitroglycerin
- Coronary plaques—location, degree of narrowing, eccentricity, involvement of side branches, length

Microvascular integrity can be assessed at the time of coronary angiography with angiographic myocardial blush scores. These scores, which measure contrast dye density and washout in the area of interest, correlate with left ventricular (LV) functional recovery after myocardial infarction (post-MI) and prognosis. In the setting of acute MI, myocardial blush scores add additional prognostic information to TIMI frame score and persistent ST-segment elevation.

Coronary angiography can be performed separately or as part of cardiac catheterization or an interventional procedure. Most patients referred for diagnostic angiography also undergo left heart catheterization and left ventriculography. When clinically indicated, patients undergoing coronary angiography will also undergo angiography of other vascular beds. For example, patients with resistant hypertension may undergo renal angiography; those with claudication may undergo lower extremity artery angiography; and those with left internal mammary artery grafting to the LAD coronary artery may undergo subclavian angiography (Fig. 9-5).

INDICATIONS

The most common indication for coronary angiography is to determine the presence, location, and severity of atherosclerotic lesions. Coronary angiography provides essential information in the diagnosis of CAD, in determining prognosis, and in decision making regarding revascularization. Neither percutaneous coronary intervention or coronary artery bypass graft can occur without coronary angiography. More rarely, coronary angiography is used to diagnose anomalies, muscular bridging, fistulas, spasm, emboli, aneurysms, and arteritis.

Indications for coronary angiography in a random sample of 100 consecutive patients at the University of North Carolina are listed in Table 9-1. The most common indication was for evaluation of symptomatic CAD—either stable angina or acute coronary syndrome. Less common indications included valvular heart disease; congestive heart failure; evaluation before heart, lung or liver transplant; periodic evaluation after heart transplant; and congenital heart disease. Other appropriate indications for coronary angiography that were not present in this cohort of patients include having survived sudden cardiac death, having a history of ventricular tachycardia, abnormal results of stress tests in high-risk occupations (e.g., pilot or bus driver), history of postrevascularization ischemia, and being a prospective heart transplant donor whose age and risk factor profile suggest possible CAD.

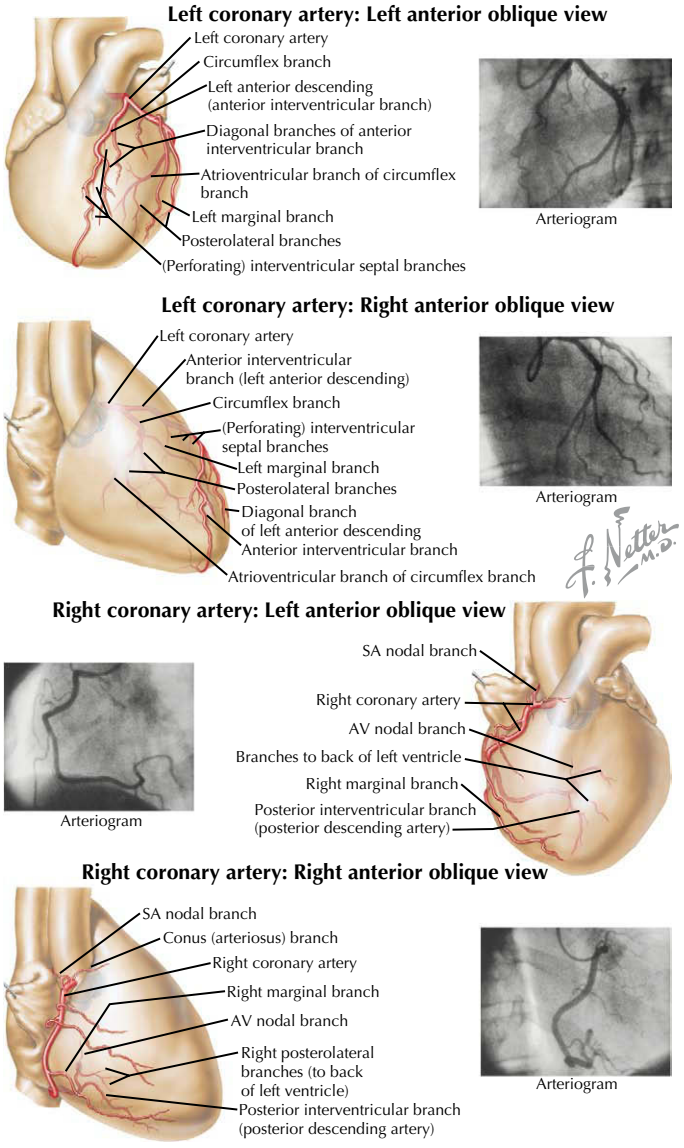


Figure 9-3 *Coronary arteries: arteriographic views.* AV, atrioventricular; SA, sinoatrial.

Use of Coronary Angiography in the Evaluation of Patients with Chest Pain

The American Heart Association and American College of Cardiology publish guidelines on the indications for coronary angiography. Use of coronary angiography in specific conditions is assigned a rating based on the weight of evidence that either (1) supports the indication (classes I and IIa), (2) argues against the indication (class III), or (3) is insufficient to support or refute the indication (class IIb). Because there are risks associated with coronary angiography, patients with class III indications should rarely, if ever, undergo the procedure. Referral for angiography with class II indications is a

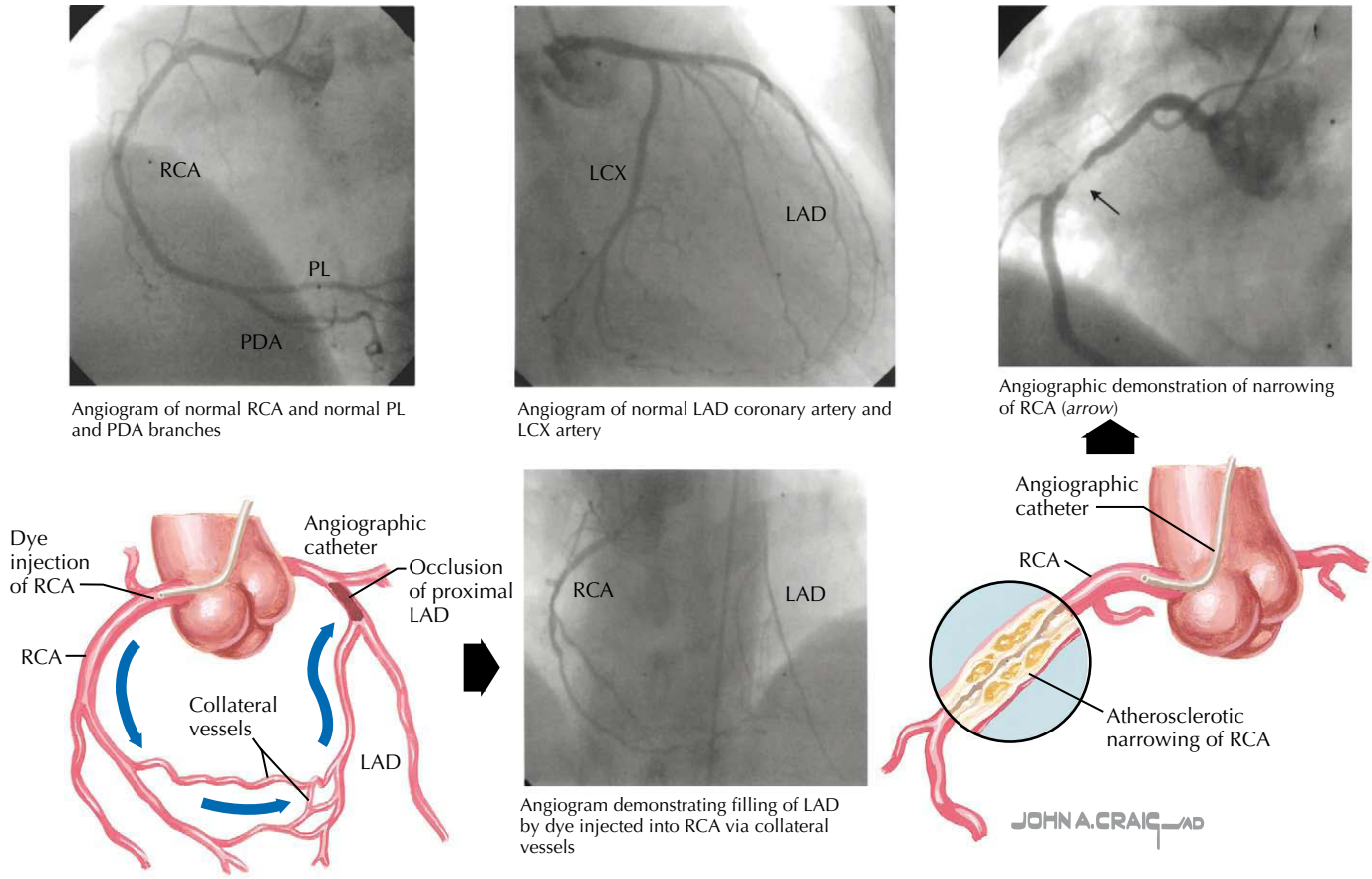


Figure 9-4 *Coronary angiography.* LAD, left anterior descending; LCX, left circumflex; PDA, posterior descending artery; PL, posterolateral; RCA, right coronary artery.

decision involving assessment of the risk-to-benefit ratio by the referring physician and the patient. Many patients with class IIa indications are referred for angiography, but it is uncommon for patients with class IIb indications to undergo coronary angiography. Despite the guidelines, marked differences exist in practice patterns among individual physicians, geographic regions within the United States, and different countries. In some areas, coronary angiography is considered the standard of care for a particular clinical scenario (such as following an uncomplicated MI), whereas noninvasive approaches are favored elsewhere.

The two most important issues in the evaluation of patients with suspected ischemic chest pain are the identification of the extent of CAD and the delineation of LV function (Fig. 9-6). This can be done either directly (e.g., cardiac catheterization) or indirectly (e.g., exercise treadmill testing). If patients have stable, exertional symptoms, an exercise treadmill test can provide diagnostic and prognostic information. In addition to ECG findings, the test provides information on symptoms during exercise, blood pressure response, and duration of exercise. Combining ECG monitoring with either nuclear imaging (to determine myocardial perfusion) or echocardiographic imaging (to determine LV function) during exercise enhances the sensitivity and specificity of treadmill testing (see Chapters 6 and 7). Imaging is essential in patients in whom the ECG response cannot be interpreted (e.g., left bundle branch block or Wolff-Parkinson-White syndrome). It is also extremely helpful in situations in which the sensitivity and/or specificity of exercise ECG is reduced, for example, in middle-aged females or in individuals with electrocardiographic evidence of LV hypertrophy. Pharmacologic stress testing coupled with imaging is available for patients unable to exercise.

Evidence for flow-limiting CAD on stress testing is an indication to proceed to coronary angiography. Occasionally, further evaluation is not needed if patient symptoms are controlled by medical therapy and if information from the stress test (e.g., duration of exercise, extent of ischemia) suggests that patient prognosis is good. Rarely, patients with normal results of stress tests are referred for coronary angiography. Generally, these are patients with typical symptoms in whom results of the stress test are thought to be falsely negative.

In selected patients with stable symptoms and in all patients with unstable symptoms, cardiac catheterization is performed without prior stress testing. Included in this group are patients with symptoms highly typical of angina, congestive heart failure, prior MI, and prior revascularization and/or with symptoms at a low level of exertion (class III or IV). In addition, patients with unstable symptoms should be referred directly for catheterization. In particular, patients with unstable angina, recent non-Q-wave MI or acute ST-elevation MI should be referred for urgent or emergent angiography, with possible use of percutaneous intervention (see Chapters 13–15).

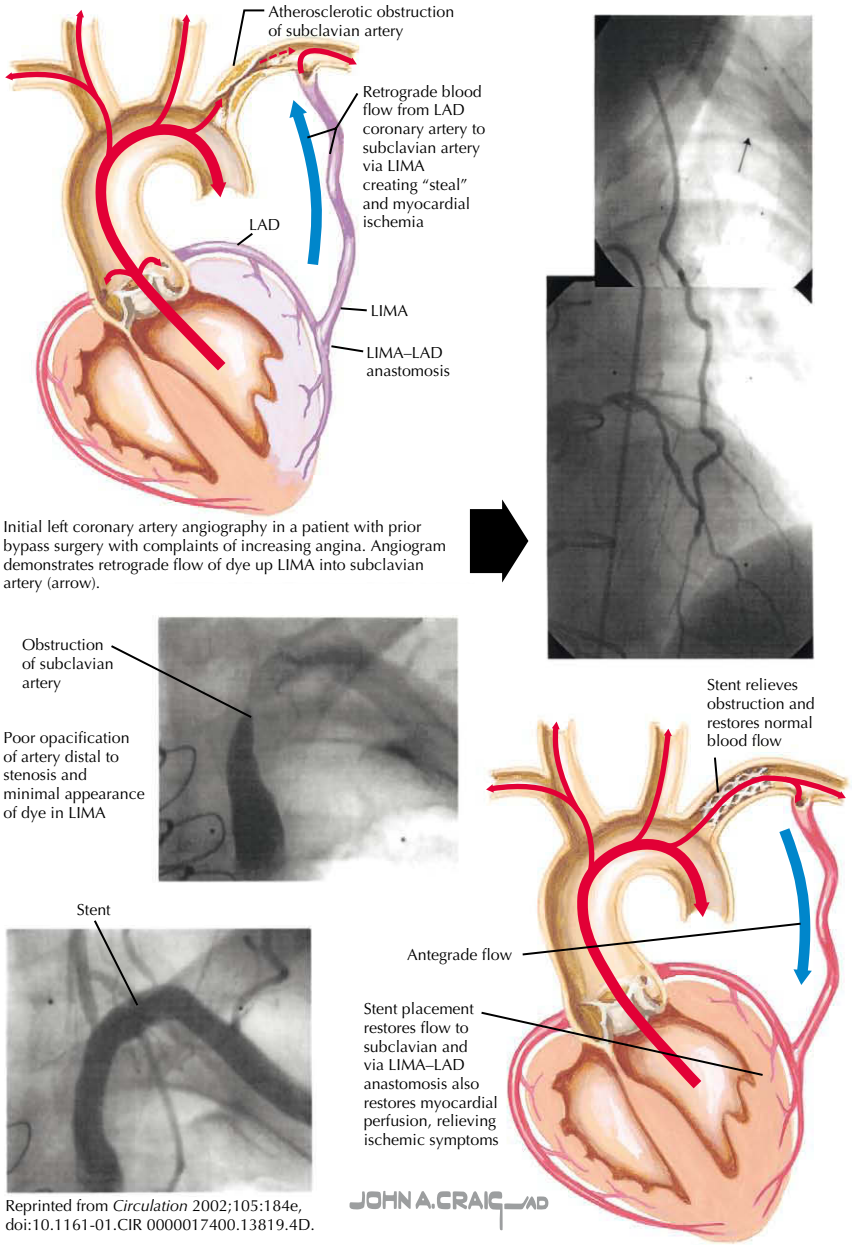


Figure 9-5 *Angiographic demonstration of subclavian steal.* LAD, left anterior descending; LIMA, left internal mammary artery.

Noninvasive coronary angiography is another modality available to evaluate CAD. This technique visualizes the coronary arteries with multidetector CT following intravenous injection of contrast dye. This technique (often referred to as CT angiography) has a high sensitivity for detecting coronary calcification and plaque, although quantification of the degree of stenosis is less accurate than with standard coronary angiography. Currently, CT angiography is primarily used in patients with a low pre-test probability of disease. Limitations of noninvasive angiography include the radiation dose, the need for relative bradycardia (although this is less of an issue with newer scanners), and intraobserver variation in interpretation. A more detailed discussion of this technique is included in Chapter 8.

CONTRAINDICATIONS

The only absolute contraindication to coronary angiography is lack of patient consent. However, relative contraindications reflect the procedure's increased risk in certain conditions. Acute renal failure or severe preexisting renal dysfunction, especially in diabetic individuals, identifies patients at high risk for contrast-induced nephropathy. Severe coagulopathy (due to comorbid diseases or medications such as warfarin), active bleeding, or both limits the ability to anticoagulate the blood of patients for interventional procedures and increases the risk of vascular complications. Decompensated heart failure can lead to respiratory failure when the patient is required to remain supine during the procedure. Electrolyte abnormalities and/or digitalis

Table 9-1 Indications for Coronary Angiography

Indications	Percentage of Patients*
Exertional angina	51
Non–ST-elevation MI	18
Congestive heart failure	9
Primary treatment of ST-elevation MI	7
Valvular heart disease	6
Cardiogenic shock	2
ST elevation after administration of thrombolytic agents (rescue angioplasty)	1
Miscellaneous	6
Annual evaluation after heart transplantation	–
Hypertrophic cardiomyopathy with chest pain	–
Constrictive pericarditis	–
Congenital heart disease	–
Preoperative evaluation for proximal aortic and/or aortic arch aneurysm repair	–
Preoperative assessment for aortic dissection repair	–
Evaluation before heart, lung, or liver transplantation	–
Ventricular arrhythmias and/or survival of sudden cardiac death	–
Abnormal stress tests in high-risk occupations (e.g., pilot)	–
Postrevascularization ischemia	–
Prospective heart transplant donor whose age and risk factor profile suggests the possibility of CAD	–
Patient who is at high risk for coronary disease when other cardiac surgical procedures (e.g., pericardectomy) are planned	–

CAD, coronary artery disease; MI, myocardial infarction.
*The percentages reflect the relative volume at the University of North Carolina based on a random sample of 100 consecutive patients.

toxicity can predispose the patient to malignant arrhythmias during contrast injection. Other relative contraindications include patient inability to cooperate, active infection, allergy to contrast agents, uncontrolled hypertension, severe peripheral vascular disease, and pregnancy. Because life-threatening complications can occur in any of these circumstances, it is essential that the risk-to-benefit ratio of coronary angiography is considered and discussed with the patient (and/or family members) and that all possible precautions are taken to minimize the potential for an adverse outcome.

LIMITATIONS

Coronary angiography outlines the vessel lumen but is unable to provide any information on wall thickness. Proper interpretation of stenosis severity involves identification of an appropriate

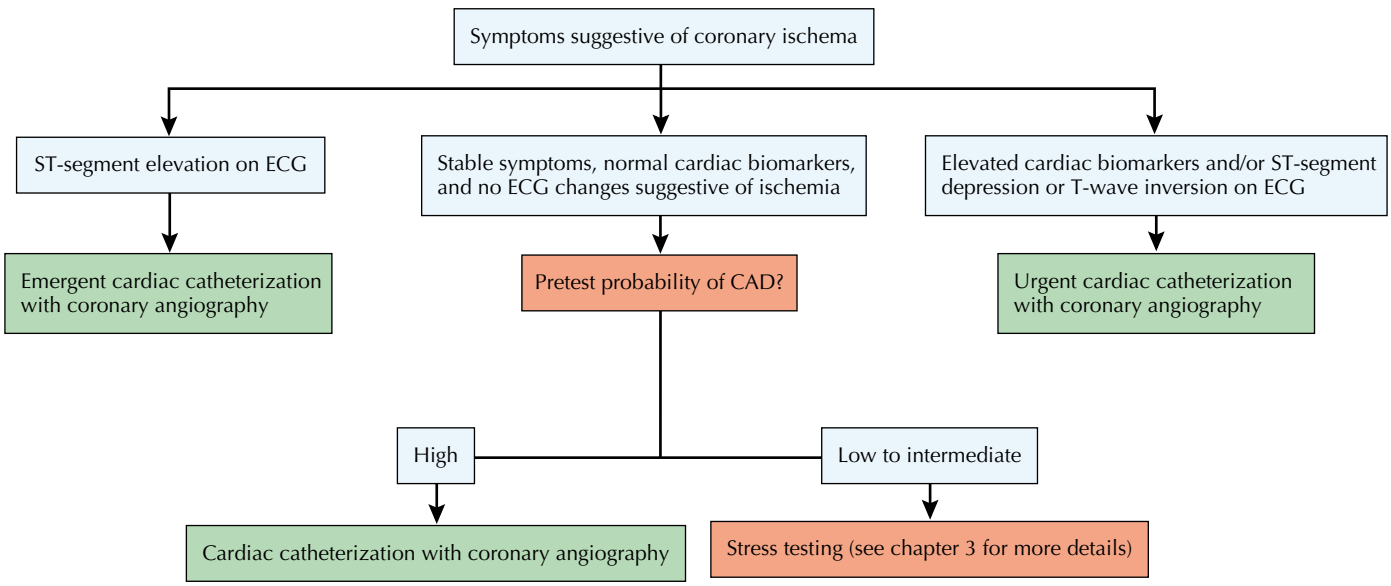


Figure 9-6 *Simplified approach to management of patients with symptoms suggestive of coronary is chemia.* CAD, coronary artery disease; ECG, electrocardiogram.

Table 9-2 Complications of Coronary Angiography*

	Year		
	1982	**1989**	**1990**
Total no. of complications	53,581	222,553	59,792
Death (%)	0.14	0.10	0.11
MI (%)	0.07	0.06	0.05
CVA (%)	0.07	0.07	0.07
Arrhythmia (%)	0.56	0.47	0.38
Vascular (%)	0.57	0.46	0.43
Total (%)	1.82	1.74	1.70

CVA, cerebrovascular accident or stroke; MI, myocardial infarction.
*Rates of complications of coronary angiography and cardiac catheterization as reported by registries of the Society for Cardiac Angiography and Intervention.
With permission from Kennedy JW. Complications associated with cardiac catheterization and angiography. Cathet Cardiovasc Diagn *1982;8:5–11; Johnson LW, Lozner EC, Johnson S, et al. Coronary arteriography 1984–1987: a report of the Registry of the Society for Cardiac Angiography and Interventions. I. Results and complications.* Cathet Cardiovasc Diagn *1989;17:5–10; and Noto TJ Jr., Johnson LW, Krone R, et al. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I).* Cathet Cardiovasc Diagn *1991;24:75–83.*

reference segment with which to compare the abnormal section. Furthermore, even with identification of a proper reference section, experienced observers are limited in their ability to consistently identify hemodynamically significant coronary stenoses.

These limitations have led to development of technologies to supplement coronary angiography, including intravascular ultrasound and pressure wire analysis. Intravascular ultrasound provides two-dimensional cross-sectional images in which the vessel's three layers (intima, media, and adventitia) can often be identified and characterized (see Chapter 2). Luminal cross-sectional area, wall thickness, and plaque area can be identified and quantified. Additionally, calcium, thrombus, and dissection planes can be imaged. Intravascular ultrasound is clinically useful in the assessment of complex coronary lesions, left main coronary artery lesions, and results of interventional procedures.

Advances in technology have allowed the attachment of pressure transducers to 0.014-in angioplasty wires, allowing determination of intracoronary pressure distal to coronary stenoses. By comparing distal coronary pressure with aortic pressure at rest and during conditions of maximal coronary hyperemia, fractional flow reserve can be calculated. Determination of fractional flow reserve is clinically useful in assessment of intermediate lesions (i.e., coronary lesions of unclear significance angiographically) and determination of adequate balloon angioplasty and/or stent placement.

COMPLICATIONS

The risk of major complications during coronary angiography, defined as death, MI, or stroke, is approximately 0.3%. If the definition is expanded to include vascular complications, arrhythmias, and contrast reactions, the risk of any complication is still less than 2%. Conditions that increase risk include shock, acute coronary syndrome, renal failure, left main CAD, severe valvular disease, increased age, peripheral vascular disease, prior anaphylactoid reaction to contrast media, and congestive heart failure. The risks of cardiac catheterization with coronary angiography are outlined in Table 9-2. Complication rates have been remarkably consistent across registries from the 1980s and, indeed, more recent registries have focused on complications associated with coronary interventions.

FUTURE DIRECTIONS

During the 50 years of diagnostic coronary angiography, continual improvement in catheters, imaging approaches, and arterial access techniques have allowed the procedure to be performed more quickly and safely. Many investigators are now examining whether noninvasive approaches to coronary artery imaging (based on improvements in MRI or CT) will lessen the need for, or even replace, diagnostic coronary angiography. Whether it is the routine use of noninvasive imaging or further modifications of invasive imaging, further reduction in morbidity and mortality rates associated with defining coronary anatomy will undoubtedly be achieved in coming years.

ADDITIONAL RESOURCE

Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol.* 1999;33:1756–1824. Executive summary available at: <http://circ.ahajournals.org/cgi/content/full/99/17/2345>; Accessed 22.02.10.

Guidelines on the use of coronary angiography.

EVIDENCE

Alderman EL, Stadius ML. The angiographic definitions of the Bypass Angioplasty Revascularization Investigation (BARI). *Coron Artery Dis.* 1992;3:1189–1207.

Nomenclature of the branches of the coronary arteries that is used in various studies.

Angelini P, Velasco JA, Flamm S. Coronary anomalies: incidence, pathophysiology, and clinical relevance. *Circulation.* 2002;105:2449–2454.

A description of various coronary anomalies.

Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation.* 1996;93:879–888.

The initial description of the widely used TIMI frame count method of assessing coronary flow.

Pijls NH, de Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703–1708.

Compares the use of fractional flow reserve to various modalities of stress testing.

Ringqvist I, Fisher LD, Mock M, et al. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). *J Clin Invest.* 1983;71:1854–1866.

Reviewed prognosis based on the extent of CAD.

Left and Right Heart Catheterization

Allison G. Dupont, Mark E. Boulware, and George A. Stouffer

10

Heart catheterization involves placing a catheter into a cardiac chamber. The primary purpose is generally to obtain hemodynamic information, although other useful information can be gained through catheterization of the atria or ventricles including a measurement of systolic function (e.g., ventriculography can provide important information on left ventricular [LV] function) and detection of abnormal intracardiac connections. Heart catheterization is distinct from coronary angiography in which a catheter is placed in the coronary ostia (and thus external to the heart), although the two procedures provide complementary information and typically are performed as a single procedure.

RIGHT HEART AND PULMONARY ARTERY CATHETERIZATION

The pulmonary artery (PA) catheter (also known as the *Swan-Ganz catheter* or *right heart catheter*) was developed in the 1970s by Dr. Harold Swan, Dr. William Ganz, and colleagues. When a PA catheter is properly placed with its distal tip in a PA, the proximal port that is approximately 30 cm from the catheter's tip generally lies in the right atrium (RA). This port can be used to transduce pressure or as central access for infusion of fluids or intravenous medications. The port at the distal tip of the catheter is used to measure PA pressure and pulmonary capillary wedge pressure (PCWP). An inflatable balloon present at the distal end of the PA catheter makes it possible for the catheter to temporarily occlude the PA and for the distal port to measure the pressure distal to the catheter. This pulmonary venous pressure, in most cases, reflects the pressure in the left atrium (LA) and the LV diastolic pressure. A thermistor at the distal tip makes it possible to measure the change in temperature of fluid injected into the proximal port of the PA catheter and to calculate cardiac output (CO), as will be described in more detail. Thus, placement of a PA catheter makes it possible to obtain information on cardiac function, including ventricular preload (RA pressure is a reflection of right ventricular [RV] preload and PCWP is a function of LV preload), afterload (systemic vascular resistance [SVR] and pulmonary vascular resistance [PVR]), and CO.

PA catheters are used primarily in three different settings: in the cardiac catheterization laboratory, in intensive care units (ICUs) and in the operating room. PA catheters are used in the cardiac catheterization laboratory in patients for whom detailed hemodynamic information is needed. Examples include patients with valvular heart disease, cardiomyopathy, and suspected intracardiac shunts. For patients with dyspnea and low CO syndromes in whom the relative contributions of systolic and diastolic function are unknown or in whom the differential diagnosis includes restrictive cardiomyopathy and pericardial constriction, right heart catheterization performed concurrently with left heart catheterization is invaluable because patients with pericardial constriction can improve dramatically with pericardiectomy (see Chapters 20, 42, and 43). There is no consensus on which patients need right heart catheterization, and even in a single catheterization laboratory there may be wide practice variation in which patients undergo right heart catheterization.

It is generally accepted that right heart catheterization can be useful for diagnosis. A separate but related question is whether it is beneficial to make clinical management decisions over hours, days, or weeks using information obtained from an indwelling PA catheter. Several randomized studies have addressed this issue for operative patients and patients in an ICU setting. These studies, which have enrolled patients with heart failure, patients undergoing high-risk noncardiac surgery, and patients with acute respiratory distress syndrome, have shown no beneficial effects of using PA catheter–derived hemodynamic information as a basis for ongoing clinical management decision making. Indeed, there has been no improvement in survival rates and an increased rate of complications in patients randomized to PA catheter–based therapeutic decisions. These studies have been criticized for several reasons, including improper patient selection (e.g., including low-risk patients who would not be expected to benefit), study design (e.g., expecting a monitoring tool to affect outcomes without specified treatment protocols), and the use of variably experienced physicians for both catheter placement and interpretation of data. Therefore, there is no clear consensus on whether PA catheters are beneficial or harmful for ongoing management in the operating room or in the ICU setting. That said, it is clear that in certain clinical settings, important initial diagnoses can be made and/or confirmed with the use of a PA catheter, as described below.

Indications for Right Heart Catheterization

Box 10-1 lists some common indications for PA catheter insertion. As with any invasive procedure, the risks and benefits should be weighed for the individual patient, and a PA catheter should be inserted only if there is a specific question that will be answered with respect to making a diagnosis and/or guiding treatment. For instance, a PA catheter may be used to determine the cause of shock in a hypotensive patient in whom the cause is not evident based on signs, symptoms, and noninvasive testing. Guidelines and consensus statements on indications for PA catheter placement and use have been formulated by numerous groups, including the American Society of Anesthesiologists, an expert panel of the European Society of Intensive Care Medicine, the American College of Chest Physicians, the American Thoracic Society, the American College of Cardiology, the Society of Critical Care Medicine, and a 1998 workshop convened by the U.S. Food and Drug Administration. The reader is referred to these documents for information on the use of PA catheters in specific indications.

Box 10-1 Common Indications for Right Heart Catheterization

- Determination of the cause of shock (vasodilatory vs. cardiogenic vs. hypovolemic)
- Management of cardiogenic shock following acute myocardial infarction
- Diagnosis and management of mechanical complications following acute myocardial infarction
- Diagnosis of pulmonary hypertension
- Determination of reversibility of pulmonary hypertension by vasodilator challenge
- Diagnosis of restrictive cardiomyopathy
- Diagnosis and treatment of congestive heart failure
- Hemodynamic monitoring in certain high-risk patients undergoing peripheral vascular, aortic, or cardiac surgery
- Determination of the cause of pulmonary edema (cardiogenic vs. noncardiogenic)
- Diagnosis and prognostic information in patients with valvular heart disease
- During the evaluation for heart, lung, or liver transplantation, since irreversible pulmonary hypertension provides information on potential benefit and risk of transplantation
- Diagnosis of constrictive pericarditis
- Diagnosis and localization of intracardiac shunts
- Determination of the hemodynamic significance of a pericardial effusion
- Quantification of LV preload
- Diagnosis of RV ischemia during myocardial infarction

LV, left ventricular; RV, right ventricular.

Contraindications to and Complications of Right Heart Catheterization

PA catheter placement is absolutely contraindicated in a small number of circumstances. Physicians who use PA catheters must be familiar with these clinical settings. A PA catheter should not be placed in a patient with a mechanical prosthetic tricuspid or pulmonic valve, because the catheter can become entrapped within the valve apparatus. Patients with right-sided endocarditis, intracardiac tumor, or thrombus also should not undergo PA catheterization. Finally, patients with a terminal illness in whom invasive measures will not affect outcome should not have this intervention.

Three categories of potential complications are associated with the use of PA catheters: (1) complications associated with central venous access (e.g., bleeding, infection, and pneumothorax); (2) catheter-associated complications; and (3) misinterpretation of the acquired data.

Although venous access complications strictly related to PA catheter placement are not any different from those associated with any procedure that involves percutaneous access of central veins, there are numerous other complications specific for PA catheter placement. One important category is related to the potential to induce either or both atrial and ventricular arrhythmias or heart block as the PA catheter is advanced through the right-sided cardiac chambers. These rhythm disturbances are usually self-limited and rarely require treatment other than changing the catheter's position. As the PA catheter crosses the tricuspid valve, it can cause trauma to the right bundle, leading to right bundle branch block, which is usually transient. This is typically inconsequential unless the patient has a preexisting left bundle branch block. In such a patient, the PA catheter–induced right bundle branch block can then lead to transient complete heart block. For this reason, in patients with a left bundle branch block, temporary pacing capabilities should be readily available in the event that complete heart block occurs.

PA catheters can also cause direct damage to the tricuspid or pulmonic valve and/or increase the risk of endocarditis involving either of these valves. An indwelling PA catheter can also be a nidus for thrombus formation, leading to an increased risk of pulmonary embolus and infarction. Pulmonary infarction can also occur from prolonged inflation of the balloon within a branch of the PA. The complication with the highest mortality rate is rupture of a PA due to either overinflation of the balloon at the distal tip of the PA catheter or repeated trauma to the PA. PA rupture is fatal in approximately 50% of cases. This complication, while rare, occurs most commonly in patients with PA hypertension. Other factors increasing the risk of PA rupture include advanced age, female sex, and frequent wedging of the balloon.

Data Obtained from Right Heart Catheterization

Right heart catheterization provides precise and detailed hemodynamic information that often cannot otherwise be obtained (Table 10-1). These data include direct measurements and calculations based upon those measurements. The pressures in the venae cavae, RA, RV, PA, and the pulmonary capillary wedge position (which is an estimation of LA pressure and LV diastolic pressure when there is no obstruction between the LA and LV) can all be directly measured using a PA catheter. CO can be calculated by either of two methods: thermodilution or the Fick method. To calculate CO by the thermodilution method, a substance cooler than blood (typically room temperature saline) is injected through the proximal port of the PA catheter. As the injected substance passes through the PA, the blood temperature decreases, and this change is measured by the thermistor at the distal tip. The change in the temperature over time is used to calculate the CO. The Fick principle, first described by Adolph Fick in 1870, states that the total uptake or release of a substance by an organ is the product of blood flow to that organ and the arteriovenous concentration of the substance. Using this principle, pulmonary blood flow can be determined using the arteriovenous difference of oxygen across the lungs and the oxygen consumption. Oxygen consumption can be assumed, but a more accurate measure of CO requires measurement of oxygen consumption. Direct measurement of oxygen consumption can be done using either a Water's hood or a metabolic cart. In comparing cardiac performance among patients of various sizes, it is useful to calculate the cardiac index (CI). CI is simply the CO divided by the body surface area (BSA):

$$CI = CO/BSA$$

SVR is a measure of afterload and can be calculated using data obtained from right heart catheterization. The equation for SVR is as follows:

Table 10-1 Hemodynamic Findings in Specific Clinical Scenarios

Clinical Situation	Catheterization Findings
Vasodilatory shock	Elevated CO, decreased SVR, decreased PCWP
Cardiogenic shock	Decreased CO, increased SVR, increased PCWP
Mitral stenosis	Increased LA pressure (PCWP) with a gradient between the LA (PCWP) and the LV (LVEDP) that persists throughout diastole, increased right heart pressures at rest and/or with exercise, prominent *a* wave on RA tracing, decreased slope of y descent
Mitral regurgitation	*Acute MR:* elevated PCWP, elevated PA pressure, prominent V wave, hyperdynamic LV function; hemodynamics can mimic constrictive pericarditis, may have hypotension/shock *Chronic, compensated MR:* normal to mildly elevated right heart pressures, V wave less prominent, normal EF *Chronic, decompensated MR:* elevated PCWP, elevated PA pressure, elevated right heart pressures, decreased EF
Restrictive cardiomyopathy	PA systolic pressure may be >50 mm Hg, RV/LV systolic pressure concordant, RVEDP/LVEDP separation >5 mm Hg, RVEDP/RV systolic pressure <⅓, dip and plateau in RV pressure, Kussmaul's sign absent
Constrictive pericarditis	Elevated RA pressure, elevated PCWP, PA systolic pressure usually <50 mm Hg, RV/LV systolic pressure discordant, RVEDP/LVEDP separation <5 mm Hg, RVEDP/RV systolic pressure >⅓, dip and plateau in RV pressure, Kussmaul's sign present
Cardiac tamponade	Elevated diastolic pressures and equalization of end-diastolic pressures, x descent preserved or prominent and y descent small or absent on RA pressure tracing, no dip and plateau on RV pressure tracing, pulsus paradoxus
Dilated cardiomyopathy	Right and left heart filling pressures typically elevated, decreased CO and index, decreased mixed venous oxygen saturation, pulsus alternans (beat-to-beat variation in systolic pressure)
Hypertrophic obstructive cardiomyopathy	Spike and dome arterial pulse, systolic intraventricular pressure gradient, elevated LVEDP, Brockenbrough's sign (aortic pulse pressure does not increase after PVC)
Aortic stenosis	Pressure gradient between the LV and aorta, elevated LVEDP, elevated PCWP, elevated PA pressures as resultant heart failure progresses, LV/aortic gradient decreases with reduction in preload, and pulse pressure increases after a PVC (negative Brockenbrough's sign), Carabello's sign (a rise in peak aortic systolic pressure by >5 mm Hg when a catheter is removed from the LV) in severe aortic stenosis
Aortic insufficiency	Wide pulse pressure, low diastolic pressure, elevated LVEDP; in severe aortic insufficiency, the LV and aortic pressures will be equal at the end of diastole and there will be premature closure of the mitral valve during diastole.

CO, cardiac output; EF, ejection fraction; LA, left atrium (atrial); LV, left ventricle (ventricular); LVEDP, left ventricular end-diastolic pressure; MR, mitral regurgitation; PA, pulmonary artery (arterial); PCWP, pulmonary capillary wedge pressure; PVC, premature ventricular contraction; RA, right atrium (atrial); RV, right ventricle (ventricular); RVEDP, right ventricular end-diastolic pressure; SVR, systemic vascular resistance.

$$SVR = (MAP - CVP)/(CO \times 80)$$

where MAP is mean arterial pressure, CVP is central venous pressure, CO is cardiac output, and 80 is a correction factor to convert units for SVR to dynes/s/cm^5. The PVR can be calculated in a manner similar to the SVR substituting (mean PA pressure – PCWP) in place of (MAP – CVP) in the above equation. The PVR is sometimes reported in Wood units as opposed to dynes/s/cm^5. In this case, one uses the same equation without the conversion factor of 80.

LEFT HEART CATHETERIZATION

Left heart catheterization is performed by advancing a catheter across the aortic valve into the LV. Left heart catheterization allows for measurement of the LV systolic and diastolic pressures and LV end-diastolic pressure. If left and right heart catheterization are done simultaneously, this can provide hemodynamic data useful in various disorders, including valvular diseases, cardiomyopathy (dilated, restrictive, or hypertrophic), and constrictive pericarditis (see Table 10-1).

Left ventriculography, performed by injection of contrast medium, provides valuable information including ejection fraction (Fig. 10-1), examination of all walls of the LV to ascertain whether wall motion is normal throughout, measurement of the presence and severity of mitral valve regurgitation (Fig. 10-2A), and determination of whether interventricular connections (e.g., ventricular septal defect; Fig. 10-2B) exist. By convention, mitral valve regurgitation is quantified by observing the degree of opacification of the LA relative to the LV. Mitral regurgitation is graded as follows:

- 1+: Contrast does not opacify the entire LA and clears with every heartbeat.
- 2+: The entire LA is faintly opacified to a degree less than that of the LV after several beats, and it is not cleared by a single beat.
- 3+: The LA is completely opacified, and the degree of opacification equals that of the LV.
- 4+: The LA is completely opacified in a single beat, and the opacification increases with each beat. In addition, in 4+ mitral regurgitation, contrast can be seen filling the pulmonary veins.

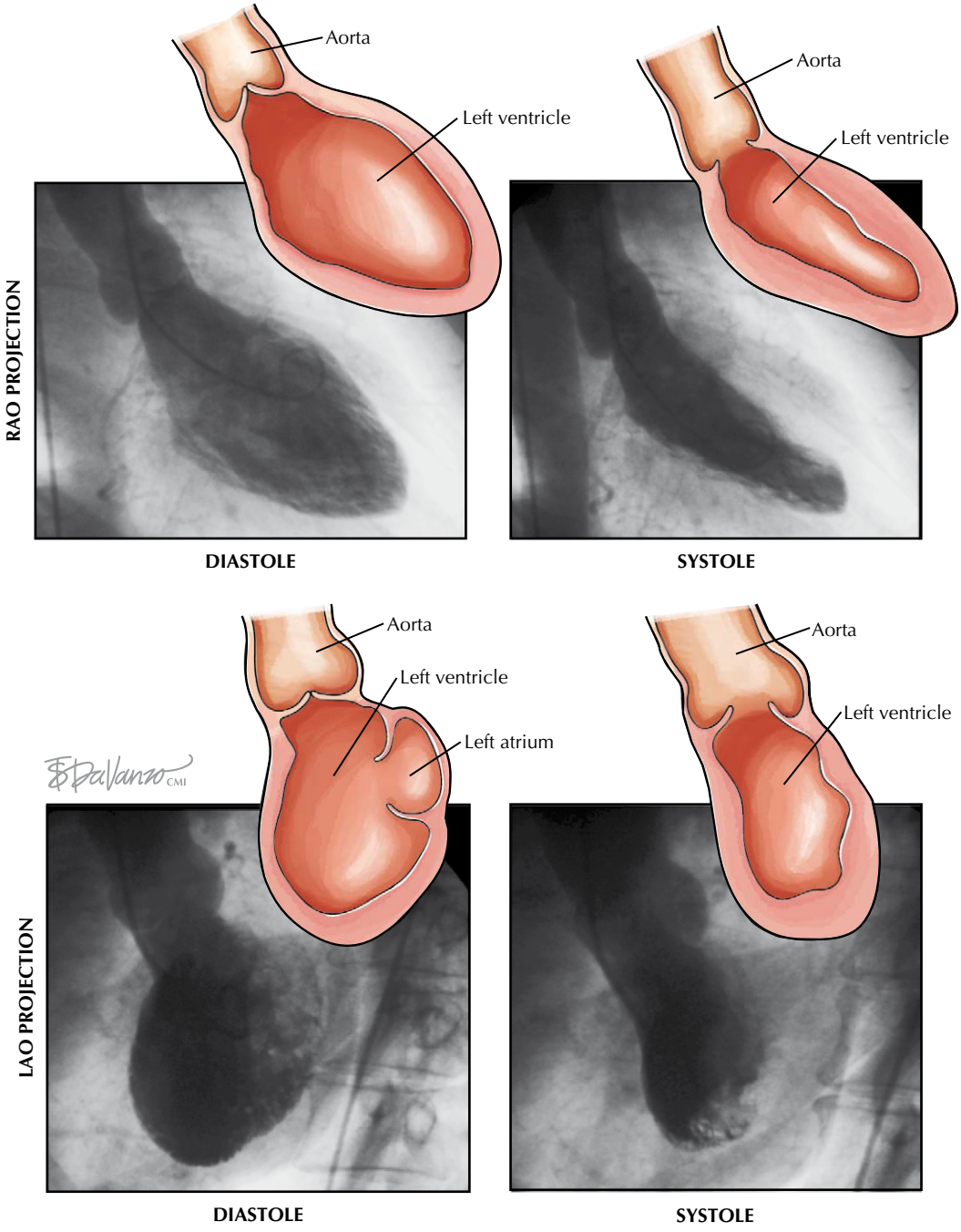


Figure 10-1 *Measurement of left ventricular function using ventriculography.* LAO, left anterior oblique; RAO, right anterior oblique.

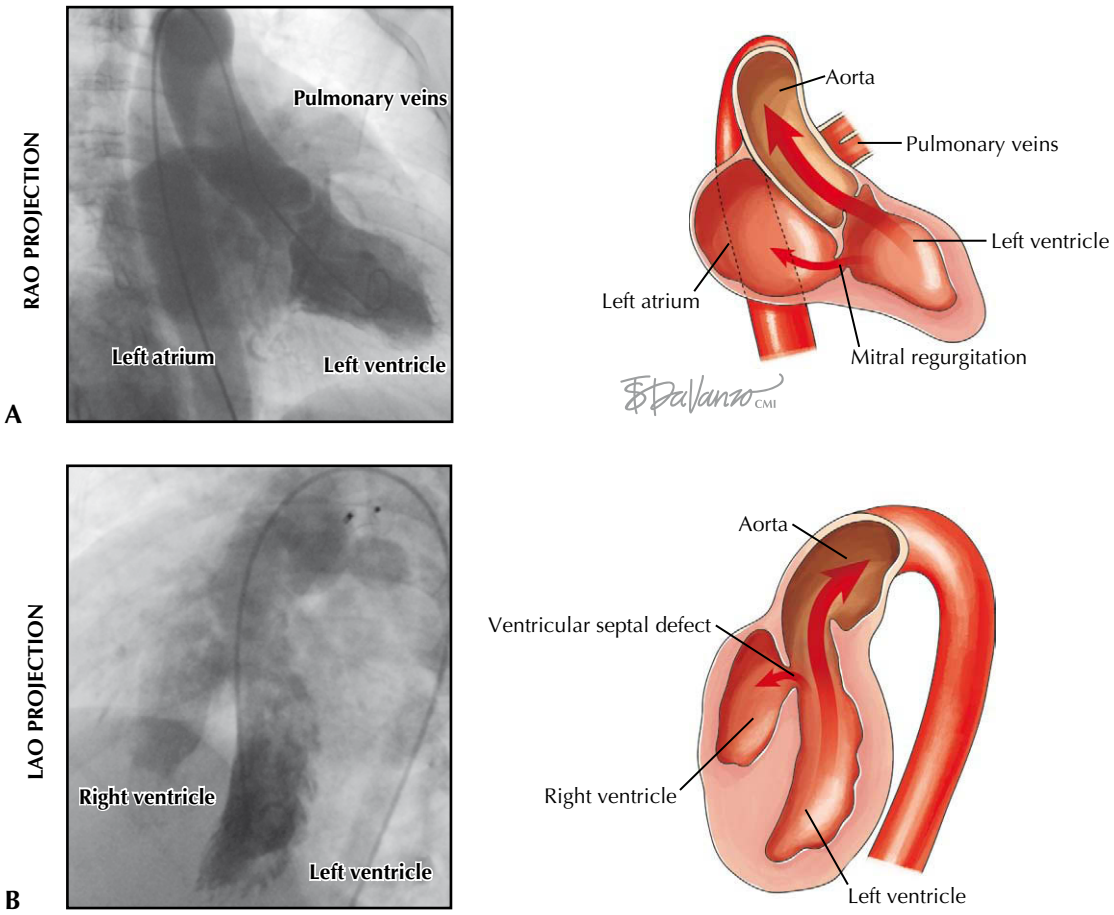


Figure 10-2 (**A**) Contrast injection into the left ventricle in a patient with severe mitral regurgitation (right anterior oblique projection; note opacification of the left atrium and pulmonary veins). (**B**) Contrast injection into the left ventricle in a patient with a ventricular septal defect (left anterior oblique projection; note that the right ventricle is opacified). LAO, left anterior oblique; RAO, right anterior oblique.

Left heart catheterization is also useful in determining whether a LV outflow tract pressure gradient is present and the etiology of this gradient. A difference in pressure between the LV apex and the aorta can be caused by a fixed obstruction at the subvalvular, valvular, or supravalvular level or because of dynamic obstruction of the aortic outflow tract in patients with features of hypertrophic obstructive cardiomyopathy (Fig. 10-3). A pressure gradient can be measured by several methods, including (a) a "pullback" across the aortic valve in which a catheter is slowly retracted from the LV into the aorta, (b) simultaneous LV and femoral arterial pressure (used as a surrogate for aortic pressure), and (c) use of a dual-lumen catheter with one lumen in the ventricle and the other recording the pressure measured from the aorta. In all of these techniques, the location of the obstruction can be estimated by slowly retracting an end-hole catheter from the LV apex and noting where the pressure decreases. Dynamic LV outflow tract obstruction—as can occur in the setting of massive septal hypertrophy with or without systolic anterior motion of the mitral valve—can be provoked using various maneuvers that decrease either preload and/or afterload (e.g., Valsalva maneuver or administration of amyl nitrate), or that increase contractility (e.g., isoproterenol infusion or inducing a premature ventricular contraction).

FUTURE DIRECTIONS

Right and left heart catheterizations have been used in the diagnosis of heart disease for more than 50 years. Over this time period the techniques and equipment have advanced to the point where it is a safe and effective procedure that is commonly used in cardiac catheterization laboratories around the world. Current research efforts are focused on obtaining a better understanding of the natural history of hemodynamic changes within the heart in patients with congenital, valvular, and cardiomyopathic conditions and in developing devices to treat structural heart disease. Examples of devices under development or in clinical use include percutaneous valves (aortic, mitral, and pulmonic), septal defect occluders (for atrial septal defects, patent foramen ovale, and ventricular septal defects), atrial appendage occluders (to reduce the risk of thromboembolism in patients with atrial fibrillation), and advanced intracardiac imaging devices (e.g., intracardiac echocardiography).

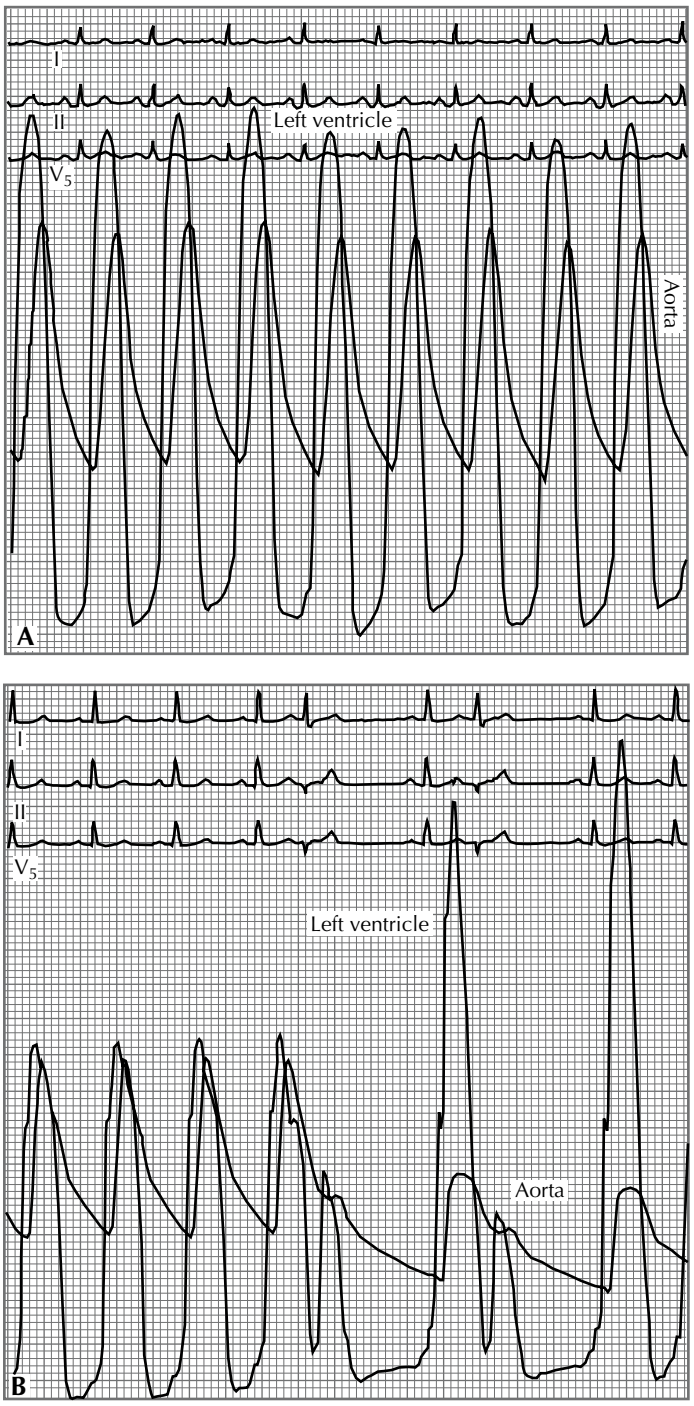


Figure 10-3 Simultaneous pressure tracings from the left ventricular apex and aorta in aortic stenosis (**A**) and hypertrophic obstructive cardiomyopathy (**B**). In this patient with aortic stenosis, there is an approximate 40 mm Hg pressure change across the aortic valve. In the patient with hypertrophic obstructive cardiomyopathy, there is minimal pressure difference under basal conditions but left ventricular pressure exceeds aortic pressure by >100 mm Hg after a premature ventricular contraction.

ADDITIONAL RESOURCE

American Heart Association. Cardiac Catheterization. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=4491>; Accessed 22.02.10.

Information on cardiac catheterization for patients and health care providers.

EVIDENCE

American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization Practice guidelines for pulmonary artery catheterization: an updated report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. *Anesthesiology.* 2003;99:988–1014.

Anon. Pulmonary Artery Catheter Consensus conference: consensus statement. *Crit Care Med.* 1997;25:910–925.

Bernard GR, Sopko G, Cerra F, et al. Pulmonary artery catheterization and clinical outcomes: National Heart, Lung, and Blood Institute and Food and Drug Administration Workshop Report. Consensus Statement. *JAMA.* 2000;283:2568–2572.

Mueller HS, Chatterjee K, Davis KB, et al. ACC expert consensus document. Present use of bedside right heart catheterization in patients with cardiac disease. American College of Cardiology. *J Am Coll Cardiol.* 1998;32:840–864.

Listed above are guidelines and consensus statements from various professional organizations and expert panels regarding the use of PA catheters.

Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA.* 2005;294:1664–1670.

A meta-analysis of studies looking at clinical outcomes in patients undergoing right heart catheterization.

Stouffer GA, ed. *Cardiovascular Hemodynamics for the Clinician.* London: Blackwell Publishing; 2007.

Provides an overview of normal cardiovascular hemodynamics and the hemodynamic changes found in various disorders including valvular, congenital, myopathic, and ischemic heart disease.

Swan HJ, Ganz W, Forrester J, et al. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med.* 1970;283:447–451.

The original description of the balloon-tipped right heart catheter.

Identifying the Patient at High Risk for Acute Coronary Syndrome: Plaque Rupture and "Immediate Risk"

11

John Paul Vavalle and Marschall S. Runge

Coronary heart disease, the clinical manifestation of coronary artery disease (CAD), is the number one killer of adults in the world and is estimated to retain this position over the next decade. In the United States alone, CAD is very prevalent. It has been estimated that as many as 100 million Americans have CAD. Among these, many have coronary heart disease, and there are approximately 12 million new cardiac events in the United States per year in individuals with CAD. Although many of those who die of coronary heart disease had been previously evaluated and treated, more than one half of patients with sudden cardiac death had no known history of coronary heart disease. Identifying such an individual involves determining the risk that an individual will have a cardiac event in the ensuing days or weeks—that is, determining the "immediate risk" of a cardiac event. Development of approaches to assign immediate risk is an area of extensive research.

It is, however, a daunting challenge, because there are no ideal screening tests to reliably define this population. A large portion of these individuals have coronary artery stenoses of less than 50% in transluminal disease, making detection by stress testing difficult. Furthermore, no reliable diagnostic tests exist to ascertain the risk of plaque rupture at a given site in a given individual.

Generally, screening strategies for coronary heart disease seek to identify those at risk before symptoms develop and lessen the burden of ischemic heart disease. Unfortunately, identifying the appropriate population to screen is difficult, and screening the entire population of individuals with CAD would be neither useful nor cost-effective. Without question, as medical technology and understanding of coronary disease expands—and concurrently national attention focuses more and more on the cost efficiency of health care—decisions about whom and how to screen will only become more complex. With a more detailed understanding of the cellular and molecular components of atherosclerosis and acute coronary syndrome, there is hope that novel screening tools with improved accuracy and specificity will be developed. This chapter focuses on the state of the art in detection of individuals at high risk and the promise for the future.

ETIOLOGY AND PATHOGENESIS

The earliest evidence of CAD is present in many Americans during late adolescence, based on autopsy studies. Clinically detectable CAD develops over decades, often silently. Multiple risk factors contribute to the development of atherosclerosis: hypertension, diabetes mellitus, smoking, age, and hyperlipidemia (Fig. 11-1). Acute coronary syndromes occur following rupture of an atherosclerotic plaque and the development of a subocclusive or totally occlusive thrombus that may lead to unstable angina or acute myocardial infarction. Many triggers for plaque rupture have been proposed, ranging from hemodynamic stress to the presence of a generalized inflammatory state to neurohormonal influences. However, the precise factors that lead to the rupture of specific plaques in a given individual have yet to be defined.

The principal problem with current methods of screening for CAD is that the majority of plaques that rupture and cause acute coronary syndrome are less than 70% in transluminal diameter and do not cause hemodynamically significant coronary obstruction until they rupture (Fig. 11-2). Thus, they are very difficult to detect with screening mechanisms that rely on reduced distal blood flow to cause changes detectable by the test (e.g., ischemic ECG changes, hypocontractility on echocardiogram, perfusion defects on nuclear scans). In fact, what many of these tests detect are narrowed, hemodynamically significant lesions that are stable and not prone to rupturing or causing acute coronary syndrome. Therefore, newer techniques to identify the vulnerable plaque prone to rupture are the focus of much research.

CLINICAL PRESENTATION

Because only approximately 20% of acute coronary events are heralded by long-standing angina, the majority of patients are asymptomatic until their major cardiac event. In theory, identifying the immediate risk of asymptomatic patients at highest risk for CAD might allow risk reduction before their event.

There are many reasons why screening for CAD has become common clinical practice, ranging from better education of the public about the dangers of CAD (resulting in more patient-initiated requests for screening) to the possibility that a noninvasive assessment will preclude a need for cardiac catheterization. In addition, physicians are eager to detect early coronary disease in their patients deemed to be at risk, so that they may intervene before the onset of symptoms or a major cardiac event (Fig. 11-3).

An important group of patients who present for CAD screening are those who wish to be "cleared" to begin an exercise program. This has become standard for many structured-exercise programs. However, little evidence supports this as common clinical practice. Additionally, for the reasons described, potentially dangerous but hemodynamically

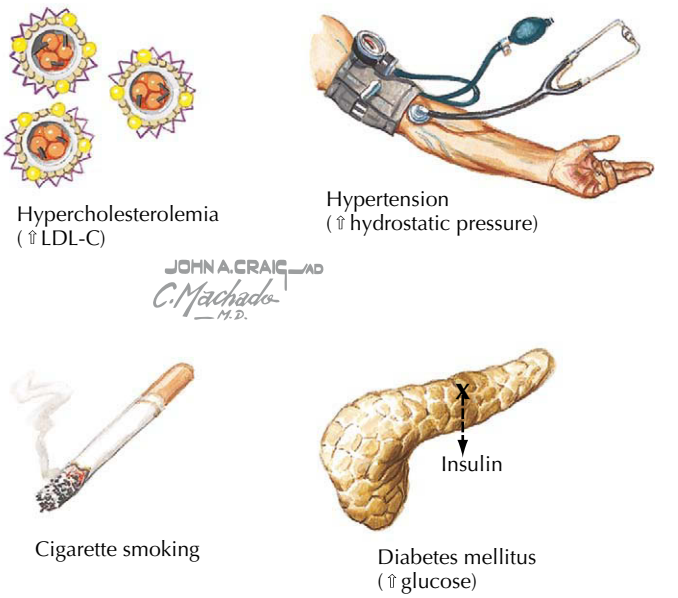


Figure 11-1 *Risk factors in coronary heart disease.* LDL-C, low-density lipoprotein cholesterol.

insignificant coronary artery lesions are not detected by standard stress or stress-imaging studies.

DIAGNOSTIC APPROACH

Clinical Epidemiology

The basic idea behind screening is that earlier detection may lead to earlier and more robust implementation of preventive strategies and better health outcomes. However, this is only true if applied to the appropriate populations that should be screened. This concept is essential to understand, because screening inappropriate populations may actually lead to harm with the inherent risks of some tests and false-positive results.

It is important to understand Bayes' theorem as it applies to medical screening tests. The post-test probability of CAD depends on the pre-test probability of disease and the sensitivity and specificity of the test being used. Testing at very low or very high pre-test probabilities may not actually change clinical decision making (see Chapter 1). In particular, for screening asymptomatic patients for CAD, patients with a very low pre-test probability are more likely to have a false-positive test result than a true-positive test result, especially if the test's specificity is poor.

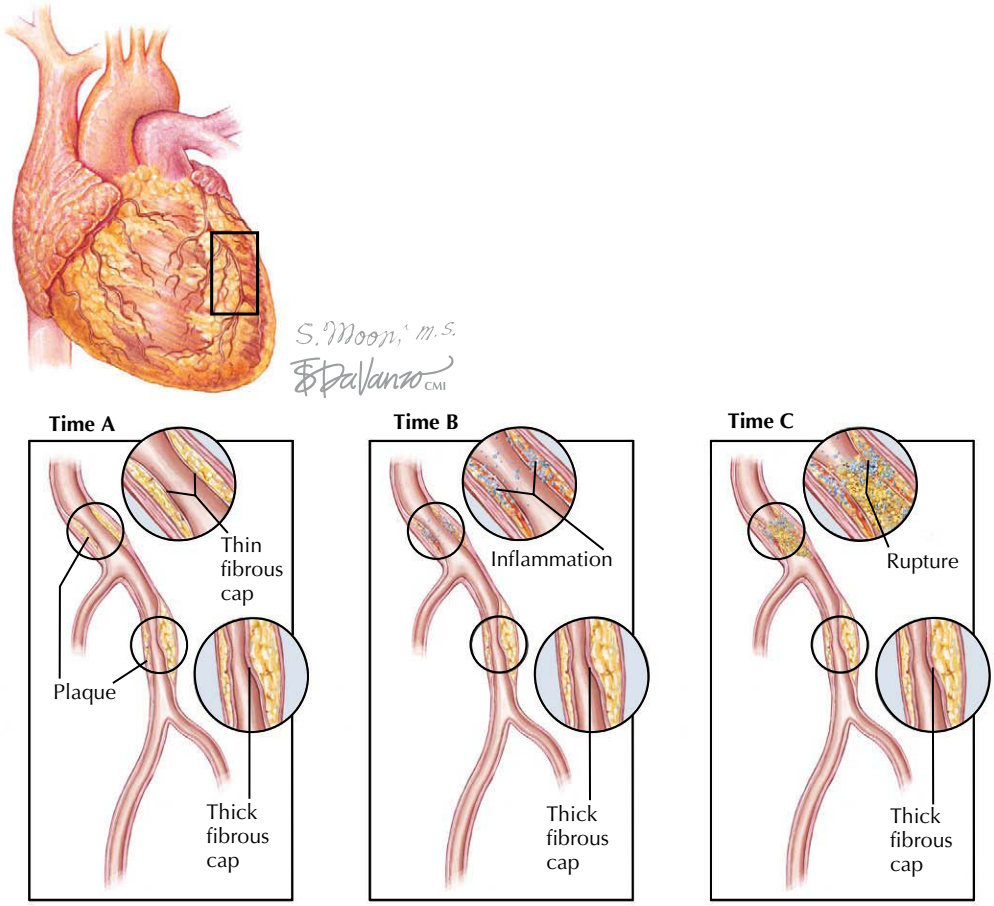


Figure 11-2 *Steps in the progression of a stable plaque (Time A) to an unstable/ruptured plaque (Time C) are shown.*

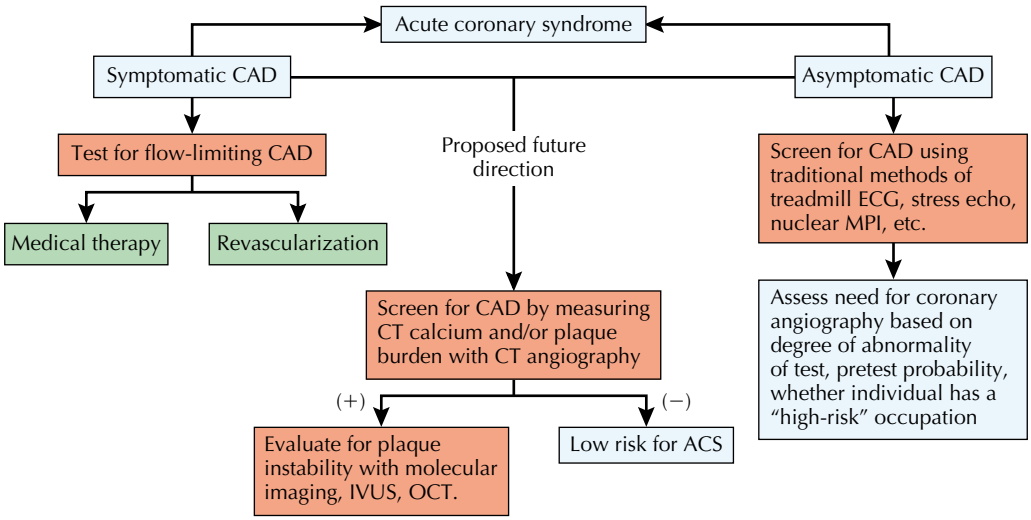


Figure 11-3 *Algorithm for differential diagnosis of acute coronary syndrome (ACS).* CAD, coronary artery disease; IVUS, intravascular ultrasound; MPI, myocardial perfusion imaging; OCT, optical coherence tomography.

Risk Scores

FRAMINGHAM RISK SCORE

There are many well-established risk factors for the development of CAD: age, smoking, hyperlipidemia, hypertension, male sex, diabetes, obesity, and physical inactivity, among others. Epidemiologic studies have allowed researchers to develop risk prediction calculators that determine the risk of coronary heart disease events based on the presence of these risk factors. One of the more commonly used risk calculators is based on the Framingham population. It provides an estimate of the 10-year risk of a cardiac event (see "National Cholesterol Education Program. Risk Assessment Tool for Estimating 10-Year Risk of Developing Hard CHD," under "Additional Resources").

Risk calculators such as the Framingham risk calculator can be used to group individuals into low-, medium-, or high-risk groups. Supplemental screening tests, as described below, may be used to further define future risk of CAD. While those in the high-risk group are most likely to have severe CAD, until it is possible to assess the potential for plaque rupture, screening these patients and uncovering CAD (see next section) while it is still asymptomatic may be of only limited benefit, since revascularization in asymptomatic patients does not confer the overall benefit of revascularization in symptomatic patients.

Screening Tests

Screening tests for CAD are used for many reasons: to diagnose CAD sufficient to cause myocardial ischemia in individuals (and who would benefit from revascularization), to determine if an individual is at high risk for vigorous activities or high-risk surgical procedures, or to determine whether known CAD in a patient with or without symptoms has progressed to a point requiring revascularization. Unfortunately, for the reasons discussed below, most conventional screening tests are not particularly effective for predicting the risk of plaque rupture in an asymptomatic or low-risk patient.

ELECTROCARDIOGRAPHY—RESTING ECG

The sensitivity of resting ECGs to detect CAD is low, yet resting-ECG abnormalities such as Q waves, ST-segment depression, bundle branch blocks, and left ventricular hypertrophy are indeed associated with worse outcomes. However, many people with normal coronary arteries have ECG changes, and a significant number of patients with CAD have normal ECGs. Furthermore, in patients who have a cardiac event who had an ECG in the year before that event, in the majority of instances the baseline resting ECG was normal.

EXERCISE TESTING—EXERCISE ECG

Exercise-ECG testing has been widely adopted for screening for CAD in asymptomatic adults. Adding exercise to ECG monitoring increases the sensitivity of the test by unmasking ischemia not detectable at rest. A positive test is reflected by at least 1 mm of flat or down-sloping ST depression. Exercise-ECG testing can only be performed in those who can exercise and do not have underlying ECG abnormalities at rest that would prevent interpretation (left bundle branch block, ST depression at rest, or a paced ventricular rhythm) (Fig. 11-4).

The Duke Treadmill Score is the most widely used validated treadmill score. Assessment of exercise time, millimeters of ST depression, and the presence or absence of angina provides a quantitative score that can be used to stratify patients into low-, moderate-, or high-risk groups. Importantly, in the development of the Duke Treadmill Score, asymptomatic patients were excluded. Thus, it is not appropriate to apply a Duke Treadmill Score to screening in asymptomatic patients.

Unfortunately, the sensitivity of exercise treadmill testing for the prediction of coronary heart disease events over the ensuing

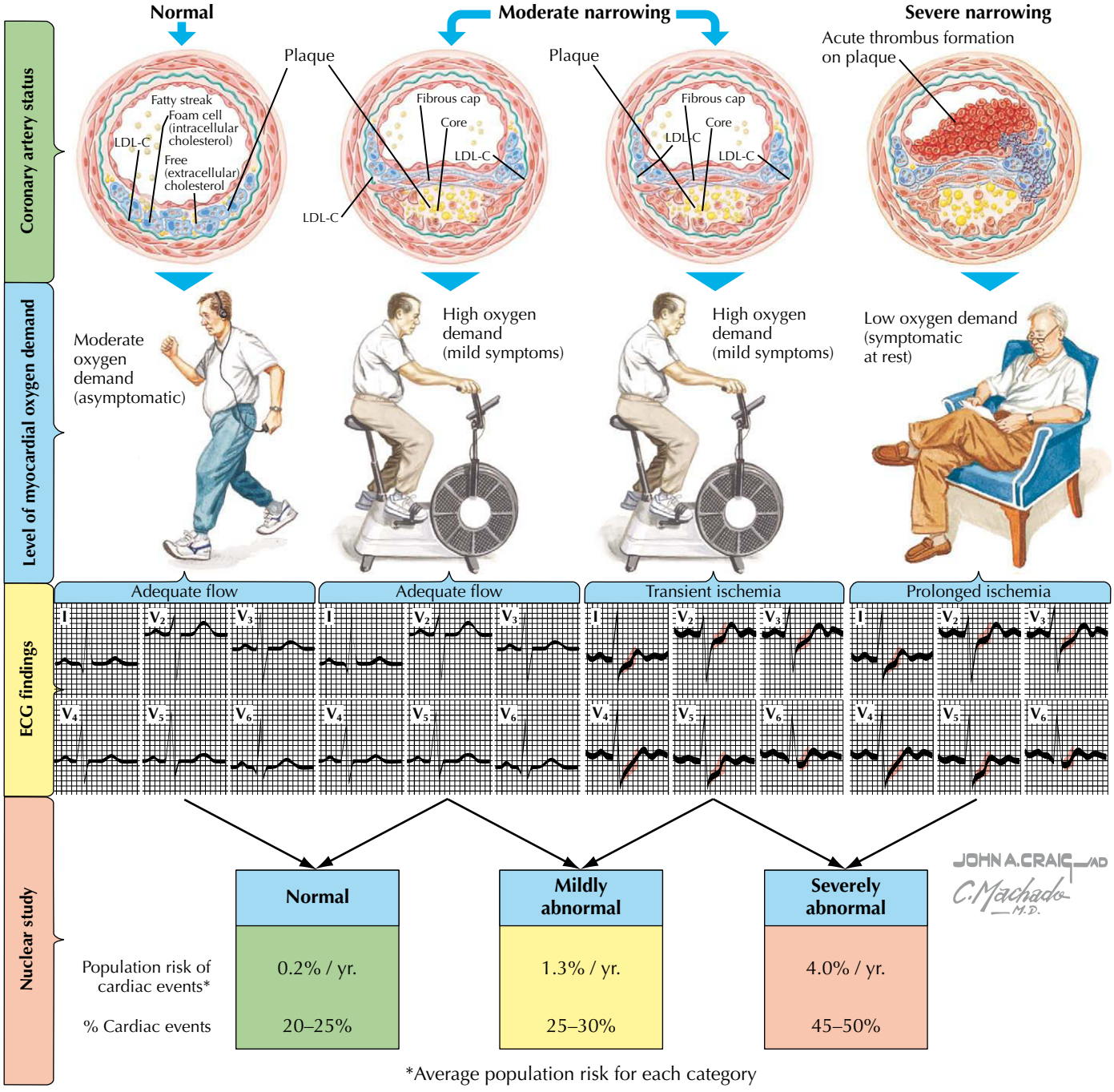


Figure 11-4 *The degrees of flow-limiting atherosclerosis and plaque rupture.* ECG, electrocardiogram; LDL, low-density lipoprotein cholesterol.

years is moderate. The ability of this test to detect severe CAD in middle-aged asymptomatic men is low. The majority of asymptomatic patients with an abnormal exercise stress test do not go on to have coronary heart disease events, and it is arguable whether there is a benefit to low- to medium-risk asymptomatic patients who undergo exercise stress testing. In studies of asymptomatic patients without risk factors, a positive result on exercise tolerance testing provided little additional predictive value. In contrast, the predictive value of exercise testing increases when the test is applied to those at higher risk who have a higher pre-test probability for disease.

Authors of a systematic review of the evidence for exercise tolerance testing to screen for CAD, performed for the U.S. Preventative Services Task Force, concluded that testing asymptomatic persons rarely detects previously unrecognized, clinically important coronary artery obstruction but does provide some additional prognostic information beyond that provided by traditional risk factors. However, the effect of this

additional information on preventive or therapeutic strategies has not been studied.

As with other screening approaches, a major limitation of exercise stress testing is that ST-segment depression detects ischemia from obstructed coronary arteries while the majority of acute coronary events occur from the rupture and sudden occlusion of a previously nonobstructive plaque.

STRESS ECHOCARDIOGRAPHY

Echocardiographic imaging can be added to stress-ECG testing to improve both sensitivity and specificity. In this test, two-dimensional echocardiography is used to visualize regional wall motion abnormalities of hypocontractility that suggest ischemia. In addition to exercise stress, for individuals who cannot exercise, a pharmacologic stress agent such as dobutamine can be used as a means to increase heart rate and contractility. In patients who can exercise, however, a treadmill or bicycle exercise stress test is preferred over chemical stress.

An advantage of adding echocardiography is that it provides information on left ventricular and valvular function. The advantages over nuclear imaging include lower cost, avoidance of radiation exposure, and ease of testing. There are limited data on the use of this test to screen for CAD in the asymptomatic population.

NUCLEAR IMAGING

Radionuclide myocardial perfusion imaging, like stress echocardiography, also demonstrates better sensitivity and specificity than exercise-ECG for the detection of CAD. This test uses a radiolabeled tracer that is taken up preferentially by viable, nonischemic myocardium. Quantitative and qualitative measurements of uptake help to identify regions of ischemia and infarction that suggest underlying coronary disease. For patients with a low pre-test probability for disease and a normal resting ECG, and who are able to exercise, nuclear stress testing is not recommended as the first test. The expense, radiation exposure, and complexity of performing the study make it a less attractive option as an initial screening test in low-risk patients. Exceptions include individuals with questionable exercise capacity, with abnormal resting ECGs, or who have had equivocal prior stress-ECG testing.

ELECTRON BEAM COMPUTED TOMOGRAPHY

Electron beam computed tomography (ECBT) has gained popularity as a noninvasive screen for CAD risk. EBCT can be used to quantify coronary artery calcification and perform coronary angiography. Numerous studies have demonstrated both positive (with a high calcium score) and negative (with very low calcium scores) correlations with the risk of major adverse cardiac events. Calcium deposition in the walls of coronary arteries occurs early in the process of atherogenesis, and the overall degree of calcification correlates well with the amount of atherosclerosis in an individual as well as the likelihood of underlying ischemia. Individuals with very low calcium scores, especially if asymptomatic, have a very low likelihood of coronary stenosis and a very low risk of major adverse cardiac events. Much of the appeal of EBCT relates to the ease of performing this test, its ready availability, and the prognostic value of the test. Radiation exposure, cost concerns, and the imprecision of its predictive value have all kept it from being widely adapted for screening the general public.

CORONARY ANGIOGRAPHY

Although coronary angiography is the gold standard for detecting and quantifying obstructive CAD (as defined by greater than 50% transluminal narrowing on arteriography), even coronary angiography does not differentiate between vulnerable and stable plaques. Coronary angiography is not recommended as a screening test in asymptomatic patients, since it is invasive, expensive, and inherently risky. Moreover, because stenotic plaques are not necessarily at highest risk for rupture and production of an acute coronary syndrome, the goal of coronary angiography in stable patients is to determine whether revascularization should be performed to reduce symptoms of myocardial ischemia. Rapid advances in noninvasive imaging approaches for quantifying coronary artery lesions include CT and magnetic resonance angiography. It is anticipated that in coming years, with technologic improvements, CT and magnetic resonance angiography may provide images similar to those obtained using invasive coronary angiography.

MANAGEMENT AND THERAPY

Widespread screening for CAD in low-risk, asymptomatic patients is not recommended based on the evidence and technology available today. Individuals with diabetes or multiple risk factors should not be considered low-risk and may merit screening for CAD, and some individuals in "high-risk" occupations (professional airline pilots, bus drivers, etc.) merit regular screening for CAD. The American College of Cardiology (ACC), American Heart Association (AHA), and United States Preventive Service Task Force (USPSTF) have published updated guidelines of the best available evidence combined with expert opinion regarding the appropriate use of cardiovascular screening tests.

Optimum Treatment

The ACC and AHA have released guidelines on the use of exercise testing in asymptomatic patients without known CAD in the ACC/AHA 2002 Guideline Update for Exercise Testing, which use four classes of recommendations (I, IIa, IIb, III). They found no class I recommendations for the use of exercise testing in this population and recommended against routine use of exercise testing to screen for CAD in asymptomatic men and women (Table 11-1). However, they did give a class II recommendation for using exercise stress testing to evaluate asymptomatic patients with diabetes who plan to start a vigorous exercise program and patients with multiple risk factors as a guide to risk reduction therapy. The ACC/AHA guidelines are summarized in Table 11-2.

The USPSTF has also released guidelines for screening using resting ECG, exercise treadmill testing (ETT), or EBCT (Table 11-3). For asymptomatic adults at low risk for coronary

Table 11-1 Exercise Testing in Asymptomatic Persons without Known CAD

Class	Description
I	None
IIa	Evaluation of asymptomatic persons with diabetes mellitus who plan to start vigorous exercise
IIb	Evaluation of persons with multiple risk factors as a guide to risk reduction therapy
IIb	Evaluation of asymptomatic men older than 45 years and women older than 55 years • Who plan to start vigorous exercise • Who are involved in occupations in which impairment might impact public safety • Who are at high risk for CAD due to other diseases (peripheral vascular disease, chronic renal failure)
III	Routine screening of asymptomatic men or women

CAD, coronary artery disease.
Adapted from ACC/AHA 2002 Guideline Update for Exercise Testing. Available at: http://www.acc.org/qualityandscience/clinical/guidelines/exercise/dirindex.htm. Accessed 04.09.08.

Table 11-3 USPSTF Recommendations on Screening for Coronary Heart Disease

Class	Recommendation
D	The USPSTF recommends against routine screening with resting ECG, ETT, or EBCT scanning for coronary calcium for either the presence of severe CAS or the prediction of CHD events in adults at low risk for CHD events.
I	The USPSTF found insufficient evidence to recommend for or against routine screening with ECG, ETT, or EBCT scanning for coronary calcium for either the presence of severe CAS or the prediction of CHD events in adults at increased risk for CHD events.

CAS, coronary artery stenosis; CHD, coronary heart disease; EBCT, electron beam CT; ECG, electrocardiogram; ETT, exercise treadmill test.
Adapted from U.S. Preventive Services Task Force (USPSTF) Screening for CAD. Available at: http://www.ahrq.gov/clinic/uspstf/uspsacad.htm. Accessed 04.09.08.

heart disease, they recommend against routine screening with resting ECG, ETT, or EBCT. For patients at increased risk for coronary heart disease events, the USPSTF found insufficient evidence to recommend for or against routine screening with ECG, ETT, or EBCT for either the presence of severe coronary artery stenosis or the prediction of coronary heart disease events (Table 11-3). Table 11-4 summarizes the categories of recommendation used by the USPSTF.

Avoiding Treatment Errors

One of the most important considerations in screening for cardiovascular diseases is selection of the appropriate test for an individual patient. There are no absolutes in defining the most appropriate population. It is important not to miss an opportunity to identify asymptomatic patients at risk of myocardial infarction in the near term, but it is also important to avoid using a low-specificity test in truly low-risk patients. Thus, the clinician should remember that the pre-test probability of disease is the most important factor in determining the post-test probability of disease to help avoid inappropriate screening of low-risk patients.

From the available evidence and recommendations, it is clear that generalized screening for very low-risk asymptomatic patients is not recommended. Screening these individuals is just as likely, or even more likely, to result in a false-positive finding than a true-positive one. This could lead to unnecessary anxiety, false labeling of disease, and inappropriate use of expensive and invasive tests and procedures. Exceptions include individuals in "high-risk occupations" (such as professional pilots or drivers)

Table 11-2 ACC/AHA Classifications of Practice Guidelines

Class	Description
I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment • IIa: Weight of evidence/opinion is in favor of usefulness/efficacy. • IIb: Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

Adapted from American College of Cardiology/American Heart Association (ACC/AHA) 2002 Guideline Update for Exercise Testing. Available at: http://www.acc.org/qualityandscience/clinical/guidelines/exercise/dirindex.htm. Accessed 04.09.08.

Table 11-4 USPSTF Recommendations and Ratings

Class	Description
A	The USPSTF strongly recommends that clinicians provide the service to eligible patients.
B	The USPSTF recommends that clinicians provide the service to eligible patients.
C	The USPSTF makes no recommendation for or against routine provision of the service.
D	The USPSTF recommends against routinely providing the service to asymptomatic patients.
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the service.

Adapted from U.S. Preventive Services Task Force (USPSTF) Screening for CAD. Available at: http://www.ahrq.gov/clinic/uspstf/uspsacad.htm. Accessed 04.09.08.

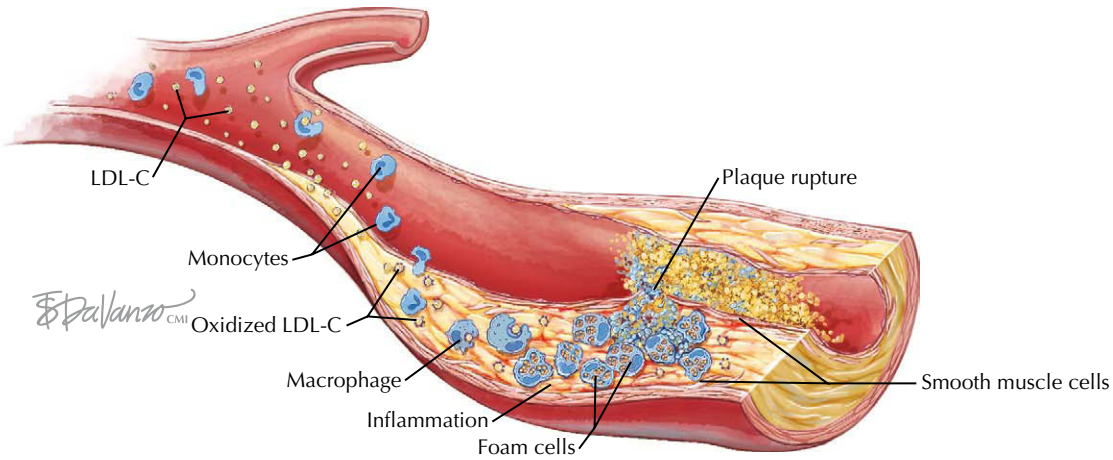


Figure 11-5 *Plaque inflammation and rupture.* LDL-C, low-density lipoprotein cholesterol.

and individuals for whom a detailed history and physical examination reveals subtle but real concerns of underlying coronary heart disease.

FUTURE DIRECTIONS

The current risk prediction models, such as the Framingham Risk Score, were developed from large epidemiologic population studies. These models work well to determine risk when applied to populations. Unfortunately, the clinician does not have the tools necessary to determine the risk of an imminent major coronary event—immediate risk—in individual patients today. The primary problem arises from the inability to detect inflamed, vulnerable plaque that is prone to rupture (Fig. 11-5). Because at least half of myocardial infarctions and acute coronary syndromes occur as a result of rupture of small, non–flow-limiting plaque, even coronary angiography cannot reliably determine the near-term risk of a coronary event. However, this topic is the focus of intensive investigation. There is much promise in molecular imaging, intracoronary imaging, genetic and metabolomic screening, as well as the identification of novel biomarkers that determine increased risk.

Molecular Imaging

Current coronary imaging modalities provide, at best, an anatomic view of plaque morphology. The goal of molecular imaging is to identify specific cellular and molecular targets that are an integral component of plaque rupture and to determine whether one or more of these targets are present in potentially unstable coronary artery lesions. Molecular imaging combines conventional imaging modalities (CT, MRI, PET) with molecular tags for specific components in plaque and allows imaging in vivo.

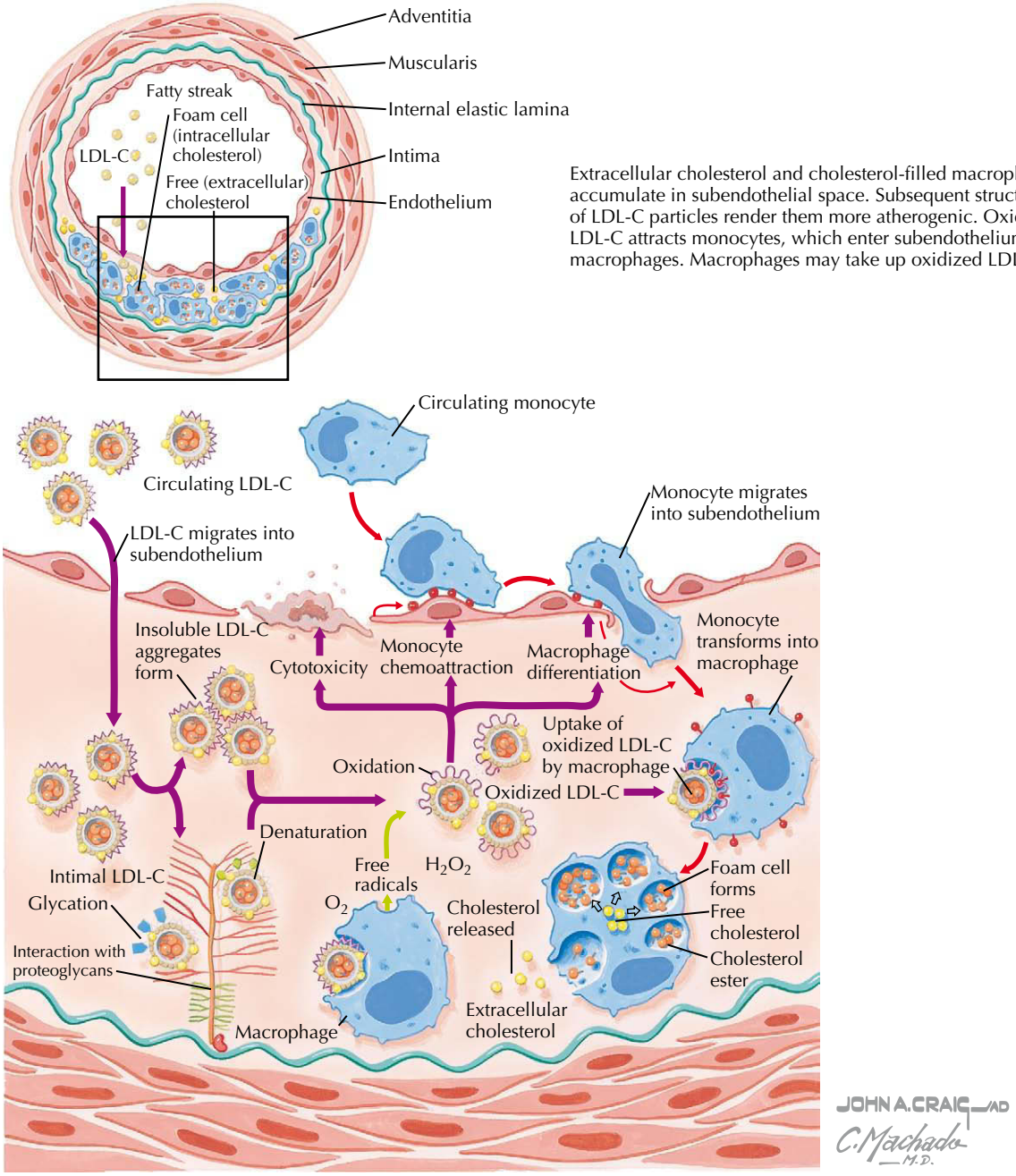
Many potential targets have been identified. One promising approach is to image subendothelial macrophages within the atherosclerotic plaque. Autopsy studies have demonstrated a disproportionate prominence of macrophages within the culprit lesions responsible for sudden cardiac death. The macrophage is the key cellular mediator in plaque inflammation and has important roles in atherogenesis development and its complications. Other potential targets include cell surface markers of apoptosis, protease enzymes, oxidized low-density lipoproteins, and other inflammatory mediators and cellular markers of angiogenesis—all of which are upregulated in unstable plaques (Fig. 11-6).

Molecular imaging seems to be on the brink of transforming our ability to identify vulnerable plaque. A better understanding of atherosclerosis biology, advances in imaging-agent chemistry such as in nanoparticle and micelle technology, as well as refinements in our imaging platforms such as single-photon emission CT and cardiac MRI, provide hope that molecular imaging for the near-term risk assessment of a cardiac event will be feasible in the coming years.

Genetic Screening

The recent decoding of the entire human genome and subsequent advances in proteomics and metabolomics have made possible the understanding of coronary heart disease at a new level. The promise of being able to identify with a simple blood test genetic factors responsible for CAD has led to much enthusiasm. Several single-nucleotide polymorphisms that confer increased risk of cardiovascular disease have already been identified. Presently, many gene-based screening tests are available and provide information that is most useful in familial cohorts and offer additional information akin to traditional cardiac risk factors.

Genome-wide association studies have identified previously unrecognized regions of the human genome that correlate with cardiac risk. These studies involve detailed comparisons of the genomes of individuals with and without cardiovascular disease. Statistically powerful correlates of coronary disease have been identified, although the odds ratios conferred are often small, on the order of a twofold increase in risk. The most important value of genome-wide association studies may be identification of novel regions of the human genome that will advance



Extracellular cholesterol and cholesterol-filled macrophages (foam cells) accumulate in subendothelial space. Subsequent structural modifications of LDL-C particles render them more atherogenic. Oxidation of subendothelial LDL-C attracts monocytes, which enter subendothelium and change into macrophages. Macrophages may take up oxidized LDL-C to form foam cells.

Figure 11-6 *Atherogenesis: Fatty streak formation.* LDL-C, low-density lipoprotein cholesterol.

understanding of the biology of atherosclerosis and coronary heart disease.

Biomarkers

For many years researchers have been searching for systemic biomarkers of inflammation that indicate increased risk. Many biomarkers have been identified and proposed as carrying an associated increased risk of CAD. Some have entered into clinical practice, such as C-reactive protein and homocysteine. Extensive biomarker panels are available for use. Unfortunately, as is the case for single-nucleotide polymorphism analysis or genome-wide association studies, while biomarker studies can help identify populations at risk, no biomarkers have been shown to advance our ability to identify individuals with vulnerable plaques.

Intravascular Ultrasound

Intravascular ultrasound (IVUS) is an imaging modality gaining wide acceptance as a tool to help understand plaque morphology and biology. IVUS is performed using a catheter with an

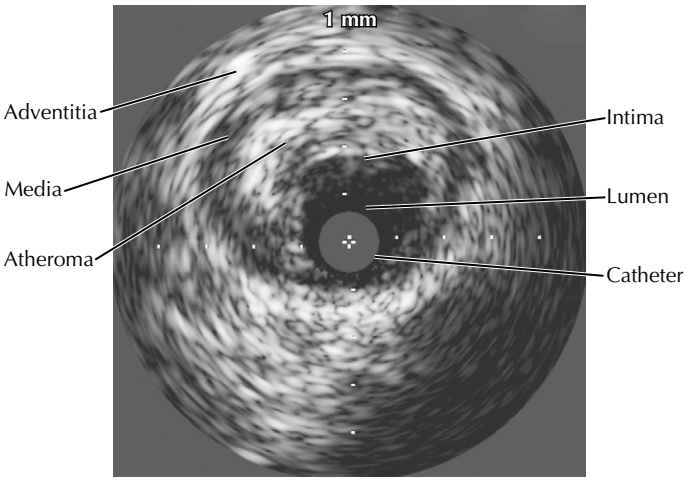


Figure 11-7 *Intravascular ultrasonogram of coronary atherosclerosis.*

ultrasound probe attached to its distal end (Fig. 11-7; see Chapter 15). Unlike angiography, which can only give a cross-sectional silhouette of the lumen, IVUS allows direct visualization of the endothelium and subendothelial space. With IVUS it is possible to visualize atherosclerotic lesions directly, to quantify the composition of lesions, and, potentially, to detect evidence of plaque instability. The plaques found to have a thin fibrous cap protecting the lipid core of the lesion are thought to be most vulnerable to rupture. Recent studies have supported the idea of a correlation between plaque structure and the risk of rupture.

Optimal coherence tomography (OCT) is another form of intravascular imaging that uses ultrasound-like technology to provide high-resolution images of atherosclerosis. It is currently under investigation but holds promise for being able to detect small and vulnerable plaques.

IVUS and OCT are invasive and expensive, and will never be ideal screening tools in the asymptomatic population given the inherent risks. However, IVUS is being used in patients already undergoing invasive coronary angiography to identify the high-risk plaque that is often not visible with conventional angiography. IVUS and OCT will be tools that help develop our understanding of plaque vulnerability.

The novel technologic advances described above will likely lead to advances in our understanding of unstable coronary syndromes and further efforts to develop useful tools for assessing coronary risk.

ADDITIONAL RESOURCES

ACC/AHA 2002 Guideline Update for Exercise Testing. Available at: <http://www.acc.org/qualityandscience/clinical/guidelines/exercise/dirindex.htm>; Accessed 22.02.10.

The American College of Cardiology and American Heart Association have published guidelines on the use of exercise stress testing.

Healthy People 2010. Available at: <http://www.healthypeople.gov/Document/HTML/Volume1/12Heart.htm>; Accessed 22.02.10.

Healthy People 2010 is a national health promotion and disease prevention initiative sponsored by the U.S. federal government. It contains useful information on prevention, detection, and risk factor modification for heart disease.

Med-Decisions.com. Available at: <http://www.med-decisions.com>; Accessed 22.02.10.

A web-based clinical decisions tool that determines a patient's 10-year risk of a major cardiovascular event based on the Framingham Risk Score.

National Cholesterol Education Program. Risk Assessment Tool for Estimating 10-Year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death). Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at: <http://hp2010.nhlbihin.net/atpIII/calculator.asp?usertype=prof>; Accessed 22.02.10.

An online risk calculator for determining the 10-year risk of major cardiovascular events.

U.S. Preventive Services Task Force—Screening for CAD. Available at: <http://www.guideline.gov/summary/summary.aspx?doc_id=4577&nbr=003367&string=Heart+AND+disease>; Accessed 22.02.10.

The U.S. Preventive Services Task Force is a federally sponsored organization that publishes screening recommendations based on a systematic review of the evidence.

EVIDENCE

Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol.* 1988;12(1):56–62.

Evaluated the angiographic appearance of coronary artery anatomy in patients whose CAD progresses to myocardial infarction and found that infarctions frequently develop from previously nonsevere lesions.

Bruce RA, Hossack KF, DeRouen TA, Hofer V. Enhanced risk assessment for primary coronary heart disease events by maximal exercise testing: 10 years' experience of Seattle Heart Watch. *J Am Coll Cardiol.* 1983;2(3):565–573.

A 10-year prospective community practice study in Seattle of risk of primary morbidity and mortality due to coronary heart disease in 3611 men and 547 women initially free of clinical manifestations of this disease.

Coplan NL, Fuster V. Limitations of the exercise test as a screen for acute cardiac events in asymptomatic patients. *Am Heart J.* 1990;119(4):987–990.

Explores the limitations of using the exercise test as a screen for acute cardiac events in asymptomatic patients.

Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data. *Circulation.* 1983;68(5):939–950.

CASS studied the effect of coronary artery bypass surgery versus medical therapy on mortality and selected nonfatal end points in patients with stable ischemic heart disease.

Fowler-Brown A, Pignone M, Pletcher M, et al. Exercise tolerance testing to screen for coronary heart disease: a systematic review for the technical support for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2004;140(7):W9–W24.

This review summarizes the evidence on the use of exercise tolerance testing to screen adults with no history of cardiovascular disease for coronary heart disease.

Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med.* 1999;130(9):719–728.

A meta-analysis of the cost-effectiveness of alternative diagnostic tests for patients at intermediate pre-test risk for coronary disease.

Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation*. 2003;108(13):1554–1559.

This study aimed to assess the role of reduced exercise capacity as an independent predictor of death in asymptomatic women, and found it to be more predictive than what had been previously established in men.

Healthy People 2010. Available at: http://www.healthypeople.gov; Accessed 06.09.08.

Healthy People 2010 provides statistics on the burden of CAD in the United States.

Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol.* 2003;42(7):318–333.

The American College of Cardiology, American Heart Association, and American Society of Nuclear Cardiology have published guidelines on the use of cardiac radionuclide imaging.

Little WC. Angiographic assessment of the culprit coronary artery lesion before acute myocardial infarction. *Am J Cardiol.* 1990;66(16): 44G–47G.

The author describes the "vulnerable" plaque as the likely culprit for myocardial infarction after rupture and thrombosis formation. Often, these lesions do not appear as significant, obstructive plaques.

Mark DB, Hlatky MA, Harrell FE Jr, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med.* 1987;106(6):793–800.

This study was designed to evaluate the prognostic value of the treadmill exercise test in 2842 patients with chest pain and developed the Duke Treadmill Score to stratify patient risk for 5-year survival.

Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA.* 2003;290(12):1600–1607.

This study sought to determine the prognostic value of exercise testing in a population-based cohort of asymptomatic women followed up for 20 years.

Pignone M, Fowler-Brown A, Pletcher M, Tice JA. Screening for asymptomatic coronary artery disease. Available at: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hsevidsyn&part=A32532>; Accessed 22.02.10.

The U.S. Preventive Services Task Force is a federally sponsored organization that publishes screening recommendations based on a systematic review of the evidence.

Siscovick DS, Ekelund LG, Johnson JL, Truong Y, Adler A. Sensitivity of exercise electrocardiography for acute cardiac events during moderate and strenuous physical activity. The Lipid Research Clinics Coronary Primary Prevention Trial. *Arch Intern Med.* 1991;151(2):325–330.

Examined whether the exercise ECG predicted acute cardiac events during moderate or strenuous physical activity among 3617 asymptomatic, hypercholesterolemic men who were followed up in the Coronary Primary Prevention Trial.

Sox HC Jr, Garber AM, Littenberg B. The resting electrocardiogram as a screening test. A clinical analysis. *Ann Intern Med.* 1989;111(6): 489–502.

Reviewed the evidence that a resting ECG predicts cardiac disease in healthy persons and discusses the role of this test in screening for CAD. It concluded that the evidence does not support doing a screening ECG in men without evidence of cardiac disease or cardiovascular risk factors.

U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services:* Report of the U.S. Preventive Services Task Force. Baltimore: Williams and Wilkins; 1996.

The U.S. Preventive Services Task Force is a federally sponsored organization that publishes screening recommendations based on a systematic review of the evidence.

U.S. Preventive Services Task Force. Screening for coronary heart disease: recommendation statement. *Ann Intern Med.* 2004;140(7): 569–572.

The U.S. Preventive Services Task Force is a federally sponsored organization that publishes screening recommendations based on a systematic review of the evidence.

Warnes CA, Roberts WC. Sudden coronary death: relation of amount and distribution of coronary narrowing at necropsy to previous symptoms of myocardial ischemia, left ventricular scarring and heart weight. *Am J Cardiol.* 1984;54(1):65–73.

Examined the amount and distribution of coronary arterial narrowing by atherosclerotic plaque at necropsy in 70 victims, aged 22 to 81 years, of sudden coronary death.

World Health Organization. Cardiovascular diseases. Available at: <http://www.who.int/mediacentre/factsheets/fs317/en/index.html>; Accessed 22.02.10.

The World Health Organization publishes statistics on the global impact of cardiovascular disease.

Chronic Coronary Artery Disease

Venu Menon and Jay D. Sengupta

12

Advances in pharmacotherapy and revascularization strategies have dramatically improved the short- and long-term outcomes for patients with atherosclerotic coronary artery disease (CAD). At the same time, the worldwide incidence of atherosclerosis and CAD—driven in large part by the exponential increases in obesity and type 2 diabetes mellitus—have also increased dramatically. These issues, the result of which is a very large population with atherosclerotic CAD, will be a major public health issue in both industrialized and developing nations for the foreseeable future.

Patients with atherosclerotic CAD can present to health care providers in many different ways. This chapter focuses on chronic stable angina. Other clinical presentations of atherosclerotic CAD (acute coronary syndromes, congestive heart failure, sudden cardiac death, and cardiogenic shock) are described in separate chapters (13, 14, 17, 23, and 30).

ETIOLOGY AND PATHOGENESIS

In contrast to oxygen extraction by skeletal muscle, oxygen extraction by cardiac tissue is near maximal, even at rest (Fig. 12-1). The heart responds to the need for increased cardiac output by increasing heart rate and contractility, both of which increase wall stress and myocardial oxygen requirements. This need for increased myocardial oxygen cannot be met by increasing the efficiency of oxygen extraction and thus must be met by increasing coronary blood flow. If a significant underlying coronary epicardial stenosis is present, blood flow at rest is maintained by compensatory dilatation of the coronary bed beyond the stenosis. This diminishes coronary flow reserve and may result in an inability to meet oxygen requirements as myocardial demand increases, creating a supply/demand mismatch. Symptoms of angina reflect myocardial ischemia and arise when the blood supply to a region of the heart cannot increase sufficiently to match myocardial oxygen demand as a result of the presence of a hemodynamically significant stenosis in the coronary artery supplying that region. Ischemia can be elicited by treadmill or bicycle exercise testing (or use of pharmacologic stress) and may be measured as loss of systolic thickening on echocardiography, diminished perfusion on single-photon emission CT, ST-segment depression on surface ECG, and angina.

Increased vasoreactivity (vasospasm on a previously narrowed arterial segment) may also result in decreased myocardial blood flow with or without increased demand. Vasoreactivity seems to be responsible for some of the circadian, seasonal, and emotional components associated with angina. Although it is thought that fixed coronary artery stenoses are the dominant contributor to stable angina, in some individuals there are clearly contributions from increased coronary vasoreactivity (both at sites of stenoses and elsewhere). The other major biologic mechanism that results in myocardial ischemia is rupture of an atherosclerotic plaque in a coronary artery, resulting in sudden diminished blood flow and acute coronary syndromes, as discussed in Chapters 13 and 14.

CLINICAL PRESENTATION

Chronic stable angina is characterized by angina that usually occurs with increased oxygen demand. Symptoms can be provoked by exertion, heavy meals, or emotional distress; they also tend to be reproducible and usually have been present over many months, or longer. As noted above, these symptoms most commonly result from fixed coronary stenoses (Fig. 12-2). Chest discomfort is typically described as a pressure or tightness, or discomfort over the left precordium, although many individuals with myocardial ischemia do not have these classic symptoms. The discomfort may radiate along the ulnar aspect of the left arm and is often accompanied by shortness of breath, nausea, and diaphoresis (Fig. 12-3). Symptoms may also radiate or be isolated to the throat, jaw, interscapular region, and epigastrium. Radiation below the umbilicus and to the occiput is uncharacteristic, as are symptoms that are well localized to a fingertip, provoked by palpation and movement, or relieved by lying down. Typically, stable anginal pain lasts for more than a few minutes and less than 10 minutes, is associated with exertion or other stresses, and is relieved by rest or the use of sublingual nitroglycerin within 1 to 2 minutes. Angina can sometimes be mistaken as indigestion, accounting for a delay in presentation or treatment. It is very important to understand that atypical presentations of angina can occur in any patient but are particularly common in diabetics, women, and the elderly. In these individuals, it is very important to evaluate further any exertion-related symptoms that may reflect an inability to increased myocardial oxygen delivery, including significant dyspnea on exertion, new or worsened fatigue with exertion, or similar symptoms.

DIFFERENTIAL DIAGNOSIS

The quality of chest pain is similar in the setting of acute unstable angina or acute myocardial infarction (MI). It is usually more intense and prolonged, but the difference may be subjective. An important difference is that the pain associated with acute MI is usually unremitting, although it may wax and wane in severity. Angina, or any symptoms reflecting a limitation of myocardial oxygen demand, may also reflect non–coronary artery etiologies, including severe aortic valve stenosis, hypertrophic cardiomyopathy, and microvascular dysfunction. Other cardiovascular causes of chest pain include pericarditis, aortic dissection, and pulmonary embolism. These may be very difficult to distinguish from angina based on the history and physical examination and often require further diagnostic evaluation. Clinicians should also attempt to distinguish angina from chest pain arising from a noncardiac etiology. The most common

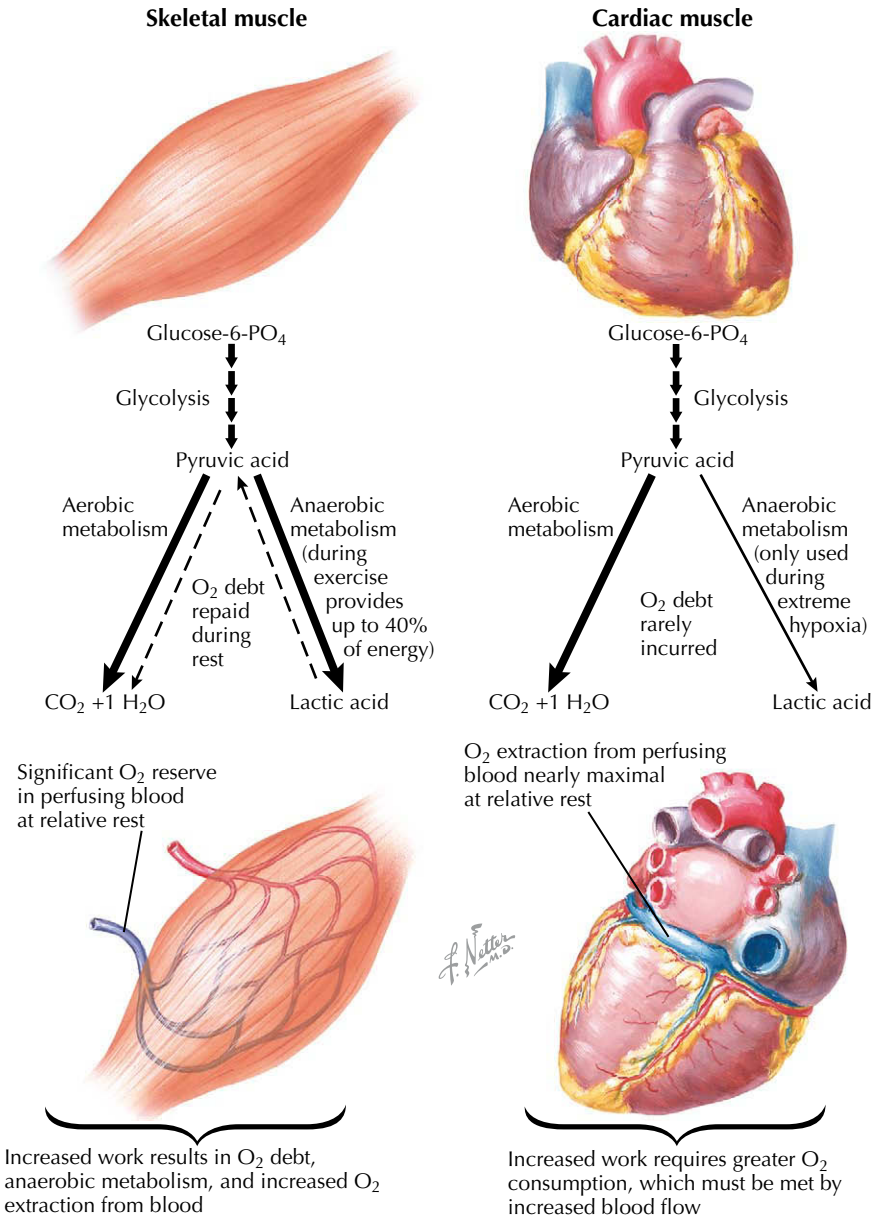


Figure 12-1 *Oxygen utilization in skeletal and cardiac muscles.*

noncardiac causes of angina-like pain are gastrointestinal conditions such as gastroesophageal reflux disease, esophageal spasm, peptic ulcer disease, biliary disease, and pancreatitis. Of these, gastroesophageal reflux disease is very common as a cause of angina-type chest pain. Pleuritis or chest pain related to other lung pathology is also common and should be considered. Cervical disk disease, costochondral syndromes, and shingles may also mimic angina. Chest discomfort is also a common manifestation in patients with panic disorder; however, this is a diagnosis of exclusion.

Because the mortality and morbidity associated with CAD is higher than many noncardiac causes of angina-like symptoms, it is important to be thorough and thoughtful before dismissing CAD as the underlying cause of an individual's symptoms.

DIAGNOSTIC APPROACH

A history suggestive of angina mandates diagnostic and prognostic evaluations. The urgency of treatment is guided by the initial presentation and clinical evaluation. A history of new-onset angina, accelerating angina, angina at a low exertional threshold, and rest angina most often means that the patient is having an acute coronary syndrome and needs immediate evaluation and therapy. In an individual who has previously had stable angina who presents with a picture of acute coronary syndrome, if there is no evidence for myocardial ischemia, it is important to include consideration of whether a noncardiac cause of increased oxygen demand (such as anemia, hyperthyroidism, severe emotional stress, or like causes) has contributed to the worsening angina in that patient. Physical examination

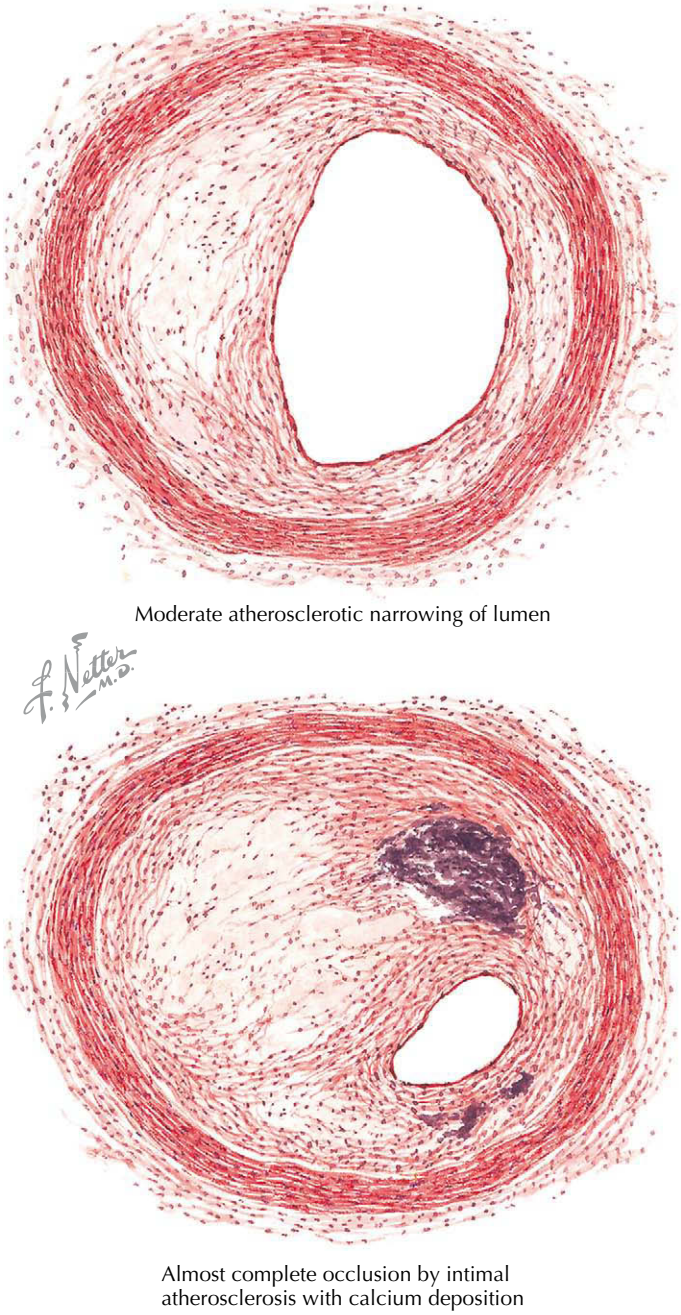


Figure 12-2 *Types and degrees of coronary atherosclerotic narrowing or occlusion.*

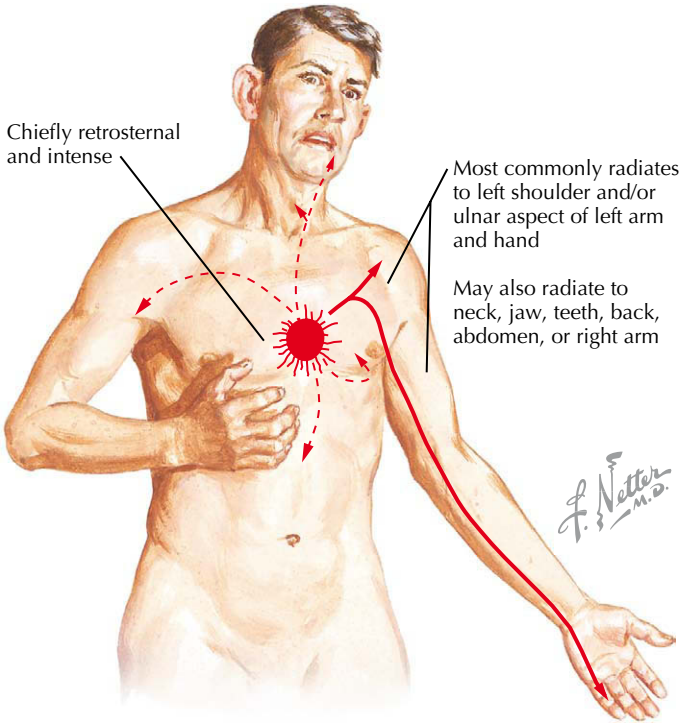


Figure 12-3 *Pain of myocardial ischemia.*

during a routine consultation is unlikely to be rewarding, but the clinician should look for clinical evidence of left ventricular (LV) dysfunction (resting tachycardia, laterally displaced apical impulse, an LV S_3, rales, jugular venous distention, positive hepatojugular reflex, pedal edema). In addition to evaluating the status of traditional cardiac risk factors (hypertension, smoking status, hyperlipidemia, diabetes), it is also important to inquire about a history of claudication, stroke, and transient ischemic attack and carefully screen for manifestations of atherosclerotic disease (audible bruits, asymmetric pulses, palpable aneurysms, ankle-brachial index). The presence of atherosclerosis in any of these areas heightens the likelihood of underlying CAD. The examiner should also look for physical and biochemical signs of the metabolic syndrome (Box 12-1), as well as stigmata of hereditary hyperlipidemic conditions (Fig. 12-4).

The next steps in the diagnostic approach should be based on the pre-test likelihood of disease. The interplay of traditional risk factors and genetic traits impacts the development of atherosclerosis (Fig. 12-5). Patients with typical angina, multiple risk factors, and/or impaired LV function with a high likelihood of disease should be considered for diagnostic coronary angiography. The few patients with a low pre-test likelihood of disease should be reassured, without further additional testing. In these individuals it is very important to emphasize risk reduction with smoking cessation and lifestyle modification.

Rather than falling into the very-high-risk or very-low-risk categories, most patients have an intermediate likelihood of epicardial CAD. In these individuals, stress testing is very useful

Box 12-1 Signs of the Metabolic Syndrome

- Abdominal obesity
  Men greater than 102 cm (>40 in)
  Women greater than 88 cm (>34.5 in)
- Blood pressure higher than 130/85 mm Hg
- Fasting glucose greater than 110 mg/dL
- HDL-C
  Men less than 40 mg/dL
  Women less than 50 mg/dL
- Triglycerides greater than 150 mg/dL

HDL-C, high-density lipoprotein cholesterol.

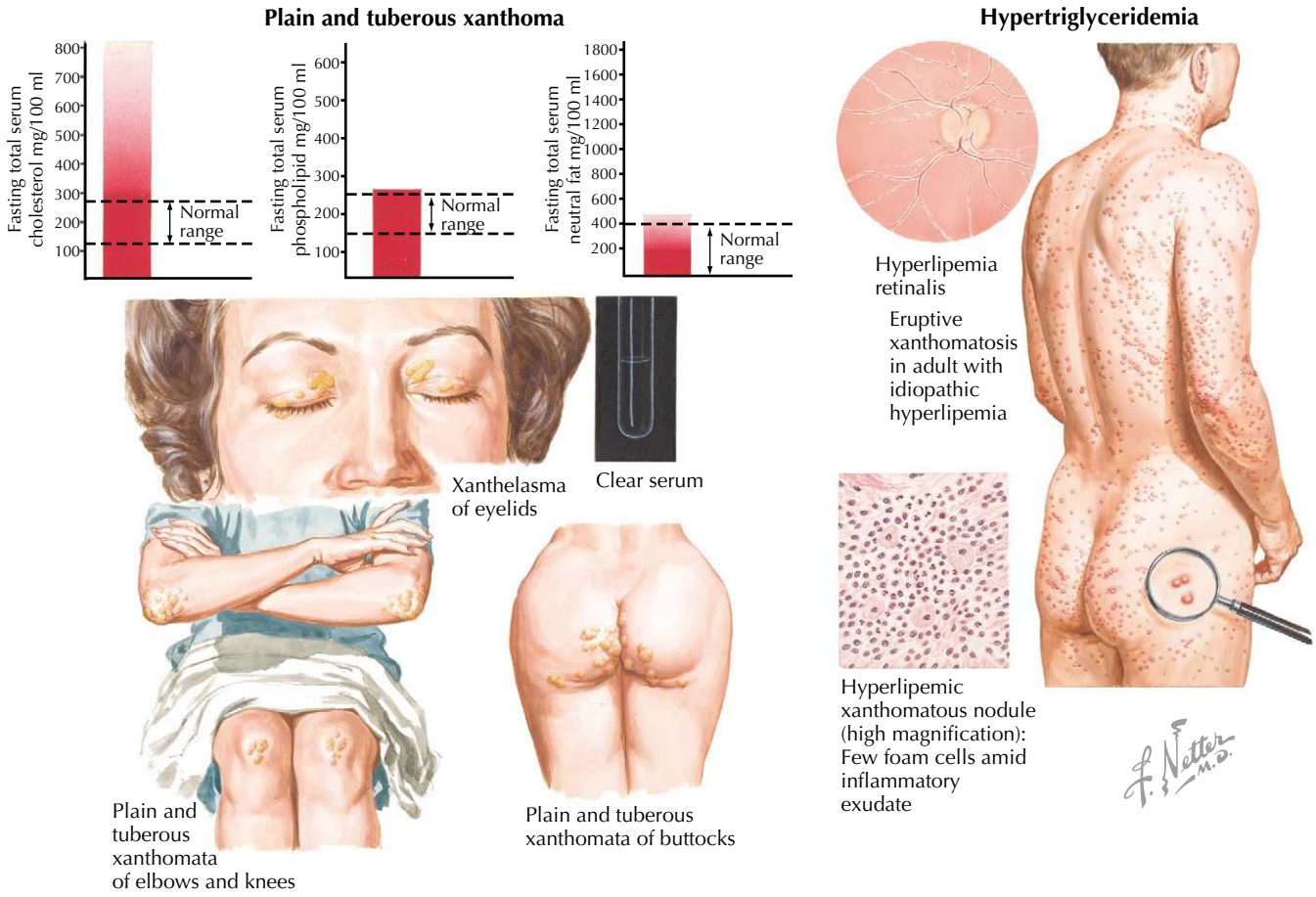


Figure 12-4 *Hypercholesterolemic xanthomatosis.*

for further risk stratification (Fig. 12-6). Patients with a normal resting ECG may be referred for standard exercise treadmill testing. As discussed elsewhere (Chapters 3 and 7), however, the diagnostic accuracy of exercise stress testing is limited. For this reason, evaluation with concomitant nuclear perfusion/stress–echocardiographic imaging studies is often preferred. In addition to the higher predictive value of stress-imaging studies compared with exercise electrocardiography, these tests also provide incremental physiologic (degree/extent of ischemia, LV function) and prognostic data. In individuals with preexcitation, paced rhythms, left bundle branch block, or baseline ST-segment abnormalities or who are taking medications (such as digoxin) that may confound stress-ECG interpretation, stress imaging is required. It should be noted that the inability to perform adequate exercise by itself is a major indicator of adverse prognosis. This subset of patients may be referred for pharmacologic stress testing with use of dipyridamole, adenosine, or dobutamine.

Patients with high-risk nuclear perfusion scans, stress-echocardiograms, and exercise tolerance test findings, as well as patients with ischemia with severe LV dysfunction, should be referred for diagnostic coronary angiography. Subjects with severe segmental LV dysfunction and absence of inducible ischemia should be evaluated to determine whether the myocardium is viable (but severely ischemic) or infarcted and not likely to benefit from revascularization. The choice of which study should be used to determine myocardial viability and the precise protocol for testing should be guided by local expertise. Low-dose dobutamine echocardiography, thallium-dipyridamole imaging, PET, and MRI are all valuable for assessment of viability. Evidence of viability should lead to referral for angiography, with the goal of attempting revascularization whenever feasible. Patients with low-risk scans may be treated medically using risk counseling and adequate follow-up.

MANAGEMENT AND THERAPY

Optimum Treatment

The treatment goals in patients with chronic stable angina are to prolong and improve quality of life. The mitigation of cardiac risk factors with lifestyle alterations and pharmacotherapy to prevent and even reverse progression of atherosclerotic disease helps to achieve these goals. Optimal medical therapy (OMT) most often involves use of a β-blocker, an angiotensin-converting enzyme (ACE) inhibitor, a statin, aspirin, and lifestyle modifications (Fig. 12-7). This combined approach can markedly reduce angina and prevent or slow the progression of CAD.

Smoking cessation should be emphasized, and referral to cessation programs should be provided. As noted elsewhere (Chapter 65), smoking cessation alone is more likely to

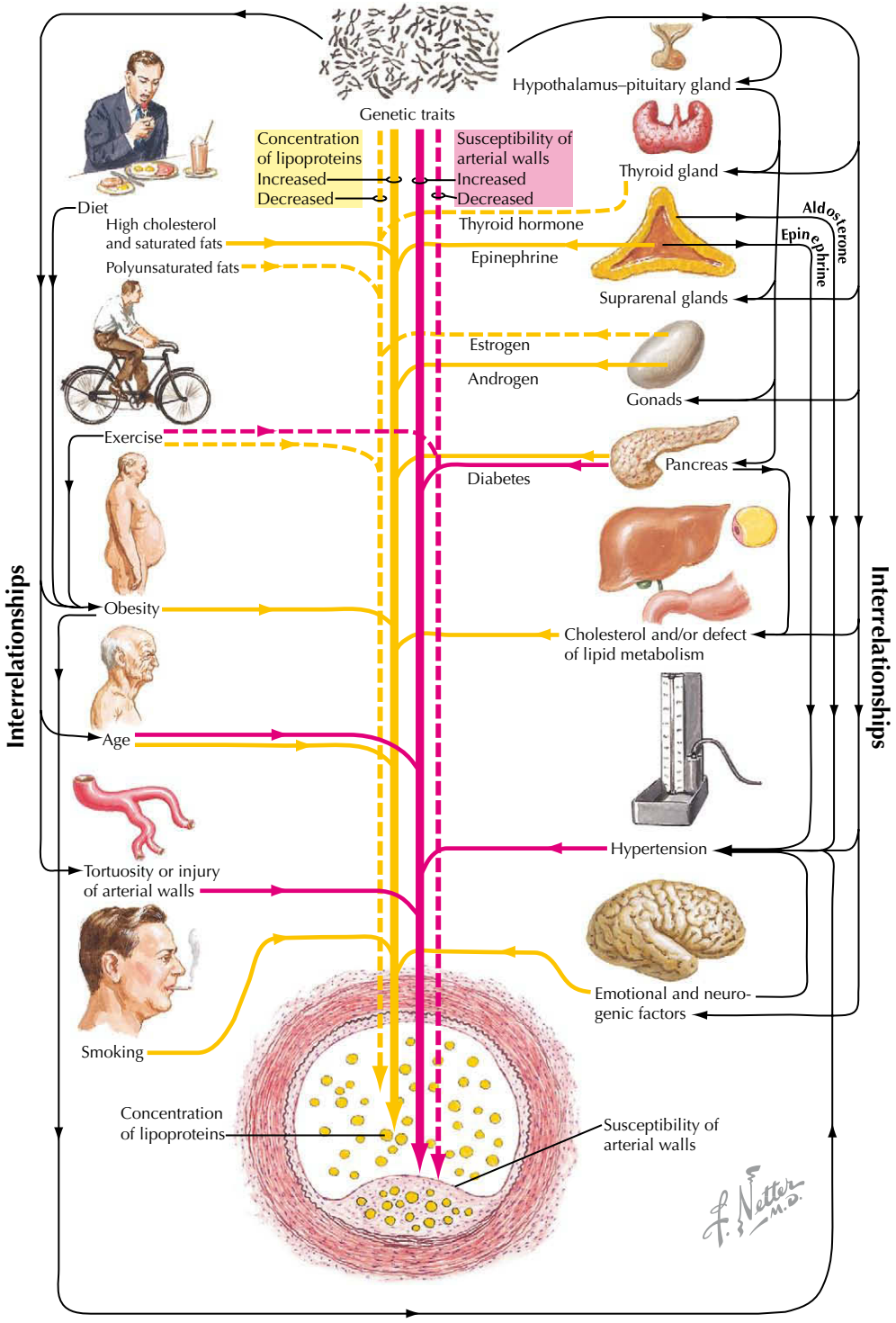


Figure 12-5 *Cardiac risk factors.*

reduce future cardiac risk than any combination of medications and revascularization procedures. Patients should also be educated about the beneficial effects of physical exercise. High-risk patients should be given a detailed exercise prescription and, in most circumstances, should initiate their exercise in a monitored setting—as provided by cardiovascular rehabilitation programs.

The Seventh Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) guidelines direct blood pressure management in hypertensive patients. The selection of antihypertensive therapy can be tailored in patients with angina to achieve both improvement in blood pressure and reduction of anginal symptoms. People with diabetes should attain tight glucose control; the

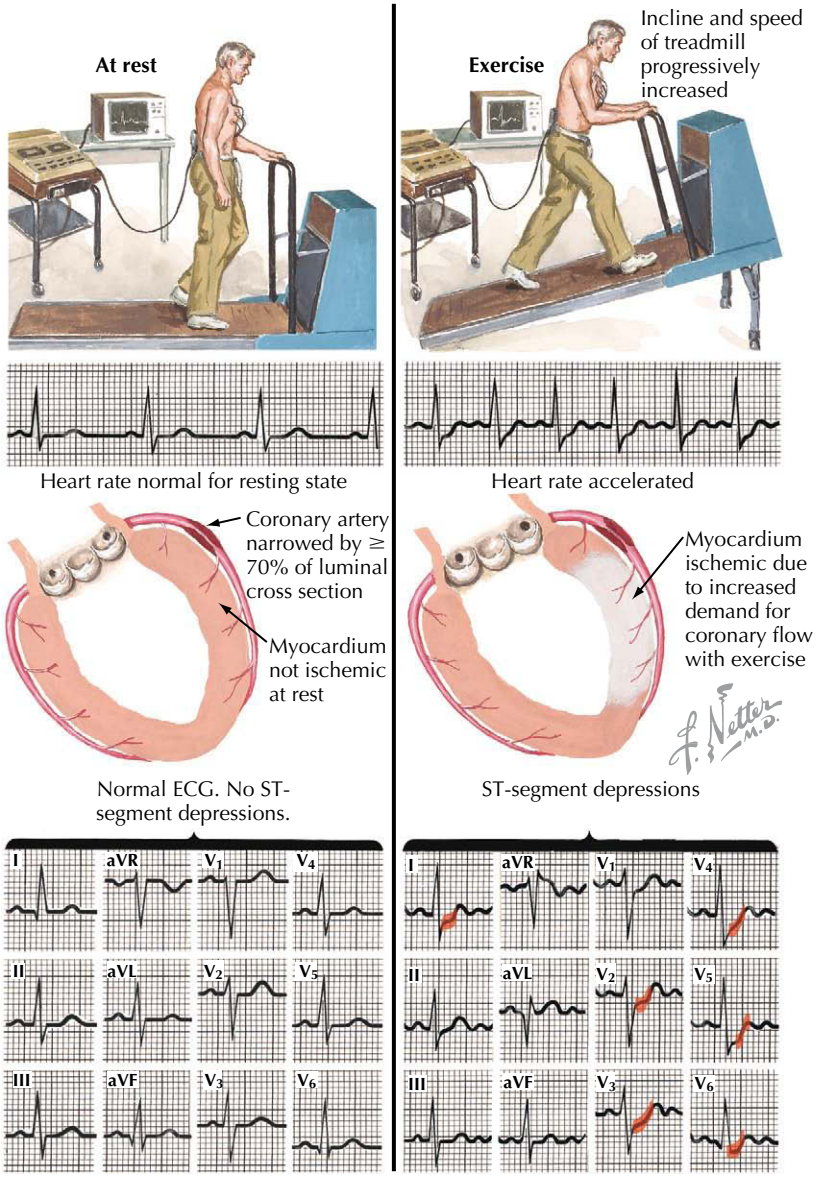


Figure 12-6 *Stress-ECG testing to detect myocardial ischemia.*

value of weight reduction must be stressed to appropriate patients. Quality assurance programs should ensure that patients with established atherosclerotic CAD be prescribed proven medical therapy (as described in the following sections on specific pharmacotherapies). Patients should be educated about the early warning signs of MI and stroke, the prompt use of aspirin and nitroglycerin, and access to the emergency medical system.

ANTIPLATELET THERAPY

All patients with atherosclerotic CAD should be treated with antiplatelet therapy. The cost and effectiveness of aspirin makes it the treatment of choice. The Swedish Angina Pectoris Aspirin Trial randomized 2035 patients with stable angina to 75 mg aspirin versus placebo. A 33% relative reduction (9% absolute reduction) in cardiovascular events was observed with aspirin therapy. Similarly, a collaborative meta-analysis suggested a 34% proportional reduction in nonfatal MI and a 26% reduction in nonfatal MI or death with antiplatelet therapy over placebo in high-risk patients. In patients with a history of MI, antiplatelet therapy prevented 18 nonfatal MIs, 5 nonfatal strokes, and 14 vascular deaths per 1000 patients treated over a mean duration of 2 years. Clopidogrel is an appropriate alternative for patients with a contraindication to aspirin. The concomitant long-term use (up to 12 months) of clopidogrel with aspirin following an acute coronary syndrome and percutaneous intervention is associated with a beneficial outcome. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) Trial evaluated dual antiplatelet therapy with aspirin and clopidogrel in patients with either clinically evident cardiovascular disease or multiple cardiovascular risk factors. Clopidogrel in addition to aspirin did not significantly reduce cardiovascular events in the overall population or high-risk primary prevention patients, although subgroup analysis demonstrated a reduction in death, MI, or stroke in patients with established cardiovascular disease. For

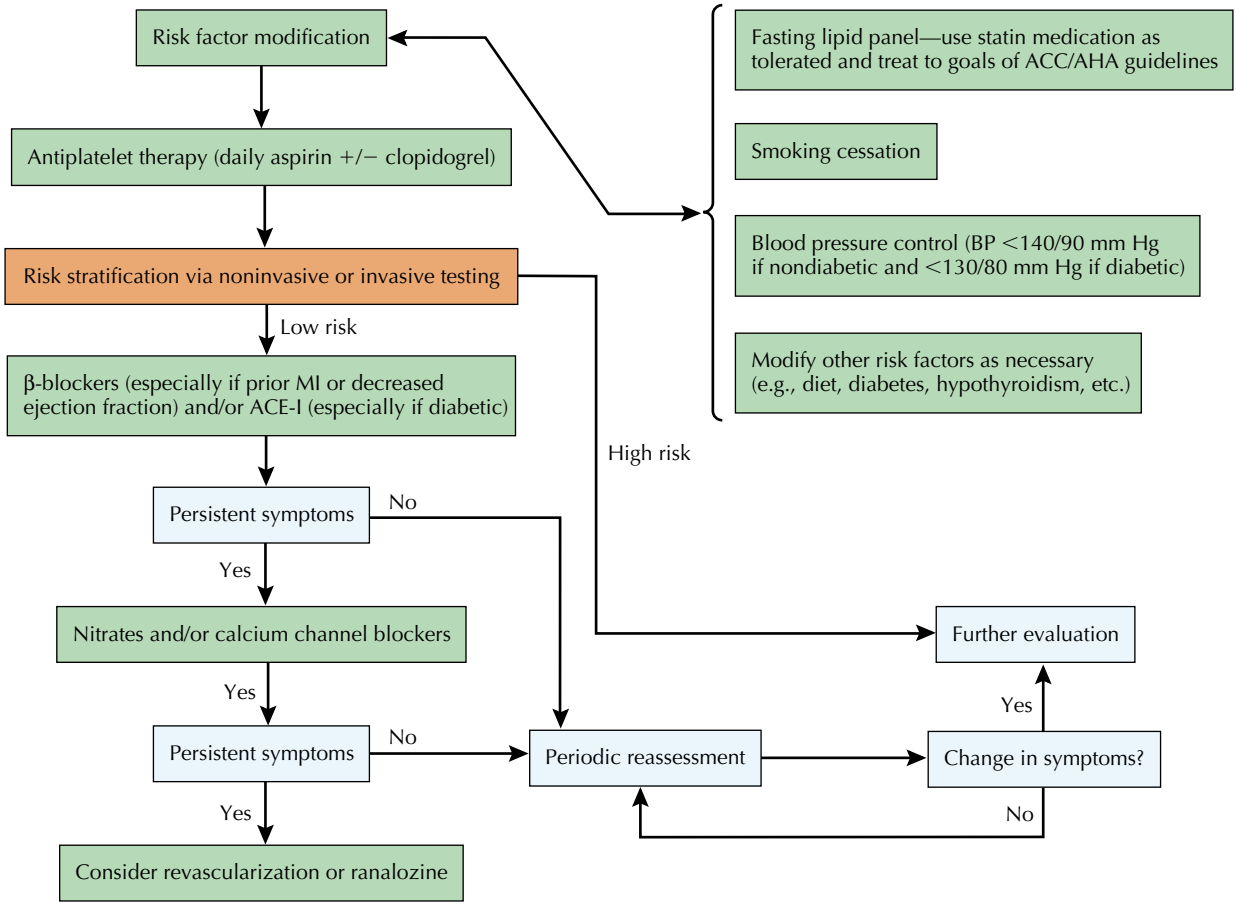


Figure 12-7 *Management of chronic coronary artery disease in clinically stable patients.* ACC/AHA, American College of Cardiology/American Heart Association; ACE-I, angiotensin converting enzyme inhibitor.

many patients with severe CAD who cannot or have not benefited from revascularization, the addition of clopidogrel to aspirin is recommended.

β-BLOCKADE

In the absence of contraindications, all patients with CAD should be prescribed a β-blocker. In the Beta Blocker Heart Attack Trial, β-blockade with propanolol reduced the combined end point of recurrent nonfatal reinfarction and fatal coronary heart disease from 13.0% in the placebo group to 10% in the treatment group, a reduction of 23% at 25 months of follow-up. In trials of stable angina, β-blockers were superior to calcium antagonists in reducing episodes of angina. The rates of cardiac death and MI were not significantly different. β-blockers are also indicated for the majority of patients with class II to IV heart failure.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

All patients with established CAD and LV dysfunction (symptomatic or asymptomatic) should be prescribed an ACE inhibitor. In three large postinfarction trials, mortality rate was lower with ACE inhibitors than with placebo, as were the rates of readmission for heart failure and reinfarction and the composite of these events. High-risk patients with preserved LV function also seem to derive benefit. In the Heart Outcomes Prevention Evaluation Study, the use of ramipril in subjects older than 55 years of age with preserved LV function significantly reduced the primary end points of MI, stroke, and cardiac death. On subgroup analysis, subjects with a history of CAD, MI, cardiovascular disease, cerebrovascular disease, or peripheral vascular disease all derived benefit. For individuals who cannot tolerate treatment with an ACE inhibitor due to side effects, treatment with an angiotensin-II receptor blocker should be considered. Although the data are not as strong as with ACE-inhibitor therapy, angiotensin-II receptor blockers probably have long-term benefits in this population.

NITRATES

Nitrates are endothelium-independent vasodilators that reduce myocardial ischemia and improve coronary blood flow. When used effectively in patients with stable angina, they improve exercise tolerance and increase the anginal threshold. Patients with frequent episodes of angina should be treated with long-acting oral nitrate therapy or with transdermal patches. If a transdermal patch is used, it is important to ensure a nitrate-free interval. Tachyphylaxis (and loss of nitrate efficacy) occurs in patients without nitrate-free intervals in their treatment regimen. Patients with angina should also be supplied with sublingual tablets or spray for breakthrough angina.

TREATMENT OF HYPERLIPIDEMIA

Low-density lipoprotein cholesterol (LDL-C) should be the primary target of therapy. Secondary causes of hyperlipidemia, such as diabetes, hypothyroidism, obstructive liver disease, and chronic renal failure, should be considered and managed effectively. Dietary fat should be restricted to 25% to 35% of daily caloric requirement (polyunsaturated fat, 20%; monounsaturated fat, 10%). All patients should receive dietary counseling and instructions for weight reduction and increased physical activity. The current National Cholesterol Education Program guidelines recommend an LDL-C target of less than 100 mg/dL for patients with established CAD. For patients at very high risk for cardiovascular events with established CAD (e.g., recent acute coronary syndrome, multiple risk factors, poorly controlled diabetes, and continued tobacco use), the suggested LDL-C goal is less than 70 mg/dL. Pharmacotherapy should be initiated with a statin. Statins decrease LDL-C by 18% to 55%, decrease triglycerides by 7% to 30%, and raise high-density lipoprotein cholesterol (HDL-C) by 5% to 15%. In a meta-analysis combining the results from three secondary- and two primary-prevention trials, treatment with a statin resulted in a 31% reduction in major coronary events and a 21% reduction in all-cause mortality rates. Women and elderly individuals derived the same reduction in coronary events as their male and younger counterparts. For subjects with triglyceride levels in the range of 200 to 499 mg/dL, concomitant treatment with niacin or fibrate (a fibric acid derivative) should be considered. These drugs may also increase HDL-C levels. Although the data for using pharmacotherapy to increase low HDL-C levels is not conclusive, many favor this approach for high-risk individuals.

A concept of global cardiovascular risk is emerging. The current evidence suggests that all patients at cardiovascular risk derive benefit from statin treatment irrespective of their measured lipid profile. There are also advocates for broad use of a combination of medications to reduce the population risk of MI and stroke. However, neither of these approaches is currently incorporated into treatment guidelines.

INDICATIONS FOR REVASCULARIZATION

Coronary artery bypass graft (CABG) improves survival in patients with severe stenosis of the left main coronary artery, three-vessel disease, or two-vessel disease with involvement of the proximal left anterior descending artery. Patients with LV dysfunction may derive more benefit but also have higher risk at the time of the procedure. When compared with percutaneous coronary intervention (PCI) in multivessel CAD, CABG provides greater freedom from angina and better target vessel revascularization—although CABG is also associated with a greater initial risk of procedural mortality, stroke, cognitive dysfunction, and early, transient deterioration in quality of life. PCI is less invasive but requires repeat procedures, mainly due to restenosis.

Trials comparing stenting (without the use of glycoprotein [GpIIb/IIIa] inhibitors) with CABG in multivessel disease reported somewhat discordant findings. The Arterial Revascularization Trial Study reported similar mortality rates for the two strategies at 1 year. The Surgery or Stent (SoS) Study reported a lower mortality rate with CABG. Given the lack of an unambiguous recommendation for revascularization for all patients with multivessel CAD, physicians caring for these patients must individualize their decision making. That said, it is recommended that patients with unprotected left main, diffuse multivessel CAD, diabetes, or severely impaired LV function be referred for CABG. An initial strategy of percutaneous intervention or CABG may be offered to patients with discrete coronary targets and preserved LV function.

Whether the use of drug-eluting stents will change the threshold for surgical referral remains to be seen. A recent study randomized patients to CABG or PCI with drug-eluting stents and examined whether there was a significant difference in major cardiovascular or cerebrovascular events at 12 months. The SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) investigators reported an increased rate of repeat revascularization in the PCI group, although rates of death and MI were similar between the two groups. The use of drug-eluting stents has decreased somewhat in the past 2 years, as a result of reports of late stent thrombosis in a small percentage of patients with drug-eluting stents (Chapter 15).

An important and somewhat controversial study, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Trial enrolled patients with chronic angina, stable CAD suitable for PCI, and inducible myocardial ischemia and compared OMT with and without PCI. LV ejection fraction less than 30% was an exclusion criterion. The results showed no benefit for PCI in terms of reducing the primary outcome, which was all-cause death or MI, when compared to OMT alone. Advocates of medical therapy for CAD have argued that PCI is overutilized, based on the COURAGE Trial results. Advocates of PCI have criticized the design of the study and the large number of patients who crossed over between the therapeutic arms. The data from the COURAGE Trial and other studies have led many to suggest that the paradigm for management of patients with chronic stable angina and relatively preserved LV function be changed to reflect the likelihood that PCI is effective for early symptom improvement but may not confer added benefit over OMT alone for the prevention of MI.

At present, American College of Cardiology/American Heart Association class I indications for PCI are symptom control, single- and double-vessel disease with a large ischemic burden or LV dysfunction, after sudden cardiac death or sustained ventricular tachycardia, and restenosis. Those with clinical angina refractory to medical therapy should be offered PCI. Subjects with refractory angina not amenable to revascularization may be considered for ranolazine, transmyocardial revascularization protocols, or enhanced external counterpulsation, but there are limited data to suggest benefit with these therapies.

Avoiding Treatment Errors

Revascularization may help to restore some degree of LV function in select patients with multivessel CAD, and it is very important to consider LV function and to assess myocardial viability when recommending for or against revascularization. Since patients with severe LV dysfunction were excluded from the COURAGE trial and no randomized studies are available

to address the particular issue of revascularizing ischemic but viable myocardium, it is important to consider these issues. Cardiac MRI and PET should be considered in such a patient to assess myocardial viability before CABG or PCI. Randomized studies currently under way will address the implications of hibernating myocardium for LV function and outcomes after revascularization.

OMT for patients with chronic CAD should include statin therapy, aspirin, β-blocker, ACE inhibitor, and clopidogrel when indicated. Goal-directed risk factor reduction with respect to blood pressure, lipid profile, and smoking cessation improves outcomes. Therapeutic lifestyle changes to monitor diet, exercise regularly, and reduce and maintain weight are important adjunctive measures. Once therapeutic goals are achieved (e.g., with respect to target LDL-C concentration), physicians and patients must be mindful that discontinuing medications or reducing dosage may alter risk and reduce the benefits of medical therapy.

FUTURE DIRECTIONS

Accurate noninvasive identification and quantification of atherosclerosis with electron beam CT, intravascular ultrasound, fractional flow reserve, carotid intimal thickness measurements, and endothelial vasoreactivity blur the traditional distinction between primary and secondary prevention of CAD. Biomarker, genetic, and proteomics research will allow prognostication with increasing accuracy as new therapeutic targets for plaque stabilization and regression are translated from bench to bedside. Treatment for fixed epicardial CAD will be altered by distal protection devices, advances in adjunctive pharmacotherapy, and, perhaps, the much-awaited conquest of restenosis with drug-eluting stents. Advances in angiogenesis and stem cell transfer will potentially revolutionize therapy. A wonderful voyage lies ahead.

ADDITIONAL RESOURCE

Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110(2):227–239.

LDL-C less than 70 mg/dL is a reasonable strategy in high-risk CAD patients based on recent clinical trials.

EVIDENCE

Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71–86.

Meta-analysis of randomized trials using antiplatelet agents to prevent high-risk vascular events such as MI, stroke, or vascular death. Aspirin or other antiplatelet agent is protective in most types of patients with increased risk of occlusive vascular events, and absolute benefit outweighs risk of major extracranial bleeding.

Beta-Blocker Heart Attack Study Group. The beta-blocker heart attack trial. *JAMA.* 1981;246:2073–2074.

Early randomized, double-blind, multicenter trial of propranolol versus placebo shortly after MI. Trial curtailed early after demonstrating significant mortality benefit of β-blocker compared to placebo.

COURAGE investigators. Optimal medical therapy with or without PCI for stable coronary disease trial has affected practice protocols. *N Engl J Med.* 2007;356(15):1503–1516.

Influential study that enrolled patients with chronic stable angina on OMT with CAD amenable to PCI. In stable CAD in patients with relatively preserved LV function, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to OMT.

Flather MD, Yusuf S, Keber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: A systematic overview of data from individual patients. *Lancet.* 2000;355;1575–1581.

Prospective analysis of use of ACE inhibitors after MI in five long-term randomized trials. The benefits of ACE inhibitors are lower rates of death, reinfarction, and readmission for heart failure. Benefits were identified over the entire range of ejection fractions found in the study participants.

HOPE investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145–153.

Assesses the role of an ACE inhibitor in patients who were at high risk for cardiovascular events but who did not have LV dysfunction or congestive heart failure. The patients enrolled typically had vascular disease or diabetes and one additional risk factor. Ramipril reduced the rates of death, MI, and stroke compared to placebo.

Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *JAMA.* 1999;281:1927–1936.

To compare the relative efficacy and tolerability of treatment with β-blockers, calcium antagonists, and long-acting nitrates for patients who have stable angina. β-blockers have similar efficacy and fewer adverse effects compared to calcium channel blockers in randomized trials of patients with chronic stable angina.

Serruys PW, Unger F, Souza JE, et al. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117–1124.

Early study that randomized patients to CABG or PCI with bare-metal stents and compared major cardiovascular or cerebrovascular events at 12 months. Stenting was associated with a greater need for repeat revascularization, which affected the primary end point.

Serruys PW, Morice MC, Kappetein AP, et al. SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360(10):1024–1026.

Randomized, multi-center trial comparing CABG or PCI with drug-eluting stents in patients with three-vessel or left main disease. Statistical noninferiority comparison for major cardiovascular or cerebrovascular events performed at 12 months showed PCI was associated with higher event rates driven by repeat revascularization procedures.

The SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): A randomized controlled trial. *Lancet.* 2002;360:965–970.

Randomized, multicenter trial comparing bare-metal stents to CABG with respect to repeat revascularization. The use of coronary stents has reduced the need for repeat revascularization when compared with previous studies that used balloon angioplasty; however, the rate remains significantly higher than in patients managed with CABG.

Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases. The epidemiologic transition and impact of urbanization. *Circulation.* 2001;104:2746–2753.

Thorough overview of the epidemiology of worldwide cardiovascular atherothrombotic disease by ethnic group and region and possible strategies for prevention.

Non–ST-Elevation Myocardial Infarction

13

Eric H. Yang and Steven R. Steinhubl

Acute coronary syndromes (ACSs) encompass a wide range of clinical disorders that share a common underlying physiology: an acute or subacute imbalance between oxygen demand and supply of the myocardium. The presenting symptoms and diagnosis of patients with an ACS depend on the duration and degree of inadequate oxygenation, and the known variation in symptomatology in patients with an ACS. For these reasons, the diagnosis of ACS can be challenging and the outcomes variable. Unstable angina, non–ST-elevation myocardial infarction (MI), ST-elevation MI, and even sudden cardiac death are potential clinical manifestations of an ACS.

The incidence and potential severity of ACS makes timely diagnosis and appropriate treatment essential for minimizing morbidity and mortality. Every year in the United States, approximately 2.5 million patients are admitted to a hospital with an ACS. Two thirds of these individuals are eventually diagnosed with unstable angina or non–ST-elevation MI. This chapter focuses on diagnosis and treatment of patients in the ACS subgroup called *non–ST-elevation ACS*. Patients diagnosed with ST-elevation MI are discussed in Chapter 14.

ETIOLOGY AND PATHOGENESIS

Several processes can result in an oxygen supply inadequate to meet myocardial demand, the hallmark of ACS. Most patients with an ACS share a common underlying pathophysiology: rupture of an atherosclerotic coronary artery plaque followed by the acute formation of a nonobstructive thrombus (Fig. 13-1). Plaque erosion, characterized by adherence of a thrombus to the plaque surface without an associated disruption of the plaque, is another mechanism of coronary thrombosis. Autopsy series have shown that the prevalence of plaque erosion—as opposed to plaque rupture—as the primary event in ACS is 25% to 40%. The frequency of plaque erosion is higher in women than in men.

Atherosclerotic lesions, composed primarily of a lipid-rich core and a fibrous cap, are extraordinarily common in adults and are present in most major arteries. Autopsy and intravascular ultrasound studies have confirmed the presence of coronary atherosclerotic lesions in most asymptomatic individuals older than 20 to 30 years of age. Why some plaques rupture and others do not is not entirely understood, although plaques prone to rupture do share certain characteristics. The presence of large, eccentric lipid cores and large numbers of inflammatory macrophages are common findings in fissured or ruptured plaques. The role of inflammatory cells and mediators that can effect the degradation and weakening of the protective fibrous cap is probably a critical component in ACS pathogenesis. The majority of lesions rupture at the site of greatest mechanical stress—shoulder regions where the fibrous cap is adjacent to normal intima—which are also often the site of greatest inflammatory activity. Importantly, neither the size of the plaque nor the degree of luminal obstruction caused by it correlates with the risk of rupture. In fact, nearly two thirds of plaques that subsequently rupture were lesions that resulted in stenoses at that site of less than 50%. In fact, the majority of atherosclerotic plaques that rupture are not flow-restricting, representing a stenosis of less than 70%. Thus, there is at most only partial overlap between the types of atherosclerotic lesions that would result in limiting angina (and be appropriate for surgical or percutaneous revascularization) and the less flow-limiting, more inflammatory atherosclerotic plaques that are most prone to rupture.

Other less common but important etiologies of ACS include intense focal spasm of epicardial coronary arteries (Prinzmetal angina) and conditions in which myocardial ischemia is secondary to a pathologic process extrinsic to the coronary arteries. Examples of the latter include an increase in myocardial oxygen demand secondary to tachycardia or fever or a decrease in myocardial oxygen supply due to systemic hypotension, severe anemia, or hypoxemia. These etiologies can result in a pattern of accelerating angina, particularly in individuals with significant underlying coronary atherosclerosis.

As illustrated in Figure 13-2, there are important differences in the pathophysiology of non–ST-elevation versus ST-elevation MI. The treatment of these two entities, and the long-term sequelae are also different.

CLINICAL PRESENTATION

Three principal presentations for ACS have been described: (1) angina that commences with a patient at rest, (2) new onset of severe angina (associated with minimal exertion), and (3) a distinct change in the frequency, duration, or threshold of a patient's prior chronic angina pattern. However, the clinical presentation of ACS can vary considerably in different patients. Up to one third of patients subsequently proven to have an MI do not have chest pain at all, and an even larger number present with chest pain symptoms that are not clearly cardiac in description. The likelihood of an atypical presentation is increased in very young or old patients, in patients with diabetes, and in women.

DIFFERENTIAL DIAGNOSIS

The clinical manifestations of myocardial ischemia can be mimicked by many other processes (see also Chapter 1). Musculoskeletal disorders involving the cervical spine, shoulder, ribs, and sternum can result in nonspecific chest discomfort and even pain syndromes that are similar to angina pectoris. Symptoms from gastrointestinal causes, including esophageal reflux with associated spasm, peptic ulcer disease, and cholecystitis, are

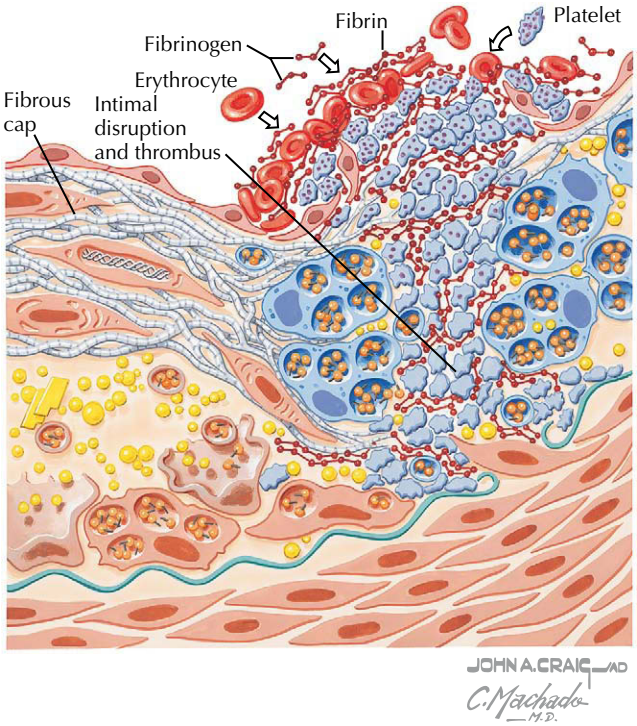


Figure 13-1 *Atherogenesis: unstable plaque formation.*

often indistinguishable from angina. Intrathoracic processes such as pneumonia, pleurisy, pneumothorax, aortic dissection, and pericarditis can produce chest discomfort. Finally, panic attacks and hyperventilation are neuropsychiatric syndromes that can be mistaken for ACS.

DIAGNOSTIC APPROACH

History and Physical Examination

Although careful evaluation of the medical history is a crucial component in determining the diagnosis of a patient with chest pain, medical history alone is an imperfect discriminator of whether a patient is experiencing an ACS, because atypical presentations are so common. Although the classic symptom of chest discomfort from cardiac angina is described as a pressure or heaviness, almost one quarter of patients with chest pain who were eventually diagnosed with myocardial ischemia described chest discomfort as sharp or stabbing. Similarly, 13% of all patients with ACS presented with a pleuritic pain component, and 7% had pain that was reproduced by palpation.

The physical examination in patients with suspected ACS is crucial for ruling out signs of hemodynamic instability and left ventricular (LV) dysfunction, because these findings identify

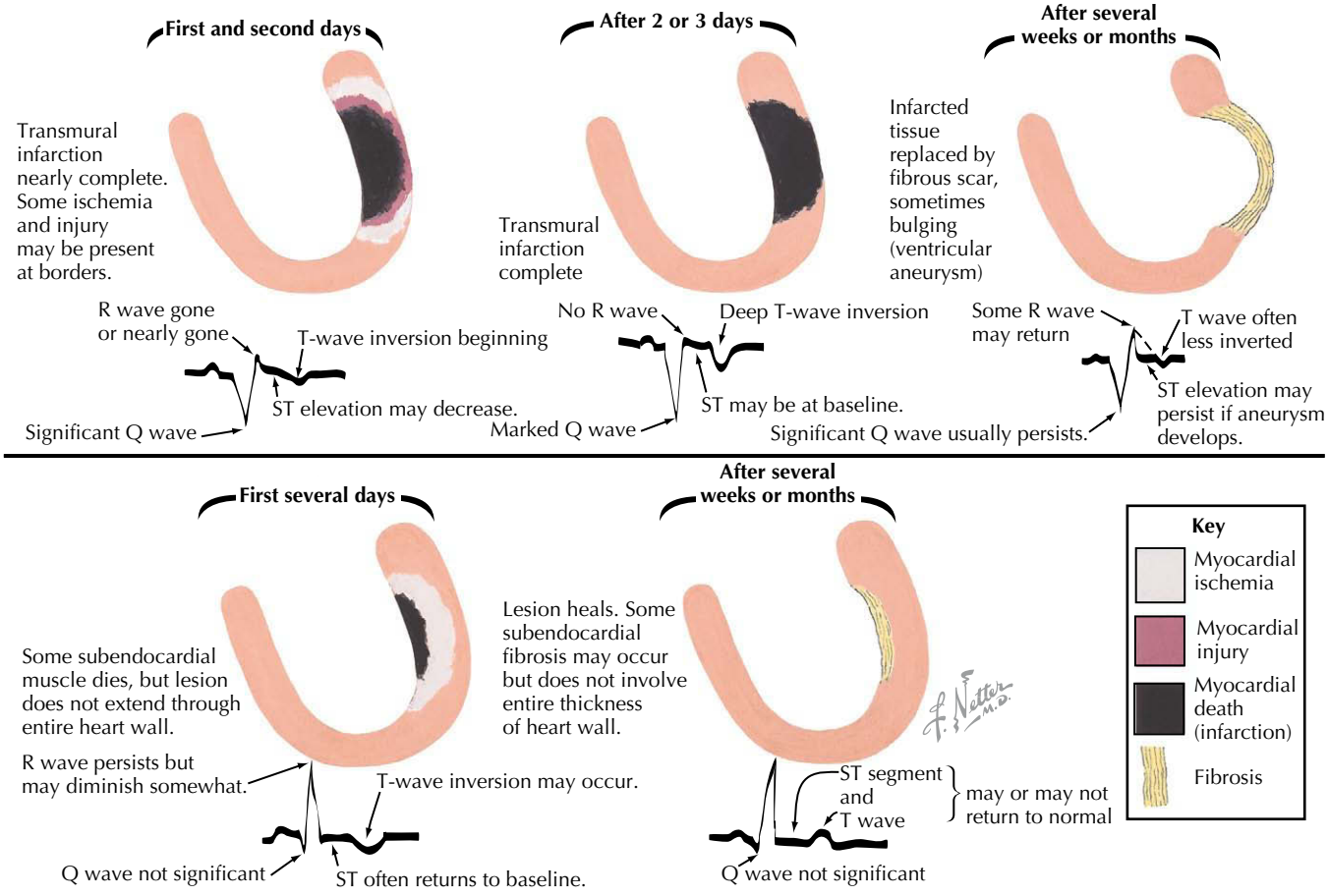


Figure 13-2 *Manifestations of myocardial infarction.*

a high-risk group of patients. In the majority of patients, examination results are normal. A thorough physical examination can help to distinguish noncardiac causes of chest discomfort and secondary causes of myocardial ischemia.

Electrocardiogram

The resting ECG is a key component for assessment of patients with suspected ACS. ST-segment and T-wave changes are the most reliable electrocardiographic indicators of myocardial ischemia (Fig. 13-2). Twelve-lead electrocardiography, performed when symptoms are present, is particularly valuable. Ideally, recordings should be obtained while symptoms are and are not present. When possible, the ECG tracing should be compared with a previous tracing, taken in the absence of chest discomfort. If transient ST-segment or T-wave changes are identified, the patient probably has acute myocardial ischemia.

It is important to note, however, that a normal ECG does *not* exclude ACS in a patient with symptoms of myocardial ischemia. Numerous studies suggest that 5% to 15% of patients with chest pain who are ultimately diagnosed with MI or unstable angina had a normal initial ECG.

The ECG is critical not only for the diagnosis of ACS but also in providing important prognostic information dependent on the type and magnitude of changes. Patients with ST-segment depression are at highest risk of death during the subsequent 6 months, whereas those with isolated T-wave changes have no more long-term risk than do persons with no ECG changes. In patients with ST-segment depression, as the level of depression and the number of leads with depressions increase, so does the risk of death or the probability of repeat MI.

Biochemical Markers of Myocardial Damage

The biochemical markers of myocardial necrosis, creatine kinase (CK) and its relatively cardiac-specific MB isoenzyme (CK-MB), as well as cardiac troponins T and I, are also essential in the diagnosis and prognosis of patients with ACS. These markers become detectable after myocyte necrosis causes the loss of cell membrane integrity, which eventually allows these intracellular macromolecules to diffuse into the peripheral circulation (Fig. 13-3).

Until recently, CK and CK-MB were the primary biochemical markers used to evaluate patients with chest pain. However, several properties of CK and CK-MB limit their predictive value, including their presence at low levels in the blood under normal conditions and in noncardiac sources, especially skeletal muscle. Therefore, in many centers cardiac troponins have become the preferred markers of myocardial necrosis. Because

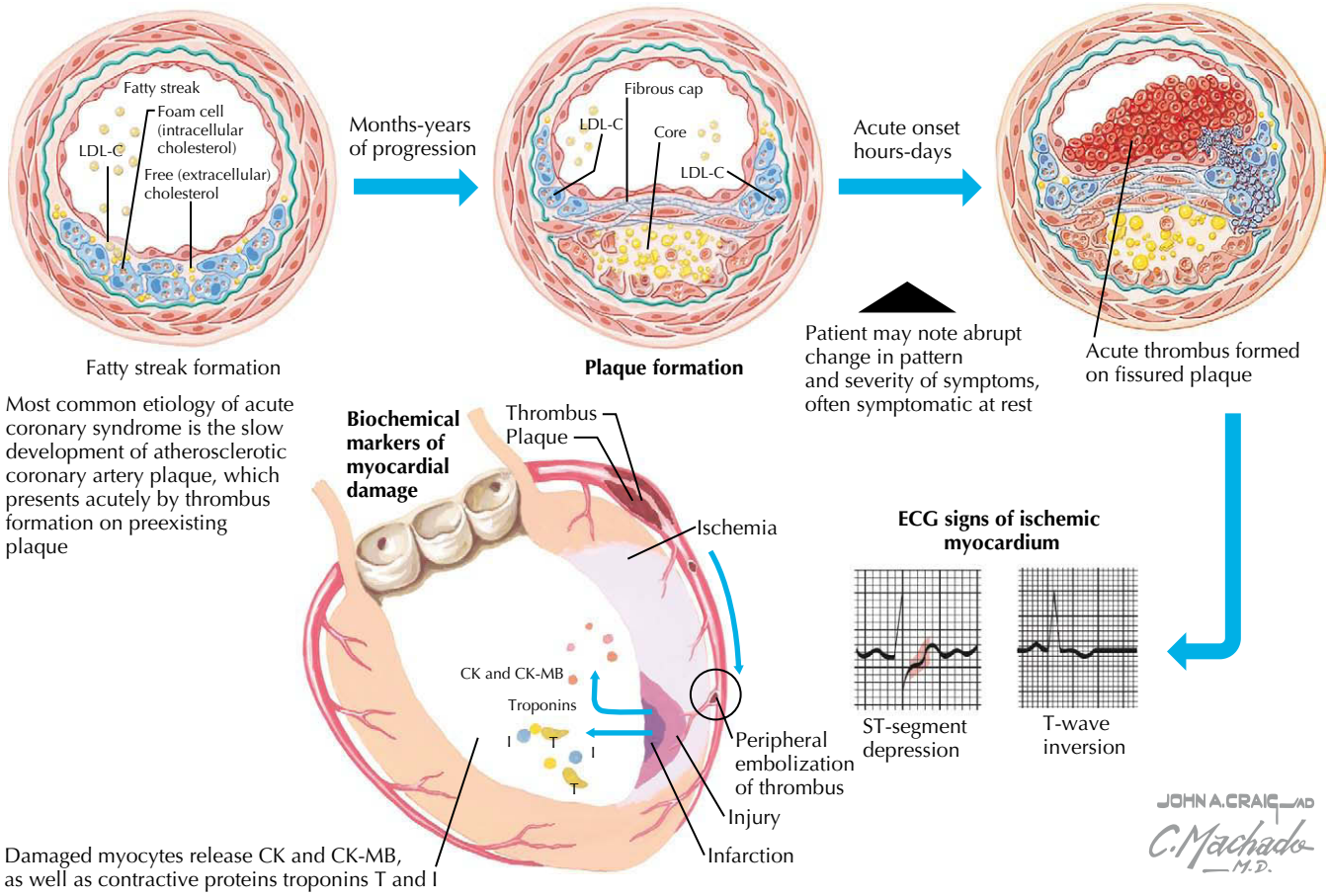


Figure 13-3 *Pathophysiology of acute coronary syndromes.* CK, creatine kinase, CK–MB, creatine kinase MB isoenzyme; ECG, electrocardiographic; LDL-C, low-density lipoprotein cholesterol.

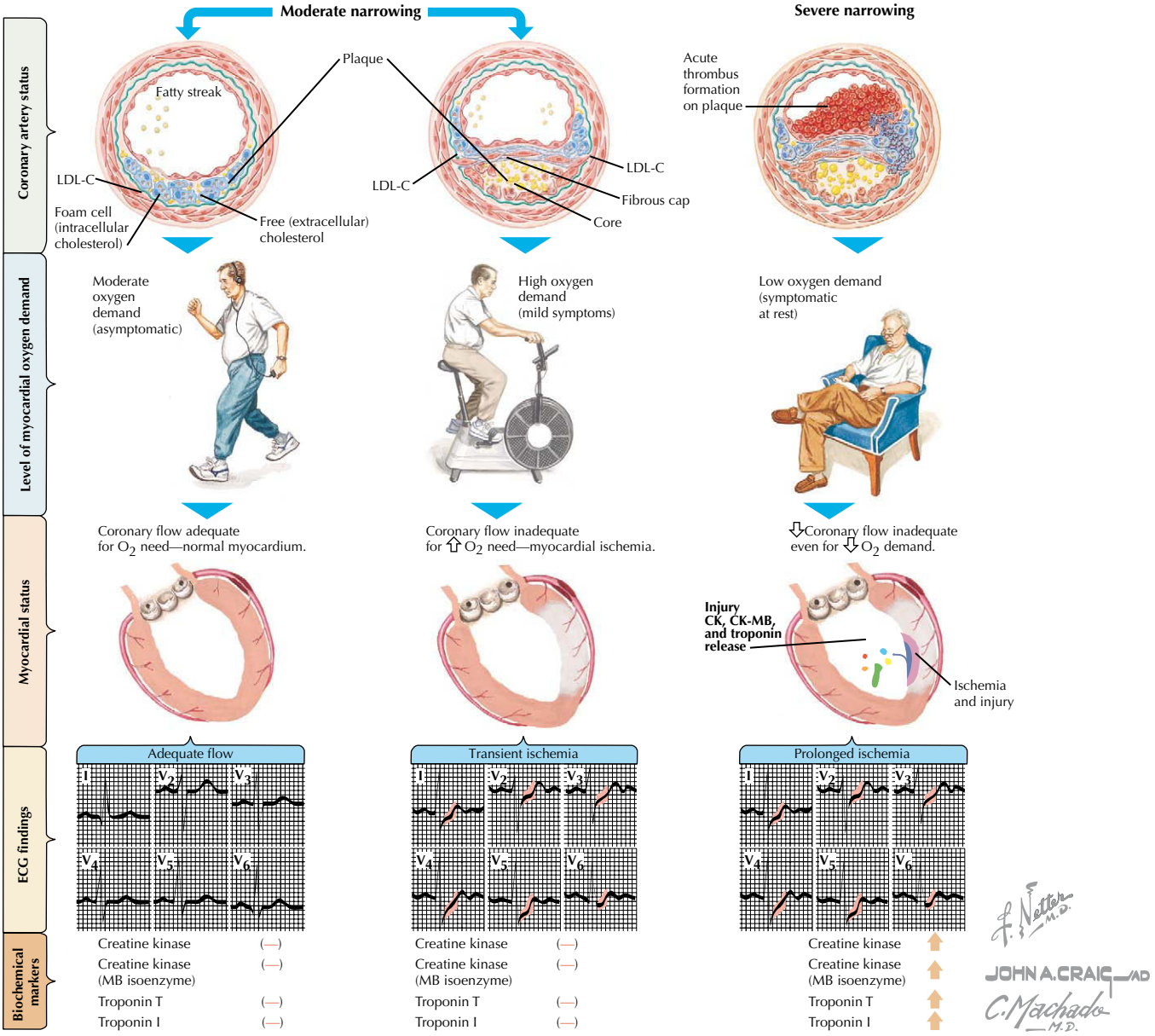


Figure 13-4 *Risk stratification for patients with coronary heart disease.* CK, creatine kinase, CK-MB, creatine kinase MB isoenzyme; LDL-C, low-density lipoprotein cholesterol.

cardiac troponins are not generally detected in the blood of healthy individuals and are cardiac-specific, they are more sensitive and specific for myocardial necrosis than CK and CK-MB. Measurement of troponins allows myocardial necrosis to be detected in approximately one third of patients with unstable angina and normal CK-MB concentrations. It should be noted that in chronic renal failure, severe hypertension, and in other less well-understood settings, there are patients in whom troponin concentrations are chronically elevated.

Because at least 3 to 4 hours are typically necessary after MI to detect an increase in peripheral blood concentrations of CK-MB or troponins, serial blood testing during the initial 6 to 12 hours after presentation is needed to safely exclude myocardial damage in patients presenting with chest pain.

MANAGEMENT AND THERAPY

Risk Stratification

The diagnosis of ACS encompasses a wide spectrum of clinical outcomes. For this reason, the optimal management is best determined by considering each patient's risk for an adverse event. In general, this risk can be categorized as the risk that the current acute presentation was caused by a thrombotic event, in the context of the long-term risk based on that particular patient's atherosclerotic disease burden. The best surrogate for early thrombotic risk is biomarker (troponin or CK-MB) positivity (Fig. 13-4). Multiple studies have confirmed the prognostic significance of elevated troponin concentrations and shown a consistent correlation between treatment benefit and troponin

status. Other markers of early thrombotic risk include ST-segment depression, dynamic ST-segment changes, and recurrent chest pain. Risk factors associated with the degree of underlying disease include advanced age, known coronary disease, and history of diabetes or multiple other classic risk factors for coronary disease (Fig. 13-5).

Many investigators have proposed specific scores—based on various clinical and laboratory criteria—to estimate risk. Thus far, none of these scores for ACS has been sufficiently sensitive, specific, and reliable to justify their use in clinical settings.

Optimum Treatment

ANTI-ISCHEMIC AGENTS

Nitrates reduce myocardial oxygen demand primarily by venodilator effects that decrease myocardial preload. They can also dilate coronary arteries and increase collateral flow. All patients with chest pain who are hemodynamically stable should receive serial sublingual nitroglycerin tablets following diagnostic electrocardiography. Early electrocardiography is critical to diagnose dynamic changes and identify whether right ventricular infarction is present. Nitrates should be used with great caution, or not at all, in patients with suspected or confirmed right ventricular infarction. If pain is not relieved after electrocardiography and use of other therapies such as β-blockers, administration of intravenous nitroglycerin should be initiated. Although nitrates reduce symptoms and myocardial ischemia, the administration of nitrates in ACS does not reduce mortality.

β-blockers competitively inhibit the effects of circulating catecholamine on cardiac β_1-receptors, thereby decreasing myocardial oxygen demand by decreasing heart rate and contractility. β-blockers should be given early, preferably intravenously, if tolerated. Oral therapy can then be maintained to achieve a resting heart rate of 50 to 60 bpm. β-blockers should be used cautiously if at all in patients with significant atrioventricular conduction delays, a history of asthma, or acute LV dysfunction. In patients who are intolerant of β-blockers, nondihydropyridine calcium channel blockers can be considered. β-blockers do reduce mortality when administered early in the course of an acute MI. Dihydropyridine calcium channel blockers should be avoided, especially in patients not receiving a β-blocker, because they can cause reflex tachycardia and therefore increase myocardial work and oxygen demand.

Morphine sulfate can be an effective adjunct when other anti-ischemic therapies have not relieved symptoms. Although morphine has some beneficial hemodynamic effects, its primary benefits are analgesia and anxiety reduction. Although these properties are important to calm a patient and decrease associated elevated catecholamine levels, the analgesic effects can mask symptoms of ongoing myocardial ischemia. In a patient who is asymptomatic following morphine administration, if objective evidence suggests ongoing myocardial ischemia, further therapy should not be delayed.

ANTICOAGULANT DRUGS

Heparin and low-molecular-weight heparin (LMWH) indirectly inhibit thrombin formation and activity, thereby facilitating thrombus resolution. Clinical trials comparing the effects of heparin plus aspirin versus aspirin alone have not shown a consistent benefit to heparin, in terms of reduction in mortality and morbidity in ACS. Larger trials have not been, and probably will not be, conducted. Based on the consensus of opinion, full anticoagulation with administration of intravenous heparin and aspirin is recommended for the initial treatment of patients with ACS and decreases the risk of death and MI by 30% to 40%.

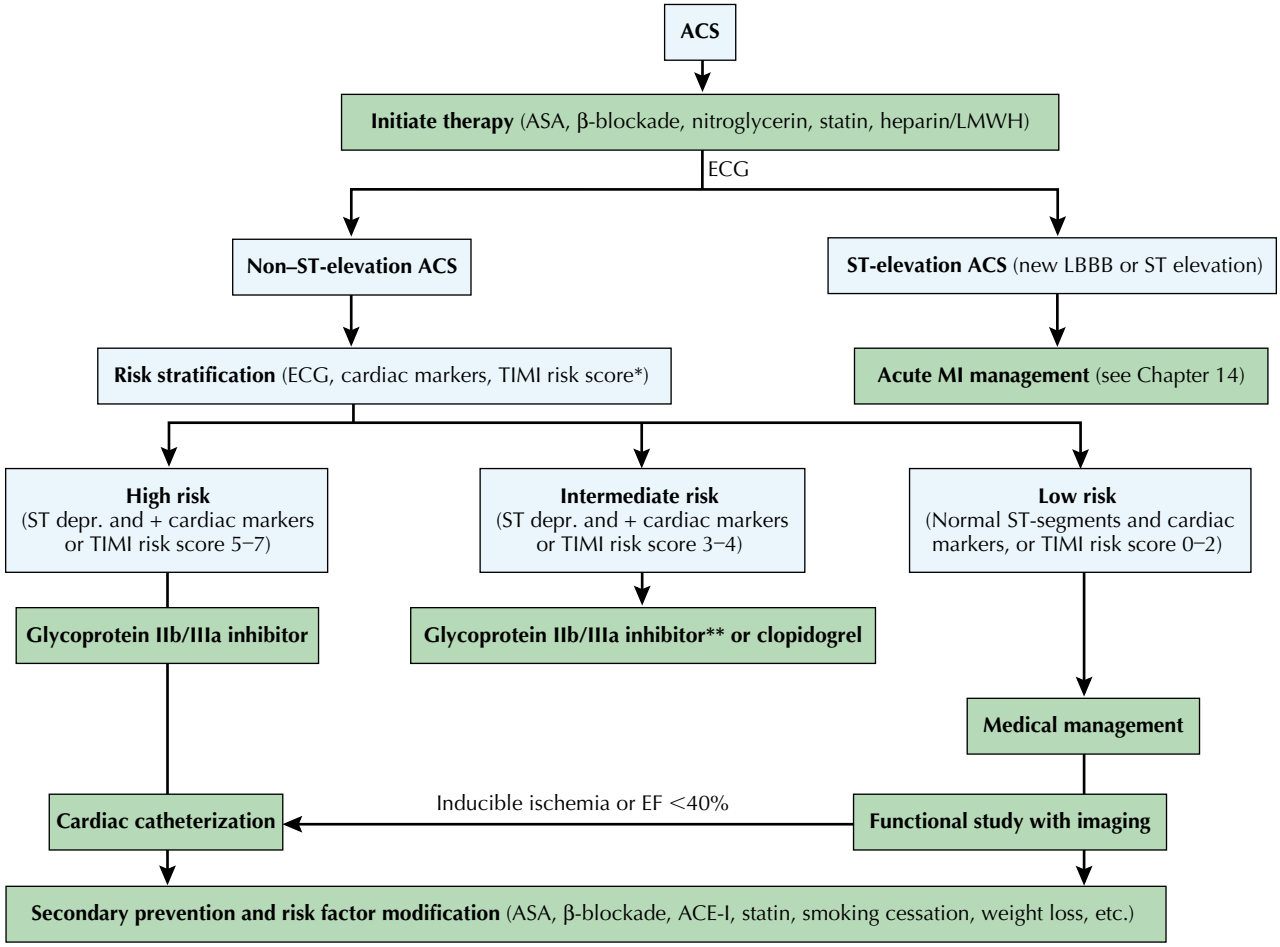
LWWH, compared with unfractionated heparin, possesses increased anti-factor Xa activity in relation to anti-factor IIa (antithrombin) activity. LMWH offers several advantages over unfractionated heparin. LMWH can be administered subcutaneously, and its anticoagulant effect is more predictable than that of heparin, so that monitoring is not required. Among the several LMWHs that are approved and available for the treatment of patients with ACS, there is variation in the ratio of anti-factor IIa (thrombin) and anti-factor Xa. How these differences influence the therapeutic benefit of LMWH is unclear. Enoxaparin is the only LMWH shown to be superior to unfractionated heparin in the treatment of patients with ACS.

Direct thrombin inhibitors have also been investigated for the management of patients with an ACS. In the ACUITY (Acute Catherization and Urgent Intervention Triage Strategy) Trial, patients with non–ST-elevation ACS undergoing an early invasive strategy were randomized to one of three treatment groups: heparin plus a glycoprotein (Gp) IIb/IIIa inhibitor, bivalirudin plus Gp IIb/IIIa inhibitor, or bivalirudin alone. The direct thrombin inhibitor bivalirudin seemed to be noninferior (i.e., therapeutically comparable) to heparin plus Gp IIb/IIIa inhibitor therapy and was associated with less bleeding. Patients with positive biomarkers who were randomized to bivalirudin therapy without a Gp IIb/IIIa inhibitor did better when pretreated with a thienopyridine. Guidelines as to the use of direct thrombin inhibitors are currently being developed.

ANTIPLATELET AGENTS

Aspirin inhibits the amplification of the platelet activation process by blocking the formation of thromboxane A_2 through the irreversible inhibition of platelet cyclooxygenase-1. Multiple placebo-controlled trials, using daily aspirin doses of 75 to 325 mg, have consistently demonstrated decreased mortality and a decrease in the rate of MI. In general, the literature suggests an approximately 50% reduction in mortality and morbidity in ACS patients treated with aspirin versus placebo. Not only does aspirin therapy provide an acute benefit, but its long-term use leads to continued reduction in mortality and morbidity from ACS in this patient group. Accordingly, aspirin therapy is the cornerstone of antithrombotic therapies in patients with ACS.

The thienopyridines irreversibly inhibit the platelet P2Y12 ADP receptor, thereby inhibiting platelet activation. Because aspirin and clopidogrel, the most commonly used theinopyridine, inhibit platelet activation by separate mechanisms, when used together they provide a synergistic antiplatelet effect. Moreover, because activation of individual platelets leads to generalized platelet activation, the aspirin-clopidogrel combination reduces amplification of platelet activation and thrombosis. The clinical benefit of this combination was demonstrated in the trial Clopidogrel in Unstable Angina to Prevent Recurrent



*TIMI risk score calculation appears in the table below.
**Abciximab should not be used in patients not expected to undergo immediate catheterization.

TIMI risk factor score

Risk factors	Risk of adverse cardiac event*	
1. Age >65	# of risk factors	% risk
2. ≥3 risk factors for CAD	0–1	4.7
3. Prior coronary stenosis ≥50%	2	8.3
4. ≥2 anginal event in past 24 hours	3	13.2
5. Aspirin use in past 7 days	4	19.9
6. ST-segment changes	5	26.2
7. Positive cardiac markers	6–7	41

* Mycocardial infarction, cardiac-related death, persistent ischemia; CAD
Low risk = score 0–2, Intermediate risk = score 3–4, High risk = score 5–7.

Figure 13-5 *Algorithm for the differential diagnosis and treatment of acute coronary syndrome (ACS).* ACE-I, angiotensin converting enzyme inhibitor; ASA, aspirin; CAD, coronary artery disease; depr., depression; EF, ejection fraction; LBBB, left bundle branch block; LMWH, low-molecular-weight heparin; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction Trial.

Ischemic Events (CURE), which enrolled more than 12,500 ACS patients. In this study, combination therapy with clopidogrel and aspirin led to a relative 20% decrease in the combined end point of death, MI, and stroke compared with aspirin alone. This decrease in mortality and major morbidity was present soon after initiation of therapy. The positive benefits of aspirin-clopidogrel therapy continued and were even more pronounced after a mean follow-up of 9 months.

Irrespective of the mechanism of platelet activation, platelet aggregation is dependent on platelet-platelet interaction through Gp IIb/IIIa receptors on the platelet surface and fibrinogen. Several direct antagonists to the platelet Gp IIb/IIIa receptor have been developed and studied in ACS patients. Abciximab, tirofiban, and eptifibatide are effective adjunctive agents in patients with an ACS. The most pronounced benefit is seen in patients who are troponin-positive or undergo a percutaneous coronary intervention (PCI) as an initial therapy for ACS. Additionally, studies of multiple oral Gp IIb/IIIa receptor antagonists have reproducibly shown a trend toward an increase in rates of death and MI, along with a significantly higher

bleeding rate, compared with patients treated with aspirin alone. These agents are not indicated in long-term therapy of patients with ACS.

CORONARY REVASCULARIZATION

Indications for and timing of revascularization of the ACS patient, either through PCI or coronary artery bypass graft surgery, remain controversial. Early trials (TIMI IIB and VANQWISH) comparing an invasive approach, which required early angiography and revascularization if indicated, with a more conservative, symptom-driven approach, showed little benefit and even suggested possible harm from use of an invasive strategy. More recent trials (FRISC II and TACTICS-TIMI 18), however, have consistently confirmed the benefit of an invasive approach. As with other therapies, the benefit of an invasive approach was primarily realized in those patients at greatest risk, particularly patients with elevated troponins. This probably explains the results of the earlier studies in which the majority of patients enrolled were clinically stable. Based on the available literature, PCI should be considered for patients presenting with an ACS who are at increased risk based on clinical findings, ECG analysis, and/or positive biomarkers.

Avoiding Treatment Errors

Non–ST-elevation ACS is an initial clinical diagnosis based on the history obtained from the patient. The clinician should not wait for ECG changes or elevations in cardiac biomarkers before initiating therapy. Once initial therapy is given, risk stratification—specifically, determining whether evidence of hemodynamic compromise or LV dysfunction is present, determining whether ischemic ECG changes are present, and laboratory analysis for biomarker positivity—should be done to direct further therapy (see Fig. 13-5).

FUTURE DIRECTIONS

Dramatic advances in our understanding of the pathophysiology of ACS have been made in recent years. As a result, patients with ACS are treated more rapidly and more efficaciously today than at any point in the past. In the years to come there will be continued improvement in antithrombotic and anti-ischemic therapies, and further research will identify those patients at greatest short- and long-term risk. By improving our ability to identify risk, both for the individual patient and for specific coronary lesions, therapies can be more appropriately directed, and complications of therapy can be minimized.

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ST-Elevation Myocardial Infarction

Martin Moser, Markus Frey, and Christoph Bode

14

The diagnosis of acute coronary syndrome (ACS) is based on findings ranging from clinical presentation to ECG and/or biochemical findings to pathologic characteristics. Patients with ACS include those whose clinical presentations cover the following range of diagnoses: unstable angina, myocardial infarction (MI) without ST elevation (NSTEMI), and MI with ST elevation (STEMI). An estimated 500,000 STEMI events per year occur in the United States.

ETIOLOGY AND PATHOGENESIS

The initial event in formation of an occlusive intracoronary thrombus is rupture or ulceration of an atherosclerotic plaque. Plaque rupture results in exposure of circulating platelets to the thrombogenic contents of the plaque, such as fibrillar collagen, von Willebrand factor, vitronectin, fibrinogen, and fibronectin. Adhesion of platelets to the ulcerated plaque, with subsequent platelet activation and aggregation, leads to thrombin generation, conversion of fibrinogen to fibrin, and further activation of platelets, as well as vasoconstriction, due in part to platelet-derived vasoconstrictors. This prothrombotic milieu promotes propagation and stabilization of an active thrombus that contains platelets, fibrin, thrombin, and erythrocytes, resulting in occlusion of the infarct-related artery (Fig. 14-1A). Upon interruption of antegrade flow in an epicardial coronary artery, the zone of myocardium supplied by that vessel immediately loses its ability to perform contractile work (Fig. 14-1B). Abnormal contraction patterns develop: dyssynchrony, hypokinesis, akinesis, and dyskinesis. Myocardial dysfunction in an area of ischemia is typically complemented by hyperkinesis of the remaining normal myocardium, due to acute compensatory mechanisms (including increased sympathetic nervous system activity) and the Frank-Starling mechanism.

CLINICAL PRESENTATION

Typical prodromal symptoms are present in many but not all patients who present with an acute MI. Of these, chest discomfort, resembling classic angina pectoris but occurring at rest or with less activity than usual, is the most common. The intensity of MI pain is variable, usually severe, and in some instances intolerable. Pain is prolonged, usually lasting more than 30 minutes and frequently lasting for hours. The discomfort is typically described as constricting, crushing, oppressing, or compressing. Often, the patient complains of a sensation of a heavy weight on or a squeezing in the chest. The pain is usually retrosternal, frequently spreading to both sides of the anterior chest, with predilection for the left side. Often the pain radiates down the ulnar aspect of the left arm, producing a sensation in the left wrist, hand, and fingers. In some instances, pain of an acute MI may begin in the epigastric area and simulate a variety of abdominal disorders. In other patients, MI discomfort radiates to the shoulders, upper extremities, neck, jaw, and even the interscapular region. In patients with preexisting angina pectoris, the pain of infarction usually resembles that of angina. However, it is generally much more severe, lasts longer, and is not relieved by rest and nitroglycerin (Fig. 14-2). In some patients, particularly the elderly, an MI is manifested clinically not by pain but by symptoms of acute left ventricular (LV) failure and chest tightness or by marked weakness or frank syncope. These symptoms may be accompanied by diaphoresis, nausea, and vomiting. More than 50% of patients with ST-segment elevation and severe chest pain experience nausea and vomiting, presumably from activation of the vagal reflex or from stimulation of LV receptors as part of the Bezold-Jarisch reflex. These symptoms are more common in patients with an inferior MI than in those with an anterior MI.

Numerous findings may be present in the patient presenting with an acute MI. LV dysfunction may also result in pulmonary edema, hypotension, and decreased peripheral perfusion with cool extremities and mottling. Evidence of LV dysfunction may be present at early stages in patients with very large areas of ischemia or with preexisting LV dysfunction from a prior MI. Additionally, patients with acute mitral valve regurgitation may present with marked evidence of LV dysfunction. Patients with mitral regurgitation secondary to dysfunction of the mitral valve apparatus (papillary muscle dysfunction, LV dilatation) may, but not always, have an audible holosystolic murmur upon presentation. A third heart sound usually reflects severe LV dysfunction with elevated filling pressures. Marked jugular venous distention and *v* waves consistent with tricuspid regurgitation are evident in right ventricular infarction.

DIFFERENTIAL DIAGNOSIS

The pain of an acute MI may simulate the pain of acute pericarditis, which is usually associated with some pleuritic features and aggravated by respiratory movements and coughing. Pleural pain is more typically sharp, knifelike, and aggravated in a cyclic fashion by each breath. These features distinguish pleural pain from the deep, dull, steady pain of an acute MI. Pulmonary embolism generally produces pain laterally in the chest, often is pleuritic, and may be associated with hemoptysis. Pain from acute dissection of the aorta is usually localized in the center of the chest or back, is extremely severe, persists for many hours, often radiating to the back or lower extremities, and reaching maximal intensity shortly after onset of the pain. Often, one or more major arterial pulses are absent. Pain arising from the costochondral and chondrosternal articulations is characterized by marked localized tenderness. The pain of an acute MI, particularly of an inferior MI, may also simulate the pain of peptic ulcer disease or stress gastritis.

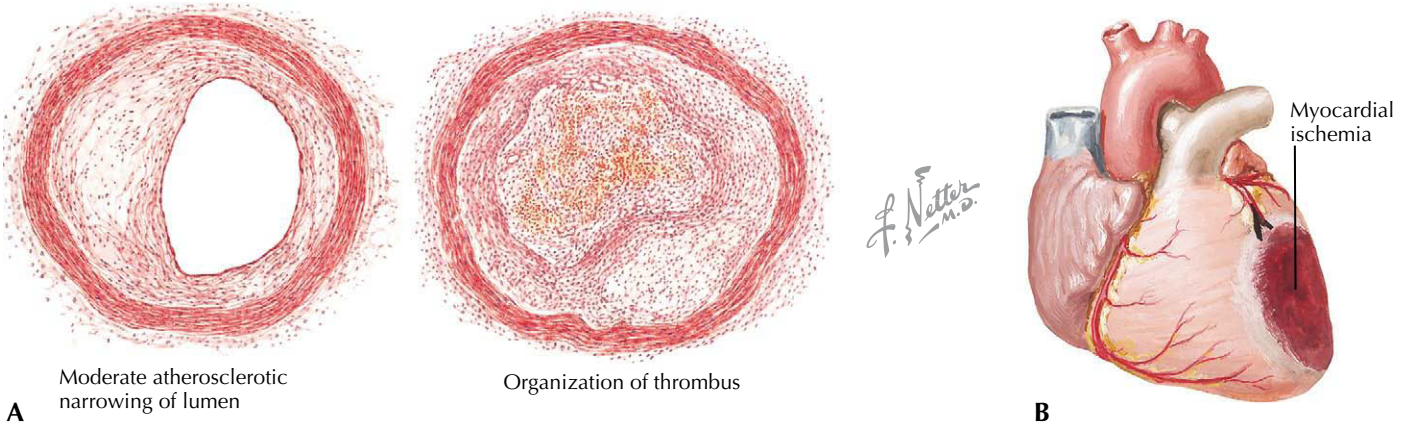

Figure 14-1 *(**A**) Pathophysiology of acute myocardial ischemia. (**B**) Myocardial ischemia.*

DIAGNOSTIC APPROACH

Electrocardiographic Findings

A pattern of ST-segment elevation, especially with associated T-wave changes and ST depression in another anatomic distribution ("reciprocal changes"), combined with chest pain persisting longer than 20 minutes is highly indicative of STEMI (Fig. 14-3). To meet the ECG criteria for STEMI the ST segment must be elevated in at least two contiguous leads by more than 0.2 mV in V_1 and V_2 in men (0.15 mV in women) and/or by more than 0.1 mV in other leads. Many factors limit the ability of ECGs to diagnose and localize an MI: the extent of the myocardial injury, the age of the infarct, the infarct's location (e.g., the 12-lead ECG is relatively insensitive to infarction in the posterolateral region of the left ventricle), conduction defects, previous infarcts or acute pericarditis, changes in electrolyte concentrations, and the administration of cardioactive drugs. In addition, some patients with an acute MI do not have significant ST changes because of the location of the infarction. For these reasons, even in the absence of STEMI ECG criteria, severe myocardial ischemia necessitating therapy may be present (see Chapter 13). With an appropriate clinical history, it may be necessary to pursue further diagnostic testing to rule out acute MI.

Serum Cardiac Markers

Before cardiac markers can be detected in serum, the myocyte cell membrane has to have disintegrated. Because this disintegration process takes time, serum markers are not useful for early detection of an acute MI. Serum markers are, however, proof of an established MI and useful indicators of risk.

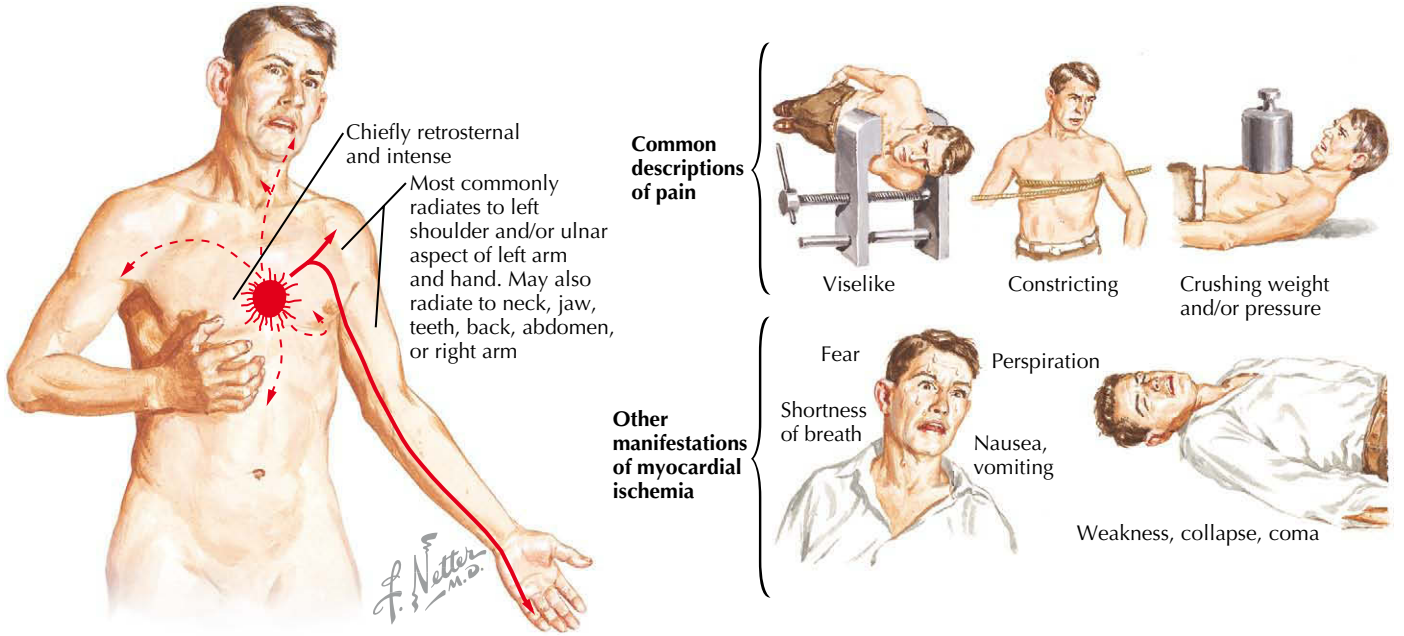

Figure 14-2 *Characteristics of chest pain in myocardial ischemia.*

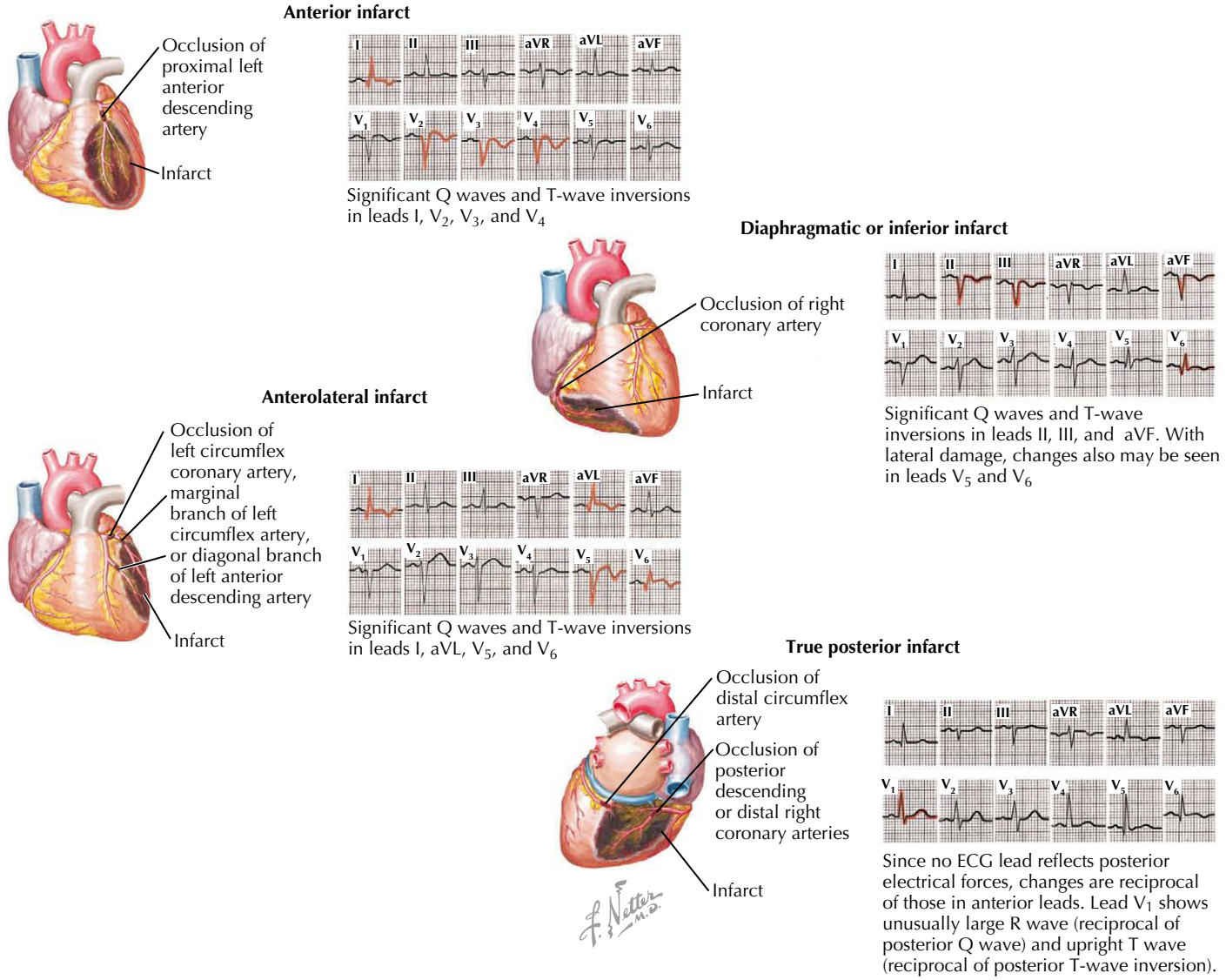

Figure 14-3 *Electrocardiogram (ECG) localization of ST-elevation myocardial infarction.*

Established serum markers used to diagnose an acute MI are creatine kinase (CK) and CK isoenzymes (CK-MB fraction), myoglobin, and cardiac-specific troponins (troponin I and troponin T). The smaller molecule myoglobin is released quickly from infarcted myocardium but is not cardiac-specific. Therefore, elevations of myoglobin that may be detected early after the onset of infarction require confirmation with a more cardiac-specific marker, such as troponin I or troponin T. The troponins are the most specific marker in clinical use. The sensitivity of troponins is quite high, but in some settings (particularly renal failure), troponin elevation can occur in the absence of myocardial injury.

Other Imaging

In STEMI patients presenting with cardiogenic shock, echocardiography can be useful in detecting correctable mechanical causes for low cardiac output—for instance, the presence of a new ventricular septum defect or papillary muscle dysfunction—and distinguishing these from global LV dysfunction. Because echocardiography can be performed at the bedside and can provide so much useful information, it is the most commonly used advanced imaging approach in patients with STEMI or ACS. Radiographic examination may show signs of LV failure and cardiomegaly. MRI can permit early recognition of an MI and an assessment of the severity of ischemic insult, although at present MRI is not used clinically in STEMI patients at most medical centers. With emphasis on early reperfusion (see "Management and Therapy"), the use of imaging techniques is extremely limited in the setting of an acute STEMI because of the time necessary for these studies.

MANAGEMENT AND THERAPY

Optimum Treatment

Several treatment options lower the mortality rate in an acute STEMI (Fig. 14-4). These options include early reperfusion (using percutaneous coronary interventions [PCIs], such as

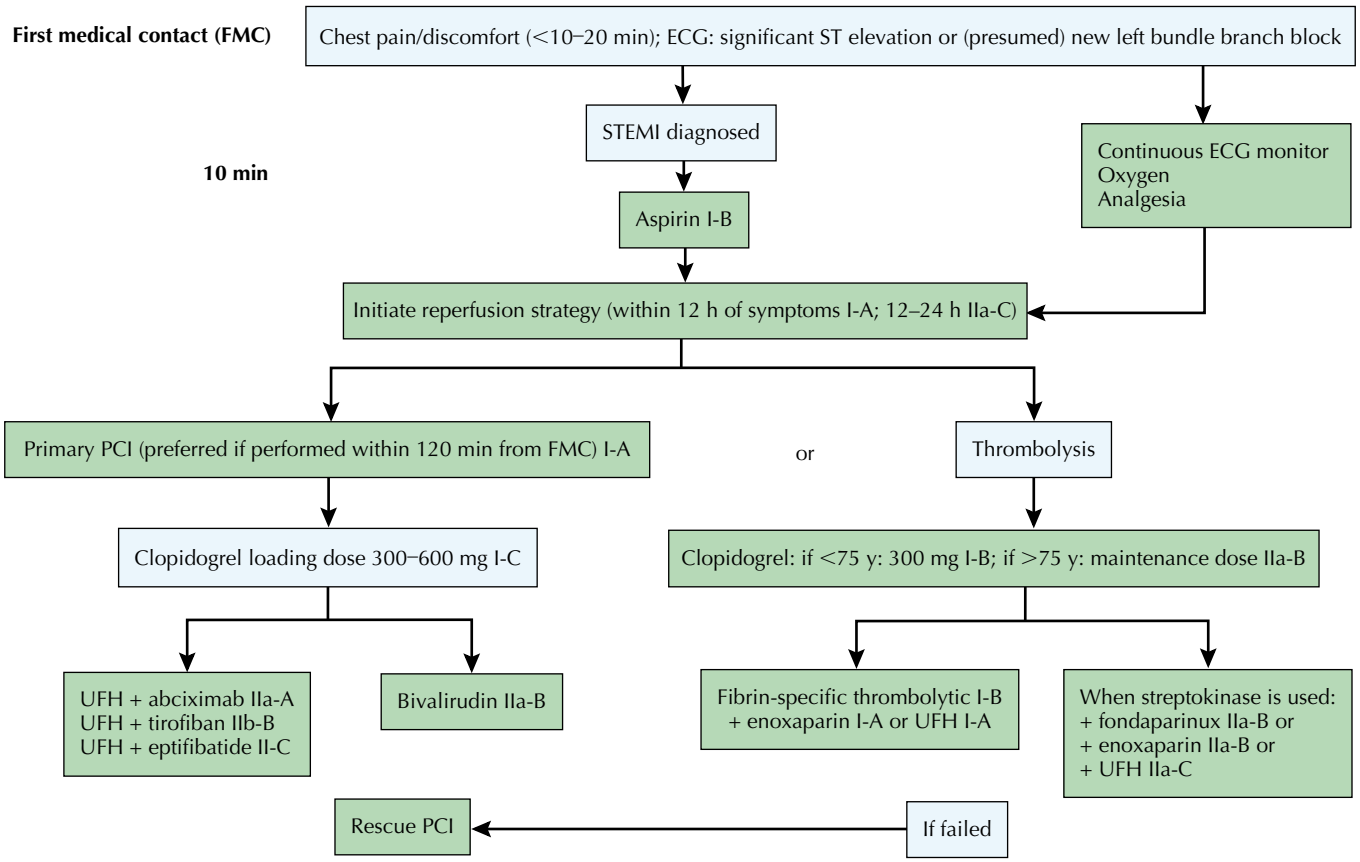

Figure 14-4 *Optimum treatment of ST-elevation myocardial infarction (STEMI).* ECG, electrocardiogram; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. See ESC STEMI Guidelines 2008 for complete classification and level of evidence recommendations.

angioplasty including stent placement; or thrombolytic therapy) and administration of aspirin and/or other platelet inhibitors, β-blockers, angiotensin-converting enzyme inhibitors, and statins. Other therapies for acute STEMI include the use of unfractionated heparin, low-molecular-weight heparin, nitrates, and antiarrhythmic agents; however, the data supporting use of these therapies are less compelling.

Reperfusion is by far the most effective treatment. Until PCI became the standard of care in hospitals with interventional cardiology programs, thrombolytic therapy was the best available reperfusion therapy. In communities without interventional capabilities where there are long transport times (discussed below) to an appropriate facility, thrombolytic therapy is indicated in the case of ST elevation or presumably new left bundle branch block (which obscures the ECG diagnosis of an MI). Various thrombolytic agents, including streptokinase, alteplase, reteplase, and tenecteplase, are all widely available. Their administration does not require specialized facilities or staff; and these agents can be administered with minimal time delay. Numerous large clinical trials have associated the use of thrombolytic therapy with preservation of LV function, limitation of infarct size, and a highly significant reduction in mortality rate. This benefit is time-dependent. When administered within 2 hours of symptom onset, fibrinolytic agents are associated with a 30% reduction in mortality rate. This benefit decreases to an 18% reduction if the fibrinolytic agents are given within 6 hours of symptom onset. Although fibrinolytic agents restore blood flow in the infarct-related artery in more than 80% of patients within 90 minutes of administration, failure to achieve complete restoration of normal coronary flow (thrombolysis in MI grade 3 flow), which may occur only in 45% to 60% of patients, represents a severe efficacy limitation of this therapy. Even after successful reperfusion, reocclusion and thus reinfarction occurs in up to 20% of patients. Therefore, only approximately 25% of patients treated with thrombolytic therapy achieve the ideal outcome of rapid and sustained normalization of flow in the infarct-related artery. Finally, fibrinolytic therapy is limited by contraindications to its use, which affect up to 30% of patients, and a risk of lethal or intracranial hemorrhage of approximately 1%.

In recent years, primary angioplasty and stent placement (PCI) have been shown to be more efficacious than thrombolytic therapy in the treatment of patients with acute STEMI (Fig. 14-5). PCI is more effective than thrombolytic therapy because it achieves both higher infarct-related artery patency rates and results in TIMI grade 3 flow more often than thrombolysis (Fig. 14-6). PCI also has advantages over thrombolytic therapy in terms of the rates of short-term mortality, bleeding

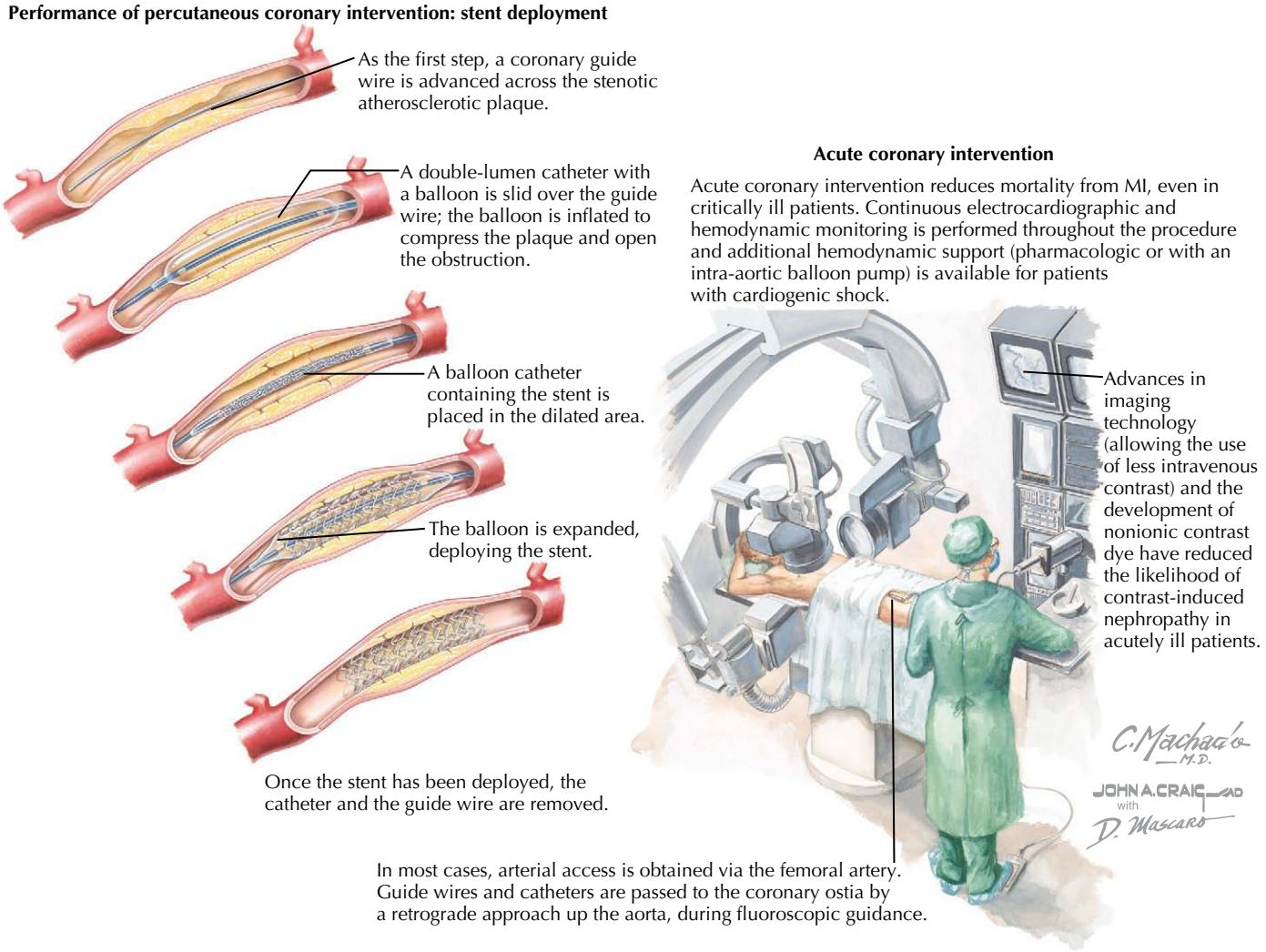

Figure 14-5 *Acute percutaneous coronary intervention (PCI) in the management of myocardial infarction (MI) with ST-elevation (STEMI).*

complications (including intracranial hemorrhage), and stroke. The benefit of primary angioplasty with regard to the rates of mortality, reinfarction, and recurrent ischemia continues over long-term follow-up. Early intervention has the additional advantage of angiographic definition of the coronary vessels, which allows early risk stratification and identification of patients at particularly high or low risk for recurrent MI or cardiovascular compromise. The use of stents in primary angioplasty adds further benefits, addressing the frequent problem of restenosis and the need for repeat revascularization. The use of drug-eluting stents is advocated in the treatment of STEMI patients in some centers because of the reduced risk of restenosis associated with drug-eluting stents. Mechanical reperfusion is superior to thrombolysis, even if longer transport times to a specialized center must be accepted. Recent studies have suggested that if a patient with an acute MI can be transported to a facility with PCI capability within 2 hours, even with the delay in initiation of definitive therapy, patients undergoing PCI (as compared with those undergoing thrombolytic therapy) have improved outcomes.

Avoiding Treatment Errors

In patients presenting with the clinical symptoms of acute MI that meet the ECG criteria for STEMI, treatment should be started immediately. It is a mistake to wait for serum cardiac markers in this situation. Serum markers may not be elevated if the patient presents early after symptom onset. Additionally, patients with a compelling clinical presentation for acute MI without ECG changes should be considered for urgent echocardiography to determine whether myocardial ischemia is present (and electrocardiographically silent).

Adjunctive Therapy

Adjunctive antiplatelet and antithrombotic therapy are cornerstones of the treatment of STEMI. The anti-ischemic potency of the adjunctive therapy is based on its anticoagulatory effects and must be balanced against the bleeding risk to the respective patient. Aspirin, an irreversible antagonist of the arachidonic acid pathway of platelet activation, is the first-choice antiplatelet

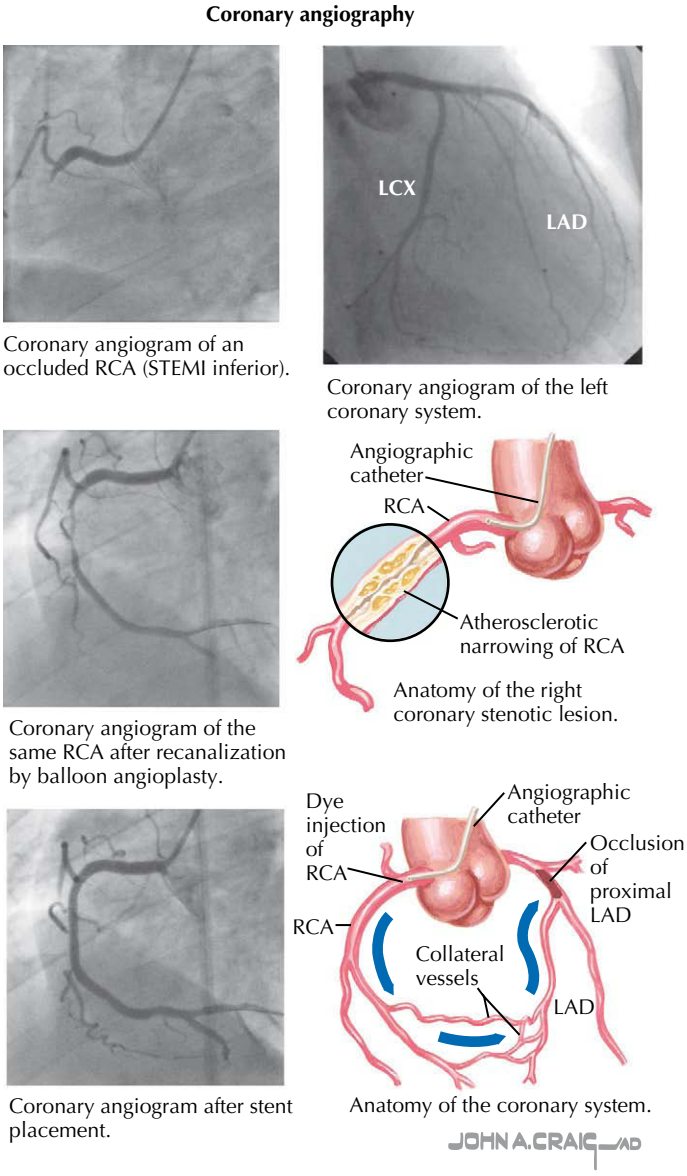

Figure 14-6 *Recanalization of an occluded right coronary artery (RCA).* LAD, left anterior descending; LCX, left circumflex; STEMI, ST-elevation myocardial infarction.

drug that every patient suffering from STEMI should receive as soon as possible independent from the planned revascularization strategy. Inhibition of additional pathways of platelet activation is beneficial. Clopidogrel, an antagonist of the ADP receptor responsible for platelet activation, decreases ischemic events and reduces mortality in STEMI patients. Clopidogrel is a prodrug and must be metabolized in the liver to be activated, resulting in a delayed onset of action. To achieve effective levels of platelet inhibition as fast as possible, a loading dose of 300 mg clopidogrel is recommended in the ACC/AHA guidelines followed by a maintenance dose of 75 mg/day (see Evidence section). It is noteworthy that a higher bolus dose (600 mg) providing even faster onset and a higher level of platelet inhibition is used in many centers. The different pathways of platelet activation lead to one final common pathway, activation of the glycoprotein (Gp) IIb/IIIa receptor. Upon activation it binds soluble fibrinogen, resulting in the formation of platelet aggregates. Gp IIb/IIIa receptor antagonists block the binding of fibrinogen to Gp IIb/IIIa and consequently inhibit platelet aggregation very effectively. Abciximab, a recombinant antibody that irreversibly blocks Gp IIb/IIIa, has been effective in clinical trials in reducing ischemic events and mortality in STEMI patients undergoing PCI. The combination of thrombolytic therapy and Gp IIb/IIIa antagonists is not recommended because of an increased bleeding risk. Data supporting the small-molecule Gp IIb/IIIa antagonists eptifibatide and tirofiban are not as compelling as those for abciximab, but these agents are considerably less expensive compared to abciximab, making the choice of the appropriate Gp IIb/IIIa antagonist sometimes challenging.

The traditional antithrombotic drug in ACS patients is unfractionated heparin. Newer anticoagulants have been developed to circumvent the disadvantages of heparin such as high interindividual variability in antithrombotic response, the need for close monitoring of the effect, and the risk of heparin-induced thrombocytopenia, a potentially life-threatening side effect. Low-molecular-weight heparins have—as a result of their decreased binding to endothelial cells and plasma proteins—a more predictable antithrombotic effect than does unfractionated heparin, and thus doses can usually be given weight-adjusted without further monitoring. Heparin or low-molecular-weight heparins should be used independently from the revascularization strategy. A novel direct antithrombin, bivalirudin, was approved for STEMI patients who undergo interventional revascularization. Compared to the standard therapy with heparin combined with a Gp IIb/IIIa antagonist, the treatment with bivalirudin alone had similar anti-ischemic properties but fewer bleeding complications. Thus, bivalirudin may be an alternative choice to Gp IIb/IIIa antagonists, particularly in patients with an increased risk for bleeding.

Hemodynamic Disturbances and Arrhythmias

LV dysfunction remains the most important predictor of death after survival of the acute phase of STEMI. In patients with STEMI, heart failure is characterized by systolic dysfunction or by both systolic and diastolic dysfunction. LV diastolic dysfunction can lead to pulmonary venous hypertension and pulmonary congestion; systolic dysfunction can result in markedly depressed cardiac output and cardiogenic shock. Mortality rates in patients with acute STEMI increase with the severity of the hemodynamic deficits.

Mechanical causes of heart failure may occur in acute STEMI: free wall rupture, pseudoaneurysm, rupture of the interventricular septum, or rupture of a papillary muscle. Arrhythmias may occur in an MI as a consequence of electrical instability. Sinus bradycardia, sometimes associated with atrioventricular block and hypotension, may reflect augmented vagal activity. Ischemic injury can produce conduction block at any level of the atrioventricular or intraventricular conduction system.

Other complications after an acute MI are recurrent chest discomfort, ischemia, and infarction. Furthermore, pericardial

effusion, pericarditis, and Dressler's syndrome may also occur. An LV aneurysm develops in fewer than 5% to 10% of patients with an STEMI (especially patients with an anterior MI). The mortality rate is up to six times higher in patients with an LV aneurysm than in patients without aneurysms. Death in patients with an LV aneurysm is often sudden and presumably related to ventricular tachyarrhythmias, which frequently occur with aneurysms.

Secondary Prevention

The concept of secondary prevention of reinfarction and death after recovery from an acute MI includes lifestyle modification, cessation of smoking, and control of hypertension and diabetes mellitus. Lipid profile modification requires drug therapy (preferably with an HMG CoA reductase inhibitor—usually one of the widely available statins) in most patients. Randomized trials of patients with a prior MI have shown that prolonged antiplatelet therapy leads to a 25% reduction in the risk of recurrent infarction, stroke, or vascular death. Indefinite angiotensin-converting enzyme inhibitor therapy is recommended for patients with clinically evident congestive heart failure, a moderate decrease in global ejection fraction, or a large, regional wall motion abnormality. MI patients with preserved LV function may also benefit from long-term therapy with an angiotensin-converting enzyme inhibitor. Meta-analyses of trials of β-adrenoceptor blockers have shown a 20% reduction in the long-term mortality rate, probably due to a combination of antiarrhythmic effect (prevention of sudden cardiac death) and prevention of a reinfarction. Note that the administration of β-adrenoceptor blockers must be carefully considered in patients with risk for LV failure or cardiogenic shock.

Though long advocated based on epidemiologic studies, the combination of estrogen plus progestin has been shown to be ineffective for long-term secondary prevention of coronary heart disease in postmenopausal women in recent years. Calcium antagonists are not routinely recommended for secondary prevention of infarction, and trials with antiarrhythmics, such as encainide, flecainide, and d-sotalol, following an MI have reported an increased risk of death. Amiodarone may improve survival after an MI in the presence of significant arrhythmias in patients with preserved LV function. Implantable cardioverter defibrillators offer a nonpharmacologic approach for prevention of cardiac arrest from ventricular arrhythmias after an MI.

FUTURE DIRECTIONS

Patients who survive the initial course of an acute MI are at increased risk because of coronary artery disease and its complications. It is imperative to reduce this risk, as well as expand preventive therapies to patients at risk who have yet to undergo a cardiac event.

ADDITIONAL RESOURCE

Braunwald E. *Heart Disease. A Textbook of Cardiovascular Medicine*, 6th ed. Philadelphia: WB Saunders; 2007.

An excellent textbook that covers not only the topic of acute myocardial infarction extensively but also most other topics in cardiology.

EVIDENCE

Antman EM, Hand M, Armstrong PW, et al. 2007. Focused update of the ACC/AHA 2004 Guidelines for the management of patients with ST-elevation myocardial infarction. *Circulation.* 2008;117(2):296–329.

Guidelines of the American College of Cardiology and the American Heart Association on how to treat patients with STEMI.

Thygesen K, Alpert JS, White HD, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation.* 2007;116;2634–2653.

The official definition of MI.

Percutaneous Coronary Intervention

Bruce R. Brodie and Tift Mann

15

In the early 1990s, the introduction of coronary stenting revolutionized percutaneous coronary intervention (PCI). Short-term procedural results improved, and the incidence of emergency coronary artery bypass graft surgery (CABG), at 3% to 5% in the 1980s, declined significantly to less than 1%. With the development of drug-eluting stents in the 2000s, the frequency of late repeat revascularization was reduced from 15% to 20% with bare-metal stents to 5% to 7% with drug-eluting stents. As a result of these improvements, and expanded indications for PCI, the number of PCI procedures has increased dramatically and the frequency of CABGs has been reduced (Fig. 15-1).

PERFORMANCE OF PERCUTANEOUS CORONARY INTERVENTION

Procedure and Equipment

PCI is performed in cardiac catheterization laboratories with the same radiographic equipment used for diagnostic coronary arteriography. Arterial access is obtained via the femoral, radial, or brachial artery (Fig. 15-2). The femoral approach is used most frequently and is the preferred method taught at most training centers. The radial approach, which has the advantage of infrequent access site bleeding complications and reduced patient morbidity due to earlier ambulation after PCI, has gained popularity in recent years. Disadvantages of the transradial approach are the significant learning curve and the potential for radial artery occlusion. The presence of a patent ulnar artery and intact palmar arch (which can be assessed by physical examination) is a prerequisite for the use of this approach and provides assurance that should radial artery occlusion occur, it will be asymptomatic.

Interventional guide catheters are slightly larger than diagnostic catheters so as to accommodate balloons, stents, and other devices. After visualization of the coronary artery and target lesion via arteriography, a coronary guide wire is advanced across the lesion and positioned in the distal vessel. A small double-lumen catheter with a distal balloon is passed over the guide wire and positioned at the lesion. An inflation device is used to expand the balloon and open the obstruction by fracturing and compressing plaque. Today, coronary stenting is an integral part of virtually all angioplasty procedures. The undeployed stent is mounted on a second balloon catheter that is passed over the guide wire to the area initially dilated. Balloon inflation expands and deploys the stent (Fig. 15-3). A high-pressure balloon catheter is then used to fully expand the stent. With continued improvements in devices it is increasingly common to insert and fully expand the stent using a single-balloon catheter without predilatation.

After PCI and after removal of catheters, hemostasis has traditionally been achieved at the access site via manual compression once the activated clotting time has returned to baseline. Recently, the use of "closure devices" at the femoral arteriotomy site has gained popularity. In this circumstance, the femoral arteriotomy site is closed with either a suture or a collagen plug immediately after the procedure, thus providing immediate hemostasis in suitable patients and allowing earlier ambulation.

Adjunctive Pharmacologic Therapy

All patients undergoing PCI receive aspirin before the procedure, and the patient is then fully anticoagulated during the procedure to prevent thrombus formation on intravascular devices. Traditionally, heparin was used as the anticoagulant of choice with the addition of platelet glycoprotein (Gp) IIb/IIIa inhibitors to provide additional protection against thrombosis in patients presenting with acute coronary syndromes, in whom the risk of a periprocedural infarction and ischemic events is increased. More recently, bivalirudin has become the anticoagulant of choice. The incidence of periprocedural ischemic events with bivalirudin is comparable to heparin in combination with a platelet Gp IIb/IIIa inhibitor, but bivalirudin has the significant advantage of a short half-life with resulting reduction in access site bleeding complications.

A major problem with stent use has been thrombus formation on unendothelialized struts. The process of endothelialization is significantly inhibited with drug-eluting stents, and it may take months for struts to become completely covered. Late stent thrombosis (LST) occurring as long as a year after drug-eluting stent deployment is a major concern with currently available devices. Because of this concern, an oral antiplatelet program of aspirin and clopidogrel should be continued for 1 year after drug-eluting stent implantation to minimize this risk. Concerns about LST and potential bleeding complications from long-term dual antiplatelet therapy have tempered the early enthusiasm for the use of drug-eluting stents (see Fig. 15-1).

Outcomes with Percutaneous Coronary Intervention

With improved technology, the availability of improved stents, and greater operator experience, outcomes of PCI procedures have improved dramatically. With proper patient selection and when performed by experienced operators, procedural success—defined as reduction in the minimal lumen diameter at the lesion site to less than 20% with normal antegrade blood flow—can be expected in greater than 95% of patients. The risk of a complication such as dissection with vessel occlusion or vessel perforation is now a rarity in the catheterization laboratory. Although this practice is controversial, some operators have advocated performing these procedures without on-site surgical backup.

Operator experience is mandatory for these procedures to be performed safely. The American Heart Association (AHA)/

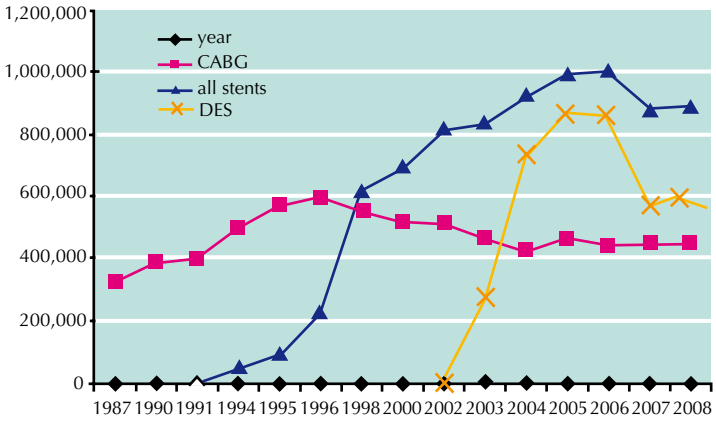

Figure 15-1 *Number of patients undergoing coronary bypass surgery and coronary stent procedures in the United States 1987–2008.* CABG, coronary artery bypass graft; DES, drug-eluting stent.

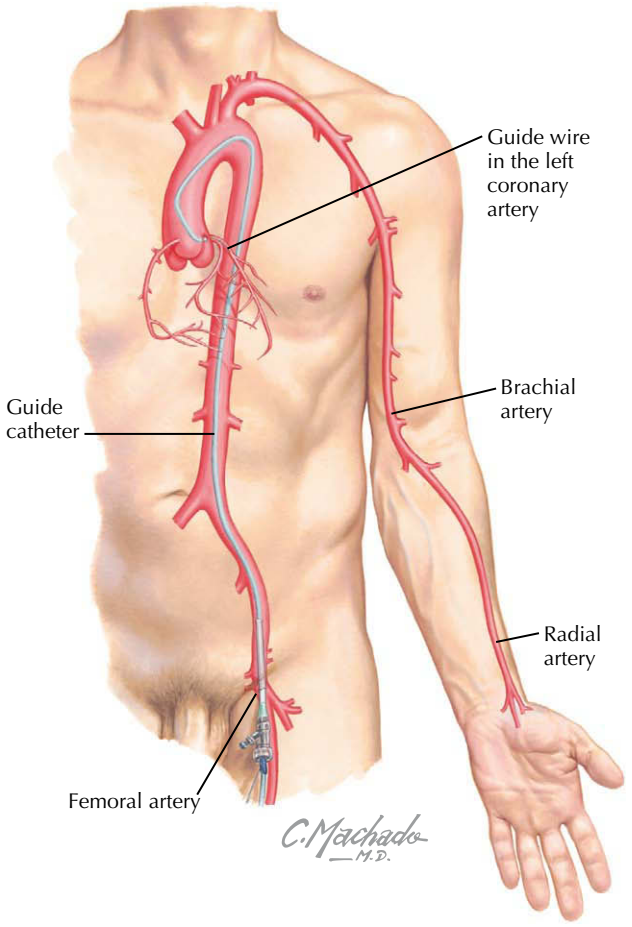

Figure 15-2 *Percutaneous coronary intervention: vascular access.*

American College of Cardiology (ACC) guidelines for PCI recommend that PCI be performed only in institutions that do more than 400 PCI procedures per year and by operators who each perform more than 75 PCI procedures per year.

Restenosis had been a major limitation of PCI before the routine use of intracoronary stents. Balloon trauma to the vessel wall induces vascular cell hyperplasia, which may result in recurrence of arterial narrowing at 3 to 6 months. The use of bare-metal stents resulted in a significant reduction in restenosis rates. The development of drug-eluting stents—stents coated with a thin polymer carrying immunosuppressive or antiproliferative agents (i.e., sirolimus, paclitaxil) that are released over time to prevent the neointimal hyperplasia that can cause restenosis—has resulted in a further decrease in restenosis. The need for late repeat revascularization has decreased from 15% to 20% with bare-metal stents to 5% to 7% with drug-eluting stents. Given the risk of LST and the need for long-term anticoagulant therapy following implantation of a drug-eluting stent, it is important to individualize stent selection. For treatment of stenoses in larger diameter coronary arteries, it may not be necessary to use a drug-eluting stent.

With these advances, many patients who previously required CABG can now be effectively treated in the catheterization laboratory. Although it is still an effective means of treating patients with complex coronary disease, CABG is now necessary in a smaller percentage of patients.

Procedural Complications

The most frequent complications with PCI relate to the arterial access site. Bleeding and hematomas occur in 3% to 5% of patients but can usually be managed conservatively and only occasionally necessitate blood transfusions or surgical intervention. Pseudoaneurysm formation at the access site occurs in less than 1% of patients and can usually be managed with ultrasound-guided compression. Retroperitoneal hemorrhage is rare but may be life-threatening, particularly if unrecognized, and may necessitate surgical intervention. It is especially important to be vigilant for evidence of retroperitoneal hemorrhage in patients who continue to receive intravenous anticoagulation after PCI. Radial artery occlusion may occur after transradial procedures, but these are virtually always asymptomatic because of the hand's dual blood supply.

Cardiac complications are surprisingly infrequent. Balloon inflations and stent deployment may result in embolization of atheromatous debris and/or thrombus formation in the distal coronary bed. The resultant myocardial infarctions (MIs) are usually small and well tolerated. The use of bivalirudin or heparin with adjunctive platelet Gp IIb/IIIa inhibitors may help reduce the frequency of periprocedural MI. Ischemia-induced arrhythmias, including ventricular tachycardia or fibrillation, usually respond to drug therapy and/or cardioversion. PCI-induced coronary dissection and/or thrombotic occlusion can result in Q-wave MI, emergency CABG, and occasionally death. Use of contemporary PCI techniques by experienced operators has decreased the frequency of these complications to less than 1%.

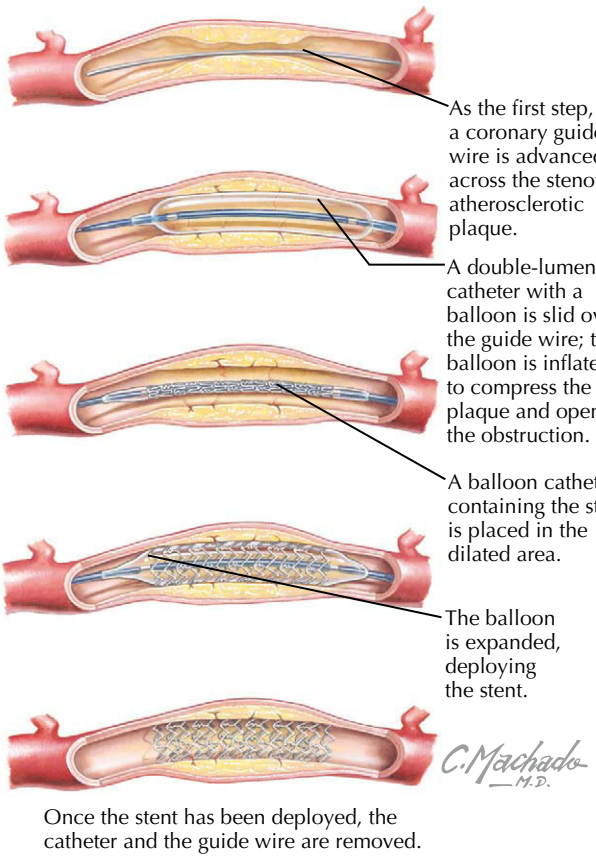

Figure 15-3 *Performance of percutaneous coronary intervention: stent deployment.*

ADJUNCTIVE DEVICES

High-Speed Rotational Atherectomy

High-speed rotational atherectomy uses a diamond-coated burr rotating at high speed to fragment plaque into small particles that are absorbed downstream (Fig. 15-4). Used primarily to treat heavily calcified lesions, ostial lesions, and bifurcation lesions, rotational atherectomy is usually combined with stenting.

Devices to Protect against Distal Embolization

Lesions that develop in saphenous vein grafts following CABG are composed of friable plaque and thrombus and are prone to distal embolization during coronary intervention. Several devices protect against distal embolization, the most common of which are coronary filters (Fig. 15-5). Filters of the current design are attached to a coronary guide wire and contained within a sheath before deployment. The filter system is positioned in the vein graft distal to the lesion, and the filter is deployed by removal of the sheath, which allows the filter to self-expand. Stenting is then performed over the coronary guide wire proximal to the filter. Atherosclerotic and thrombotic

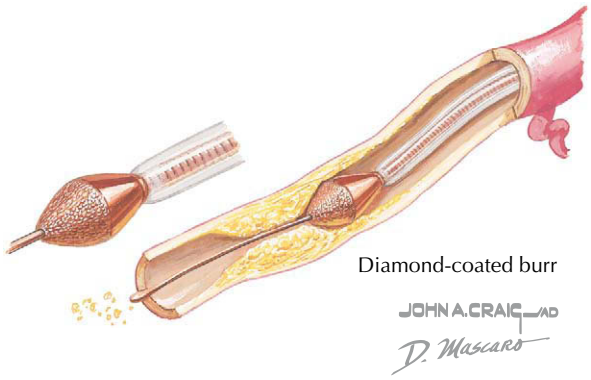

Figure 15-4 *Rotational atherectomy.*

debris, dislodged during stent deployment, are caught in the filter rather than embolizing downstream to the microvascular circulation, where they could potentially cause myocardial damage. After completion of the stent procedure, the filter is removed with a retrieval sheath.

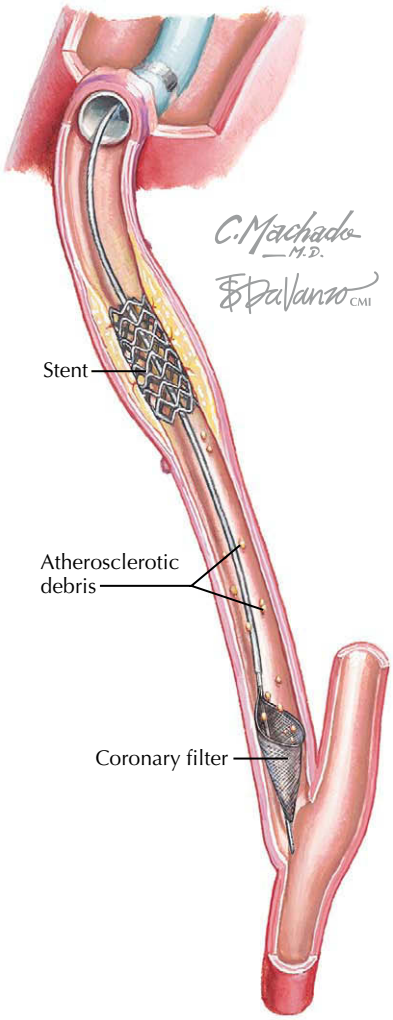

Figure 15-5 *Distal protection device: coronary filter.*

A proximal protection device (in contrast to the filter, which is a distal protection device) has been developed to provide protection against distal embolization in lesions that are not suitable for protection with filters. Both proximal and distal protection devices reduce periprocedural MI when used with PCI in saphenous vein grafts.

Devices to Remove Thrombus

Thrombus is frequently present at the site of obstructive coronary lesions, especially in patients with ST-segment elevation MI (STEMI) and other acute coronary syndromes. Thrombi may embolize into the distal coronary bed and compromise outcomes with PCI. The most commonly used thrombectomy devices are aspiration devices, which have a lumen for passage of the device over a coronary wire and a second lumen with a distal opening that is used for manual aspiration of thrombotic material. These devices are frequently used to treat STEMI patients who have a large thrombus burden. Select studies have demonstrated improved outcomes by using thrombectomy devices in this setting.

Another device for removal of thrombus is the rheolytic thrombectomy system. This device involves a unique catheter with an extra lumen through which high-speed saline is injected backwards into the catheter. This creates a low-pressure zone (Bernoulli principle) that pulls the surrounding thrombus into the catheter through holes in the end of the catheter. Saline jets then break the thrombus into microparticles and propel them out of the catheter proximal lumen. This device is particularly effective in managing lesions with a very large thrombus burden.

Intravascular Ultrasound

Intravascular ultrasound (IVUS) is performed with a transducer that is passed over a coronary guide wire into the coronary artery. IVUS allows visualization of atherosclerotic plaque and the vessel wall and provides diagnostic information not available from coronary angiography alone (Fig. 15-6). It is used before PCI to evaluate lesion severity and vessel size, to help determine the need for adjunctive devices, and to help size the stent. After PCI, IVUS is frequently used to assess the adequacy of stent deployment and to ensure complete stent apposition to the vessel wall. In the present era of drug-eluting stents, optimum stent deployment and complete stent apposition are thought to be extremely important in minimizing the risk of early and late stent thrombosis, and IVUS has been used with increasing frequency for this purpose. Serial IVUS studies are also used for research purposes to quantitate coronary plaque volume and measure progression or regression of plaque volume in response to experimental therapies.

Cutting Balloon

The cutting balloon has been proposed as an alternative to standard balloon angioplasty for the treatment of technically difficult lesions, such as those that occur within a stent, at sites of arterial bifurcation or at the ostia of coronary arteries, and in small coronary arteries. The most commonly used cutting balloon has three cutting blades or atherotomes that cause a controlled dissection and may provide a better opening as compared with standard balloon angioplasty. A similar cutting device has been introduced that uses three or four spiral nitinol struts mounted on a semicompliant balloon. This device cuts the plaque with balloon inflation and may provide a more predictable outcome.

Coronary Doppler Flow Wire

The coronary Doppler flow wire is an important tool that can be used to evaluate the functional severity of an intermediate coronary artery stenosis. A sensor-tipped angioplasty guide wire is positioned distal to the coronary lesion, and the flow velocity reserve is determined after adenosine-induced hyperemia. The results can predict inducible ischemia with stress testing and are useful in determining the need for PCI.

INDICATIONS

Coronary revascularization with PCI can provide symptomatic relief from angina for patients with obstructive coronary artery disease (CAD) and may improve survival in selected patients. Indications for PCI have been outlined in the AHA/ACC/Society for Coronary Angiography and Interventions guidelines for PCI. The decision to perform PCI involves weighing the likelihood of procedural success and long-term benefits against the benefits of alternative strategies of medical therapy and CABG. The likelihood of procedural success and late benefit is highly dependent on lesion and patient selection, as well as operator and institutional experience.

Patient Selection

Patients with obstructive CAD who are asymptomatic or have only mild angina, and who have no or minimal ischemia during stress testing, can often be treated medically. However, asymptomatic patients who have significant myocardial ischemia during stress testing and severe obstructive CAD at catheterization are at high risk of cardiovascular morbidity and should be considered for revascularization with either PCI or CABG.

Patients with stable angina and significant obstructive CAD in one or two vessels generally have improved symptoms and a better quality of life when treated with PCI compared with medical therapy. However, PCI does not reduce the frequency of death or reinfarction in most patients with stable angina. PCI is generally preferred as the revascularization strategy over CABG in patients with single- or double-vessel CAD if the lesions are suitable for PCI.

In patients with multivessel disease, both CABG and PCI are options. Most trials comparing PCI with CABG have shown similar rates of death and MI but less need for repeat procedures in those patients who have undergone CABG. Whether to choose CABG or PCI depends on the presence of comorbid disease that may affect surgical risk, lesion characteristics that may affect PCI outcome, and patient preference, weighing the initial risk and morbidity of open heart surgery against the increased need for repeat revascularization procedures after PCI. Diabetic patients with multivessel disease generally have better survival rates with CABG than with PCI.

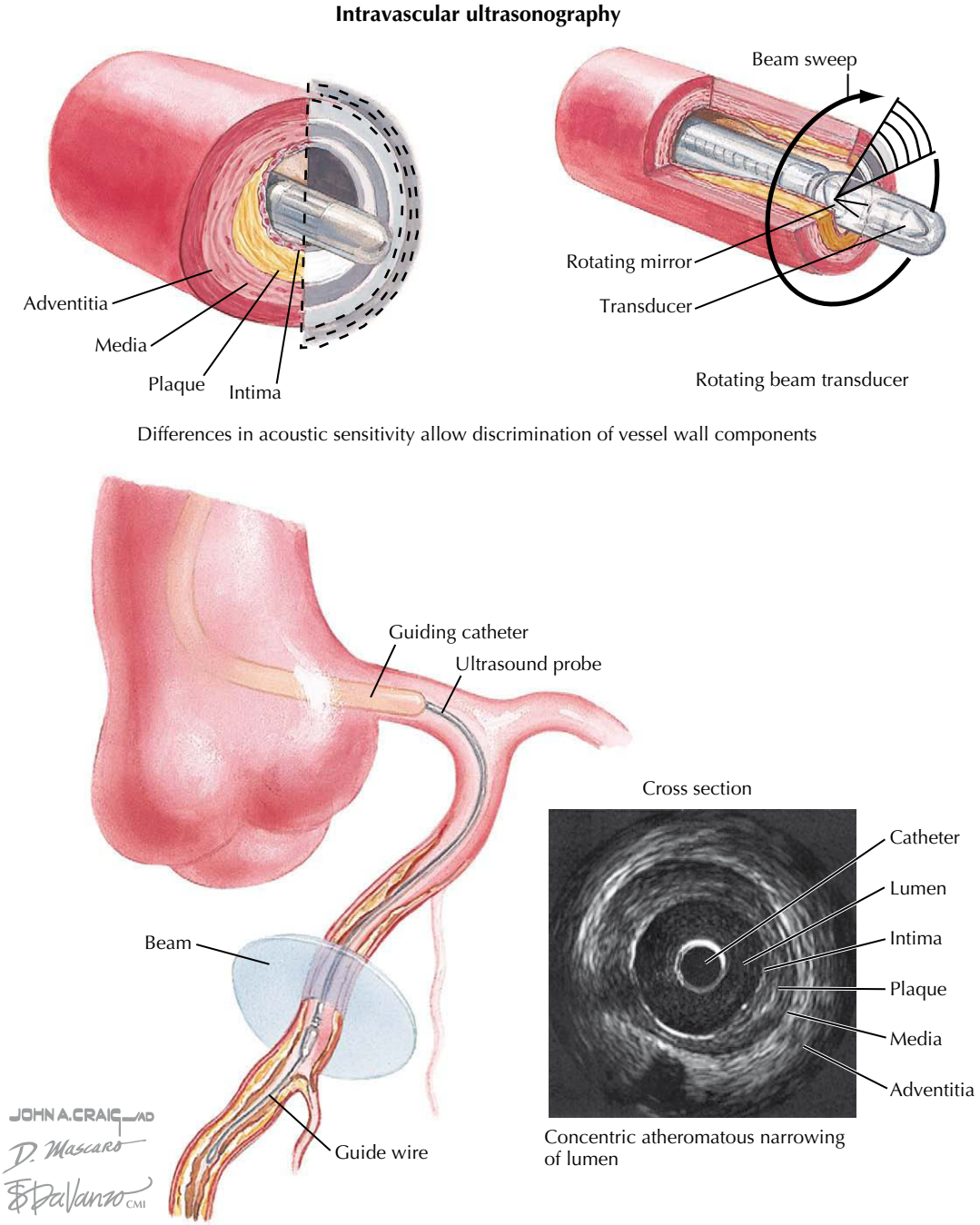

Figure 15-6 *Intravascular ultrasonography.*

Patients who present with acute coronary syndromes benefit significantly if they undergo urgent PCI. Patients with unstable angina and non-STEMI treated invasively (with PCI) have significantly reduced major events (death or MI) as compared with those patients treated with medical therapy alone. Patients presenting with unstable angina or non-STEMI should undergo urgent evaluation with coronary angiography followed by triage to PCI, CABG, or medical therapy depending on the coronary anatomy and coexisting medical conditions.

Patients with STEMI derive the greatest benefit from PCI. PCI for patients with STEMI (primary PCI) has clear advantages over fibrinolytic therapy, with significant reductions in death, reinfarction, and stroke, and has become the preferred reperfusion strategy when it can be performed by experienced personnel in a timely fashion. Primary PCI has special advantages in patients with cardiogenic shock and in patients ineligible for thrombolytic therapy. In patients who present to non-PCI hospitals, when there is delay in transfer for primary PCI, there has been controversy whether the best option is fibrinolytic therapy given locally or transfer for primary PCI. Recently, there has been a nationwide effort to reduce transfer times so that most STEMI patients can be treated with primary

PCI. STEMI patients who are treated with fibrinolytic therapy but fail to reperfuse, as evidenced by persistent chest pain and lack of ECG ST-segment resolution, are candidates for rescue PCI, which can improve outcomes. PCI performed early or within a few days after successful fibrinolytic therapy may reduce the frequency of recurrent ischemic events.

Coronary Lesion Selection

Coronary artery lesion characteristics are an important factor in deciding whether patients should be treated with PCI, CABG, or medical therapy. Complex coronary lesions include very long lesions, lesions with excessive tortuosity or calcification, extremely angulated lesions, some bifurcation lesions, ostial lesions, degenerative vein grafts, small vessel size, and chronic total occlusions. The presence of such lesions can make PCI more difficult and can compromise long-term outcomes. When there are complex coronary lesions and the likelihood of a favorable outcome with PCI is reduced, other alternatives, such as medical therapy or CABG, may become more attractive.

The development of obstructive disease in saphenous vein grafts after CABG is an increasingly common problem. Lesions in saphenous vein grafts are characterized by diffuse, friable plaque and thrombus and have increased frequency of distal embolization with PCI. Focal lesions in vein grafts can usually be treated with stenting using distal protection to prevent distal embolization (described above), but diffuse degenerative lesions in multiple saphenous vein grafts are often best treated with repeat CABG.

Previously, the standard treatment strategy for lesions of the left main coronary artery has been CABG. However, improved PCI techniques and the availability of drug-eluting stents have made stenting of left main coronary artery lesions feasible. It is likely that treatment of left main lesions with PCI will increase.

FUTURE DIRECTIONS

The most important problem in interventional cardiology is that of late stent thrombosis following drug-eluting stent implantation. While the drug coating on these stents very effectively reduces intimal hyperplasia and thus restenosis, it also prevents endothelialization. This is true for all currently approved drug-eluting stents. Thus, these stents (and their struts) may remain exposed to the circulation months after implantation. The requirement for long-term antiplatelet therapy is problematic; it is expensive and exposes the patient to potential significant bleeding complications. Even short-term interruption of antiplatelet therapy for elective noncoronary surgical procedures in patients with drug-eluting stents has been associated with risk of stent thrombosis, and clinical decisions regarding how to balance this risk with the risk of postponing surgery can be difficult.

The next generation of drug-eluting stents may help with the problem of stent thrombosis. Different or less potent antiproliferative drugs could impede intimal hyperplasia while allowing endothelialization of the stent. Other areas under investigation include bioabsorbable stents and stents covered with drug only on the abluminal surface.

Ongoing studies are also addressing technical issues related to PCI. New wires and devices that may facilitate crossing chronic total occlusions are being studied in clinical trials. New stents are being designed to specifically address bifurcation lesions as well as small vessels. New stent platforms are being evaluated to allow easier delivery to complex lesions. Advances in adjunctive pharmacology are also anticipated.

Together, these approaches offer the promise of continued improved outcomes for patients who undergo PCI.

ADDITIONAL RESOURCE

King SB, Yeung AC, eds. *Interventional Cardiology.* New York: McGraw-Hill, 2007.

Provides an excellent general reference for PCI and interventional cardiology.

EVIDENCE

ACCF/SCAI/STS/AATS/AA/ASNC. 2009 Appropriateness Criteria for Coronary Revascularization, Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3062638>; Accessed 22.02.10.

Provides detailed guidelines for the selection of patients for coronary revascularization with either PCI or CABG.

Douglas JS, King SB III. Percutaneous coronary intervention. In: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P, eds. *Hurst's The Heart*, 12th ed., New York: McGraw-Hill; 2008:1427–1457.

Provides detailed information regarding criteria for selection of patients for PCI, adjunctive therapies used with PCI, and techniques for performing PCI. It also serves as an excellent general reference.

2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2008;51:172–209.

Provides the current standard of care for the selection of patients for PCI and the use of adjunctive therapies with PCI.

Coronary Artery Bypass Surgery

Michael E. Bowdish, Sharon Ben-Or, Michael R. Mill, and Brett C. Sheridan

16

Cardiovascular disease is the leading cause of death of both sexes in the United States and all industrialized nations and is increasingly becoming an important cause of death in developing countries. Approximately 500,000 people die in the United States as a result of cardiac disease yearly; 148,000 of them are younger than 65. In 2008, approximately 770,000 Americans presented with a new myocardial infarction (MI), and approximately 430,000 had a recurrent MI. Acute and chronic coronary syndromes result in inadequate delivery of oxygen to the myocardium and subsequent disturbances in oxidative metabolism. Insufficient coronary flow of nutrients to myocardial cells results in angina. If prolonged, myocardial ischemia leads to myocardial cell death. The most straightforward solution to this interruption of blood flow through coronary arteries is to bring new or additional blood flow through alternative pathways, thus bypassing the obstructed coronary arteries. The development of coronary artery bypass graft (CABG) surgery was fostered by this understanding.

ETIOLOGY AND PATHOGENESIS

The presence of risk factors for atherosclerosis—advanced age, genetic predisposition, male sex, hypertension, diabetes mellitus, renal disease, hyperlipidemia, and cigarette smoking—all result in a propensity for the normally thin intima of coronary arteries to increase in both thickness and smooth muscle cell content. This earliest stage of atherosclerosis is caused by the proliferation of smooth muscle cells; the formation of a tissue matrix of collagen, elastin, and proteoglycan; and the accumulation of intracellular and extracellular lipids. Thus, the first phase of atherosclerotic lesion formation is focal thickening of the intima with an increased presence of smooth muscle cells and extracellular matrix. Intracellular lipid deposits also accumulate. Next, lesions called *fatty streaks* form. A fatty streak is an accumulation of intracellular and extracellular lipid that is visible in diseased segments of affected arteries. As the lesion evolves, a fibrous plaque can form from continued accumulation of fibroblasts covering proliferating smooth muscle cells laden with lipids and cellular debris. Plaques progress in complexity as ongoing cellular degeneration leads to ingress of blood constituents and calcification. The plaque's necrotic core may enlarge and become calcified. Hemorrhage into the plaque may disrupt the smooth fibrous surface, causing thrombogenic ulcerations. Clot organization on the plaque surface often occludes, or nearly occludes, the arterial lumen, further decreasing blood flow (see also Chapter 2).

Just as the rapidity of atherosclerotic lesion formation varies from individual to individual, the presentation of ischemic heart disease also varies. Objective evidence of myocardial ischemia is identified with concurrent coronary angiographic evidence of flow-limiting atherosclerotic lesions. The need for surgical treatment usually arises from presentation of an individual with an acute coronary syndrome and multivessel coronary artery disease (CAD) or with stable but debilitating angina (see Chapters 13 and 14). Examples of indications for urgent CABG include postinfarction angina, ventricular septal defect, acute mitral regurgitation, free wall rupture, and/or cardiogenic shock in patients admitted to the hospital with acute MI. Each of these acute conditions warrants surgical intervention and revascularization.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of myocardial ischemia includes atherosclerotic and nonatherosclerotic causes of epicardial coronary artery obstruction. Nonatherosclerotic causes include congenital anomalies, myocardial bridges, vascularities, aortic dissection, aortic valve stenosis, granulomas, tumors, and scarring from trauma, as well as vasospasm and embolism. Many of these entities may also be indications for CABG.

Other diseases mimicking angina include esophagitis due to gastrointestinal reflux, peptic ulcer disease, biliary colic, visceral artery ischemia, pericarditis, pleurisy, thoracic aortic dissection, and musculoskeletal disorders.

DIAGNOSTIC APPROACH

Although patients with ischemic heart disease present with a spectrum of clinical urgency, diagnostic evaluation relies on objective evidence of ischemia, assessment of disease burden, and determination of whether the coronary anatomy is amenable to surgical revascularization. The diagnostic approach begins with a complete history and extensive physical examination (see Chapter 1). It is important to note that the physical examination is an insensitive tool and may not assist in the diagnosis of chronic ischemic heart disease. Many patients with chronic ischemic heart disease have no physical findings related to the disease, and even when present, physical findings are often not specific for CAD. Because coronary atherosclerosis is common, any physical finding suggestive of heart disease should raise the suspicion of chronic ischemic heart disease.

Diagnostic evaluation includes multiple approaches. Laboratory studies should be performed to assess for the presence of cardiac risk factors such as diabetes mellitus, hyperlipidemia, renal insufficiency, hepatic insufficiency, and hyperthyroidism. Electrocardiography can document myocardial ischemia during chest pain or with physiologic or pharmacologic stress testing. A stress test may also be used to detect CAD or assess the functional importance of coronary lesions. Test results are positive if the patient has signs or symptoms of angina pectoris with typical ischemic ECG changes. The predictive value of the ECG for detecting myocardial ischemia varies in different clinical settings, but the sensitivity and specificity of electrocardiography are typically less than 70%. The predictive value of stress testing is improved by combining electrocardiography with

nuclear or echocardiographic imaging. In individuals who cannot exercise, stress can be induced by administration of the synthetic catecholamine dobutamine, which mimics exercise. Vasodilator drugs such as dipyridamole and adenosine are often used to accentuate flow variations that can occur in individuals with CAD. With vasodilation, these drugs also can cause increased heart rate, increased stroke volume, and an increase in myocardial oxygen demand. Wall motion abnormalities at rest or with stress may be assessed by transthoracic echocardiography, nuclear imaging, or by MRI (see Chapters 3, 7, and 8).

The gold standard for evaluating coronary anatomy to determine the suitability for surgical revascularization is coronary angiography. Coronary angiography allows accurate assessment of coronary atherosclerosis, including quantification of disease location and severity. Studies on the relationship between coronary artery stenoses and myocardial ischemia support the notion that lesions that reduce the coronary artery's cross-sectional area by 70% or more (50% in diameter) significantly limit flow, especially during periods of increased myocardial oxygen demand. If detected, such lesions are considered compatible with symptoms or other signs of myocardial ischemia. Because atherosclerosis is not uniform, coronary angiography is, to a certain degree, imprecise. The coronary artery's cross-sectional area at the point of atherosclerotic lesion must be estimated from two-dimensional diameter measurements and in several planes. When compared with autopsy findings, stenosis severity is usually underestimated by coronary angiography. Additionally, coronary angiography does not consider that serial coronary artery lesions may incrementally reduce flow to distal beds by more than is predicted by any single lesion. A series of apparently insignificant lesions may reduce myocardial blood flow substantially.

In choosing a diagnostic approach, noninvasive stress testing is performed first in evaluating patients with suspected coronary atherosclerosis, as long as they have not presented with an unstable coronary syndrome. Although the risks of both stress testing and coronary angiography are low, in patients with stable angina, or in patients being assessed following MI, the risk of stress testing is lower than that of coronary angiography. Mortality rates for stress testing average 1 per 10,000 patients compared with 1 per 1000 for coronary angiography. The physiologic demonstration of myocardial ischemia and its extent form the basis of the therapeutic approach, irrespective of coronary anatomy. Mildly symptomatic patients who have small areas of ischemia at intense exercise levels have an excellent prognosis and are usually treated medically, particularly if left ventricular (LV) function is normal or near normal. Knowledge of coronary anatomy is not necessary to make this therapeutic decision. For this reason, in stable patients noninvasive assessment of myocardial ischemia and its extent is appropriate before considering coronary angiography.

Patients with profound symptoms of myocardial ischemia during minimal exertion are more likely to have severe diffuse multivessel coronary atherosclerosis or obstruction of the left main coronary artery. The likelihood that revascularization will be required is high, and coronary angiography should be performed as soon as possible. Patients with severe unstable angina should not undergo stress testing because of the increased risk in this population. Coronary angiography is recommended as the initial diagnostic study in these patients. Patients with angina or evidence of ischemia in the early post-MI period are considered to be unstable angina patients and, likewise, should also undergo coronary angiography instead of stress testing. Other indications for coronary angiography include situations in which noninvasive testing will be inaccurate, such as for many patients with left bundle branch block on ECG or those who are unable to exercise and difficult to image noninvasively.

MANAGEMENT AND THERAPY

With an indication for surgical myocardial revascularization, management evolves into an issue of timing (emergent, urgent, or elective) and surgical approach (traditional revascularization with cardioplegic arrest and cardiopulmonary bypass [CPB] support versus off-pump CABG [OPCABG]) (Box 16-1; Fig. 16-1). The merits of percutaneous revascularization versus surgical revascularization in specific patient presentations are discussed in Chapter 15. The decision to proceed with CABG emergently is made when coronary angiography confirms the diagnosis of occlusive CAD with hemodynamic instability and/or ongoing myocardial ischemia despite intensive medical treatment. Although the increased myocardial perfusion that results from placement of an intra-aortic balloon pump (IABP) can be useful in the short term, patients who require an IABP for control of myocardial ischemia should undergo revascularization as soon as safely possible. Urgent procedures are performed during the same hospital admission secondary to unstable symptoms and severely obstructed coronary anatomy. Patients with stable angina patterns, hemodynamic stability, and less threatening coronary anatomy may undergo elective CABG.

Box 16-1 The Indications for Coronary Artery Bypass Surgery

- Left main coronary disease
- Triple-vessel disease with normal or diminished ejection fraction
- Two-vessel disease with involvement of the proximal left-sided anterior descending coronary artery with normal or diminished ejection fraction
- Unstable (crescendo) angina
- Post–myocardial infarction angina
- Life-threatening ventricular arrhythmias with greater than 50% left main disease or triple-vessel disease
- Acute coronary occlusion after percutaneous coronary intervention
- Persistent symptoms despite maximal medical therapy
- Coronary artery disease and the need for heart surgery for other indications (i.e., valve replacement surgery)
- Mechanical complications of acute myocardial infarction
  - Ventricular septal defect
  - Acute mitral regurgitation
  - Free wall rupture
  - Cardiogenic shock

Data from Brown ML, Sundt TM, Gersh BJ. Indications for revascularization. In: Cohn LH, ed. *Cardiac Surgery in the Adult.* New York: McGraw Hill; 2007.

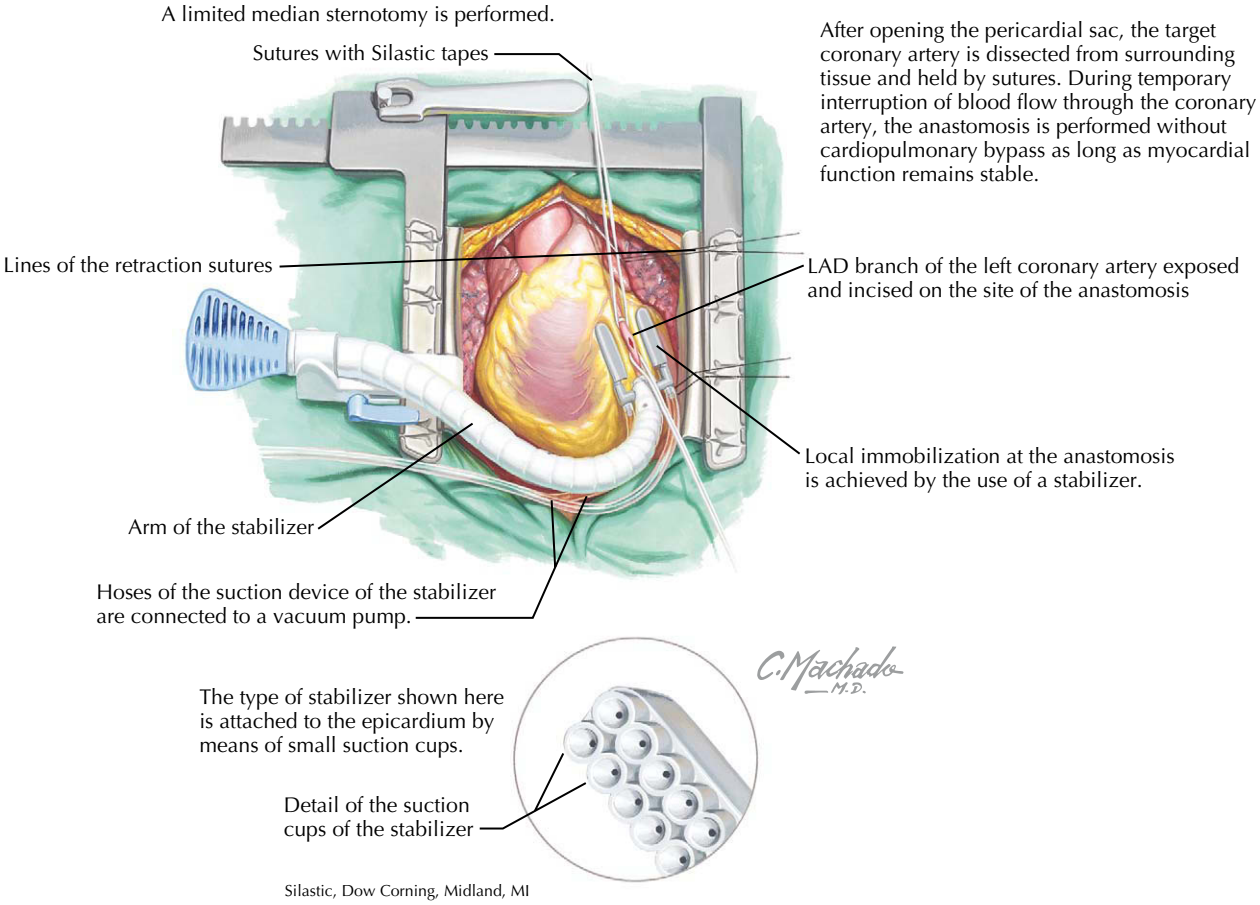

Figure 16-1 *Off-pump coronary artery bypass grafting.* LAD, left anterior descending.

Optimum Treatment

The gold standard for CABG is complete myocardial revascularization. CABG often allows more complete revascularization than is possible using percutaneous coronary revascularization approaches. CABG is traditionally performed with an arrested, still heart with circulatory support provided by CPB. CPB systems include a pump (most commonly a roller pump), a membrane oxygenator, and an open reservoir. Operating on the arrested heart permits careful examination of diseased vessels and selection of optimal sites for anastomosis of grafts to coronary vessels as small as 1.5 mm in diameter.

Initial studies suggested that because of the potential detrimental effects of CPB, the widespread use OPCABG would result in improved outcomes. Subsequent studies have demonstrated that when surgery is conducted as expeditiously as possible and CPB time is minimized, outcomes for conventional CABG versus OPCABG are virtually identical.

Obtaining optimal outcomes for CABG involves attention to several important technical details. The traditional surgical revascularization technique involves placement of an aortic cross-clamp on the ascending aorta to control the surgical field. Cross-clamping the aorta results in myocardial ischemia. To minimize myocardial injury, the heart is protected both by the use of cardioplegia solutions and by cooling the heart to reduce metabolic demand. Blood and crystalloid cardioplegia are both used, with indications for each determined by surgeon preference and the presence or absence of acute ischemia. Hypothermic (4°C) oxygenated blood and cardioplegic solutions are administered by both anterograde and retrograde approaches to rapidly cool the heart. Hypothermic systemic perfusion provides enhanced right-sided ventricular protection, in that retrograde cardioplegia via the coronary sinus may provide limited delivery to the right ventricle. Retrograde cardioplegia is of importance particularly in patients with impaired right-sided ventricular function, proximal right coronary artery occlusion, prolonged ischemic times, or when right-sided ventricular metabolic demand is increased. Because ventricular stretch impairs postoperative ventricular function, an LV vent can be used to decompress the left ventricle if it distends during CPB. Following completion of anastomoses, approximately 100 mL of crystalloid cardioplegia solution at 4°C are delivered through each graft to the myocardium if inadequate myocardial protection is a concern. Cardioplegic redosing via the aortic root or coronary sinus is performed every 20 minutes throughout the cross-clamp period and is accompanied by strict vigilance to topical cooling, which ensures adequate maintenance of tissue hypothermia during the cross-clamp period.

After cross-clamp application and inducement of cardioplegia, distal anastomoses are performed first. The vessels on the heart's inferior surface (right coronary artery, posterior

descending artery, LV branch) are grafted before other vessels. Then, proceeding in a counterclockwise direction, grafts are placed as needed for the posterior marginals, the middle marginals, the anterior marginals, the ramus intermedius, the diagonals, and, last, the left-sided anterior descending artery. The internal mammary artery anastomosis to the left anterior descending artery (or alternately, to the most important distal target) is performed last. Proximal anastomoses are then performed with the formation of aortotomies that are subsequently enlarged with a 4-mm punch. If the ascending aorta has substantial atherosclerotic disease (detected either by inspection or transesophageal echocardiography), embolic risk is minimized by the procedure being performed without a cross-clamp. Many surgeons place stainless-steel washers (that can be visualized by fluoroscopy) on the proximal graft anastomotic sites to assist with later catheterizations. Once proximal and distal anastomoses are completed, the aorta and grafts are de-aired with subsequent removal of the aortic clamp. This initiates myocardial reperfusion, and preparations are made for weaning the patient from CPB.

The heart is allowed to reperfuse in an unloaded beating state as electrolyte, acid-base, and hematocrit values are corrected and inotropic agents are started, if indicated. In general, the need for inotropic agents is determined by preoperative or intraoperative factors. Preoperative factors include advanced age, low ejection fraction, high pulmonary artery pressures, high LV end-diastolic pressure, or high central venous pressures. Intraoperative factors that prompt the need for inotropic assistance include incomplete revascularization, severe distal disease, prolonged CPB or cross-clamp times, poor myocardial protection, and poor LV contractility seen by visual inspection after cross-clamp removal. Intraoperative transesophageal echocardiography can be helpful in determining the need for inotropic agents after weaning from CPB.

An alternative approach to traditional CABG is to operate on the beating heart—so-called OPCABG. The placement of stabilizing devices on the targeted coronary artery makes this technique technically feasible (Fig. 16-1, lower). The coronary artery is briefly occluded (10–20 minutes), or intracoronary shunts are used to allow anastomosis of the graft to the coronary artery distal to the atherosclerotic obstruction. The targeted coronary artery is stabilized, and blood pressure is aggressively controlled with volume and inotropic agents delivered during anesthesia. OPCABG requires continued communication with the anesthesiologist throughout the procedure. Although hemodynamically and technically more challenging, this procedure allows for pulsatile antegrade flow through the coronary artery and systemic circulation without the added insults of hypothermia, CPB, and the obligatory proinflammatory blood–artificial surface interface.

Minimally invasive surgery is another less widely adapted technique. In brief, this approach incorporates the concept of OPCABG with a limited-access incision. A limited left-sided anterolateral thoracotomy is performed through the fourth intercostal space without resection or dissection of the ribs. After opening of the pericardial sac, the target coronary artery is dissected from surrounding tissue and held by sutures at a short distance proximal and distal to the anastomosis that was snared over a piece of pericardium for temporary interruption of blood flow. The anastomosis is performed without CPB as long as myocardial function remains stable. A stabilizer permits local immobilization at the anastomosis site. This procedure has less utility than the other procedures because minimal exposure limits options with hemodynamic instability and multivessel disease. In most cases, this technique limits the surgeon to the use of the internal mammary artery and, usually, grafting of the left anterior descending coronary artery. Thus, minimally invasive CABG is most appropriate for single-territory myocardial revascularization.

Avoiding Treatment Errors

Avoiding treatment errors in CABG is multifactorial. An initial important issue is to determine the suitability of a given patient for CABG. Second, CABG requires meticulous attention to surgical technique. In addition, conduit choice is vital to long-term patency of grafts and ultimately long-term survival. For instance, the use of an internal mammary artery is superior to the use of vein grafts alone. In addition, survival is improved with bilateral internal mammary grafting as opposed to left internal mammary artery and vein grafting. Finally, excellent postoperative care is a necessity for success in any cardiac surgical program.

FUTURE DIRECTIONS

As noted, OPCABG has reputed advantages in smaller, single-institution prospective series, as well as retrospective analysis of larger thoracic surgery databases. Advantages of OPCABG seem to include fewer neurologic, pulmonary, and renal sequelae. Although the absence of circulatory support with CPB is the prevailing explanation for less end-organ injury, the absence of global ischemia-reperfusion may also contribute. The potential disadvantage of OPCABG is incomplete myocardial revascularization or compromised distal conduit–coronary anastomosis due to the increased technical difficulty of operating on the moving heart. For all CABG subtypes, revascularization should not be compromised. Conversion from off- to on-pump may be necessary to complete revascularization. The ongoing National Institutes of Health–sponsored, multicenter, prospective controlled trial evaluating traditional CABG versus OPCABG, is addressing these issues.

With rapidly growing incidence of heart failure and a limited number of donors for heart transplantation, techniques to improve LV function in the context of myocardial revascularization have evolved. Surgical restoration of normal LV shape and volume following MI has gained widespread appeal. The National Institutes of Health is sponsoring a multicenter, prospective, randomized trial to examine the influence of LV endoaneurysmorrhaphy and CABG on morbidity and mortality rates compared with medical treatment or CABG alone.

Advances in robotic technology, off-pump multivessel techniques, and closed-chest CPB systems have prompted exploratory use of remote CABG techniques (Fig. 16-2). One study compared percutaneous intervention to limited-access beating-heart minithoracotomy single-vessel coronary revascularization for proximal left-sided anterior CAD. The results were favorable for this hybrid surgical, less-invasive approach.

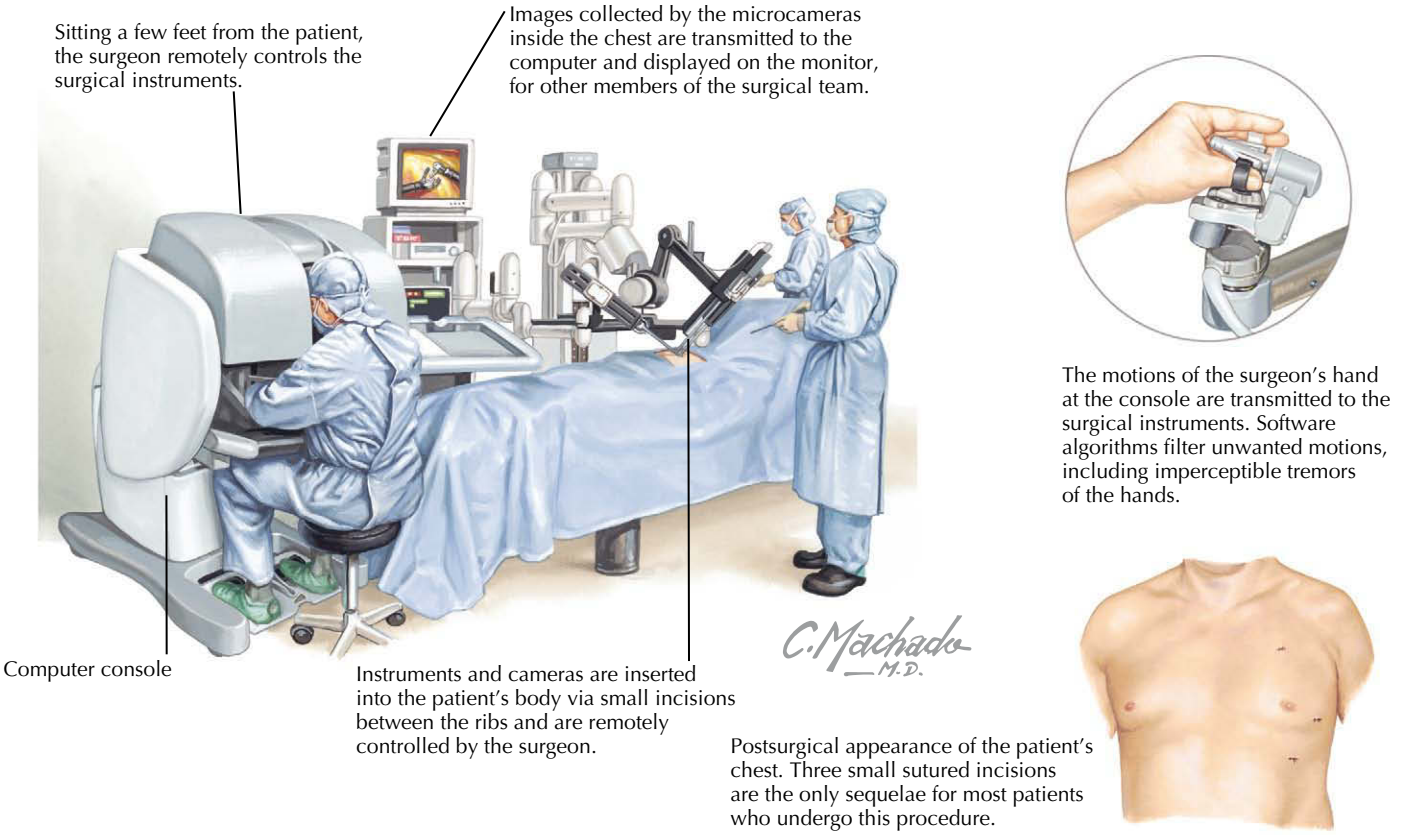

Figure 16-2 *Remote-access minimally invasive coronary artery bypass grafting.*

The ultimate goal for robotic CABG is complete multivessel revascularization using an off-pump approach without sternotomy or even minithoracotomy. This requires that conduit harvesting, conduit preparation, target vessel preparation, control, and anastomosis are all performed remotely from a master control unit. Although two-vessel CABG has been successfully performed with this approach in Europe, limitations remain. New technologies in facilitated anastomotic devices, integrated real-time imaging, and guidance control systems will be mandatory to realize the vision of robotic multivessel CABG.

ADDITIONAL RESOURCE

Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). American College of Cardiology Website. Available at: <http://www.acc.org/qualityandscience/clinical/guidelines/cabg/index.pdf>. Accessed 12.11.09.

A comprehensive examination of the data surrounding CABG. Also provides state-of-the-art recommendations regarding indications, treatment, risks, and outcomes. Vital reference for anyone involved caring for patients with CAD.

EVIDENCE

Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal mammary artery graft on 10 year survival and other cardiac events. *N Engl J Med.* 1986;314:1–6.

Study from Cleveland Clinic showing superiority of internal mammary artery grafting versus all-vein grafting.

Lytle BW, Blackstone EH, Sabik JF, et al. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg.* 2004;78:2005–2014.

Study from Cleveland Clinic showing superiority of bilateral internal mammary artery grafting at 20 years.

Puskas JD, Kilgo PD, Lattouf OM, et al. Off-pump coronary artery bypass provides reduced mortality and morbidity and equivalent 10-year survival. *Ann Thorac Surg.* 2008;86:1139–1146.

Study from Emory University analyzing outcomes of OPCABG.

Cardiogenic Shock after Myocardial Infarction

17

Venu Menon and Jay D. Sengupta

Cardiogenic shock (CS) is characterized by hypotension and end-organ hypoperfusion as a result of low cardiac output. CS remains the most common cause of death after presentation with a myocardial infarction (MI). This clinical state occurs in 5% to 8% of patients hospitalized with ST-elevation myocardial infarction (STEMI) and 2.5% of patients with non-STEMI. The incidence of CS has decreased only slightly over time, and the mortality rate remains high at near 50% despite advances in interventional and pharmacologic management.

ETIOLOGY

CS after an MI is most commonly secondary to severe left ventricular (LV) dysfunction. This may result from a large-index MI or from acute injury in subjects with prior LV dysfunction. In the SHOCK (SHould we revascularize Occluded Coronaries for cardiogenic shocK) Trial, predominant LV failure accounted for four out of five of all such cases. Approximately one third of the patients enrolled in the study had evidence of a prior MI.

Several unique clinical entities may also present with acute hemodynamic collapse. Mechanical complications associated with shock include acute mitral regurgitation related to papillary muscle dysfunction or rupture, ventricular septal rupture (VSR), or free-wall rupture. Right ventricular (RV) failure due to RV infarction in isolation or in combination with LV failure can also present in this manner. The clinician should also be aware of iatrogenic shock resulting from inappropriate administration of medications such as β-blockers. Occult hemorrhage due to procedure-related complications or in conjunction with therapy using antithrombotic, antiplatelet, and fibrinolytic agents can also cause hypotension and shock.

DIFFERENTIAL DIAGNOSIS

Several nonischemic and extracardiac etiologies must be considered in patients with hypotension and suspected cardiogenic shock. Acute myocarditis secondary to infections or toxins can lead to the development of CS within hours of the first signs of illness. Takotsubo cardiomyopathy, or apical ballooning syndrome, is another cause of acute LV dysfunction, typically in response to emotional or physical stress, and can present as CS. The differential diagnosis should also include acute aortic dissection, which can be associated with aortic valve regurgitation, coronary artery dissection, aortic rupture, and tamponade. Cardiac tamponade can also occur secondary to a focal myocardial hematoma following cardiac surgery or trauma or from a circumferential pericardial effusion from malignancy, infarction, or infection. A pulmonary embolism may cause volume and pressure overload of the right ventricle and obstruction of RV outflow leading to hemodynamic collapse. Myocardial depression secondary to septic shock must also be excluded.

PATHOGENESIS

Predominant Left Ventricular Failure

CS is traditionally defined as an unsupported systolic blood pressure less than 90 mm Hg with normal to elevated LV filling pressures and evidence of end-organ hypoperfusion. Acute ischemia due to plaque rupture/thrombosis can result in acute myocardial dysfunction. Decreased cardiac output on the basis of inadequate LV stroke volume in the setting of MI can lead first to decreased systemic systolic blood pressure. Hypotension can then lead to further reduction in coronary perfusion pressure and further worsening of myocardial ischemia. There may also be cardiac ischemia due to fixed flow-limiting stenoses in epicardial coronary arteries remote from the infarct-related vessel. Ischemia thus begets ischemia resulting in a progressive spiral of hemodynamic collapse culminating with death. In this traditional paradigm of CS, vasoconstriction from falling cardiac output was thought to be the major mechanism by which the neurohormonal system compensates for hypotension. The recognition that many patients have unexpected vasodilation and low systemic vascular resistance in this setting has led to modification of this conceptual design. Observational evidence suggests that inflammatory cytokines such as interleukin-6 (IL-6), IL-1, and tumor necrosis factor-α are elevated in patients with CS to the same levels seen in patients with a septic state. These findings suggest that MI may result in a systemic inflammatory response syndrome as previously observed with infection or trauma that results in myocardial depression and hypotension independent of ischemic necrosis (Fig. 17-1). These findings are also of importance when considering the diagnostic evaluation of CS patients and optimal therapy (see below).

Right Ventricular Failure

RV dysfunction commonly occurs when there is infarction of the territory supplied by the acute marginal branches of the right coronary artery (Fig. 17-2). This typically results in hypotension with clear lung fields and is often accompanied by bradyarrhythmic complications, including high-grade atrioventricular block and even complete heart block. ST-segment elevation in right-sided ECG leads V_3 and V_4 is a very specific finding for RV infarction. A right-sided ECG should be obtained in all patients presenting with an acute inferior MI and in any patients suspected of having RV infarction. With RV infarction, the right-sided filling pressures become acutely elevated, since

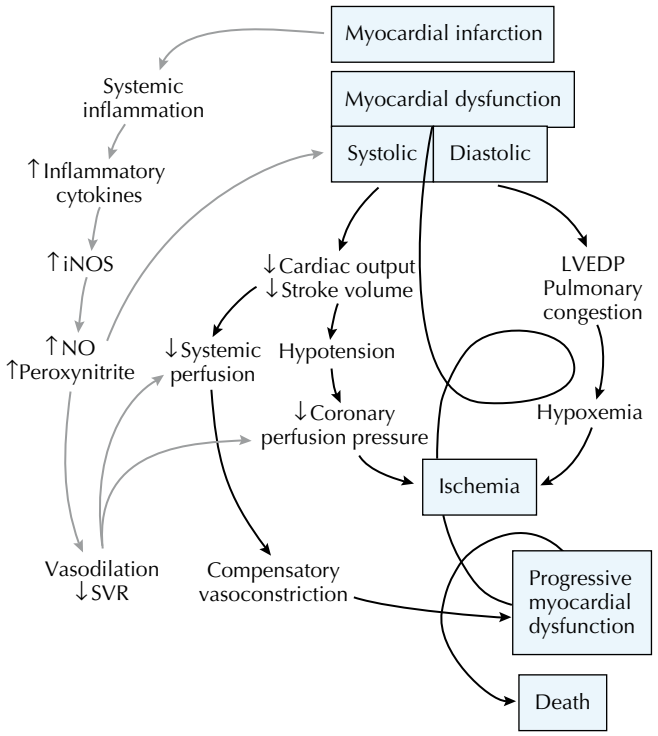

Figure 17-1 *Classic paradigm of cardiogenic shock with recent observation that inflammatory mediators contribute to a vicious cycle of hypotension and further ischemia.* iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; SVR, systemic vascular resistance. Adapted from Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation.* 2003;107; 2998–3002.

there is reduced forward flow through the pulmonary circulation into the left side of the heart. Elevation in RV end-diastolic pressure may also negatively impact LV filling by causing a "bowing" of the interventricular septum into the LV cavity. As a result, the left ventricle is underfilled and cardiac output further reduced. Reperfusion of the right coronary artery improves RV function, restores conduction, and can often result in normalization of hemodynamics.

Mitral Regurgitation

The anatomy of the mitral valve as depicted in Figure 17-3 reveals how mitral leaflet closure depends on papillary muscle function. Each mitral valve leaflet is connected by chordae tendineae to both the posteromedial and anterolateral papillary muscles. The posteromedial papillary muscle is at greater risk from ischemic damage, since it has a single blood supply from the posterior descending artery, whereas the anterolateral papillary muscle usually receives dual blood supply from the left anterior descending and circumflex arteries. Consequently, inferior and posterior MIs are more likely to cause papillary muscle dysfunction/rupture and resultant severe mitral regurgitation. Additional risk factors for papillary muscle rupture include age, female sex, first MI, hypertension, and single-vessel disease. The jet of mitral regurgitation in this situation is eccentric and directed away from the affected flail mitral leaflet. In contrast, ischemic mitral regurgitation results from a restricted posterior mitral leaflet with resultant central to posteriorly directed mitral regurgitation.

The natural history of acute severe mitral regurgitation from papillary muscle rupture is dismal, with three quarters of patients dying within 24 hours and only 6% surviving longer than 2 months. The severity of mitral regurgitation results in marked elevations in left atrial and pulmonary capillary wedge pressures leading to pulmonary edema and hypoxia. In the SHOCK Registry, despite having a higher mean LV ejection fraction, the cohort of patients with acute severe mitral regurgitation had similar in-hospital mortality to patients with LV failure. There was a trend toward improved in-hospital survival in patients who underwent surgical repair in addition to revascularization as compared with those treated with revascularization alone (40% to 71%, $P = 0.003$). Ischemic mitral regurgitation in the setting of an acute MI may be difficult to recognize initially. For this reason, it is critical to keep this potential diagnosis in mind in the evaluation of MI patients with CS. At present, it is still recommended that these patients undergo surgery to repair or replace the mitral valve, coupled with revascularization, urgently or emergently.

Ventricular Septal Rupture

CS due to VSR complicating acute MI has a mortality rate exceeding 75%. Classically described as a late complication, it can also present early. The median time from MI to VSR was only 16 hours in the SHOCK Registry. Both anterior and inferior MIs can give rise to VSR. Inferior infarctions cause septal rupture in the basal inferior septum that are complex and serpiginous and usually extend into the right ventricle. In contrast, anterior infarctions cause rupture in the apical septum. As with ischemic mitral regurgitation/papillary muscle rupture, the mainstay of management for peri-MI VSR is surgical; however, mortality remains high in patients who have surgery. Outcomes with apical septal VSR are better than with inferoseptal VSR since the surgical technique is simpler. Endovascular devices are being increasingly used in this situation, especially in patients with significant surgical comorbidity.

Free-Wall Rupture

Cardiac rupture is a catastrophic complication of MI. Predisposing factors are advanced age and female sex. Three types have been described from a series of 50 autopsies in 1975. Type I rupture occurs typically within 24 hours after MI and is characterized by a slit through a normal-thickness infarct. Type II rupture occurs more often in posterior infarcts and is a localized erosion of the infarcted myocardium. Type III rupture is most commonly seen in anterior infarcts and occurs in severely expanded, thinned, and dilated infarcts. Rupture usually results in instantaneous death. In some patients, the rupture may be contained to form a pseudoaneurysm. The treatment in both cases is emergency cardiac surgery.

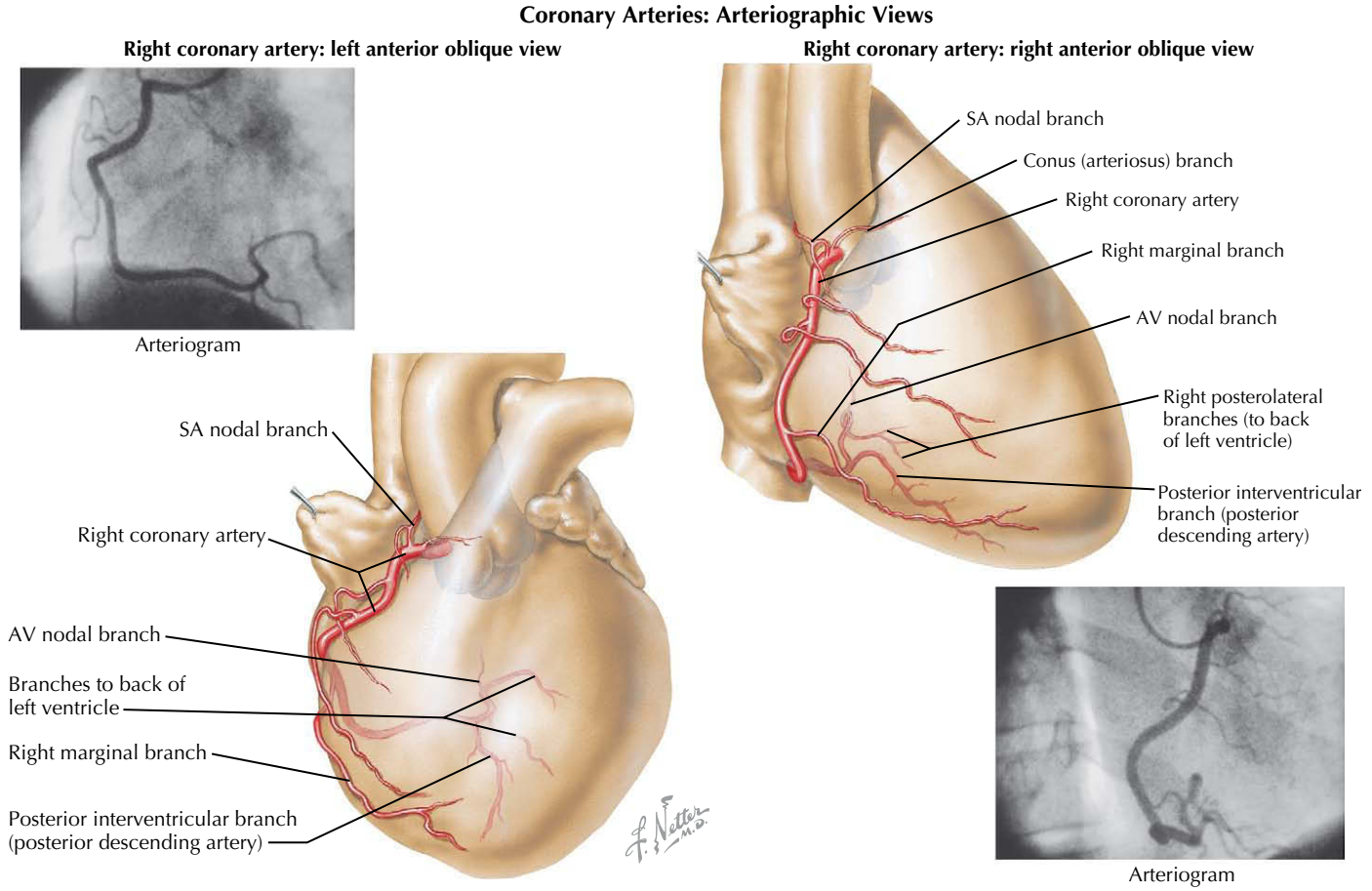

Figure 17-2 *Angiographic views of the right coronary artery (RCA) and illustration of normal areas perfused by the RCA.* AV, atrioventricular; SA, sinoatrial.

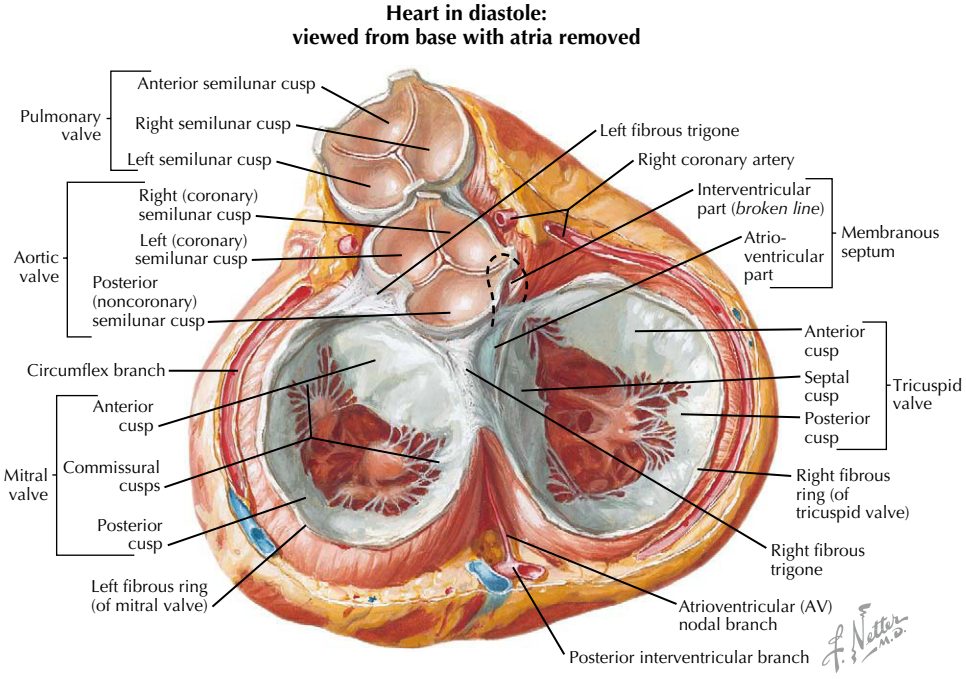

Figure 17-3 *Structural relationships of the pericardium, heart, valves, and fibrous skeleton.*

It is likely that the incidence of both VSR and free-wall rupture decreased first with the routine use of thrombolytic therapy and further with the use of percutaneous coronary intervention (PCI) in acute MI. However, both are still seen and must be diagnosed and treated early for there to be any reduction in mortality from these mechanical complications of MI.

CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH

The clinical signs and symptoms of CS derive from the underlying pathophysiology. Patients presenting with MI complain of chest pain. Recurrent chest pain may imply ongoing ischemia or reinfarction but may also reflect mechanical complications such as papillary muscle rupture, VSR, or free-wall rupture. Symptoms associated with ischemia include nausea, emesis, restlessness, and agitation. End-organ hypoperfusion associated with the redistribution of blood to vital organs by means of selective vasoconstriction results in cool and clammy peripheries. There may also be evidence of decreased urine output and mental status changes.

The elevated LV filling pressures give rise to pulmonary edema and resultant dyspnea and tachypnea with associated bilateral rales on physical examination. Often, the development of respiratory failure can be sudden and dramatic. Laboratory evaluation may demonstrate evidence of acute kidney and liver dysfunction as well as lactic acidosis.

Cardiopulmonary examination may give clues into the etiology of hemodynamic collapse. A diffuse point of maximal impulse, loud S_3 gallop, and elevated jugular venous pressure with rales on lung examination are specific findings associated with underlying heart failure. A new holosystolic murmur would lend suspicion for mitral regurgitation (although in the acute setting the murmur may be difficult to detect), VSR, or RV failure with functional tricuspid regurgitation as a result of RV dilatation and volume overload. A precordial thrill may help to differentiate VSR. Evidence of hypotension with reduced pulse pressure, pulsus paradoxus, and distant heart sounds could indicate the presence of tamponade physiology related to free-wall rupture.

Echocardiography is a powerful diagnostic tool in patients who present after MI. In CS, this imaging modality can provide detailed information about the etiology and supplement findings from the history and physical examination. The echocardiogram can provide information regarding the LV and RV size and function, as well as the presence of valvular and structural complications.

MANAGEMENT AND THERAPY

Optimum Treatment

The management of CS after an MI revolves around early reperfusion of the occluded coronary artery with a goal of complete revascularization in the setting of severe multivessel coronary artery disease. Coronary angiography followed by revascularization is preferred over fibrinolytic therapy (Fig. 17-4). In the SHOCK Trial, a strategy of early revascularization resulted in 132 lives saved at 1 year per 1000 patients treated, as compared with initial medical therapy followed by no or late revascularization as clinically determined. The benefit was noted in patients younger than 75 years of age, and the survival benefits persisted at long-term follow-up. In the setting of shock, the time window for benefit with revascularization is greater than that established with primary reperfusion for STEMI. The SHOCK Trial enrolled patients within 36 hours of their index MI, and patients throughout the time window benefited. Certain patients over the age of 75 years also seem to derive benefit from revascularization in observational registries when selected by experienced physicians. The modality of revascularization should be guided by the extent and severity of coronary artery disease. PCI with stent implantation should be used in patients with single-vessel and two-vessel disease amenable to revascularization. In addition to opening the infarct-related artery, multivessel PCI should strongly be considered for other severely stenotic lesions in the acute setting. Patients with severe obstruction in three coronary vessels or severe left main trunk stenosis may be considered for emergency bypass surgery, especially if PCI is not feasible.

A Swan-Ganz catheter (SGC) for hemodynamic monitoring is a useful tool in CS. There is no evidence for survival benefit in patients with an SGC when independently studied;

Acute coronary intervention reduces mortality from MI, even in critically ill patients. Continuous electrocardiographic and hemodynamic monitoring is performed throughout the procedure, and additional hemodynamic support (pharmacologic or with an intra-aortic balloon pump) is available for patients with cardiogenic shock.

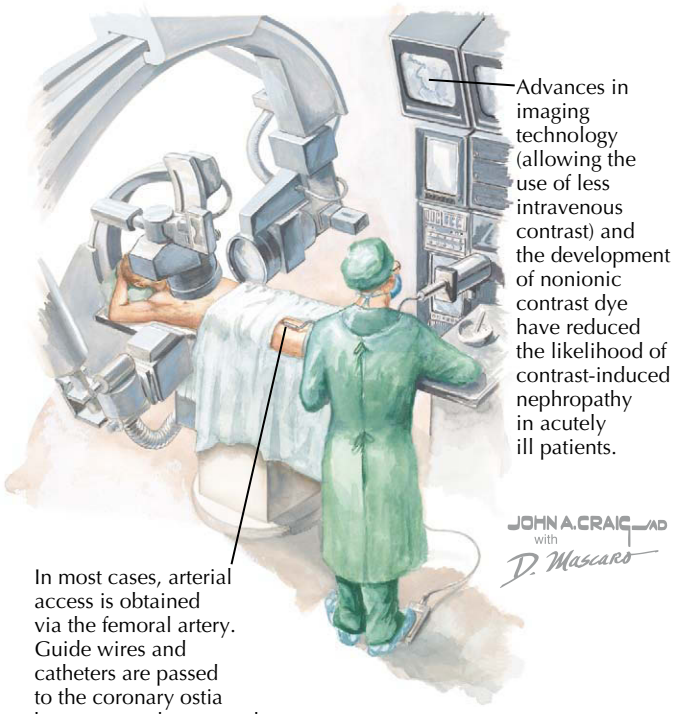

Figure 17-4 *Acute coronary intervention.*

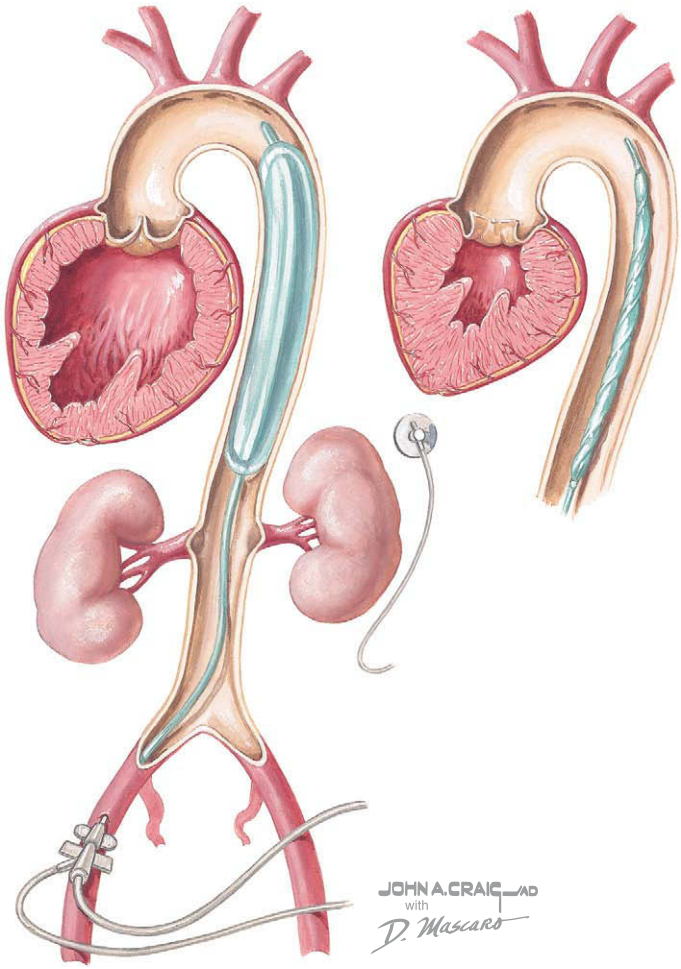

Figure 17-5 *Intra-aortic balloon counterpulsation pump.*

however, it is useful for diagnosis and management. When the cause of hypotension is unclear, the SGC can confirm the presence of reduced cardiac output with elevated intracardiac filling pressures distinguishing cardiogenic from alternative etiologies for shock. The presence of RV failure, papillary muscle rupture, and VSR can be further characterized by SGC hemodynamic patterns. In addition, the hemodynamic response to intra-aortic balloon pump (IABP) insertion and medication changes can be followed closely in real time.

The IABP is another important adjunctive measure in CS management (Fig. 17-5). It functions by inflating in diastole and deflating in systole as triggered by ECG or pressure waveform during the cardiac cycle. The IABP creates a vacuum effect during systole that reduces afterload on the left ventricle. During diastole, the IABP augments diastolic blood pressure, theoretically increasing coronary perfusion pressure. The current American College of Cardiology/American Heart Association Guidelines support the use of IABPs as a stabilizing measure in CS.

The expression of inducible nitric oxide synthase may play an important role in the genesis and outcome after shock. However, the multicenter randomized trial testing the nitric oxide synthase inhibitor L-*N*(G)-monomethyl arginine did not show reduction in mortality from CS.

The general approach to a patient with MI and cardiogenic shock is to stabilize the oxygenation, blood pressure, and rhythm while proceeding urgently to coronary angiography. Once the anatomy of the obstructive coronary artery disease is determined, the approach to revascularization can be decided. When cardiac catheterization is not readily accessible, fibrinolytic therapy may be considered for reperfusion in STEMI and early shock within 3 hours of initial symptom onset. The patient is then transferred to a center with cardiac catheterization and coronary care unit capabilities (Fig. 17-6).

Avoiding Treatment Errors

Patients with large infarct territories or hemodynamic instability following an MI benefit from monitoring in an intensive care setting to diagnose complications and guide management. Early identification of mechanical complications facilitates appropriate surgical intervention. Caution must be applied with routinely used medications to avoid iatrogenic shock. Patients with RV infarction are notoriously sensitive to reductions in preload. The administration of nitroglycerin in such cases may result in hypotension and exacerbation of ischemia. Similarly, patients with RV infarct may require a surprisingly high volume of fluid replacement (several liters) to achieve hemodynamic stability. Fluid replacement must be individualized in these patients, monitoring mean blood pressure to be certain sufficient fluid has been given, and carefully following the patient for evidence of fluid overload by physical examination and measurement of oxygen saturation. A patient with large infarct territory and severe LV dysfunction can manifest with tachycardia to maintain adequate cardiac output. The administration of a β-blocker may result in reduced cardiac output and hemodynamic collapse in these patients. In the COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction) Trial, early β-blockade in patients with acute MI was associated with an increase in CS. Overly aggressive use of angiotensin-converting enzyme inhibitors may also lead to iatrogenic hypotension.

FUTURE DIRECTIONS

Patients with persistent shock despite revascularization have a poor prognosis. Eligible patients may be considered for cardiac transplantation. Selection of patients for mechanical support in CS is challenging. The possibility of ventricular recovery with revascularization alone must be weighed against prompt establishment of adequate cardiac output to prevent end-organ dysfunction. As more data become available with LV assist devices and artificial heart models, it will be easier to select patients who would benefit from mechanical support. Smaller mechanical-assist devices that can be implanted percutaneously will be developed. Mechanical support is most commonly used as a bridge to cardiac transplantation, but technologic advancements will allow for greater utilization for long-term support, or so-called destination therapy. Stem cell breakthroughs may provide additional options to repair and regenerate myocardial tissue and restore cardiac function. This is being evaluated in several ongoing clinical trials.

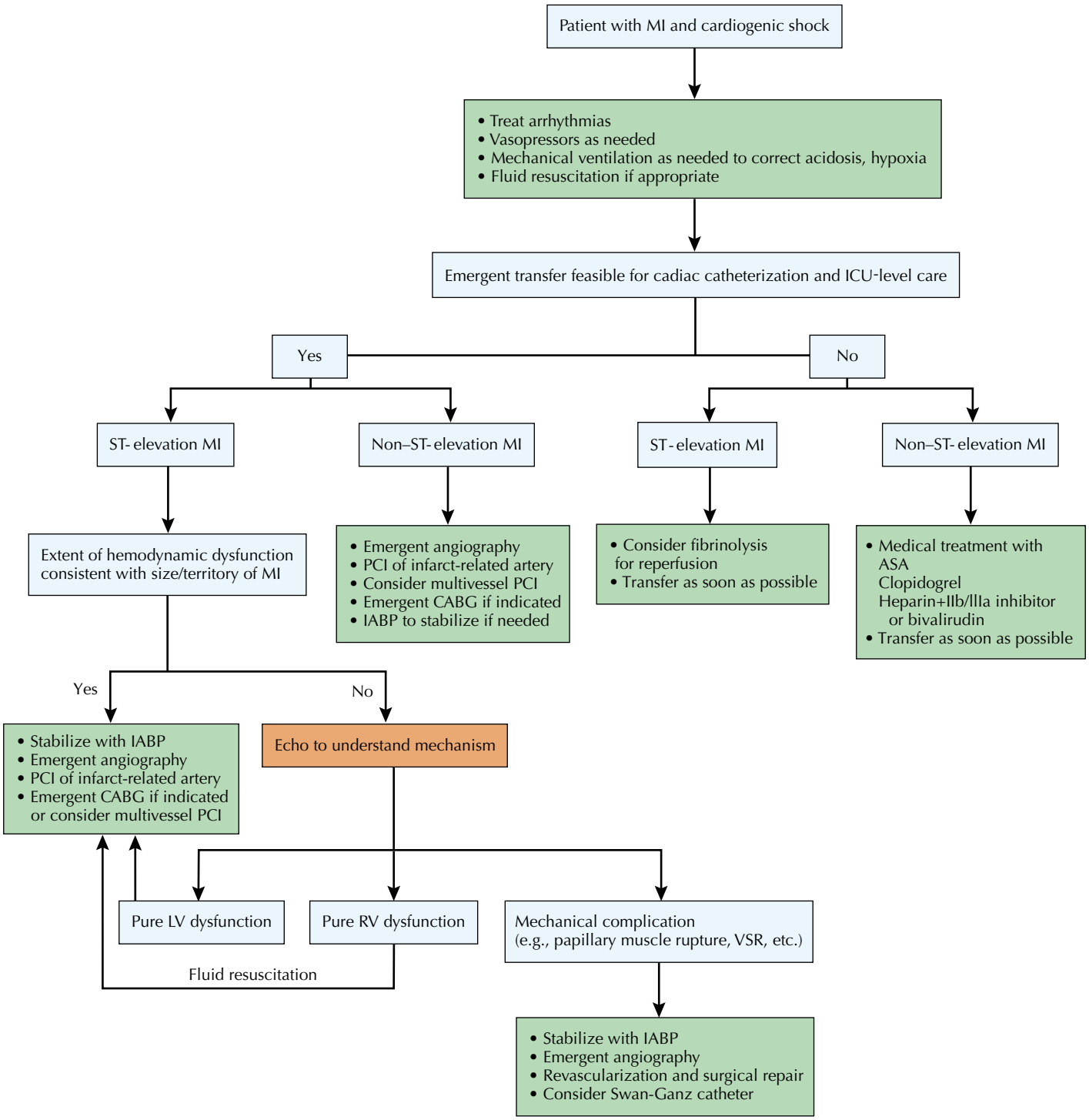

Figure 17-6 *General approach to treatment of acute myocardial infarction (MI) and cardiogenic shock.* ASA, aspirin; CABG, coronary artery bypass graft surgery; IABP, intra-aortic balloon counterpulsation pump; ICU, intensive care unit; LV, left ventricular; PCI, percutaneous coronary intervention; RV, right ventricular; VSR, ventricular septal rupture.

ADDITIONAL RESOURCES

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Thorough overview of pathophysiology and cellular pathways that propagate hypotension during cardiogenic shock after MI.

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EVIDENCE

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Dilated Cardiomyopathy

Patricia P. Chang

18

The word cardiomyopathy stems from Greek roots: *kardia* (heart), *mys* (muscle), and *pathos* (suffering). Dilated cardiomyopathy (DCM) is the most common type of systolic heart failure (HF) and has multiple etiologies. Given the number of Americans with HF (approximately 5.3 million), the cost of their care (an estimated direct and indirect cost of $34.8 billion in 2008), and the fact that more than half of these individuals have DCM and systolic HF, understanding the underlying causes of cardiomyopathy and its treatment are of great importance.

The clinical presentation of an individual with DCM is typically with symptoms and signs of HF, regardless of the etiology of the DCM. The prognosis for individuals with DCM has improved as treatment has evolved to include many medications as well as electrophysiology devices and surgical therapies. Despite medical progress, the prevalence of DCM will continue to grow, since this is the common final stage of many cardiovascular diseases. This chapter describes the causes of DCM and general treatment options.

ETIOLOGY AND PATHOGENESIS

DCM is characterized by dilatation and impaired contraction of either the left ventricle or both ventricles, as a result of altered structure or function in diseased cardiomyocytes. Before the heart becomes dilated and weak, there is either an index event (e.g., a myocardial infarction [MI] or acute myocarditis) that leads to impaired ventricular contractility, or progression of underlying disease (e.g., severe valvular regurgitation) that leads to ventricular pressure overload causing systolic dysfunction. Because of ventricular systolic dysfunction, gradual compensatory responses of the cardiomyocytes lead to cardiac remodeling (Fig. 18-1). Initially the cardiomyocytes respond by becoming hypertrophied, but the poorly functioning ventricle gradually dilates to handle the progressive volume overload. In most cases, contractility is impaired initially and primarily in the left ventricle, but as systolic dysfunction progresses, the right ventricle also becomes enlarged and hypokinetic. Rarely, the cardiomyopathic process will affect primarily the right ventricle at the outset of the DCM.

In DCM and other types of HF there is an imbalance between the activation and effects of the vasoconstrictor hormones versus endogenous vasodilators. The effects of the vasoconstrictor hormones predominate in HF as a result of activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). These vasoconstrictor hormones (e.g., norepinephrine, angiotensin II) worsen hemodynamics by increasing vascular resistance and afterload, and hence myocardial work, resulting in progressive ventricular remodeling through abnormal cellular growth and other effects. Activation of the RAAS also produces salt and water retention, further elevating filling pressures and resulting in symptoms and signs of HF. Angiotensin II acts on the angiotensin II type 1 (AT1) receptor to cause vasoconstriction, sodium retention, and other physiologic effects.

In contrast, activation of the vasodilating natriuretic peptide system (e.g., atrial and B-type natriuretic peptides [ANPs, BNPs]) is beneficial in HF, resulting in vasodilation and sodium excretion. In decompensated HF patients, the vasodilatory systems are simply overwhelmed by the vasoconstricting neurohormones.

Interventions to prevent decompensated HF have focused on these neurohormonal targets in an effort to restore the balance of these competing systems and to reverse acute decompensated HF. Blocking the RAAS and sympathetic nervous system (e.g., by administrating angiotensin-converting enzyme [ACE] inhibitors and β-blockers) and augmenting the natriuretic peptide system (e.g., pharmacologic dosing of BNP) all have positive therapeutic effects in patients with DCM and systolic HF.

Of the many causes of DCM (Table 18-1), the most common in the United States is ischemic heart disease. After an MI, the infarct scar may expand to develop into a large area of nonfunctioning myocardium during the first hours and days after an acute MI. During this time, left ventricular (LV) systolic function may be maintained by hypercontractility of the noninfarcted portion of the left ventricle. Longer term, over days to months to years, global remodeling occurs, resulting in a dilated and poorly contractile ventricle. In some cases, a ventricular aneurysm may form (Fig. 18-2). Because coronary artery disease (CAD) is such a frequent cause of DCM—contributing to approximately two thirds of all cases of HF—the nomenclature for DCM is often subdivided into ischemic cardiomyopathy (ICM) versus nonischemic cardiomyopathy. To be classified as an ICM, the burden of coronary disease must be in proportion to the systolic dysfunction. The definition of ICM is thus based on systolic dysfunction in patients with a history of MI, patients who have undergone revascularization procedures (coronary artery bypass surgery or percutaneous coronary intervention), patients with 75% or greater stenosis of the left main or proximal left anterior descending artery, and patients with 75% or greater stenosis of two or more epicardial vessels.

Other common etiologies for DCM are end-stage hypertensive heart disease (Fig. 18-3) and valvular heart disease ("valvular cardiomyopathy"). Less common etiologies include cardiotoxins such as alcohol and anthracycline and herceptin chemotherapies; abnormal metabolic state or endocrinopathies such as thyroid disease, diabetes, acromegaly, adrenal cortical insufficiency, pheochromocytoma; autoimmune diseases such as connective tissue diseases (e.g., scleroderma, systemic lupus erythematosus) and giant cell myocarditis; infiltrative diseases such as sarcoidosis, hemochromatosis, and amyloidosis; nutritional deficiencies; peripartum state; and familial/genetic diseases (e.g., muscular dystrophies, MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke] syndrome, and other recently discovered associated chromosomal abnormalities).

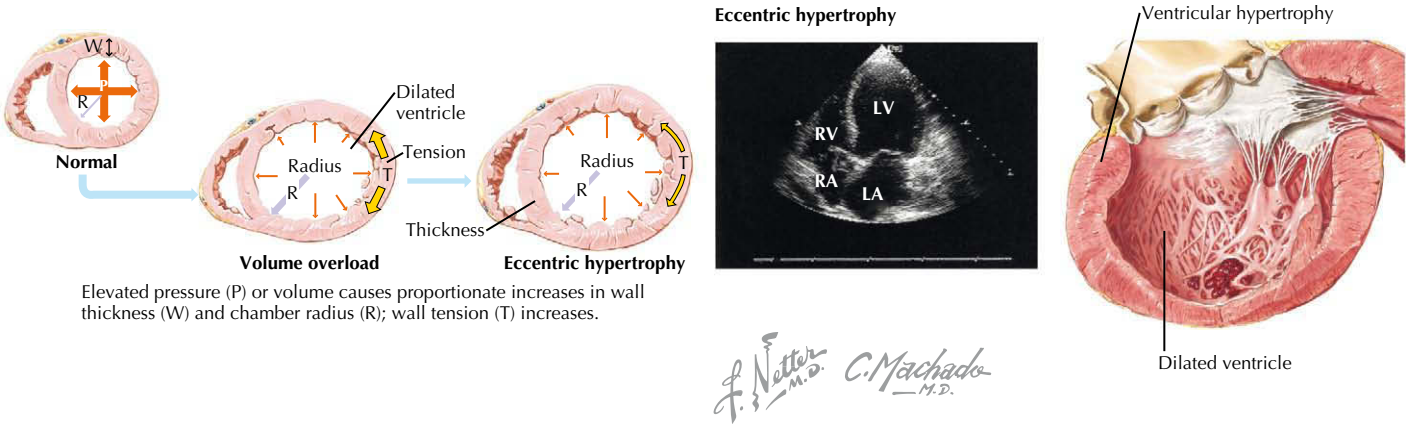


Figure 18-1 *Cardiac remodeling secondary to volume overload.* LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table 18-1 Etiologies of and Evaluation for Dilated Cardiomyopathy

Etiology	Targeted Evaluation
Ischemic heart disease (coronary artery disease)	Coronary angiography (gold standard), noninvasive coronary imaging (CT or MRI), stress test
Hypertension*	Physical examination (not helpful when end-stage)
Valvular heart disease	Physical examination, echocardiography, cardiac MRI
Infectious (e.g., viral; Chagas disease; Lyme disease)	Coxsackie B antibody titers Enterovirus PCR HIV antibody *Trypanosoma cruzi* antibody (IgM, IgG) Lyme antibody
Cardiotoxins (e.g., alcohol, anthracycline; excess catecholamines; heavy metals—lead, arsenic, cobalt)	Cumulative dose exposure Serum levels when available (e.g., lead)
Metabolic/endocrine (e.g., hypothyroidism, hyperthyroidism; diabetes mellitus; acromegaly; adrenal insufficiency; pheochromocytoma)	TSH Glucose, HbA1c Physical exam GH, cortisol, urine metanephrines
Connective tissue disease (e.g., systemic lupus erythematosus; scleroderma*; dermatomyositis; polyarteritis nodosa; rheumatoid arthritis)	ANA ± ENA and other specific rheumatologic markers
Infiltrative (e.g., Wilson's disease; sarcoidosis*; hemochromatosis*; amyloidosis*)	Free copper, ceruloplasmin Ferritin, transferrin SPEP, UPEP ACE level
Metabolic/nutritional (e.g., magnesium deficiency; kwashiorkor; anemia; beriberi; selenium deficiency)	Serum levels where available (e.g., magnesium, selenium) CBC, ferritin
Peripartum cardiomyopathy	Temporal relationship to pregnancy
Giant cell myocarditis	Endomyocardial biopsy
Muscular dystrophies (e.g., Duchenne; Becker-type; myotonic dystrophies)	Genetics
Familial (e.g., X-linked)	Family history, genetics
Idiopathic	(Diagnosis of exclusion)

*Diseases that can belong to more than one type of cardiomyopathy (e.g., hypertrophic or restrictive).
ACE, angiotensin-converting enzyme; ANA, anti-nuclear antibody; CBC, complete blood count; ENA, extractable nuclear antigens; GH, growth hormone; HbA1c, hemoglobin A1c; Ig, immunogobulin; PCR, polymerase chain reaction; SPEP, serum protein electrophoresis; TSH, thyroid-stimulating hormone; UPEP, urine protein electrophoresis.

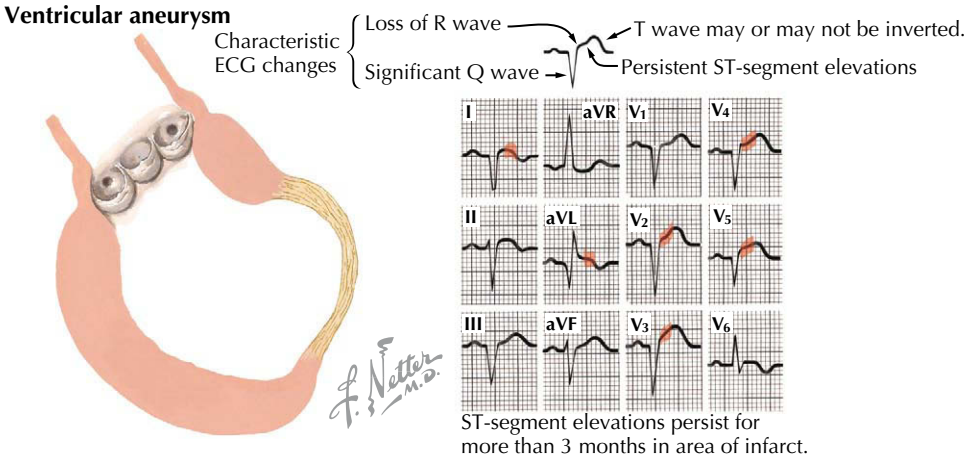


Figure 18-2 *Dilated cardiomyopathy after myocardial infarction.* ECG, electrocardiographic.

When the etiology is thought to be an infectious agent because of a viral prodrome, the specific pathogen is often not identified, in which case the generic term "viral myocarditis" is commonly used. Histologically there is usually a diffuse inflammatory response with lymphocytes infiltrating the myocardium (Fig. 18-4). Specific pathogens that have been associated with DCM development include viruses such as Coxsackie B virus, enterovirus, adenovirus, parvovirus, HIV, and cytomegalovirus; and parasites such as trypanosomiasis in Chagas disease (the most common cause of infectious cardiomyopathy in South America) and Lyme disease. Although no specific bacterium or fungus has been known to cause cardiomyopathy, acute

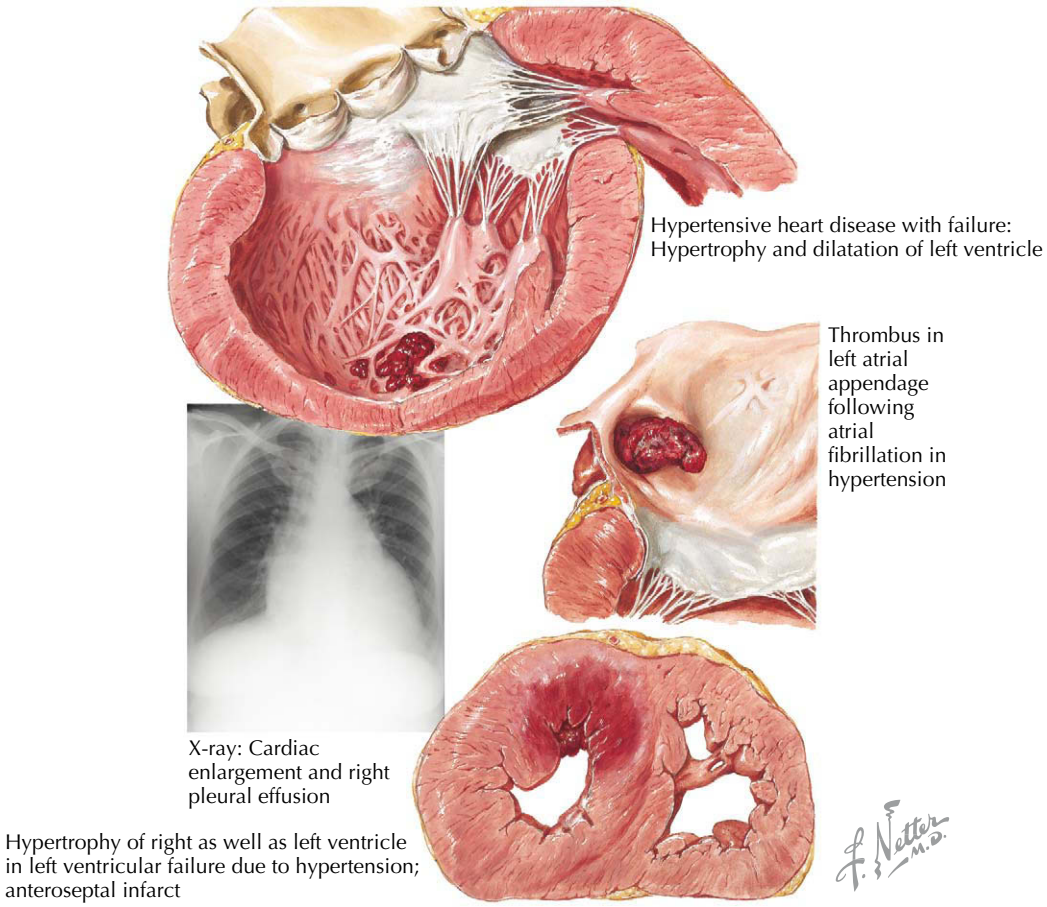


Figure 18-3 *Hypertension and cardiomyopathy.*

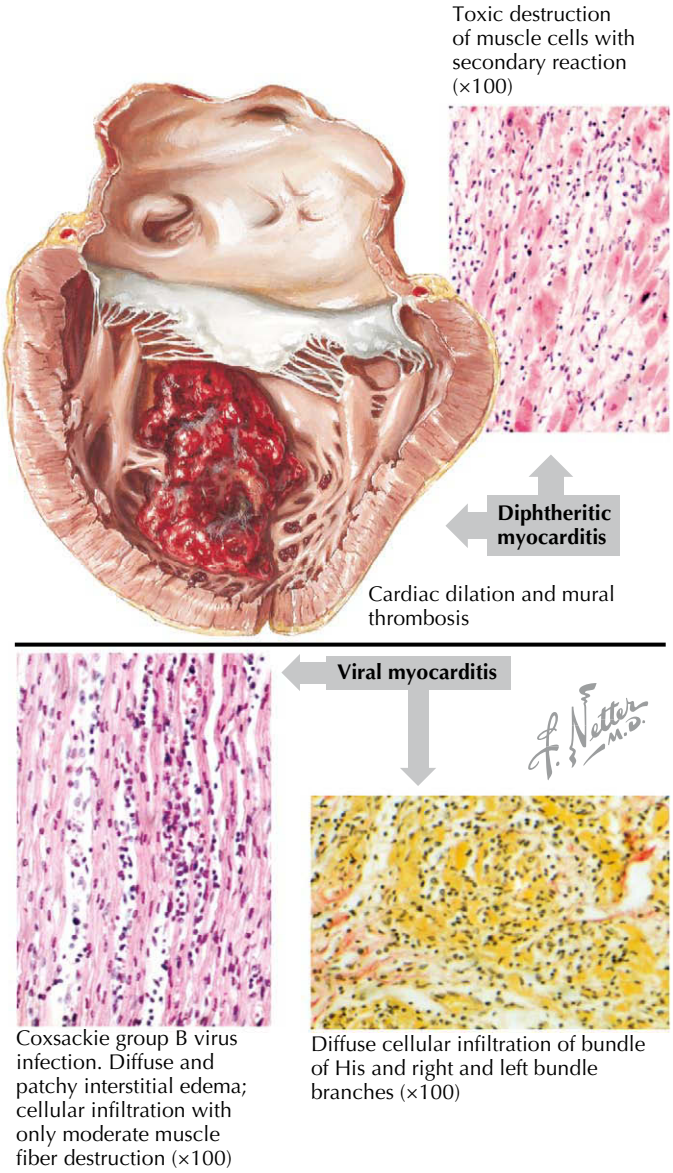


Figure 18-4 *Diphtheritic and viral myocarditis.*

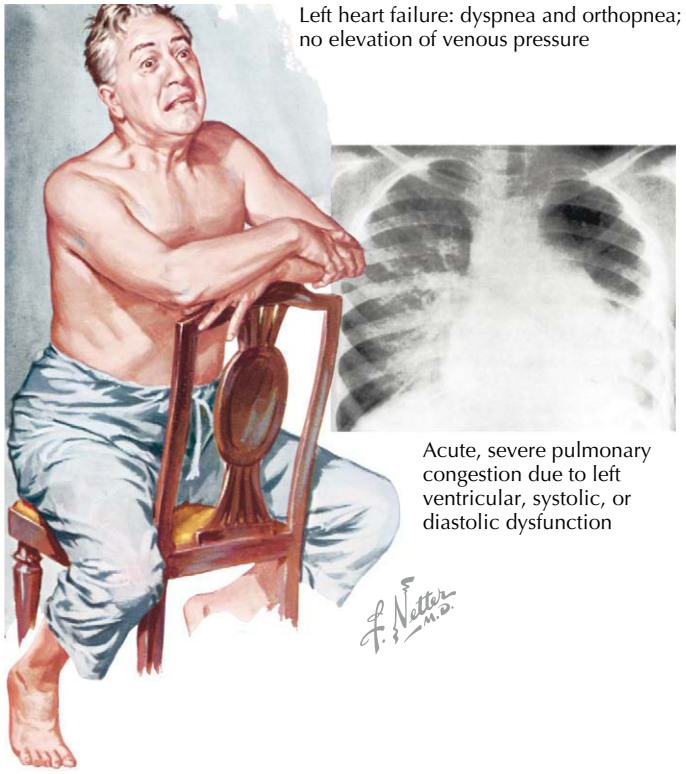


Figure 18-5 *Left heart failure and pulmonary congestion.*

ventricular systolic dysfunction has been seen in the setting of sepsis, presumably due to the effect of endotoxins or other mediators.

When no specific cause is found the DCM is described as "idiopathic cardiomyopathy." This is a common designation; in most studies, it is second only to ischemia in the etiology of DCM. It is quite possible that a genetic susceptibility to environmental factors (ranging from infectious or toxic exposures to factors such as hypertension, diabetes, and cigarette smoke) contributes to the etiology of idiopathic cardiomyopathy. Some authors have suggested that genetic abnormalities may be important in up to 30% of cases of idiopathic DCM. Some familial conditions that predispose to DCM have already been described, such as the muscular dystrophies (e.g., Duchenne, Becker), X-linked DCM (e.g., other dystrophin gene mutations), and autosomal-dominant forms of familial DCM (e.g., lamin A/C gene mutation). With advances in our knowledge of genetics, it is anticipated that this list will grow rapidly in coming years.

CLINICAL PRESENTATION

Patients with DCM can present with a variety of HF symptoms and signs. Traditionally, clinical findings can be classified as left-sided (Fig. 18-5) and right-sided (Fig. 18-6). Because the most common cause of right-sided HF is left-sided HF, most patients with DCM have a combination of both left- and right-sided findings. Decades ago the New York Heart Association (NYHA) developed a functional classification (which was originally based on the left-sided symptom of dyspnea) that is still used.

As the DCM progresses toward end-stage disease, the more severe symptoms often reflect a low-output state and hypoperfusion with or without congestion. The Forrester classification, developed in 1977 to characterize the clinical and hemodynamic status of patients with acute MI, has been adopted to describe the HF patient in terms of perfusion (warm or cold) and congestion (dry or wet). Symptoms and signs of congestion ("wet") include shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, morning cough, peripheral edema, rales, ascites, hepatic congestion, and jugular venous distention. Hypoperfusion ("cold") can be manifested symptomatically as nausea, vomiting, early satiety, altered mental status, acidosis, worsening renal or hepatic function, reduced capillary refill, cold and clammy skin, hypotension, and a narrow pulse pressure.

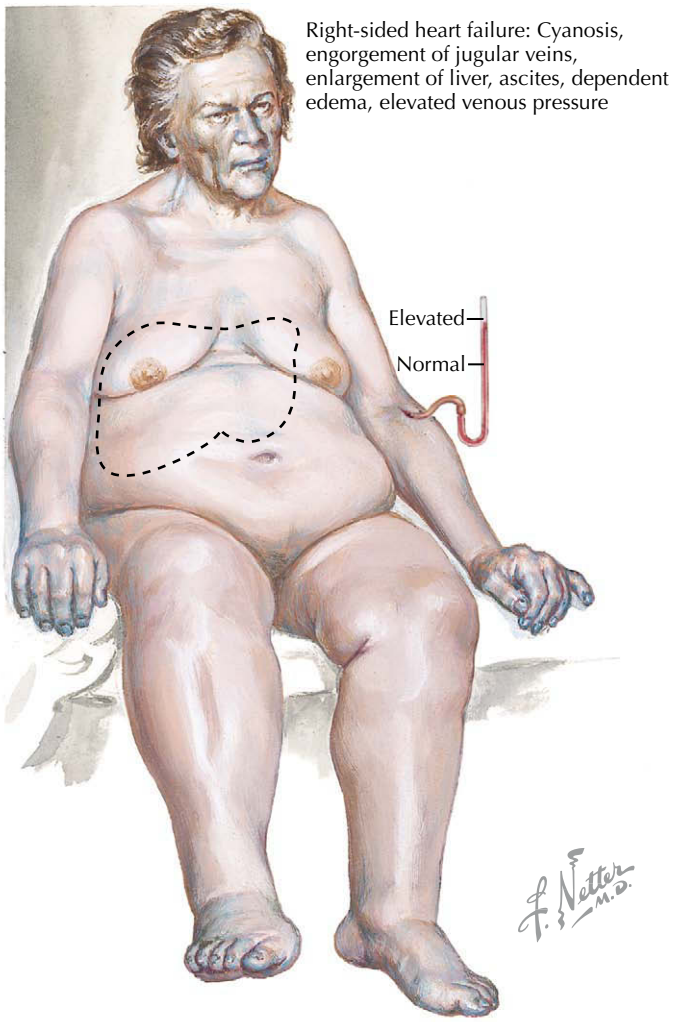


Figure 18-6 *Right-sided heart failure in a patient with dilated cardiomyopathy.*

An important goal is to reduce the prevalence of HF by prevention—particularly related to ischemia, toxin exposure, and other controllable etiologies. The American College of Cardiology (ACC) and the American Heart Association (AHA) published a new approach to the classification of HF that emphasizes its evolution and progression and defined four stages of HF in its first guidelines for the evaluation and management of chronic HF in 2001. In particular, asymptomatic patients were considered in Stage A HF if they have no apparent structural or functional abnormalities of the pericardium, myocardium, or cardiac valves but are at high risk for developing HF because of the presence of conditions strongly associated with HF. Stage A HF patients include individuals with hypertension, CAD, valvular disease, diabetes mellitus, history of cardiotoxic drug therapy or alcohol abuse, personal history of rheumatic fever, or family history of cardiomyopathy. Patients with Stage B, C, or D all have a structural abnormality of the heart with varying symptomatology that correlates to NYHA classes I through IV (Table 18-2). Although survival from DCM has improved, patients with advanced HF (NYHA classes III–IV) still make up approximately 10% to 15% of the affected population, half of whom have refractory HF (Stage D), where the prognosis is still poor.

Table 18-2 ACC/AHA Staging of Heart Failure Compared to the NYHA Functional Classification

ACC/AHA Stage	NYHA Functional Classification
A. At high risk of developing HF but without structural heart disease or symptoms of HF	None
B. With structural heart disease but without signs or symptoms of HF	I. Asymptomatic
C. With structural heart disease and prior or current symptoms of HF	II. Symptomatic with moderate exertion III. Symptomatic with minimal exertion
D. With structural heart disease and refractory HF symptoms requiring specialized interventions	IV. Symptomatic at rest

ACC, American College of Cardiology; AHA, American Heart Association; HF, heart failure; NYHA, New York Heart Association. *Adapted from Farrell MH, Foody JM, Krumholz HM.* JAMA *2002;287:890–897.*

DIFFERENTIAL DIAGNOSIS

Many of the symptoms of DCM are also common to other end-organ diseases, such as lung disease (dyspnea), cirrhosis (ascites, peripheral edema), renal failure (volume overload), and hypothyroidism (fatigue). Physical examination and laboratory data can distinguish individuals with noncardiac etiologies from patients with DCM. A second issue concerns underdiagnosis of DCM. The diagnosis of DCM in young patients is often delayed because new-onset asthma or chronic bronchitis/pneumonia—either of which results in dyspnea and fatigue as the main presenting symptoms—are far more common than DCM. Similarly, low-output symptoms are sometimes unrecognized. Nausea and vomiting, for instance, are presumed to have a gastrointestinal rather than cardiac origin, and a cholecystectomy for presumed symptomatic cholelithiasis may be unnecessarily performed. Other cardiac diagnoses mimicking DCM include angina, diastolic HF including hypertrophic and restrictive cardiomyopathies, hypertensive heart disease, and valvular disease without systolic dysfunction. A diagnostic algorithm is outlined in Fig. 18-7.

DIAGNOSTIC APPROACH

A complete history and physical examination is extremely important for the assessment of patients with DCM and HF. Of course the history is only helpful if the patient has symptoms, and the physical examination provides clues only if abnormal findings are present. Yet a normal history or physical examination does not necessarily mean a normal heart. Because DCM often has a subclinical phase, asymptomatic LV dysfunction is

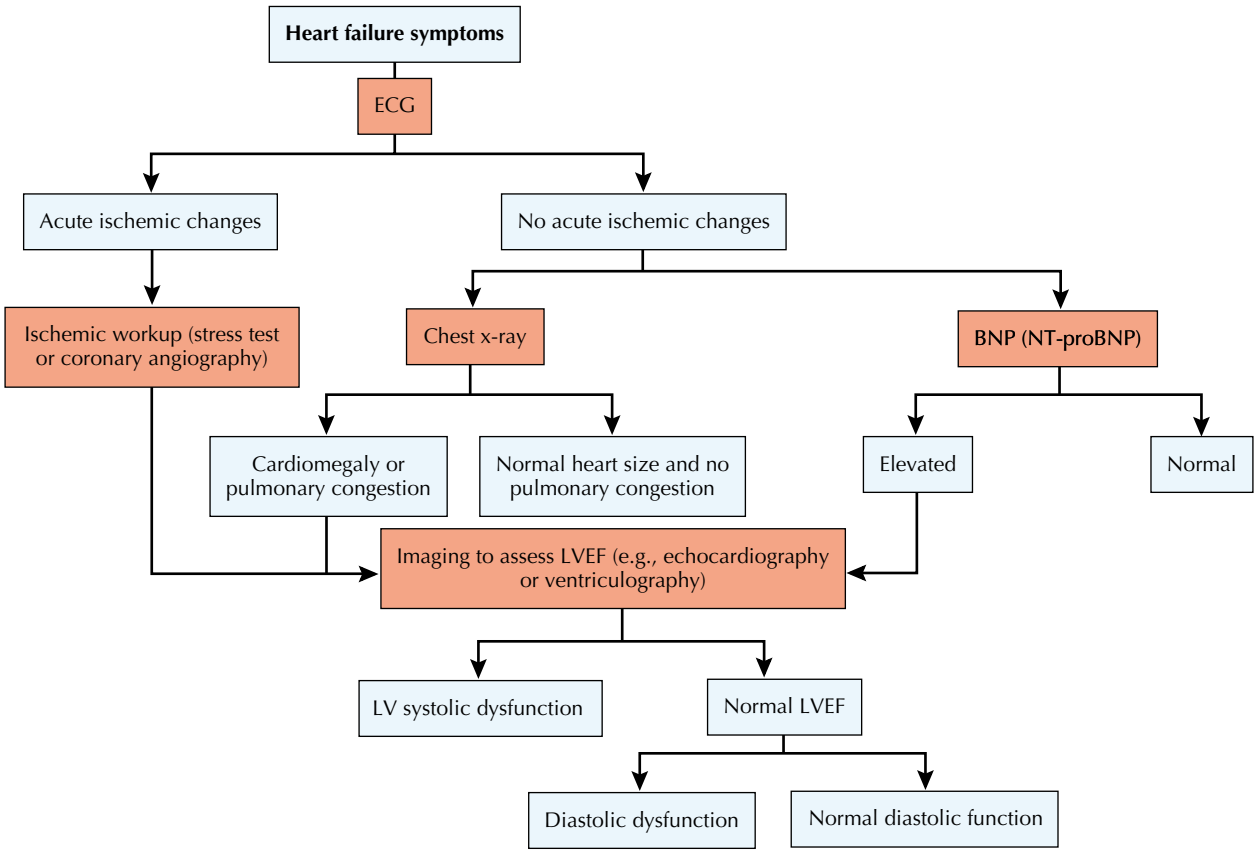


Figure 18-7 *Simplified diagnostic algorithm for heart failure.* Symptoms of dilated cardiomyopathy will vary widely depending on the patients. If both the chest x-ray and B-type natriuretic peptide (BNP) are normal, further diagnostic workup with cardiac imaging can still be considered based on pre-test probability of cardiac dysfunction. ECG, electrocardiogram; LV, left ventricular; LVEF, left ventricular ejection fraction.

often not detected by physical examination and, instead, may be discovered from abnormal findings on diagnostic tests used for other reasons. For example, cardiomegaly on a screening chest x-ray or a left bundle branch pattern on ECG (or any abnormalities of conduction, chamber size, or ischemia) should lead to further cardiac evaluation.

Echocardiography is the standard noninvasive assessment of chamber size and cardiac function. Echocardiography is widely available, well tolerated, and relatively inexpensive compared with other modalities. More precise LV ejection fraction (LVEF) estimates can be obtained from nuclear ventriculography (also known as *radionuclide ventriculography* or *cardiac blood pool multigated acquisition*), angiographic left ventriculography during coronary catheterization, and newer noninvasive modalities such as cardiac MRI and cardiac CT.

Biomarkers have also been used for confirming the diagnosis of DCM and HF in general. Natriuretic peptides, of which the most well known are BNP, N-terminal proBNP (NT-proBNP), and ANP, are very useful. BNP and NT-proBNP are endogenous natriuretic peptides that are activated in response to ventricular volume and pressure expansion. ANP is activated in response to atrial expansion. Elevated circulating levels of these peptides correlate with symptoms and NYHA class. For instance, BNP values are higher with increasing severity and higher filling pressures, as well as with lower LVEF. They have also been used prognostically as a therapeutic guide and for risk stratification in terms of future HF and mortality.

The diagnostic approach to DCM should include confirmation of the diagnosis through history taking, physical examination, and an assessment of heart function and estimate of LVEF (by echocardiography or other noninvasive technique). Determination of the etiology of DCM should prioritize diagnostic testing based on the type of cardiomyopathy suspected (Table 18-3). Because ischemic heart disease is the most common cause of DCM and HF, the presence of significant CAD should be excluded as part of the evaluation for all DCM patients. Depending on the presentation, this may involve a noninvasive stress-imaging test, noninvasive imaging of the coronary arteries (by CT or MRI), or both. If DCM is present and a patient has not undergone coronary angiography before, most experts recommend proceeding with coronary angiography because (1) the false-negative rate of noninvasive stress-imaging studies is 10% to 15% under the best of circumstances, and (2) patients with DCM and significant CAD may benefit significantly from revascularization.

Some of the specific tests may only apply to certain types of DCM; for example, cardiac MRI may be useful only for myocardial viability (ICM) or diffuse patchy defects (sarcoidosis).

Table 18-3 Diagnostic Approach for Unexplained Cardiomyopathy

Evaluation		Rationale and/or Common Findings
History	Past medical history	Etiology
	Family history	Familial
Cardiac assessment	Physical examination	+S_3, ±S_4, ±murmur, left- and right-sided HF signs/symptoms
	Electrocardiography	Abnormal ST and T wave, old MI
	Echocardiography	Dilated LV; systolic dysfunction ± diastolic dysfunction; valve disease
	Nuclear ventriculography	Dilated LV; systolic dysfunction
	Stress test	CAD
	Coronary angiography or cardiac CT angiography	CAD
	Right heart catheterization	↓cardiac output, ↑ filling pressures
	Cardiac MRI	CAD, myocardial viability, fibrosis
Other testing	Blood tests:	Etiology
	TSH	
	Glucose, HbA1c	
	ANA ± ENA	
	HIV antibody	
	SPEP, UPEP	
	Free copper, ceruloplasmin	
	Serologies:	Etiology
	Coxsackie B antibody titers	
	Enterovirus PCR	
	Trypanosoma cruzi antibody (IgM, IgG)	

ANA, anti-nuclear antibody; CAD, coronary artery disease; CT, computed tomography; ENA, extractable nuclear antigens; HbA1c, hemoglobin A1c; HF, heart failure; HIV, human immunodeficiency virus; Ig, immunoglobulin; LV, left ventricle; MI, myocardial infarction; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SPEP, serum protein electrophoresis; TSH, thyroid-stimulating hormone; UPEP, urine protein electrophoresis.

Endomyocardial biopsy is now rarely performed to determine the etiology of the cardiomyopathy but may be very helpful to diagnose certain conditions in which specific therapies are useful, such as giant cell myocarditis or acute fulminant myocarditis, for which immunosuppression might be indicated. When the etiology of a nonischemic cardiomyopathy is uncertain, blood testing should at least include thyroid-stimulating hormone, antinuclear antibody, serum protein electrophoresis, urine protein electrophoresis, HIV, ferritin, or transferrin. Right heart catheterization is generally not needed in the diagnostic workup of DCM but can be useful to distinguish between a high-output versus low-output state.

MANAGEMENT AND THERAPY

Specific treatment should be directed to the underlying cause of the DCM if a cause was identified, especially if that cause can be reversed. Ultimately, treatment is directed to managing HF symptoms and reversing the cardiac remodeling when possible. Therapy has become standardized based on numerous clinical trials on different therapies for systolic HF that improve survival and decrease morbidity. As detailed in Chapter 23 and in practice guidelines from the ACC/AHA, the Heart Failure Society of America, and the European Society of Cardiology, standard treatment includes behavioral and lifestyle modifications, such as low-salt diet, fluid restriction, weight monitoring, and minimizing coronary risk factors; medications, both oral and intravenous; electrophysiologic devices, such as implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy; and surgical therapies where indicated, such as revascularization, valve surgery, mechanical cardiac support, and cardiac transplantation.

Optimum Treatment

There are currently five accepted core performance measures developed by the ACC/AHA, of which the first four are widely used by the Joint Commission on Accreditation of Healthcare Organizations and the Centers for Medicare and Medicaid Services for assessing the quality of clinical care of HF patients. These are (1) evaluation of LV systolic function before arrival, during hospitalization, or planned after discharge; (2) administration of an ACE inhibitor or angiotensin receptor blocker (ARB) to patients with LV systolic dysfunction (LVSD); (3) discharge instructions given to patient or caregiver addressing all of the following: activity level, diet, discharge medications, follow-up appointment, weight monitoring, and what to do if symptoms worsen; (4) adult smoking cessation advice or counseling; and (5) anticoagulation therapy for eligible patients with atrial fibrillation. Although adherence to these performance measures seems to be related to improved quality of care, it is likely that over time these core measures will be revised to further improve the care of patients with HF. Optimum treatment is considered to include optimizing evidence-based medications to at least target doses as tolerated and the appropriate use of the various electrophysiologic devices or surgical therapies when needed.

With many medications proven to help patients with HF, the challenges of polypharmacy include patient compliance, cost, and minimizing medication-related complications. In general,

β-blockers and ACE inhibitors should be prescribed for all patients with DCM, since these classes have the greatest impact on survival and reversing cardiac remodeling with potential improvement in LVEF. ACE inhibitors have a class effect, but it is believed that not all β-blockers are equally effective. β-blockers with the most evidence for improving HF survival include extended-release metoprolol succinate, carvedilol, and bisoprolol. Doses of both ACE inhibitors and β-blockers should be titrated up to target doses (e.g., enalapril to 10 mg twice daily, metoprolol succinate to 200 mg daily). Although loop diuretics may not improve mortality, they are commonly needed to maintain euvolemia and are important in the symptomatic treatment of patients with HF. Interestingly, the aldosterone blockers spironolactone and eplerenone (which are considered diuretics) decrease HF mortality, although they result in modest, at best, diuresis in patients with HF. ARBs can be used as an alternative to an ACE inhibitor (e.g., for patients with ACE inhibitor–related cough) or as an adjunct (e.g., for more blood pressure control or afterload reduction). The combination of hydralazine and nitrate should be considered for patients intolerant of an ACE inhibitor or ARB (e.g., significant renal dysfunction) or as adjunctive therapy for African Americans, or if congested. Digitalis is the only "inotrope" that is not proarrhythmic. Although digitalis does not reduce mortality, in one study it was shown to reduce the frequency of recurrent hospitalization in patients with decompensated HF.

Unlike most other cardiomyopathies, there is a role for electrophysiology therapies in DCM when the LVEF is 35% or less (see also Chapter 32). Use of an ICD is indicated for primary and secondary prevention for both ischemic and nonischemic DCM. The timing of ICD insertion is different depending on the etiology: greater than 40 days post-MI or after revascularization for patients with ICM, and greater than 3 months for patients with nonischemic DCM on optimal therapy. Because approximately 30% of patients with chronic HF have ventricular dyssynchrony, cardiac resynchronization therapy (CRT) with biventricular pacemakers can improve symptoms and reduce mortality in patients with NYHA class III through IV symptoms and a basal QRS duration greater than 120 milliseconds. In general, CRT should only be considered if patients remain symptomatic even after medical therapy has been optimized. Recent evidence, for example from the Multicenter Automatic Defibrillator Implantation Trial (MADIT-CRT), has suggested a possible role for CRT in asymptomatic or minimally symptomatic patients (NYHA class I-II).

Finally, various surgical therapies should be considered when appropriate for patients with DCM. Whether revascularization with coronary bypass grafting should be pursued in all DCM patients with multivessel coronary disease and LVEF less than 35% is under investigation in the STICH Trial (Surgical Treatment for Ischemic Heart Failure; results expected in 2010). Ventricular restoration (the Dor procedure) has been frequently used to surgically manipulate and minimize cardiac remodeling (also part of the STICH Trial). Since DCM causes mitral annular dilatation that often results in severe mitral regurgitation, mitral valve repair or replacement can be considered in those who appear particularly symptomatic from the valvular disease.

The ultimate cure of the patient with end-stage DCM is cardiac transplantation (Chapter 24). Over 85,000 cardiac transplants are performed worldwide, with about 2000 transplantations per year performed in the United States. There are a variety of mechanical cardiac support devices that can be used as an alternative or bridge to transplantation. Some of these devices are intended to be temporary as a bridge to recovery or to transplantation (e.g., extracorporeal membrane oxygenation, intra-aortic balloon pumps). Ventricular assist devices (VADs) can provide prolonged support either as bridge to transplant (temporary) or as destination therapy (permanent) for the patient who is not eligible or interested in heart transplantation. Older generations of VADs provided pulsatile flow (volume displacement pumps), but newer generations provide continuous flow (axial pumps).

Avoiding Treatment Errors

The patient with DCM should be carefully monitored with close follow-up. Patients must be monitored for medication-related complications such as hyperkalemia with ACE inhibitors, ARBs, and aldosterone blockers; hypokalemia with diuretics; hypotension with any medication that can lower blood pressure; or other medication-related issues. Care providers should ensure timely referral for specific therapies for refractory or Stage D HF (e.g., VAD or cardiac transplantation before a patient is truly end-stage). Objective assessments of advanced or end-stage disease should include frequent and reproducible noninvasive assessment of functional capacity (e.g., a 6-minute walk or a cardiopulmonary exercise stress test that measures peak exercise O_2 consumption [Vo_2]), or an invasive assessment of hemodynamics (right heart catheterization). Several prognostic models have been used in patients with DCM to aid in making timely referrals for VAD/transplantation. The Heart Failure Survival Score has been used for risk stratification and includes ischemic etiology, resting heart rate, LVEF, mean blood pressure, intraventricular conduction delay, peak exercise Vo_2, and serum sodium.

FUTURE DIRECTIONS

As medical technology continues to evolve, tools will be developed for both diagnostics and therapeutics for DCM. Genetic advances will allow easier diagnosis of otherwise unexplained DCM presumed to be familial. Although purely investigational at this time, treatment with new drugs, stem cells, and total artificial hearts may provide even more hope to the end-stage patient.

Acknowledgment: We would like to thank Kirkwood F. Adams, Jr., and Stephanie H. Dunlap for their contributions to the earlier edition of this chapter.

ADDITIONAL RESOURCES

American Heart Association website. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3004550>; Accessed 22.02.10.

Provides access to the most up-to-date versions of HF guidelines (most developed in conjunction with the ACC).

European Society of Cardiology website. Available at: <http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/GuidelinesList.aspx>; 2008 Accessed 22.02.10.

Provides access to their HF guidelines.

Fonarow GC, Abraham WT, Albert NM, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA* 2007;297(1):61–70.

This study challenges the accepted clinical performance measures for HF with respect to its relationship to clinical outcomes.

Heart Failure Society of America. Available at: <http://www.hfsa.org>; Accessed 22.02.10.

Contains many helpful resources about HF for health professionals, patients, and their families, including the Society's versions of HF guidelines.

EVIDENCE

Bonow RO, Bennett S, Casey DE Jr, et al. ACC/AHA Clinical Performance Measures for Adults with Chronic Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures): endorsed by the Heart Failure Society of America. *J Am Coll Cardiol.* 2005;46(6):1144–1178.

Describes the clinical performance measures that were developed for assessing and improving the quality of clinical care of chronic HF.

European Society of Cardiology; Heart Failure Association of the ESC (HFA); European Society of Intensive Care Medicine (ESICM), Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail.* 2008;10(10):933–989.

These guidelines provide current recommendations for treatment of chronic HF based on available data and consensus opinion (Classes I, IIa, IIb, III; Levels A, B, C).

Heart Failure Society of America. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail.* 2006;12(1):10–38.

These guidelines provide current recommendations for treatment of chronic HF based on available data and consensus opinion (Classes I, IIa, IIb, III; Levels A, B, C).

Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation.* 2005;112(12):e154–e235.

These guidelines provide current recommendations for treatment of chronic HF based on available data and consensus opinion (Classes I, IIa, IIb, III; Levels A, B, C).

Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. *J Heart Lung Transplant.* 2006;25(9):1024–1042.

These guidelines provide current recommendations for evaluating patients for heart transplantation based on available data and consensus opinion (Classes I, IIa, IIb, III; Levels A, B, C).

Hypertrophic Cardiomyopathy

19

Parag Kale and Richard A. Walsh

Hypertrophic cardiomyopathy (HCM) is the accepted term for a form of unexplained left ventricular (LV) hypertrophy that is attributable to mutations in genes encoding cardiac sarcomere proteins. Although the presentation of HCM within families varies in part because of the presence of known triggers such as hypertension, HCM is distinct from myocardial hypertrophy that develops solely in response to this sort of stimulus (Fig. 19-1). The cardinal histologic feature of HCM is myofibrillar disarray occupying 20% or more of at least one pathologic tissue block.

The annual mortality rates from HCM are approximately 6% in patients diagnosed while children and approximately 3% in patients diagnosed as adults. Patients who are older at diagnosis are often symptomatic but, in general, demonstrate slower disease progression and a more favorable prognosis. However, the 1-year mortality rate associated with HCM dramatically rises in older patients presenting with New York Heart Association (NYHA) Class III or IV congestive heart failure. Other adverse prognostic indicators are a history of atrial fibrillation or hypertension, use of digoxin and diuretics, and ECG evidence of myocardial infarction (MI). Syncope and a family history of sudden death are most predictive of sudden death. By contrast, the presence or absence of LV outflow tract obstruction may not be associated with prognosis.

ETIOLOGY AND PATHOGENESIS

Various terms have been used to describe the phenotype of HCM. These include *hypertrophic obstructive cardiomyopathy*, *idiopathic hypertrophic subaortic stenosis*, *asymmetric septal hypertrophy*, and *muscular subaortic stenosis*—all based on the misconception that dynamic outflow tract obstruction was the key pathologic determinant of the hypertrophy (Fig. 19-2).

It is now accepted that despite the presence or absence of outflow tract obstruction, the principal abnormality is impaired ventricular compliance as a consequence of inappropriate myocardial hypertrophy and diastolic dysfunction. The nonobstructive form of HCM accounts for approximately 75% of cases.

Epidemiology

HCM is inherited in an autosomal-dominant pattern in 50% to 75% of cases. Its prevalence is thought to be 1 per 500 in the general U.S. population and higher in African American individuals. Three age peaks of presentation have been proposed: adolescence, the early 40s, and the early 60s. The clinical presentation of HCM (syncope, sudden cardiac death, severe effort-related chest discomfort, or dyspnea) tends to be most dramatic when HCM presents in adolescence, and more dramatic when the presentation is in the 40s than in the 60s. There is a male predominance in younger patients, whereas there may be an equal or higher prevalence in females in the older population. Clinical presentation with dyspnea, atrial fibrillation, and hypertension is more common in elderly individuals. Echocardiographic differences in two series highlight ovoid LV shape in elderly persons as opposed to reversed septal curvature with a crescent-shaped cavity in persons 40 years or younger. Posterior septal movement, as opposed to systolic anterior motion of the mitral valve, may contribute to higher outflow velocities in elderly individuals. ECG findings of Q waves in the anterior and lateral leads are often seen in the younger group. The genetic basis for HCM is addressed in Chapter 72, Genetics in Cardiovascular Disease.

CLINICAL PRESENTATION

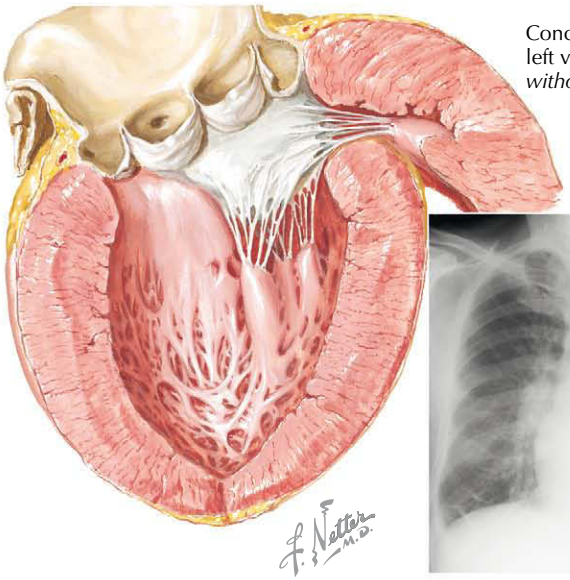
Some patients with HCM are asymptomatic, and the diagnosis is made after an episode of sudden cardiac arrest. The most common initial symptoms are dyspnea, chest pain, and syncope. Dyspnea is usually exertional and is reported in more than 90% of patients with HCM. Angina occurs in 75% of patients, and MI has been documented in 15% of cases at autopsy. Syncope occurs in approximately 50% of patients. There is no relation between the outflow tract gradient severity and syncopal symptoms except in some circumstances (atrial fibrillation in patients with a significant outflow gradient, see discussion below), suggesting that the most common etiology of syncope in HCM is arrhythmic.

Clinical Syndromes/Variants

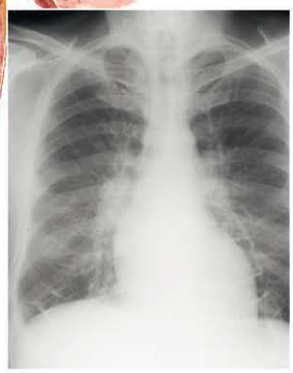
Apical hypertrophy is a rare manifestation of HCM, usually presenting in a more benign fashion. The diagnosis is often suggested by very characteristic ECG findings; typically the ECG shows giant negative T waves in the precordial leads. The configuration of the left ventricle is different from that of the usual form of HCM. In patients with apical hypertrophy, an end-diastolic left ventriculogram in the right anterior oblique projection has a characteristic "spadelike" appearance, so called because the LV cavity in this projection resembled the spade in a deck of playing cards. Patients with Costello's syndrome have HCM and mental and growth retardation, possibly related to advanced parental age and autosomal-dominant inheritance. Distinctive craniofacial findings, resembling those of lysosomal storage disorders, are also present. Other features of this syndrome include acanthosis nigricans, verrucous papillomata of the nose, hyperextensibility of the digits, and soft skin with excess wrinkling over the dorsum of the hands and deep creases on the palms and soles.

DIFFERENTIAL DIAGNOSIS

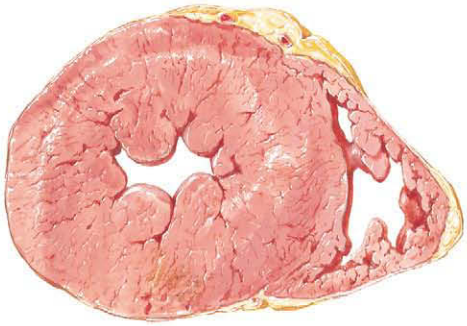
LV hypertrophy (mimicking HCM) may also be present in patients with long-standing systemic hypertension (Fig. 19-3), outflow obstruction secondary to valvular heart disease (e.g., aortic stenosis or coarctation of the aorta), and infiltrative



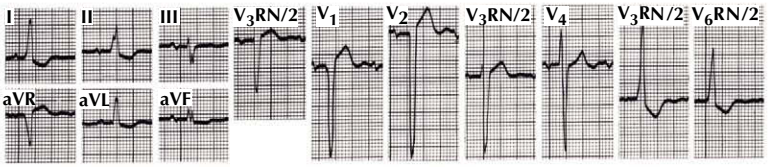
Concentric hypertrophy of left ventricle in hypertension *without* cardiac failure



Cardiac hypertrophy in chronic hypertension (x-ray evidence may be minimal)

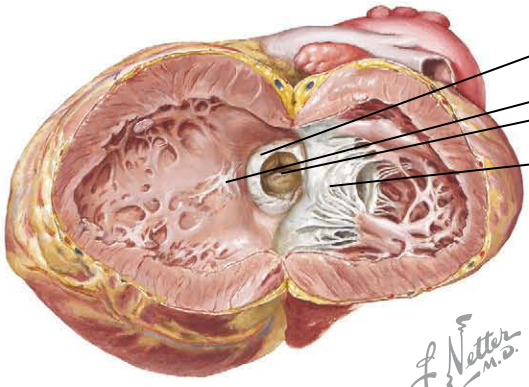


Cross-section of heart with greatly hypertrophied left ventricle and relatively normal right ventricle in uncomplicated hypertensive heart disease



Electrocardiographic evidence of left ventricular hypertrophy may or may not be present (tall R waves in V_4, V_5, and V_6; deep S waves in V_3R, V_1, V_2, III, and aVR; depressed ST and inverted T in V_5, V_6, I, II, aVL, and aVF)

Figure 19-1 *Left ventricular hypertrophy in hypertension.*

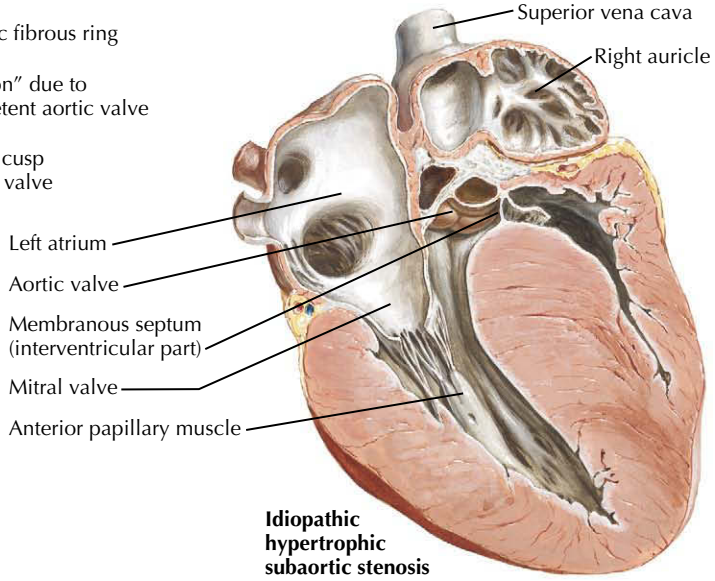


Subaortic fibrous ring

"Jet lesion" due to incompetent aortic valve

Anterior cusp of mitral valve

Fibrous subaortic stenosis



Idiopathic hypertrophic subaortic stenosis

Figure 19-2 *Anomalies of the left ventricular outflow tract that can mimic valvular aortic stenosis.*

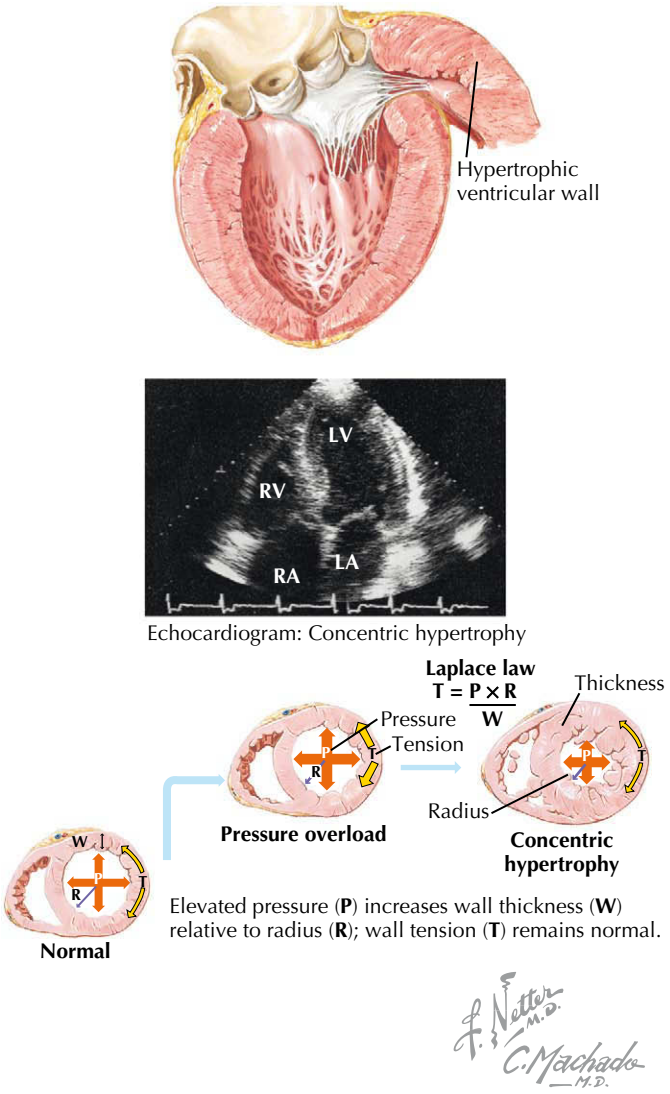


Figure 19-3 *Left ventricular concentric hypertrophy.* LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

disorders of the myocardium. At times, distinguishing these conditions from HCM clinically, or even by echocardiography, can be very difficult. Tips for making this diagnostic distinction include the following: (1) in patients with aortic stenosis the gradient is fixed, unlike in patients with HCM in whom the gradient is dynamic and may fluctuate with each heartbeat; and (2) the pattern of hypertrophy seen in patients with hypertension is concentric as opposed to the pattern seen in patients with HCM, which is often distinctive, as described later in this chapter.

DIAGNOSTIC APPROACH

Physical Examination

The carotid impulse of the patient with the obstructive form of HCM is rapid in upstroke, bifid, and followed by a prominent dicrotic notch. This "spike-and-dome" pulse pattern is caused by rapid ventricular emptying secondary to increased LV contractility, followed by abrupt flow reduction secondary to systolic anterior motion of the mitral valve, causing partial occlusion of the outflow tract. The jugular venous pulse in sinus rhythm is characterized by prominent *a* waves. The outflow murmur characteristically is systolic and heard best along the left sternal border without radiation to the carotid arteries. Because the outflow tract gradient is dynamic, the murmur can be altered by various physical and pharmacologic maneuvers (see Chapter 1). It increases with amyl nitrate, Valsalva maneuvers, and upright posture, and decreases with administration of phenylephrine, squatting, and isometric handgrip.

Mitral regurgitation occurs in almost all patients with obstructive HCM. The systolic anterior motion of the mitral valve that is common in HCM results in incomplete coaptation of the mitral valve leaflets and resulting valvular regurgitation. There is also a direct relation between the LV outflow pressure gradient and the severity of mitral regurgitation. Mitral regurgitation in nonobstructive HCM is usually mild and occurs in approximately 30% of patients.

Atrial fibrillation is the most common arrhythmia seen with HCM. Paroxysmal and then persistent atrial fibrillation occurs in at least 20% of patients. Its incidence increases with age. Sequelae commonly associated with atrial fibrillation include embolic phenomena and precipitation of heart failure. The latter is especially true when onset is before 50 years of age in patients with obstructive HCM. Patients with HCM may also experience syncope or presyncope with the onset of rapid atrial fibrillation.

Heart failure symptoms can mainly be attributed to diastolic LV dysfunction because of impaired and asynchronous LV relaxation and increased wall stiffness. Other contributory factors are outflow obstruction, atrial fibrillation, and myocardial ischemia. LV systolic function may deteriorate in patients with end-stage HCM, leading to severe symptoms of heart failure.

Electrocardiography

The most common abnormalities seen in patients with HCM are ST-segment and T-wave abnormalities. LV hypertrophy is also common, with QRS complexes usually tallest in the midprecordial leads.

Echocardiography

Now accepted as the imaging study of choice, echocardiography is generally used to confirm the diagnosis of HCM. Various patterns of LV hypertrophy have been identified. Concentric hypertrophy occurs because of left ventricle pressure overload, as in patients with aortic stenosis. Eccentric hypertrophy usually is a result of left ventricle volume overload, as in mitral or aortic regurgitation (see Fig. 19-3). Septal thickening at least 1.5 times the posterior wall thickness in diastole is a diagnostic criterion for HCM. A "ground-glass" or "speckled" appearance may be seen in portions of the hypertrophied myocardium, but such a pattern is often absent in confirmed cases of HCM. Anteriorly, the outflow tract of the left ventricle is constituted by the septum and, posteriorly, by the mitral valve anterior leaflet. The leaflets may be enlarged and produce a pressure gradient secondary to

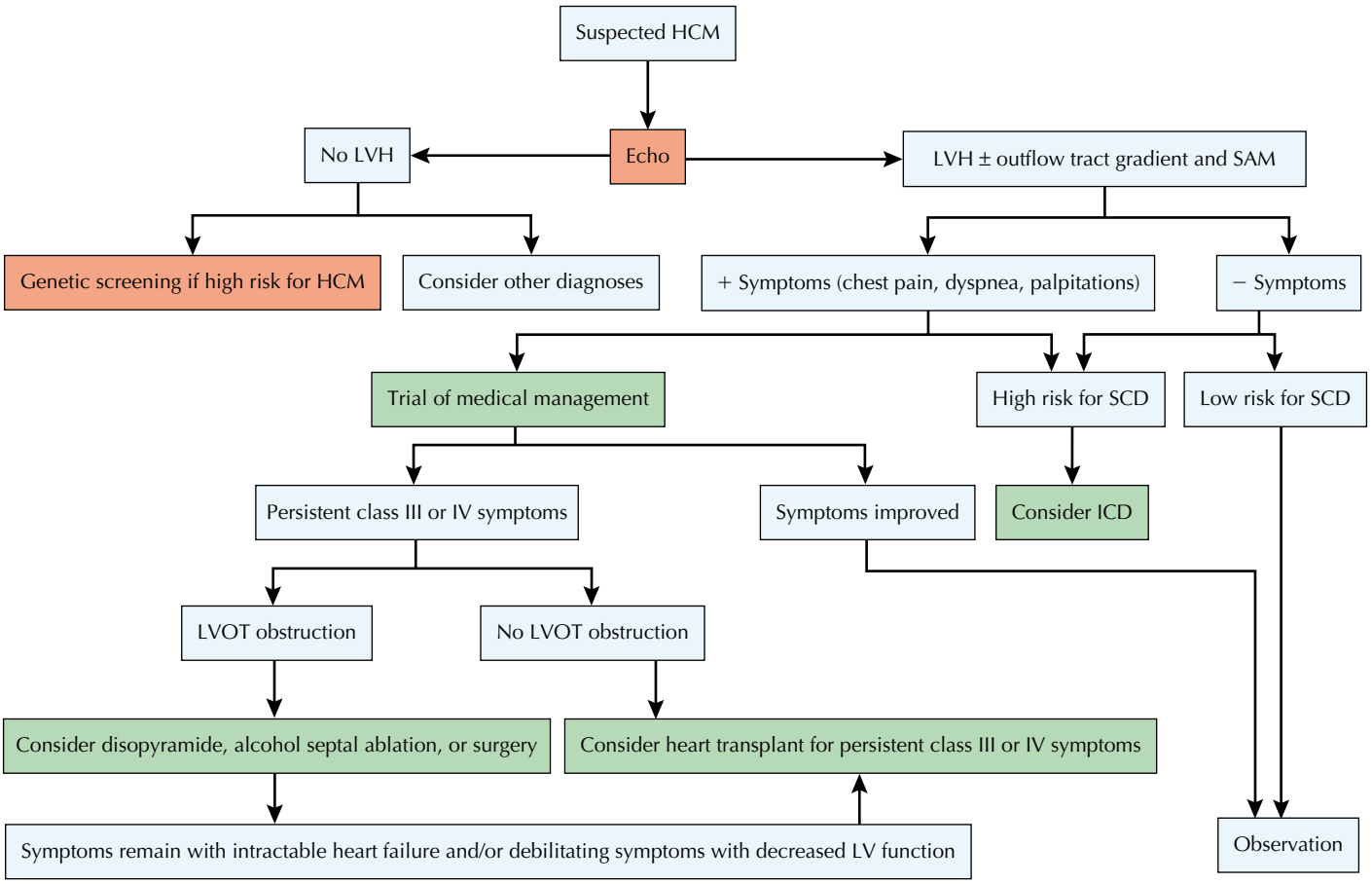


Figure 19-4 *Diagnostic algorithm for suspected hypertrophic cardiomyopathy (HCM).* ICD, implantable cardioverter defibrillator; LV, left ventricular; LVH, LV hypertrophy; LVOT, LV outflow tract; SAM, systolic anterior motion; SCD, sudden cardiac death.

abnormal systolic anterior motion of the anterior leaflet. Mitral regurgitation is usually noted in association with the outflow gradient. Although for many years echocardiography has been considered the "gold standard" for diagnosis of HCM, the wide variance of echocardiographic findings in individuals with identical mutations (see Chapter 72) has led some experts to rely on genetic, echocardiographic and other imaging data when evaluating individuals with suspected HCM (Fig. 19-4).

Cardiac Catheterization

Characteristic hemodynamic findings have been described in HCM patients with resting or provocable outflow tract gradients and augmented LV systolic contraction. A decrease in the aortic pulse pressure is often noted in the postpremature ventricular contraction beat (Braunwald sign).

Exercise and HCM

Although the most common cause of death in athletes is trauma, cardiovascular conditions rank second, and HCM constitutes 80% of this subset (see Chapter 69). HCM gained widespread public recognition after postmortem diagnosis in a number of high-profile athletes who died suddenly while engaged in competitive sports. Most athletes with HCM are asymptomatic and therefore difficult to diagnose without imaging studies. Although expert opinion varies somewhat, in general, an individual with typical HCM should not engage in competitive sports.

Athletes with a genetic predisposition should undergo serial echocardiography every 12 to 18 months until age 18, because phenotypic expression may not occur until later in adolescence or in adult life when physical maturation is complete. There is no evidence to justify routinely precluding genotype-positive/phenotype-negative individuals of any age from most activities or employment.

MANAGEMENT AND THERAPY

Optimum Treatment

MEDICAL MANAGEMENT

Conventional therapy focuses on management of symptoms with use of negatively inotropic drugs, such as β-blockers and verapamil, with the idea that this approach will improve diastolic function in HCM. Generally, treatment results in a reduction of exertional symptoms. Initial treatment considerations are usually independent of the presence of a gradient.

Box 19-1 Predictors of the High-Risk Subgroup of HCM

- Prior cardiac arrest
- Sustained ventricular tachycardia
- Family history of sudden or premature HCM-related death
- Nonsustained ventricular tachycardia found on surveillance Holter monitoring
- Syncope-presyncope thought not to be neurocardiogenic in origin
- LV outflow gradient ≥ 50 mm Hg
- Substantial LVH (wall thickness ≥ 20 mm)
- Left atrial enlargement (>45 mm)
- Hypotensive BP response to exercise

BP, blood pressure; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy.

β-blockers are usually the first-choice drug class and have a salutary effect on symptoms. Verapamil may be considered when β-blockers are ineffective or not tolerated. Disopyramide may be effective in decreasing outflow gradient and in improving symptoms and exercise tolerance and also may provide some protection against atrial fibrillation in HCM patients.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR THERAPY

The implantable cardioverter defibrillator (ICD) can be highly effective in the prevention of sudden death and therefore prolongs the survival of the high-risk patient with HCM (Box 19-1). Sudden cardiac death or aborted cardiac arrests may occur in patients who have little functional impairment. Marked LV hypertrophy alone may not justify prophylactic ICD use. However, marked LV hypertrophy plus an additional risk factor (e.g., family history of sudden death, syncope, chest pain, nonsustained ventricular tachycardia, failure of systolic blood pressure [SBP] to increase with exercise) identifies a higher risk subset that should be considered for prophylactic implantation of an ICD.

SURGICAL THERAPY

Subaortic ventricular myotomy was first performed on two patients in 1961, with subsequent reduction in outflow tract gradient and clinical improvement. In the ensuing decades, the popularity of surgical treatment for HCM has varied. In general, surgery is only considered when debilitating symptoms persist despite maximal pharmacologic therapy. Myocardium from the proximal septum just beyond the mitral leaflets is resected to reduce the outflow gradient. This operation has many advantages: low mortality rate (<2%), reduced symptoms, improved functional capacity, and durable results; symptomatic improvement persists for 5 or more years after surgery in 70% of patients. An alternative to surgical myomectomy is alcohol ablation of the septum (see below). Though not widely available, this procedure is available at several centers in the United States and Europe as an alternative to open-chest surgery. If there is a need for mitral valve repair/replacement in addition to septal myomectomy, alcohol ablation is contraindicated.

Heart Transplantation

Heart transplantation is an option for end-stage HCM patients with deterioration in LV systolic function who exhibit debilitating symptoms and in whom heart failure develops. Patients with nonobstructive HCM whose symptoms are refractory to pharmacologic therapy are also candidates for transplantation.

Avoiding Treatment Errors

Certain classes of drugs should be avoided in patients with HCM. These include nitrates and other direct-acting vasodilators.

Other Treatment Considerations

TREATMENT OF ERECTILE DYSFUNCTION IN PATIENTS WITH HCM

Sildenafil citrate and other members of this drug family are commonly used in the treatment of erectile dysfunction. There is very little information regarding its safety in patients with HCM. Two case reports indicate potential negative effects of the use of sildenafil in these patients. One adverse effect that can occur with administration of sildenafil in patients with HCM is atrial fibrillation, possibly caused by drug-induced arterial vasodilatation producing an increased gradient across the LV outflow tract, with a resultant acute increase in LV end-diastolic pressure and left atrial hypertension. Another report was of decreased SBP after administration of sildenafil, possibly due to a marked reduction in LV dimensions, associated with increases in the ejection fraction and subaortic gradient.

PERMANENT PACING

The enthusiasm for permanent pacing in all patients with HCM (to reduce LV outflow tract obstruction) has diminished over recent years. The decreased outflow obstruction and reduction in gradient after right ventricular (RV) pacing is complicated by significant decreases in stroke volume and aortic pressure. Synchronized atrial and RV apical stimulation reduced subaortic gradients substantially (by 43% in one study) without altering aortic pressure or cardiac output. An optimum atrioventricular (AV) interval during dual-chamber pacing can be determined by maintenance of early RV apical activation and optimal LV filling pressures. In some patients this approach has proven useful. Pacing has not been shown to affect mortality rates in patients who are at various levels of risk for sudden arrhythmic death. There may be a substantial placebo effect, because there is poor correlation between reduction in outflow tract gradients and symptoms. Therefore, permanent pacing should still be considered a viable alternative for the elderly individual subgroup as an alternative to surgical or ablative approaches. In this and other settings, permanent pacing may offer benefit to some patients.

ALCOHOL ABLATION OF THE SEPTUM

In this procedure, approximately 1 to 4 mL of absolute alcohol is injected selectively into the septal perforator branch of the

left anterior descending artery via a percutaneous catheter. The resultant MI reduces the thickness of the proximal septum. Thus, the outflow tract dimension is increased and the gradient is reduced. Although considered an alternative to surgery, this procedure is associated with complications such as high-grade AV block, coronary dissection, and anterior wall MI.

Additionally, the resultant scar is a substrate for potentially lethal ventricular tachyarrhythmia, and no randomized controlled studies have rigorously evaluated the benefit of this procedure. Therefore, surgery, which has equivalent morbidity and mortality rates, remains the gold standard. The results of ongoing trials of septal ablation will clarify the role of this approach in the treatment of patients with HCM.

FUTURE DIRECTIONS

None of the existing pharmacologic therapies for HCM induces a regression of hypertrophy and fibrosis or reduces mortality rate. Interestingly, simvastatin induces regression of cardiac hypertrophy and fibrosis as well as improves LV filling pressures in a transgenic rabbit model. A clinical trial is needed to study the benefit of statins and other pharmacologic approaches in humans with HCM.

With the rapid growth of molecular genetics, new genetic forms are increasingly being identified. Genetic testing may provide insight into better risk stratification and identification of individuals with HCM or their family members, who are at risk for sudden death.

Newer devices with combined functions of dual-chamber pacing, antitachycardia overdrive pacing, defibrillation, and event recording are likely to have important roles in alleviating symptoms, preventing sudden death, and providing information about the causes of sudden death in patients with HCM.

ADDITIONAL RESOURCES

Hansen MW, Merchant N. MRI of hypertrophic cardiomyopathy: Part 1, MRI appearances. *Am J Roentgenol.* 2007;189(6):1335–1343.

Hansen MW, Merchant N. MRI of hypertrophic cardiomyopathy: Part 2, differential diagnosis, risk stratification, and posttreatment MRI appearances. *Am J Roentgenol.* 2007;189(6):1344–1352.

This two-part series describes the use of MRI as an additional modality in patient evaluation. The technique is valuable in patients in whom echocardiography is limited by poor acoustic windows. MRI has the potential of enhancing the understanding of the morphologic characteristics of HCM and distinguishing it from other forms of cardiomyopathy such as amyloidosis. Additionally, the presence of delayed enhancement following gadolinium administration is associated with other clinical markers of increased risk and can identify a subset of patients with increased risk of sudden cardiac death. MRI is also useful in following patients after surgical myomectomy and septal ablation.

Pelliccia A, Zipes DP, Maron BJ. Bethesda Conference #36 and the European Society of Cardiology Consensus Recommendations revisited: a comparison of U.S. and European criteria for eligibility and disqualification of competitive athletes with cardiovascular abnormalities. *J Am Coll Cardiol.* 2008;52(24):1990–1996.

Outlines the recommendations of the 36th Bethesda Conference and compares them with the European Society Consensus Recommendations. While the patients with HCM remain excluded from most competitive sports, their gene-positive/phenotype-negative relatives are also restricted by the European guidelines but not by the Bethesda Conference.

EVIDENCE

Awan GM, Calderon E, Dawood G, Alpert MA. Acute symptomatic atrial fibrillation after sildenafil citrate therapy in a patient with HOCM. *Am J Med Sci.* 2000;320:69–71.

Case report describing a patient with hypertrophic cardiomyopathy who developed symptomatic atrial fibrillation on two occasions after ingesting sildenafil citrate.

Fifer MA, Vlahkes GJ. Management of Symptoms in Hypertrophic Cardiomyopathy. *Circulation.* 2008;117:429–439.

Reviews the pathophysiology of symptoms in HCM and the literature supporting medical, device, and surgical management.

Johnson JP, Golabi M, et al. Costello syndrome: Phenotype, natural history, differential diagnosis, and possible cause. *J Pediatr.* 1998; 133:441–448.

Describes the syndrome on the basis of eight patients and reviews the literature on 29 previously reported cases.

Maron BJ. Hypertrophic cardiomyopathy a systematic review. *JAMA.* 2002;287:1308–1320.

An extremely well-written and exhaustive review of the subject by Dr. Maron, who has published extensively on HCM and is a recognized expert in the field. The data current to 2002 are nicely summarized.

Maron BJ, Mitchell JH. Revised eligibility recommendations for competitive athletes with cardiovascular abnormalities. *J Am Coll Cardiol.* 1994;24:848–850.

A more current publication by Pelliccia et al. is available (see additional resources above).

Stauffer JC, Ruiz V, Morard JD. Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. *N Engl J Med.* 1999; 341:700–701.

Case report of a man presenting with near syncope 2 hours after taking sildenafil; highlights the danger of using sildenafil in this population. Despite an increase in oral verapamil dosage, there was a documented increase in outflow tract gradient from 16 mm Hg to 54 mm Hg and a decrease in LV dimension following the use of sildenafil as measured by echocardiography. Further Holter monitoring for 24 hours after sildenafil documented a fourfold increase in premature ventricular contractions as well as six episodes of nonsustained ventricular tachycardia.

Ten Berg JM, Suttorp MJ, Knaepen PJ, et al. Hypertrophic obstructive cardiomyopathy: initial results and long term follow-up after Morrow septal myectomy. *Circulation.* 1994;90:1781–1785.

This study involved 38 patients with HCM in The Netherlands who underwent septal myomectomy. There was demonstrated safety, without perioperative deaths and a significant reduction in outflow tract gradient from 72 mm Hg to 6 mm Hg. These patients were all followed for a mean period of 6.8 years after surgery, with 92% of the patients reporting an improvement in quality of life and NYHA class.

Zieman SJ, Fortuin NJ. Hypertrophic and restrictive cardiomyopathies in the elderly. *Cardiol Clin.* 1999;17:159–172.

The article highlights the differences in HCM diagnosed in the older population with certain genetic mutations, such as in the gene that encodes cardiac myosin-binding protein C (a less crucial protein in force development), which are phenotypically expressed beyond the 40s and are associated with a more benign clinical course. The elderly patients, while more symptomatic as compared with younger patients with HCM, tend to have a slower progression of the disease and a more favorable prognosis with 1- and 5-year survival rates of 95% and 75%, respectively.

Restrictive Cardiomyopathy

Thomas M. Bashore

20

Cardiomyopathies are generally classified into three forms: dilated, hypertrophic, and restrictive. The restrictive form is the least common endomyocardial disease and is characterized by variable degrees of diastolic dysfunction out of proportion to systolic dysfunction. Clinically, restrictive cardiomyopathy is often and easily confused with constrictive pericarditis. Differentiating between them is a challenge but very important because of the implications for prognosis and treatment. Restrictive cardiomyopathy and constrictive pericarditis can both be present in the same patient, further complicating the diagnosis and therapeutic decision making. Because constrictive pericarditis is eminently more treatable than restrictive cardiomyopathy, the distinction is critical.

Restrictive cardiomyopathy was originally described in 1961 as *constrictive cardiomyopathy*. This was later changed to the more accurate term, *restrictive cardiomyopathy*, which describes a stiff myocardium usually resulting from an infiltrative process. Diastolic heart failure is now recognized to be a common process, often affecting the elderly and those with hypertension and increased systemic arterial stiffness. Although the etiology for diastolic dysfunction is restrictive cardiomyopathy in some patients, more commonly diastolic dysfunction and diastolic heart failure arise from other causes.

ETIOLOGY AND PATHOGENESIS

A variety of disease states produce the clinical manifestation of a restrictive cardiomyopathic process (Box 20-1). Myocardial fibrosis, myocardial infiltration by specific proteins, endomyocardial scarring, and cardiac muscle hypertrophy all may present as diastolic dysfunction.

Noninfiltrative Causes

Idiopathic restrictive cardiomyopathy is associated with patchy endomyocardial fibrosis, increased cardiac mass, and enlarged atria (Fig. 20-1). It is more common in older adults but may be seen in children. In adults, 5-year survival is approximately 64%, but mortality may be higher in children. Occasionally, the cardiomyopathy is accompanied by skeletal muscle myopathy, and in some patients with restrictive cardiomyopathy, a clear familial component is present. Idiopathic restrictive cardiomyopathy is also found in families with no skeletal muscle involvement, however, and as an autosomal-dominant disorder in patients with Noonan's syndrome. Conduction system disease such as atrioventricular (AV) block may also be present and in some cases precedes clinical myocardial dysfunction.

Infiltrative Causes

Clinically, the most common variety of restrictive cardiomyopathy is from amyloidosis, the deposition of unique, twisted, β-pleated sheets of fibrils formed by various proteins (Fig. 20-1, middle). Cardiac amyloidosis can be present in several different circumstances. Primary amyloidosis is caused by deposition of an amyloid protein composed of portions of an immunoglobulin light chain (designated *AL* for light chain–associated amyloidosis) produced by a monoclonal population of plasma cells. Primary amyloidosis can be the consequence of multiple myeloma but it is also found in patients without multiple myeloma. Secondary amyloidosis, sometimes called *reactive systemic disease*, is caused by the production of a nonimmunoglobulin protein and termed *AA* (for amyloid-associated). Familial amyloidosis is an inherited autosomal-dominant trait resulting from a variant prealbumin protein, transthyretin. More than 80 point mutations have been described, and familial amyloidosis may present as a cardiomyopathy, a progressive neuropathy, or a nephropathy. It is four times more common in blacks than in whites. In some cases, the heart is the only affected organ. Senile systemic amyloidosis is produced by an atrial natriuretic-like protein or transthyretin. Its frequency increases with age. Scattered amyloid deposits in the aorta or the atria are almost universally found in individuals older than 80 years, whereas only a small minority of the elderly has evidence of restrictive cardiomyopathy due to amyloidosis.

Regardless of the specific etiology, the overall size of the left ventricular (LV) chamber is normal or small, and at least early in the disease, systolic function is preserved even in individuals with very significant diastolic dysfunction. The greater the myocardial thickness, the more amyloid present and the worse the prognosis.

In amyloidosis secondary to immunocyte dyscrasias, cardiac involvement is common and the most frequent cause of death. In amyloidosis secondary to other diseases, cardiac involvement is much less common, often only manifesting as smaller perivascular deposits that do not cause diastolic dysfunction. About one in four individuals with familial amyloidosis has overt cardiac involvement, and even in these individuals, neurologic and renal dysfunction often dominate the clinical picture. Senile amyloidosis is rarely responsible for clinical cardiac dysfunction.

Symptomatically, patients with cardiac amyloid present with severe diastolic dysfunction and predominantly right-sided heart failure. Late in the course there may be progressive loss of LV systolic function and pulmonary congestion. Amyloid deposits in the atria are demonstrated by a markedly thickened interatrial septum and loss of atrial function. Most patients also experience arrhythmias and conduction system disease. Peripheral neuropathy is common, and orthostatic hypotension may be a major feature. Orthostasis is worsened by amyloid involvement in the adrenals and nephrotic syndrome due to renal involvement. Syncope is a common and ominous symptom.

Sarcoidosis is a granulomatous disease of unknown cause (Fig. 20-1, lower). Of the multiple organ systems commonly involved, including the heart, the most important is usually the lungs, where this involvement manifests as diffuse scarring, pulmonary hypertension, and cor pulmonale. Myocardial

Box 20-1 Classification of Restrictive Cardiomyopathy

Common

Noninfiltrative
Idiopathic restrictive cardiomyopathy

Infiltrative
Amyloidosis
Sarcoidosis

Endomyocardial
Endomyocardial fibrosis
Radiation fibrosis
Anthracycline toxicity

Uncommon

Noninfiltrative
Familial cardiomyopathy
Hypertrophic cardiomyopathy
Scleroderma
Pseudoxanthoma elasticum
Diabetic cardiomyopathy

Infiltrative
Gaucher's disease
Hurler's syndrome
Fatty infiltration

Storage diseases
Hemochromatosis
Fabry's disease
Glycogen storage disease

Endomyocardial
Hypereosinophilic syndrome
Carcinoid heart disease
Metastatic cancers
Ventricular noncompaction
Drug-induced fibrosis (serotonin, methysergide, ergotamine, mercurial agents, busulfan, toxic effect of anthracyclines)

With permission, modified from Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *N Engl J Med*. 1997;336:267–276. (Copyright Massachusetts Medical Society. All rights reserved.)

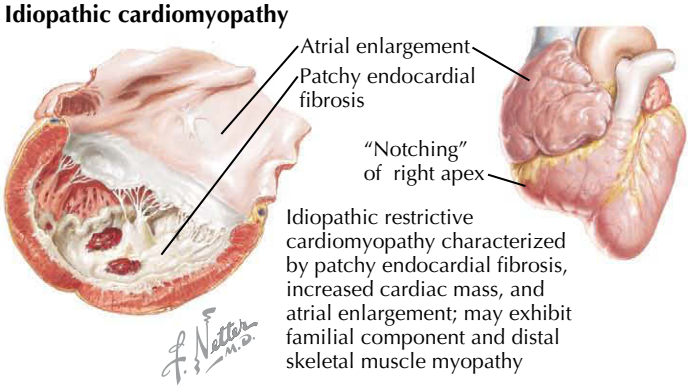
involvement causes a restrictive or a dilated cardiomyopathy in less than 5% of systemic sarcoidosis patients. More commonly, focal involvement may result in heart block, congestive failure, ventricular arrhythmias, or sudden cardiac death. The noncaseating granulomas have a propensity for involving the interventricular septum (hence the high incidence of heart block) and the LV free wall. The scattered nature of granulomas contributes to the failure of right ventricular (RV) biopsies to detect the disease in about half the patients. MRI is much more sensitive for detection of cardiac involvement in patients with known sarcoidosis.

Clinically, patients with sarcoidosis generally present with syncope from conduction system disease or cor pulmonale from both the pulmonary manifestations and cardiac involvement. Myocardial involvement may be gradually progressive, although it can be fulminant and lead rapidly to death.

Endomyocardial Causes

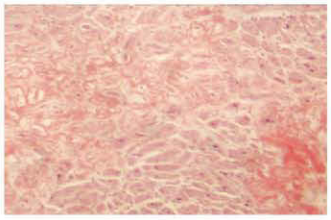
Endomyocardial fibrosis (sometimes called *Becker's disease*) occurs most commonly in Africa, especially in Uganda and

Idiopathic cardiomyopathy

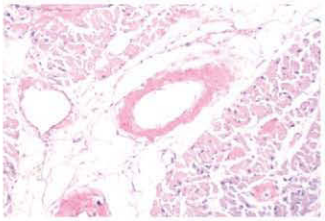


Idiopathic restrictive cardiomyopathy characterized by patchy endocardial fibrosis, increased cardiac mass, and atrial enlargement; may exhibit familial component and distal skeletal muscle myopathy

Amyloidosis

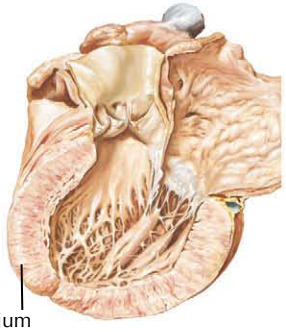


Focal deposition of amyloid around muscle cells of heart with dead myocardial fibers

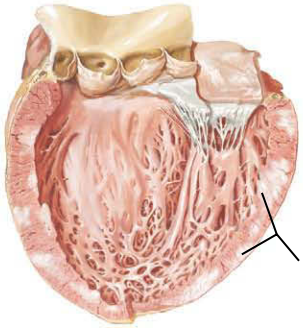


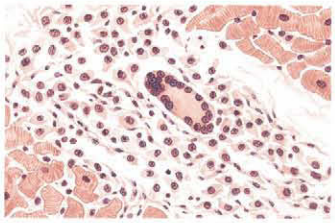
Perivascular amyloid deposits in myocardium (×40)

Amyloidosis is the most common form of restrictive cardiomyopathy. Characterized by deposition of amyloid protein throughout the myocardium, causing thickening and diastolic dysfunction



Sarcoidosis





Granuloma with giant cell in heart wall

Sarcoidosis exhibits myocardial involvement in a small percentage of patients with the systemic disease. Granulomas in myocardium lead to diastolic dysfunction, congestive heart failure, heart block, ventricular arrhythmias, and sudden cardiac death.

Figure 20-1 *Idiopathic and infiltrative causes of restrictive cardiomyopathy.*

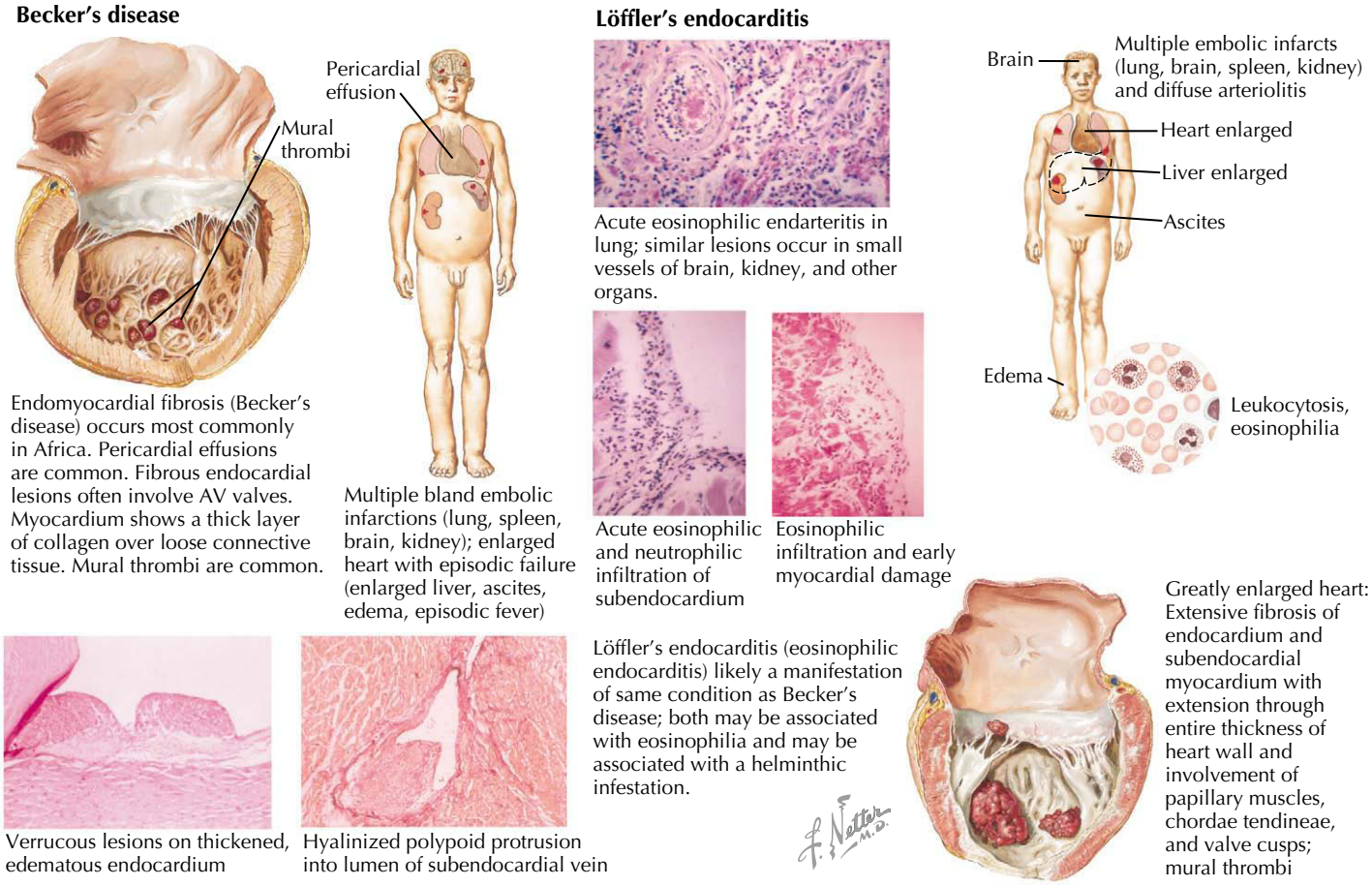


Figure 20-2 *Endomyocardial causes of restrictive cardiomyopathy.* AV, atrioventricular.

Nigeria (Fig. 20-2, left). In equatorial Africa, it is responsible for 10% to 20% of deaths from heart disease. Pericardial effusions are common and may be large. Fibrous endocardial lesions are frequently noted in the ventricular inflow tracts and often involve the AV valves, resulting in valvular regurgitation. The involved myocardium demonstrates a thick layer of collagen tissue overlying a layer of loosely arranged connective tissue. Fibrous and granulomatous tissue may extend into the myocardium. Either or both ventricles may be involved, and when the disease process is extensive, papillary muscles and chordae may be matted with a mass of thrombus and tissue, filling the cavity. Clinical manifestations depend on the extent of involvement of the right ventricle, the left ventricle, or both. Eosinophilic endocarditis (Löffler's endocarditis) is probably an earlier manifestation of this same process (Fig. 20-2, lower). Both diseases are associated with eosinophilia. Epidemiologic evidence suggests that Löffler's endocarditis is related to worm (helminth) infestation. It is thought that it is during the initial (necrotic) phase of hypereosinophilia that myocardial damage occurs. This is then followed after a year or more by a thrombotic phase and finally a fibrotic, restrictive phase. Clinically, the initial phase is characterized by fever, weight loss, rash, and congestive heart failure (CHF). Localized thickening of the posterolateral LV wall and limited mitral valve movement may be noted. In some instances, the LV apex is virtually obliterated by thrombus. Later, a restrictive pattern with AV regurgitation dominates the hemodynamics, and pericardial effusions, sometimes quite large, are seen.

Patients with Churg-Strauss syndrome (asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormalities, and/or extravascular eosinophils) may also develop endomyocardial fibrosis. The intracytoplasmic granular content of activated eosinophils may be toxic to the myocardial and endothelial cells, resulting in the damage observed.

Prior radiation therapy is an important cause of restrictive cardiomyopathy. It is believed that radiation may cause long-lasting injury to the capillary endothelial cells, leading to cell death, capillary rupture, and microthrombi. Cardiac complications usually occur many years after the initial insult and can vary widely, with constrictive pericarditis a more common manifestation than restrictive cardiomyopathy. Pericarditis with effusion, coronary artery fibrosis (especially ostial) with myocardial infarction, valvular stenosis or regurgitation, conduction system disease, and myocardial fibrosis may result from excessive radiation exposure. The severity of cardiac involvement is proportional to the radiation dose (more common at doses greater than 45 Gy) and to the mass of myocardium exposed. Cardiac radiation exposure is most common following therapy for Hodgkin's disease or breast cancer and, despite attempts to shield the heart from radiation, is still a concern. Additionally, although damage

to the myocardium from chemotherapy (which many of these same patients receive) ultimately causes systolic dysfunction, diastolic dysfunction can be present. Separating the effects of radiation from the consequences of chemotherapy is not always possible.

The most common cardiotoxic chemotherapeutic agents are the anthracyclines. After anthracycline exposure, cardiac toxicity usually is delayed and results in a dilated cardiomyopathy. Early manifestations of primarily diastolic dysfunction may herald the cardiotoxicity. There is a nonlinear increase in cardiotoxicity as the cumulative dose increases, with a 7% incidence with doxorubicin doses over 550 mg/m^2. Cytotoxicity from anthracylines seems to be due to the inhibition of an enzyme necessary for DNA repair and to generation of free radicals that damage cell membranes, in part by lipid peroxidation. The heart may not detoxify the free radicals because only a small amount of catalase, needed to convert hydrogen peroxide to water, is present. The anthracyclines also chelate iron and generate tissue-damaging hydroxyl radicals locally. Therefore, dexrazoxane, a drug that hydrolyzes to form a carboxylamine capable of removing the iron from the anthracycline-iron complex, is often used as a cardioprotectant in patients receiving anthracyclines. Other toxic drugs that have been implicated in the development of myocardial fibrosis include methysergide, ergotamine, mercurial agents, and busulfan.

Other Causes

Less common causes of restrictive cardiomyopathy include certain inherited diseases. The most prominent is Fabry's disease, an X-linked recessive disorder caused by deficiency of the lysosomal enzyme α-galactosidase. The accumulation of lysosomal glycolipids in cardiac tissue results in a severe restrictive cardiomyopathy. Some patients with Fabry's disease also have involvement of the cardiac valves, the skin, the kidneys, and the lungs.

Hypertrophic cardiomyopathy can present in a similar manner as a restrictive cardiomyopathy. Many mutations in sarcomeric proteins have been identified in genetic studies of hypertrophic cardiomyopathy (see Chapter 19), and there is variability in the degree of diastolic dysfunction depending on both the genotype as well as concomitant diseases (hypertension, diabetes). Generally, it is not difficult to distinguish hypertrophic cardiomyopathy from other causes of restrictive cardiomyopathy.

Other inherited diseases are rare and, hence, less commonly a cause of restrictive cardiomyopathy. In Gaucher's disease (characterized by a deficiency of the enzyme β-glucosidase, with accumulation of cerebrosides in various organs), there may be both myocardial dysfunction and hemorrhagic pericardial effusion. In Hurler's syndrome, a deposition of mucopolysaccharide in the myocardium can cause a restrictive process. The cardiac valves and the coronary arteries may also be involved. Hemochromatosis, arising from inherited (autosomal-recessive) or acquired etiologies, is characterized by iron deposition in many organs, including the heart. Myocardial damage may result from direct tissue damage by the free-iron moiety, not from the infiltration of iron. Many reports have described massive trabeculations in the left ventricle toward the apex with large sinus recesses between the trabeculae—a pattern that defines ventricular noncompaction. Noncompaction is a genetic disorder that may present with any or all of the features of a restrictive cardiomyopathy. Cardiac MRI is usually definitive.

Carcinoid heart disease primarily affects the right heart and is characterized by fibrous plaque that virtually coats the tricuspid and pulmonic valves and the RV endocardium. Valvular stenosis and regurgitation result, and RV dysfunction is common. The cardiac involvement in patients with carcinoid correlates with serotonin concentrations.

CLINICAL PRESENTATION

In addition to some of the unique clinical presentations described earlier, as a general rule, patients with restrictive cardiomyopathy present with congestion and low-output symptoms. Dyspnea, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, ascites, and overall fatigue and weakness are common. Angina can be a presenting symptom if coronary arteries are involved. Atrial fibrillation is common, and heart block is a particularly common occurrence in patients with amyloidosis or sarcoidosis. Up to one third of patients may present with thromboembolic complications. Unlike in a dilated cardiomyopathy, right-sided heart failure is often more prominent than left-sided heart failure early in the course of restrictive cardiomyopathy.

DIFFERENTIAL DIAGNOSIS

Most patients present with right heart failure out of proportion to left heart failure and have normal or near-normal cardiac size on examination and chest x-ray. Though not specific for restrictive cardiomyopathy, this constellation of symptoms, signs, and findings should always raise the possibility of restrictive cardiomyopathy. The differential diagnosis of restrictive cardiomyopathy includes several cardiac causes: constrictive pericarditis, chronic RV infarction, RV dysfunction from RV pressure or (less likely) RV volume overload, intrinsic RV myocardial disease, or tricuspid valve disease. Additionally, discerning restrictive cardiomyopathy from primary hepatic causes, including cirrhosis, can be challenging, since both can present with evidence of right heart failure, ascites, and marked hepatic dysfunction. Upon further evaluation, however, the results of the examination and echocardiography usually narrow the differential diagnosis to restrictive cardiomyopathy and constrictive pericarditis. These two entities affect hemodynamics in a subtly different manner, and distinguishing the two can be challenging but is extremely important given the prognosis and treatment options.

Normal Hemodynamics

Intracardiac pressures are a reflection of the contraction and relaxation of individual cardiac structures and the changes imparted to them by the pleural and pericardial pressures (Fig. 20-3). Changes in either pleural or pericardial pressure can be reflected in the intracardiac pressure. With inspiration, the intrapleural pressures drop and the abdominal cavity pressure increases. Blood flow through the right side of the heart increases, whereas blood return to the left side of the heart

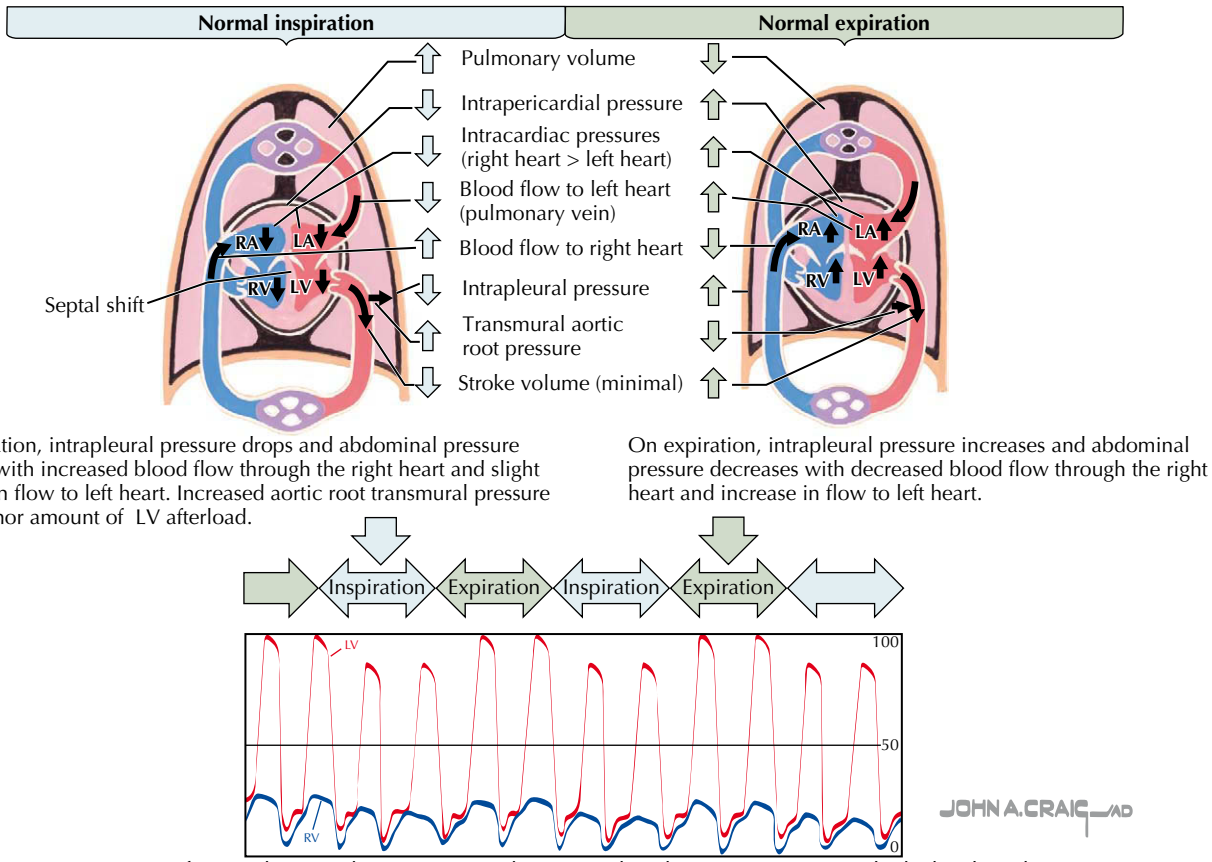


Figure 20-3 *Normal cardiac blood flow during inspiration and expiration.* LA, left atrium; LV, left ventricle/ventricular; RA, right atrium; RV, right ventricle/ventricular.

decreases slightly. The fall in the intrapleural pressures with inspiration also increases the transmural aortic root pressure, effectively increasing the impedance to LV ejection. The reverse occurs during expiration. Normally, inspiration lowers the right atrial and the systolic RV pressures slightly more than it lowers the left heart pressures. In severe lung disease, such as asthma, left heart filling is more profoundly affected, and these changes are exaggerated. The very negative inspiratory intrapleural pressures and very positive expiratory pressures result in marked swings in LV filling. A paradoxical pulse (fall in systemic pressure with inspiration) may thus result from lung disease alone.

The normal atrial and ventricular waveforms are shown in upper Figure 20-4. With atrial contraction, the atria become smaller and the atrial pressures rise (*a* wave). With the onset of ventricular contraction, the AV valves bulge toward the atria, and a small *c* wave is typically detectable on hemodynamic tracings. Although many findings can be seen by careful inspection of the jugular veins on physical examination, the *c* wave typically cannot be seen. As ventricular contraction continues, the AV annular ring is pulled into the ventricular cavity and the atria go into their diastole, resulting in enlargement of the atria and a decrease in the atrial pressures (*x* descent). Passive filling of the atria during ventricular systole produces a slow rise in the atrial pressures (the *v* wave) until the AV valves reopen at the peak of the *v* wave, and the pressure then falls rapidly as the ventricles actively relax (the *y* descent). Passive filling of the ventricles continues while the AV valves are open until atrial contraction again occurs, and the cycle repeats.

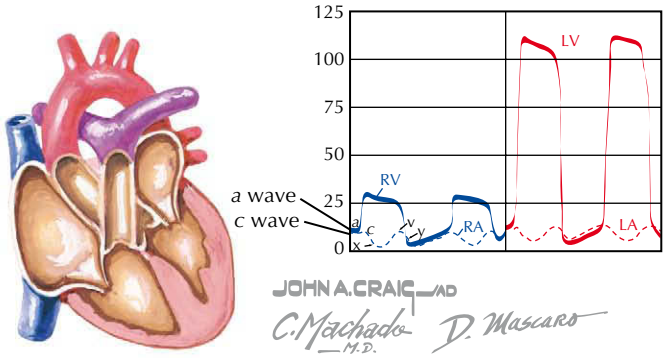
Following ventricular systole, ventricular diastole can be divided into an initial active phase (a brief period when the ventricle fills about halfway) and a passive filling phase. The nadir or lowest diastolic pressure during ventricular diastole occurs during the early active relaxation phase (suction effect).

Constrictive Pericarditis Physiology

Constrictive pericarditis (Fig. 20-4, middle) and restrictive cardiomyopathy (Fig. 20-4, lower) alter the normal intracardiac pressures in several ways as described in the figures. Please refer to Chapter 43, which covers these and expected respiratory changes with cardiac flow in detail.

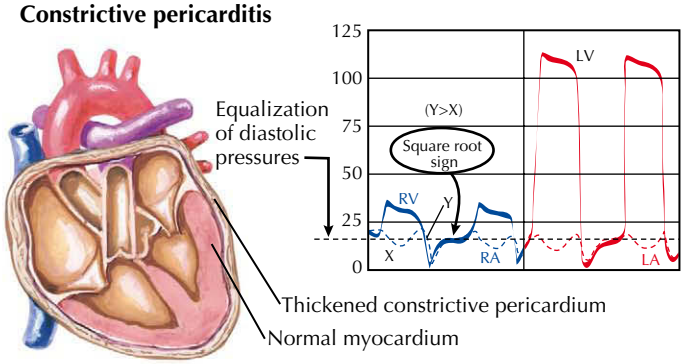
Because the atrial and ventricular septi are normally unaffected by the pericardial process, in a restrictive cardiomyopathy, both the RV systolic and LV systolic pressures should fall with inspiration. If constrictive pericarditis is present, with inspiration the RV systolic pressure and area of the RV pressure tracing will rise as the LV systolic pressure and area of the LV pressure tracing falls, demonstrating ventricular interdependence. It is critical to demonstrate ventricular interdependence to diagnose constriction. In addition, in constrictive

Normal



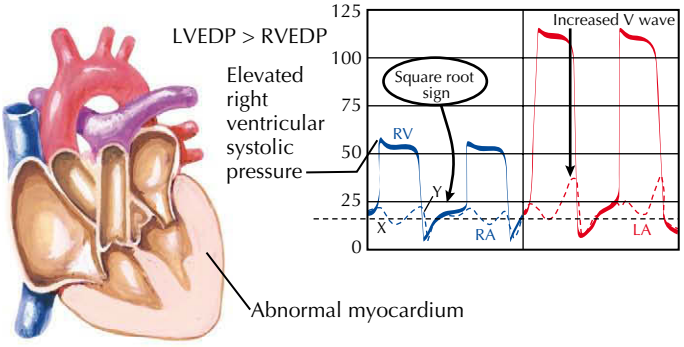
Atrial contraction reduces atrial volume and increases atrial pressure (*a* wave). Ventricular contraction closes the AV valve and creates the *c* wave. The AV ring is pulled into the atria, and atrial relaxation ensues with pressure decrease (*x* descent). Passive atrial filling causes *v* wave until AV valves open and pressure drops rapidly (*y* descent) while ventricles relax. Following ventricular systole, an active and passive diastolic filling phase follows, with ventricular pressure lowest in the active phase.

Constrictive pericarditis



High atrial pressures when AV valves open result in rapid early filling (rapid *y* descent) until filling abruptly stops (square root sign). There is equalization of late diastolic pressures. The right ventricular diastolic is usually > one third the right ventricular systolic.

Restrictive cardiomyopathy



Restrictive cardiomyopathy exhibits high atrial pressures with early and rapid diastolic filling. Left heart diastolic pressures are higher than the right heart, and LVEDP is greater than RVEDP. A large *v* wave in left atrium reflects poor left atrial compliance. Pulmonary hypertension results, and the RV systolic pressure is elevated.

Figure 20-4 *Comparisons of normal and pathologic intracardiac pressures.* AV, atrioventricular; LA, left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; RA, right atrial; RV, right ventricular; RVEDP, right ventricular end-diastolic pressure.

pericarditis the RV and pulmonary arterial systolic pressures are usually normal, and there is equalization of the RV and LV end-diastolic pressures. The high RV end-diastolic pressure results in the RV end-diastolic pressure being greater than one third of the RV systolic.

Restrictive Cardiomyopathy Physiology

In restrictive cardiomyopathy, the atrial pressures are high, and there is also early and rapid diastolic filling. This can produce the "square root" sign in the diastolic filling pattern of the RV or LV similar to that seen in constrictive pericarditis. The end-diastolic LV pressure, however, should be consistently higher (>5 mm Hg) than that of the end-diastolic RV pressure. Pulmonary hypertension and RV systolic hypertension are common findings not present in constriction (Fig. 20-4). The elevated RV systolic pressure means that the RV end-diastolic pressure will not be greater than one third of the RV systolic pressure. In a patient with myocardial restriction but a normal pericardium, a normal inspiratory decrease in all intracardiac pressures is expected, and there is a normal concordant fall in the RV and LV systolic pressures. This lack of demonstrable ventricular interdependence helps confirm restrictive physiology.

DIAGNOSTIC APPROACH

Procedures that will aid in the differential diagnosis of restrictive cardiomyopathy are outlined in Table 20-1.

Electrocardiography

The ECG in patients with restrictive cardiomyopathy is often abnormal but usually nonspecific. Low voltage may be a prominent feature, especially in amyloidosis. The QRS pattern often simulates myocardial infarction with poor R wave progression in the precordial leads or a pseudoinfarction pattern in the inferior leads. If pulmonary hypertension is present, evidence of RV hypertrophy may be noted. Interatrial conduction delays (notched P waves) and evidence of atrial enlargement are also common. AV heart block is common in sarcoidosis. High-grade AV block is less commonly seen in amyloidosis, but first-degree AV block is often present. Atrial arrhythmias, especially fibrillation, are common, although rarely a presenting symptom; sick sinus syndrome is also common. Ventricular tachyarrhythmias are frequent with disease progression and in amyloidosis may be a harbinger of sudden cardiac death.

Blood Tests

There are no specific markers for restrictive cardiomyopathy, and often blood tests are unrevealing. That being said, patients presenting with a restrictive cardiomyopathy should be screened for all systemic diseases that may be contributory. Specific findings may provide direction for therapeutic intervention. A complete blood count with differential can exclude anemia and eosinophilia as causes or contributors to heart failure. The sedimentation rate is usually reduced in patients with right heart failure, so an elevated sedimentation rate may suggest an

Table 20-1 Differential Diagnosis of Restrictive Cardiomyopathy versus Constrictive Pericarditis

Examination Procedure	Restrictive Cardiomyopathy	Constrictive Pericarditis
Physical examination	Kussmaul's sign is occasionally present. Paradoxical pulse is absent. Apical impulse is prominent. S_3 and S_4 are present. Regurgitant AV valve murmurs are common.	Kussmaul's sign is common. Paradoxical pulse may be present. Apical impulse retracts or is absent. Pericardial knock may be present. Regurgitant AV valve murmurs are rare.
Chest x-ray	Enlarged atria Pulmonary edema at times	Normal heart size Occasional pericardial calcium
ECG	Low voltage Atrial hypertrophic P waves Conduction disease is common. Atrial fibrillation is common.	Occasional low voltage P waves reflect interatrial conduction delay. Conduction defects are rare. Atrial fibrillation is occasionally present.
Echocardiography	Small LV cavity with large atria Increased wall thickness; sparkling texture Thickened cardiac valves at times Septal notch movement is rarely seen. Little septal movement with inspiration Thickened atrial septum <15% inspiratory decrease in MV velocity In PV: D>S (S/D ratio <1) TV inflow velocity with inspiration: Mild decrease in E wave No change in peak TR velocity Myocardial Ea <8.0 cm/s (reduced) M-mode slope of inflow color velocity edge <100 cm/s	Mild or no atrial enlargement Normal wall thickness Abrupt septal notch in early diastole Septal movement to left ventricle with inspiration Normal atrial septum >25% inspiratory decrease in MV velocity In PV: S>D In PV: inspiratory decrease in S and D waves TV inflow velocity with inspiration: Decreased inflow E wave Increased peak TR velocity Myocardial Ea >8.0 cm/s (normal or increased) M-mode slope of inflow color velocity edge >100 cm/s
Cardiac catheterization	LVEDP − RVEDP >5 mm Hg Pulmonary hypertension Dip and plateau in RA and RV are common. RVEDP < ⅓ RV systolic Late inspiratory RV/LV systolic pressure in phase (concordant) Area of LV pressure tracing/area of RV pressure tracing ratio declines with inspiration. Paradoxical pulse is rare.	Equalization of pressures LVEDP − RVEDP <5 mm Hg PA systolic rarely >40 mm Hg Dip and plateau in RA and RV are common. RVEDP > ⅓ RV systolic Late inspiratory RV/LV systolic pressure discordant Area of LV/area of RV pressure tracing is unchanged with inspiration. Paradoxical pulse is more common.
CT/MRI	LA enlargement, LV hypertrophy, thickened atrial septum	Occasionally thickened pericardium or calcium

AV, atrioventricular; CT, computed tomography; ECG, electrocardiogram; LA, left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; MRI, magnetic resonance imaging; MV, mitral valve; PA, pulmonary artery; PV, pulmonary vein; RA, right atrial; RV, right ventricular; RVEDP, right ventricular end-diastolic pressure; TR, tricuspid regurgitant; TV, tricuspid valve.

inflammatory process such as sarcoidosis. Although only rarely helpful, an elevated angiotensin-converting enzyme (ACE) level may be present in sarcoidosis. If signs of systemic illness such as multiple myeloma are present, measures of serum and urine electrophoresis in search of a monoclonal gammopathy are appropriate. Renal failure should be excluded, because it may suggest Fabry's disease or renal involvement from another systemic process. A 24-hour urine for total protein may be indicated to exclude a nephrotic syndrome, especially if the serum albumin is low. Hemochromatosis is characterized by an elevated plasma iron level, a normal or low total iron-binding capacity, elevated serum ferritin, high saturation of transferrin, and urinary iron. Carcinoid syndrome is associated with high levels of circulating serotonin and urinary 5-hydroxyindoleacetic acid. Endemic forms of endomyocardial fibrosis have been related to high levels of cerium and low levels of magnesium.

Chest X-ray

The chest x-ray in most restrictive cardiomyopathies reveals a normal heart size and enlarged atria. With pulmonary hypertension, an enlarged right ventricle may be seen. Pericardial calcium is usually not present. Mediastinal nodes may be prominent if sarcoidosis is a consideration. Diastolic heart failure should be suspected in all patients with a relatively normal heart size and pulmonary edema.

Echocardiography

Echocardiography is usually revealing and frequently diagnostic. Ventricular Doppler filling patterns can be assessed, and changes in the patterns with respiration recorded. Pulmonary venous and hepatic venous flow patterns in concert with mitral

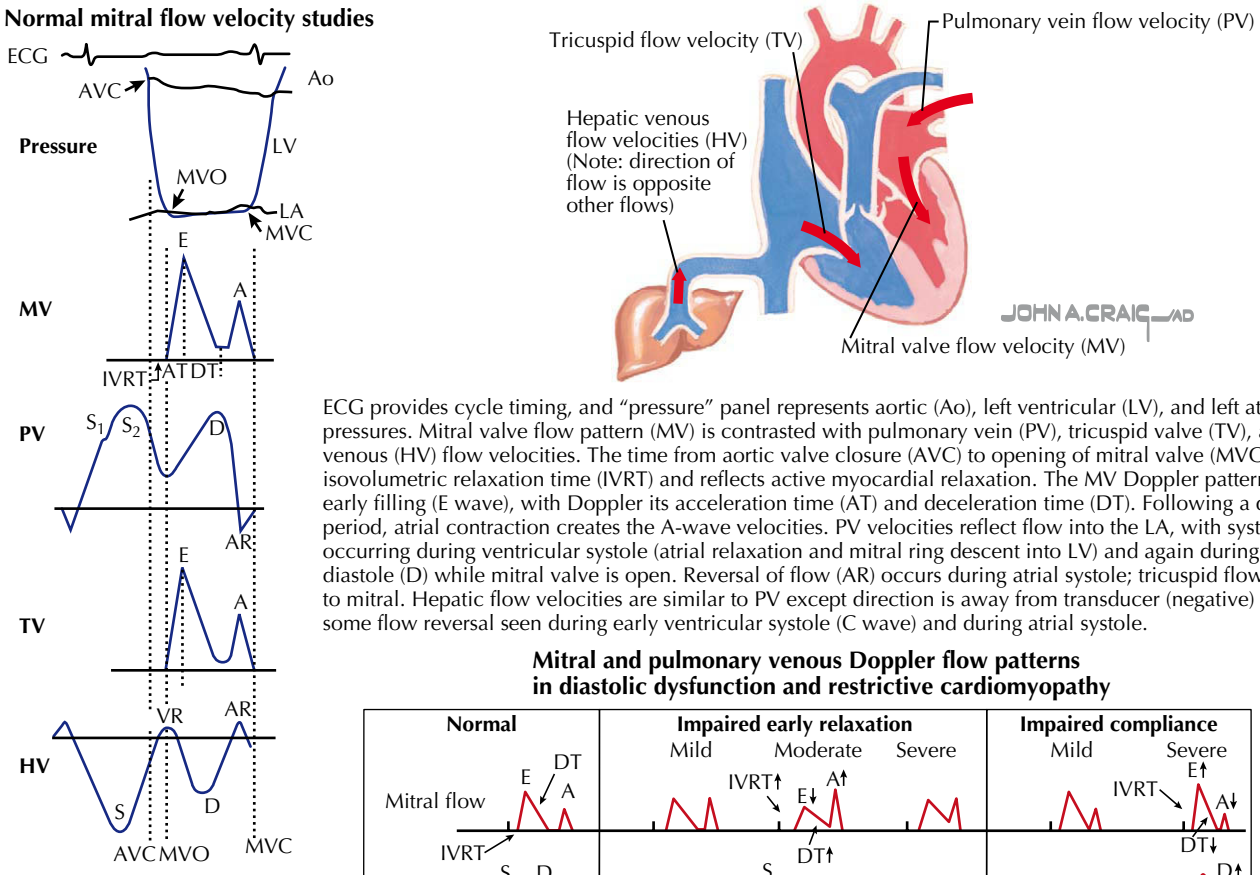


Figure 20-5 *Doppler flow studies: comparison of mitral and pulmonary vein flow velocities.* ECG, electrocardiogram; MVC, mitral valve closure; VR, ventricular relaxation. (Modified with permission from Klein AL, Scalia GM. Disease of the pericardium, restrictive cardiomyopathy and diastolic dysfunction. In: Topol EJ, ed. *Comprehensive Cardiovascular Medicine.* Philadelphia: Lippincott–Raven; 1998:669–716.)

flow patterns provide additional information. Transesophageal echocardiography is usually not necessary.

The classic restrictive cardiomyopathy two-dimensional echocardiographic image includes severe biatrial enlargement and thickened LV walls, often with a speckled or unusual myocardial texture if an infiltrative process is present. There is often thickening of the interatrial septum in amyloidosis. There is no ventricular septal bounce or septal shifting with inspiration, which might be seen in constrictive pericarditis. Patients with endomyocardial fibrosis usually have involvement of the ventricular apices and the subvalvular apparatus. In endomyocardial fibrosis, the ventricles may be virtually obliterated by the collagen tissue and thrombus. The echocardiogram in patients with ventricular noncompaction most often visualizes massive trabeculations in the LV apical region with large sinuses between. The echocardiogram can also exclude hypertrophic cardiomyopathy as a cause.

ECHOCARDIOGRAPHY/DOPPLER PATTERNS

Doppler filling patterns, especially during respiration, help differentiate constrictive pericarditis from restrictive cardiomyopathy (see Table 20-1). Normal Doppler echocardiographic patterns and definitions are shown in Figure 20-5. The time from aortic valve closure to mitral valve opening represents the isovolumic relaxation time. The E-wave acceleration time is the

time from the opening of the mitral valve to the peak flow; the time from the peak flow to diastasis is the E-wave deceleration time. Normal atrial contraction results in an A wave, reflecting the acceleration of blood flow into the left ventricle; the A-wave velocity may be increased in diastolic dysfunction. The tricuspid flow pattern reflects right-sided filling and usually mirrors the mitral flow pattern.

The Doppler pulmonary venous flow pattern characterizes filling of the left atrium from the pulmonary veins. Normally, the left atrium fills during ventricular systole in concert with atrial diastole and while the mitral ring is being pulled toward the left ventricle. The left atrium fills again during ventricular diastole while the mitral valve is open to the ventricle. Normally, about an equal amount of left atrial (LA) filling occurs during ventricular diastole and ventricular systole (S = D). Under normal circumstances, when the atrial kick occurs, some reversal of flow is seen in the pulmonary vein because of the rapid rise in LA pressure. Relative to the transducer, hepatic flow is negative but is similar to pulmonary venous flow. The flow reversal pattern in the hepatic veins during atrial systole—and during the *c* wave when the tricuspid valve bulges into the atrium at the onset of ventricular systole—is usually more prominent than that in the pulmonary veins.

Figure 20-5 (bottom) shows the mitral pattern of impaired early relaxation and contrasts the findings seen with impaired LV compliance. The E-wave velocity is normally greater than the A-wave velocity, but if early relaxation is impaired, the rate of initial filling (E wave) is reduced, the isovolumic relaxation time and the mitral deceleration time increased, and there is reversal of the E/A ratio. The pulmonary venous flow is similarly blunted in ventricular diastole, and ventricular systolic filling of the left atrium from the pulmonary vein is greater than the diastolic filling. The S/D ratio is therefore greater than 1.

In restrictive cardiomyopathy the issue is not impaired early LV filling but abnormal LV compliance and restricted late filling. Because the left ventricle fills mostly in early diastole in a restriction, the E wave is prominent, and the time to fill the ventricle is reduced (a shortened isovolumic relaxation time). Because of the rapidly rising LV diastolic pressures, the deceleration time is shorter, and the contribution from the atrial kick to the late flow velocities is reduced (the E is much more prominent than the A). The pulmonary venous pattern reflects this, with rapid flow during early ventricular diastole and little flow into the stiff left atrium during ventricular systole. Thus, the S/D ratio of the pulmonary venous flow pattern is much less than 1. Hepatic venous flow patterns again resemble the pulmonary venous flow.

Tissue Doppler measures have now improved on the diagnosis of restrictive cardiomyopathy. Tissue Doppler uses the same pulse wave sampling as with flow velocity, but it is modified to filter the low-amplitude reflections. When the transducer is placed on the mitral annulus or at the myocardium near the mitral annulus, the velocities record the longitudinal movement of the heart in systole and diastole. Because the transducer is at the apex, movement toward the apex is recorded as a positive wave (Sa). When the ventricle goes into diastole, the movement away from the transducer is recorded as a negative wave (Ea). If Ea is reduced (<10 cm/s), it implies impaired early relaxation. If the E wave of the mitral flow pattern is prominent (rapid filling of the left ventricle) while the Ea wave of the tissue Doppler is reduced, it means that there must be an elevated LA pressure. In other words, if there is more pressure pushing the blood into the left ventricle than anticipated from the LV pulling blood, then the LA pressure is presumed to be elevated. This ratio (E/Ea) has thus been used to provide an estimate of the LA pressure. In general, a ratio of 15 or greater has a 90% predictive value of a mean pulmonary capillary wedge pressure greater than 15 mm Hg. The E/Ea ratio has the added advantage of being useful in atrial fibrillation and sinus tachycardia.

Another method for demonstrating the rapid early flow into the left ventricle in restriction is the use of color M-mode propagation velocity. As the left ventricle relaxes, there are intracavitary pressure gradients that promote the propagation of flow from the mitral orifice to the LV apex. By placing an M-mode cursor on the edge of the color-flow envelope, a propagation velocity (first aliasing contour) can be recorded (Vp). A reduced Vp (<40 cm/s) implies impaired relaxation.

A schematic review of the various echo/Doppler patterns that might be observed in a patient with restrictive cardiomyopathy is shown in Figure 20-6.

Because similar diastolic mitral inflow patterns may occur in constrictive pericarditis, patterns during inspiration are the key to differentiating constriction from restriction. There is usually little respiratory change in the mitral and pulmonary venous flow patterns in restrictive cardiomyopathy, but there is a significant (>25%) inspiratory drop in the maximal velocity of these flow patterns in constriction. The increased inspiratory filling of the right ventricle with constrictive pericarditis results in the increased RV pressure described above, and that increased pressure can be recorded in the tricuspid regurgitant jet velocity with inspiration. In restriction, the RV systolic pressure falls normally with inspiration.

Making the distinction even more difficult, pericardial constriction and restrictive cardiomyopathy may occur together, and in this circumstance, the above findings less clearly distinguish the two. The presence of atrial fibrillation makes Doppler flow patterns less complete (lacking an atrial component) and can complicate differentiating pericardial constriction and restrictive cardiomyopathy. Overall, it is estimated that equivocal echocardiographic patterns are present in up to one third of the patients with possible constrictive pericarditis. The use of tissue Doppler adds some additional useful information in differentiating constriction from restriction with a peak Ea greater than 8.0 cm/s or an M-mode of the velocity color-flow pattern greater than 100 cm/s, suggesting constriction rather than restriction.

Cardiac Nuclear Imaging

First-pass and multigated radionuclide angiography can provide ventricular volume data and a time-activity curve reflecting the ventricular volumetric changes of each heartbeat. Because of beat-to-beat variations and difficulties with describing late filling parameters, diastolic radionuclide angiographic information is confined primarily to early filling measurements. Diastolic filling can be described with early filling parameters (peak filling rate, time to peak filling rate, first third filling time) with some accuracy, but these same data are similar to the data from

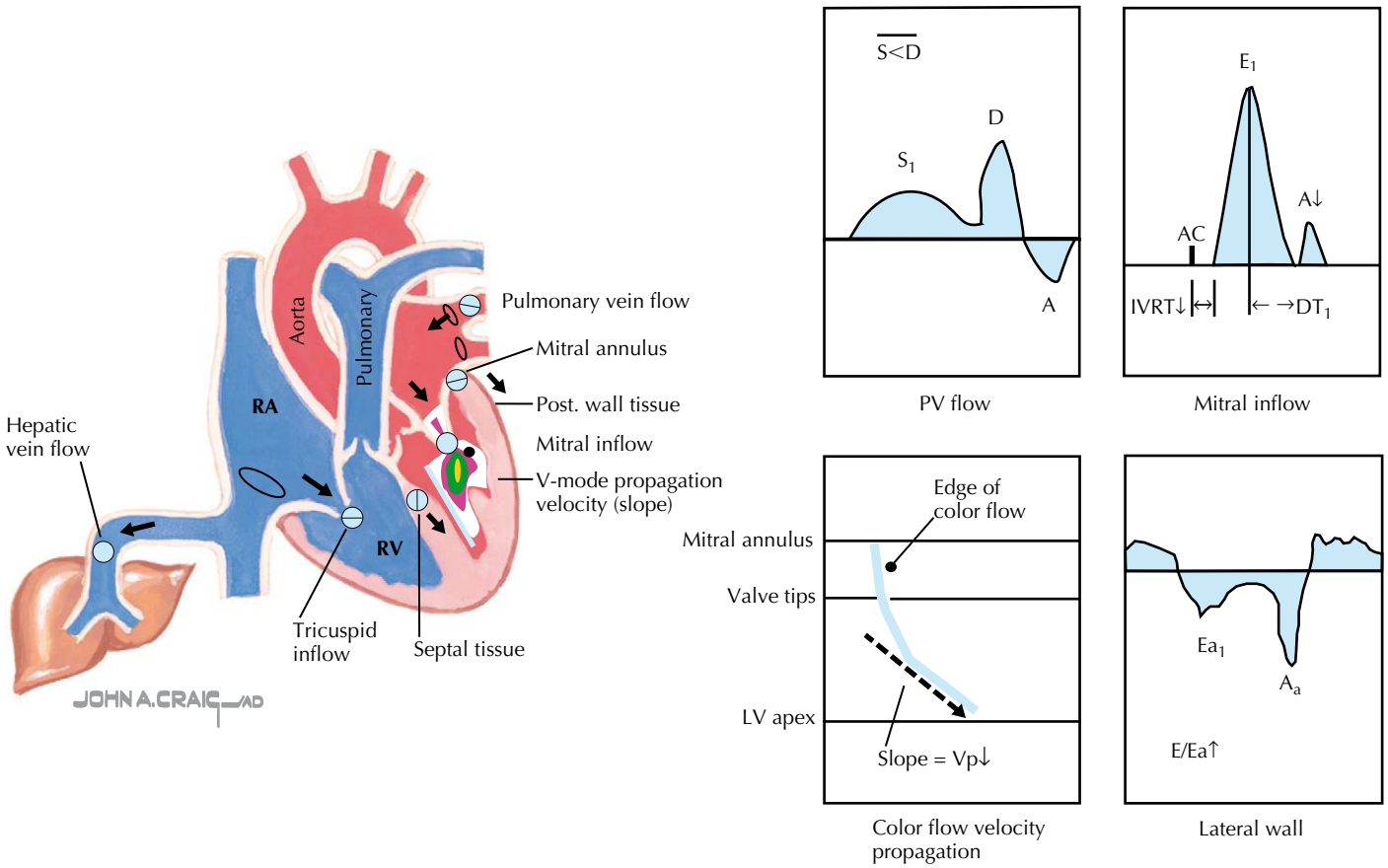


Figure 20-6. *Diastolic abnormalities in restrictive cardiomyopathy.* There is more rapid filling in early diastole in the pulmonary venous (PV) flow (S<D) and in the mitral inflow (E>A). The high left atrial pressure results in the mitral valve opening earlier than after aortic closure (↓isovolumic relaxation time). Color flow velocity into the left ventricle (LV) is reduced (↓velocity propagation [Vp]) and the driving force pushing blood into the LV (E velocity) is greater than that pulling blood into the LV (Ea). Thus, the E/Ea ratio is increased. D, diastolic velocity; DT, deceleration time; RA, right atrium; RV, ventricle; S, systolic velocity.

echocardiography/Doppler studies and are not widely used clinically. The dissociation between systolic and diastolic function can be well demonstrated using nuclear imaging and may be useful in patients in whom echocardiography/Doppler studies are difficult or nondiagnostic.

In patients with amyloidosis, technetium-99m pyrophosphate myocardial imaging may be abnormally positive, and indium-labeled anti-myosin antibody scans can also be abnormal. In patients with familial cardiac amyloid polyneuropathy, meta-iodobenzylguanidine scintigraphy assessments for sympathetic denervation have been proposed but are only occasionally of use because of low specificity. Segmental perfusion defects are occasionally seen with perfusion imaging (thallium-201 or technetium-99m sestamibi) in sarcoidosis; gallium-67 scans may also localize inflammation in this disorder.

Computed Tomography and Magnetic Resonance Imaging

Cardiac anatomic features and their relationship to the lungs are best described by CT and MRI. Pericardial thickening is poorly described by echocardiography, but both CT and MRI can detect pericardial thickening of 2 mm or more. However, a normal pericardium does not exclude constrictive pericarditis. A thickened interatrial septum suggests amyloidosis. Additionally, CT and particularly MRI may provide evidence of an infiltrative process (e.g., amyloid, sarcoid) in patients with restrictive cardiomyopathy. Because the disease process is not always uniform, patients with negative endocardial biopsy results (see below) should undergo imaging of the heart by CT or MRI.

Cardiac Catheterization and Endomyocardial Biopsy

Because of confusion created by the noninvasive tests, cardiac catheterization is often an important adjunct in distinguishing between restrictive cardiomyopathy and constrictive pericarditis. Although many of the subtle findings listed herein can be helpful in determining whether restriction or constriction is more likely, more often than not only some of these findings can be documented.

The relationship between right and left heart filling pressures during inspiration is key to understanding the hemodynamics

(Table 20-1). A right heart–only procedure is inadequate for differentiating constriction from restriction: simultaneous ventricular pressure measurements are often critical to the diagnosis, because the right heart pressure waveforms may be similar in both disease states. Kussmaul's sign (lack of fall of the right atrial pressure with inspiration) may be seen in both diseases. In constriction, portions of the coronary arteries may also be encased in the pericardium and can seem to be frozen because they do not move with the rest of the beating heart.

In restrictive cardiomyopathy the LV end-diastolic pressure should be more than 5 mm Hg higher than the RV end-diastolic pressure at all phases of respiration, and pulmonary hypertension should be present (see Fig. 20-4). Hence, the RV end-diastolic pressure should be less than a third of the RV systolic pressure despite an elevated RV end-diastolic pressure. Unfortunately, lung disease may also be present in the same patient, and other causes of pulmonary hypertension may make this criterion less specific. The pulmonary vascular resistance is normal or near normal in both constrictive pericarditis and restrictive cardiomyopathy unless there is associated lung disease. Elevated pulmonary resistance implies that the left heart may not be solely responsible for the observed pulmonary hypertension. A prominent LA (or pulmonary capillary wedge) *v* wave may be present in restriction because of abnormal LA compliance and may or may not be associated with mitral valve regurgitation. An elevated *v* wave is unlikely in the pulmonary wedge tracing in constriction. The ventricular systolic pressures should be tracked together with inspiration, and both should fall in restrictive disease. The late inspiratory RV systolic pressure may actually rise in constrictive pericarditis.

Endomyocardial biopsy is often of limited value in dilated cardiomyopathy, but it may be helpful in restrictive cardiomyopathy. In cardiac amyloidosis, histochemical staining helps distinguish the primary AL type (κ or λ immunoglobulin light chains) from the less common AA (nonimmunoglobulin protein A) or secondary amyloidosis. Senile cardiac amyloidosis may have extensive or minor deposits, and its prevalence increases with age. Sarcoidosis is spotty and may be missed by percutaneous biopsy. Fabry's disease is distinctive, with deposition of glycolipid in the affected lysosomes, and the diagnosis is often first detected on myocardial biopsy. Other diseases that result in a restrictive process cause myocardial fibrosis of a general nature, with interstitial fibrosis, loss of myofibrils, and vacuolation of cytoplasm. Myocardial biopsy is often not diagnostic in these circumstances.

MANAGEMENT AND THERAPY

Optimum Treatment

DIASTOLIC HEART FAILURE

The treatment of diastolic heart failure centers on reducing symptoms and assessing whether therapy can be directed at the underlying process (Box 20-2). When diastolic pressures are elevated, diuretics are used to treat pulmonary and systemic congestion. However, the stiff ventricle is dependent on adequate preload, and the overzealous use of diuretics can result in hypotension, reduced renal blood flow, and renal dysfunction. Increased bowel edema may reduce the absorption of furosemide. Commonly, patients with restrictive cardiomyopathy present for hospitalization when oral diuretics are ineffective, and it is essential in this circumstance to give diuretics and other medications intravenously. Aquapharesis is helpful at times. Oral torsemide is a preferred diuretic when bowel edema is present. Spironolactone is a useful adjunct, especially if liver congestion and ascites are present. Maintenance of slow heart rates improves diastolic time and allows for adequate diastolic filling. β-blockers can improve rate control. Calcium channel blockers are also used routinely under the assumption that they can both improve myocardial diastolic dysfunction in addition to helping control ventricular rate in patients with atrial fibrillation, thereby improving cardiac function. Sinus rhythm should be maintained if possible, because the atrial contribution to output may be significant in diastolic dysfunction. ACE inhibitors may also improve myocardial relaxation and are often useful despite relatively normal ventricular systolic function. Angiotensin receptor blockers have also been reported to provide

Box 20-2 Therapy in Restrictive Cardiomyopathy

General

- Diuretics (furosemide, torsemide); occasionally aquapharesis
- Spironolactone
- Slow heart rate
  - In sinus rhythm: β-blockers
  - Antiarrhythmics to maintain sinus rhythm if possible
  - In atrial fibrillation: β-blockers, calcium channel blockers
- Improve diastolic relaxation
  - Calcium channel blockers
  - β-blockers
  - ACE inhibitors and possibly ACE receptor blockers
- Control systemic blood pressure
- Avoid digitalis preparations
- Anticoagulation
- Cardiac transplantation

Specific

- Amyloidosis
  - Alkylating agents
  - Interferon (?)
  - Steroids
  - Colchicine
- Hypereosinophilic syndrome
  - Steroids
  - Hydroxyurea
- Sarcoidosis
  - Steroids and other anti-inflammatories
  - Pacemaker if heart block present
- Hemochromatosis
  - Phlebotomy
  - Desferrioxamine
  - Liver transplantation
- Fabry's disease
  - α-galactosidase enzyme replacement
- Carcinoid syndrome
  - Somatostatin analogues
  - Serotonin antagonists
  - α-adrenergic blockers
  - Surgical valve replacement

ACE, angiotensin-converting enzyme.

symptomatic relief and can be used in concert with ACE inhibitors. Systemic blood pressure control is important to reduce the cardiac workload and decrease any stimulus for further LV hypertrophy. However, hypotension is usually a more difficult clinical problem than hypertension in restrictive cardiomyopathy. Digoxin may result in increased arrhythmias, especially in patients with amyloidosis, and should generally not be used.

The use of the Doppler flow pattern may tailor therapy. For instance, fusion of the mitral inflow E and A waves implies inadequate diastolic time; therefore, heart rate reduction is needed. A pseudonormal or restrictive pattern (E>A) implies high diastolic filling pressures and the need for further therapy with ACE inhibitors, calcium blockers, and diuretics. If the PR interval is prolonged, dual-chamber pacing may maximize the relationship of the atrial kick to ventricular contraction. Anticoagulation with warfarin is often recommended to reduce the risk of atrial appendage thrombi in patients with continuous or paroxysmal atrial fibrillation (see also Chapter 28) or if there is evidence for LV thrombus.

Gradually, medical therapy tends to fail. Cardiac transplantation in selected patients may be the only option. Unfortunately, following cardiac transplantation, amyloidosis has been reported to recur in the transplanted heart, suggesting that cardiac transplantation is not appropriate for patients with systemic amyloidosis.

SPECIFIC THERAPY

Therapies directed at the underlying cause of the restrictive process are quite limited. The prognosis for primary amyloidosis is poor, with a median survival time of approximately 2 years despite the use of alkylating agents and other approaches. Interferon has been tried with little success, although the combination of steroids and interferon shows some promise. Combination therapy with melphalan, prednisone, and colchicine may relieve some of the noncardiac and renal aspects of the disease. The restrictive cardiomyopathy due to light-chain deposition, though, has been reported to be reversible, and this variant may have a better prognosis after remission of the plasma cell dyscrasia. Liver transplantation (or combined liver-heart transplantation) may be an option in familial amyloidosis (but only this form of amyloidosis), because the circulating transthyretin that causes the disorder is manufactured in the liver. Thus far, the experience in transplanting these patients is limited. Autologous stem cell transplantation has had some limited success in amyloidosis and may be an option in selected cases.

Corticosteroids and hydroxyurea are used in the early stages of the hypereosinophilic syndrome. There has also been some success with interferon in this disease. Surgery can debride the fibrous plaque, and valve replacement may be indicated.

Corticosteroids and other inflammatory agents are used in sarcoidosis. Heart block can be treated with permanent pacing; implantable defibrillators help patients susceptible to severe ventricular tachyarrhythmias.

Enzyme replacement (β-glucosidase) and liver transplantation has improved some patients with Gaucher's disease.

Hemochromatosis is generally managed by phlebotomy, chelating agents such as desferrioxamine, or both. Heart transplantation and combined heart-liver transplantation have also been used in patients whose hemochromatosis is refractory to standard therapy.

Fabry's disease can now be treated with intermittent intravenous infusion of the enzyme α-galactosidase A, and early studies of its use to improve cardiac function are encouraging.

Carcinoid syndrome is treated with somatostatin analogues, serotonin antagonists, and α-adrenergic blockers. Surgical tricuspid and/or pulmonary valve replacement is an option, especially in patients under 65 years of age.

Avoiding Treatment Errors

There are several important issues for patients with suspected or confirmed restrictive cardiomyopathy. First, it is critically important to be certain that the patient does indeed have restrictive cardiomyopathy. Many patients with pericardial constriction benefit enormously from pericardiectomy. Patients with hypertrophic cardiomyopathy have other treatment options. Patients with end-stage liver disease may benefit from liver transplantation. Second, a variety of treatment options exist, depending on the causes of the restrictive cardiomyopathy, so it is important to make a precise diagnosis of the underlying cause of restriction if at all possible. Third, optimal care requires very close monitoring of patients to maintain intravascular volumes at a point that provides for patient comfort and ambulation but avoids hypotension and the downward spiral that occurs with worsening renal failure. Finally, in patients with severe restrictive cardiomyopathy, it is important for the physician to discuss treatment options and prognosis so that the patient and family can be involved in end-of-life decisions.

FUTURE DIRECTIONS

The definition of diastolic heart failure must be further standardized. Abnormalities of ventricular active relaxation and compliance are often dissociated from systolic dysfunction. Diastolic dysfunction may precede systolic dysfunction in many diseases, especially diseases with concentric hypertrophy, such as aortic stenosis and systemic hypertension. The prevalence of normal systolic and diastolic dysfunction in heart failure studies varies from 14% to 75%, depending on how they are defined. Abnormalities of early diastolic relaxation clearly differ from those of late diastolic compliance.

Clinically, the elderly present with diastolic dysfunction more commonly than younger individuals. Despite this, the prognosis in patients with diastolic dysfunction is far better than in patients with systolic dysfunction, unless an infiltrative process is present.

Diastolic dysfunction need not be present with even profound systolic dysfunction. Many patients who have a poor LV ejection fraction suffer no symptoms of congestion for many years. Only when diastolic dysfunction manifests do congestive symptoms emerge.

Diastolic dysfunction from a restrictive cardiomyopathy suggests that a definable etiology is present, although it is often difficult to identify. Early detection might improve the dismal outcome, so sensitive tests continue to be sought. Exercise measures of diastolic function may be possible that demonstrate early abnormalities not evident at rest. Cardiac MRI is perhaps

the most promising new imaging modality, with improved imaging of all cardiac chambers. MRI may help distinguish epicardial restriction from pericardial constriction and better identify patients for whom pericardial stripping may help. It also may provide better definitions of tissue characteristics and thus allow more precise diagnoses in infiltrative disorders.

Therapy remains the greatest challenge. Although some advances have been made in symptomatic treatment, until satisfactory therapy is available for diseases such as amyloidosis, the outlook for most patients with restrictive cardiomyopathy will remain grim.

ADDITIONAL RESOURCES

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Excellent overall up-to-date review of the major clinical issues in restrictive cardiomyopathy.

U.S. National Library of Medicine and the NIH. Restrictive cardiomyopathy. <http://www.nlm.nih.gov/medlineplurs/ency/article/000189.htm.> Accessed 17.02.10.

Designed primarily for patient information. Provides outline review of various condition and some imaging.

EVIDENCE

Asher CR, Klein AL. Diastolic heart failure: Restrictive cardiomyopathy constrictive pericarditis, and cardiac tamponade: Clinical and echocardiographic evaluation. *Cardiol Rev.* 2002;10:218–229.

An excellent practical review of approaches to distinguishing restrictive cardiomyopathy from pericardial constriction and tamponade.

Frank H, Globits S. Magnetic resonance imaging evaluation of myocardial and pericardial disease. *J Magn Reson Imaging.* 1999;10:617–626.

Provides an overview of imaging approaches for restrictive cardiomyopathy and related entities.

Palka P, Lange A, Donnelly JE, Nihoyannopoulos P. Differentiation between restrictive cardiomyopathy and constrictive pericarditis by early diastolic Doppler myocardial velocity gradient at the posterior wall. *Circulation.* 2000;102:655–662.

The Doppler characteristics that can differentiate restriction and constrictive pericarditis are described in detail in this classic article.

Quinones MA. Assessment of diastolic function. *Prog Cardiovasc Dis.* 2005;47:340–355.

A recent, comprehensive review of approaches to distinguishing the etiology of diastolic dysfunction.

Talreja DR, Nishimura RA, Oh JK, Holmes DR. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. *J Am Coll Cardiol.* 2008;51:315–319.

An outstanding state-of-the-art review of invasive characterization of constrictive pericarditis, which includes key differentiating findings from restrictive cardiomyopathy.

Hereditary Cardiomyopathies

José Ortiz and Richard A. Walsh

21

The World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of the Cardiomyopathies has expanded the definition of cardiomyopathies from disorders intrinsic to the myocardium (for which no other primary cause was evident) to include myocardial damage regardless of etiology. The focus of this chapter, however, is on cardiomyopathies intrinsic to the myocardium.

There are five categories of cardiomyopathic heart disease, based on morphologic and hemodynamic characteristics: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC), and nonclassifiable cardiomyopathies (such as noncompaction and mitochondrial cardiomyopathy).

Numerous genetic mutations, either de novo or with a clear familial transmission, are associated with each of these categories of cardiomyopathy. A familial cause has been found in about 50% of patients with HCM, 35% with DCM, and 30% with ARVC (Tables 21-1, 21-2, and 21-3). As yet, no specific genetic mutations have been found in restrictive cardiomyopathy; however, it is likely that genetic abnormalities predisposing to restrictive cardiomyopathy will be found, given the numerous reports of families with multiple cases of the disease.

The first evidence of a gene defect associated with an intrinsic heart muscle disease was published in 1990. The discovery of a mutation in the gene encoding the β-myosin heavy chain (Table 21-1; Fig. 21-1), with resultant familial HCM, was followed by discoveries of gene mutations for the entire spectrum of cardiomyopathies. This chapter focuses on the breadth of mutations that affect the myocardium, whereas Chapter 72 addresses the general topic of genetics in cardiovascular diseases.

ETIOLOGY AND PATHOGENESIS

Familial Dilated Cardiomyopathy

The phenotype for familial DCM is divided into three groups (Table 21-2; Fig. 21-1), two that are based on the type of genetic transmission and Barth's syndrome (previously included among "X-linked" cardiomyopathies), which is considered a third group because of its peculiar mitochondrial involvement.

AUTOSOMAL-DOMINANT TRANSMISSION

Autosomal-dominant transmission accounts for most cases of familial DCM, which may present either as heart failure or as a conduction abnormality. Ten genetic loci have been mapped for cardiomyopathy without conduction system disease. Seven of these genes are known: actin (chromosome 15q14), desmin (chromosome 2q35), δ-sarcoglycan (chromosome 5q33), β-sarcoglycan (chromosome 4q12), cardiac troponin T (chromosome 1q3), β-myosin heavy chain (β-MHC, chromosome 14q11), and α-tropomyosin (chromosome 15q22); see Table 21-1. Mutations in the α-tropomyosin gene are associated with familial HCMs. Actin, a sarcomeric protein, leads to DCM if the mutation affects its binding to dystrophin (at the sarcolemma level) or to HCM if the mutation affects the myosin-binding region. Mutations of the β-MHC and of cardiac troponin T genes are thought to produce DCM by causing reduced force generation by the sarcomere. In particular, the β-MHC mutation disrupts interactions between actin and myosin or with a hinge area within myosin that transmits movement. Mutations in cardiac troponin T decrease the power of contraction by reducing the ionic interactions between cardiac troponins T and C. The α-tropomyosin mutation interferes with the integrity of the thin filaments. Other mutations are involved either with the stability of the sarcomere or the sarcolemma, or with signal transduction.

Cardiomyopathy with conduction system disease is associated with five mapped loci and one identified gene, lamin A/C, on chromosome 1q21, which encodes a nuclear envelope intermediate filament protein. This mutation also causes Emery-Dreifuss muscular dystrophy.

X-LINKED TRANSMISSION

Characterized by elevated amounts of serum creatine kinase muscle isoforms, the disease-causing gene of X-linked transmission leads to a severe reduction or absence of dystrophin, a cytoskeletal protein, in the heart. This gene is responsible for Duchenne's and Becker's muscular dystrophies as well. The mutations cluster in the 5′ portion of the gene affecting the N-terminal actin-binding region of the dystrophin protein.

MITOCHONDRIAL INHERITANCE (BARTH'S SYNDROME)

Seen most often in male infants, mitochondrial inheritance also follows an X-linked genetic transmission but is considered a separate category because it is characterized by abnormal mitochondrial function, neutropenia, and 3-methylglutaconic aciduria. The responsible gene was found to encode the protein tafazzin. Although the role of tafazzin is unknown, its mutation results in many clinical disorders, including DCM, hypertrophic DCM, endocardiac fibroelastosis, and left ventricular (LV) noncompaction, with or without Barth's syndrome features. There are also reports linking abnormalities of energy production and mitochondrial DNA mutations to cardiomyopathies. In at least two families, HCMs that have evolved to severe DCMs have been linked to transfer RNA–lysine defects.

Hypertrophic Cardiomyopathy

Familial HCM with autosomal-dominant inheritance encompasses most of the cases of HCM (see Table 21-1; Fig. 21-1).

Table 21-1 Gene Defects Associated with Hypertrophic Cardiomyopathy

Gene Product	Chromosome	Risk of Frequent Sudden Death	FHC	Remarks
Myofilaments				
β-myosin heavy chain	14q11.2–q12	High (R403Q, R453C, R719W)	Yes	Degree of hypertrophy correlates with risk of sudden death.
Myosin light chain-1	3p21	Low	Yes	Papillary muscle thickening, rare cases
Myosin light chain-2	12q23–q24.3	Low	Yes	Papillary muscle thickening, rare cases
Thin-filament proteins				
Troponin T	1q3	High (Int15G1_A, ΔE160, R92Q, 179N)	Yes	High risk of sudden death, mild or absent hypertrophy; 13 different mutations reported on the *cTnT* gene
Troponin I	19q13.4	High (ΔK183)	Yes	Apical variant of HCM, occasionally DCM-like features in elderly patients
Actin	15q14	Low	Yes	Some mutations might also cause primary DCM.
α-tropomyosin	15q22	High (V95A)	Yes	Usually favorable prognosis, high phenotypic variability
Other defects associated with FHC				
Myosin-binding protein C	11p11.2	Low	Yes	Benign clinical course, progressive hypertrophy with rather late onset
Titin	Spontaneous	Not applicable	Yes	Only one patient reported
Other defects associated with HCM				
AMP-activated protein kinase γ 2	7q3	Low	No	Associated with Wolff-Parkinson-White syndrome
α-myosin heavy chain	Spontaneous	Low	No	Late onset, rare

DCM, dilated cardiomyopathy; FHC, familial hypertrophic cardiomyopathy; HCM, hypertrophic cardiomyopathy.
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The first gene for familial HCM was mapped to chromosome 14q11.2–14q12. Familial HCM can be caused by mutations in nine different genes encoding sarcomere proteins expressed in cardiac muscle. There are now more than 100 point mutations in the sarcomeric proteins known to cause HCM.

Left Ventricular Noncompaction

Two inheritance patterns of LV noncompaction have been described: One is an X-linked form, seen in males. The mutation has been localized to the gene *TAZ*, which encodes tafazzin, as described above in the section "Mitochondrial Inheritance (Barth's Syndrome)." The other inheritance pattern is a dystrophin-associated protein gene mutation. The gene that encodes α-dystrobrevin, which maps to the chromosome 18q12, has structural properties as well as nitric oxide signaling functions. Its deletion causes cardiomyopathy in mutant mice, supporting its deletion as a cause of ventricular dysfunction.

Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic RV dysplasia presents as a familial disease in at least 30% of patients (see Table 21-3; Fig. 21-1). It is mostly inherited in an autosomal-dominant fashion, and mutations in plakoglobin (chromosome 17q21), desmoplakin (chromosome 6p23–p24), and ryanodine (chromosome 1q42) have been reported to be causative.

CLINICAL PRESENTATION

Patients with hereditary cardiomyopathy have a spectrum of clinical manifestations, from discovery in the asymptomatic patient during the screening of a patient's relatives to the patient presenting with sudden cardiac death or heart failure. It is important to note that the reasons for widely varying phenotypes in family members with the same structural protein mutation have yet to be fully elucidated.

Many patients, regardless of the type of cardiomyopathy, present with classic heart failure symptoms, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, angina, syncope, edema, evidence of low cardiac output (fatigue, weakness, exercise intolerance), and conduction abnormalities. Symptoms depend on the degree of ventricular dysfunction, valvular involvement, and cardiac arrhythmias (if present), and the cardiac chamber involved. Presentation, clinical course, and prognosis also vary according to the altered gene and the mutation responsible for the disease. Less understood variables may affect genetic background and alter the clinical course of the disease.

HCM deserves special consideration, because sudden death may be the initial presentation in a young, otherwise healthy patient. As seen in Table 21-1, the risk of sudden death correlates reasonably well with the type of genetic mutation and the degree of LV outflow obstruction and hypertrophy (see also Chapters 19 and 30). Studies linking the incidence of sudden deaths in athletes have shown different results according

Table 21-2 Gene Defects Associated with Dilated Cardiomyopathy

Gene Product	Chromosome	Skeletal Involvement	Frequent Sudden Death or Rapid Progressive Heart Failure	Remarks	Mutations of the Same Gene Cause Primary MD
DCM with mainly LV dysfunction					
Troponin T	1q3	Not reported	SD, HF (Δk210)	Early-onset ventricular dilation	HCM
δ-sarcoglycan	5q33–q34	None/subclinical	SD, HF (Δk238)	Early-onset ventricular dilation	Limb girdle MD 2F
β-sarcoglycan	4q12	May be severe	HF	May be the initiating deficiency and lead to multiple defects in sarcoglycan expressions	Limb girdle MD 2E
β-MHC	14q11.2–q12	None	HF (S532P, F764L)	Early-onset ventricular dilation	HCM
Actin	15q14	Not reported		Defect located in dystrophin-binding region	HCM
NK	1q32	Not reported		First to second decade, incomplete penetrance	
NK	2q31	None	HF	Native American family, incomplete penetrance	
NK	9q13–q22	None		Large Italian family, incomplete penetrance	
NK	10q21–q23	Not reported		Mitral valve prolapse, occasionally sudden death	
DCM with early conduction disease					
Lamin A/C	1q21.3	None/mild	SD	Frequently in DCM with conduction abnormalities	Emery-Dreifuss MD, limb girdle MD 2B
Desmin	2q35	None/severe		Syncope, can develop severe skeletal myopathy	Desmin myopathy
NK	2q14–q22	Not reported		Frequently ventricular tachycardia	
NK	3p22–p25	Not reported		Associated with sick sinus syndrome and stroke	
NK	6q23	Severe		Associated with adult-onset limb girdle MD	
DCM with sensorineural hearing loss					
NK	6q23–q24	None		Associated with juvenile sensorineural hearing loss	
tRNA-Lys	Mitochondrial DNA	Mild	Involvement of organs with high oxidative metabolism: heart, cochlea, brain, skeletal muscle		
DCM with rapid progression in young men					
Dystrophin	Xp21	Mild	HF	Rapid progression to end-stage HF	Becker's and Duchenne's MD
Tafazzin	Xq28	Mild	HF	Usually fatal in infancy, rare survival to adulthood	Barth's syndrome, endocardial fibroelastosis

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricular; MD, muscular dystrophy; MHC, myosin heavy chain; NK, not known; SD, sudden death.
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Table 21-3 Gene Defects Associated with Arrhythmogenic Right Ventricular Cardiomyopathy

Gene Product	Chromosome	Inheritance	Remarks
Plakoglobin	17q21	Autosomal recessive	Associated with palmoplantar keratoderma and woolly hair (Naxos disease)
Desmoplakin	6p23–p24	Autosomal recessive	Associated with palmoplantar keratoderma and woolly hair (Naxos disease)
Ryanodine receptor	1q42	Autosomal dominant	Identification of four different mutations in independent families
NK	2q32	Autosomal dominant	
NK	3p23	Autosomal dominant	
NK	10p12–p14	Autosomal dominant	
NK	14q12	Autosomal dominant	
NK	14q23	Autosomal dominant	

NK, not known.
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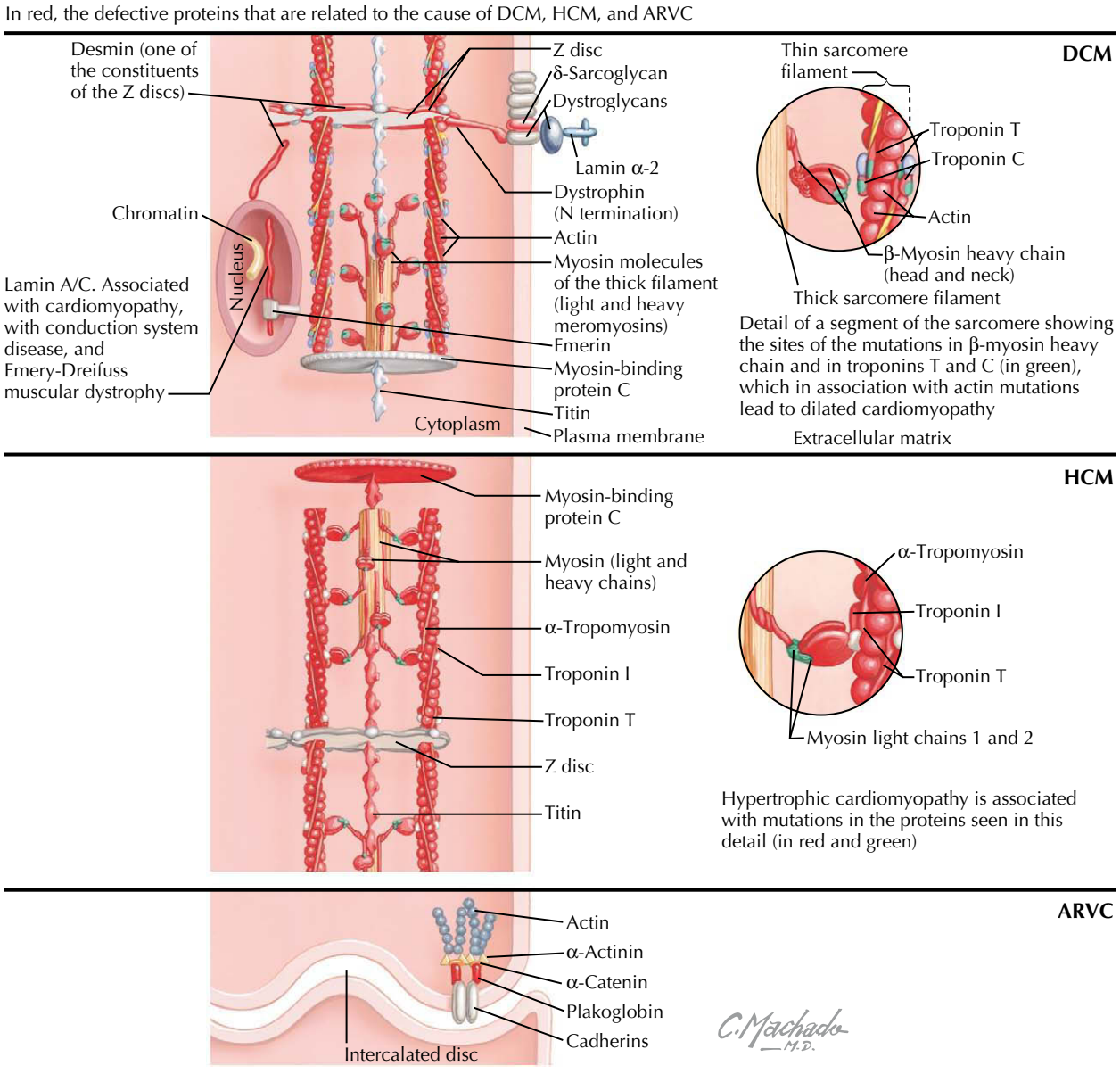


Figure 21-1 *Interaction of affected proteins in dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC; cardiac muscle cell).*

to the country of origin of the patient population. This may be the result of the relative frequency of the various genotypes that affect the likelihood of sudden death. Atrial fibrillation, considered by some to be a sign of disease progression, may add to treatment difficulties by predisposing the patient to stroke and worsening heart failure caused by the difficult-to-control ventricular response, the impact on diastolic filling, or both. Patients may also progress to a dilated phase, with symptoms indistinguishable from those of patients with any cause of DCM.

Patients with genetically determined DCM most commonly present with symptoms between the ages of 18 and 50 years. Genetically determined DCM occurs more frequently in men than in women and more frequently in black individuals than in white individuals. Without cardiac transplantation, about 50% of patients die within 5 years of the date of diagnosis. As with acquired cardiomyopathy, patients succumb to progressive heart failure or sudden death from ventricular tachyarrhythmias. DCM can also be associated with genetic systemic disorders such as glycogen storage disorders, mucopolysaccharidosis, neuromuscular disorders, and fatty acid disorders. In patients with any of these disorders, symptoms related to the systemic disorder are often found upon presentation.

Patients with DCM sometimes present with conduction system disease. For these patients, the age at death is usually in the third decade of life. The cardiomyopathy is disproportionate to the electrical abnormality, which may have started as mild conduction disease and progressed to complete heart block over several years.

Patients with LV noncompaction have deep trabeculations in the LV endocardium, and hypertrophy, dilation, or both can develop. Patients may also have septal defects, a pulmonic stenosis, or a hypoplastic left ventricle.

Patients with arrhythmogenic RV dysplasia typically undergo progressive replacement of the RV myocardium with fibrofatty tissue. Patients present with significant arrhythmias of RV origin, ranging from premature beats to sustained ventricular fibrillation and sudden death.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC APPROACH

Patients with a significant family history of cardiomyopathy usually do not represent a diagnostic dilemma, and a genetic evaluation should be obtained promptly after the onset of symptoms. Diagnosis starts with a well-focused history, an appropriate physical examination, and ECG, usually followed by echocardiography and right- and left-heart catheterizations. Myocardial biopsy should be performed whenever an inflammatory or viral cardiomyopathy is suspected. Even in cases in which a clear familial inheritance is well documented, the initial workup should exclude secondary causes of cardiomyopathies, such as coronary artery disease and hypertension, which may act alone or in combination with the genetic disorder. All patients with DCM should undergo a complete neuromuscular evaluation to exclude an associated muscular pathology. Conversely, patients with any type of muscular dystrophy should undergo a cardiac evaluation to assess for the presence of a concomitant cardiomyopathy.

MANAGEMENT AND THERAPY

Optimum Treatment

Specific treatments for familial cardiomyopathy are not available. Supportive management for these individuals continues to be based on therapies that have proven useful in the treatment of heart failure. The main goals of therapy are to halt/reverse the progressive ventricular functional deterioration and to prevent sudden cardiac death. β-blockers and angiotensin-converting enzyme inhibitors are considered the cornerstone of treatment for genetic DCMs and should be given at the maximum doses tolerated. Patients intolerant of angiotensin-converting enzyme inhibitors may benefit from angiotensin receptor blocker therapy. In general, the same cautions around the use of inotropes and diuretics in HCM are present in any familial cardiomyopathy characterized by preserved systolic function and diastolic dysfunction. For example, although positive inotropic agents are very useful for patients with acutely decompensated cardiomyopathy who are not responding to less-aggressive therapy, they are contraindicated in patients with HCM and normal systolic function (or hyperkinesis). Similarly, diuretic agents should be used cautiously in HCM because patients with HCM are preload-dependent, and even relative volume depletion can further impair their already altered diastolic function.

For moderate to severe heart failure, the aldosterone antagonist spironolactone has decreased morbidity and mortality. For patients with severe conduction abnormalities, especially left bundle branch block, biventricular pacing (also know as *resynchronization therapy*) may help to relieve symptoms. Improvement in functional mitral regurgitation and the freedom to use β-blockade without the risk of bradycardia may be two of the most important benefits of this minimally invasive procedure.

Implantable cardiac defibrillators (ICDs) are the mainstay of antiarrhythmic therapy. Multiple antiarrhythmic agents have been studied in patients with cardiomyopathy, but there are almost no data supporting the use of these agents. Of all the drugs, only amiodarone has shown a marginal decrease in sudden cardiac death in dilated nonischemic cardiomyopathies. Conversely, ICD therapy provides significant mortality benefit in patients with an LV ejection fraction less than 35%, regardless of the etiology. Because of their extremely low predictive value, diagnostic electrophysiology studies help little in the decision of whether to use an ICD, especially in patients with DCM.

Lifestyle modifications such as a regular physical exercise program improve well-being and endothelial function and should be encouraged. Surgical options (before heart transplantation) may improve the quality of life and even reduce mortality rate. Despite the usually complicated early postoperative period, high-risk surgeries such as mitral valve repair or replacement can be performed. Partial ventriculectomies, aneurysm resections, latissimus dorsi cardiomyoplasty, and other surgeries have been performed with mixed or negative results, and these procedures are not generally recommended.

Finally, a patient's condition may become refractory to standard management and require more aggressive means, including ventricular-assist devices (as a bridge to recovery/

transplantation) and, eventually, cardiac transplantation. This is especially true for patients with hereditary DCM.

Specific therapies for patients with DCM and HCM are discussed in Chapters 18 and 19, respectively. Periodic screening of family members is indicated and strongly encouraged and, importantly, there is not an obvious "cutoff" time beyond which further vigilance is not needed. First-degree relatives of DCM patients, even relatives with no apparent findings at initial screening, should be rescreened every 3 to 5 years. The medical history of every new patient should include a detailed cardiac family history of at least first- and second-degree relatives, and an examination, ECG, and echocardiography should be conducted for all relatives. Particular attention should be paid to those relatives with abnormal findings that do not necessarily fit the criteria for cardiomyopathy (such as bundle branch block or LV enlargement with normal LV systolic function). Relatives with these abnormal findings may have a high risk of development of cardiomyopathy. The presence of isolated LV enlargement may be a key indicator or an early stage of disease. When LV enlargement is discovered in a relative, further screening should be performed every 1 to 3 years, depending on the degree of dilation. Because of the variable degree of phenotypic expression and the severity of outcomes, it is advisable for families to receive genetic counseling from a specialist.

Avoiding Treatment Errors

Despite significant advances in knowledge regarding the mechanisms of heart failure, no available therapeutic agents can "cure" the pathophysiologic changes associated with cardiomyopathies. Changes in pathophysiologic function are particularly challenging in cases wherein genetic alteration is the basis of the syndrome. While significant symptom reduction and near-normalization of ventricular contraction may be achieved with medical therapy, under no circumstances should this treatment be discontinued. Discontinuation of treatment has been shown to result in worsening LV function even beyond the pretreatment condition.

FUTURE DIRECTIONS

Despite several promising small observational studies, several new therapeutic strategies such as immunoabsorption of antimyocardial antibodies, anticytokine therapy, and endothelial blockade have not proven successful in the management of cardiomyopathic heart failure. Numerous new molecular-based approaches are in various stages of development.

ADDITIONAL RESOURCES

Hershberger RE, Lindenfeld J, Mestroni L, et al. Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline. *J Cardiac Fail.* 2009;15:83–97.

An update of genetic cardiomyopathies that includes strategies to best evaluate, counsel, treat, and refer patients suspected of having a genetic basis for their disease.

Genetic Health. Heart Disease: What Is Cardiomyopathy? Available at: <http://www.geneticheath.com/HD_What_is_Cardiomyopathy.shtml>; Accessed 23.02.10.

Website for patients and families explaining in easy-to-understand language the basics of cardiomyopathy.

Walsh RA, ed. *Molecular Mechanisms of Cardiac Hypertrophy and Failure.* London: Taylor & Francis; 2005:746.

Reviews current knowledge of the mechanisms contributing to heart failure. Discusses key advances in molecular and cell biology, biochemistry, and pharmacology, focusing on advances that have a direct bearing on current clinical studies

EVIDENCE

Arbustini E, Morbini P, Pilotto A. Familial dilated cardiomyopathy: from clinical presentation to molecular genetics. *Eur Heart J.* 2000;21:1825–1832.

A stepwise approach for genetic screening based on clinical presentation, gender, and some baseline laboratory tests.

Crispell KA, Hanson EL, Coates K, et al. Periodic rescreening is indicated for family members at risk of developing familial dilated cardiomyopathy. *J Am Coll Cardiol.* 2002;39:1503–1507.

Evaluates the role of clinical rescreening of family members at risk for familial dilated cardiomyopathy and shows the value of rescreening several years (around 6) after the initial evaluation.

Davies MJ. The cardiomyopathies: An overview. *Heart.* 2000;83:469–474.

Summary of the more typical findings of each type of cardiomyopathy. An easy-to-follow review.

Franz WM, Müller OJ, Katus HA. Cardiomyopathies: from genetics to the prospect of treatment. *Lancet.* 2001;358:1627–1637.

Discussion about the four types of cardiomyopathies with an in-depth review of the genetic alterations as well as the current approaches to therapy.

Kamisago M, Sharma SD, DePalma SR, et al. Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. *N Engl J Med.* 2000;343:1688–1696.

Genetic causes of dilated cardiomyopathy are reviewed. Four family pedigrees are used to further understand the genetic transmission of the abnormal mutations.

Lowes BD, Gilbert EM, Abraham WT, et al. Myocardial gene expression in dilated cardiomyopathy treated with beta blocking agents. *N Engl J Med.* 2002;346:1357–1365

Study that reviews the value of β-blockers not only for symptom control in heart failure but also in altering the expression of myocardial genes that regulate contractility and pathologic hypertrophy.

Maisch B, Ristic AD, Hufnagel G, et al. Dilated cardiomyopathies as a cause of congestive heart failure. *Herz.* 2002;27:113–134.

Review of dilated cardiomyopathies with a summary of each one of the most common types as well as an approach to diagnosis and treatment.

Towbin JA, Bowles NE. The failing heart. *Nature.* 2002;415:227–233.

Review article that discusses molecular and genetic mechanisms of cardiomyopathies. Approaches to diagnosis and therapy are discussed.

Myocarditis

Daniel J. Lenihan

22

Myocarditis is an inflammatory process that can involve one or more components of the myocardium including cardiomyocytes, the interstitium, and the coronary vasculature. This inflammatory process may result from infectious processes, responses to pharmacologic or toxic agents, hypersensitivity reactions, or physical damage. Myocarditis may also be a cardiac manifestation of a systemic disease.

The clinical course of myocarditis is as diverse as its etiologies. Most patients have a subclinical, self-limited course, but myocarditis may also have fulminant, acute, or chronic presentations. The burden of myocarditis as a clinical entity is difficult to ascertain, at least in part because of its diversity and the elusiveness of diagnosis; for similar reasons, the ideal diagnostic and therapeutic approach to myocarditis has been elusive. The future is likely to be more promising. Recent data have established a causal link between the chronic effects of viral myocarditis and dilated cardiomyopathy. New treatments for dilated cardiomyopathy and heart failure have focused on immunomodulating therapy partly based on this knowledge. Further elucidation of the pathogenesis of myocarditis will probably affect the management of left ventricular (LV) dysfunction and heart failure.

ETIOLOGY AND PATHOGENESIS

In North America and Europe, the majority of cases of myocarditis probably result from viral infection. Many viruses have been associated with myocarditis (Box 22-1). Initial serologic studies suggested that enteroviruses, such as coxsackie B, are common causes of viral myocarditis. However, the application of direct molecular techniques to endomyocardial biopsy specimens, and perhaps changing epidemiology, has led to increasing recognition of adenoviruses, parvovirus, and hepatitis C as etiologic agents. In HIV infection, there is often evidence of myocarditis when cardiac decompensation occurs, although it is unclear whether HIV or opportunistic infections are responsible.

The molecular mechanisms of myocardial injury in viral myocarditis remain incompletely understood. The initial phases of injury probably depend on viral attachment to myocytes and direct cell damage by the virus, resulting in myocyte necrosis. The finding of a common membrane receptor for adenoviruses and coxsackieviruses supports this hypothesis and the preponderance of these viruses as causative agents. Following the initial injury, host immune response to the virus probably has an important role in myocardial injury. Animal models have shown that after the initial phase of entry and proliferation of the virus in the myocyte cytoplasm, inflammatory cells (including natural killer cells and macrophages) infiltrate with subsequent release of proinflammatory cytokines. T lymphocytes are activated through classic cell-mediated immunity. Cytotoxic T cells recognize viral protein fragments on the cell surface in a major histocompatibility complex-restricted manner. Molecular mimicry can occur when antigens intrinsic to the myocyte cross-react with viral peptides, inducing persistent T-cell activation. Cytokines, including tumor necrosis factor, interleukin (IL)-1, IL-2, and interferon γ have been identified as important mediators of chronic inflammatory disease. These cytokines can cause myocyte damage, resulting in fewer contractile units with a resulting worsening of systolic function. Autoantibodies to myocyte components are often found in patients with myocarditis, although most studies measuring autoantibody levels were in patients with idiopathic dilated cardiomyopathy. Even so, it is likely that cellular immunity has more of a role in the pathogenesis of myocarditis than does humoral immunity.

Rarely, bacterial infections, through spread from endogenous sources (Fig. 22-1), can produce focal or diffuse myopericarditis. One of the earliest recognized causes of myocarditis was diphtheria. Up to 20% of diphtheria patients have cardiac involvement, and myocarditis is the leading cause of death with this infection. The toxin produced by the diphtheria bacillus injures myocardial cells (Fig. 22-2). In South and Central America, the most common cause of infectious myocarditis is the protozoan *Trypanosoma cruzi*—the causative agent of Chagas' disease.

Sarcoidosis, a systemic granulomatous disorder of unknown etiology, involves the myocardium in at least 20% of cases. Cardiac involvement ranges from a few scattered lesions to extensive involvement (Fig. 22-3). As a result, endomyocardial biopsy may be diagnostic but is frequently unreliable in confirming myocarditis. Giant cell myocarditis is a rare but highly lethal form of myocarditis of suspected immune or autoimmune etiology that may be associated with other inflammatory conditions such as Crohn's disease. Although the cumulative studies on immunosuppressive therapy for myocarditis are not positive (see below), the above causes of myocarditis do often respond to immunosuppression. Peripartum cardiomyopathy has been associated with a greater than 50% rate of myocarditis on endomyocardial biopsy, although the etiology remains unknown.

Hypersensitivity reactions resulting in myocarditis are characterized by eosinophilia and a perivascular infiltration of the myocardium by eosinophils and leukocytes. Any drug may cause hypersensitivity myocarditis, but clinically this condition is rarely recognized. Therefore, a high index of suspicion should be maintained.

There are also a number of medications and toxins that can cause myocarditis. Cocaine use, for instance, produces myocyte necrosis—mostly from profound sympathetic overstimulation. Anthracyclines (used as chemotherapeutic agents) are direct myocardial toxins with a dose-dependent effect that can profoundly affect the heart, even at low doses.

CLINICAL PRESENTATION

The clinical course of a patient with myocarditis is variable. In up to 40% of patients, the disease is self-limited (Box 22-2). Some patients have a defined prodromal viral illness with fever

Box 22-1 Selected Etiologies of Myocarditis*

Infectious

Viral (coxsackievirus, adenovirus, HIV, hepatitis C, parvovirus)
Bacterial (meningococcus, *Corynebacterium diphtheriae*)
Protozoal (*Trypanosoma cruzi*)
Spirochetal (*Borrelia burgdorferi*)
Rickettsial (*Rickettsia rickettsii*)
Parasitic (*Trichinella spiralis, Echinococcus granulosus*)
Fungal (*Aspergillus, Cryptococcus*)

Inflammatory Diseases

Sarcoidosis
Giant cell myocarditis
Scleroderma
Systemic lupus erythematosus
Hypersensitivity reactions
Serum sickness (antibiotics, tetanus toxoid, acetazolamide, phenytoin)

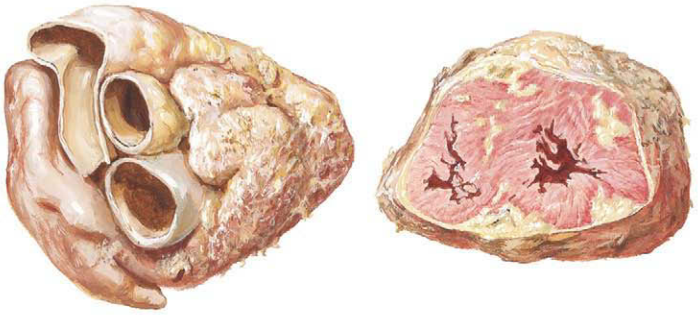
Toxic Exposures

Cocaine
Anthracyclines

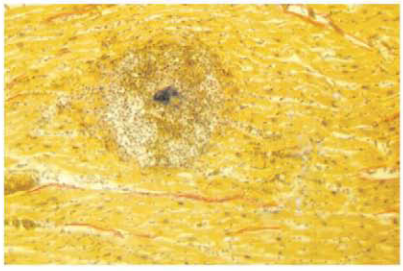
*Examples are shown in each category, but this is not an all-inclusive list.

and arthralgia. Often cardiac symptoms are nonspecific and include fatigue, dyspnea, and chest pain with pleuritic features. Other patients present more acutely with progressive cardiac decompensation from heart failure and require intensive support. In some instances, the presentation of patients with focal myocarditis mimics that of acute myocardial infarction (MI)—but with normal coronary arteries. Patients may present with symptoms of arrhythmia, including palpitations or syncope. Sudden death may also occur with myocarditis and is presumed to be secondary to arrhythmia, because even focal inflammation in the cardiac conduction system can be significant. Chronic immune-mediated myocardial injury, or persistent myocyte viral gene expression, may cause progressive dilatation and resultant LV dysfunction after the resolution of a clinically apparent or subclinical illness.

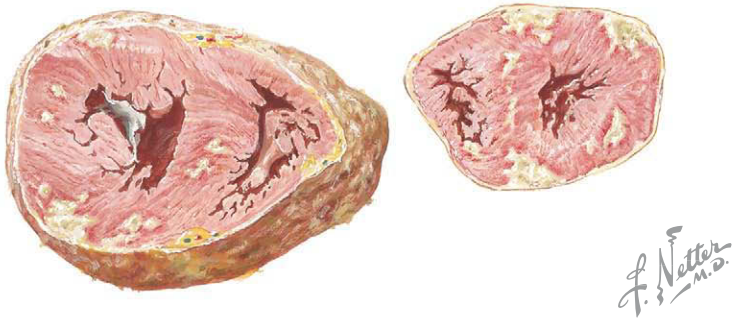
Physical findings in mild cases of infectious myocarditis may include low-grade fever, and a pericardial friction rub may be audible. Physical features of the underlying etiology, such as erythema nodosum (sarcoidosis) and erythema chronica migrans (Lyme disease), can be important clues in determining the cause of myocarditis and should be elicited. If heart failure is evident, there may be a third heart sound, jugular venous distention, or evidence of pulmonary edema. Sinus tachycardia is usually prominent and out of proportion to temperature elevation.



Heart serially sectioned, revealing multiple intramural and subepicardial abscesses with pericarditis



Abscess in heart muscle. Central mass of bacteria surrounded by leukocytes, destroyed muscle, and dilated blood vessels



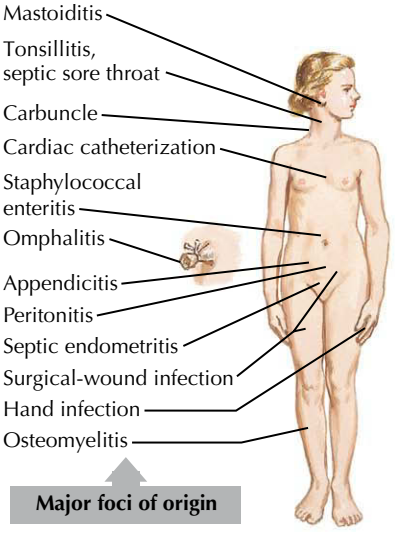


Figure 22-1 *Septic myocarditis and myopericarditis.*

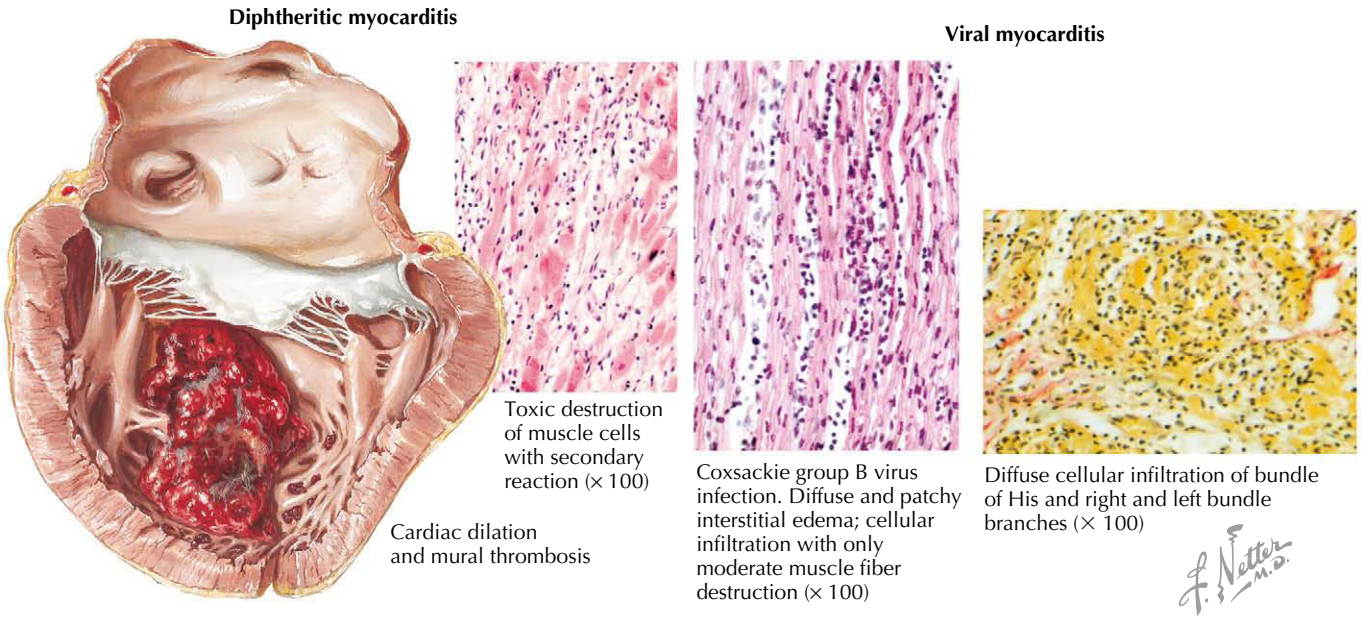


Figure 22-2 *Diphtheritic and viral myocarditis.*

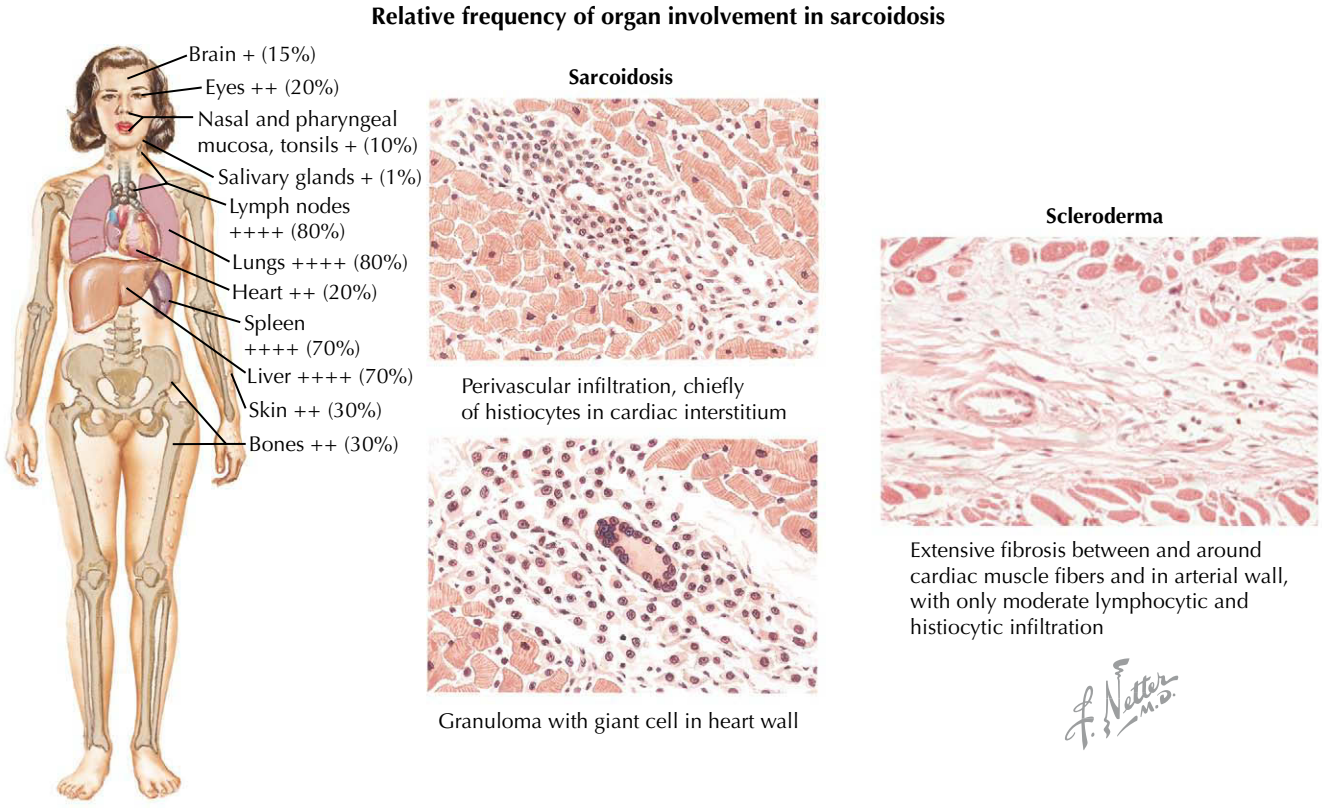


Figure 22-3 *Myocarditis in sarcoidosis and scleroderma.*

Box 22-2 Clinical Presentations of Myocarditis

- Unexplained fever or viral syndrome
- Asymptomatic LV dysfunction
- Symptomatic LV dysfunction
- Acutely decompensated heart failure
- Acute MI with normal coronaries
- Sudden cardiac death
- Arrhythmias

LV, left ventricular; MI, myocardial infarction.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of myocarditis depends mainly on the presentation of the illness. Many illnesses are potentially implicated with or are thought to be causal of myocarditis (see Boxes 22-1 and 22-2). In terms of other causes of LV dysfunction or heart failure, the more common causes include long-standing hypertension, coronary artery disease, valvular heart disease, or inherited cardiomyopathy. Myocarditis, with evidence of LV dysfunction, is typically a diagnosis of exclusion after the other myriad causes of the clinical presentation have been considered.

DIAGNOSTIC APPROACH

Few reliable diagnostic tests are available for myocarditis; therefore, clinical suspicion is vital (Box 22-3). Creatine kinase-MB fraction and cardiac troponin I and troponin T concentrations are often increased, confirming the presence of myocardial cell injury. There may be evidence of a systemic infection with an increased white blood cell count and sedimentation rate. Blood cultures may confirm a bacterial etiology, but in viral infections this is frequently not possible. Acute and convalescent titers for viruses (such as coxsackie B and Epstein-Barr) may provide some evidence of recent infection, especially if there is a two- to fourfold increase in neutralizing antibody titers to a virus (or spirochetes in the case of Lyme disease). Other laboratory testing may confirm a systemic immunologic disease associated with myocarditis, such as sarcoidosis (angiotensin-converting enzyme [ACE] level) or connective tissue diseases (antinuclear antibodies). Typical ECG findings include nonspecific ST-segment and T-wave abnormalities, atrial and ventricular arrhythmias, atrioventricular blocks, widened QRS complexes from intraventricular conduction delays, and, rarely, Q waves. Intraventricular conduction abnormalities are associated with diffuse myocarditis and often predict a poor prognosis. As noted, some patients with myocarditis present with classic ECG findings of MI but have normal coronary arteries. There are no specific radiographic findings in myocarditis; however, findings of cardiomegaly or pulmonary edema are often present. Echocardiography is useful to assess the global and regional LV function, as well as diastolic filling abnormalities. Echocardiography can also demonstrate findings resulting from myocarditis, including increased wall thickness, ventricular thrombi, valvular abnormalities, and pericardial involvement. Cardiac catheterization may exclude the presence of coronary disease or confirm the hemodynamic disturbances of heart failure. Nuclear imaging techniques, such as antimyosin antibody scanning, can identify myocardial inflammation but are not widely available. MRI may detect tissue alterations associated with myocarditis, and recent data suggest that contrast-enhanced images may be a preferred test (Fig. 22-4).

Box 22-3 Diagnostic Testing Useful to Establish the Diagnosis of Myocarditis

- Cardiac markers (CK-MB and troponins)
- Serologic tests for viral, spirochetal, or parasitic etiologies
- Blood cultures (for infectious causes)
- Markers of inflammation or underlying inflammatory disease (erythrocyte sedimentation rate, antinuclear antibodies, ACE level)
- Echocardiography
- Endomyocardial biopsy
- Cardiac catheterization
- Nuclear and magnetic resonance imaging

ACE, angiotensin-converting enzyme; CK-MB, creatine kinase MB fraction.

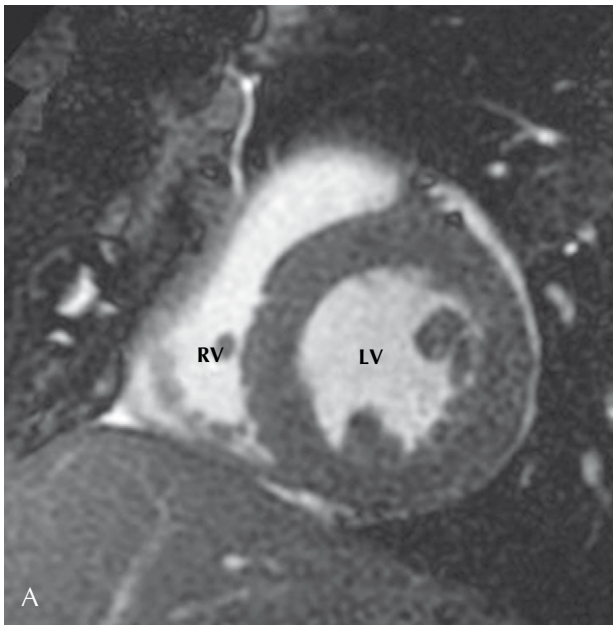
The only gold standard to confirm myocarditis is endomyocardial biopsy. This method has a small, defined risk to the patient, as well as disparities in interpretation. An expert panel of cardiac pathologists formulated the Dallas criteria to standardize the histologic diagnosis of myocarditis on endomyocardial biopsy. They concluded that the histologic hallmark of myocarditis is an inflammatory myocardial infiltrate with associated evidence of myocytolysis. Borderline myocarditis was defined as an inflammatory infiltrate without clear evidence of myocyte necrosis. The positive predictive value of endomyocardial biopsy using these criteria is low (10%); however, it can be marginally increased with more samples. These criteria probably underestimate the true incidence of myocarditis. Because there can be sampling error due to nonuniformity of myocarditis throughout the myocardium or patchy infiltrates as well as interobserver variability in interpretation, a negative result does not exclude the diagnosis of myocarditis. Confirming the presence of viral genomes by polymerase chain reaction or in situ hybridization is a relatively new development that has the potential for significant improvement of diagnosis and assessment of prognosis. Promising studies on the use of MRI for the diagnosis of myocarditis have also recently been reported.

MANAGEMENT AND THERAPY

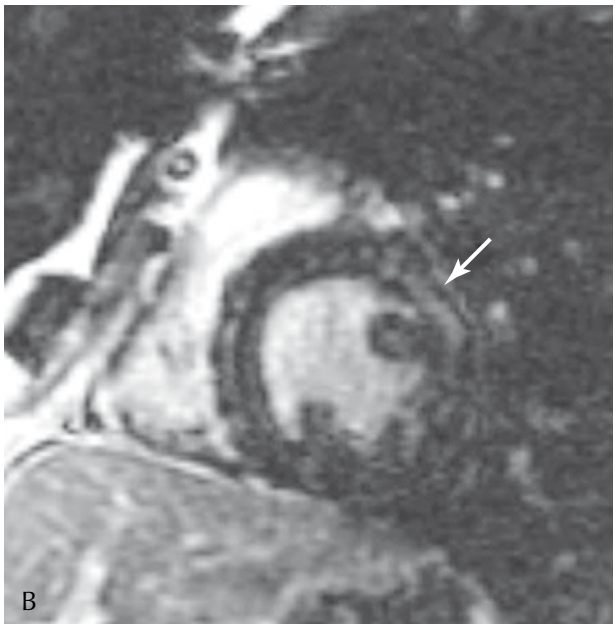
Optimum Treatment

NONPHARMACOLOGIC THERAPY

The treatment of patients with myocarditis is largely supportive. Activity should be restricted to bed rest or a minimal amount until active myocarditis is resolved. At least in animal models of myocarditis, exercise during an active period of cardiac inflammation results in increased myocardial damage. Athletes should refrain from sports for a 6-month period until heart size and function have returned to normal. Those with arrhythmias should refrain from athletic activities until the arrhythmias resolve. Salt restriction (typically emphasized in the management of heart failure) should be recommended for this



(**A**) **White blood:** Short-axis MRI of the heart shows normal wall thickness and wall motion throughout the left ventricle. (Courtesy of G. Gladish, MD.)



(**B**) **Delayed enhancement:** Short-axis myocardial delayed enhancement image shows hyperenhancement (*arrow*) in the midwall of the anterolateral segment of the left ventricle. There is also patchy midwall enhancement of the septum. (Courtesy of G. Gladish, MD.)

Figure 22-4 *Short-axis imaging.* LV, left ventricle; RV, right ventricle.

population, especially in patients with LV systolic dysfunction. In the rare cases that progress to severe heart failure, supportive care may include an LV-assist device or even cardiac transplantation. All unnecessary medications should be eliminated because of the potential that one may be responsible for a hypersensitivity reaction resulting in myocarditis.

PHARMACOLOGIC THERAPY

The etiology established in a patient with myocarditis dictates the specific treatment plan. For instance, in myocarditis caused by diphtheria, antitoxin should be administered immediately upon confirmation of the diagnosis. In the treatment of Lyme myocarditis, antibiotic therapy is used, although its efficacy is not established. Efforts at treatment of Chagas' disease have focused on vector control and immunoprophylaxis.

Patients with dilated cardiomyopathy secondary to myocarditis are treated with conventional therapies for LV dysfunction, including ACE inhibitors, β-blockers, diuretics for volume overload, spironolactone for severe heart failure, and digoxin if symptoms persist. During the acute phase of myocarditis, digoxin should be used with caution based on the notion that there is an increased sensitivity to digitalis in myocarditis and, hence, an increased likelihood of digitalis toxicity.

Immunosuppressive Therapy

Because the long-term effects of viral myocarditis are believed to be due in part to immune-mediated mechanisms, immunosuppressive therapy has been studied. The multicenter, U.S. National Institutes of Health–sponsored Myocarditis Treatment Trial evaluated the role of immunosuppressive therapy using prednisone with either cyclosporine or azathioprine in those with endomyocardial biopsy-proven myocarditis and an LV ejection fraction less than 45%. There was no significant change in LV ejection fraction at 28 weeks and no survival difference between those treated with immunosuppression and controls in this prospectively randomized study. Smaller studies evaluating the role of intravenous immunoglobulins (IVIGs) provided mixed results in myocarditis, but a large-scale randomized study failed to demonstrate a significant effect. Therefore, until evidence is presented with randomized placebo-controlled studies of IVIG in the treatment of acute myocarditis, IVIG therapy should be considered only when the likelihood of benefit is greater, such as in systemic autoimmune disease or biopsy-proven myocarditis with decompensation.

Avoiding Treatment Errors

If myocarditis is suspected, exercise should be minimized until the acute phase of illness is resolving, as has been shown by animal research. Efforts to uncover the underlying cause should be pursued, since treatments may differ depending on the etiology. The treatment of heart failure in any individual patient should be based on standard therapy for heart failure, but caution should be used when adding digoxin.

FUTURE DIRECTIONS

Future therapy for myocarditis will probably be directed at the specific mechanisms of myocardial injury. The common pathway for many causes of myocarditis is the host immune response, so antiviral drugs and virus-specific vaccines may well prove to be efficacious.

Immune-modulating therapy for heart failure is also under active investigation based on the hypothesis that these

treatments may have a role in myocarditis or even idiopathic dilated cardiomyopathy. Proinflammatory cytokines may contribute to disease progression in heart failure by their direct toxic effects on the heart. Several studies suggest that tumor necrosis factor α, a cytokine with negative inotropic properties, is potentially an important therapeutic target for heart failure patients, especially those with more severe decompensation. Although inhibitors of tumor necrosis factor α have been investigated in treating heart failure from LV dysfunction in initial studies, follow-up large-scale studies did not demonstrate benefit. Given the large number of potential etiologies of myocarditis, it could well be the case that some etiologies of the disease respond to immunomodulation while others do not. Further studies, with more accurate pre-enrollment characterization of the underlying etiology, should address this issue. Other forms of immunomodulating therapy, including plasma exchange and immunoabsorption, are also being investigated and perhaps may prove to be useful adjuncts to established therapy.

ADDITIONAL RESOURCES

Feldman AM, McNamara D. Myocarditis. *N Engl J Med.* 2000;343:1388–1398.

An extensive review of the literature with recognized experts in the treatment of myocarditis.

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Gullastad L, Halfdan A, Fjeld J, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. *Circulation.* 2001;103:220–225.

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This is the initial large-scale study that failed to show a significant benefit of prednisone for the treatment of myocarditis.

McNamara D, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation.* 2001;103:2254–2259.

An important study that describes the lack of notable benefit for IVIG in a broad population of patients with possible myocarditis. Of note, the low percentage of patients that had biopsy-proven myocarditis may have influenced the results.

Management of Heart Failure

Carla S. Dupree

23

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with (diastolic HF) or eject (systolic HF) blood. Most commonly, HF results from myocardial muscle dysfunction with accompanying dilation or hypertrophy of the left ventricle (LV), remodeling, and neurohormonal activation.

There are an estimated 23 million people with HF worldwide. In the United States, the prevalence is high. An estimated 5.3 million Americans have HF, and 660,000 new cases of HF are diagnosed per year. The incidence of HF increases significantly with age. HF results in over 1 million hospitalizations annually and is the most common cause of hospitalization for patients aged 65 years and older. The annual health care cost of patients with HF is projected to exceed $34 billion in 2008. With appropriate therapy, patients with HF can be stabilized and have significant improvement in their symptoms. However, despite therapeutic advances, the mortality rate is high, about 50% at 5 years. HF is recorded in one out of every eight death certificates. It is likely that the broader use of evidence-based approaches for the treatment of patients with HF will lead to reduction in mortality. More aggressive efforts for risk factor modification, especially for coronary heart disease risk factors, are of importance given that HF following myocardial infarction (MI) is common. Studies have demonstrated that treating hypertension, vascular disease, or high-risk diabetics significantly reduces the incidence and development of HF.

Risk factors for developing HF include a history of atherosclerotic vascular disease, smoking, hypertension, diabetes, obesity, valvular disease, hyperlipidemia, physical inactivity, excessive alcohol intake, exposure to cardiotoxins, family history of cardiomyopathy, and sleep-disordered breathing.

The American College of Cardiology/American Heart Association update in 2005 presented a new combined clinical and pathophysiologic classification for HF based on four stages:

A, high risk for developing HF
B, asymptomatic with myocardial dysfunction
C, prior or current symptoms with myocardial dysfunction
D, refractory, end-stage

The focus of this chapter is on those individuals who do have evidence of myocardial dysfunction or HF—patients in stages B, C, and D.

ETIOLOGY AND PATHOGENESIS

Coronary artery disease (CAD) accounts for 50% of the incidence of HF worldwide. Patients with a previous MI can develop both decreased systolic performance and diastolic impairment due to interstitial fibrosis and scar formation. Hibernating myocardium due to severe CAD can also cause systolic HF, which is potentially reversible with revascularization. Hypertension is a common cause of HF, especially in African Americans and older women. Valvular heart disease accounts for approximately 10% to 12% of cases of HF. A common cause of initially unexplained HF (following exclusion of CAD) is idiopathic cardiomyopathy. Familial cardiomyopathies may account for up to one third of cardiomyopathies thought to be idiopathic. Other etiologies of dilated cardiomyopathy (Chapter 18) include thyroid disease, chemotherapy (anthracyclines, e.g., doxorubicin and trastuzumab [Herceptin]), myocarditis (Chapter 22), infection due to HIV, diabetes, alcohol, cocaine, connective tissue disease, systemic lupus erythematosus, peripartum cardiomyopathy, and arrhythmias. Hypertrophic (Chapter 19) and restrictive (Chapter 20) cardiomyopathies can cause HF, but this is less common.

Systolic Heart Failure

Systolic HF (ejection fraction [EF] = 40%) results in a reduction in cardiac output that is perceived as "hypovolemia" by the kidneys and triggers activation of the renin-angiotensin-aldosterone system (RAAS). With RAAS activation, salt and water retention occurs. Initially, this results in increased preload, transiently improving cardiac output. Over longer periods of time, chronic activation of the RAAS results in volume overload and symptoms of HF. Declining blood pressure due to decreased cardiac output also triggers activation of the sympathetic nervous system. Increased levels of angiotensin II, aldosterone, catecholamines, endothelin, and vasopressin result in systemic vasoconstriction. The short-term benefit of vasoconstriction—increased perfusion of critical organs—is followed by worsening HF due to chronically increased LV afterload. Sympathetic nervous system activation can also precipitate ventricular arrhythmias, a common cause of death in patients with HF.

HF generally follows an injury to the myocardium (due to ischemia, a toxic effect, or an increased volume or pressure load on the LV). LV remodeling, a maladaptive response, follows, with resulting changes in cardiac size, shape, and function (Fig. 23-1). Myocyte length increases, with a resulting increase in chamber volume, which preserves stroke volume. Myocyte hypertrophy can also occur, along with a loss of myocytes due to apoptosis or necrosis, and fibroblast proliferation and fibrosis. The heart remodels eccentrically in systolic HF, becoming less elliptical and more spherical and dilated. The mitral valve annulus often becomes dilated, resulting in mitral regurgitation and further increased wall stress.

The success of angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), β-blockers, and aldosterone antagonists in reducing mortality in patients with HF is in large part due to their ability to block neurohormonal activation and subsequently attenuate and even reverse remodeling.

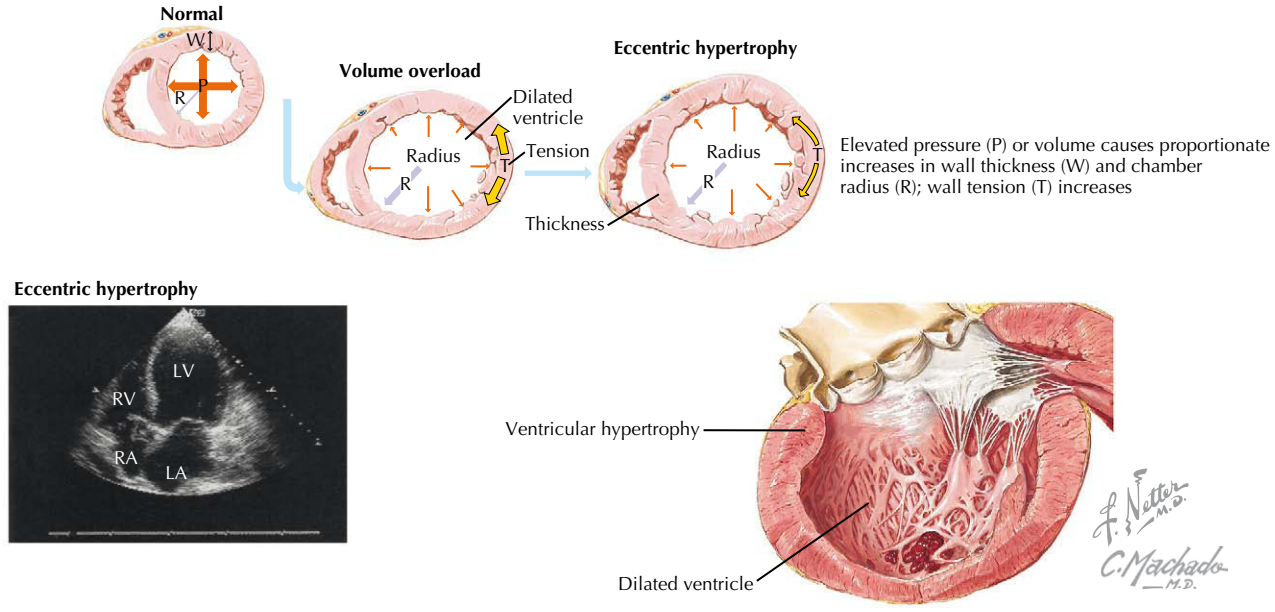


Figure 23-1 *Cardiac remodeling secondary to volume overload.* LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Diastolic Heart Failure

Diastolic heart failure (DHF) is characterized by normal LV volume, concentric remodeling, normal LV systolic function, and abnormalities of diastolic function. DHF accounts for 40% to 50% or more of HF cases. DHF affects older patients, especially women. Ischemic heart disease and hypertension are the most common causes of isolated DHF. In the typical patient with DHF, the ventricular size is normal. However, if DHF occurs as a result of mitral or aortic valve regurgitation, or because of a high-output state (such as anemia or thiamine deficiency), ventricular dilation may be present. The morbidity and mortality of patients with DHF is similar to that of patients with HF due to systolic dysfunction.

Hypertrophic and restrictive cardiomyopathies can result in a clinical presentation consistent with DHF (see Chapters 19 and 20), as can constrictive pericarditis. Indeed, distinguishing these entities can be difficult, requiring extensive noninvasive and invasive hemodynamic assessment.

DHF is generally characterized by a normal end-diastolic volume, hypertrophy of the cardiomyocytes, and increased wall thickness resulting in a concentric pattern of LV remodeling as compared with the increased cardiomyocyte length, increased end-diastolic volume, and eccentric remodeling seen in systolic HF (Fig. 23-2). There is increased extracellular matrix, abnormal calcium handling, and activation of the RAAS and sympathetic nervous system. Together, these pathophysiologic changes result in impaired ventricular relaxation, high LV diastolic pressure, high left atrial filling pressures, and resulting symptoms and signs of HF.

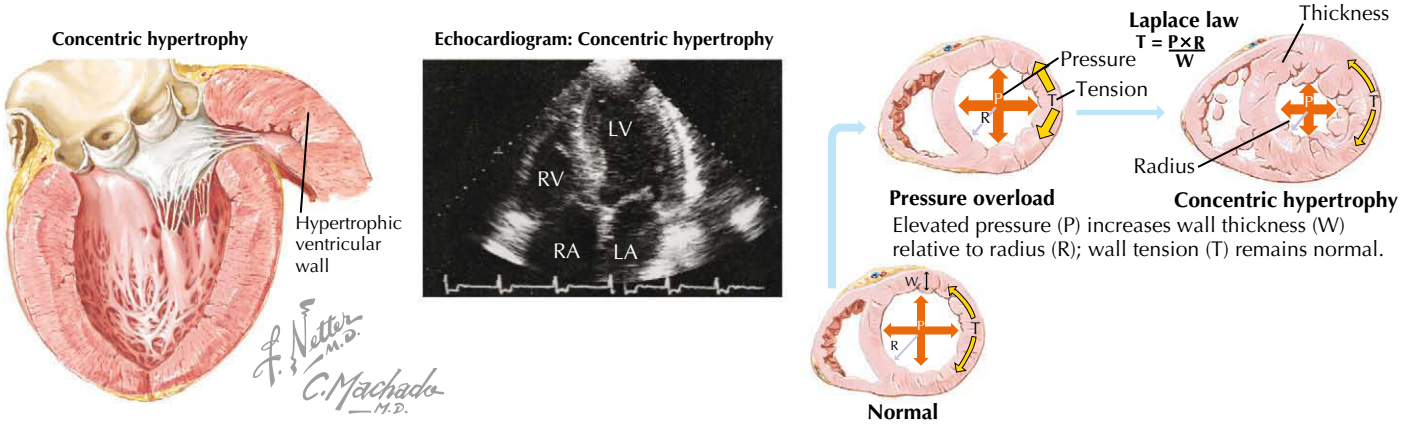


Figure 23-2 *Diastolic heart failure due to hypertension.* LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

CLINICAL PRESENTATION

The presentation of patients with HF includes signs and symptoms of pulmonary congestion, systemic fluid retention, exercise intolerance, or inadequate organ perfusion. Symptoms include dyspnea on exertion, exercise intolerance, orthopnea, paroxysmal nocturnal dyspnea, cough, chest pain that may or may not represent angina, weakness, fatigue, volume overload or pulmonary hypertension, nocturia, insomnia, depression, and weight gain. Patients with end-stage disease may also complain of nausea, abdominal pain, oliguria, confusion, and weight loss. Physical examination findings that should be assessed include jugular venous pressure, rales, wheezing, pleural effusion, displaced point of maximal intensity, right ventricular heave, increased intensity of P_2 due to pulmonary hypertension, S_3, S_4, murmurs, hepatomegaly, hepatojugular reflux, low-volume pulses, and peripheral edema. Patients with end-stage disease may also exhibit pulsus alternans, ascites, cool, pale extremities, and cachexia.

The clinical presentation may be indistinguishable between patients with systolic and diastolic HF (Fig. 23-3). The cardiac silhouette is usually enlarged in both circumstances, with cardiomegaly due to ventricular dilation in systolic HF and from hypertrophy in patients with DHF. An assessment of LV function is essential for determining the appropriate approach to therapy.

DIFFERENTIAL DIAGNOSIS

The difficulty in arriving at a new diagnosis of HF lies in its vague symptoms and examination mimickers (Box 23-1).

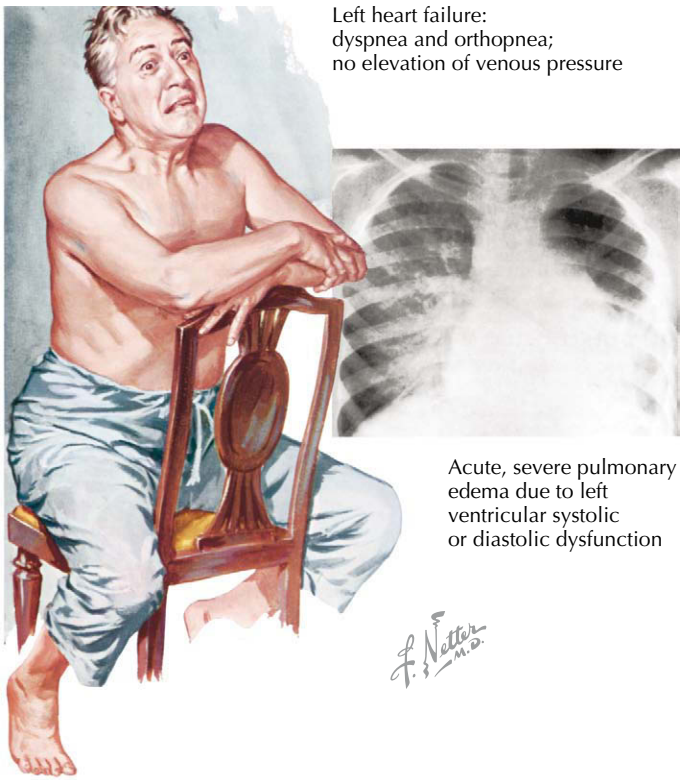


Figure 23-3 *Left heart failure and pulmonary edema.*

Box 23-1 Differential Diagnosis

Myocardial ischemia
Pulmonary disease
Sleep-disordered breathing
Obesity
Deconditioning
Thromboembolic disease
Anemia
Hepatic failure
Renal failure
Hypoalbuminemia
Venous stasis
Depression
Anxiety and hyperventilation syndromes

Symptoms of dyspnea and exercise intolerance can be attributed to many diagnoses: lung disease (including chronic obstructive lung disease, reactive airways diseases, thromboembolic pulmonary disease, and pulmonary hypertension), thyroid disease, arrhythmias, anemia, obesity, deconditioning, and cognitive disorders. Signs of volume overload are not specific to HF. Sodium-avid states of nephrosis and cirrhosis, as well as pericardial disease, can present with similar findings of jugular venous distention, hepatomegaly, and edema.

DIAGNOSTIC APPROACH

The diagnosis is made by taking a careful history, performing a directed examination, and assessing systolic and diastolic ventricular function. Laboratory evaluation (electrolytes, glucose, calcium, magnesium, lipid profile, complete blood count, albumin, liver functions tests, urinalysis, thyroid function), ECG, CXR, and pulmonary function testing will eliminate most noncardiac diagnoses.

Additional directed tests include iron studies (ferritin and total iron binding capacity) to screen for hereditary hemochromatosis, antinuclear antibody and other serologic tests for lupus, viral serologies and antimyosin antibody if myocarditis is suspected, evaluation for pheochromocytoma, serum protein electrophoresis, urine protein electrophoresis, and thiamine, carnitine, and selenium levels.

Measurement of serum brain natriuretic peptide (BNP >400 pg/mL) or N-terminal prohormone BNP (pro-BNP >450 pg/mL in individuals younger than 50 years, >900 pg/mL in individuals 50–75 years old, or >1800 pg/mL in patients over 75 years old) can be very helpful in the acute setting. These markers correlate with elevated filling pressures and are particularly helpful in the evaluation of patients with dyspnea. Although an elevated BNP or pro-BNP level does not rule out pulmonary causes of dyspnea, normal levels (BNP <100 pg/mL or proBNP <300 pg/mL) argue against HF as the predominant cause of dyspnea. Even though levels are generally higher in cases of systolic HF, these tests cannot distinguish between systolic and DHF.

Determining the Type and Degree of Left Ventricle Dysfunction

Echocardiography is the most common method for initial assessment of LV function. EF, valve function, hypertrophy,

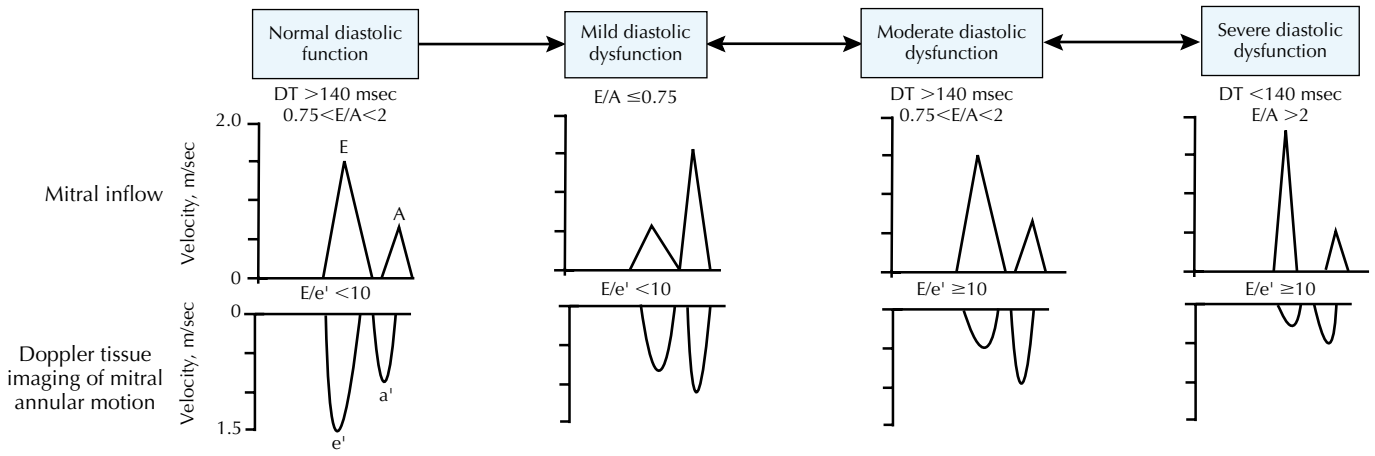


Figure 23-4 *Echo-Doppler criteria for assessment of diastolic function.* From Bursi F, Weston SA, Redfield MM, et al: Systolic and diastolic heart failure in the community. *JAMA;* 2006:296(18):2209–2216. Copyright American Medical Association.

and diastolic function can all be assessed. Most patients with DHF have impaired LV relaxation, with or without a quantifiable reduction in LV compliance, and preserved EF. The most reproducible and validated method of diagnosing diastolic dysfunction combines echocardiographic two-dimensional M-mode Doppler measurements of mitral valve inflow with the sensitive, relatively load-independent measure of LV relaxation (e´ velocity) obtained by tissue Doppler imaging of the mitral annulus. This approach has resulted in four classifications of diastolic function: normal, mild dysfunction (impaired relaxation, normal filling pressure), moderate dysfunction (impaired relaxation or pseudonormal with moderately elevated filling pressure), and severe dysfunction (restrictive) (Fig. 23-4). Reversibility can be determined with the Valsalva maneuver. An E/e´ ratio that exceeds 15 correlates with elevated filling pressure.

Radionuclide ventriculography can be used to determine EF in obese patients and in those with significant chronic obstructive pulmonary disease. The first-pass technique can quantify right ventricular EF as well. Cardiac MRI is a newer imaging modality that allows very accurate assessment of LV function (and EF) in all patients, provides an assessment of myocardial viability, and can identify infiltrative disease. In recent years it has become clear that there is a risk in gadolinium administration to patients with moderate to severe kidney disease, which is common in HF, including patients on dialysis. In these patients, gadolinium administration is associated with the severe syndrome of nephrogenic systemic fibrosis. Therefore, gadolinium administration should be avoided in these patients. Pacemakers and defibrillators are contraindications for MRI.

Defining the Etiology of Heart Failure

The degree of reversibility and, hence, the progression and management of HF differ depending on the underlying cause. Many underlying causes of HF are largely reversible. Treatment of uncontrolled hypertension, thyroid disease, and active ischemia may result in significant improvement in LV function. However, the prognosis is worse in patients with prior transmural MI and systolic dysfunction; patients who are older, are male, have right ventricular dysfunction and a marked reduction in LV systolic function; and patients who have hyponatremia, anemia, high BNP levels, elevated troponin, renal dysfunction, or New York Heart Association (NYHA) class III or IV HF.

Ischemic heart disease should be excluded in every patient, because revascularization of hibernating myocardium can result in significant improvement in systolic function. Focal wall motion abnormalities most commonly indicate CAD, but not always. However, global LV dysfunction does not rule out an ischemic cause and the presence of coronary stenoses amenable to revascularization. Testing options include cardiac catheterization and exercise or pharmacologic echocardiographic or nuclear stress testing. Patients with left bundle branch block should not be evaluated with stress echocardiography because the conduction delay can result in a false-positive test result. Newer imaging techniques include CT angiography, which can identify CAD; cardiac MRI, which can also provide assessment of viability; and PET, which provides both myocardial perfusion and viability.

Determining NYHA classification is important for assessing prognosis, for medical management, as an indication for device placement, and for longitudinal follow-up and evaluation of response to therapy.

MANAGEMENT AND THERAPY

As a first step, it is important to correct precipitating factors, such as dietary noncompliance, ischemia, uncontrolled hypertension, atrial fibrillation, hypoxemia, thyroid disease, anemia, and the presence and causes of medication nonadherence, including financial indigence. An overall approach to management is presented in Figure 23-5.

Revascularization should be considered in ischemic patients. Observational studies suggest that patients with reversible ischemia, even with marked systolic dysfunction, improve with revascularization. The largest and best designed study to

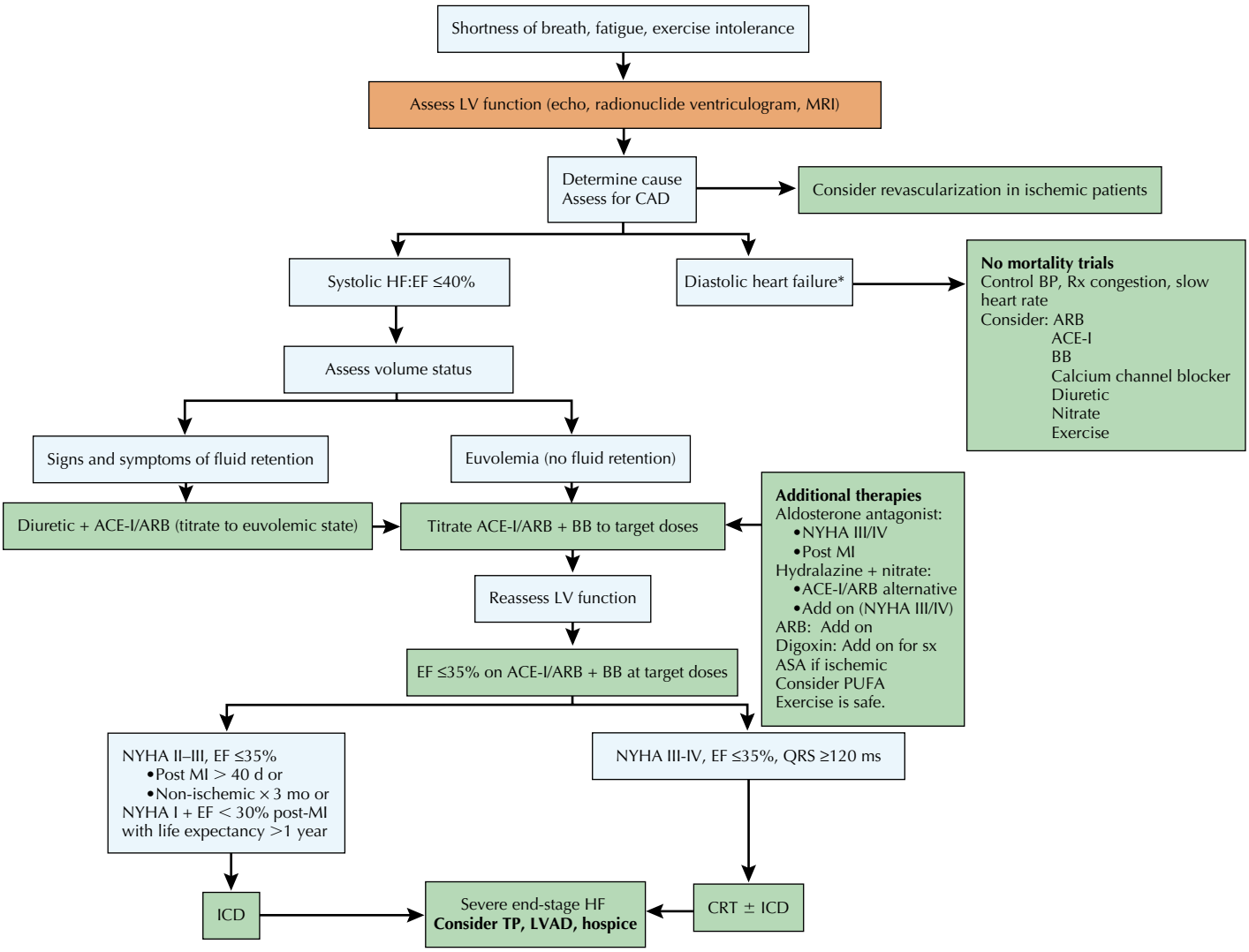


Figure 23-5 *Algorithm for management of heart failure.* ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ASA, aspirin; BB, β-blocker; BP, blood pressure; CAD, coronary artery disease; CRT, chronic resynchronization therapy; echo, echocardiogram; EF, ejection fraction; HF, heart failure; ICD, implantable defibrillator; LV, left ventricle; LVAD, left ventricular assist device; MI, myocardial infarction; MRI, magnetic resonance imaging; NYHA, New York Heart Association (class); PUFA, polyunsaturated fatty acids; QRS, QRS interval; Rx, treat; sx, symptoms; TP, transplant. *Diastolic heart failure is also referred to as heart failure with preserved ejection fraction (HFpEF).

date, the U.S. National Institutes of Health–sponsored Surgical Treatment for IsChemic Heart failure (STICH) trial will ultimately demonstrate whether revascularization is superior to medical therapy for patients with ischemic cardiomyopathy and markedly depressed LV systolic function. Notably, the STICH trial also proposed that surgical restoration of ventricular size and shape will improve outcomes in the study population. The results of this portion of the study are already available and do not support the above hypothesis. In patients with anterior hypokinesia, no additional benefit was observed with surgical ventricular reconstruction plus coronary artery bypass grafting (CABG) compared to CABG alone. Follow-up is ongoing in hypothesis one, comparing revascularization to medical therapy.

Optimum Treatment for Systolic Heart Failure

For systolic HF, blockade of the RAAS with ACE-I or ARB therapy is recommended in all patients. Improved survival, decreased frequency of hospitalization, and improved quality of life have been demonstrated in patients with NYHA classes I to IV HF and in post-MI patients treated with target doses of ACE-Is or ARBs (Table 23-1). Contraindications to ACE-I or ARB therapy include moderate to severe aortic stenosis, bilateral renal artery stenosis, and hyperkalemia (K >5.5 mmol/L). ACE-I therapy can cause intractable cough or, rarely, angioedema. An ARB can generally be substituted for ACE-I therapy, and several studies indicate that ARB therapy is efficacious

Table 23-1 Drug Therapy for Systolic Heart Failure

Medication	Starting Dose	Target Dose
Angiotensin-Converting Enzyme Inhibitors		
Generic		
Enalapril	2.5 mg twice daily	10 mg twice daily
Lisinopril	2.5–5 mg/day	20–40 mg/day
Ramipril	1.25–2.5 mg/day	10 mg/day
Trandolapril	1 mg/day	4 mg/day
Fosinopril	5–10 mg/day	40 mg/day
Quinapril	5 mg twice daily	20 mg twice daily
Captopril	6.25 mg 3 times daily	50 mg 3 times daily
Nongeneric		
Perindopril	2 mg/day	8–16 mg/day
Angiotensin Receptor Blockers (All Nongeneric)		
Valsartan	20–40 mg twice daily	160 mg twice daily
Candesartan	4–8 mg/day	32 mg/day
Losartan	25 mg/day	50–100 mg/day
β-blockers		
Generic		
Bisoprolol*	1.25 mg/day	10 mg/day
Carvedilol*	3.125 mg twice daily	25–50 (>85 kg) mg twice daily
Metoprolol succinate ER*	12.5–25 mg/day	200 mg/day
Metoprolol tartrate	12.5–25 twice daily	100 mg twice daily
Nongeneric		
Carvedilol-CR*	10 mg/day	80 mg/day
Aldosterone Antagonists		
Generic		
Spironolactone	12.5–25 mg/day	25–50 mg/day
Eplerenone	12.5–25 mg/day	25–50 mg/day
Nitrate + Hydralazine		
Generic		
Isosorbide dinitrate	10–20 mg 3 times daily	40–60 mg 3 times daily
Hydralazine	10–25 mg 3 times daily	75–100 mg 3 times daily
Nongeneric		
Bidil (20 mg/37.7 mg)	½–1 tablet 3 times daily	2 tablets 3 times daily
Digoxin (Generic)	0.125 mg/day	0.125 mg/day

*Preferred.

in this population. If the reason for discontinuation of ACE-I therapy was angioedema, it is important to recognize that, though very rare, angioedema has been reported with ARB therapy. Both agents have an equivalent effect on renal function. In patients with significant renal dysfunction and hyperkalemia (K >5.5 mmol/L), the combination of isosorbide dinitrate (160 mg daily in four divided doses) and hydralazine (300 mg daily in four divided doses) is an alternative, although not as effective as ACE-I therapy. All patients with CAD should be treated with aspirin (81–325 mg/day) unless there is a contraindication. Patients who have had percutaneous intervention should also be treated with clopidogrel.

β-blockers should be added to ACE-I therapy in all patients who do not have evidence of fluid overload. Improved survival and EF and reductions in sudden death and hospitalizations have been demonstrated in patients with NYHA class II to IV symptoms and in all post-MI patients at target doses (see Table 23-1). Contraindications include severe reactive airway disease in patients receiving inhaled daily β-agonists, severe bradycardia, or advanced heart block. β-blockers should be started at a low dose and titrated every 2 weeks. Most patients require diuretic therapy during β-blocker initiation and may require up-titration to prevent fluid overload. β-blockers should not be initiated or titrated in patients showing volume overload; these patients should be treated for fluid overload first. Side effects (transient fatigue, weight gain, and diarrhea) are more common with the first few doses. If patients have difficulty tolerating the drug, dose titration can be slowed by increasing the time between titrations, increasing the dose by a smaller amount, or increasing the evening dose first in patients on twice-daily dosing. Although target doses should be the goal, lower doses (i.e., carvedilol 6.25 mg twice daily) also confer a mortality and morbidity benefit. Studies indicate that at least 80% of patients tolerate β-blocker therapy. ACE-I and β-blocker up-titration can be alternated, rather than titrating ACE-I to the target dose before adding a β-blocker. β-blockers can be safely added during hospitalization once the patient is euvolemic. The OPTIMIZE-HF Hospital Registry demonstrated a significantly lower 60- to 90-day post-discharge mortality rate in patients who were newly started or continued on a β-blocker as compared with patients who had never received a β-blocker. Patients whose β-blocker was stopped during the hospitalization and not restarted before discharge had the highest mortality rate, 2.3-fold higher as compared with patients who continued to receive a β-blocker.

Aldosterone antagonists should be added to therapy in patients with NYHA class III (previously class IV) chronic HF and in post-MI patients with an EF less than 40%. Therapy should only be initiated in patients whose potassium is less than 5 mmol/L, serum creatinine 2.5 mg/dL or less, and creatinine clearance above 30 mL/min. The serum potassium level often increases with treatment, especially in diabetic and older patients, and regular monitoring is necessary. Potassium and creatinine should be reassessed at least 1 week and 1 month after initiation or change in dose.

The combination of isosorbide dinitrate and hydralazine added to standard therapy of an ACE-I or ARB and β-blocker therapy may provide an additional mortality and morbidity benefit in NYHA class III and IV African American patients. The target doses in the A-HeFT Trial were isosorbide dinitrate, 40–60 mg three times daily, and hydralazine, 75–100 mg three times daily.

Diuretics such as hydrochlorothiazide, furosemide, and bumetanide are prescribed in most patients to alleviate fluid overload. Because they activate the RAAS, the minimal effective dose should be used. In patients with severe HF, combination therapy (a loop diuretic and hydrochlorothiazide or metolazone) can be used, but potassium and magnesium levels must be carefully monitored.

Digoxin reduces hospitalization and improves symptoms. However, there is no survival benefit. Higher serum concentration (1.2 ng/mL or greater) is associated with poor outcome. Therefore, low-dose digoxin, generally 125 μg daily, is recommended, with a target concentration of less than 1 ng/mL. Digoxin doses should be reduced by half and monitored closely if amiodarone or warfarin is initiated.

Nitrates reduce preload and are prescribed as antianginal agents. At higher doses, systemic and pulmonary vasodilatation occurs. Nitrate tolerance can be prevented acutely by increasing the dose and long term by allowing a nitrate-free interval of at least 8 hours. The addition of hydralazine also mitigates nitrate tolerance.

Amlodipine and felodipine are used to treat hypertension and angina unresponsive to β-blockers and nitrates. Clinical trials have demonstrated a neutral effect of these agents on mortality. Nifedipine, verapamil, and diltiazem should not be used in patients with systolic HF because of their negative effect on contractility.

TREATMENT OF ACUTE HEART FAILURE

Intravenous bolus diuretic therapy is commonly used to treat acute decompensated HF with volume overload. Continuous furosemide infusion has been found to result in a steadier diuresis, particularly in patients who are resistant to initial bolus intravenous diuretics. Generally, it is recommended that an infusion be initiated at a dose of 3 to 10 mg/hr of furosemide with adjustments based on response. Metolazone, spironolactone, intravenous chlorthalidone (500 mg twice daily), or low-dose dopamine can be added in refractory cases.

In the absence of symptomatic hypotension, one should consider nitroglycerin, nitroprusside, or nesiritide in patients who are refractory to diuretics. Nitrate therapy is particularly effective in acute MI with pulmonary edema. Compared with nitroglycerin, nitroprusside is a more powerful afterload-reducing agent for the same degree of preload reduction. A recent retrospective study from the Cleveland Clinic found that administration of nitroprusside to patients with a cardiac index of 2 L/min/m^2 or less and pulmonary capillary wedge pressure of 18 mm Hg or less resulted in greater hemodynamic improvement, higher vasodilator doses at discharge, and a lower mortality rate (25% vs. 44%, odds ratio 0.48; $P = 0.005$) as compared with patients who did not receive nitroprusside. There was no increase in inotropic support, renal dysfunction, or rehospitalization rate in the patients who received nitroprusside. The Cleveland Clinic protocol initiates nitroprusside at 10 to 40 μg/min without a bolus and recommends titrating the dose up to a maximum dose of 400 μg/min with a target mean arterial pressure of 65 to 70 mm Hg. As nitroprusside is gradually weaned after 24 to 72 hours, these investigators added captopril, and isosorbide dinitrate plus hydralazine and up-titrated these medications to target doses: captopril 50 mg three times daily; isosorbide dinitrate 60 mg three times daily; and hydralazine 100 mg four times daily.

Nesiritide is a balanced venous and arterial vasodilator. Concurrent diuretic therapy is necessary because the natriuretic and diuretic effects are modest. Nesiritide is favored by some because it is less arrhythmogenic than dobutamine. Clinical trials have demonstrated improved hemodynamics and symptoms. However, there are concerns about a potential adverse impact on mortality and a potential risk of worsening renal function. A post hoc pooled analysis of 862 patients from three randomized controlled trials comparing nesiritide with noninotropic vasodilator therapy noted a trend toward an increase in the risk of 30-day mortality among patients receiving nesiritide (7.2% vs. 4%, $P = 0.059$). However, a larger meta-analysis did not find an increased risk of death with nesiritide. An ongoing study is addressing the effect of nesiritide on mortality. In regard to the effect of nesiritide on renal function, a post hoc review of data from 1269 patients enrolled in clinical trials comparing nesiritide to vasodilator or inotropic therapies found a greater degree of worsening renal function, defined as a rise in serum creatinine greater than 0.5 mg/dL among patients treated with nesiritide (21% vs. 15%, relative risk 1.54, 95% confidence interval 1.19–1.98). There was no difference between the groups in the need for dialysis (2%). Several other studies using lower doses have demonstrated a neutral effect of nesiritide on renal function. In most centers that treat high-acuity HF, nesiritide therapy is considered for patients who have volume overload, are not responding to intravenous diuretics, and are not hypotensive. Generally, the recommended starting dose is 0.005 to 0.01 μg/kg/min with no bolus. Renal function must be closely monitored in patients receiving nesiritide.

Intravenous inotropes, such as dobutamine or milrinone, may be useful for symptom relief in patients with advanced systolic HF and volume overload or who have diminished peripheral perfusion, referred to as *low-output syndrome*. Dobutamine is an inotrope with limited vasodilator activity. Milrinone, a phosphodiesterase inhibitor, is both an inotrope and a systemic vasodilator. Although both medications may worsen hypotension in patients with severe HF, this effect may be more pronounced in low-output HF patients who are treated with milrinone. However, for patients with both high pulmonary vascular resistance as well as high systemic vascular resistance, milrinone is the preferred agent since it reduces pulmonary vascular resistance as well as systemic vascular resistance. Both dobutamine and milrinone are arrhythmogenic, precipitating both atrial and ventricular arrhythmias. With either agent, one should consider starting at low doses—dobutamine 1 μg/kg/min and milrinone 0.1 μg/kg/min with no bolus. Heart rate, assessment of angina, and heart rhythm must be monitored. If systolic pressure is less than 90 mm Hg or mean arterial pressure is less than 65 mm Hg, nitroglycerin, nitroprusside, milrinone, and nesiritide should be used with caution. Although routine invasive hemodynamic monitoring is not recommended, placement of a Swan-Ganz catheter should be considered in patients whose filling pressures are unclear, who are refractory to standard therapy, who have symptomatic hypotension (i.e., systolic pressure <80 mm Hg) or worsening renal function, or who need documentation of improved hemodynamics when an inotrope is considered for chronic therapy. Because intermittent chronic administration of dobutamine or milrinone has not resulted in improved outcomes in patients with HF, chronic infusion should only be administered as a bridge to transplantation in transplant-listed patients who have implantable cardioverter defibrillators (ICDs) or as palliative therapy in end-stage patients.

Device Therapy for Systolic Heart Failure

ICDs are indicated in all patients who have survived a cardiac arrest. Device implantation should be considered for those patients with a life expectancy of at least 1 year. ICD placement reduces mortality in NYHA class II and III patients with an EF of 35% or less, whether the HF is ischemic or nonischemic. ICD placement is also recommended in class I ischemic patients with an EF of 30% or less. Biventricular pacemakers improve quality of life in approximately 70% of class III and IV patients with EF of 35% or less and a prolonged QRS duration (120 milliseconds or longer), as well as increase survival and reduce hospitalization. Trials are continuing in patients with class II symptoms. These devices should be considered only in optimally treated patients, that is, those receiving ACE-I and β-blocker therapy. It is important to reassess LV function after reaching the target or maximum tolerated doses of these medications before device implantation. Occasionally, a marked improvement in LV function and EF will occur following optimization of medical therapy, obviating the need (and/or indication) for device placement.

LV-assist devices are most often used as a bridge to cardiac transplantation but are also approved as destination therapy for end-stage patients who are not transplantation candidates.

Treatment of Diastolic Heart Failure

There are no completed randomized trials to guide optimization of a medical regimen for treating patients with diastolic HF on the basis of survival. However, several studies have demonstrated an improvement in symptoms and morbidity using several approaches. Candesartan, an ARB, reduced subsequent HF hospitalizations in patients admitted for a cardiac reason whose EF was more than 40%. Nebivolol, a β_1-selective β-blocker with nitric oxide–dependent vasodilating properties, significantly reduced the combined outcome of mortality and cardiovascular hospitalization in patients 70 years and older admitted with HF regardless of EF. The Treatment of Preserved Cardiac function heart failure with an Aldosterone antagonist Trial (TOPCAT) is enrolling patients with symptoms and LVEF ≥45%. The composite endpoint is cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure.

All experts agree that blood pressure control is essential. ARBs, ACE-Is, β-blockers, calcium channel blockers, and aldosterone antagonists have all been demonstrated to cause regression of LV hypertrophy and can be considered for treatment of patients with LV hypertrophy and DHF. Agents that reduce preload, such as diuretics and nitrates, are also commonly prescribed. Nitrates can be used to treat ischemia. Calcium channel blockers, particularly verapamil, improve ventricular relaxation. Agents that decrease heart rate (increasing diastolic filling time), including verapamil, diltiazem, and β-blockers, are usually beneficial. Smaller studies have demonstrated a benefit of daily moderate exercise.

Though not yet studied in randomized, prospective trials, it seems that maintaining atrial contraction is important in patients with DHF. Atrial contraction contributes up to 50% of ventricular filling in patients with decreased compliance, explaining why the loss of atrial contraction in atrial fibrillation results in acute decompensation. Cardioversion, treatment with antiarrhythmic agents, or radiofrequency ablation are options that should be considered on an individual basis.

Avoiding Treatment Errors

Prescribing an ACE-I plus an ARB plus an aldosterone antagonist is not recommended because of the increased danger of hyperkalemia. Regular monitoring of potassium and renal function, at least every 6 months in stable patients and more often in decompensated patients or when medications are changed, is strongly recommended in patients receiving any of these drugs.

Routine administration of nonsteroidal agents is not recommended in patients with HF because of the increased risk for fluid retention and worsening renal function. Nifedipine, verapamil, and diltiazem should not be used in patients with systolic HF because of their negative effect on contractility. Digoxin does not have a benefit in patients with DHF unless they are in atrial fibrillation.

Drug Cost

HF patients take an average of nine to ten medications daily. The huge financial cost of medications often leads to medication nonadherence. Even if patients have insurance or receive Medicare Part D benefits, nongeneric medications can be costly. It is important to determine how patients pay for their medications and to estimate their monthly drug bill. Prescribing generics when available will reduce cost (see Table 23-1). A number of large chain stores offer many generic medications for reduced pricing—as low as $4 per prescription per month. Mail-order companies may also offer reduced pricing.

Nonpharmacologic Strategies

Daily exercise, salt restriction to less than 2.5 to 3 g/day, fluid restriction, and daily weight measurements should all be in the patient's care plan. Obese HF patients benefit from weight loss, and all HF patients benefit from smoking cessation and reduced alcohol intake, or if the etiology of the HF is alcohol, complete abstention. Every patient should receive an annual flu shot. Patients and their families should be educated about the symptoms and signs of the disease, prognosis, medications, and when to contact a health professional.

HF specialists can be helpful in the care of complex HF patients. Those who may benefit include patients who remain severely limited on an optimized medical regimen, do not tolerate medication up-titration, are transplantation candidates (refractory HF, EF <20%, without significant comorbid disease, compliant, psychologically stable with good social support), or are candidates for clinical trials or an LV-assist device.

Treatment of Comorbid Disease

Aggressive management of hypertension, diabetes mellitus, obstructive sleep apnea, and depression is part of routine care. Treatment of atrial fibrillation in patients with systolic heart

failure with either rate control or rhythm control results in similar outcomes. β-blockers are excellent agents for rate control. Common antiarrhythmic agents include amiodarone with thyroid and liver function monitoring every 6 months and sotalol and dofetilide with dosing based on renal function. Sotalol and dofetilide initiation is done in the hospital because of the potential for proarrhythmia. Data on long-term outcomes of atrial flutter or fibrillation ablation are not yet available. Two trials have evaluated the effect of statins and fish oil in patients with systolic heart failure. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) randomized 5011 symptomatic patients with ischemic cardiomyopathy, 60 years of age and older, provided that the investigator thought they did not need treatment with a cholesterol-lowering drug, to rosuvatatin 10 mg daily versus placebo. Mean low-density lipoprotein was 137 mg/dL. During a median follow-up of 32.8 months, total mortality was not affected, but the number of cardiovascular hospitalizations was significantly reduced in the group that received rosuvastatin.

In contrast, GISSI-HF randomized 5574 patients with chronic HF irrespective of cause (40% ischemic, 33% had a history of MI) or EF (10% EF ≥40% EF) to rosuvastatin 10 mg daily versus placebo. Mortality and cardiovascular hospitalization were not reduced after a median follow-up of 3.9 years. However, 33% of patients were not compliant with statin therapy. Another arm of GISSI-HF randomized 7975 patients with symptomatic HF of any cause (50% ischemic) or EF (10% EF ≥40% EF) to N-3 polyunsaturated fatty acid (1 g daily) versus placebo. Approximately 22% were receiving a statin as well. Mortality was decreased by 9% in the polyunsaturated fatty acid group. In absolute terms, 56 patients treated for a median duration of 3.9 years will prevent one death or treatment of 44 patients will avoid one death or hospital admission for cardiovascular reasons. It is likely that the benefits of statin therapy are much greater in patients with coronary heart disease, and there are no large-scale data to support initiating statin therapy in nonischemic patients. Whether to discontinue statins in patients with ischemic cardiomyopathy is less clear and has not been studied.

FUTURE DIRECTIONS

Genetic variation of disease modifiers such as ACE and β-adrenergic receptors influences ACE-I and β-blocker effectiveness. The investigation of functional genomics will allow pharmacologic therapeutics to be tailored to an individual's specific genetic background. Identification of candidate genes, pathways, and relatively common polymorphisms that may predispose patients to increased risk for sudden cardiac death will improve risk stratification such that ICDs can be targeted to those patients most likely to derive benefit. Disease prevention by aggressive modification of risk factors and early detection will continue to have an enormous impact on cardiovascular disease leading to HF.

ADDITIONAL RESOURCES

American Heart Association [home page on the Internet]. <http://www.americanheart.org>; Accessed 18.02.10.

Contains many helpful resources about HF for health professionals, patients, and their families.

Heart Failure Society of America [home page on the Internet]. <http://www.hfsa.org>; Accessed 18.02.10.

Contains helpful information about HF for health professionals, patients, and their families.

EVIDENCE

American Heart Association [home page on the Internet]. <http://www.americanheart.org>; Accessed 18.02.10.

Provides the latest epidemiology data on the prevalence, incidence, mortality, hospitalization, and costs related to heart failure.

Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. *JAMA.* 2006;296(18):2209–2216.

A prospective study that describes the demographic and echocardiographic characteristics and prognosis of 556 HF patients living in Olmsted County, Minnesota. Heart failure with preserved EF was associated with a high mortality rate, comparable to that of patients with reduced EF. Echocardiographic classification of diastolic dysfunction is also reviewed.

Heart Failure Society of America. HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail.* 2006;12(1):e1–e12.

These guidelines provide current recommendations for treatment of HF based on evidence-based data and consensus opinion.

Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation, endorsed by the Heart Rhythm Society. *Circulation.* 2005;112(12):e154–e235.

These guidelines provide current recommendations for treatment of heart failure based on evidence-based data and consensus opinion.

Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med.* 2004;351:2049–2057.

Addition of hydralazine/isosorbide dinitrate to a standard HF treatment regimen showed a significant reduction in mortality, hospitalization, and improvement in quality of life.

Cardiac Transplantation and Mechanical Circulatory Support Devices

24

Michael E. Bowdish, Michael R. Mill, and Brett C. Sheridan

Cardiac transplantation developed as an outgrowth of research into heart preservation to allow safe open heart surgery. In 1961, Shumway and Lower published their seminal article describing the technique of orthotopic cardiac transplantation in a canine model, with successful functioning of the transplanted heart for several days. While Shumway was preparing to begin a human clinical trial of cardiac transplantation, Christiaan Barnard, a South African surgeon who had worked in the United States learning the techniques of immunosuppression and surgical transplantation, shocked the world in December 1967 by performing the first human-to-human heart transplant in Capetown. His patient lived for 18 days before succumbing to infectious complications. Shumway performed the first successful cardiac transplantation in the United States in January 1968, beginning what has become the longest ongoing program of cardiac transplantation in the world.

Activity in cardiac transplantation exploded after these initial successes. However, a dismal initial 1-year survival rate of 22% led most programs to abandon the procedure. Early transplant patients died of both immune rejection of the transplanted heart and infectious complications. Two major developments allowed surgeons and those caring for cardiac transplant patients to balance more successfully the complications of graft rejection versus systemic infection. The development in 1971 of the cardiac bioptome by Caves, combined with Billingham's pathologic grading system for rejection, removed much of the treatment guesswork and permitted accurate diagnosis of rejection and rational strategies for maintenance immunosuppression and treatment of rejection. Cardiac transplantation improved rapidly again with the introduction of cyclosporine A in 1980. This calcineurin inhibitor dramatically reduced the incidence of rejection.

More recently, further investigation into basic mechanisms of transplant rejection resulted in triple-drug immunosuppressive regimens that used smaller doses of prednisone, azathioprine, and cyclosporine, allowing better rejection control with fewer infectious complications and adverse effects from these powerful immunosuppressive agents. Newer agents, such as tacrolimus, mycophenolate mofetil, and sirolimus, as well as the use of induction therapy, are now part of the antirejection armamentarium, and drugs continue to be developed.

INDICATIONS

Generally accepted indications for cardiac transplantation include the presence of end-stage heart disease not amenable to standard medical or surgical therapy, New York Heart Association (NYHA) class III or IV heart failure on maximal medical therapy, and an estimated 1-year life expectancy of less than 50%. As other therapeutic approaches have improved—from coronary artery bypass grafting to percutaneous interventions to advances in medical therapy for congestive heart failure—patients who need transplantation are generally older and sicker, and have multiple comorbidities. In addition, the spectrum of individuals considered for cardiac transplantation today has been broadened to include elderly patients, children, and newborns. The most common indications for cardiac transplantations in the adult population are cardiomyopathies and end-stage coronary artery disease (CAD). A minority of transplants are performed in patients with valvular heart disease, congenital heart disease, and as retransplants (e.g., for graft vasculopathy). In children the leading diagnoses are dilated cardiomyopathies and congenital heart disease (see Section VIII).

Potential transplant patients undergo an intensive screening process by a multidisciplinary team of cardiothoracic surgeons, cardiologists, transplant coordinators, social workers, dietitians, physical therapists, psychologists/psychiatrists, and financial counselors. The screening ensures not only that the patient needs the transplant but also that he or she is physically and mentally able to comply with the rigorous post-transplantation medical regimen and has the appropriate social support to undergo transplantation successfully.

DONORS

Transplant donors are individuals who are brain dead but continue to have adequate cardiac function to temporarily support other organ function. Most die of catastrophic intracranial events or trauma. The hearts are carefully evaluated with respect to cause of death, need for cardiopulmonary resuscitation, and use of inotropic support; they undergo electrocardiography and echocardiography to ensure adequate ventricular and valvular function. In men aged older than 45 years, women aged older than 55 years, and patients with other risk factors for CAD, cardiac catheterization and coronary angiography are frequently performed. Donors undergo thorough serologic testing to rule out transmissible diseases, and their medical and social histories are evaluated.

DONOR-RECIPIENT MATCHING

Patients accepted for transplantation are placed on a national waiting list maintained by the United Network for Organ Sharing (UNOS). UNOS has a contract with the U.S. government to act as the organ procurement and transplantation network. Patients are placed on the waiting list by size, ABO blood type, medical urgency status, and waiting time. When a suitable donor is identified, UNOS generates a list that ranks potential recipients by distance from the donor hospital (to

minimize the organ ischemic time during travel and implantation), size, ABO type, medical urgency, and waiting time. An organ is then offered to a prospective recipient's transplant center. If the transplant physicians believe that the organ is suitable for their patient, arrangements are made to procure the organ and perform the transplantation. On occasion, a potential recipient is precluded from transplantation because of ongoing infection or another potentially reversible contraindication. If the initial center does not accept the organ, it is offered sequentially to all patients on the local list, followed by patients in ever-enlarging geographic circles until the nation is covered. Given the number of patients actively awaiting transplantation, the majority of hearts are placed within their local or regional areas. Other available organs are likewise matched with potential recipients.

DONOR PROCEDURE

After all the organs are placed, procurement surgeons arrive at the donor hospital, and a coordinated procedure allows simultaneous procurement of all usable organs, often including the heart, lungs, liver, kidneys, and pancreas and occasionally including the small intestine. The heart explant procedure depends on whether the heart alone will be used or whether the lungs will also be used separately or as a combined heart-lung transplant. After initial dissection of the aorta and superior and inferior venae cavae, placement of a cardioplegia cannula in the ascending aorta, and completion of the other teams' initial dissections, the donor is systemically heparinized. The superior vena cava is tied off, the left atrial (LA) appendage is amputated, and the inferior vena cava is partially transected to decompress the heart and prevent ventricular distention. The aorta is then cross-clamped, and cardioplegia is infused while the heart is lavaged with ice-cold saline (Fig. 24-1).

Simultaneously, the other organs are flushed with their own preservative solutions and lavaged with cold saline. After completing the cardioplegia infusion, the superior and inferior venae cavae are transected. If only the heart is to be used, the pulmonary veins and pulmonary arteries are divided at the pericardium, and the aorta is divided. If the lungs are to be used, the left atrium is divided at the midatrial level, leaving enough cuff of the left atrium for cardiac implantation and cuffs around the pulmonary veins for lung implantation. The pulmonary trunk is divided at its bifurcation to leave enough length on the pulmonary arteries for the lung implantation. If a combined heart-lung transplant is planned, the two organs are resected en bloc by dividing the cavae, aorta, and trachea and dissecting the heart-lung block from its mediastinal attachments. The organs are then stored in ice-cold saline in multiple layers of plastic bags to ensure sterility, and they are packed in an ice-filled cooler for transportation to the transplanting center.

RECIPIENT PROCEDURE

Two approaches to orthotopic cardiac transplantation are widely used. In the traditional Shumway and Lower technique, a biatrial anastomosis is performed whereby the donor and recipient atrial cuffs are sewn together. This technique does not require separate caval anastomoses, and therefore saves time. An alternative technique, the bicaval technique, was developed in the 1990s and consists of sewing separate caval anastomoses. Purported advantages of this technique primarily relate to improved atrial function, decreased need for permanent pacing, and decreased tricuspid regurgitation. However, in an outcomes analysis of the UNOS database between 1999 and 2005, no survival difference was identified between recipients of bicaval versus biatrial orthotopic cardiac transplantation.

Biatrial Technique

The operation is performed through a standard median sternotomy using cardiopulmonary bypass with aortic and bicaval cannulation. The initial dissection and cannulation are performed while the heart is being transported to the recipient hospital. When the new heart arrives, cardiopulmonary bypass is instituted at moderate systemic hypothermia (~32°C), and caval tapes are secured around the caval cannulas. The aorta is cross-clamped and then divided just above the level of the aortic valve. The pulmonary trunk is divided above its respective valve, and the atria are divided at the midatrial level, with removal of the atrial appendages and preservation of the posterior atrial cuffs containing the pulmonary veins on the left and the cavae on the right. The donor heart is prepared by freeing the pulmonary artery from the aorta and the roof of the left atrium. The pulmonary venous orifices are interconnected to create a cuff for the LA anastomosis. Excess LA tissue can be removed to create a better size match for this anastomosis. The oval fossa of the donor heart is examined for a patent foramen ovale. If identified, it is closed. The LA anastomosis is then fashioned with a suture in a continuous running fashion. The suture line is begun at the base of the donor LA appendage, just above the recipient left superior pulmonary vein (see Fig. 24-1).

The donor right atrium is opened from the orifice of the inferior vena cava through the right atrial appendage and then sewn to the recipient atrial cuff. Next, the donor and recipient pulmonary trunks are cut to appropriate lengths. The pulmonary trunks are then anastomosed end to end with a running suture. Systemic rewarming is begun, and the donor and recipient aortas are trimmed and anastomosed with a running suture. The heart is de-aired, the suture line is secured, the patient is placed in a steep Trendelenburg position, and the cross-clamp is released, thus ending the donor heart ischemic time. During rewarming and reperfusion, the right side of the heart is de-aired, the caval tapes are removed, and the donor superior vena cava is oversewn. With rewarming and reperfusion, a spontaneous normal sinus rhythm usually develops. Regardless, temporary atrial and ventricular pacing wires are placed should temporary atrioventricular sequential pacing be needed postoperatively. After the onset of forceful ventricular contractions and completion of de-airing maneuvers, inotropic support is begun. Depending on the donor heart ischemic time and size, the recipient's pulmonary vascular resistance, and the preoperative use of antiarrhythmic drugs (especially amiodarone), additional inotropic support or vasoconstrictive agents are sometimes necessary. The patient is then weaned from cardiopulmonary bypass. Heparin is reversed with protamine sulfate, and the heart is decannulated. After ensuring adequate hemostasis, chest drains are placed, and the sternotomy is closed.

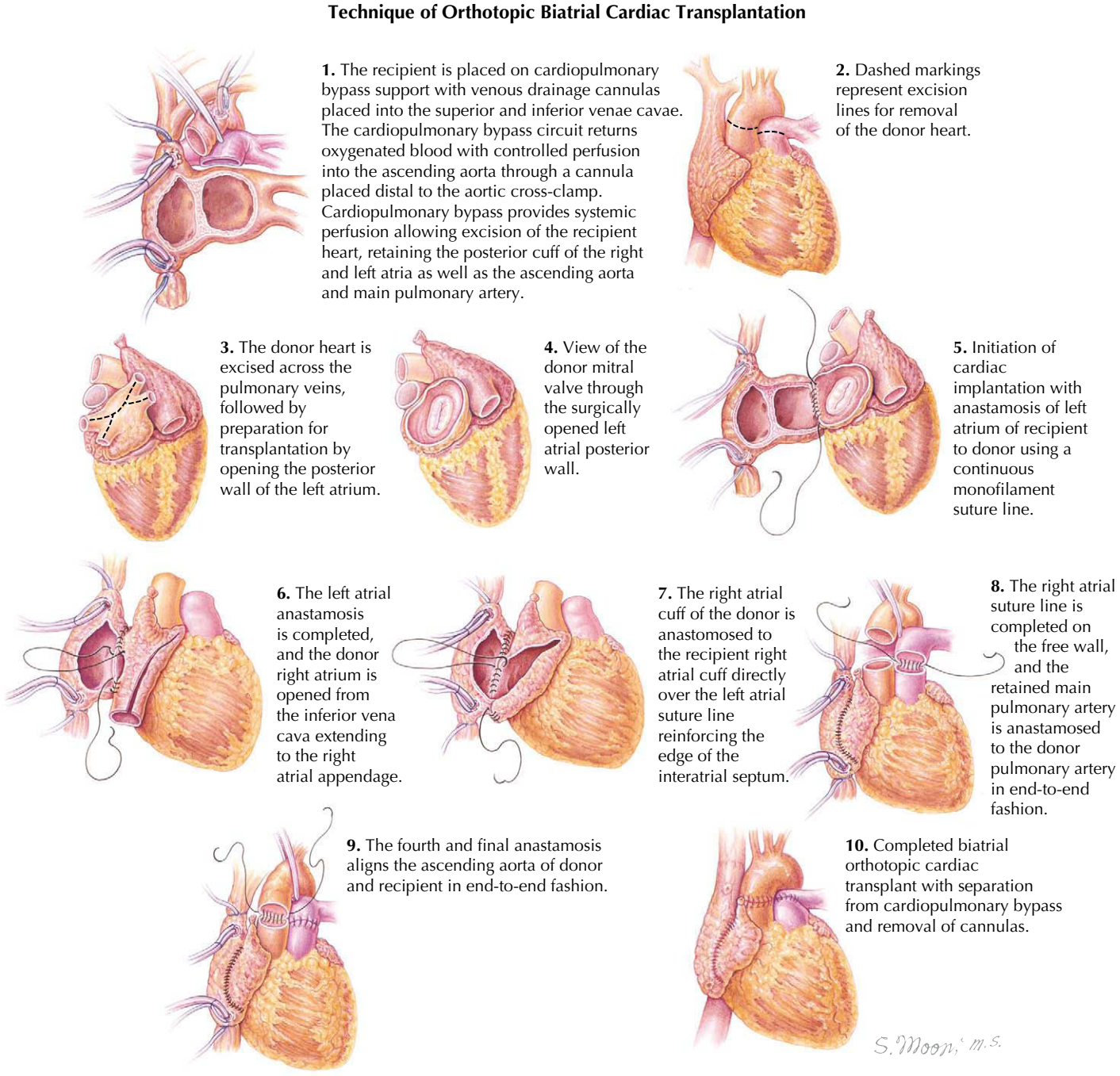


Figure 24-1 *Technique of biatrial cardiac transplantation.*

Bicaval Technique

The operation is fundamentally the same as the biatrial technique. The differences in cardiectomy include developing the groove between the right and left atria to allow their separation. During excision of the heart, the superior vena cava is divided just above the level of the right atrium, and the inferior vena cava is divided just below the coronary sinus. After the aorta and pulmonary artery have been divided, a LA cuff is then created starting at the dome of the left atrium, carrying the incision inferiorly above the orifices of the right and left pulmonary veins (Fig. 24-2). During implantation, the LA cuff is sewn in a similar manner. Some surgeons place a vent through the right side of the LA suture line to assist in de-airing and to prevent warm blood from accumulating in the heart during the remainder of the implantation. Next, the recipient and donor inferior venae cavae are anastomosed, followed by the superior venae cavae. The pulmonary artery and aortic anastomosis are then completed similarly. An alternative is to complete the LA, inferior vena cava, and aortic anastomoses and then release the cross-clamp, completing the remaining right-sided anastomoses with the heart beating and reperfused to decrease ischemic time.

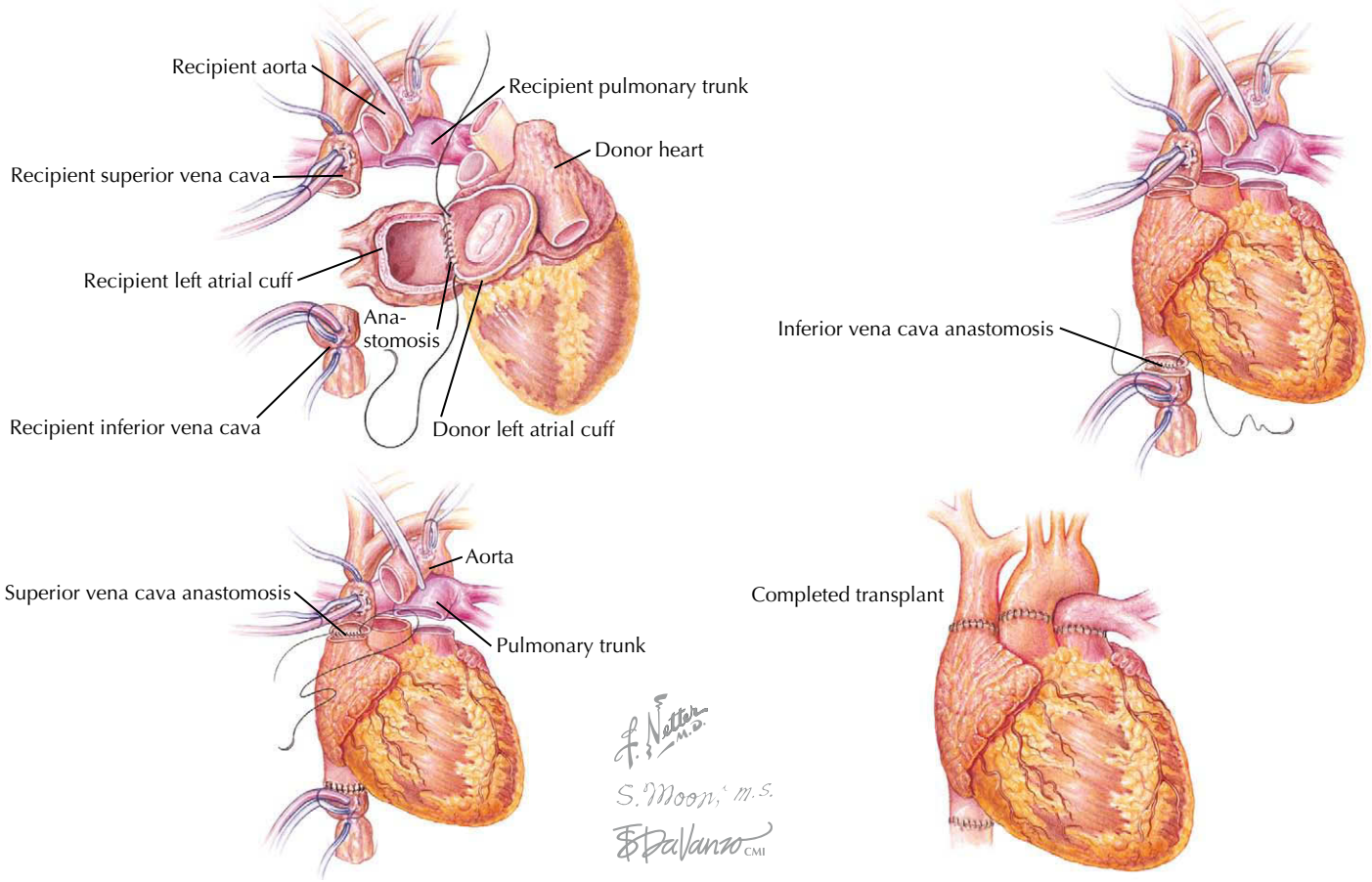


Figure 24-2 *Technique of bicaval cardiac transplantation.*

Weaning from cardiopulmonary bypass is the same as with the biatrial technique.

POSTOPERATIVE MANAGEMENT

The initial postoperative treatment of cardiac transplant recipients is similar to that of open heart surgery patients, especially in terms of fluid and electrolyte management, ventilator care and weaning, and pain control. The major differences include isolation precautions because of the increased infection risk and immunosuppression to prevent rejection. Multiple protocols for transplant immunosuppression and rejection monitoring exist. Most rely on initial triple-drug immunosuppression with a calcineurin inhibitor (cyclosporine or tacrolimus), a purine synthesis inhibitor (azathioprine or mycophenolate mofetil), and prednisone. The doses of calcineurin inhibitors are monitored and adjusted based on daily serum concentrations, the standard doses of purine synthesis inhibitors are decreased if leukopenia or pancytopenia develops, and steroids are tapered by schedule in the absence of rejection. Most programs use a protocol of endomyocardial biopsies, supplemented when indicated by echocardiography, right-sided heart catheterization, or both to diagnose rejection and monitor response to therapy. With significant rejection or hemodynamic compromise, patients are treated with bolus steroids. If this is ineffective or if a pattern of recurrent rejection develops in the patient, other treatment protocols are used. During follow-up examinations, patients are monitored for the development of arrhythmias, immunosuppressive side effects, and signs and symptoms of infection. Routine electrocardiograms often show two P waves: one from the recipient right atria and one from the donor right atria. This can be misdiagnosed as atrial fibrillation or premature atrial contractions. The correct diagnosis is established by confirming that one set of P waves (from the donor) is synchronous with the QRS complex. Routine chest radiography is vital to detect new infiltrates that most commonly represent preclinical pneumonias or early malignancies. Aggressive evaluation of these infiltrates is mandatory, because immunosuppressive agents increase infection risks and can accelerate growth of malignancies. Early detection and treatment can mean the difference between survival and death. Chronic renal insufficiency is a common adverse effect of long-term calcineurin inhibitor use and can be ameliorated by dose modulation. Likewise, chronic hypertension is a common result of the use of calcineurin inhibitors and steroids and can necessitate treatment with multiple agents to control blood pressure. Hyperlipidemia occurs with both agents also, and evidence suggests all transplant patients should be routinely treated with statins. Calcineurin inhibitors and steroids are also diabetogenic and usually necessitate aggressive therapy with insulin for adequate control. The frequency of endomyocardial biopsies gradually decreases in the absence of rejection; by 1 year, they are only performed with

clinical suspicion of rejection or as part of the annual examination.

RESULTS OF CARDIAC TRANSPLANTATION

Data on more than 80,000 cardiac transplant procedures from approximately 225 centers (all centers in the United States, mandatory for UNOS membership and voluntary for international centers) have been collected and analyzed by the International Society of Heart and Lung Transplantation and UNOS since 1983. In 2008, the Twenty-fifth "Official Adult Heart Transplant Report" was released by the International Society for Heart and Lung Transplantation. The number of heart transplant procedures reported to the registry annually has leveled at approximately 3200, following a decline from approximately 4500 procedures in the mid-1990s. More than 50% of the reporting centers perform more than 10 transplants annually. The primary indication for adult heart transplantation has changed slightly over the last 5 years, with a shift from an equal split between coronary heart disease and nonischemic cardiomyopathy to a significantly greater proportion of patients with nonischemic cardiomyopathy (50% vs. 34%). The remaining indications are adult congenital heart disease (3%), retransplantation (2%), and valvular heart disease (2%). Recipients older than 60 years now compose almost 25% of all recipients annually. In addition, a significant increase in the number of recipients on left ventricular assist devices (LVADs) at the time of transplant has occurred (22% currently vs. 11% during 1999–2001). Also, fewer recipients are now hospitalized immediately before transplantation (44% vs. 72%), probably reflecting the current practice of using an LVAD or inotropes in the outpatient setting as a bridge to transplant. Donor utilization has become more liberal over the last decade, with an increase in the mean donor age from 23 years in 1983 to 30.2 years in 2008. In addition, whereas donors older than 50 years were rare before 1986, they now account for more than 12% of donors.

Postoperative immunosuppression has changed somewhat over the last decade, with increased use of perioperative antilymphocyte antibodies (37% in 1997 vs. 51% in 2007). Tacrolimus is now the most commonly used calcineurin inhibitor, while mycophenolate mofetil remains the predominant antiproliferative agent. Sirolimus use remains low at approximately 13%, with little change in recent years. Prednisone use has decreased over the last 6 years but is still used by 63% of patients at 1 year post-transplant.

Survival after cardiac transplantation remains excellent. The 1-, 5-, and 10-year survival rates are currently 82%, 70%, and 50%, respectively. After an initial drop in survival during the first 6 months, the survival curve then decreases at a linear rate of approximately 3.5% per year beyond 15 years after transplant. However, it does not appear that there is a point where the slope of the survival curve decreases to reach that of the general population. Risk factors for 1-year mortality include the requirement of dialysis or prolonged mechanical ventilation at the time of transplant, having an infection treated with intravenous antibiotics within 2 weeks of transplant, requirement of short-term extracorporeal mechanical circulatory support, adults with congenital heart disease, preoperative use of a pulsatile ventricular assist device, recipient age, donor age, donor heart ischemic time, donor body mass index (inverse), transplant center volume (inverse), recipient pulmonary artery diastolic pressure, and recipient pretransplant bilirubin and creatinine levels.

At 7 years post-transplant, approximately 90% of recipients have no functional limitations, and many have returned to full-time work. In the first year after transplantation, non-cytomegalovirus infection, graft failure, and acute rejection are the most common causes of death. After 5 years, allograft vasculopathy accounts for 33% of deaths, followed by malignancies (23%) and non-cytomegalovirus infections (11%). Post-transplant morbidities remain significant. By 10 years after transplantation, 99% of survivors have hypertension, 14% have severe renal insufficiency, 93% have hyperlipidemia, 37% have diabetes, and 53% have angiographic allograft vasculopathy.

MECHANICAL CIRCULATORY SUPPORT DEVICES

Over the past 20 years, mechanical circulatory support devices (MCSDs) have been developed with the goal of supporting patients with advanced heart failure as a bridge to transplantation, bridge to recovery, and alternative to transplantation. MCSDs are defined as mechanical pumps that assist or replace the left, right, or both ventricles of the heart to pump blood. The current generation of devices allows a spectrum of support ranging from short- to intermediate- to long-term duration. Depending on hemodynamic parameters, devices can be tailored for partial or complete left ventricular support, right ventricular support, or biventricular support. Device positions range from paracorporeal pumps, to intracorporeal pumps with transcutaneous drive lines, to completely implantable systems. Device technology has also advanced, becoming progressively smaller, more reliable, less thrombogenic, and with lower infection risks. First-generation devices rely mostly on large pneumatic or electric drives, second-generation on axial flow technology, and third-generation, which are just beginning clinical trials, primarily on magnetically levitated drives.

Patient Selection and Indications

Patient selection remains paramount to success with MCSDs, and a multidisciplinary approach should be utilized. Indications for mechanical circulatory support are similar to heart transplantation. Clinical indications for MCSD are both acute and chronic (Fig. 24-3). Acute indications include refractory cardiogenic shock after myocardial infarction, acute myocarditis, and failure to wean from cardiopulmonary bypass. The use of short-term MCSDs to treat acute heart failure falls outside the scope of this chapter and will not be discussed further, but it should be mentioned that MCSDs can be used with acceptable results in these patient populations at experienced centers.

Chronic indications are similar to those of heart transplantation and include ischemic cardiomyopathy, idiopathic cardiomyopathy, valvular cardiomyopathy, and congenital heart disease. Generally accepted hemodynamic criteria for MCSD in these patients include NYHA class IV heart failure refractory to medical therapy, cardiac index less than 2 L/min/m^2, pulmonary capillary wedge pressure greater than 25 mm Hg, systolic blood

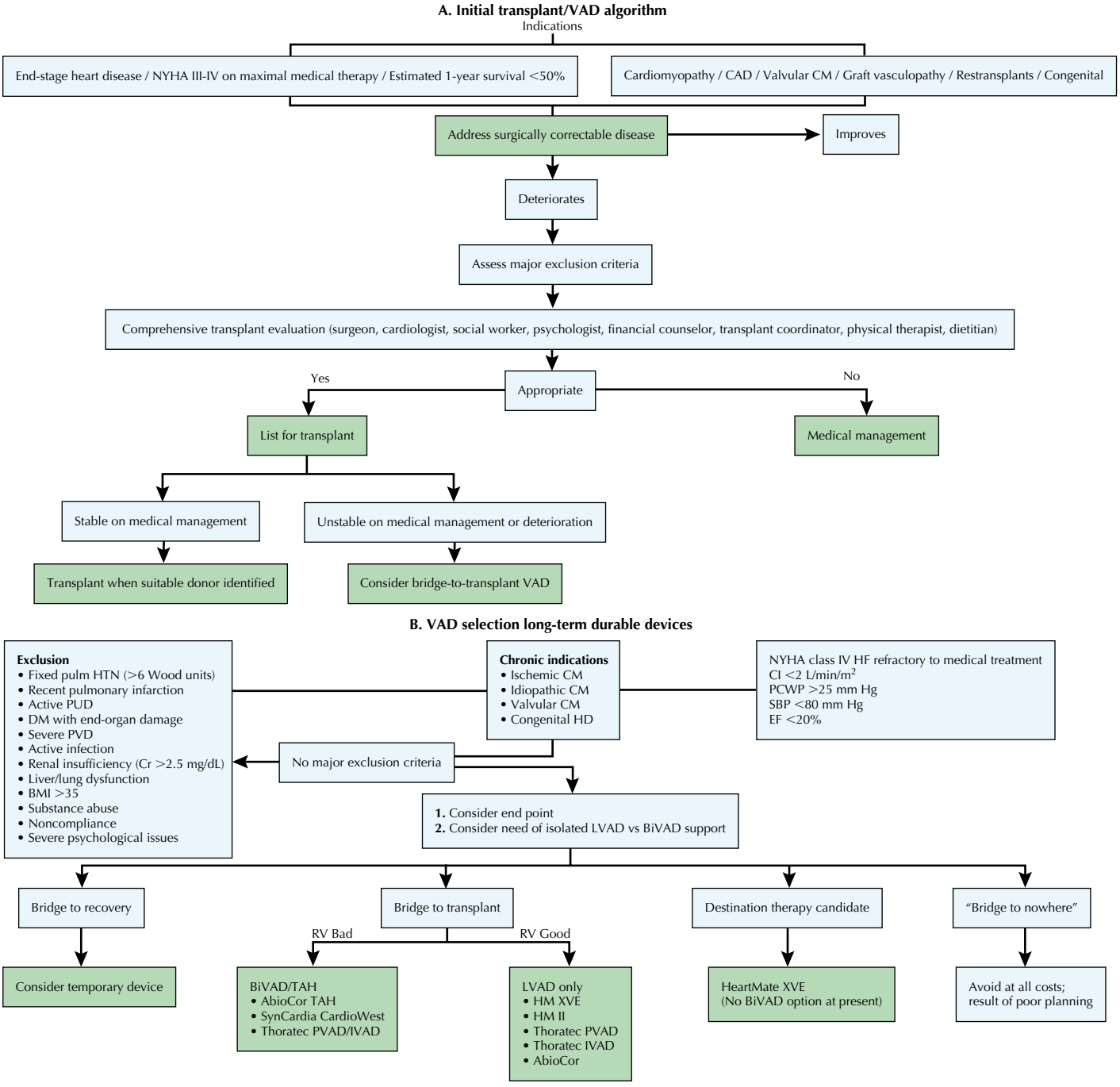


Figure 24-3 *Ventricular assist device selection.* BiVAD, biventricular assist device; BMI, body mass index; CAD, coronary artery disease; CI, cardiac index; CM, cardiomyopathy; Cr, creatinine; DM, diabetes mellitus; EF, ejection fraction; HD, heart disease: HF, heart failure; HM, HeartMate; HTN, hypertension; IVAD, implantable ventricular assist device; LVAD, lead ventricular assist device; NYHA, New York Heart Association (class); PCWP, pulmonary capillary wedge pressure; PUD, peptic ulcer disease; Pulm, pulmonary; PVAD, paracorporeal ventricular assist device; PVD, peripheral vascular disease; RV, right ventricle; SBP, systolic blood pressure; TAH, total artificial heart; VAD, ventricular assist device; XVE, extended lead vented electric.

pressure less than 80 mm Hg, and an ejection fraction of less than 20%. Exclusion criteria for MCSD in these patients remain a subject of debate but generally include evidence of fixed pulmonary hypertension (>6 Wood units), recent pulmonary infarction, active peptic ulcer disease, diabetes with end-organ damage, severe peripheral vascular disease, active infection, renal insufficiency (creatinine >2.5 mg/dL), significant liver or lung dysfunction, recent malignancy, excessive obesity (body mass index >35), active substance abuse, history of noncompliance, and severe psychosocial issues.

Patients with chronic indications for MCSD can be considered for a long-term, or durable, device. An end point for

Table 24-1 FDA-Approved Durable Mechanical Circulatory-Assist Devices Currently in Use

Company	Device	Support	Position	Type of FDA Approval
Abiomed	AbioCor Total Artificial Heart	Total artificial heart	Intracorporeal	Approved under a Humanitarian Device Exemption for those who are not transplant candidates and not LVAD destination therapy candidates
SynCardia Systems Inc.	SynCardia CardioWest	Total artificial heart	Intracorporeal	Approved as a bridge to transplant in patients at risk for imminent death with biventricular failure
Thoratec Corporation	Thoratec PVAD	Left and right	Extracorporeal	Approved for left, right, or biventricular support as a bridge to transplantation
	Thoratec IVAD	Left and right	Intracorporeal	Approved for left, right, or biventricular support as a bridge to transplantation (only biventricular device approved for home discharge)
	HeartMate XVE	Left	Intracorporeal	Approved as a bridge to transplantation and as destination therapy for those who are not transplant candidates
	HeartMate II	Left	Intracorporeal	Approved as a bridge to transplantation

FDA, U.S. Food and Drug Administration; IVAD, implantable ventricular assist device; LVAD, left ventricular assist device; PVAD, paracorporeal ventricular assist device; XVE, extended lead vented electric.

mechanical circulatory support should be considered preoperatively, with the caveat that the end point can change depending on patient status after device implantation. Possible end points include bridge to recovery, bridge to transplantation, and destination therapy (alternative to transplantation). For example, one may intend a device to be a bridge to recovery and find that cardiac function does not improve; these patients are then often candidates for consideration for either bridge-to-transplantation or destination therapy. We would caution against the use of durable devices in the acute setting before a full evaluation has been completed to avoid the dreaded end point of "bridge to nowhere."

FDA-Approved, Long-Term Durable Mechanical Circulatory Support Devices

Devices for long-term durable circulatory support that have been approved by the U.S. Food and Drug Administration (FDA) are shown in Table 24-1.

ABIOCOR

The AbioCor (Abiomed, Inc., Danver, MA) is approved by the FDA under a Humanitarian Device Exemption for use in patients who are not transplant candidates and not LVAD destination therapy candidates. It is implanted selectively at only a few centers in the United States. The device is a total artificial heart employing transcutaneous energy transmission. Thromboembolic and bleeding complications have been high with this device, and its use is limited.

SYNCARDIA CARDIOWEST

The SynCardia CardioWest (SynCardia Systems, Inc., Tucson, AZ) device is a temporary total artificial heart, the modern version of the Jarvik 7 artificial heart first implanted into Barney Clark in 1982. It is approved for use as a bridge to transplant for transplant-eligible patients dying from end-stage biventricular failure. This biventricular, pneumatic, pulsatile blood pump completely replaces the patient's native ventricles and all four cardiac valves orthotopically. In a nonrandomized prospective study at five U.S. centers, 81 patients received the artificial heart device with a rate of survival to transplantation of 79%, and overall 1-year survival of 70%. Bleeding events occurred in 62% of patients, infectious events in 77%, and neurologic events in 27%.

THORATEC PARACORPOREAL AND IMPLANTABLE VENTRICULAR ASSIST DEVICES

The Thoratec Paracorporeal Ventricular Assist Device (PVAD; Thoratec Corp., Pleasanton, CA) has been a mainstay of mechanical circulatory support programs. Based on designs from the 1970s, it has been approved as a bridge to transplantation since 1995. It can be used in the right, left, or biventricular positions. Relatively easy to implant, it can be used in a wide range of patient sizes given the paracorporeal location of the ventricles. It is connected by inflow cannulas to the right atrium and/or left ventricular apex and outflow cannulas to the pulmonary trunk and/or aorta. These cannulas exit the skin in the epigastrium, are connected to one or more pneumatically driven pumps containing mechanical inflow and outflow valves, and lie on the patient's abdomen. Although patients can be ambulated with this device, its paracorporeal position limits its wide-ranging applicability and appeal. The Implantable Ventricular Assist Device (IVAD; Thoratec Corp.) is similar to the Thoratec PVAD system, although the ventricles in the IVAD are implantable to allow for patient discharge with biventricular support. In a study of 38 patients receiving the IVAD device, 18 patients were discharged home. Support to successful outcome was 70% for those treated as a bridge to transplantation.

HEARTMATE XVE

The HeartMate XVE (Thoratec Corp.) is an implantable, electrically driven device that can fully sustain circulation. The inflow cannula connects to the left ventricular apex, and the outflow cannula connects to the aorta. The pump is implanted

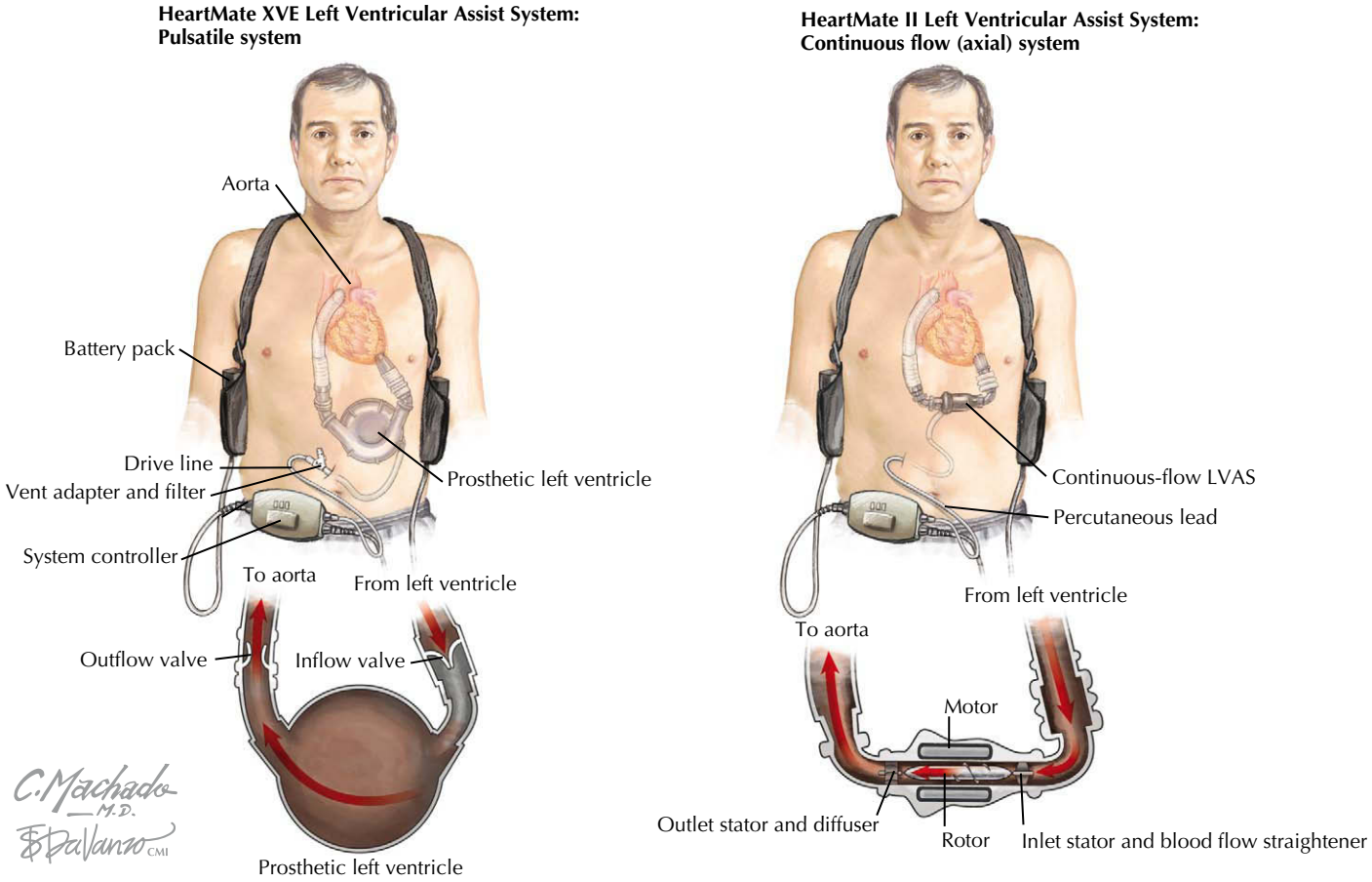


Figure 24-4 *HeartMate XVE and II left ventricular assist systems.* LVAS, left ventricular assist system; XVE, extended lead vented electric.

in an abdominal wall pocket, and a single transcutaneous cable exits the right epigastrium and connects to a wearable external driver (Fig. 24-4). The patient can be fully mobile while wearing the portable controller and two rechargeable batteries. Many patients have been supported more than 1 year with this device. Its notable feature is a "flocked" surface lining the pump chamber that promotes formation of a pseudointima, which reduces the need for anticoagulation and is associated with fewer neurologic events than the other devices. It has been approved as a bridge to transplantation since 1998, and it received FDA approval in 2003 for use as destination therapy in patients with intractable stage IV heart failure who are not candidates for transplantation. In the destination therapy trial, 129 patients with end-stage heart failure who were not cardiac transplant candidates were randomized to either HeartMate XVE support or optimal medical management. Survival rates at 1 year were 52% in the LVAD group and 25% in the medical therapy group. Survival of the device group was limited primarily by device-related complication, including a high rate of infection and device-related failure.

HEARTMATE II

The HeartMate II (Thoratec Corp.) was developed to overcome some of the limitations of pulsatile volume-displacement devices, such as the HeartMate XVE (including large pump size and limited long-term mechanical durability). The HeartMate II device employs continuous-flow, rotary-pump technology (see Fig. 24-4). One advantage of these pumps is a smaller size, with the potential to extend MCSD therapy to smaller patients (adolescents and some women). Another advantage is the potential for greater durability given that this device has only a single moving part (the rotor). Implantation is similar to the HeartMate XVE; however, a much smaller abdominal wall pocket is needed due to the smaller device size. In a prospective multicenter trial without a concurrent control group, 133 patients underwent implantation of the HeartMate II device. The principal outcome (transplant or alive at 6 months) was reached in 75% of patients, and the incidences of device failure and infection were lower than in the HeartMate XVE destination therapy trial. Given these results, this device was recently approved by the FDA for use as a bridge to transplantation. A destination therapy trial is under way.

Results from the Interagency Registry for Mechanically Assisted Circulatory Support

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, funded by the U.S. National Heart, Lung and Blood Institute (NHLBI), is a registry for patients who receive durable FDA-approved MCSDs for treatment of advanced heart failure. It was established to advance

understanding and application of mechanical circulatory support so as to improve the duration and quality of life for individuals with advanced heart failure. It represents a unique collaboration of the NHLBI as the funding and scientific support agency, the FDA as the regulatory agency, and the Center for Medicaid and Medicare Services as the federal reimbursement agency, to establish a common language through which benefit and progress with respect to these devices can be expressed.

INTERMACS went live on June 23, 2006, and as of December 31, 2007, 89 centers were able to enroll patients into its database. The first report of INTERMACS was released in November 2008. It is important to note that this report only represents recipients of pulsatile devices, since the HeartMate II had not yet been approved by the FDA during this reporting period.

During the first 18 months of accrual, 420 patients undergoing MCSD were enrolled. Patients were enrolled under four basic indications: bridge to transplantation, bridge to recovery, destination therapy, and bridge to candidacy. The actuarial survival for the entire cohort was 90% at 1 month and 56% at 1 year. One-year actuarial survival for destination therapy patients was 61%, and those requiring isolated LVAD support had 67% 1-year survival. Preoperative risk factors for early death were critical cardiogenic shock, older age, ascites at the time of implant, higher level of bilirubin, and placement of a biventricular assist device or total artificial heart. Interestingly, the initial "strategy" at implant had no discernible effect on survival (bridge to transplant vs. bridge to recovery vs. bridge to candidacy).

FUTURE DIRECTIONS

Cardiac transplantation is an established, safe, durable, and reliable therapy for patients with end-stage heart disease. Its application is limited only by an inadequate supply of donor organs, mandating careful selection of recipients to ensure the best results in the use of this scarce resource. Initiatives for improvements in cardiac transplantation include development of a more scientific method to evaluate heart recipients and donors through development of a Heart Allocation Score and a Donor Risk Index. In addition, there are initiatives to standardize donor management among the regional Organ Procurement Organizations (OPOs), since donor selection and management varies widely geographically with cardiac donation rates ranging from 4% to 60%, depending on the OPO. Advances in immunosuppression and immunomodulation will probably occur in the areas of co-stimulatory blockade and modification of antibody-mediated rejection. New research suggests that B-cell regulation, in addition or as opposed to T-cell regulation, affects the development of chronic allograft vasculopathy. However, drugs to target these mechanisms remain in their infancy and require better understanding before they can be used clinically. Unfortunately, despite early enthusiasm, stem cell therapy for advanced heart failure remains far from a clinical reality.

MCSDs continue to evolve. The new, smaller rotary pumps seem to have increased durability and lower infection rates than the pulsatile flow devices. However, the outcomes of trials utilizing these devices in the setting of destination therapy remain to be published. Future developments in MCSDs will undoubtedly continue, especially from the aspects of decreasing infections and thromboembolic events. Percutaneously placed or peripherally placed ventricular assist devices that either fully or partially support the patient are also possibilities, perhaps moving the MCSD therapy to "less sick" patients before they progress to refractory heart failure. Given the epidemic of heart failure, research interest and clinical activity will continue, and it is likely that the future holds significant advances.

ADDITIONAL RESOURCE

Baumgartner WA, Reitz BA, Achuff SC, eds. *Heart and Heart-Lung Transplantation.* Philadelphia: W.B. Saunders; 1990.

A comprehensive review of heart transplantation from the leaders in the field.

EVIDENCE

Deng MC, Naka Y. *Mechanical Circulatory Support Therapy in Advance Heart Failure.* London: Imperial College Press; 2007.

State-of-the-art overview of MCSDs and their role in the care of patients with advanced heart failure from leaders in the field at Columbia University in New York, NY.

International Society for Heart and Lung Transplantation. Available at: <http://www.ishlt.org>; The Scientific Registry of Transplant Recipients. Available at: <http://www.ustransplant.org>; United Network for Organ Sharing. Available at: <http://www.unos.org>; Accessed 23.02.10.

Useful websites for information about U.S. organ donation, trends, and outcomes

Kirklin JK, Naftel DC, Stevenson LW, et al. INTERMACS database for durable devices for circulatory support: first annual report. *J Heart Lung Transplant.* 2008;27:1065-1073.

First report of the INTERMACS database. INTERMACS is funded by the U.S. NHLBI. It was established to advance the understanding and application of mechanical circulatory support so as to improve the duration and quality of life for individuals with advanced heart failure. It represents a unique collaboration of the NHLBI as the funding and scientific support agency, the FDA as the regulatory agency, and the Center for Medicaid and Medicare Services as the federal reimbursement agency, to establish a common language through which benefit and progress with respect to these devices can be expressed.

Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med.* 2007;357:885-896.

Report showing that a continuous-flow LVAD can provide effective hemodynamic support for a period of at least 6 months in patients awaiting heart transplantation, with improved functional status and quality of life. This report led to FDA approval of the HeartMate II device as a bridge to transplantation in April 2008.

Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart disease. *N Engl J Med.* 2001;345:1435-1443.

Seminal article showing a survival benefit of LVADs in patients with advanced heart failure who are not candidates for heart transplantation as compared with optimal medical management. This report led to FDA approval of the HeartMate XVE device as destination therapy.

Taylor DO, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-fifth Official Adult Heart Transplant Report—2008. *J Heart Lung Transplant.* 2008;27:943-956.

Most recent registry report from the International Society for Heart and Lung Transplantation.

Stress-Induced Cardiomyopathy

25

Christopher D. Chiles and Charles Baggett

Stress-induced cardiomyopathy represents a syndrome of transient left ventricular (LV) dysfunction from a variety of psychological or physiologic stressors. Patients in the critical care setting are particularly vulnerable, but ambulatory patients subject to severe emotional distress may also develop stress-induced cardiomyopathy. In the intensive care setting, sepsis, respiratory failure, intracranial hemorrhage, and pancreatitis are a few of the described precipitators. The most recognized form of stress-induced cardiomyopathy is takotsubo cardiomyopathy. The majority of this chapter focuses on this specific pattern of cardiomyopathy.

Takotsubo cardiomyopathy was originally described in the early 1990s. The name "takotsubo" stems from a narrow-necked Japanese fishing pot used for trapping octopi that resembles findings seen on the left ventriculogram in individuals with this entity (Fig. 25-1). Subsequent reports have documented the syndrome in the United States and Europe, where it is also known as *transient LV apical ballooning* and colloquially as "*broken heart syndrome*."

Takotsubo cardiomyopathy affects women more often than men, with a mean age of 62 to 75 years, and accounts for roughly 2% of suspected acute coronary syndrome cases. The prognosis is favorable, with an estimated in-hospital mortality rate of 1% and a low rate of recurrence.

ETIOLOGY AND PATHOGENESIS

Although numerous associations exist between putative etiologies and stress-induced cardiomyopathy, the pathogenesis of disease is not well understood. This is the case even for takotsubo cardiomyopathy, probably the best studied of the stress-induced cardiomyopathies. Because a variety of clinical circumstances have been temporally associated with stress-induced cardiomyopathy, it has been proposed that mediators such as excess catecholamines, histamines, and/or cytokines—resulting from a variety of stresses—could cause coronary artery spasm, microvascular dysfunction, or direct myocardial depressant effects. Any combination of these could result in the transient ECG changes, depressed LV function, and elevated cardiac biomarkers that characterize stress-induced cardiomyopathy.

Observational studies indicate that the majority of cases of takotsubo cardiomyopathy are preceded by either emotional (14% to 38%) or physiologic (17% to 77%) stress. Such an association would be consistent with the notion that increased catecholamine levels could cause microvascular dysfunction or myocardial toxicity. Four studies have documented elevated plasma norepinephrine levels at presentation in 26 of 35 patients with takotsubo cardiomyopathy. Another report measured the magnitude of plasma catecholamine release in takotsubo cardiomyopathy compared to Killip class III myocardial infarction (MI) patients. Concentrations of both epinephrine (1264 vs. 376 pg/mL) and norepinephrine (2284 vs. 1100 pg/mL) were higher in takotsubo cardiomyopathy. Further support for a causative effect of catecholamines, and resulting microvascular dysfunction, includes findings of transient myocardial perfusion abnormalities consistent with stunned myocardium or multivessel coronary artery vasospasm in patients with takotsubo cardiomyopathy. Additionally, endomyocardial biopsy data show histologic signs of catecholamine toxicity.

CLINICAL PRESENTATION

Many patients with stress-induced cardiomyopathy present with severe LV dysfunction and are, as a result, critically ill. Symptoms on presentation may include dyspnea, chest pain, or ventricular arrhythmias.

The most common chief complaint in takotsubo cardiomyopathy is chest pain at rest (33% to 71%), with shortness of breath, syncope, and shock also reported. Important in the clinical presentation may be the history of severe emotional distress, such as death of a family member, or other significant psychological stress. Chronic obstructive pulmonary disease exacerbation, panic attack, arguments, and other emotionally charged situations have been reported as triggering scenarios. Cardiogenic pulmonary edema may develop, particularly with fluid resuscitation in the setting of sepsis, pancreatitis, trauma, or the postoperative period—settings consistent with the diagnosis of stress-induced cardiomyopathy.

ECG findings typically mimic those in ST-segment elevation MI (STEMI) or other forms of acute coronary syndrome. The presentation of stress-induced cardiomyopathy may also result in ECG changes similar to those seen in intracranial hemorrhage, stroke, or head trauma; deep symmetric T-wave inversions in the precordial leads with a prolonged QT interval have been associated with stress-induced cardiomyopathy in some reports. Acute systolic heart failure (3% to 46%) and dynamic intraventricular obstruction due to hyperdynamic basal segments (13% to 18%) may also be part of the presentation.

DIFFERENTIAL DIAGNOSIS

Stress-induced cardiomyopathy typically presents with respiratory distress or pulmonary edema, in conjunction with LV dysfunction, ECG abnormalities, and elevated cardiac biomarkers. The clinical presentation of takotsubo cardiomyopathy is similar to STEMI.

Acute coronary syndromes are far more common than stress-induced cardiomyopathy. For this reason, the clinician evaluating a patient with a recent history of emotional or physical stress should still consider the likelihood that the patient's underlying physiology is that of ST-elevation or non-ST elevation MI. The diagnosis of stress-induced cardiomyopathy most often involves ruling out significant coronary artery disease by angiography. Acute pulmonary embolism should also be considered. The possibility of myocarditis may be more difficult to distinguish from takotsubo cardiomyopathy at times. Either the

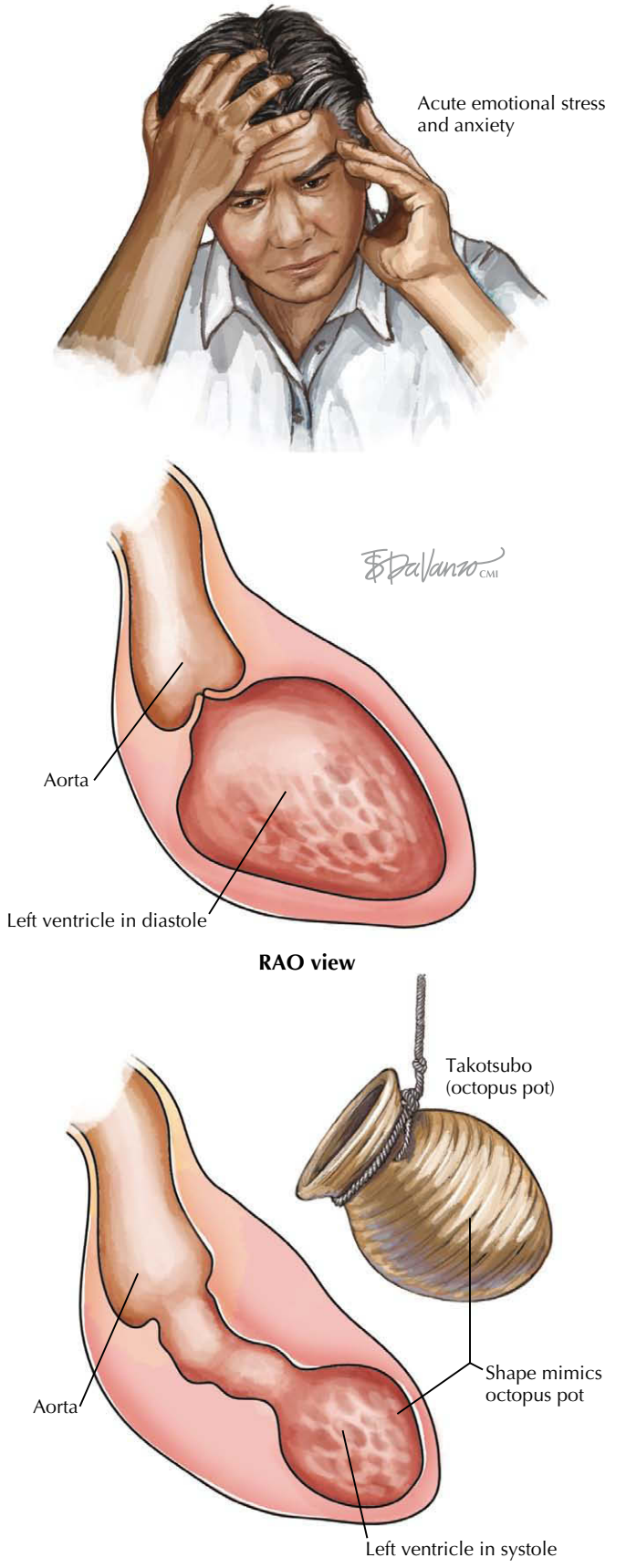


Figure 25-1 *Octopus pot.* RAO, right anterior oblique.

characteristic pattern of wall motion abnormality or the rapidly improving clinical course will distinguish takotsubo or any stress-induced cardiomyopathy from an acute coronary syndrome or myocarditis.

DIAGNOSTIC APPROACH

The diagnosis of stress-induced cardiomyopathy depends upon a history of a severe stressor and the lack of evidence to support the diagnosis of an acute coronary syndrome. The appropriate history permits the clinician to then pursue the diagnosis of stress-induced cardiomyopathy using appropriate diagnostic studies.

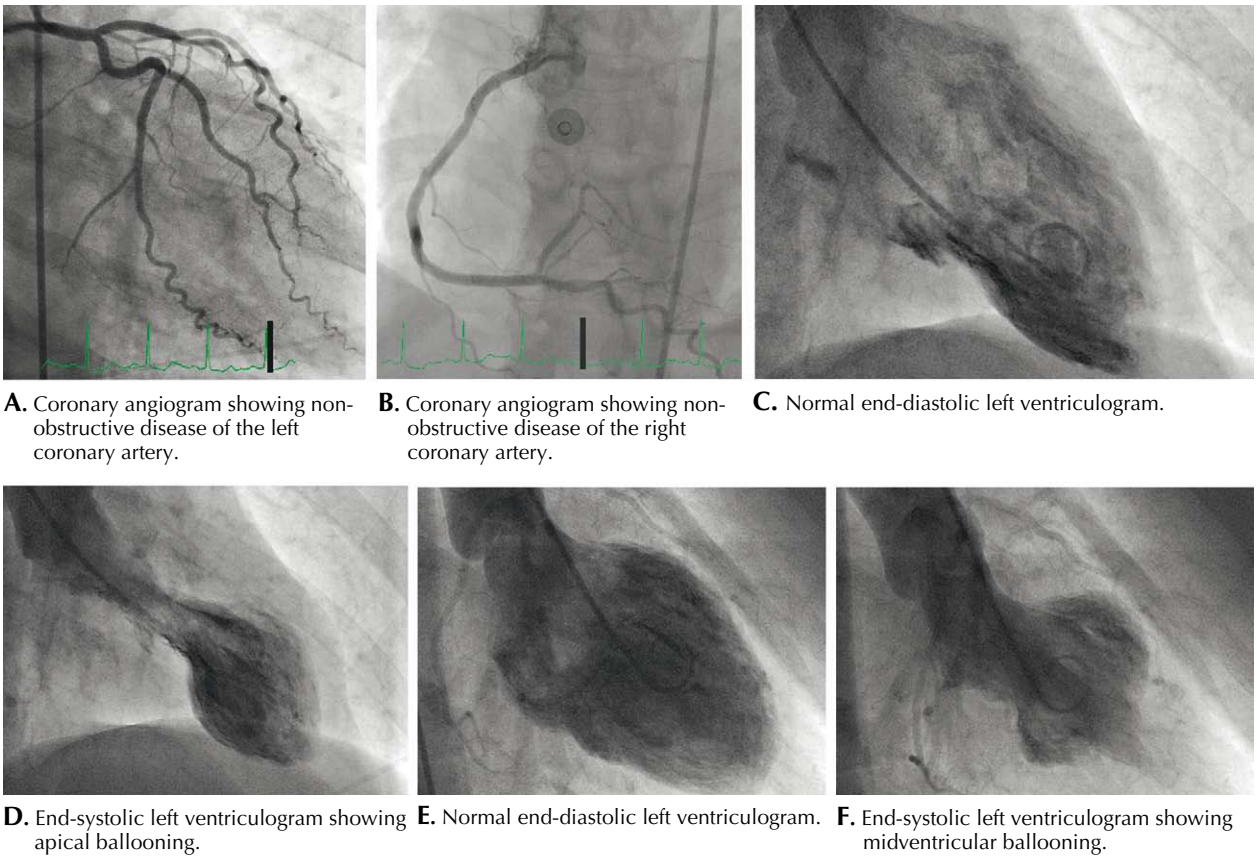
In the spectrum of stress-induced cardiomyopathy, the diagnosis of takotsubo cardiomyopathy is best characterized based on criteria developed at the Mayo Clinic. If all four of the below criteria are met, the diagnosis of takotsubo cardiomyopathy can be confirmed.

1. Transient akinesis or dyskinesis of the LV apical and midventricular segments with regional wall motion abnormalities extending beyond a single epicardial vascular distribution
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3. New ECG abnormalities (either ST-segment elevation or T-wave inversion)
4. Absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, obstructive coronary artery disease, hypertrophic cardiomyopathy, or myocarditis

ECG

As noted, ECG is an important initial diagnostic tool in stress-induced cardiomyopathy. The most common ECG abnormalities are ST-segment and T-wave abnormalities. Findings range from nonspecific ST-segment and T-wave changes to deep, inverted T waves with concomitant QT prolongation or ST-segment elevation and/or depression in a pattern similar to that seen in acute MI.

ST-segment elevation at presentation is reported in greater than 81% of takotsubo cardiomyopathy cases. Anterior ST changes are more common than inferior or lateral ST abnormalities. Additional findings may include right and left bundle branch blocks, T-wave inversions, pathologic Q waves, and prolonged corrected QT segments. Ogura and colleagues (2003) compared specific 12-lead ECG findings in takotsubo cardiomyopathy and acute anterior MI. Q waves and inferior lead reciprocal changes were more common in acute anterior MI than in takotsubo cardiomyopathy. T-wave inversion in precordial leads, a ratio of ST-segment elevation in V_4 to V_6 and V_1 to V_3 of greater than 1.0, and QT dispersion were more common in takotsubo cardiomyopathy. Absence of inferior lead reciprocal changes combined with the ratio of ST-segment elevation in V_4 to V_6 and V_1 to V_3 was the most powerful predictor of takotsubo cardiomyopathy, with a specificity of 100% and overall accuracy of 91%.



A. Coronary angiogram showing nonobstructive disease of the left coronary artery.

B. Coronary angiogram showing nonobstructive disease of the right coronary artery.

C. Normal end-diastolic left ventriculogram.

D. End-systolic left ventriculogram showing apical ballooning.

E. Normal end-diastolic left ventriculogram.

F. End-systolic left ventriculogram showing midventricular ballooning.

Figure 25-2 *Takotsubo cardiomyopathy.*

Cardiac Biomarkers

The incidence of positive cardiac biomarkers at presentation in patients with takotsubo cardiomyopathy ranges between 56% and 100%. Troponin I or T is the most sensitive biomarker. In two case series, 100% of individuals with takotsubo cardiomyopathy were found to be troponin-positive. The most common pattern of cardiac biomarker elevation is a small, rapid increase with peak levels typically measured at presentation. While the incidence of biomarker elevation is less well described in other forms of stress-induced cardiomyopathy, many patients with critical illness–related cardiomyopathy have modest rises in cardiac troponin.

Cardiac Catheterization

Takotsubo cardiomyopathy typically presents with chest pain and ST-segment elevation on electrocardiogram, necessitating emergent diagnostic coronary angiography. Even when the diagnosis of takotsubo cardiomyopathy is suspected, initial management should proceed in accordance with current STEMI guidelines.

According to a review of multiple case series, all patients with takotsubo cardiomyopathy had either no angiographically detectable coronary artery disease or nonobstructive coronary artery disease defined as a stenosis of less than 50%. The classic description of takotsubo cardiomyopathy on left ventriculogram is apical dyskinesis in the absence of obstructive coronary artery disease (Fig. 25-2A–D). However, midventricular dyskinesis is also recognized as an atypical presentation accounting for up to 40% of takotsubo cardiomyopathy cases (Fig. 25-2E and F). Coronary angiography has also been utilized in some cases to show inducible multivessel coronary artery vasospasm and abnormal flow (based on thrombolysis in MI frame counts) in all three epicardial coronary arteries.

Intensive care unit patients with multisystem failure and stress-induced cardiomyopathy may be unable to safely undergo coronary angiography. Patients with trauma, intracranial bleeding, pancreatitis, and the like are poor candidates for revascularization, with its concurrent use of anticoagulation. In these settings, the risk-to-benefit ratio of cardiac catheterization precludes proceeding with an invasive evaluation. Importantly, in many of these cases the clinical presentation may not mimic STEMI as in takotsubo cardiomyopathy; thus, the sense of urgency for angiography is mitigated.

Transthoracic Echocardiography

Transthoracic echocardiography is recommended for initial evaluation and serial follow-up of LV function with suspected

stress-induced cardiomyopathy. In takotsubo cardiomyopathy, a mean LV ejection fraction (EF) ranges between 39% and 49%, but may be as low as 20%. The EF rapidly increases over days to weeks to a mean follow-up LV EF of 60% to 76%. The return of normal global and regional LV function can confirm the diagnosis of stress-induced cardiomyopathy.

Cardiac Magnetic Resonance Imaging

Routine use of cardiac MRI is not generally required although it has been recently examined in clinical studies. One study of takotsubo cardiomyopathy patients who underwent cardiac MRI showed 26% had right ventricular (RV) wall abnormalities. Those with RV dysfunction had an overall lower LV EF than did patients with normal RV function (40% to 48%). Follow-up cardiac MRI showed typical improvement of LV function as well as resolution of RV function.

Endomyocardial Biopsy

Four studies evaluated endomyocardial biopsy in the acute phase of takotsubo cardiomyopathy, and each found no convincing evidence of myocarditis. Biopsy is not routinely recommended in any form of stress-induced cardiomyopathy.

MANAGEMENT AND THERAPY

Optimal Treatment

There are limited data on optimal medical management for stress-induced cardiomyopathy. Observations based on prospective and retrospective case series support the use of a medical regimen analogous to that recommended for treatment of patients with cardiomyopathy and systolic dysfunction. This includes initiation of a β-blocker (when the patient is euvolemic), an angiotensin-converting enzyme inhibitor, aspirin, and diuretics, as needed. Marked improvement in LV dysfunction over days to weeks is typical for patients with stress-induced cardiomyopathy. Anticoagulation to prevent thrombosis from significant LV dysfunction may be considered until LV function improves. Patients should be monitored for atrial and ventricular arrhythmias, heart failure, and mechanical complications while in the hospital.

Avoiding Treatment Errors

Hypotension in patients with takotsubo cardiomyopathy is rare. Nevertheless, this clinical scenario warrants the timely evaluation for an intraventricular pressure gradient by either left heart catheterization or transthoracic echocardiography. Such a gradient can occur with apical and midventricular systolic dyskinesis if the LV base is hyperkinetic. Prompt diagnosis of this complication is important, because treatment differs from hypotension in the absence of intraventricular obstruction. In this setting, treatment must focus on maintaining an adequate end-diastolic LV volume and decreasing the intraventricular pressure gradient. Maintenance of end-diastolic LV volume is achieved by avoiding excessive diuresis and fluid resuscitation if pulmonary congestion is absent. β-blocker therapy increases diastolic filling time and may decrease the magnitude of the gradient. β_1 agonists (particularly dobutamine) should be specifically avoided in the setting of hypotension with dynamic intraventricular obstruction. If hemodynamics do not improve with fluids and β-blockers, then phenylephrine can increase mean arterial pressure and reduce the gradient. Finally, placement of an intra-aortic balloon pump can mechanically support the patient, although there is a small possibility that decreased afterload can worsen the interventricular gradient.

FUTURE DIRECTIONS

Diagnosis of stress-induced cardiomyopathy depends on meeting criteria (particular biomarker positivity and LV dysfunction) in the presence of an appropriate clinical scenario and the absence of significant coronary artery disease. Advances in imaging may ultimately prove to be valuable tools in assessing stress-induced cardiomyopathy. With recent technologic advances for imaging the coronary arteries (the use of 64-slice coronary CT angiography to exclude significant coronary stenoses) and improved knowledge of the role of catecholamines and other vasoactive molecules, it may be possible to diagnose stress-induced cardiomyopathy more accurately in the future. Nuclear medicine techniques, including ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, could help clarify regional adrenergic receptors in stress-induced cardiomyopathy. A recent rat model of takotsubo cardiomyopathy may provide further insights into the pathogenesis. Studies of the potential role of the endocrine, central neural, and autonomic nervous systems may also be useful.

While much remains to be understood regarding the pathophysiology of stress-induced cardiomyopathy, today's therapeutic approaches are effective. This, combined with the generally favorable prognosis and the likelihood that LV dysfunction typically resolves within weeks, suggests that the most important advances in the future will be in the area of early and accurate diagnosis of stress-induced cardiomyopathy.

ADDITIONAL RESOURCE

"Uptodate" Online Medical Resource. Available at: <http://www.uptodate.com/home/index.html>; 2008 Accessed 23.02.10.

An evidence-based, peer-reviewed medical information resource providing a synthesis of the literature, the latest evidence, and specific recommendations for patient care.

EVIDENCE

Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation.* 2008;118:2754-2762.

Provides details regarding the mouse model of disease and the potential for estrogen replacement as a therapy.

Bybee KA, Kara T, Prasad A, et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-

segment elevation myocardial infarction. *Ann Intern Med.* 2004;141: 858-865.

A review of seven case series that proposes specific Mayo criteria for the clinical diagnosis of takotsubo cardiomyopathy due to its characteristic presentation.

Kurowski V, Kaiser A, von Hof K, et al. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanism, and prognosis. *Chest.* 2007;132:809.

Reports demographic, clinical, and outcomes data on takotsubo cardiomyopathy.

Ogura R, Hiasa Y, Yakahashi T, et al. Specific Findings of the standard 12-lead ECG in patients with 'takotsubo' cardiomyopathy: comparison with the findings of acute anterior myocardial infarction. *Circ J.* 2003;67:687-690.

Describes the 12-lead ECG findings in takotsubo cardiomyopathy and acute anterior MI, and identifies which are most specific and most accurate for the diagnosis of takotsubo cardiomyopathy.

Bradyarrhythmias

Fong T. Leong and J. Paul Mounsey

26

In adults, bradycardia refers to a ventricular rate that is less than 60 bpm. This figure is somewhat arbitrary and does not necessarily connote disease. For instance, it is common to find healthy athletes with resting heart rates of approximately 40 bpm. In general, bradycardia becomes a clinical issue if it correlates with symptoms—syncope, dizziness, exercise intolerance, breathlessness, angina, fatigue, or mental confusion. These correlations can be difficult to establish. Fatigue, for example, is a common complaint and may be merely coincidental with, and not caused by, slow heart rates.

ETIOLOGY AND PATHOGENESIS

It is simplest to regard bradycardia as a manifestation of quite a few noncardiac and cardiac causes (Box 26-1). When due to cardiac causes, bradycardia may be further categorized according to the site(s) of delay or block within the cardiac conduction system: the sinus node, the atrioventricular (AV) node, the bundle of His, and the bundle branches/Purkinje network. Conditions that alter the autonomic inputs to the sinus and AV nodes, diseases that interrupt the blood supply or the electrophysiology of these structures, or drugs that modify the ionic properties of conductive cardiomyocytes can all lead to bradycardia. By far, sinus node dysfunction and AV block (either nodal or infranodal) account for the majority of clinically significant bradyarrhythmias. Reflex-mediated syncope (subtypes of which retard the heart to varying extents) is described in Chapter 31. In this chapter, we focus on the cardiac causes of bradyarrhythmia (Fig. 26-1).

Sinus Node Dysfunction

In sinus node dysfunction (SND) there is delay or loss of impulse propagation from the sinoatrial (SA) node to the atria. Although congenital forms of this condition do occur, SND is mainly a disease of the elderly. The associated bradyarrhythmia is often progressive and also unpredictable in terms of how slow the heart rate may become. In addition, at the time of diagnosis, 17% of patients with SND have coexistent AV node dysfunction. In those with solitary sinus node disease, new AV conduction abnormalities develop at a rate of approximately 2.5% per year.

Four different clinical presentations of SND have been described. These subtypes of SND are not mutually exclusive and may overlap.

INAPPROPRIATE SINUS BRADYCARDIA

Persistent sinus bradycardia that does not improve with exercise is an early sign of SND. On the screening ECG, the PR interval is normal and the QRS complex is narrow, unless there is bundle branch block (BBB) that is either concomitant with the bradycardia or dependent on it (deceleration-dependent BBB).

SINUS ARREST

In sinus arrest, the sinus node fails to depolarize, resulting in an atrial pause. The P-P interval encompassing this pause is not an exact multiple of the basic P-P interval (Fig. 26-2), indicating that the abnormality is not simply a blocked sinus impulse. Sinus pauses exceeding 3 seconds are highly suggestive of SND. Conversely, it is not uncommon to encounter asymptomatic sinus pauses of 2 seconds or less in the well-conditioned athlete or even in normal individuals.

SINOATRIAL EXIT BLOCK

In SA exit block, the SA node does fire automatically, but the impulse either fails to propagate into the atria (because of a conduction barrier within or around the SA node) or does so after a delay. In the former scenario, the atria are not depolarized, and the expected P wave fails to materialize. Like AV block, SA exit block can be graded as first, second, or third degree, with second-degree SA block further classified into Mobitz type I (Wenckebach) or Mobitz type II. Type II SA block is the most common. In this circumstance, the failure of the sinus impulse to exit the node is intermittent, and the atrial pause produced is an exact multiple of the prevailing P-P interval (see Fig. 26-2). In Wenckebach SA block, the P-P interval shortens progressively before the dropped beat. With third-degree SA block, the ECG only records the escape rhythm (see Fig. 26-2). If no P waves are present, it is impossible to distinguish (by ECG criteria alone) third-degree SA block from prolonged sinus arrest. Clinically, this distinction is not important; what matters is whether the patient is symptomatic. In first-degree SA block, there is an abnormally long interval between the sinus impulse and atrial capture. This condition, too, cannot be diagnosed from the surface ECG.

TACHY-BRADY SYNDROME

Also known as *sick sinus syndrome*, tachy-brady syndrome is a common manifestation of SND. Here, the cardiac rhythm is interrupted by alternating periods of supraventricular tachyarrhythmias (most commonly atrial fibrillation) and bradycardia. Typically, the bradycardia is seen immediately after spontaneous termination of the tachycardia, and it may take the form of a prolonged sinus arrest, SA block, or a junctional escape rhythm. Because bradycardia occurs suddenly, patients frequently experience dizziness or syncope. Indeed, the highest incidence of syncope associated with SND probably occurs in this group. Note that it is also possible for tachycardia to be initiated during spontaneous bradycardia or sinus arrest, perhaps because of the increased dispersion of refractoriness when the heart slows down. Some individuals with tachy-brady syndrome have periods of marked tachycardia and other, unassociated periods of marked bradycardia.

Box 26-1 Causes of Bradycardia

Noncardiac Causes

Drugs
β-blockers
Calcium channel blockers
Antiarrhythmic drugs (e.g., amiodarone, ibutilide, flecainide, lidocaine)
Digoxin
Adenosine
Opiate overdose
Lithium
Ivabradine
Clonidine

Neurogenic
Reflex-mediated syncope
Raised intracranial pressure
Increased ocular pressure (e.g., during eye surgery)
Neuromuscular disorders (e.g., myotonic dystrophy, Friedreich's ataxia)
Guillain-Barré syndrome
Dysautonomia (e.g., Shy-Drager syndrome)

Endocrine and Metabolic
Hypothyroidism
Acidosis
Electrolyte abnormalities
Anorexia nervosa
Porphyria

Environmental and Infection-related
Hypothermia
Lyme disease
Chagas disease
Envenomation (e.g., snakebite)
Diphtheria
Acute rheumatic fever
Organophosphate insecticides

Others
Physiologic
Iatrogenic (e.g., following aortic valve replacement or supraventricular tachycardia ablation)
Collagen vascular disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis)
Congenital

Cardiac Causes

Sinus node dysfunction
Atrioventricular node dysfunction
Hisian and infra-Hisian block
Myocardial infarction (especially inferior)
Myocarditis
Myocardial infiltration: cardiac sarcoidosis, hemochromatosis, cardiac amyloidosis, Wegener's granulomatosis

Atrioventricular Block

AV block occurs when there is a delay or nonconduction of an atrial impulse to the ventricles. It can result from normal or abnormal cardiac electrophysiology, can be transient (e.g., following inferior myocardial infarction) or permanent, and can occur at any or several levels of the AV node–His–Purkinje axis. Based on the ECG, AV block may be graded as first, second, or third degree, depending on whether AV conduction is merely delayed, intermittently blocked, or completely blocked. This classification has clinical implications, because the site of AV block (and hence the patient's prognosis) may be inferred with reasonable accuracy from the rhythm. It is important to note that when the atria and ventricles beat independently of each other, AV dissociation occurs (Fig. 26-3). In clinical parlance, this term is applied when the ventricular rate, driven by a subsidiary pacemaker, is the same or faster than the atrial rate. Because of this, the ventricles are functionally refractory to the slower atrial impulses.

FIRST-DEGREE ATRIOVENTRICULAR BLOCK

First-degree AV block is defined as a PR interval greater than 0.2 seconds. Each P wave is followed, after a constant delay, by a QRS complex (see Fig. 26-3). In that sense, the label "AV block" is incorrect, because no P waves are actually "blocked." Because the PR interval reflects the time between the earliest recorded atrial activity and the onset of ventricular depolarization, first-degree AV block can arise from conduction delay in the AV node (the commonest mechanism), abnormally slow intra-atrial conduction (less common), or, even less often, His-Purkinje disease (in which case the evoked QRS complex will be broad). In individuals with dual AV node physiology, transient, abrupt, first-degree AV block may be seen when antegrade conduction jumps from the fast pathway (used normally) to the slow pathway (see Chapter 27). In the presence of concomitant organic heart disease (e.g., cardiac involvement from myotonic dystrophy or aortic root abscess from endocarditis), first-degree AV block may evolve unpredictably into higher degrees of heart block. Serial ECGs over time will reveal if there is progression of the first-degree AV block. Isolated first-degree heart block is benign and carries no increased mortality.

SECOND-DEGREE ATRIOVENTRICULAR BLOCK

In second-degree AV block, there is intermittent interruption of AV conduction, so that some P waves are not followed by QRS complexes. Two types are recognized: Mobitz types I and II.

In Mobitz type I (Wenckebach) AV block, the delay in AV conduction increases with each successive impulse; in other words, the PR interval lengthens with each beat until a P wave is blocked (see Fig. 26-3). After the dropped ventricular beat, AV conduction recovers and the cycle repeats. Although the PR interval increases progressively, the magnitude of increment decreases during the Wenckebach cycle. Typically, the first P wave after the pause is associated with a normal PR interval, whereas the second P wave is associated with the greatest PR increment. When the evoked QRS complex is narrow, the site of Wenckebach AV block is almost always nodal in location. Wenckebach block at the level of the His bundle is rare. Even if the QRS complex is broad, the block is still more likely to be within the AV node, but in this circumstance it is also possible that the block is distal to the bifurcation of the His bundle. Mobitz type I block is often physiologic and can be observed during sleep. Uncommonly, Mobitz I block can be incessant. In this case, symptoms of fatigue or, rarely, syncope may require treatment.

P wave	PR interval	QRS complex and rhythm	Diagnosis
Normal axis and rhythm. Each P wave followed by a QRS	Constant and ≤200 ms	QRS complex generally narrow but may be wide if there is BBB; each QRS preceded by a P wave	Sinus bradycardia
Disappears intermittently and unpredictably	Constant, except for the pause(s)	QRS may be absent, narrow, or broad following the missing P wave, with variation reflecting escape rhythm.	Sinus arrest or exit block (+/− junctional or ventricular escape)
Absent. No fibrillatory waves evident	Not applicable	Narrow and regular	Junctional bradycardia
Normal axis and rhythm. Rate <60/min. Each P wave followed by a QRS	Constant and >200 ms	QRS complex generally narrow but may be wide if there is BBB; each QRS preceded by a P wave.	Sinus bradycardia with 1st degree heart block
Normal axis and rhythm. Rate may be < or ≥60/min. Not every P wave followed by a QRS	Lengthens progressively, until P wave fails to initiate QRS. Pattern then repeats.	QRS complex generally narrow but may be wide if there is BBB; fewer QRSs than Ps; irregular rhythm; QRS complexes 'dropped' in cyclical manner	Sinus rhythm with Mobitz type I (Wenckebach) block
Normal axis and rhythm. Rate may be < or ≥60/min. Not every P wave followed by a QRS	Constant, except for the pause(s). PR after the dropped QRS is same as before.	QRS complex typically wide; fewer QRSs than Ps. QRS rhythm varies according to P/QRS ratio, but is generally regular.	Sinus rhythm with Mobitz type II block
Normal axis and rhythm. Rate may be < or ≥60/min. No relationship between Ps and QRSs	Not applicable as there is no relationship between Ps and QRSs.	QRS complex may be narrow or broad, depending on origin of escape rhythm. QRS < P wave rate. Rhythm is usually regular.	Sinus rhythm with complete heart block
Normal axis and rhythm. Rate <60/min. No relationship between Ps and QRSs	Not applicable as there is no relationship between Ps and QRSs.	QRS complex generally narrow. QRS rate = P wave rate. Regular rhythm	Bradycardia with isorhythmic AV dissociation

Figure 26-1 *Diagnostic algorithm for bradyarrhythmias (QRS rate <60 bpm).* AV, atrioventricular; BBB, bundle branch block.

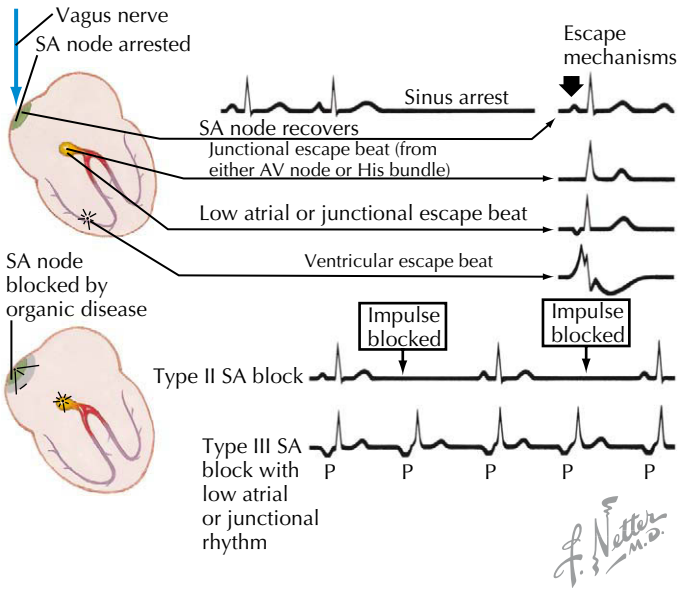
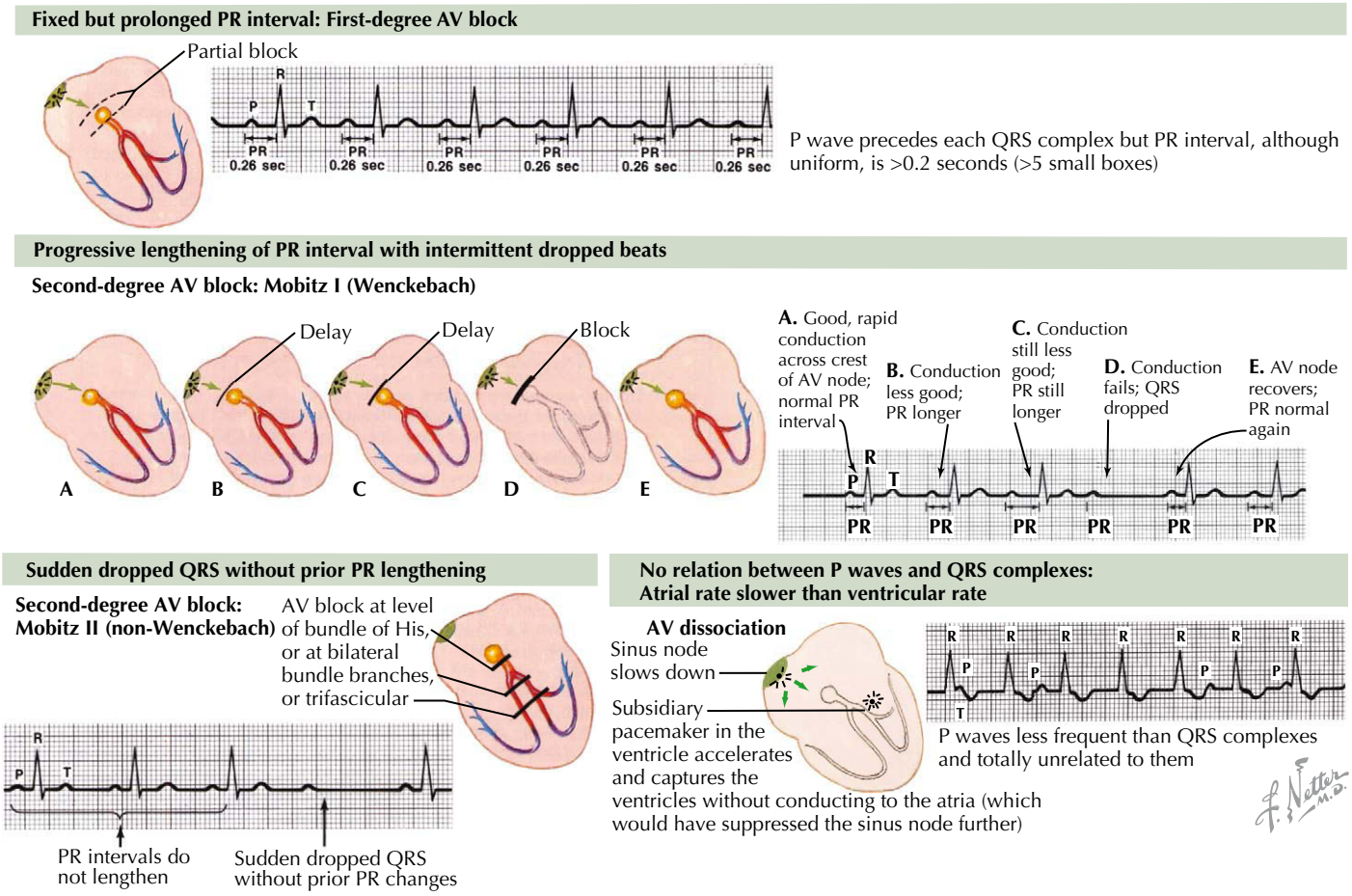


Figure 26-2 *Sinus arrest and sinoatrial exit block.* AV, atrioventricular; SA, sinoatrial.

In Mobitz type II AV block, the PR interval is constant and does not change until the block occurs (see Fig. 26-3). Typically, bifascicular block or BBB is also present—usually right (R) BBB with left anterior fascicular block (LAFB). In a majority of these cases the site of block is at or below the level of the His bundle. When Mobitz type II block is seen with narrow QRS complexes (a rare combination), the block is generally within the bundle of His. Mobitz type II block can be differentiated from a non-conducted atrial ectopic beat by (1) its uniform P-wave configuration, (2) its constant P-P interval, and (3) the observation that the P-P interval encompassing the blocked P wave is twice as long as the prevailing P-P duration. If two or more consecutive atrial beats are blocked but others conduct to the ventricles, then the term *advanced type II AV block* is used. The distinction between Mobitz type I and type II AV block is important because type II block often progresses to complete heart block (thus compromising prognosis), whereas Wenckebach block rarely does so.

The question arises whether it is possible to designate fixed 2:1 AV block as either type I or type II if the basic pattern has only one conducted P wave in it. Although it is not always



Features of two types of atrioventricular block

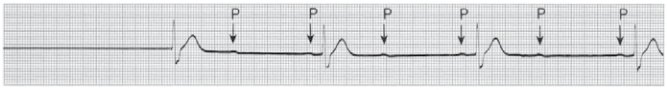
	"High"	"Low"
Site of block	AV node	Bundle of His, bilateral bundle branch, or trifascicular
Type of escape rhythm	Junctional escape rhythm Narrow QRS Adequate rate (40–55 beats/min)	Ventricular escape rhythm Wide QRS Inadequate rate (20–40 beats/min) Risk of asystole
Underlying pathology	Right coronary artery disease, inferior infarction, edema around AV node	Left anterior descending coronary artery disease, large anteroseptal infarction, or chronic degeneration of conduction system
Rhythm before complete block	Preceded by Mobitz I (Wenckebach) second-degree AV block	Preceded by Mobitz II second-degree AV block

Figure 26-3 *Atrioventricular conduction abnormalities.* AV, atrioventricular.

possible to distinguish the two, if the block worsens during exercise or with atropine and improves with vagal stimulation, it is likely to reside below the AV node and hence to be indicative of the type II AV block. The converse observations will be true of type I AV block. In addition, if the PR interval is normal but the QRS complex is broad, type II block is again likely. However, if the PR interval is prolonged and associated with a BBB, or if the PR interval and QRS complex are both normal (Fig. 26-4), then the site of block can only be defined using intracardiac electrode recordings.

COMPLETE OR THIRD-DEGREE AV BLOCK

Third-degree AV block is characterized by the failure of all atrial impulses to reach the ventricles (Fig. 26-5). The site of block can be inferred from the features of the escape rhythm



In the situation in which every other P wave is blocked, it is impossible to tell whether the PR interval is progressively increasing (since there is never more than one completed PR interval at a time). Thus, one cannot differentiate between Mobitz I and Mobitz II, and it is unclear whether the site of the block is at the AV node or in the His–Purkinje system. If this differentiation is clinically vital, intracardiac electrophysiologic study is necessary.

Figure 26-4 *Second-degree atrioventricular block.*

Box 26-2 Fascicular Block

ECG Criteria for Left Anterior Fascicular Block

1. Left axis deviation (–45 degrees or less*)
2. RS pattern in leads II, III, aVF
3. QR pattern in aVL
4. Peak of R wave in aVL precedes peak of terminal R wave in aVR.
5. Peak of initial R wave in lead III precedes peak of initial R wave in lead II.

ECG Criteria for Left Posterior Fascicular Block

1. Right axis deviation (120 degrees or greater)
2. S_IQ_{III} pattern, with RS in lead I and QR complexes in leads II, III, and aVF

*–45 degrees indicates a negative axis.
ECG, electrocardiographic.

distal to the choke point. Complete block of the AV node unmasks an escape pacemaker in the His bundle. In the absence of antecedent BBB, the rhythm produced has (1) narrow QRS complexes, (2) a heart rate of 40 to 60 bpm, and (3) a rate that increases with exercise or atropine. With block at or below the His bundle, the escape rhythm arises from a ventricular pacemaker and (1) has a wide QRS complex, (2) a heart rate of 20 to 40 bpm, and (3) a rate that fails to accelerate with atropine. Note that the escape rate is not necessarily critical to the patient's safety. Instead, it is the site of origin of the escape rhythm that matters. A subsidiary pacemaker distal to the bundle of His can stop at any time (resulting in ventricular standstill) and is vulnerable to overdrive suppression (from, for example, a spontaneous burst of pause-dependent ventricular tachycardia). In contrast, narrow complex escape rhythms are more stable.

CONCEALED HIS EXTRASYSTOLES

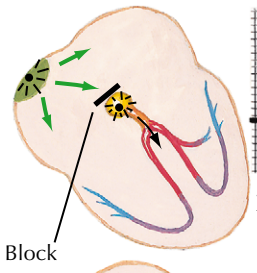
Rarely, premature junctional beats that do not conduct to the atria or the ventricles (and hence remain "concealed" on the surface ECG) may penetrate the AV node retrogradely and cause conduction delay or even blockade of the subsequent atrial beat. This shows as first-degree or Mobitz type II AV block, respectively. Confirmation of this diagnosis requires His bundle recordings.

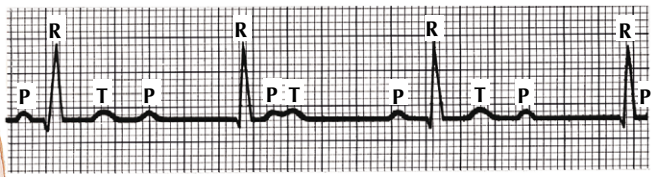
Chronic Multifascicular Blocks

A conduction disturbance of the right bundle branch or one of fascicles of the left (L) bundle branch is also known as a fascicular block (Box 26-2). By this definition, bifascicular block

No relation between P waves and QRS complexes: QRS rate slower than P rate: Third-degree (complete) AV block

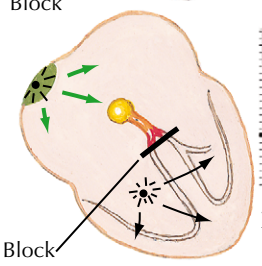
1. Atrial impulse blocked at AV node. Ventricles driven by an escape pacemaker in bundle of His (relatively fast, narrow complex escape rhythm)

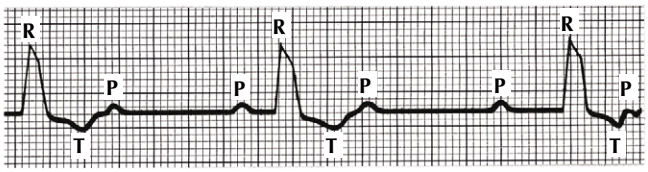




Atria and ventricles depolarize independently. QRS complexes less frequent; regular at 40 to 55 beats/min but normal in shape.

2. Atrial impulses blocked below the His bundle. Ventricles driven by a subsidiary ventricular pacemaker (slow broad complex escape rhythm)





Atria and ventricles depolarize independently. QRS complexes less frequent; regular at 20 to 40 beats/min but wide and abnormal in shape.

Figure 26-5 *Complete atrioventricular (AV) block.*

Table 26-1 Recommendations for Permanent Pacing in Chronic Bifascicular Block

Class	Recommendation	Level of Evidence*
I	Permanent pacemaker implantation is indicated for advanced second-degree AV block or intermittent third-degree AV block.	B
	Permanent pacemaker implantation is indicated for type II second-degree AV block.	B
	Permanent pacemaker implantation is indicated for alternating bundle-branch block.	B
IIa	Permanent pacemaker implantation is reasonable for syncope not demonstrated to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia.	B
	Permanent pacemaker implantation is reasonable for an incidental finding at electrophysiologic study of a markedly prolonged HV interval (≥100 ms) in asymptomatic patients.	B
	Permanent pacemaker implantation is reasonable for an incidental finding at electrophysiologic study of pacing-induced infra-His block that is not physiologic.	B
IIb	Permanent pacemaker implantation may be considered in the setting of neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with bifascicular block or any fascicular block, with or without symptoms.	C
III	Permanent pacemaker implantation is not indicated for fascicular block without AV block or symptoms.	B
	Permanent pacemaker implantation is not indicated for fascicular block with first-degree AV block without symptoms.	B

*Evidence is ranked as: (1) Level A if the data were derived from multiple randomized clinical trials that involved a large number of individuals; (2) Level B if data were derived either from a limited number of trials that involved a comparatively small number of patients or from well-designed data analyses of nonrandomized studies or observational data registries; and (3) Level C if the consensus of experts was the primary source of the recommendation. See Evidence Section for more details.
AV, atrioventricular.

can be associated with any of the following: (1) RBBB + LAFB, (2) RBBB + left posterior fascicular block (LPFB), or (3) LBBB alone. Similarly, disease of all three ventricular fascicles can present as (1) alternating RBBB and LBBB, or (2) RBBB + LAFB alternating with RBBB + LPFB. Confusingly, the latter combinations are not generally referred to as "trifascicular block." Instead, the term *trifascicular block* is commonly used to indicate abnormal PR prolongation with concurrent bifascicular block (the AV node/His bundle regarded as an independent "fascicle"). Terminology aside, multifascicular blocks are clinically relevant because of the small but finite risk (~1% per year) of progression to complete heart block. This risk is lower in individuals who have the common RBBB + LAFB combination, as compared with those who have the rare RBBB + LPFB dyad. Indications for pacing in chronic fascicular block are listed in Table 26-1.

DIAGNOSTIC APPROACH

The clinical evaluation of bradycardia focuses on (1) correlating the documented rhythm disturbance with symptoms and (2) ascertaining the site of conduction block—given the importance of this in predicting the natural history, prognosis, and treatment of the bradyarrhythmia. To this end, a careful patient history and 12-lead ECG of the bradyarrhythmia are absolutely vital. Sometimes it may be necessary to supplement the ECG with an atropine challenge or vagal stimulation to help differentiate nodal from infranodal conduction block. Exercise testing is also valuable because it can provide objective evidence of chronotropic incompetence and can also confirm the level of block in second-degree heart block. When the suspected bradyarrhythmia is intermittent or if symptom correlation is unclear, long-term rhythm recording is necessary. This can be done with an ambulatory Holter recorder (that documents the rhythm continuously for 24–72 hours), a patient-activated event monitor (typically kept by the patient for 1–3 months and activated at the time of symptoms), or an implantable loop recorder (inserted subcutaneously and capable of nonstop rhythm recording for up to 3 years). Very rarely, invasive electrophysiology studies are required, usually because documentation of suspected high-grade AV block as the cause of dizziness or blackouts cannot be obtained noninvasively.

MANAGEMENT AND THERAPY

Optimum Treatment

In the absence of torsades de pointes (see Chapter 31), documented asystole of 3 or more seconds, or a ventricular escape rhythm of less than 40 bpm, asymptomatic bradycardia does not require medical intervention. Symptomatic bradycardia, however, is most often treated with implantation of a permanent pacemaker (Tables 26-1, 26-2, and 26-3). The role of drugs for chronotropic support is limited and is confined to emergency use. Atropine (used during acute resuscitation to abolish vagal slowing of the heart) and isoproterenol (sometimes used until pacing is established) are examples of drugs given for this purpose.

Avoiding Treatment Errors

With bradyarrhythmias, a careful assessment of the patient's symptoms, review of the drug history, and interpretation of the relevant ECG tracings are usually all that is necessary to avoid over- or undertreating the patient.

Table 26-2 Recommendations for Permanent Pacing in Sinus Node Dysfunction

Class	Recommendation	Level of Evidence*
I	Permanent pacemaker implantation is indicated for SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms.	C
	Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence.	C
	Permanent pacemaker implantation is indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions.	C
IIa	Permanent pacemaker implantation is reasonable for SND with heart rate <40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented.	C
	Permanent pacemaker implantation is reasonable for syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiologic studies.	C
IIb	Permanent pacemaker implantation may be considered in minimally symptomatic patients with chronic heart rate <40 bpm while awake.	C
III	Permanent pacemaker implantation is not indicated for SND in asymptomatic patients.	C
	Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia.	C
	Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy.	C

*Evidence is ranked as: (1) Level A if the data were derived from multiple randomized clinical trials that involved a large number of individuals; (2) Level B if data were derived either from a limited number of trials that involved a comparatively small number of patients or from well-designed data analyses of nonrandomized studies or observational data registries; and (3) Level C if the consensus of experts was the primary source of the recommendation. See Evidence Section for more details.
SND, sinus node dysfunction.

Table 26-3 Recommendations for Permanent Pacing in Acquired Atrioventricular Block in Adults

Class	Recommendation	Level of Evidence*
I	Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block.	C
	Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia.	C
	Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 sec or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.	C
	Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients with AF and bradycardia with 1 or more pauses of ≥5 sec.	C
	Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level after catheter ablation of the AV junction.	C
	Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with postoperative AV block that is not expected to resolve after cardiac surgery.	C
	Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms.	B
	Permanent pacemaker implantation is indicated for second-degree AV block with associated symptomatic bradycardia regardless of type or site of block.	B
	Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of ≥40 bpm if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node.	B
	Permanent pacemaker implantation is indicated for second- or third-degree AV block during exercise in the absence of myocardial ischemia.	C

Continued

Table 26-3 Recommendations for Permanent Pacing in Acquired Atrioventricular Block in Adults—cont'd

Class	Recommendation	Level of Evidence*
IIa	Permanent pacemaker implantation is reasonable for persistent third-degree AV block with an escape rate >40 bpm in asymptomatic adult patients without cardiomegaly.	C
	Permanent pacemaker implantation is reasonable for asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiologic study.	B
	Permanent pacemaker implantation is reasonable for first- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise.	B
	Permanent pacemaker implantation is reasonable for asymptomatic type II second-degree AV block with a narrow QRS. When type II second-degree AV block occurs with a wide QRS, including isolated right bundle-branch block, pacing becomes a class I recommendation.	B
IIb	Permanent pacemaker implantation may be considered for neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease.	B
	Permanent pacemaker implantation may be considered for AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn.	B
III	Permanent pacemaker implantation is not indicated for asymptomatic first-degree AV block.	B
	Permanent pacemaker implantation is not indicated for asymptomatic type I second-degree AV block at the supra-His (AV node) level or that which is not known to be intra- or infra-Hisian.	C
	Permanent pacemaker implantation is not indicated for AV block that is expected to resolve and is unlikely to recur (e.g., drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms).	B

*Evidence is ranked as: (1) Level A if the data were derived from multiple randomized clinical trials that involved a large number of individuals; (2) Level B if data were derived either from a limited number of trials that involved a comparatively small number of patients or from well-designed data analyses of nonrandomized studies or observational data registries; and (3) Level C if the consensus of experts was the primary source of the recommendation. See Evidence Section for more details.
AF, atrial fibrillation; AV, atrioventricular; LV, left ventricular.

FUTURE DIRECTIONS

Important questions on the diagnosis, prognosis, and optimal treatment of bradyarrhythmias include (1) whether genetic abnormalities (yet to be defined) can be useful in assessing and establishing the timing of treatment in these patients, and (2) how best to determine the contribution of bradycardia to symptoms in patients with unclear presentation. It seems unlikely that pharmacologic approaches will be able to match the success of cardiac pacemakers in preventing symptoms and mortality and morbidity in patients with bradyarrhythmias. In the last decade, significant advances have been made in pacemaker size and durability, and it is likely that advances in pacemaker design will continue.

ADDITIONAL RESOURCES

Fisher JD, Aronson RS. Rate-dependent bundle branch block: occurrence, causes and clinical correlations. *J Am Coll Cardiol.* 1990;16:240–243.

An excellent review of rate-dependent BBB.

Harrigan RA, Pollack ML, Chan TC. Electrocardiographic manifestations: bundle branch blocks and fascicular blocks. *J Emerg Med.* 2003;25:67–77.

Well-illustrated review of infranodal blocks.

Krahn AD, Klein GJ, Yee R, Skanes AC. The use of monitoring strategies in patients with unexplained syncope—role of the external and implantable loop recorder. *Clin Auton Res.* 2004;14(suppl 1):55–61.

Describes the use of loop recorders in unexplained syncope.

EVIDENCE

Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2008;117:e350–e408.

Latest consensus guidelines on the management of bradyarrhythmias.

Supraventricular Tachycardia

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Supraventricular tachycardia (SVT) is an abnormally rapid heart rhythm originating above or within the atrioventricular (AV) node. SVT is a tachyarrhythmia generally caused by a reentrant electrical circuit or a focal atrial origin and can be classified as AV nodal reentrant (AVNRT), AV reentrant (AVRT), or atrial tachycardia (AT). Symptoms can be varied but often include the sudden onset and termination of palpitations, with minimal associated physical examination findings. Knowledge of ECG characteristics of various SVTs may aid in the diagnosis and treatment of each. Depending on multiple factors including symptomatology, risk, and patient preference, medical therapy or catheter ablation should be considered. This chapter provides an overview of the various mechanisms of SVT, their clinical presentations including ECG recognition, acute and chronic treatments, and prognoses.

ETIOLOGY AND PATHOGENESIS

The different types of SVT can be divided into categories based on their site of initiation and mechanisms responsible for maintenance of the SVT. Potential sites of initiation of SVT include the sinus node, the atrium, the AV node, and the His bundle. Atrial arrhythmias may also originate from venous structures that directly communicate with the atria such as the pulmonary veins or superior vena cava. For the majority of SVTs, maintenance of the rhythm involves a reentry circuit. The circuit generally involves two separate pathways through which electrical impulses can cycle in a circular manner, generating rapid atrial and ventricular contractions. The reentry circuit usually occurs within the AV node itself or involves the AV node and an AV pathway consisting of a muscle bundle that directly connects the atrium and the ventricle. Less common reentry circuits may involve the sinus node. The other major mechanism involves abnormal automaticity where a cardiac tissue normally lacking automaticity becomes spontaneously active. Focal AT is an example of abnormal automaticity.

This chapter discusses the three categories of SVT (AVNRT, AVRT, and AT). The other major atrial arrhythmias, atrial fibrillation and atrial flutter, are discussed in Chapter 28.

CLINICAL PRESENTATION

Patients diagnosed with SVT are usually asymptomatic at the time of initial evaluation but have sought care because of tachycardia-related symptoms before evaluation. Occasionally, individuals will present with an ominous symptom such as syncope, which is observed in approximately 15% of patients with SVT. Syncope associated with an SVT usually occurs either just after the onset of tachycardia, or with a pause after the termination of the episode. Rarely, sudden cardiac death is a presentation of SVT. Sudden cardiac death is almost always limited to individuals with Wolff-Parkinson-White (WPW) syndrome who also have atrial fibrillation and in whom rapid atrial fibrillation has degenerated to ventricular fibrillation and hemodynamic collapse. Fortunately, the incidence of death in this instance is low; most studies suggest the rate of death from SVT is 0.15% to 0.45% per patient-year.

Much more commonly, however, patients report more benign but bothersome symptoms including palpitations, lightheadedness, dyspnea, cardiac awareness, decreased exercise tolerance, presyncope, or chest discomfort. The history of onset and termination, the frequency and duration of the episodes, as well as possible inciting circumstances may be helpful in distinguishing the type of SVT.

Abrupt onset and termination of episodes and termination by vagal maneuvers is suggestive of either AVRT or AVNRT, both of which involve the AV node. Statistically, these together account for approximately 90% of SVTs. Episodes that begin and end gradually ("warming up" and "cooling down") tend to be associated with automatic tachycardias such as sinus tachycardia or ATs. Any described irregularity of the palpitations could predict atrial fibrillation, variably conducted atrial flutter, multifocal AT, or AT with block.

DIFFERENTIAL DIAGNOSIS

Atrioventricular Nodal Reentrant Tachycardia

MECHANISM

Excluding atrial fibrillation and atrial flutter, the most common SVT is AVNRT, accounting for approximately 60% of cases. AVNRT is characterized by the presence of two distinct pathways within the AV node that facilitate reentry by allowing an electrical impulse to cycle in one direction, creating a reentrant loop or circuit. The presence of two pathways is often referred to as *dual AV nodal physiology*. One pathway has a short conduction time but a long refractory period (fast pathway); the second has a long conduction time but a short refractory period (slow pathway). The differing conduction times and refractory periods of each pathway allow the electrical impulse to cycle in only one direction, using one pathway in the anterograde direction and one pathway in the retrograde direction. The pathways are joined into one final common pathway before impulses exiting the AV node to continue to the bundle of His (Figs. 27-1 and 27-2).

Typical or common AVNRT, which accounts for 95% of cases, employs the slow pathway in the anterograde direction and the fast pathway in the retrograde direction of the circuit. This is also termed *slow-fast tachycardia*. Conversely, in atypical or uncommon AVNRT, the anterograde limb of the circuit is rapidly conducting and the retrograde limb is slowly conducting, otherwise called *fast-slow tachycardia*.

Initiation of typical AVNRT is usually caused by a critically timed single premature atrial beat. Under normal circumstances, sinus beats are initially conducted down both the fast and slow pathways. The signal through the fast pathway reaches the final

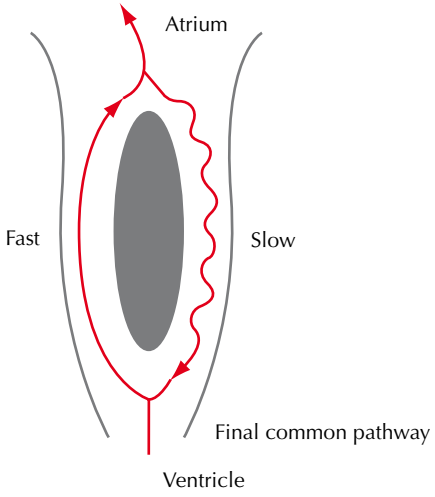

Figure 27-1 *Representation of dual-pathway physiology.*

common pathway before the impulse in the slower conducted limb and proceeds to exit the AV node. When the conduction through the slow pathway ultimately reaches the final common pathway, it collides with the fast pathway, which is now refractory, unable to support any impulse. The collision essentially extinguishes the slowly conducted impulse.

In the case of a critically timed atrial premature beat, however, the circumstances may be present to initiate AVNRT. Following a normal sinus beat that was conducted over the fast pathway, the fast pathway remains refractory longer than the slow pathway (fast pathway: rapid conduction, long refractory period; slow pathway: slow conduction, short refractory period). When a premature atrial beat reaches the AV node and finds the fast pathway refractory, it is transmitted anterogradely down the slow pathway. Upon reaching the final common pathway, the fast pathway has now recovered and is able to accept the impulse. The fast pathway is activated, conducting the impulse retrogradely, depolarizing the atria and then reentering the slow

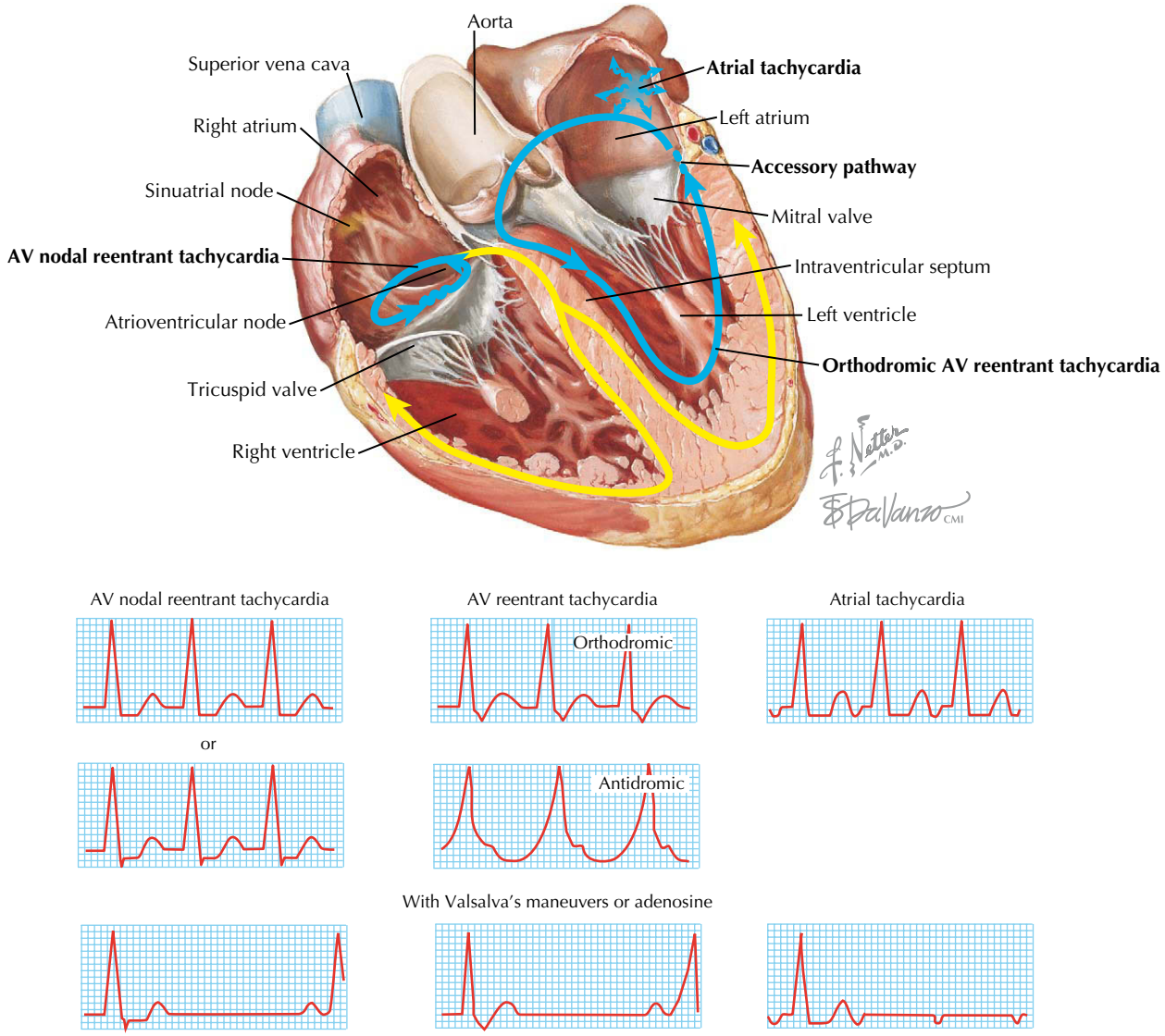

Figure 27-2 *Typical electrocardiographic recordings and anatomic representation of the common supraventricular tachycardias.* AV, atrioventricular. From Delacretaz E. Clinical practice. Supraventricular tachycardia. *N Engl J Med.* 2006;354:1039–1051.

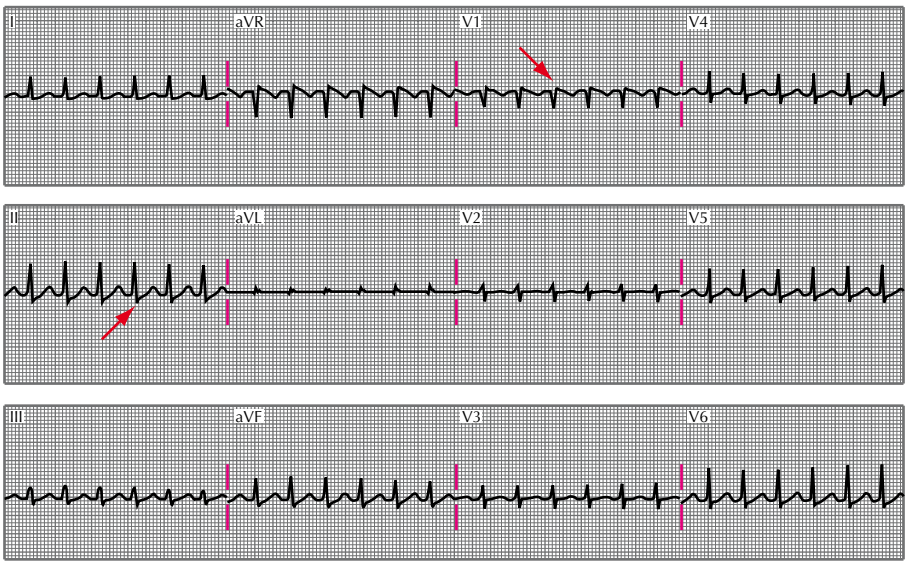

Figure 27-3 *Atrioventricular nodal reentrant tachycardia.* Arrows show pseudo-S waves in II and pseudo-R waves in V_1.

pathway to conduct anterogradely again. This creates a sustained reentrant tachycardia.

In a similar fashion, remembering that the slow and fast pathways serve equal but opposite functions in atypical as compared with typical AVNRT, a ventricular premature beat may initiate the reentrant tachycardia by entering the slow pathway and conducting retrogradely. The circuit is then created in a manner similar to that described for common AVNRT.

ECG RECOGNITION

Typical and atypical AVNRTs usually present as a narrow-complex tachycardia, although concomitant aberrancy/bundle branch block can rarely create a wide-complex tachycardia. Several differences in ECG characteristics may help distinguish between typical and atypical AVNRTs: P-wave morphology (width), P-wave location, and mechanism of initiation.

It should first be noted that the P-wave axis for both types is similar. In both, activation of the atria occurs in an inferior-to-superior direction (retrograde conduction of the fast pathway in typical or the slow pathway in atypical AVNRT). This produces a negative (inverted) P-wave axis in the inferior leads II, III, and aVF. The AV node is located posteriorly, creating posterior-to-anterior activation of the atria and therefore producing a positive (upright) P-wave axis in lead V_1. P-wave width, on the other hand, differs in the two forms. In typical AVNRT, the P wave tends to be narrow, whereas in atypical AVNRT, it is wider because of the differences in anatomic location of the fast and slow pathways that activate the atria.

Typical AVNRT can be distinguished from atypical AVNRT on an ECG by comparing the location of the P wave in relation to the QRS complex. In typical AVNRT, near-simultaneous conduction to the ventricles via the slow pathway anterogradely and to the atria via the fast pathway retrogradely may rarely make P wave visible on the ECG because they are inscribed in the QRS complex. When visualized, the P waves occur in close proximity to the QRS, creating a short RP interval (RP interval less than half the RR interval). This can sometimes manifest as a "pseudo-S wave" in the inferior leads II, III, and aVF, and a "pseudo-R wave" in lead V_1 (Fig. 27-3). Typical AVNRT, therefore, is an example of a "short-RP" tachycardia. In contrast, P waves are clearly visible in atypical AVNRT. Due to retrograde conduction through a slow pathway, the presence of the P wave occurs later than the QRS complex, resulting in an RP interval that is frequently longer than half the RR interval, called a *long RP tachycardia* (Fig. 27-4).

Another ECG feature that may help to distinguish typical from atypical AVNRT is the mode of initiation of the reentrant circuit. Though obviously difficult to obtain on a standard 12-lead ECG, should a rhythm strip be available that demonstrates an initiating atrial premature beat, the diagnosis is more likely typical AVNRT. A ventricular premature beat is more likely to precipitate an atypical AVNRT (Table 27-1).

Atrioventricular Reentrant Tachycardia

MECHANISMS

Approximately 30% of SVTs result from the presence of an accessory AV connection causing an AV reentrant circuit. Similar to the mechanisms described with AVNRT, AVRT requires the presence of two distinct pathways: the normal AV conduction system, which almost always serves as the anterograde limb of the circuit, and an AV accessory pathway (AP) that usually forms the retrograde limb. The presence of two circuits with different conduction velocities and different refractory periods sets up the milieu for the possibility of a reentrant rhythm when initiated by a critically timed atrial or ventricular premature beat.

An AP is composed of a congenitally acquired abnormal muscle bundle joining the atrium and the ventricle, allowing direct electrical communication between them. The pathway may be capable of both anterograde and retrograde conduction

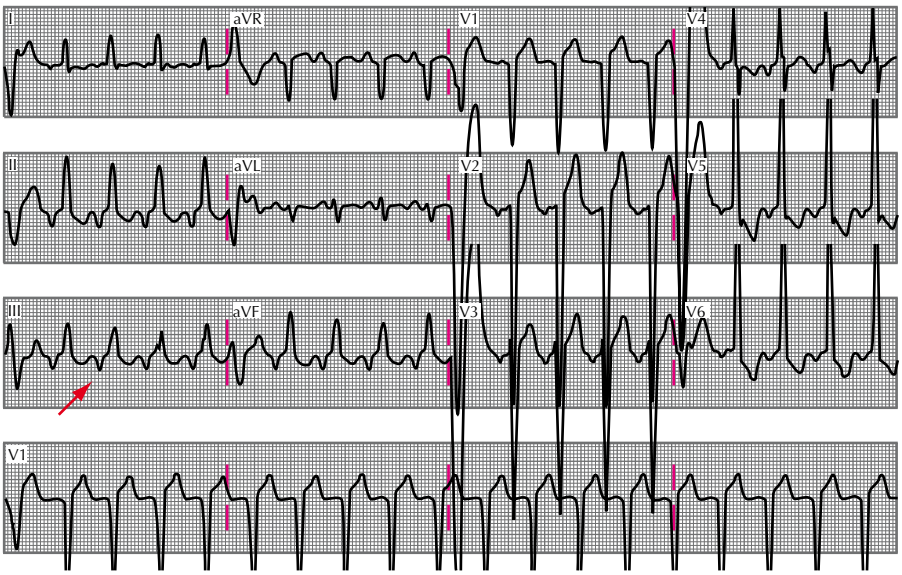

Figure 27-4 *Long RP tachycardia with inverted P waves highlighted by arrow.*

or may conduct only in one direction. Unlike the normal conduction system, which contains a "slowing mechanism" (the AV node), APs do not contain any means for delaying conduction. Therefore, when the AP conducts anterogradely (from atrium to ventricle), the electrical impulse arrives at the ventricle rapidly, preceding the arrival of the impulse conducted through the normal conducting system. This is known as "preexcitation" of the ventricle. The fusion of the impulse conducted through both circuits produces a characteristic ECG pattern during sinus rhythm referred to as the *WPW pattern*, consisting of a short PR interval and a delta wave (Fig. 27-5). The delta wave occurs because a portion of the ventricles are activated instantaneously via the AP. The remainder of the QRS is normal, because it is activated via the AV node and His-Purkinje system. It is notable that patients are given the diagnosis of WPW syndrome only when they have both a WPW ECG pattern and tachyarrhythmias. Many patients with the WPW pattern may never experience tachycardia and therefore do not have the WPW syndrome.

When an AP conducts only in a retrograde direction (from ventricle to atrium), there is no ventricular preexcitation, resulting in a normal-appearing ECG in sinus rhythm. This is referred

Table 27-1 Clinical Clues to the Differential Diagnosis of Supraventricular Tachycardia

Tachycardia	Prevalence	Usual Presentation	Electrocardiographic Characteristics
Atrioventricular nodal reentrant			
Common	Common	Paroxysmal	P waves hidden, pseudo-R in V_1, pseudo-S in II or III
Uncommon	Uncommon	Paroxysmal	Inverted P waves, RP > PR
Accessory pathway–mediated supraventricular			
Orthodromic atrioventricular reentrant	Common	Paroxysmal	Inverted P waves,* RP < PR, QRS alternans
Atrial fibrillation (Wolff-Parkinson-White)	Common	Paroxysmal	Irregularly irregular, variable QRS configuration
Antidromic atrioventricular reentrant	Rare	Paroxysmal	Inverted P waves, wide and bizarre QRS
Permanent junctional reciprocating	Rare	Incessant	Inverted P waves,* RP > PR
Sinus node reentrant	Uncommon	Paroxysmal	Upright P waves, RP > PR
Unifocal atrial			
Reentrant	Uncommon	Paroxysmal	Upright, biphasic, or inverted P waves; RP > PR
Automatic	Rare	Incessant	Upright, biphasic, or inverted P waves; RP > PR; variable atrial rate
Multifocal atrial	Common	Incessant	Variable P waves, variable rate, variable PR intervals

*The electrocardiographic lead or leads showing inverted P waves are related to the site of the earliest atrial activation during tachycardia.
From Ganz LI, Friedman PL. Supraventricular tachycardia. N Engl J Med. *1995;332:162–173.*

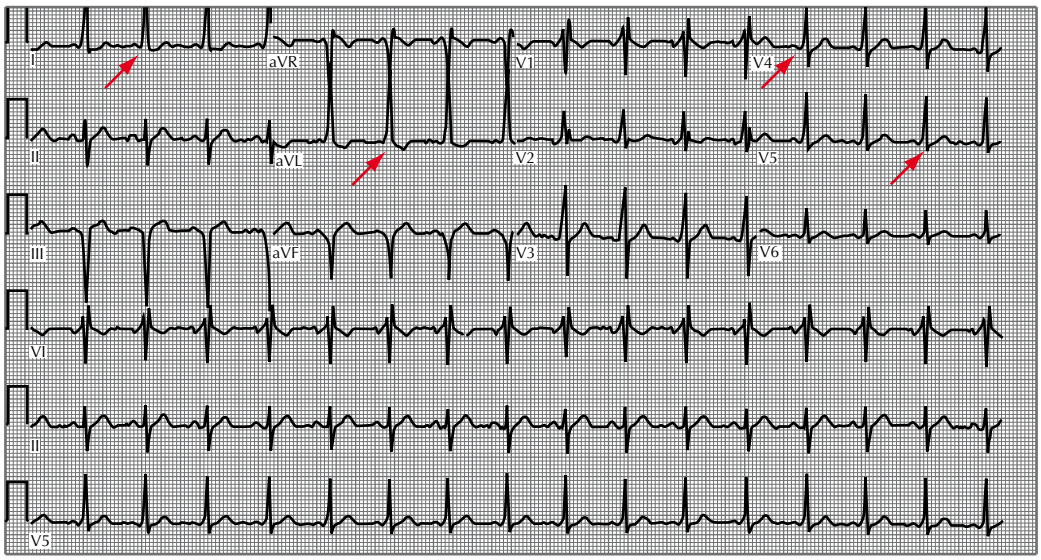

Figure 27-5 *Wolff-Parkinson-White pattern with delta waves highlighted by arrows.*

to as a "concealed" pathway, because it is only apparent when there is tachycardia. Occasionally, a pathway that conducts anterogradely may appear concealed if intrinsic AV nodal conduction is rapid or if the AP is located far from the sinus node. In these cases, the normally conducted impulse reaches the ventricle more quickly than the AP impulse, and a delta wave may be difficult to appreciate on the ECG. Slowing or blocking AV nodal conduction, for example with adenosine, may help to expose such a pathway.

The reentrant loop created by the normal conducting system and an AP allows AVRT to occur. AVRT can be further classified into two subtypes: orthodromic (OAVRT) or antidromic (AAVRT). If the electrical impulse travels anterogradely down the AV node and then retrogradely up the AP, it is termed *orthodromic reciprocating tachycardia*, which accounts for 90% to 95% of tachycardias in patients with WPW syndrome. In AAVRT, the impulse travels in the reverse direction, with anterograde conduction down the AP followed by retrograde propagation up the AV node.

There is also a relatively uncommon variant of OAVRT in which the retrograde impulse propagation in the AP is unusually slow. Slow conduction through both limbs of the reentrant loop (the AV node and the AP) creates a stable, incessant circuit leading to a persistent tachycardia called *permanent junctional reciprocating tachycardia* (PJRT). Because it is often incessant, PJRT may lead to a tachycardia-mediated cardiomyopathy, which may be the presenting scenario leading to this diagnosis.

Of patients with WPW syndrome, approximately 10% to 30% experience atrial fibrillation, a rhythm that can potentially produce ventricular rates that exceed 300 bpm, posing an obvious threat of hemodynamic compromise. The rapid, disorganized atrial activity of atrial fibrillation can bombard an anterograde AP, a pathway with a short refractory period that typically shows rapid, nondecremental conduction. The pathway, in turn, can propagate the electrical impulses to the ventricle, producing rapid ventricular depolarization. This can be particularly hazardous in patients with multiple APs. Under such circumstances, atrial fibrillation with an extremely rapid ventricular response can potentially degenerate into ventricular fibrillation, leading to sudden death.

The refractory period of the AP is a key determinant in the development of ventricular fibrillation. APs with longer refractory periods pose less risk, because they become inexcitable at faster heart rates. Risk stratification can be performed noninvasively via stress testing or administration of intravenous medications such as procainamide that block conduction in pathways with long refractory periods but not short ones. The disappearance of the delta wave at relatively low exercise heart rates or with the drug administration is indicative of a long refractory period. Intermittent presence of preexcitation on a resting ECG—that is, ECGs with and without preexcitation on different days—is also thought to indicate low risk. Unfortunately, the noninvasive tests have limited sensitivity and specificity, and the gold standard to determine risk is an invasive electrophysiologic study that allows accurate definition of the characteristics of the accessory pathway(s).

ECG RECOGNITION

The ECG findings of an anterograde AP during sinus rhythm include the short PR interval and the delta wave of ventricular preexcitation (WPW pattern) as described above. Atrial or ventricular premature beats may initiate AVRT with a mechanism similar to that described with AVNRT. The tachycardia will be orthodromic or antidromic; the two types show distinctly different ECG morphologies (Fig. 27-6).

OAVRT demonstrates a narrow QRS complex (i.e., without delta waves) with rates ranging from 150 to over 250 bpm. In OAVRT, because the ventricles are depolarized through the normal conducting system, there is no preexcitation of the ventricle and therefore no delta wave is seen. P waves will generally appear within the ST-T wave segment, with an intermediate RP interval. Though often difficult to distinguish from AVNRT,

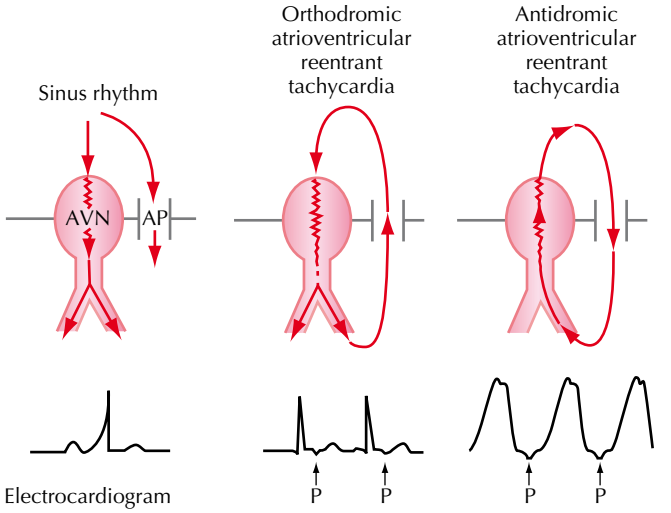

Figure 27-6 *Mechanism of atrioventricular reentrant tachycardia in patients with the Wolff-Parkinson-White syndrome.* AVN, atrioventricular node; AP, accessory pathway. From Ganz LI, Friedman PL. Supraventricular tachycardia. *N Engl J Med.* 1995;332:162–173.

the difference in the RP interval (intermediate vs. short) may be helpful in making the diagnosis by ECG. Additionally, ST-segment depression in either the inferior or precordial leads resembling that of cardiac ischemia may be present in OAVRT and may be a clue to the AP's location.

The ECG of AAVRT demonstrates a wide-complex QRS due to full preexcitation of the ventricles by the anterograde conduction over the AP. The rhythm is regular with rates up to 250 bpm, and P waves are usually obscured by the wide QRS complex. Due to retrograde activation of the atria via a relatively slow AV nodal system, when P waves are identified they are retrograde with a relatively long RP interval. Though a diagnostic challenge, this longer RP interval may be helpful in distinguishing AAVRT from AVNRT with aberrancy.

The rate associated with PJRT is generally slower than the other AVRTs, ranging from approximately 120 to 150 bpm. Anterograde ventricular activation is via the AV nodal system, so the QRS is narrow. Because of a slowly conducting retrograde AP, retrograde inverted P waves are easily seen in the inferior leads, and the RP interval is characteristically long.

Atrial fibrillation in WPW syndrome is characterized by a rapid, irregular rhythm with a wide-complex QRS due to a fully preexcited ventricle caused by anterograde conduction down the AP(s). With extremely rapid ventricular rates, the irregularity may be difficult to recognize and could be challenging to initially distinguish from ventricular tachycardia (Fig. 27-7).

Atrial Tachycardia

MECHANISMS

SVTs arising from an atrial focus other than the sinus node are ATs. The two most common ATs are atrial fibrillation and atrial flutter (Chapter 28). The remainder of ATs represents only 10% of presenting SVTs.

Unifocal ATs may arise from distinct anatomic locations within the atria. Common origins include the crista terminalis of the right atrium, the atrial septum, the mitral valve annulus, and the pulmonary veins. ATs are usually paroxysmal but are sometimes incessant, and atrial rates are generally slower than 250 bpm. Incessant ATs, like PJRT, may produce a tachycardia-induced cardiomyopathy.

AT is caused by abnormal automaticity, triggered activity, or intra-atrial reentry. Automaticity is the spontaneous generation of action potentials (and therefore myocardial depolarization) and is the mechanism by which the normal heart rhythm is generated. When automaticity occurs in myocardial tissue that is not normally automatic (e.g., atrial or ventricular myocardium), this is called *abnormal automaticity* and results in a tachyarrhythmia. Notably, increased sympathetic tone enhances automaticity, so in automatic ATs a wide variation in rate may occur depending on autonomic tone, and rates may exceed 250 bpm during exercise.

Triggered activity is generated by an interruption in repolarization that then "triggers" another action potential causing enhanced depolarization of atrial tissue. This is probably the mechanism of AT induced by digoxin toxicity, which causes intracellular calcium overload. The resulting AT has variable ventricular conduction because of digoxin's influence on the AV node.

Reentrant AT results from abnormalities in intra-atrial conduction and refractoriness, and tachycardias are sustained by reentry. The commonest reentrant ATs are atrial flutter and atrial fibrillation. Unlike other reentrant SVTs described above, however, atrial reentry is usually precipitated by underlying structural heart disease or scars from cardiac surgery.

ECG RECOGNITION

ATs produce a P wave before the QRS, the morphology of which is different from that produced from the sinus node and is dependent on the site of origin (see Fig. 27-7). The PR interval is dependent on the rate of the tachycardia, although

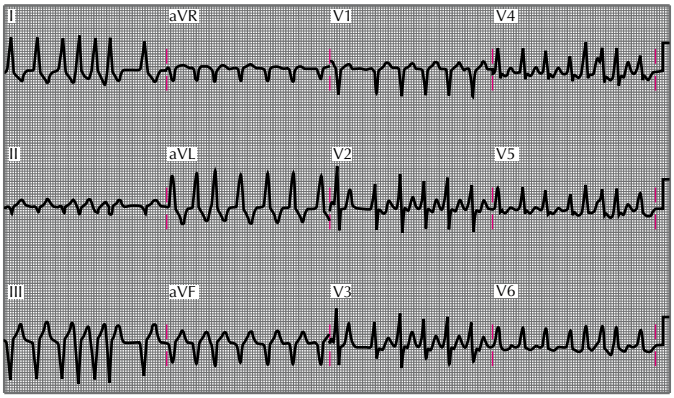

Figure 27-7 *Wolff-Parkinson-White syndrome with rapid atrial fibrillation.*

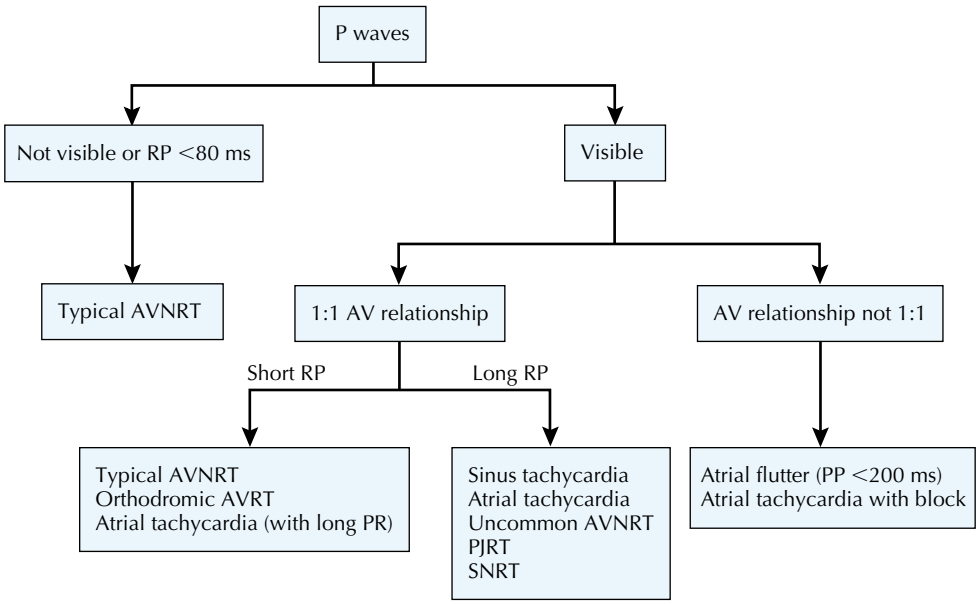

Figure 27-8 *Diagnosis of narrow-complex supraventricular tachycardia.* AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; PJRT, permanent junctional reciprocating tachycardia; PP, PP interval; RP, RP interval; SNRT, sinus node reentrant tachycardia.

the RP interval is usually long. An isoelectric baseline between P waves may help to distinguish this tachycardia from atrial flutter along with an atrial rate that is generally slower. The presence of AV block in the setting of abnormal P-wave morphology rules out AV reciprocating tachycardias (AVNRT or AVRT), because those tachycardias require a 1:1 AV relationship.

Multifocal AT is an irregular tachycardia that may be confused with atrial fibrillation. ECG diagnosis of multifocal AT is made based on the irregular rhythm with three or more different P-wave morphologies and rates faster than 100 bpm. Commonly there is variation in the PR intervals and variability in AV block. Isoelectric intervals between P waves and rates typically slower than atrial fibrillation may help distinguish the two (Fig. 27-8).

MANAGEMENT AND THERAPY

Optimum Treatment

ACUTE MANAGEMENT

In a hemodynamically stable patient with a narrow-complex tachycardia, vagal maneuvers including Valsalva or carotid massage should be the initial branch in the algorithm for management of SVT. Because the majority of SVTs depend on the AV node as part of their reentry circuit, slowing conduction in the AV node should help to slow or break the tachycardia. Vagal maneuvers do this by increasing parasympathetic tone and sympathetic withdrawal.

If the maneuvers fail to terminate the tachycardia, administration of intravenous AV-nodal–blocking agents should be the next step in treatment. Potential drug choices include adenosine, non-dihydropyridine calcium channel blockers such as verapamil or diltiazem, or β-blockers (metoprolol or esmolol). Among these, adenosine is the preferable agent because of its rapid onset and short half-life. Approximately 90% of SVTs can be terminated with 12 mg of adenosine if they are due to AVNRT or AVRT. Occasionally, ATs are also adenosine-sensitive. A continuous ECG should be performed during the adenosine administration, since the pattern of termination or response may be diagnostic. A tachycardia that terminates with a P wave shortly after a QRS complex probably indicates AVNRT or AVRT, whereas a terminal QRS complex favors AT as the diagnosis. AV block with continuation of a rapid atrial rate is diagnostic of AT.

Caution is warranted with adenosine use in patients with bronchospastic disease and in heart transplant patients who may have an exaggerated response to adenosine and, hence, a risk of prolonged asystole. Adenosine use in WPW syndrome with rapidly conducted atrial fibrillation may be deadly; by blocking AV-nodal conduction, atrial impulses are preferentially transmitted down a rapidly conducting AP, leading to an increase in ventricular rate and the potential to develop ventricular fibrillation. Therefore, in a wide-complex tachycardia, unless SVT with aberrancy is known, adenosine should be avoided (Fig. 27-9).

If SVT continues despite adenosine or if adenosine is contraindicated, intravenous verapamil, diltiazem, or a β-blocker may terminate the tachycardia. Calcium channel blockers, though rarely terminating an AT, may be preferable to provide symptomatic relief by reducing the ventricular rate in this type of SVT. The disadvantages of these agents are their relatively longer half-life, as well as their negative inotropic and hypotensive effects. Concomitant doses of these agents may provoke bradycardia after termination of the tachycardia. As with

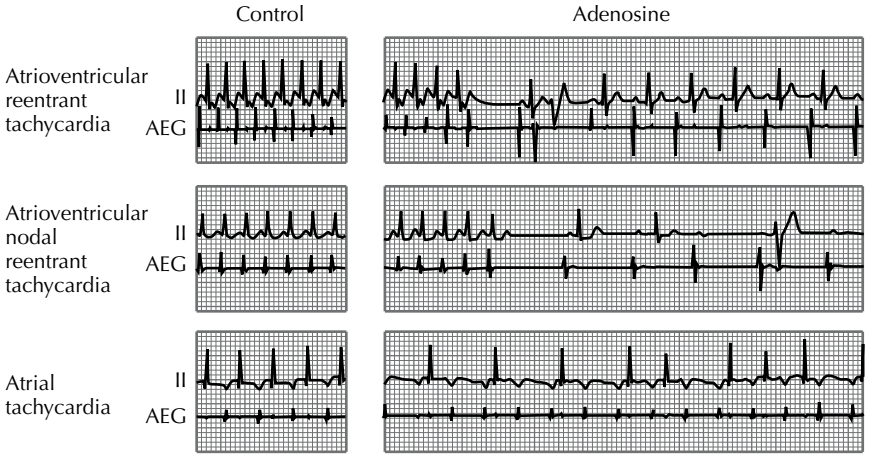

Figure 27-9 *Effect of adenosine on atrioventricular reentrant tachycardia, atrioventricular nodal reentrant tachycardia, and atrial tachycardia.* AEG, atrial electrogram. From Ganz LI, Friedman PL. Supraventricular tachycardia. *N Engl J Med.* 1995;332:162–173.

adenosine, calcium channel agents should be avoided in WPW with atrial fibrillation.

Acute management of WPW with atrial fibrillation depends on hemodynamic stability. If unstable, electric cardioversion is recommended. If stable, it is reasonable to administer intravenous drugs that lengthen the refractory period of the AP such as procainamide, ibutelide, or flecainide. It cannot be overemphasized that adenosine, calcium channel blockers, or β-blockers should be avoided in this arrhythmia.

LONG-TERM TREATMENT

The decision for pharmacologic treatment versus catheter ablation for SVT largely depends on the patient's symptom burden and response to medications, as well as the risk attributed to the arrhythmia if untreated. For patients with infrequent episodes of prolonged but relatively well-tolerated tachycardia that are not responsive to vagal maneuvers, a "pill-in-the-pocket" approach may be reasonable in those with AVNRT and with AVRT without preexcitation. This approach entails the self-administration of one dose of a rapid-acting AV-node–blocking medication with onset of the tachycardia in an attempt to terminate it. The combination of a single dose of 120 mg of diltiazem with a single dose of 80 mg of propranolol has a beneficial effect without substantial risk of bradycardia or hypotension. In patients without structural heart disease, systolic dysfunction, or coronary artery disease, a single dose of the antiarrhythmic drug flecainide is also an option.

Frequent, recurrent episodes of tachycardia may require prophylactic options including medical or radiofrequency catheter ablation therapy. In those with AVNRT or OAVRT with a concealed pathway, AV-nodal–blocking drugs such as verapamil, β-blockers, or digoxin may be efficacious in preventing tachycardic episodes for approximately 30% to 60% of patients. If these agents are unsuccessful, a class IC (flecainide or propafenone) or class III antiarrhythmic (amiodarone or sotalol) may be considered. Although these may be more effective in preventing SVT, there are generally more potential side effects attributed to these drugs that must be weighed against their benefits.

Medical therapy in those with WPW syndrome can be considered, although catheter ablation is the treatment of choice. Unless the AP is proven to have a long refractory period, verapamil and digoxin are contraindicated because of the risk of precipitating a rapid ventricular response during atrial fibrillation. Class IC agents are effective by slowing anterograde conducting pathways, with improved efficacy with the addition of a β-blocker.

Patients with SVT who cannot tolerate medical therapy, whose condition is refractory to it, or who would prefer not to take medications should consider radiofrequency catheter ablation. This can be used either as a first- or second-line option of treatment, achieving resolution of tachycardia in approximately 95% of patients following ablation of a pathway associated with the tachycardia. Particularly in WPW patients who are at risk for rapidly conducted atrial fibrillation due to a fast AP, catheter ablation should be the initial treatment. Decisions to pursue ablation for other forms of SVT should be driven by patient preference, lifestyle or occupational issues, drug efficacy, the presence of structural heart disease, and the availability of an experienced operator to perform the procedure.

An electrophysiology study is generally performed to localize and define the characteristics of various pathways before the actual ablation. Ablation for AVNRT usually targets the slow pathway of the reentry circuit, successfully alleviating tachycardia in approximately 95% of individuals following the procedure. The major risk of catheter ablation of the AV node slow pathway is the risk of heart block (0.5%), occasionally necessitating permanent pacing. In WPW syndrome, catheter ablation of APs also carries a 95% success rate, although there is a possibility that an AP will recur in approximately 5% of individuals, requiring a second procedure. Left lateral AP ablation, as opposed to other anatomic locations, tends to be most successful. Heart block is a risk only when the pathway is located close to the AV node, and this is an uncommon location for an AP. Focal AT ablation targets the origin of the tachycardia and is successful approximately 90% of the time, with an 8%

recurrence. Because of the incessant nature of some ATs, catheter ablation should be considered the initial therapy because of the risk of developing a tachycardia-associated cardiomyopathy. The same is true of PJRT.

Avoiding Treatment Errors

As noted, it is critically important to emphasize that adenosine, calcium channel blockers, and β-blockers are absolutely contraindicated in the treatment of WPW with atrial fibrillation. Use of these agents in this particular arrhythmia risks conversion to ventricular fibrillation and death.

Care should be taken to ensure that a patient does not have bilateral carotid stenosis before carotid massage for vagal stimulation. It should be noted that patients with heart transplant may have an exaggerated response to adenosine, risking asystole. Adenosine should also be used with caution in those with bronchospastic disease.

Prognosis and Special Populations

Prognosis for most SVTs is excellent. Most carry little risk of morbidity, particularly if treated either medically or with ablation. Few exceptions are noted: PJRT, incessant ATs, or inappropriate sinus tachycardia may lead to the development of a tachycardia-induced cardiomyopathy. Elimination of the tachycardia generally carries a good prognosis for recovery of ventricular function. Any of the SVTs may cause hemodynamic compromise or syncope during prolonged episodes or in cases of hypovolemia. In general, however, the risk of death under such circumstances is minimal.

The exception in which the risk of sudden cardiac death is still low but nevertheless increased is WPW syndrome, estimated at 0.15% to 0.4% over 3 to 10 years' follow-up. For this reason, risk stratification in special populations with WPW syndrome bears careful consideration. Athletes with WPW, for instance, represent a population with a heightened risk for sudden cardiac death. The increased incidence of atrial fibrillation in athletes, as well as the heightened adrenergic state imposed during physical activity, predisposes these individuals to rapidly conducted atrial fibrillation leading to ventricular fibrillation and death. Though not necessarily a population particularly predisposed to sudden death, pilots or persons in other high-risk occupations with WPW syndrome also deserve careful risk stratification with consideration for catheter ablation.

SVT in pregnancy adds some risk to the usual treatment because of the fear of potential effects on the fetus. Because pregnancy may exacerbate SVT symptoms in approximately 20% of women with SVT, women with symptomatic SVT should consider catheter ablation before becoming pregnant, if possible. In those with minimal symptoms, no treatment is recommended. If urgent conversion of AVNRT is necessary and vagal maneuvers do not suffice, then adenosine administration is considered safe for both mother and fetus, as is direct current cardioversion. For preexcited atrial fibrillation, procainamide is acceptable treatment. Should prophylactic medication be necessary, digoxin, propranolol, or metoprolol are recommended as category B drugs in pregnancy without known significant effects on the fetus, particularly during the second and third trimesters. Other antiarrhythmics, except for sotalol, are generally considered category D (contraindicated) and should be avoided.

FUTURE DIRECTIONS

Indications for catheter ablation of SVTs have increased with advances in ablation technology including new endocardial mapping techniques. Further advances in ablation catheter design and energy modalities including cryoablation and highly focused ultrasound should theoretically improve the ability to treat SVT via catheter ablation.

ADDITIONAL RESOURCES

Page RI. Treatment of arrhythmias during pregnancy. *Am Heart J.* 1995; 130:871–876.

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Wellens HJ. 25 years of insights into the mechanisms of supraventricular arrhythmias. *Pacing Clin Electrophysiol.* 2003;26:1916–1922.

Summarizes technologic developments that have contributed to accurate diagnosis and therapy for SVT.

EVIDENCE

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Provides an excellent review of AVNRT, including information on clinical and ECG diagnosis and medical and invasive treatments.

Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Supraventricular Arrhythmias). *Circulation.* 2003;108:1871–1909.

Provides class I, II, and III recommendations for treatment of SVT.

Calkins H, Yong P, Miller JM, et al. Catheter ablation of accessory pathways, atrioventricular nodal reentrant tachycardia, and the atrioventricular junction: final results of a prospective, multicenter clinical trial. The Atakr Multicenter Investigators Group. *Circulation.* 1999;99: 262–270.

The study evaluated the safety and efficacy of radiofrequency ablation on SVT, particularly variables that would predict complication or death from ablation.

Chen SA, Chiang CE, Yang CJ, et al. Sustained atrial tachycardia in adult patients. Electrophysiological characteristics, pharmacological response, possible mechanisms, and effects of radiofrequency ablation. *Circulation.* 1994;90:1262–1278.

This is a study that evaluated mechanisms and characteristics of atrial tachycardia in adults. Pharmacologic and ablative therapies to terminate atrial tachycardia were studied.

Delacretaz E. Clinical practice. Supraventricular tachycardia. *N Engl J Med.* 2006;354:1039–1051.

Provides an excellent review on differential diagnosis, ECG recognition, and treatment of SVT.

Ganz LI, Friedman PL. Supraventricular tachycardia. *N Engl J Med.* 1995;332:162–173.

Provides an excellent review of ECG recognition and treatment of SVT.

Atrial Fibrillation

Anil K. Gehi and J. Paul Mounsey

28

Atrial fibrillation (AF), a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation, is the most common sustained cardiac rhythm abnormality. The increase in the prevalence of AF is probably due to a combination of factors, including the aging of the population, a rising prevalence of chronic heart disease, and more frequent diagnosis by way of enhanced monitoring devices.

AF increases in prevalence with age, with rates of 5% to 10% reported in those older than 80 years. It is more common in men and less common among African Americans. Often AF is associated with structural heart disease, although a significant proportion of patients have no detectable heart disease.

DEFINITION AND CLASSIFICATION

On ECG, AF is characterized by the replacement of P waves with rapid oscillating or fibrillatory waves that vary in amplitude, shape, and timing associated with an irregular ventricular response (Fig. 28-1). The rapidity of the ventricular response to AF depends on properties of the atrioventricular (AV) node, the level of autonomic tone, the presence of accessory conduction pathways, and the effects of various medications. AF may occur in association with other arrhythmias, including atrial flutter or atrial tachycardia.

Several classification schemes have been used to describe the pattern of AF, such as acute, chronic, paroxysmal, and constant. The preferred classification is to use the term *recurrent* when a patient has had two or more episodes of AF. If the episodes terminate spontaneously, AF is designated *paroxysmal*. If episodes last beyond 7 days, AF is designated *persistent*. If cardioversions of AF fail or are not attempted, AF is designated as *permanent*. The designation of *lone AF* generally applies to young individuals without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension.

ETIOLOGY AND PATHOGENESIS

Histologically, the atria in patients with AF are frequently found to demonstrate patchy atrial fibrosis. Potential triggers of fibrosis may include inflammation or atrial stretch in response to heart disease such as valvular disease, hypertension, or heart failure. However, just as atrial stretch may lead to AF, AF itself worsens atrial stretch as a result of poor atrial contractility.

The onset and maintenance of AF require an initiating event in the setting of an anatomic substrate. Currently existing data support two schools of thought regarding the genesis of atrial fibrillation: (1) the automatic-focus hypothesis and (2) the multiple-wavelet hypothesis. The focal origin of AF gained credibility when it was found that often a focal source could be identified and that ablation of this source could abolish AF. It was established that cardiac muscle with preserved electrical properties extends into the pulmonary veins of the left atrium. Most often the pulmonary veins were the source of automatic foci that, when they propagate rapidly through an appropriate anatomic substrate, could lead to AF. The multiple-wavelet hypothesis proposes that fractionation of the electrical wavefronts in the atria leads to daughter wavelets of electrical activity. A large atrial mass in addition to other factors increases the number of wavelets, thereby leading to sustained AF. It is likely that these mechanisms are not mutually exclusive and may coexist in the same patient to a varying degree along a spectrum of disease.

AF acutely has adverse hemodynamic consequences as a result of loss of synchronous atrial mechanical activity, irregularity of ventricular response, rapid heart rate, and impaired coronary arterial blood flow (Fig. 28-2). Loss of atrial contraction may most markedly affect cardiac output in those with impaired diastolic filling who are most dependent on atrial function, such as those with left ventricular hypertrophy (LVH) or hypertension.

Persistently elevated ventricular rates can produce tachycardia-induced cardiomyopathy. Importantly, control of the ventricular rate may reverse the cardiomyopathic process.

AF is associated with a significantly increased risk of thromboembolic stroke (see Fig. 28-2). Reduced blood flow velocity in the left atrial appendage due to loss of organized mechanical contraction leads to stasis and thrombus formation. Thrombus formation generally requires continuation of AF for approximately 48 hours. However, even after cardioversion, atrial stunning (and minimally effective mechanical function of the atria) may be present for as long as 3 to 4 weeks, depending on the duration of AF.

CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH

AF may be related to multiple causes (Box 28-1), including acute causes such as binge alcohol intake, surgery, myocardial infarction, pericarditis, pulmonary disease, or hyperthyroidism (see Fig. 28-1). Most often, treatment of these conditions will lead to resolution of the AF. AF has been associated with obesity and obstructive sleep apnea. Multiple cardiovascular conditions are associated with AF, including valvular heart disease, heart failure, coronary artery disease, hypertension (particularly with LVH), hypertrophic cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, and pericardial disease. In these conditions, treatment of the underlying cause does not usually abolish the AF. Familial AF has been increasingly recognized and is probably a result of genetic abnormalities leading to abnormal function of cardiac ion channels. Finally, approximately 30% to 45% of cases of paroxysmal AF and 20% to 25% of persistent AF occurs in patients without underlying predisposing conditions and is classified as lone AF.

AF may present clinically in a variety of manners, including the sensation of palpitations or by its hemodynamic or thromboembolic complications. Aside from the functional impairment associated with stroke, AF in and of itself, in

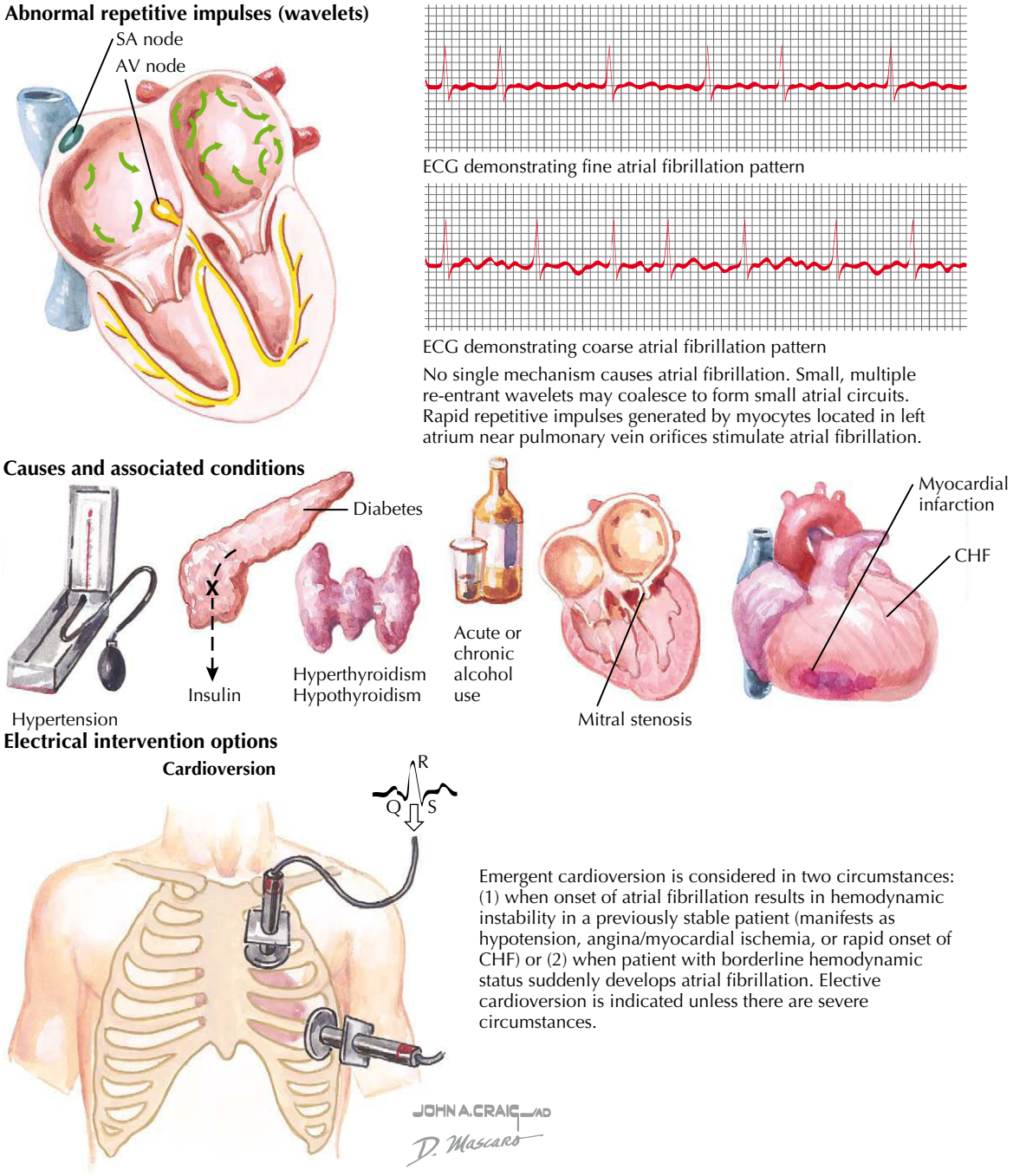


Figure 28-1 *Atrial fibrillation.* AV, atrioventricular; CHF, congestive heart failure; ECG, electrocardiogram; SA, sinoarterial.

general, considerably impairs quality of life. That said, many individuals with AF appear to be completely asymptomatic.

The initial evaluation of AF involves characterizing the pattern of episodes (i.e., paroxysmal or persistent), determining its cause and associated cardiac- or noncardiac-associated conditions, and its tolerability. This can usually be accomplished with a thorough history and physical, ECG, echocardiogram, and basic tests of thyroid function. For further investigation of the pattern of arrhythmia, one may consider a Holter or other telemetric recording.

MANAGEMENT AND THERAPY

Optimum Treatment

There are three fundamental aspects to management of AF: rate control, prevention of thromboembolism, and rhythm control. Both control of the ventricular rate and prevention of thromboembolism are essential to any patient with AF. Based on numerous studies of the potential benefit of rhythm control, an effort to control rhythm should be primarily directed by symptoms associated with AF.

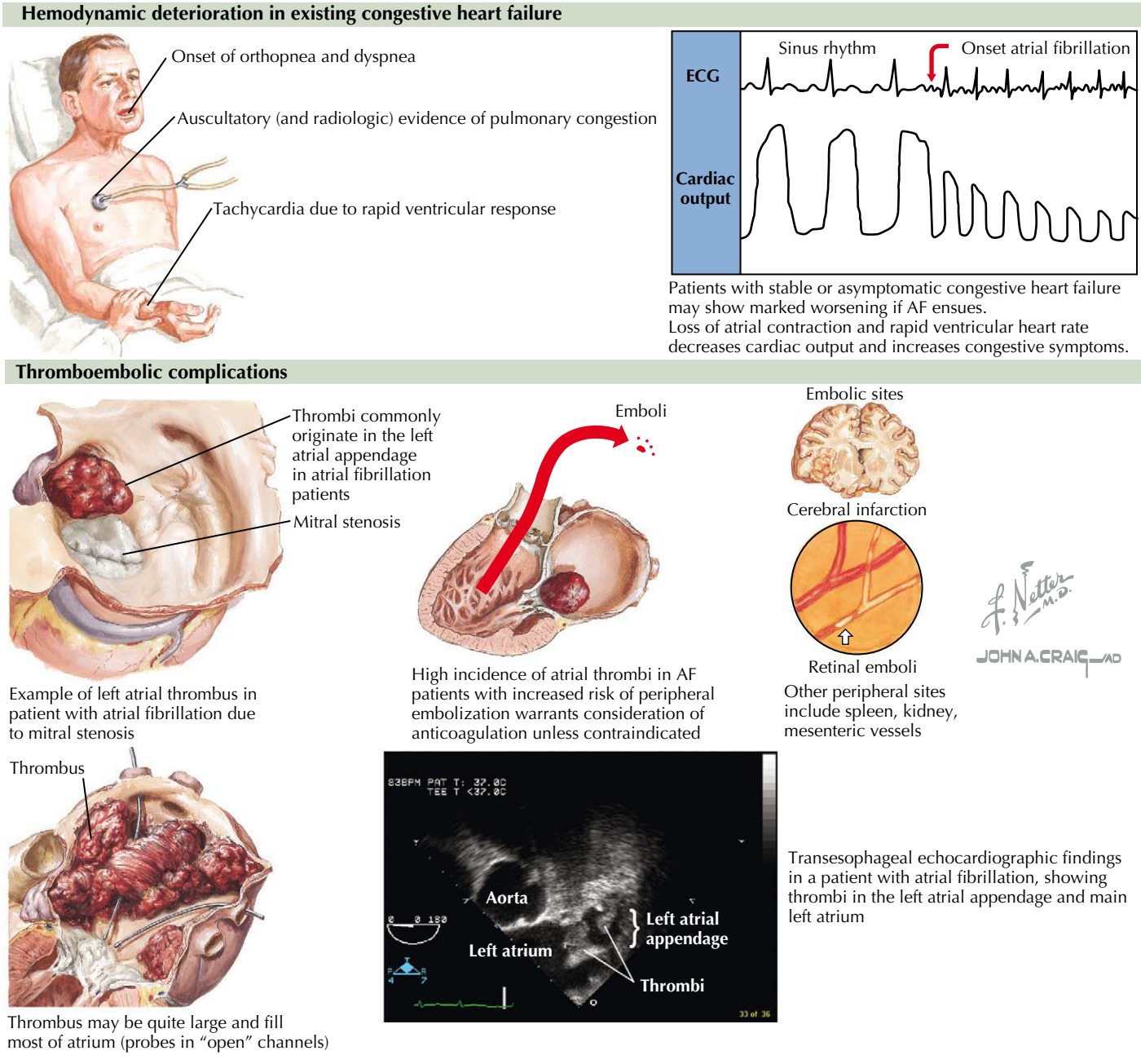


Figure 28-2 *Complications of atrial fibrillation (AF).* ECG, electrocardiogram.

RATE CONTROL

There is no strict definition of adequate rate control, although it is recommended that achieving ventricular rates slower than 80 bpm at rest and slower than 110 bpm during moderate exercise is a reasonable goal. Monitoring the heart rate over an extended period as with a Holter or another such telemetric device may be useful to evaluate the adequacy of rate control. Patients who are hemodynamically compromised as a result of rapid ventricular rates during AF require prompt attention. In addition, inadequacy of rate control may lead to tachycardia-induced cardiomyopathy and should be considered in any patient with idiopathic heart failure and rapid AF. It is essential to assess the heart rate with exercise in all patients when assessing adequacy of rate control.

Drugs that prolong the refractory period of the AV node are generally effective agents for rate control. β-blockers and non-dihydropyridine calcium channel blockers (verapamil or diltiazem) are considered the first-line agents for rate control. Multiple β-blockers have been studied and proven to be effective, including metoprolol, atenolol, nadolol, and carvedilol. Care should be taken when initiating β-blockers in patients with AF and heart failure who have a reduced ejection fraction.

Box 28-1 Underlying Etiologies of Atrial Fibrillation

Cardiac

- Mitral valvular heart disease
- Systolic or diastolic LV dysfunction
- Heart failure
- Hypertension
- Diabetes
- Myocardial infarction
- Hypertrophic cardiomyopathy
- Pericarditis
- Wolff-Parkinson-White syndrome
- Sick sinus syndrome
- Congenital heart disease
- Post coronary artery bypass surgery

Noncardiac

- Acute or chronic alcohol ingestion (holiday heart syndrome)
- Hyper- or hypothyroidism
- Alterations in vagal or sympathetic tone
- Pulmonary embolism
- Sepsis, pneumonia
- Chronic obstructive pulmonary disease
- Obesity
- Obstructive sleep apnea
- Lone atrial fibrillation

LV, left ventricular.

Verapamil and diltiazem are also effective agents. These agents should be avoided in patients with systolic heart failure (particularly if the left ventricular ejection fraction is <40%) because of their negative inotropic effects. However, these agents may be preferred over β-blockers in patients with bronchospastic pulmonary disease. Digoxin is effective at slowing the heart rate at rest but does not slow the heart rate during exercise. In addition, digoxin has a narrow therapeutic window with many potential side effects. Digoxin is thus not considered first-line therapy for rate control except in patients with severe left ventricular dysfunction or in patients who are sedentary. It may be most useful as an add-on agent in patients already on β-blockers or calcium channel blockers whose heart rates are not adequately controlled. Amiodarone has sympatholytic and calcium channel–blocking properties and is safe in critically ill patients. Amiodarone is considered a reasonable alternative for heart rate control in patients who are critically ill or have heart failure. Its long-term use should be balanced against the known side effects of amiodarone, albeit that these are less common at the low doses needed for rate control (and rhythm control; see below) for AF.

As a last resort in patients inadequately treated with antiarrhythmic and negative chronotropic agents, AV nodal ablation with permanent pacemaker implantation is a definitive option.

PREVENTION OF THROMBOEMBOLISM

Several epidemiologic studies have demonstrated that there is a gradation of risk for thromboembolism in patients with nonvalvular atrial fibrillation. From these studies, several risk classification schemes have been proposed to risk-stratify patients into high-risk or low-risk groups. Probably most useful is the $CHADS_2$—a risk classification scheme that integrates several elements of prior studies into a risk index based on five features: cardiac failure, hypertension, age, diabetes, and stroke (doubled) (Fig 28-3). Thus, by assigning 1 point each for a history of heart failure, hypertension, diabetes, or age over 75 and 2 points for a history of stroke or transient ischemic attack, one can compute a score between 0 and 6. Using this scoring system, the yearly risk of stroke varies from 1.9% for a $CHADS_2$ score of 0 to 18.2% for a $CHADS_2$ score of 6.

Multiple studies have demonstrated the safety and efficacy of oral anticoagulation and platelet inhibition in patients with AF who are at high risk for stroke. Those with AF who have low rates of stroke when treated with aspirin (<2% per year, $CHADS_2$ score of 0) do not gain significant benefit from anticoagulation to outweigh the potential risks of therapy. However, those with high risk for stroke (>6% per year, $CHADS_2$ score >1) strongly benefit from anticoagulation with warfarin dose adjusted to achieve an intensity of the international normalized ratio (INR) of 2.0 to 3.0. It remains somewhat controversial whether routine anticoagulation should be recommended in patients at intermediate risk for stroke (2% to 6%, $CHADS_2$ score = 1). The current recommendation is that this decision should be made on an individual basis based on discussions between the patient and treating physician of risks and benefits (see Fig. 28-3).

RHYTHM CONTROL

Several randomized clinical trials have compared outcomes of a rate-control and anticoagulation strategy versus a rhythm-control (using pharmacologic agents) and anticoagulation strategy in patients with AF. Although a rhythm-control strategy may be expected to have theoretical advantages over rate-control strategies through the addition of atrial contraction and the regularization of ventricular contraction, these studies did not support this hypothesis. Instead, there was no overall difference in mortality and an increase in hospitalization in the rhythm-control group, mostly as a result of admissions for cardioversion. It may be that deleterious effects of antiarrhythmic drugs offset the benefits of sinus rhythm. Or it may be that pharmacologic agents are not effective enough at rhythm control to demonstrate a benefit. Nevertheless, the implication of these studies is that a rhythm-control strategy should be an individualized decision based on the nature, intensity, and frequency of symptoms associated with AF, patient preferences, and response to treatment.

Should one make the decision to embark on a rhythm-control strategy in the patient with symptomatic AF, there are many approaches (see Fig. 28-3). In patients with recurrent paroxysmal atrial fibrillation, several antiarrhythmic drugs may be effective. For those with no or minimal heart disease, flecainide, propafenone, or sotalol is recommended as initial therapy because these drugs are generally well tolerated and have few side effects. Flecainide and propafenone are contraindicated in patients with coronary artery disease or significant LVH (>1.3 cm septal wall thickness). Sotalol should be used with caution in those with renal insufficiency. If these drugs are not tolerated or ineffective, second-line pharmacologic agents include dofetilide or amiodarone. A decision for long-term

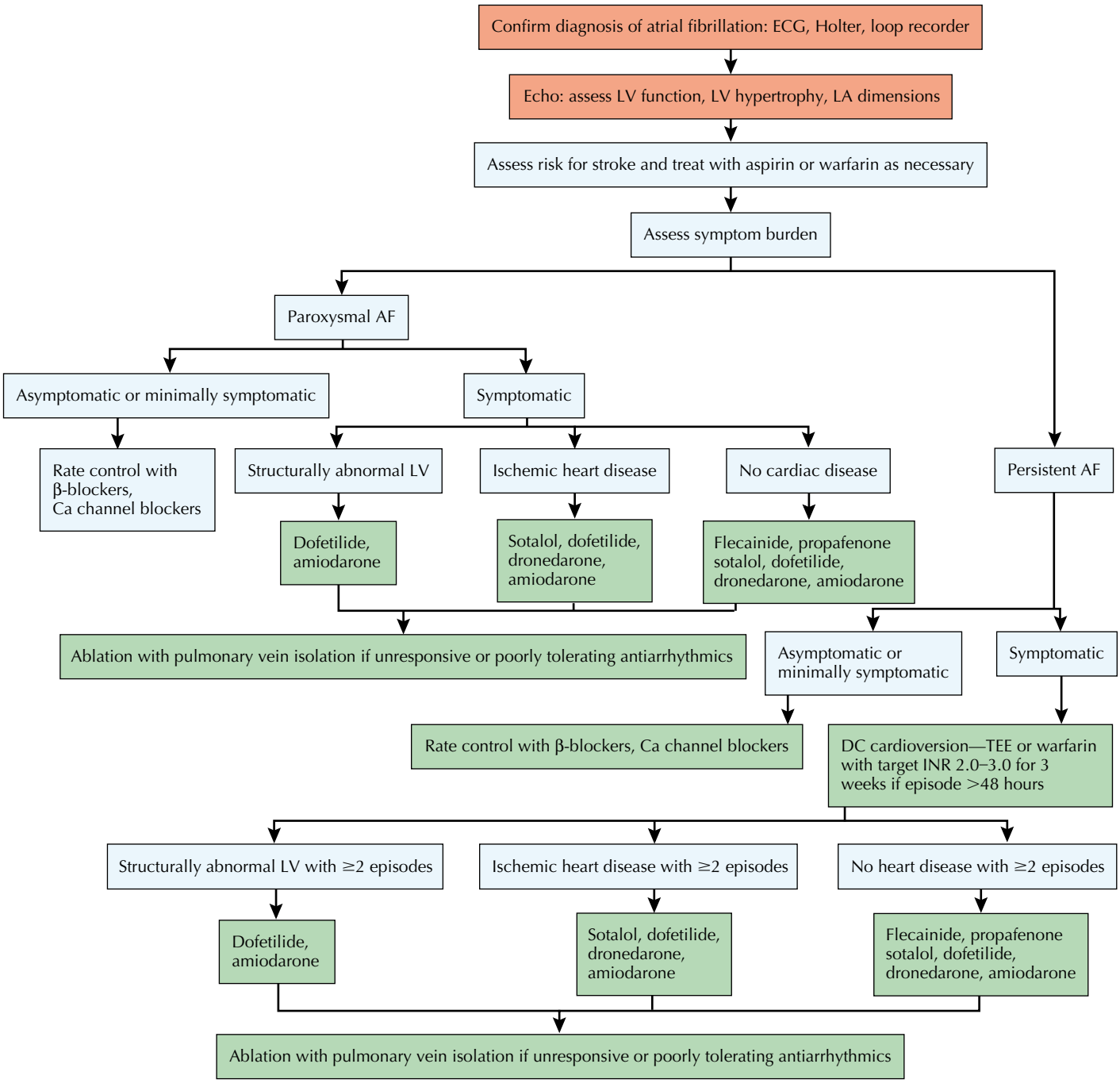


Figure 28-3 *Management and therapy for atrial fibrillation (AF).* Ca, calcium; DC, direct current; ECG, electrocardiogram; INR, international normalized ratio; LA, left atrium; LV, left ventricle/ventricular; TEE, transesophageal echocardiography.

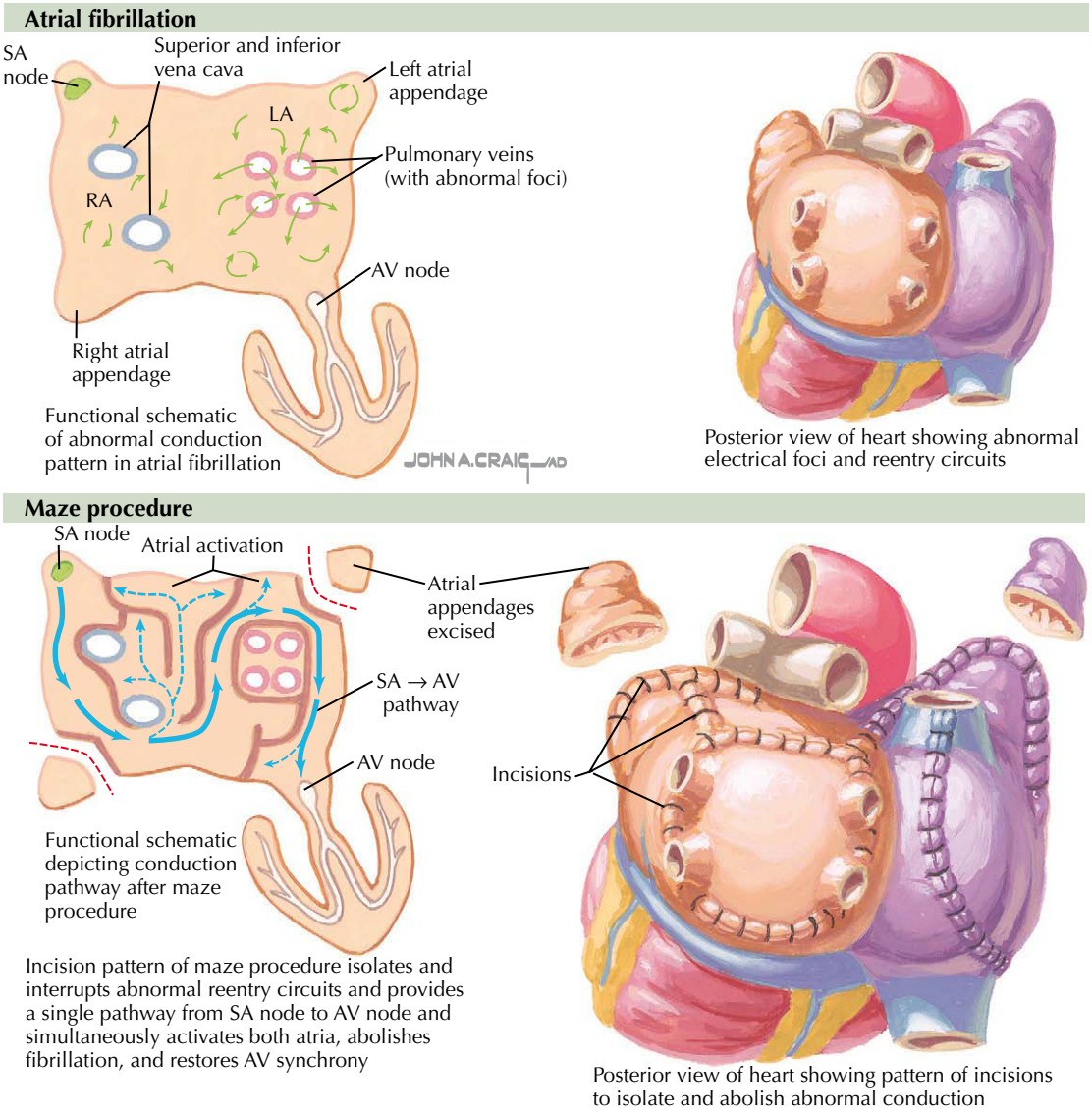


Figure 28-4 *Surgical management of atrial fibrillation.* AV, atrioventricular; LA, left atrium; RA, right atrium; SA, sinoatrial.

amiodarone therapy should be based on discussions of the risk-to-benefit ratio with the patient. Dofetilide requires hospitalization for initiation and should be used with caution in those with renal insufficiency. As an alternative when first-line agents are ineffective, catheter or surgical ablation can be considered (see Fig. 28-3). Ablation is discussed in detail in Chapter 33 but is a highly effective method of rhythm control in AF, particularly in patients with paroxysmal AF.

Recently, an additional antiarrhythmic, dronedarone, has been approved for the treatment of recurrent atrial fibrillation. Dronedarone is an amiodarone analog, which is not associated with the many side effects of amiodarone. A large clinical trial showed that dronedarone reduced the risk of cardiovascular hospitalization in patients with AF. However, dronedarone is limited in that it is contraindicated in patients with significant heart failure.

In a patient with persistent AF, a first attempt at rhythm control may be made with cardioversion alone, especially in the patient with no or minimal heart disease. Direct-current cardioversion under adequate anesthesia is a highly effective means to restore sinus rhythm acutely (see Fig. 28-1). However, pharmacologic cardioversion with ibutilide or dofetilide is a reasonable alternative. For patients with AF of 48 hours' duration or longer (or when the duration of AF is unknown), anticoagulation (INR 2.0 to 3.0) is recommended for at least 3 weeks before and 4 weeks after cardioversion, regardless of the method used for cardioversion. As an alternative to anticoagulation prior to cardioversion, a transesophageal echocardiogram can be performed to exclude the presence of left atrial thrombus. Even in those individuals with no evidence of a left atrial thrombus, anticoagulation after cardioversion is still necessary.

If AF recurs in the patient with persistent AF, an antiarrhythmic drug may be effective in maintaining sinus rhythm following cardioversion. Again, flecainide, propafenone, or sotalol is recommended as initial therapy in patients with no or minimal heart disease. Sotalol is recommended as the initial agent in

patients with coronary artery disease. Dofetilide or amiodarone is the only option in patients with heart failure. If patients do not respond to a first-line pharmacologic agent, second-line agents can be tried. As an alternative, catheter or surgical ablation can be considered.

Surgical ablation is based on the concept that barriers to atrial conduction at critical locations would prevent sustained AF (Fig. 28-4). Using cut-and-sew techniques to create atrial barriers has been termed *the maze procedure*. The maze procedure has gone through multiple iterations. Newer techniques utilize bipolar radiofrequency, cryoablation, or microwave energy as alternatives to the cut-and-sew technique. Despite a high reported success rate, the maze operation has not been widely adopted except in patients with a history of AF who are undergoing cardiac surgery, such as those with valvular disease.

Catheter ablation initially emulated the surgical maze procedure by utilizing radiofrequency ablation to produce linear lines of electrical isolation in the atrial endocardium. With the observation that potential within the pulmonary veins often provoked AF, there has been increasing enthusiasm for catheter-based treatment of AF. The technique of ablation has continued to evolve with a primary focus being electrical isolation of the pulmonary veins, although other approaches are often used in conjunction. Catheter ablation has developed into a promising therapy for patients resistant to pharmacologic therapy, although its long-term efficacy will require further study.

Avoiding Treatment Errors

Management of AF should focus on the three principles of rate control, prevention of thromboembolism, and rhythm control. Once rate control and prevention of thromboembolism are addressed, a rhythm-control strategy should be adopted in patients with recurrent AF who have disabling symptoms. Most common errors arise when one of these principles of management is not adequately addressed. In the case of failure to address stroke prophylaxis, a relatively common error, the consequences can be devastating.

FUTURE DIRECTIONS

The management of AF will undoubtedly change. Newer anticoagulants being developed—such as direct thrombin inhibitors—if proven safe and efficacious, will simplify the prevention of thromboembolism. Techniques of catheter ablation are undergoing tremendous change. In the future, more sophisticated tools will make catheter ablation a more simplistic, safer procedure, and ablation techniques will probably lead to enhanced efficacy in eliminating AF altogether. As this happens, ablation will probably be used more and more frequently, perhaps even in patients with minimal symptoms of AF.

ADDITIONAL RESOURCES

Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339:659–666.

Seminal description of the source of ectopic foci that initiate atrial fibrillation.

Klein AL, Grimm RA, Murray RD, et al. For the Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med.* 2001;344:1411–1420.

Study describing the use of transesophageal echocardiography to obviate the need for anticoagulation before a cardioversion of AF.

Wyse DG, Waldo AL, DiMarco JP, et al. For the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825–1833.

Largest study thus far comparing the alternative strategies of rate or rhythm control with anticoagulation in the management of atrial fibrillation

EVIDENCE

Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation). Developed in collaboration with the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol.* 2006;48:149–246.

Latest comprehensive guidelines for the management of AF developed by the major cardiology societies.

Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke. Results from the National Registry of Atrial Fibrillation. *JAMA.* 2001;285:2864–2870.

Seminal study describing the use of a point scoring system to predict the risk for stroke in patients with AF.

Ventricular Tachycardia

Eugene H. Chung, Richard G. Sheahan, and J. Paul Mounsey

29

Ventricular tachycardia (VT) refers to a cardiac rhythm with a rate greater than 100 beats per minute (bpm) originating from the distal conduction system (distal to the His bundle) or ventricular myocardium. With few exceptions, VT presents with a wide QRS tachycardia on ECG. Although wide-QRS-complex tachycardia is not synonymous with VT, 80% of patients with a wide-complex tachycardia have VT as a diagnosis. VT is usually found in patients with underlying structural heart disease, predominantly coronary artery disease (CAD) and myocardial ischemia. It is often associated with hemodynamic instability and thus may cause symptoms such as chest pain, dyspnea, palpitations, or syncope, or lead to sudden cardiac death (SCD). The severity of symptoms determines the urgency of treatment.

This chapter reviews the pathogenesis, diagnosis, and treatment of VT. SCD, which most commonly results from VT, is addressed in greater detail in Chapter 30.

ETIOLOGY AND PATHOGENESIS

The type of VT, prognosis, and management of the arrhythmia are dependent on the presence of structural heart disease. The risk of sustained monomorphic VT is higher in patients with severe left ventricular (LV) dysfunction and extensive scarring. VT is also associated with myocardial ischemia, congestive heart failure, infiltrative cardiomyopathy, and high catecholamine states (Fig. 29-1). Any wide-complex tachycardia in a patient with a history of ischemic heart disease should be managed as VT until proven otherwise. In such a patient the mechanism is most often a reentry circuit in a region of healed myocardial infarction (MI). In these areas, gap junctions are often disrupted leading to slow and disorderly conduction by surviving cardiomyocytes. This physiology can lead to initiation and maintenance of reentrant circuits. Intracardiac recordings in the electrophysiology laboratory from the VT site of origin during sinus rhythm demonstrate fractionated low-amplitude electrograms that become continuous during VT. Sustained monomorphic VTs due to reentry can be reliably induced and terminated with ventricular programmed stimulation.

Patients with VT but no ischemic heart disease may still have reentry as the underlying cause. Patients with dilated cardiomyopathy (DCM), up to 60% of the time, have multiple patchy areas of fibrosis in the left ventricle on autopsy that can result in reentrant VT. Other mechanisms are possible in nonischemic cardiomyopathy; however, including enhanced automaticity or triggered activity, which can render these patients especially vulnerable to early or delayed after-depolarizations induced by QT interval–prolonging medications and/or metabolic abnormalities. Bundle branch reentry tachycardia, caused by a macroreentrant circuit involving the His-Purkinje system may also be responsible for wide-complex tachycardia in DCM patients (see below). In fact, a monomorphic wide-complex tachycardia arises from bundle branch reentry up to 40% of the time in patients with DCM.

DIFFERENTIAL AND ECG DIAGNOSIS

VT must be distinguished from other wide-complex tachycardias: supraventricular tachycardia (SVT) with bundle branch block, preexcitation of the ventricle during SVT due to anterograde conduction over an accessory pathway (antidromic reciprocating tachycardia), or ventricular pacing. The decision that a wide-complex tachycardia is VT is extremely important, because misdiagnosis can delay lifesaving treatment.

Many diagnostic algorithms exist for distinguishing VT from other wide-complex tachycardias. These can be confusing and very often unhelpful. ECG clues that, if present, favor VT, are reviewed below. The two main groups of diagnostic criteria relate to abnormalities of QRS morphology and identification of independent P-wave activity.

QRS Morphology

If the QRS morphology changes during the tachycardia relative to baseline, then the diagnosis is probably VT. Intraventricular conduction is always abnormal in VT and results in broadening of the QRS. In general, the QRS duration is usually longer than 120 milliseconds in VT with the caveat that VTs originating from the His-Purkinje system can, on rare occasion, have a normal QRS duration. Wellens and colleagues (1978) found that approximately 70% of VTs have a QRS duration longer than 140 milliseconds in patients with a right bundle branch block pattern. VTs with a left bundle branch pattern generally have a QRS duration longer than 160 milliseconds. Generally, a VT with right bundle branch block morphology (predominantly positive QRS complex in lead V_1) suggests an LV origin, whereas a VT with left bundle branch block morphology (predominantly negative QRS in lead V_1) suggests right ventricular (RV) origin (Fig. 29-2A). VT with a right bundle branch block pattern will not have a typical RS wave. The R wave is single or biphasic (QR or RS) or triphasic (with initial R wave taller than the smaller r´ and an S wave in between that crosses the baseline). V_6 typically demonstrates small r and large S waves. In VT with a left bundle branch block pattern, the duration of the initial R wave exceeds 30 milliseconds, and the beginning of the QRS to the nadir of the S wave exceeds 70 milliseconds. The S wave may be notched or slurred. Since SVT with aberration is due to a functional bundle branch block, the QRS should resemble a typical bundle branch block, and the S wave is neither notched or slurred. If V_6 is used, a qS pattern suggests VT. Though sometimes useful, these findings have limited sensitivity and specificity.

Change in the frontal plane QRS axis of more than 40 degrees, especially toward the "Northwest quadrant" between

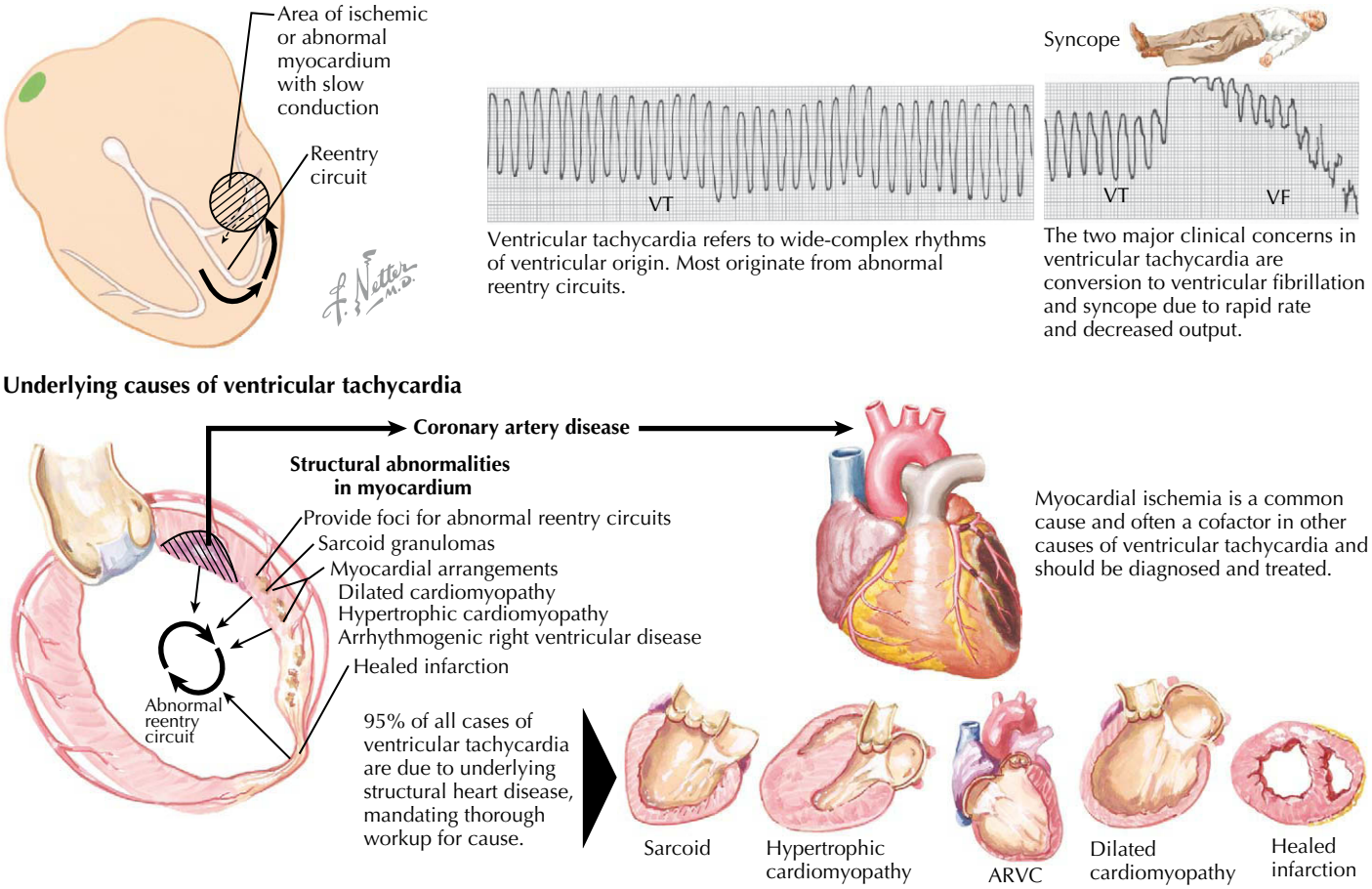


Figure 29-1 *Mechanisms of ventricular tachycardia (VT).* ARVC, arrhythmogenic right ventricular cardiomyopathy; VF, ventricular fibrillation.

–90 and –180 degrees (normal is –30 to 90 degrees), is highly suggestive of VT. The presence of a qS pattern in lead V_6 favors VT as a cause of wide-complex tachycardia. Concordance refers to uniform direction of the QRS complexes in the precordial leads, either all positive or all negative; for example, in VT with right bundle branch block pattern, the QRS is upright in all precordial leads (Fig. 29-2B).

Independent P-wave Activity

Atrioventricular (AV) dissociation indicates independent P-wave activity, and its presence is diagnostic of VT (Fig. 29-3A). The sinus rate is usually slower than the ventricular rate. The P waves should be upright in leads I and II if the origin is the sinus node. Variable deflections within the ST segment are suggestive of AV dissociation, and all 12 leads should be analyzed. AV dissociation can be difficult to discern, and its absence does not exclude VT, because the patient may have underlying atrial fibrillation (in up to one third of cases), or there may be retrograde ventricle-to-atrial conduction resulting in AV association in VT.

A fusion beat occurs when a sinus beat conducts to the ventricles via the AV node concurrent with a beat arising from the ventricles (Fig. 29-3B). The resulting QRS complex has an intermediate appearance between a normal beat and a VT beat. A capture beat occurs when the ventricle is depolarized via the AV node resulting in a narrow (normal-appearing) QRS (Fig. 29-3C). The presence of capture and/or fusion beats indicates AV dissociation and if present points to a diagnosis of VT. Their absence, however, does not exclude VT.

Additional Criteria

Two simplified approaches have been reported. One study used bundle branch pattern criteria and set VT as the default diagnosis (rather than SVT as in other criteria) and found a sensitivity of 96%. Another more recent algorithm has been reported that restricted ECG analysis to aVR (Fig. 29-4).

CLINICAL PRESENTATION

Most patients presenting with symptomatic VT, especially those older than 40 years of age, have underlying ischemic heart disease. The next most common substrate is cardiomyopathy, acquired or inherited, followed by valvular heart disease, channelopathies, and congenital heart disease. Symptoms associated with VT depend on many factors, including the VT rate, presence of structural heart disease, and medications.

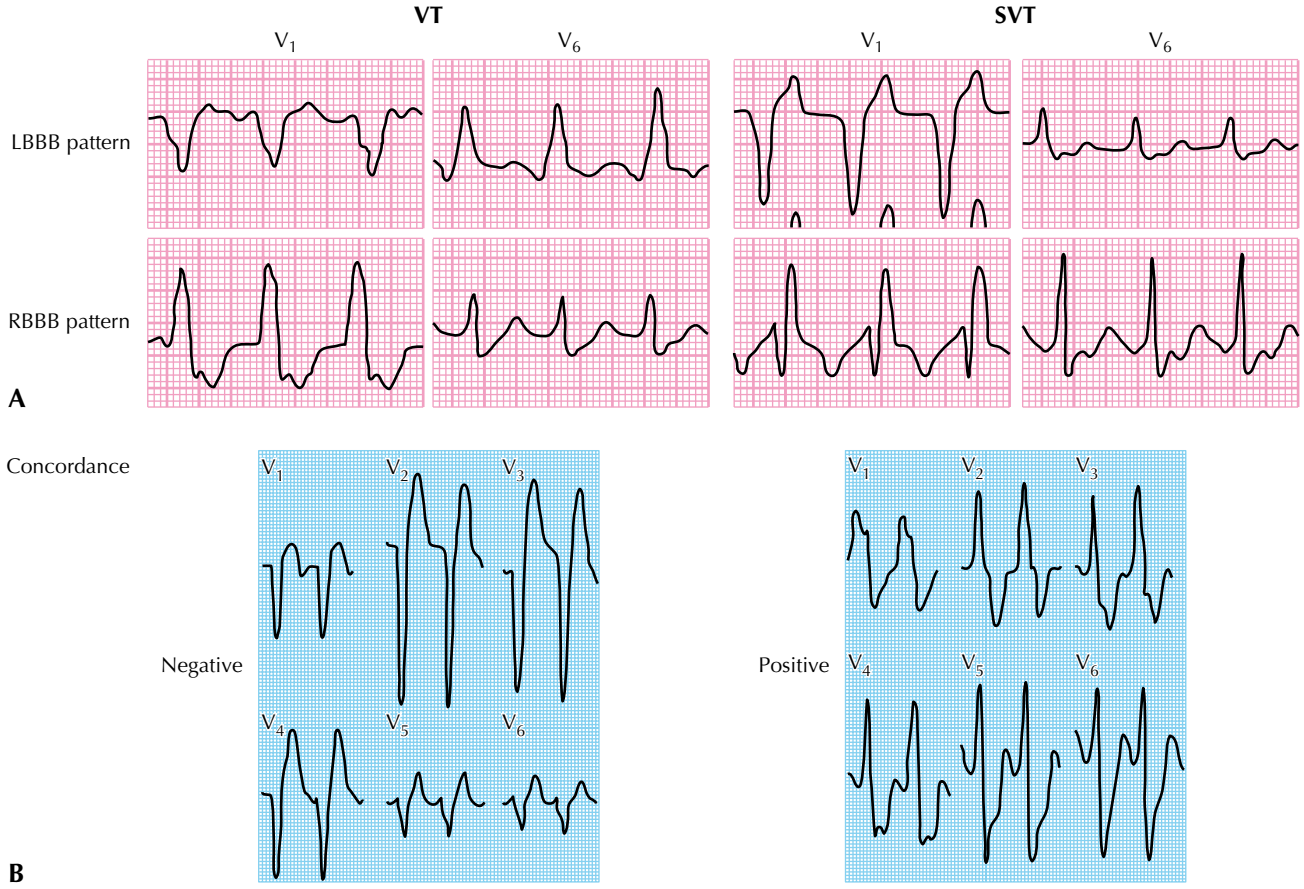


Figure 29-2 *Changes in QRS morphology in ventricular tachycardia (VT) and in supraventricular tachycardia (SVT).* (**A**) Typical patterns seen with left bundle branch block (LBBB) and in right bundle branch block (RBBB). (**B**) Typical patterns of positive and negative concordance in QRS complexes. See text for details.

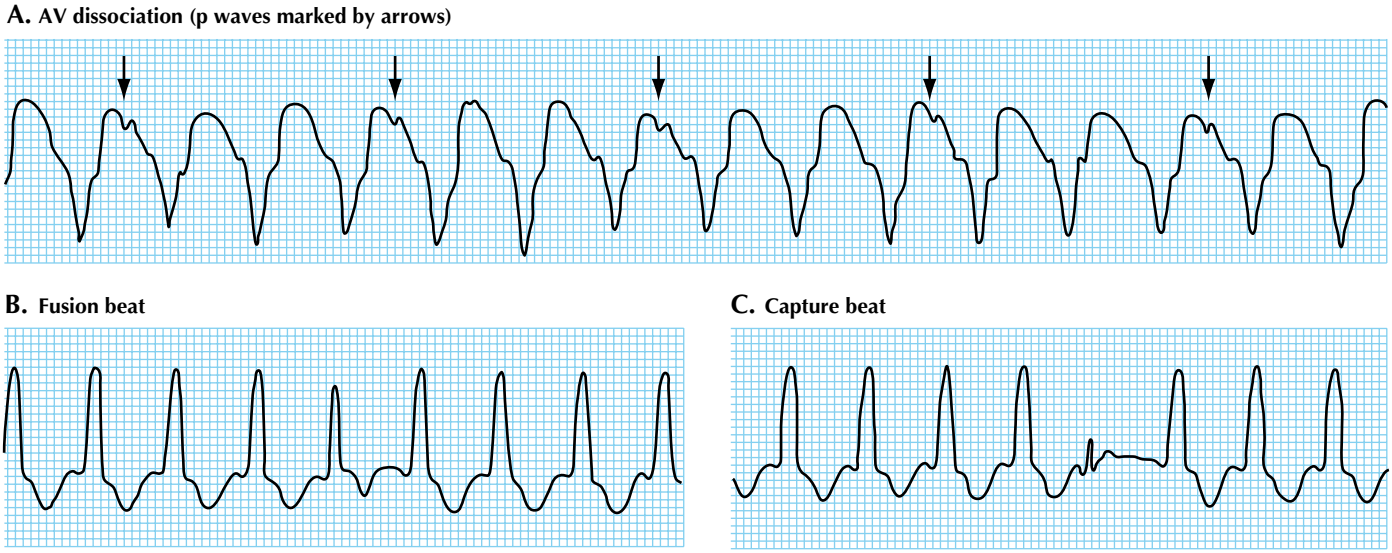


Figure 29-3 *Electrocardiographic signs of independent P-wave activity.* AV, atrioventricular.

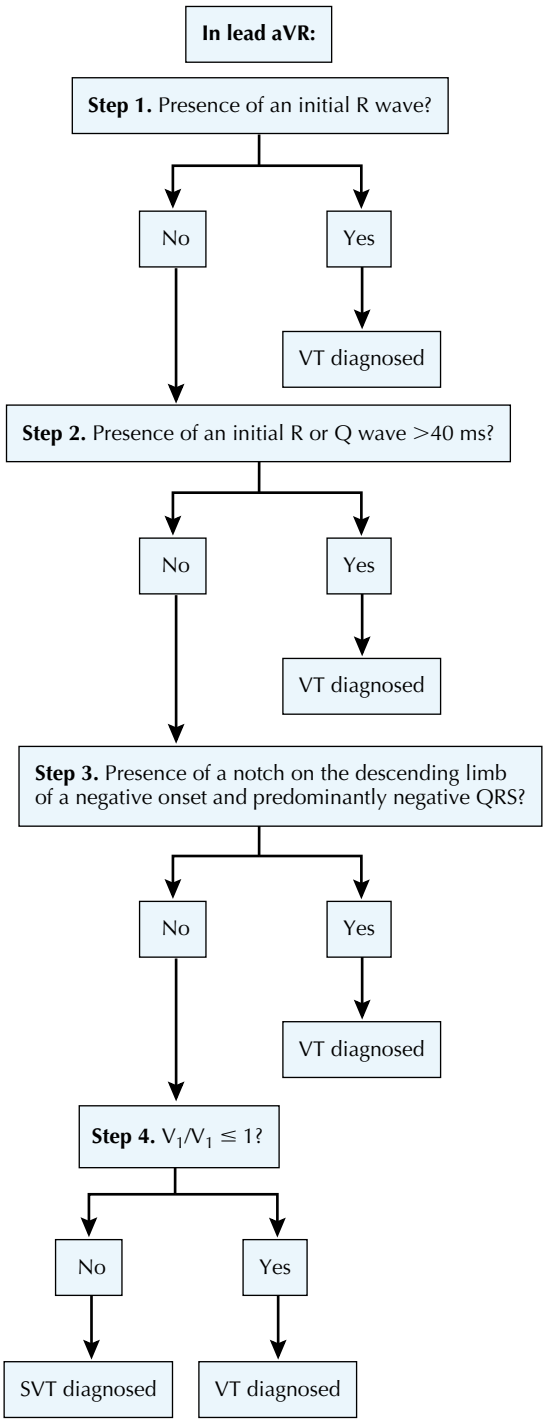


Figure 29-4 *New aVR algorithm for diagnosing wide-complex tachycardia.* SVT, supraventricular tachycardia; VT, ventricular tachycardia. Modified from Vereckei A, Duray G, Szénási G, et al. New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. *Heart Rhythm.* 2008;5:89–98.

Hemodynamics may be stable in a patient presenting with VT, and thus they are not reliable for establishing the diagnosis. Exercise-induced VT in a normal heart may be better tolerated than even a slow VT in patients with a low ejection fraction (EF). Anemia or preexisting orthostatic hypotension in a patient with VT will usually result in early hemodynamic compromise. Patients may present with a range of symptoms: palpitations (regular or irregular), dizziness, shortness of breath, chest pain, presyncope, syncope, congestive heart failure, or SCD. "Cannon" A waves may present on physical examination, suggesting AV dissociation.

DIAGNOSTIC APPROACH

Some maneuvers may aid in differentiating SVT from VT in the hemodynamically stable patient. During an episode of tachycardia, carotid massage or Valsalva maneuver increases vagal stimulation and is most useful for tachyarrhythmias *other* than VT. Vagal stimulation can slow conduction over the AV node and thereby can terminate an AV nodal reentrant tachycardia or AV reentrant tachycardia, or unmask atrial flutter waves. Although the termination of a wide-complex tachycardia with intravenous adenosine favors a diagnosis of SVT with aberrancy, adenosine-responsive VT has been reported in patients with normal LV function and, thus, responsiveness to adenosine does not rule out VT. However, the idea that the absence of a response to adenosine rules in a diagnosis of VT is also a fallacy. The most common reason adenosine fails to terminate an adenosine-sensitive arrhythmia is that an insufficient dose reaches the heart before the drug is inactivated in the circulation. Moreover, adenosine can precipitate hemodynamic compromise in a patient whose condition is already tenuous and promote ventricular fibrillation (VF), and thus it should only be used with caution in a patient in whom VT is the most likely diagnosis (see Chapter 27).

ACUTE MANAGEMENT AND THERAPY

Optimum Treatment

Acute management combines stabilizing the patient and terminating the VT and takes priority over the diagnostic evaluation. If the patient is maintaining a pulse but is presyncopal, hypotensive, or in severe respiratory distress, the patient should, after appropriate sedation, receive a synchronized external direct current (DC) cardioversion. If synchronization is difficult because of the width of the QRS complex, then unsynchronized defibrillation should be performed. Patients who are pulseless and/or unresponsive should be immediately treated according to the Advanced Cardiac Life Support guidelines with cardiopulmonary resuscitation and high-energy defibrillation.

If the VT is well tolerated, agents such as intravenous procainamide, lidocaine, amiodarone, and magnesium may be given. Procainamide is more effective than lidocaine unless the VT is in the context of acute myocardial ischemia or infarction. Amiodarone often requires 24 to 48 hours for effect and rarely converts monomorphic VT acutely. Amiodarone may have to be administered concurrently with or after another drug (such as procainamide) has converted the rhythm. Intravenous magnesium is most useful in torsades de pointes. If the VT fails to terminate, a synchronized DC cardioversion should be performed, but only after the patient has received adequate and appropriate sedation. Potential precipitating causes such as

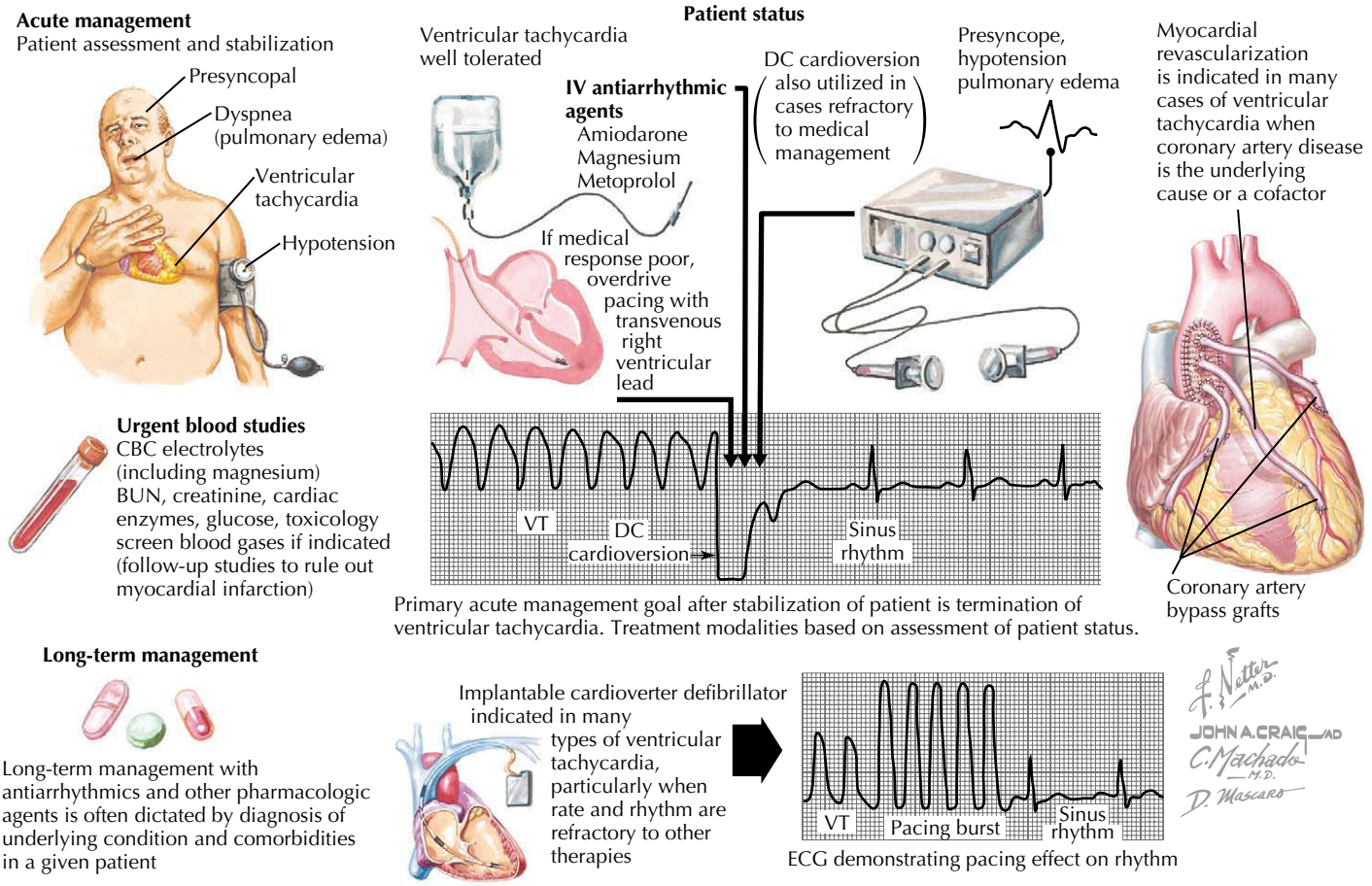


Figure 29-5 *Management of ventricular tachycardia (VT).* BUN, blood urea nitrogen; CBC, complete blood count; DC, direct current; ECG, electrocardiogram; IV, intravenous.

myocardial ischemia, congestive heart failure, hypoxia, electrolyte disturbances, and/or drug toxicities should be addressed. Subsequent management of the patient with VT depends on the etiology and the absence of reversible causes. Blood samples should be urgently obtained for complete blood count, electrolytes including magnesium, blood urea nitrogen, creatinine, cardiac markers, blood glucose, and toxicology screen. When appropriate, an arterial blood gas measurement should also be obtained (Fig. 29-5).

For patients with an implantable cardioverter defibrillator (ICD), therapies should be delivered within the first 30 seconds to few minutes of arrhythmia onset. Interrogation of the device will usually provide sufficient information to determine whether the arrhythmia precipitated overdrive pacing or defibrillation was indeed VT, as well as the frequency and treatment of like (and other) tachyarrhythmias. A recurrent need for shocks requires exploration of precipitating triggers, programming of the ICD, and adjunctive antiarrhythmics if indicated. If a patient has presumed VT that has not triggered the ICD to initiate either overdrive pacing or cardioversion, there are several possible explanations. The VT rate could be slower than the programmed detection rate, or the arrhythmia could be mistaken for SVT by the ICD. If the ICD cannot be urgently reprogrammed by experienced personnel, the patient should be treated as if no ICD were present. The ICD should then be evaluated as soon as possible thereafter.

Avoiding Treatment Errors

In general, a patient with a new wide-complex tachycardia should be presumed to have VT until proven otherwise, and intravenous verapamil or diltiazem should be avoided. Such drugs can precipitate hemodynamic compromise in a patient whose condition is already tenuous and promote VF. AV-nodal–blocking drugs of any kind are absolutely contraindicated unless there is a very high index of suspicion that the diagnosis is SVT. Treatment of VT with AV-nodal blockers can be disastrous. Treatment of SVT with antiarrhythmic drugs (as if it is VT) is not.

LONGER TERM MANAGEMENT AND THERAPY

Optimum Treatment

The long-term approach to preventing recurrent VT and SCD combines risk stratification, antiarrhythmic medications, and/or ICDs. Primary and secondary prevention of SCD is discussed in more detail in Chapter 30.

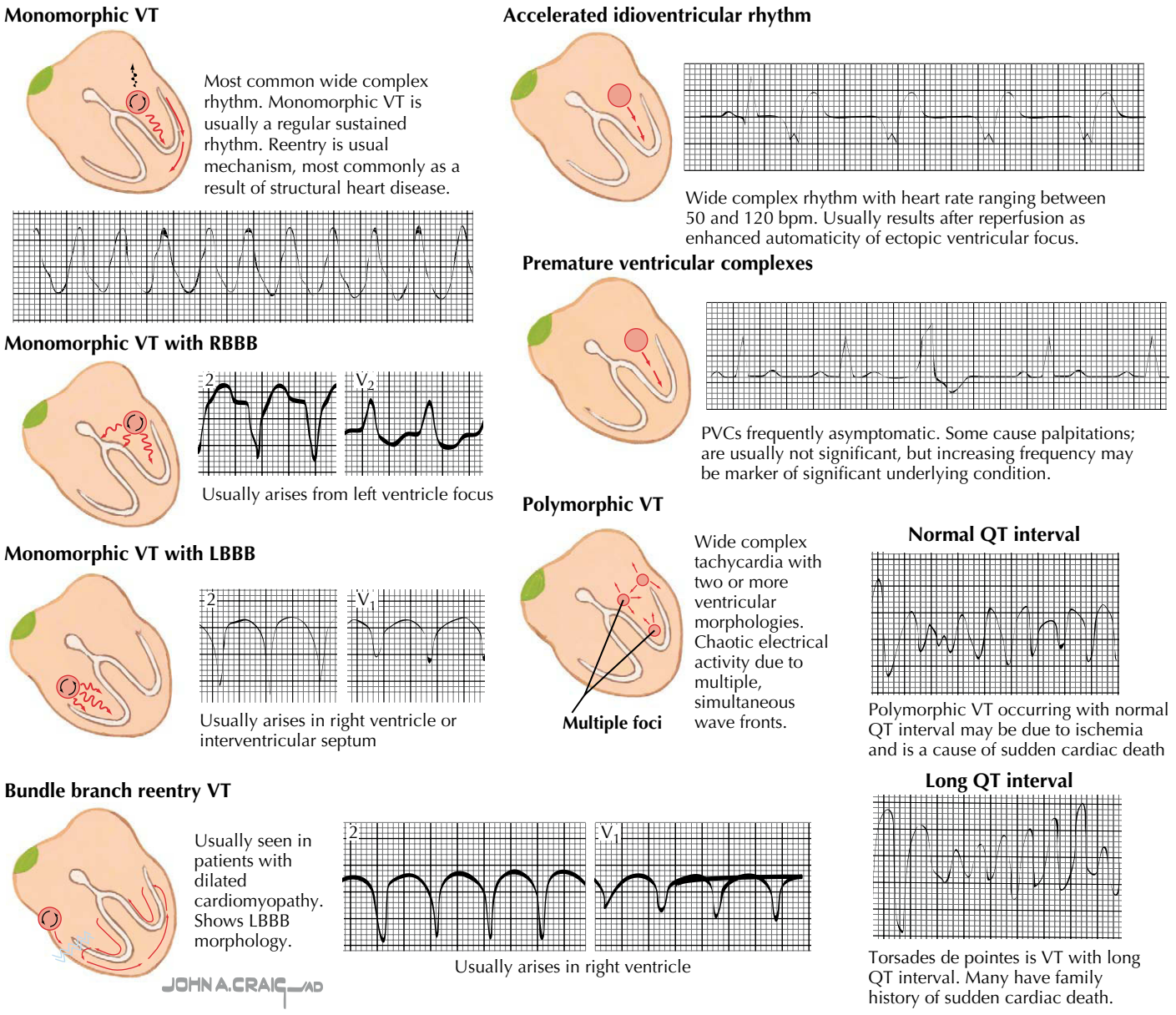


Figure 29-6 *Types of ventricular tachycardia (VT).* LBBB, left bundle branch block; PVCs, premature ventricular complexes; RBBB, right bundle branch block.

Patients with a history of sustained VT and depressed LV function or a history of a cardiac arrest clearly benefit from ICD implantation. If recurrent VT develops after the ICD is placed, resulting in multiple shocks, amiodarone can be used to slow down the VT cycle length and possibly permit overdrive pacing as a means of termination of subsequent episodes via the ICD. If amiodarone is not effective, β-blockers, sotalol, procainamide, and mexiletine are options. These are usually, however, not as effective as amiodarone. Medication-refractory, hemodynamically stable VT can be studied in the electrophysiology laboratory. By utilizing activation mapping and three-dimensional (3D) electroanatomic mapping techniques, the circuit can often be localized and transected with several radiofrequency ablation lesions. In patients with ischemic heart disease or DCM, multiple circuits may be present, rendering radiofrequency ablation very difficult. In patients with complex recurring VT, which is hemodynamically poorly tolerated, scar mapping in sinus rhythm with linear ablations, which connect scar tissue, may be effective in decreasing the frequency of VT.

The next sections review specific types of VT, associated conditions, and long-term management approaches. Figure 29-6 shows examples of different types of VT.

Monomorphic Ventricular Tachycardia

Monomorphic VT is the most common wide-complex rhythm. It is usually a regular sustained rhythm originating from the

ventricles. The mechanism depends on the underlying etiology.

CORONARY ARTERY DISEASE

Patients who have a healed MI without ongoing ischemia may present with VT, even years after the original MI. (Polymorphic VT is usually seen in this population with ongoing ischemia or infarction and is discussed later in this chapter.) Viable myocardial tissue within the scar provides an area where the slowed conduction that is critical to the maintenance of a VT reentrant circuit may occur. Ventricular aneurysms are also associated with VT. Patients who present with VT and CAD initially require an ischemic evaluation and, if necessary, revascularization. In patients for whom revascularization is possible, an evaluation of the need for placement of an ICD for secondary prevention should be performed following revascularization. An ICD is superior to amiodarone or other antiarrhythmic agents in decreasing mortality in patients with CAD and VT. In patients who have recurrent VT, episode frequency can be reduced by antiarrhythmic agents such as amiodarone or sotalol and/or radiofrequency ablation.

DILATED CARDIOMYOPATHY

VT may occur in patients with DCM. Coexistent CAD must be excluded. Patients with DCM and no significant CAD should undergo ICD implantation without further evaluation, because an electrophysiology study (EPS) is often not useful in these cases. ICDs are also superior to amiodarone in prolonging survival in DCM patients.

One circumstance that requires special consideration is individuals in whom bundle branch reentrant VT is suspected. Bundle branch reentrant VT presents as VT with a left bundle branch block morphology. Bundle branch reentrant VT occurs with His-Purkinje dysfunction and a prolonged HV interval (i.e., the time from the His bundle electrogram to the earliest recorded ventricular activation). Retrograde conduction over the left bundle branch activates transseptal conduction, which then activates the right bundle branch, establishing the reentrant circuit. Although most patients with bundle branch reentrant VT do require ICD placement, radiofrequency ablation of the right bundle branch may completely or largely prevent VT recurrences, reducing the frequency of ICD discharges and prolonging device life.

In general, patients with DCM (especially those with VT) should be treated with the maximum tolerated doses of β-blockers and angiotensin-converting enzyme inhibitors. Amiodarone or sotalol may also help patients with recurrent VT or atrial arrhythmia who have already received ICD therapy. The diagnosis of tachycardia-induced cardiomyopathy should be considered in patients with DCM and persistent atrial arrhythmias. LV size and function may return to normal or near normal with control of atrial tachyarrhythmias.

HYPERTROPHIC CARDIOMYOPATHY

VT in hypertrophic cardiomyopathy requires ICD placement. Risk factors for SCD are syncope, nonsustained VT, family history of SCD, insufficient blood pressure response with exercise, and interventricular septal thickness greater than 30 mm as determined by echocardiography. Patients with two or more risk factors should receive a prophylactic ICD even in the absence of VT. Amiodarone does not improve mortality but may reduce recurrent tachyarrhythmias. Where possible, β-blockers should be prescribed. Sotalol or dofetilide may also help patients with frequent ICD discharges. Septal alcohol ablation has been employed in recent years to relieve symptomatic patients of LV outflow tract obstructions, but this procedure carries a risk of subsequent complete heart block. Additionally, it creates a septal scar that may serve as a nidus for future tachyarrhythmias. In individuals for whom septal alcohol ablation is performed to control symptoms, ICD placement is generally indicated.

SARCOIDOSIS

Sarcoid granulomas can infiltrate anywhere in the ventricular myocardium and become foci for abnormal automaticity, or they may disrupt ventricular depolarization and repolarization. VT with sarcoidosis requires an ICD. β-blocker therapy is also generally required in these patients.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic RV cardiomyopathy (ARVC; also called *arrhythmogenic RV dysplasia*) is a condition of segmental or diffuse replacement of the RV myocardium with fatty and fibrofatty tissue. Fatty tissue replacement is most severe in areas near the epicardium and mid-myocardium in the RV free wall, but the disease may progress to the left ventricle. ARVC is inherited as an autosomal-dominant condition; it is estimated that half the patients who have ARVC have a family history of it. It is an important cause of SCD in young persons with VT and apparently normal hearts. Classic findings on ECG in sinus rhythm are right bundle branch block, inverted T waves in leads V_1 to V_3, and a terminal notch in the QRS in V_1 to V_3 ("epsilon wave"). VT in ARVC requires an ICD. Because the RV free wall is usually abnormal in these patients, the ICD lead must be placed in the RV septum to avoid myocardial perforation through the fatty RV wall and potential alterations in the sensing and capture thresholds during the course of this progressive condition. Radiofrequency ablation has equivocal results, given the progression of myocardial replacement.

RIGHT VENTRICULAR OUTFLOW TRACT VENTRICULAR TACHYCARDIA

RV outflow tract VT is a rare catecholamine-induced tachycardia that typically occurs in young patients with structurally normal hearts and is often induced by exercise. The ECG shows a left bundle branch block with a right or normal axis. An automatic or triggered mechanism is probably responsible for this tachycardia. RV outflow tract VT not only responds to adenosine and β-blockers, but it is also one of the rare VTs that responds to verapamil and adenosine. SCD rarely occurs in these patients, and for this reason they may be treated

pharmacologically. For recurrent episodes, an EPS with radiofrequency ablation should be performed. During EPS, isoproterenol is frequently required to initiate and/or maintain the tachycardia for mapping the VT origin, but the tachycardia can usually be cured.

IDIOVENTRICULAR LEFT VENTRICULAR TACHYCARDIA (FASCICULAR TACHYCARDIA)

Idioventricular left ventricular tachycardia typically occurs in young, predominantly male patients with structurally normal hearts. This VT is unique in that it is responsive to verapamil. The ECG usually shows almost classic right bundle branch block with left-axis deviation. The earliest ventricular activation usually occurs at the LV apex or in the mid-left ventricular septum. During mapping, a discrete electrical potential can often be identified. The arrhythmia is thought to result from a triggered mechanism. If the patient remains symptomatic despite pharmacologic therapy, an EPS and radiofrequency ablation are needed, including mapping of the earliest activation and identification of a discrete potential. SCD is rare. Although treatment with verapamil can be useful, it should only be considered in consultation with a cardiac electrophysiologist, given that verapamil is contraindicated for other forms of VT.

Nonsustained Ventricular Tachycardia

Nonsustained monomorphic VT (NSVT) is defined as a wide-complex tachycardia of at least three beats lasting less than 30 seconds. Some patients are asymptomatic; others may experience palpitations, dyspnea, chest pain, dizziness, presyncope, or syncope. Management of NSVT depends on the rhythm's etiology and the presence of underlying structural heart disease. Asymptomatic patients with NSVT and no structural heart disease usually do not require further evaluation.

For patients with CAD and NSVT, an ischemic evaluation is required, and revascularization should be performed if necessary. Any proarrhythmic medication should be withdrawn. If no reversible cause for the VT is found, then further management hinges on LV function. Based on several studies, patients with NSVT and diminished LV function often are treated with ICD placement. For patients with left ventricular ejection fractions between 35% and 40%, the decision is generally individualized based on that individual's overall risk profile. The Multicenter Unsustained Tachycardia Trial (MUSTT, 1999) and Multicenter Automatic Defibrillator Implantation Trial (MADIT I, 1996), which studied post-MI patients with NSVT, EF less than 35% to 40%, and inducible VT on EPS, showed a significant decrease in mortality from ICD placement versus antiarrhythmic therapy. The MADIT II (2002) Study showed that post-MI patients with EF less than 30% and couplets or over 10 premature ventricular complexes (PVCs) per hour who did not undergo EPS also benefited from ICD therapy. In those with NSVT and DCM (EF < 36%), the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE, 2004) Study showed survival benefit for those receiving an ICD.

Adjunctive therapy with β-blockers and antiarrhythmics such as sotalol or amiodarone may be required for symptomatic patients. Flecainide is contraindicated in patients with CAD and should generally be used only in patients with structurally normal hearts. In patients with NSVT and a structurally normal heart who remain symptomatic or are intolerant to medications, radiofrequency ablation using careful mapping with a 3D electroanatomic system is also an effective strategy.

Polymorphic Ventricular Tachycardia

Polymorphic VT is a wide-complex tachycardia that has two or more ventricular morphologies. Patients presenting with acute myocardial ischemia may have polymorphic VT, and the possibility of ongoing ischemia should be addressed immediately. Electrolytes should be obtained and corrected. Although these patients' QTc interval on ECG is within the normal range, they are at very high risk for VF and should be monitored in a coronary care unit. If the polymorphic VT persists, consideration should be given to implanting an ICD and initiating an antiarrhythmic drug. In the absence of ischemia, polymorphic VT with DCM, hypertrophic cardiomyopathy, sarcoidosis, or ARVC is associated with a poor prognosis. Almost always, ICD implantation and subsequent therapy with a β-blocker or other antiarrhythmic are indicated.

In patients with a structurally normal heart and a negative ischemic evaluation, a polymorphic VT should prompt careful evaluation of the underlying ECG to exclude acquired or congenital long QT syndrome. Torsades de pointes is a polymorphic VT most commonly found in patients with a prolonged QT interval. Patients should be carefully assessed for metabolic derangements (i.e., hypomagnesemia, hypokalemia) or medications that may prolong the QT interval as well as relevant past medical history. For patients with symptomatic long QT syndrome and a family history of SCD, an ICD with atrial pacing capacity should be implanted. The addition of β-blockers should be considered in those with long QT syndrome type 1 (see Chapter 30).

Accelerated Idioventricular Rhythm

Accelerated idioventricular rhythm (AIVR) is a wide-complex rhythm with a heart rate between 60 and 110 bpm. AIVR is an arrhythmia often observed after reperfusion therapy of acute MI and occasionally seen in other situations. AIVR results from enhanced automaticity of an abnormal ectopic ventricular focus. This focus discharges earlier than the sinus node. AIVR is generally well tolerated and requires no therapy. Increasing discharges from the sinus node at a rate faster than the ectopic focus will overcome the AIVR. Therefore, atropine or atrial pacing should be considered. AIVR is not associated with an increased risk for development of VF or increased mortality.

Premature Ventricular Complexes

PVCs are premature QRS complexes originating from the ventricular myocardium. Bigeminy refers to alternating normal and premature (and wide) QRS complexes, and trigeminy refers to two normal beats for every PVC. PVCs may be a marker for significant underlying conditions such as CAD, congestive heart failure, DCM, hypertrophic cardiomyopathy, infiltrative conditions, sarcoidosis, and ARVC. They may be a precursor to one

of the outflow tract VTs, but they may be multifocal as well. In the absence of CAD or structural heart disease, PVCs are generally benign. In the symptomatic patient, a β-blocker should be considered. Ambulatory ECG monitoring can document the PVC burden. Patients are at increased risk of a tachycardia-induced cardiomyopathy when 20% or more of recorded beats are ventricular ectopy. For patients whose symptoms persist and who have frequent PVCs (>5% of recorded beats), pharmacologic therapy with flecainide or sotalol and/or radiofrequency ablation should be considered.

FUTURE DIRECTIONS

In a patient presenting with a new wide-complex tachycardia, the diagnosis of VT should be excluded first from the ECG before other diagnoses are considered. Initial management decisions are driven by the patient's hemodynamic stability. Long-term therapy with ICDs has been well established through numerous clinical trials. The majority of patients presenting with VT have underlying CAD, and thus revascularization (when indicated) and aggressive risk factor modification is important for primary and secondary prevention. The presence of structural heart disease remains the best prognostic barometer for those at risk of VT. Antiarrhythmic drugs are often required to suppress recurrent symptomatic arrhythmias. For patients with medically refractory VT, catheter ablation techniques continue to rapidly improve, particularly in the area of electroanatomic mapping. Finally, developments in pharmacogenetics may improve the likelihood of identifying patient populations who would benefit from certain antiarrhythmic agents.

ADDITIONAL RESOURCES

Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure (SCD-HeFT). *N Engl J Med.* 2005;352:2022–2025.

The SCD-HeFT Trial included both ischemic and nonischemic cardiomyopathy patients. In these patients with EFs less than or equal to 35% and NYHA class II or III heart failure, overall mortality was significantly reduced in the ICD group (compared to amiodarone).

ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2005;112(suppl 1):IV-1–IV-203. Available at: <http://circ.ahajournals.org/content/vol112/24_suppl/#_AMERICAN_HEART_ASSOCIATION_GUIDELINES_FOR_CARDIOPULMONARY_RESUSCITATION_AND_EMERGENCY_CARDIOVASCULAR_CARE>; Accessed 23.02.10.

This report provides the latest guidelines from the American Heart Association.

Edhouse J, Morris F. ABC of clinical electrocardiography: broad complex tachycardia Part I. *Br Med J.* 2002;324:719–722.

The first of a series of reviews on the basics of electrocardiography.

Griffith MJ, Garratt CJ, Mounsey JP, et al. Ventricular tachycardia as default diagnosis in broad complex tachycardia. *Lancet.* 1994;343:386–388.

This paper proposes using VT as the default diagnosis when evaluating a new broad-complex tachycardia in contrast to most algorithms, which are based on a default diagnosis of SVT.

Wellens HJ, Bar FW, Lie K. The value of the electrocardiogram in the differential diagnosis of a tachycardia with widened QRS complex. *Am J Med.* 1978;64:27–33.

This was a retrospective case study that helped establish criteria to distinguish ventricular ectopy from aberrantly conducted SVT.

EVIDENCE

Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med.* 1999;341:1882–1890.

The MUSTT Study, along with MADIT, examined post-MI patients with NSVT, EF less than 35% to 40%, and inducible VT on EPS and showed a significant decrease in mortality from ICD placement as opposed to antiarrhythmic therapy.

Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation.* 1991;83:1649–1659.

Reports the stepwise Brugada criteria for diagnosing VT.

Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med.* 2004;350:2151–2158.

In those with NSVT and DCM (EF < 36%), the DEFINITE Study showed survival benefit for those receiving an ICD.

Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med.* 1996;335:1933–1940.

The MADIT Study, along with MUSTT, examined post-MI patients with NSVT, EF less than 35% to 40%, and inducible VT on EPS and showed a significant decrease in mortality from ICD placement as opposed to antiarrhythmic therapy.

Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877–883.

The MADIT II Study showed that post-MI patients with EF less than 30% and couplets or over 10 PVCs per hour who did not undergo EPS also benefited from ICD therapy.

Vereckei A, Duray G, Szénási G, et al. New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. *Heart Rhythm.* 2008;5:89–98.

Presents a new and simplified algorithm using aVR for differentiating VT from SVT and compares it to previously published approaches.

Sudden Cardiac Death

Eugene H. Chung and J. Paul Mounsey

30

Sudden cardiac death (SCD) is defined as any death from a cardiac cause occurring within an hour of symptom onset. SCD occurs in 300,000 to 450,000 individuals in the United States annually, which translates to an overall incidence of 0.1% to 0.2% per year. The term *SCD* is also used to refer to an event from which an individual is resuscitated or spontaneously recovers—events probably more appropriately termed *cardiac arrest*. SCD has many potential etiologies (Box 30-1). Patients with coronary artery disease (CAD) and prior myocardial infarction (MI) have an annual incidence of SCD of up to 30% and are responsible for approximately 70% of fatal arrhythmias. Other high-risk groups include patients with prior cardiac arrest, congestive heart failure, cardiomyopathy (dilated, infiltrative, or hypertrophic), valvular heart disease, myocarditis, and congenital heart disease. Screening patients potentially at risk for SCD and addressing their risk factors is the crux of primary prevention. Secondary measures aim to prevent recurrent events in survivors of aborted SCD (Fig. 30-1).

ETIOLOGY AND RISK FACTORS

The pathogenic electrical events leading to SCD are most commonly ventricular tachycardia (VT), ventricular fibrillation (VF), and eventually asystole (Fig. 30-2). Approximately 80% of SCDs involve VT, VF, or torsades de pointes; the remaining 20% are due to bradyarrhythmias. SCD is most commonly associated with underlying structural heart disease. Less than 20% of out-of-hospital victims of SCD recover to hospital discharge. The likelihood of resuscitation diminishes 10% for every minute of delay. It has been estimated that 50% of those who survive a cardiac arrest will die within 3 years. This underscores the importance of primary and secondary prevention.

CAD accounts for 70% to 80% of SCD cases, especially in Western societies in patients over the age of 35. As such, two of the leading risk factors are previous heart attack and documented CAD. In those with chronic ischemic disease, the most powerful predictor is an ejection fraction (EF) less than 40%. Following CAD, patients with nonischemic cardiomyopathies (hypertrophic and dilated) and EF less than 40% are at the highest risk. Additional major risk factors for SCD include congestive heart failure of any etiology and prior history of cardiac arrest. Channelopathies, which result in an increased risk for cardiac arrhythmias, and congenital heart disease are less common causes of SCD.

DIFFERENTIAL DIAGNOSIS

The most common etiologies are discussed in the sections that follow (see also Box 30-1).

Ischemic Heart Disease

Overwhelmingly, the most common cause of SCD is ischemic heart disease resulting from coronary atherosclerosis. Arteritis, dissection, spasm, and congenital coronary anomalies are very rare causes associated with myocardial ischemia. CAD has been attributed to 70% to 80% of all SCDs. In a study of 84 survivors of out-of-hospital cardiac arrest, immediate coronary angiography revealed significant disease of probable etiologic significance in 71% of patients; approximately one half of these patients had complete occlusions. Acute occlusion of the left anterior descending or left circumflex coronary artery portends a higher risk of SCD. Patients with angina and prior MI are at much higher risk than those without any clinical manifestation of CAD. Unfortunately, SCD can be the first manifestation of CAD in one third of CAD patients.

Causes of SCD in the CAD population include myocardial ischemia or infarction, heart failure, electrolyte imbalance, drug toxicity, or primary (no precipitating cause identified). The probable mechanisms for VT or VF in patients with CAD are acute ischemia and reentry via myocardial scar, especially in those with a prior infarct. A meta-analysis of four non–ST-elevation MI (NSTEMI) trials found the risk of sustained or unstable ventricular arrhythmias (VT or VF) to be 2.1% (vs. 10% in ST-segment elevation MI, STEMI) during the initial hospital admission. Patients with VT and VF had the highest mortality rate in the first 30 days (>60%) post-MI, followed by patients with VF only (>45%), followed by patients with VT only (>30%). This trend was consistent at 6 months, correlating to a 5- to 15-fold increase in mortality within 6 months in patients with these arrhythmias. Patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) Trial, which studied fibrinolytic therapies for STEMI, demonstrated higher overall incidences of sustained arrhythmias than in NSTEMI patients: specifically, 3.5% for VT only, 4.0% for VF only, and 2.6% for both VT and VF. Of these arrhythmias, 80% to 85% occurred within the first 48 hours ("early"). In-hospital mortality and 1-year mortality (for those who survived longer than 30 days) after discharge of these patients were much higher among those with VT, VF, or VT and VF (18.6%, 24%, or 44% in-hospital, and 7.2%, 2.9%, or 7.1% 1 year, respectively) than patients without these arrhythmias (4.2% in-hospital, 2.7% 1-year). Patients with "late" (after the first 48 hours) ventricular arrhythmias had increased mortality at 1 year (24.7% for VT, 6.1% for VF, 4.7% for VT and VF) and were more likely to have had a previous MI, previous bypass surgery, and a longer time from the onset of MI and receiving treatment.

Nonischemic Cardiomyopathy

IDIOPATHIC DILATED CARDIOMYOPATHY

Ten to fifteen percent of SCD cases are attributable to cardiomyopathies not associated with CAD. In patients with dilated cardiomyopathies, the presence of nonsustained VT, syncope, and/or advanced heart failure are high-risk predictors. SCD is

Box 30-1 Major Etiologies of Sudden Cardiac Death

Ischemic heart disease
Coronary atherosclerosis (myocardial ischemia or infarction)
Congenital coronary anomalies
Arteritis
Dissection
Coronary spasm

Nonischemic heart disease
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Arrhythmogenic RV dysplasia or cardiomyopathy
Congenital heart disease (tetralogy of Fallot, Ebstein's anomaly, transposition of great arteries)

Primary electrophysiology disorders
Long QT syndrome
Brugada syndrome
Idiopathic VF
Catecholaminergic polymorphic VT
Commotio cordis
Metabolic derangements

RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

the major cause (up to 72% in some studies) of death in patients with nonischemic cardiomyopathy. Most fatal arrhythmias are thought to be tachyarrhythmias, mainly polymorphic, and less commonly monomorphic, VT. The primary mechanism of polymorphic VT and VF is unknown, but subendocardial scarring and interstitial and perivascular fibrosis are probably involved. A particular type of monomorphic VT (see Chapter 29) caused by bundle branch reentry is characteristic of nonischemic cardiomyopathy. In bundle branch reentry, a "macro" reentrant circuit involving both bundles, the Purkinje system, and the myocardium can be documented.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is an autosomal-dominant inherited disorder estimated to affect 1 in 500 adults (see Chapter 19 and Figure 30-3). The overall risk of SCD in patients with HCM is estimated at 1% to 4% per year, but within subgroups of patients with this disease the risk of SCD varies substantially. All first-degree relatives of a patient with HCM who had SCD must be screened. Generally, patients with

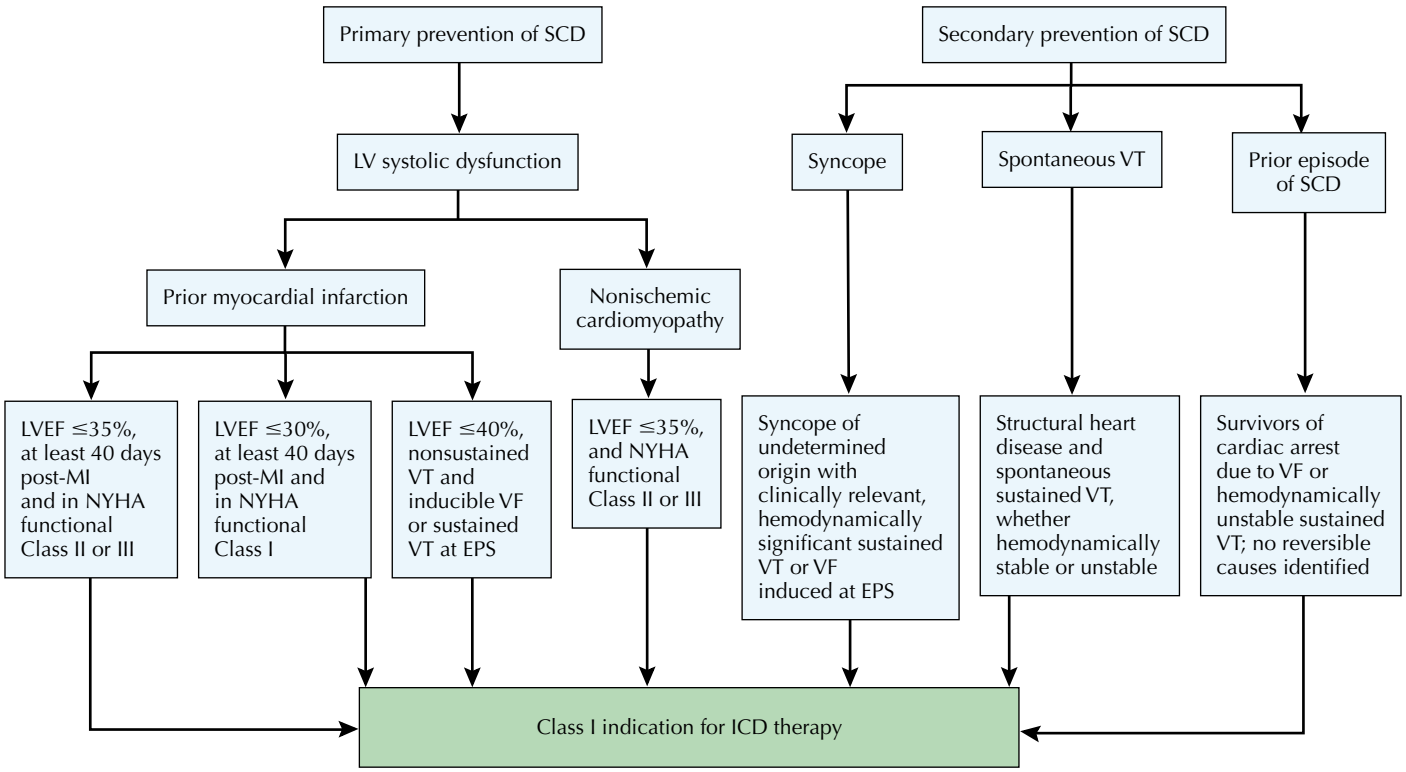


Figure 30-1 *Treatment algorithm for ICD-based primary and secondary prevention of sudden cardiac death (SCD).* DCM, dilated cardiomyopathy; EPS, electrophysiologic study; ICD, implantable cardiac defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.

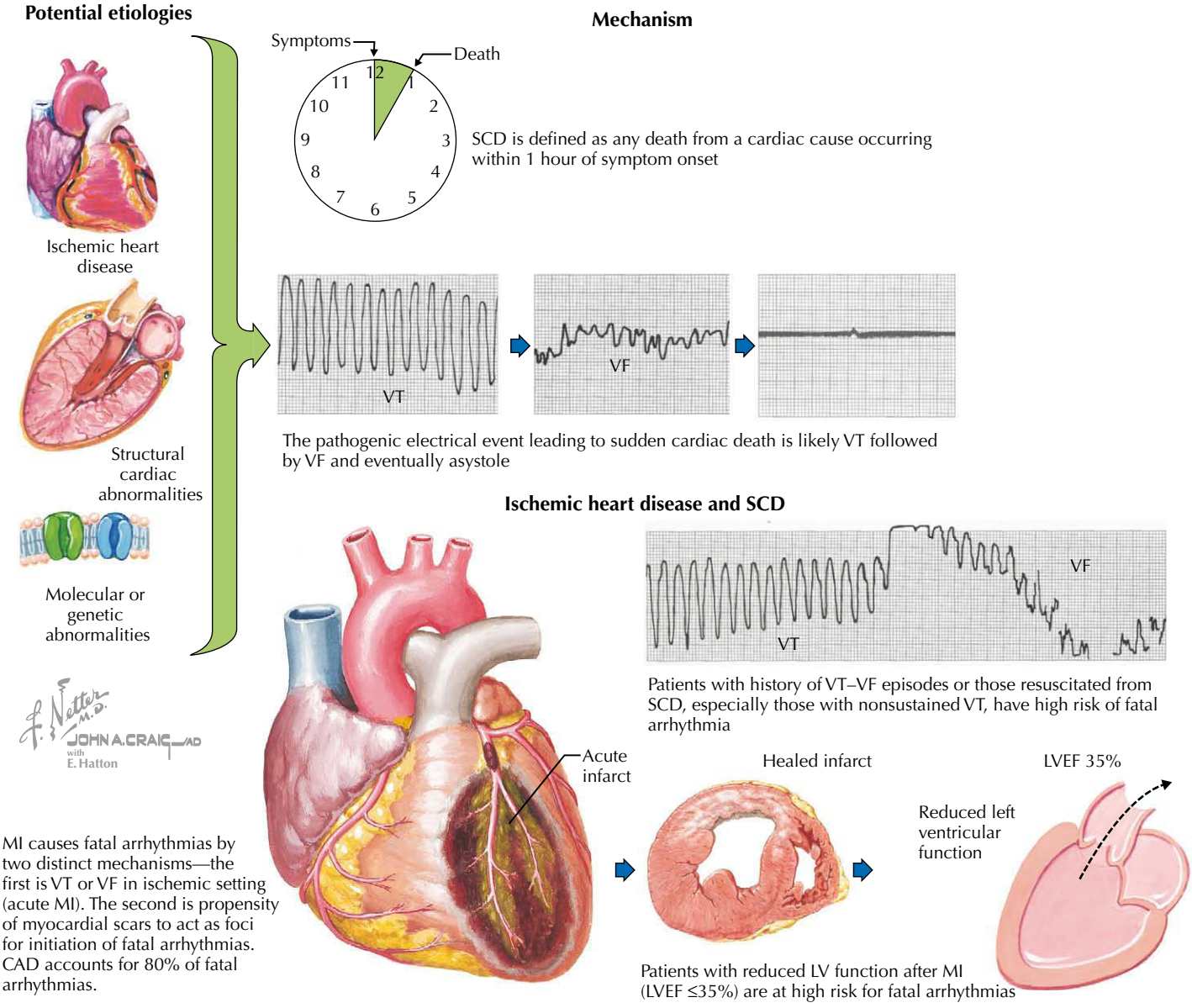


Figure 30-2 *Mechanisms of sudden cardiac death (SCD): Ischemic heart disease.* CAD, coronary artery disease; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction, VF, ventricular fibrillation; VT, ventricular tachycardia.

HCM who are at highest risk for SCD are those with recurrent syncope, nonsustained VT on Holter monitoring, extreme left ventricular hypertrophy on echocardiogram (>30 mm), abnormal blood pressure response to exercise, and a positive family history of SCD from HCM. Careful evaluation for HCM is of utmost importance in young individuals because HCM is the most common cause of SCD in young athletes in the United States (Fig. 30-3, top). Genetic testing of first-degree relatives of an individual whose gene mutation has been identified may help establish risk but remains a controversial screening modality. Screening should include a detailed history and physical examination, ECG, and echocardiography.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA AND CARDIOMYOPATHY

Arrhythmogenic right ventricular dysplasia and cardiomyopathy (ARVD/C) is an autosomal-dominant condition in which the right ventricular (RV) myocardium is replaced by fatty or fibrofatty tissue. The left ventricle may be involved in later stages of the disease. SCD incidence in ARVD/C is 2% and usually presents before age 50.

The ECG may reveal left bundle branch morphology and left-axis deviation during VT, and epsilon waves and T-wave inversions in leads V_1 through V_3 during sinus rhythm

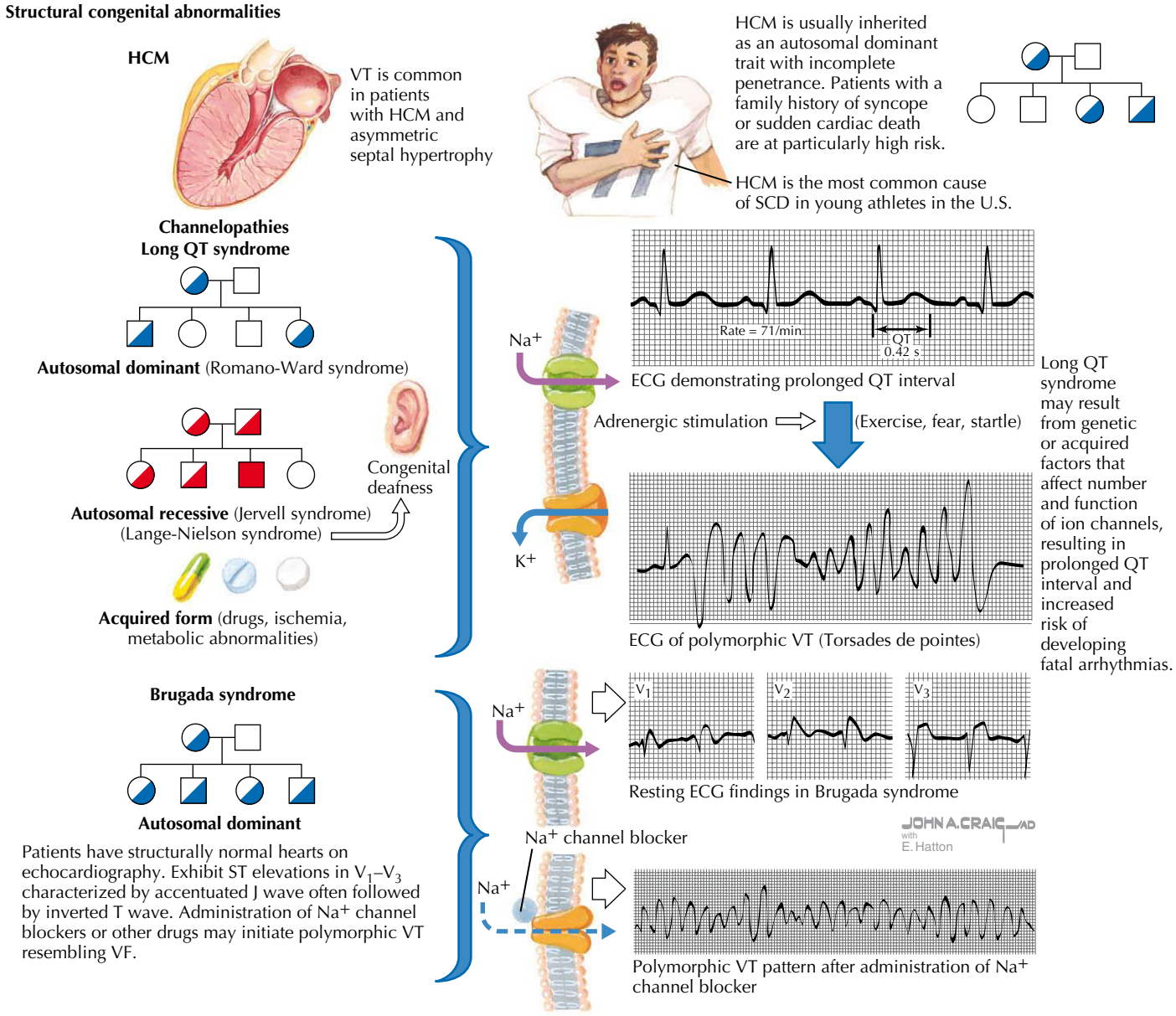
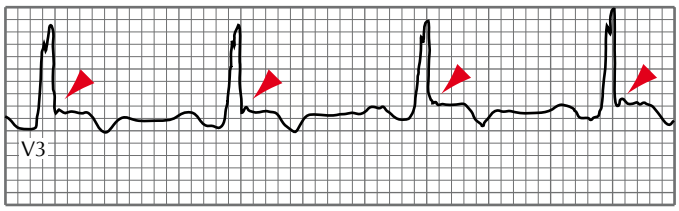


Figure 30-3 *Mechanisms of sudden cardiac death (SCD): Inherited cardiomyopathies.* ECG, electrocardiogram/electrocardiographic; HCM, hypertrophic cardiomyopathy; K^+, potassium; Na^+, sodium; VF, ventricular fibrillation; VT, ventricular tachycardia.

(Fig. 30-4). The most useful imaging study to confirm the diagnosis of ARVD/C is MRI, which classically shows fatty infiltration of the myocardium, RV dilatation or dyskinesia, or both, but if nondiagnostic, additional confirmatory tests may be required.

OTHER CONGENITAL ANOMALIES

Coronary artery anomalies are uncommon but account for a disproportionate percentage of deaths in young athletes. The mechanism of SCD is thought to be ischemia from coronary spasm or abnormal tension placed on the ectopic coronary artery by the ascending aorta and the pulmonary trunk (Fig. 30-5). The most consistently fatal anomaly occurs when the left



Epsilon waves (marked by the red arrowheads) are notches in the terminal portion of the QRS complex that reflect slowed intraventricular conduction.

Figure 30-4 *Epsilon wave in arrhythmogenic right ventricular dysplasia or cardiomyopathy.*

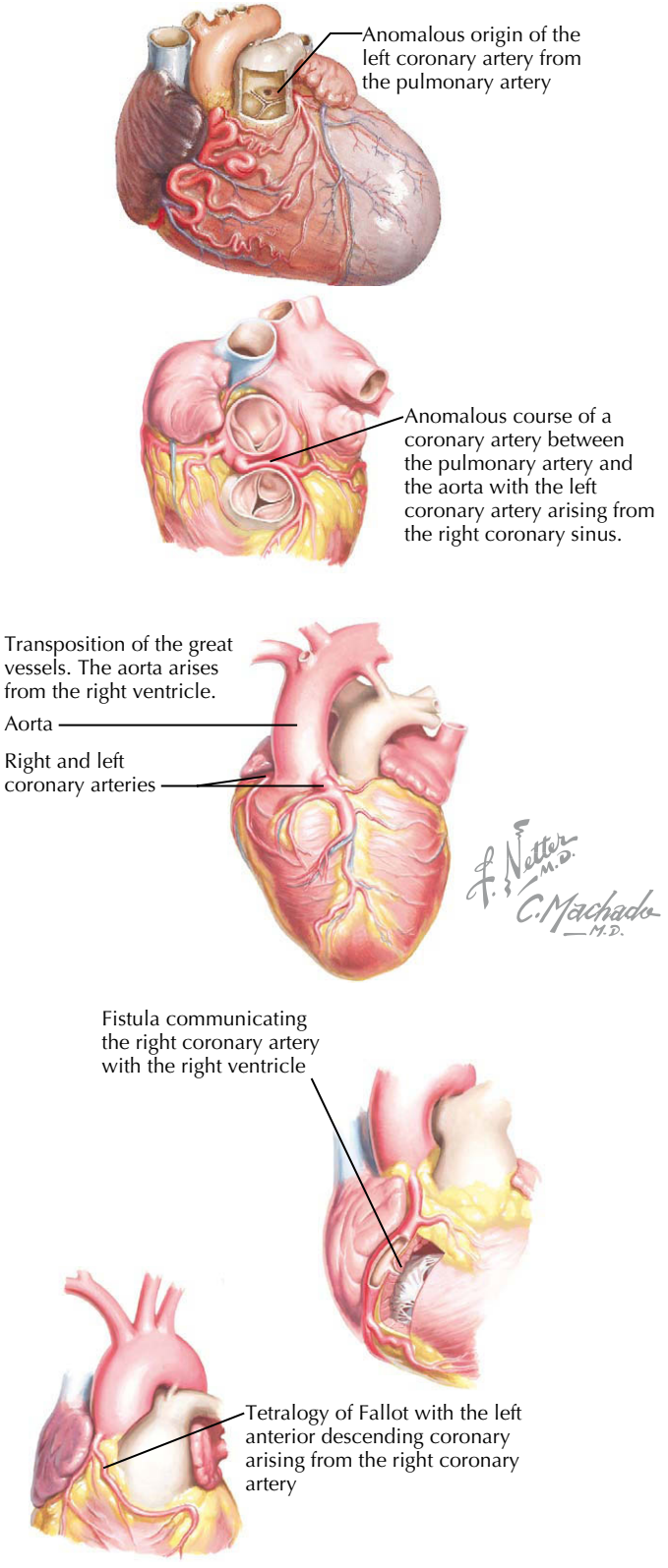


Figure 30-5 *Congenital coronary artery anomalies.*

coronary artery originates from the right coronary sinus and courses between the aorta and the pulmonary artery.

Other infrequent congenital diseases associated with an increased risk of SCD are mitral valve prolapse, aortic stenosis, Ebstein's anomaly, coarctation of the aorta, tetralogy of Fallot, transposition of the great arteries, and Eisenmenger's physiology. When surgical correction is possible, the risk of SCD decreases but is not eliminated.

Primary Electrophysiology Disorders

LONG QT SYNDROME

Channelopathies account for up to 5% to 10% of SCDs annually but generate considerable interest because these patients have structurally normal hearts. The most recognized of the channelopathies are manifested by prolongation of the QT interval with a concomitant increased risk of VT and SCD. Long QT syndrome (LQTS) encompasses patients with QTc intervals greater than 440 milliseconds (Fig. 30-3, middle) and can be congenital or acquired. The annual incidence of SCD is between 1% to 2% and approximately 9% in affected individuals with syncope. Life-threatening arrhythmia presents as torsades de pointes. Torsades de pointes, or "twisting of the point," is polymorphic VT associated with a prolonged QT interval, R-on-T premature ventricular contractions, and long-short coupled R-R intervals.

Multiple forms of LQTS have been recognized and associated with at least 12 different genes. LQTS1 and 2 are due to potassium channel defects. Potassium channels are responsible for cardiac repolarization; loss of function results in prolongation of repolarization and thus lengthening of the QT interval. SCD can occur with exercise stress or unexpected auditory stimulation (sudden loud sounds or a phone ringing in the middle of the night have been reported to cause SCD in LQTS). LQTS3 results from a gain of function in the cardiac sodium channel gene *SCN5A* that is associated with rapid cardiac depolarizations. Too much repolarization upsets the balance between depolarization and repolarization and results in QT prolongation. SCD occurs during sleep. β-blockers are a mainstay of treatment in all patients with congenital LQTS, regardless of symptoms, since they mitigate the effect of enhanced sympathetic activity. Animal studies and registry data have shown β-blockers to be most efficacious in LQTS1 and least efficacious in LQTS3. This finding is probably due to the differing roles of sympathetic stimulation by genotype.

Acquired LQTS is reversible QT prolongation due to secondary causes (medications, electrolyte abnormalities, or ischemia). It is unclear whether there is always a genetic predisposition to the acquired form of LQTS, but cases have been described wherein patients with apparent acquired LQTS have a subtle genetic abnormality.

BRUGADA SYNDROME

Brugada syndrome, an autosomal-dominant disease, causes 20% of SCD in young people with structurally normal hearts. The most common recognized cause is a loss-of-function mutation in *SCN5A* that results in early repolarization of the RV

myocardium. However, in most patients the genetic abnormality has not been recognized. SCD is associated with rest or nocturnal settings and elevated temperatures (e.g., febrile illness or hot tubs). Diagnosis is based on symptoms and 12-lead ECG showing ST elevations of more than 2 mm in leads V_1 through V_3, characterized by an accentuated J wave (often followed by a negative T wave) (Fig. 30-3, lower). Type 1 pattern, shown in Figure 30-3, is diagnostic of Brugada syndrome. Type 2 pattern has a "saddleback" ST elevation in the right precordial leads, and type 3 pattern has either a coved or saddleback appearance with ST elevation of more than 1 mm. Sodium channel blockade with flecainide or procainamide can unmask Brugada ECG patterns when the diagnosis is in doubt. Electrophysiology study (EPS) should be considered in patients with spontaneous type 1 pattern regardless of symptoms, and if positive for inducible VT, an implantable cardioverter defibrillator (ICD) should be considered. In patients with type 1 pattern provoked by a sodium channel blocker, EPS is recommended in those with a family history of SCD. Any patient with a history of syncope or cardiac arrest and a type 1 pattern should be considered for an ICD.

OTHER ELECTRICAL DISORDERS

In Wolff-Parkinson-White syndrome, rapid conduction of atrial fibrillation or flutter down an accessory pathway can lead to rapid ventricular rates and degenerate to VF. Patients with Wolff-Parkinson-White syndrome are at higher risk of SCD if multiple pathways are present, and if the R-R interval during preexcited atrial fibrillation is less than 250 milliseconds (or 240 bpm). Short QT syndrome, characterized by a QT interval of less than 300 milliseconds, is caused by gain-of-function mutations in genes encoding potassium channels. It presents with syncope, atrial fibrillation, or VT, and typically affects young healthy patients with structurally normal hearts. Bradyarrhythmias can result in SCD and are discussed in Chapter 26. Other potential but rare causes of SCD include catecholaminergic polymorphic VT, idiopathic VF, and congenital heart block (which results in VF).

COMMOTIO CORDIS

Commotio cordis is SCD from blunt, nonpenetrating chest blows, occurring in an individual without structural anomalies in the heart and without traumatic injury to the sternum, the ribs, or the heart. Chest impact during the 15 to 30 milliseconds preceding the peak of the T wave can induce VF. The harder the projectile, the more reliably VF was induced in swine model experiments. The overall survival rate is less than 25%, and when cardiopulmonary resuscitation was initiated after 3 minutes (38 patients) in one study, only 3% survived. Prevention with protective sporting equipment, softer baseballs, and rapid bystander cardiopulmonary resuscitation (including immediate access to automated external defibrillators) represent the best strategies. Teenaged boys are particularly at risk given the sports they play and the underdevelopment of their chest walls.

SUDDEN CARDIAC DEATH IN YOUNG ATHLETES

SCD in young (age <35 years) athletes is very rare, with U.S. incidence at approximately 1 in 200,000. The three most common etiologies in the United States are HCM, commotio cordis, and coronary anomalies. In athletes older than 35 years, CAD remains the most common cause of SCD. Screening centers on the history and physical; any athlete who reports prior exertional syncope or near syncope must undergo further cardiac evaluation. Routine use of ECG and echocardiography remains controversial. The 36th Bethesda Conference provided recommendations for athletic participation in patients at risk of SCD (see Chapter 69 for additional information).

DIAGNOSTIC APPROACH

Early response is critical, and patients are far more likely to survive to hospital discharge if bystander cardiopulmonary resuscitation and early defibrillation are available. Thus, advanced cardiac life support and the rapid-response system must be activated as soon as possible. The evaluation of survivors of SCD should include a detailed history and physical examination, including the circumstances of the SCD, medication and drug history, a family history of SCD, and potential risk factors. Diagnostic testing may include any combination of ECG, echocardiography, cardiac catheterization, CT, MRI, telemetry monitoring, stress testing (exercise or pharmacologic), and EPS. During an EPS, attempts are made to induce VT. The EPS is more sensitive in patients with ischemic than nonischemic heart disease, but recent trials have shown that the predictive value of induced VT is significantly less than initially proposed. Nonetheless, multiple studies have verified the predictive power of the EF in both primary- and secondary-prevention patients. Unless a clearly reversible cause is found, the vast majority of SCD survivors will require ICD implantation to prevent further events. Attempts to reduce SCD must be centered on prevention, because mortality is so high.

SUMMARY OF ICD TRIALS

Results of multiple clinical trials have helped define the role of ICDs in primary and secondary prevention of SCD. EF is the most potent predictor of SCD, and ICDs are superior to antiarrhythmic drug therapy in most cases. Recent important trials are briefly reviewed below (Tables 30-1 and 30-2).

Primary Prevention

Several trials have sought to identify patients at risk of SCD and assess the role of ICD or antiarrhythmic therapy as primary prevention measures. The broad categories of patients have consisted of (1) history of myocardial ischemia or infarction, or both, and (2) congestive heart failure of any etiology. The first of these studies, the Multicenter Automatic Defibrillator Implantation Trial (MADIT I, 1996), directly compared ICD versus amiodarone in patients with prior MI, EF ≤35%, and an

Table 30-1 Summary of Major Implantable Cardioverter Defibrillator Trials—Primary Prevention

Trial	Inclusion Criteria	Key Findings
Multicenter Automatic Defibrillator Implantation Trial (MADIT I, 1996)	Prior MI, EF ≤35%, nonsustained VT, abnormal EPS (VT induced)	ICDs reduced overall mortality by 54% compared with medical therapy.
Multicenter Unsustained Tachycardia Trial (MUSTT, 1999)	Prior MI, EF ≤40%, nonsustained VT	Cardiac arrest or death from arrhythmia was significantly lower in those receiving an ICD compared with those receiving no therapy or those with EPS-guided antiarrhythmic drug therapy.
MADIT II, 2002	Prior MI, EF ≤30%,	These patients have a high risk of SCD regardless of the presence of nonsustained VT or the results of EPS.
Defibrillator in Acute Myocardial Infarction Trial (DINAMIT, 2004)	MI within preceding 6–40 days, EF ≤35%,	ICD did not reduce overall mortality in patients with recent MI. ICD was associated with reduced arrhythmic death, but that was offset by increased rate of nonarrhythmic death.
CABG Patch (1997)	Planned CABG, EF <36%, abnormal SAECG	ICD at time of revascularization did not improve overall therapy compared with medical therapy.
Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE, 2004)	Nonischemic dilated cardiomyopathy, EF ≤35%, nonsustained VT	Significant reduction in all-cause mortality in NYHA class III heart failure patients, trend toward significance in all study patients receiving ICD.
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT, 2005)	Ischemic or nonischemic cardiomyopathy, class II and III heart failure, EF ≤35%	ICD group had 23% reduction in overall mortality. Amiodarone without ICD did not confer survival benefit.

CABG, coronary bypass grafting; EF, ejection fraction; EPS, electrophysiologic study; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NYHA, New York Heart Association; SAECG, signal-averaged ECG; VT, ventricular tachycardia.

abnormal EPS. It was stopped early, because the ICD group had a 55% reduction in total mortality. The Multicenter Unsustained Tachycardia Trial (MUSTT, 1999) enrolled a patient population similar to MADIT I but with an EF ≤40%. The study's goal was to compare medical therapy with EPS-guided therapy (antiarrhythmic drug or ICD). The incidence of arrhythmic death was significantly lowered in those receiving an ICD. MADIT II (2002) evaluated patients whose MI had occurred at least 30 days before the trial began, whose bypass surgery or percutaneous coronary intervention had taken place at least 3 months before, or both, and who had EFs ≤30%. No other risk stratification was undertaken. This trial was also stopped early, since the ICD group showed a marked 29% reduction in all-cause mortality as compared with the conventional medical therapy group. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT, 2004) evaluated whether early ICD implantation in an immediate (6–40 days, average 18 days) post-MI population confers benefit. While arrhythmic deaths were more frequent in the non-ICD arm of the study, no significant benefit in all-cause mortality was noted. The Coronary Artery Bypass Graft Patch (CABG Patch, 1997) Trial also examined the potential benefit of an early (epicardial) ICD system implantation at the time of bypass surgery. Patients had EFs less than 36% and a positive signal-averaged ECG (a more detailed ECG that averages recordings taken over a period of 20 minutes). There was no significant benefit in overall mortality, emphasizing the powerful effect of coronary revascularization in SCD prevention. The ICD group did have a relative 45% reduction in arrhythmia-associated death.

Based on the primary-prevention trials' results, current guidelines recommend ICD implantation for primary prevention in patients with ischemic cardiomyopathy (EF ≤35%) whose MI occurred at least 40 days before implantation or whose revascularization occurred at least 3 months before.

Table 30-2 Summary of Major Implantable Cardioverter Defibrillator Trials—Secondary Prevention

Trial	Inclusion Criteria	Key Findings
Cardiac Arrest in Hamburg (CASH, 1994)	Survivors of SCD	ICDs reduced overall mortality by 23% compared with either amiodarone or metoprolol and 63% reduction compared with propafenone.
Canadian Implantable Defibrillator Study (CIDS, 2000)	Cardiac arrest survivors due to VT or VF or syncope thought due to arrhythmia	Patients at highest risk of death benefited most from ICD. Age, poor ventricular function, and poor functional status predict risk.
Antiarrhythmics Versus Implantable Defibrillators (AVID, 1997)	Resuscitated VF or sustained VT with syncope or sustained VT with chest pain and EF ≤40%	ICD therapy was associated with 39%, 27%, and 31% reductions in mortality at 1, 2, and 3 years, respectively, compared with antiarrhythmic drug therapy.

CABG, coronary bypass grafting; EF, ejection fraction; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

To examine the role of ICD in patients with nonischemic cardiomyopathy, the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE, 2004) Trial enrolled patients with EFs less than 35% and nonsustained VT. Patients receiving an ICD demonstrated a strong but not quite significant trend in reduction of all-cause mortality. The Sudden Cardiac Death Heart Failure Trial (SCD-HeFT, 2005) included both ischemic and nonischemic cardiomyopathy patients. In these patients with EFs ≤35%, and New York Heart Association (NYHA) class II or III heart failure, overall mortality was significantly reduced in the ICD group (compared with amiodarone). In the latest guidelines, any patient meeting SCD-HeFT critieria qualifies for an ICD.

In patients who are candidates for cardiac resynchronization therapy, the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) Trial demonstrated significant reduction in all-cause mortality. Cardiac resynchronization therapy is reviewed in Chapter 32.

Secondary Prevention

For survivors of SCD without a reversible cause, ICD implantation is extremely beneficial in preventing death from VT or VF. Three randomized controlled trials have assessed the role of ICDs in secondary prevention. Two meta-analyses confirmed a significant reduction (25%–28%) in overall mortality with an ICD compared with amiodarone, especially in patients with an EF ≤35%.

The Cardiac Arrest Survival in Hamburg (CASH, 2000) Trial compared an ICD to metoprolol, propafenone, or amiodarone. A 23% reduction in mortality ($P = 0.08$) was seen in the ICD group as compared with metoprolol or amiodarone. Propafenone was stopped prematurely in the study because of increased mortality rates. The Canadian Implantable Defibrillator Study (CIDS, 2000) did not show significant reduction in total mortality with an ICD compared to amiodarone after 5-year follow-up. Further analysis showed that the highest-risk patients (having two of the following: EF ≤35%, NYHA class III or IV heart failure, age >70 years) did derive a significant survival benefit with an ICD. Both CASH and CIDS may have lacked the statistical power to demonstrate significant mortality benefit. In the Antiarrhythmic Drug Versus Defibrillator (AVID, 1997) Trial, over 1000 patients who had survived cardiac arrest and who had an EF ≤40% were randomized to ICD or medical therapy with amiodarone or sotalol. Survival was significantly higher in the ICD group, and there was over 50% reduction in arrhythmic death. Additionally, the improved survival was seen most in patients with an EF of 20% to 35%.

MANAGEMENT AND THERAPY

Optimum Treatment

A summary of the current guidelines is shown in Box 30-2. Patients with ischemic cardiomyopathy and an EF less than 35% should receive an ICD after optimization of anti-ischemia therapy and after at least 40 days have passed since MI or 3 months after revascularization, or both. For patients with a previous MI and an EF between 35% and 40%, but a history of nonsustained VT or syncope, an EPS should be performed.

Box 30-2 Summary of Indications for Implantable Cardioverter Defibrillator

- Documented cardiac arrest due to VF and not due to a reversible cause (secondary prevention)
- Documented sustained VT, spontaneous or induced during EPS, not associated with acute MI or reversible cause (secondary prevention)
- Documented prior MI, EF ≤35%, and inducible sustained VT or VF on EPS; the MI must have occurred more than 4 weeks before, and the EPS must be performed more than 4 weeks after the MI (MADIT I criteria)
- Documented prior MI and EF ≤30% (MADIT II criteria)
- At least 40 days have passed since the most recent MI
- Ischemic dilated cardiomyopathy, documented prior MI, NYHA class II or III heart failure, and EF ≤35% (SCD-HeFT criteria)
- At least 3 months have passed since revascularization (CABG or PCI)
- Optimization of medical therapy
- Expected survival with a good functional status of at least 1 year

Exclusions include:

- Prior MI within the past 40 days (DINAMIT criteria)
- Hypotension or cardiogenic shock while in a stable baseline rhythm
- CABG or PCI within the past 3 months
- Symptoms or findings that would make the patient a candidate for revascularization
- Noncardiac disease associated with expected survival or less than 1 year or irreversible brain damage

CABG, coronary bypass grafting; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; EF, ejection fraction; EPS, electrophysiologic study; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

If the patient has inducible VT, an ICD should be implanted. Medical therapy, including angiotensin-converting enzyme inhibitors, β-blockers, antiplatelet agents, and lipid-lowering therapy, should be optimized.

For patients with persistent nonischemic cardiomyopathy, NYHA class II heart failure and an EF ≤35%, an ICD should be placed. EPSs are not predictive of recurrent arrhythmias in most patients in this group. In the case of bundle branch reentry VT, radiofrequency ablation (see Chapter 33) may be beneficial, although patients in this group will still require ICD placement if the EF is ≤35%. Other specific diseases require more aggressive approaches. In patients with Wolff-Parkinson-White syndrome and SCD, radiofrequency ablation is necessary. Patients with a family history of SCD who have findings of HCM, arrhythmogenic RV dysplasia, LQTS, or Brugada syndrome should undergo ICD placement, and any agent known to precipitate acquired LQTS should be discontinued immediately. Finally, patients without a demonstrable cause for documented VF or VT are still at risk for SCD and should be offered ICD therapy.

β-blockers have a favorable effect on prevention of SCD and other benefits in patients with congestive heart failure. The

Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure showed a 41% decrease in SCD in heart failure patients with an EF below 40% (mean ~28%) with β-blocker therapy. A β-blocker may be added to amiodarone in most cases without causing worrisome bradycardia. The combined post hoc analysis of the European Myocardial Infarction Amiodarone Trial and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial revealed a 61% decrease in SCD in post-MI patients treated with both β-blockers and amiodarone, although no change in overall mortality was noted.

Avoiding Treatment Errors

Implantation of ICDs has become a routine procedure for cardiac electrophysiologists, but they should be implanted by experienced operators. Rare procedural complications include pneumothorax, cardiac tamponade, bleeding, or infection.

When compared with antiarrhythmic therapy, ICDs are clearly superior in the prevention of SCD. Individualization of medical treatment must be balanced with adherence to the latest guidelines to identify and treat patients who are most likely to benefit from ICD therapy.

FUTURE DIRECTIONS

Ongoing research involves finding genetic, electrical, and biochemical markers for increased risk of SCD. Although the EF is a powerful predictor of those at risk of SCD, its measurement can be variable depending on the testing modality used and the physiologic state of the patient. Follow-up data from SCD-HeFT has shown that over 80% of patients had not required therapy from their prophylactic ICD. Development of an SCD "risk score," much like the CHADS2 index that guides oral anticoagulation in atrial fibrillation patients or the TIMI risk score for guiding management of NSTEMI, may be the best means of stratifying risk and controlling costs. Such a score could incorporate a combination of invasive and noninvasive studies such as the EPS, signal-averaged ECG, microvolt T-wave alternans, heart rate variability, maximum oxygen consumption, and serum B-type natriuretic peptide. To enhance survival of out-of-hospital cardiac arrests, the rapid-response system must be expanded as much as possible by teaching basic life support in the schools and increasing the availability of automated external defibrillators.

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Syncope

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31

Syncope is a transient loss of consciousness with an inability to maintain postural tone. Typically, it is quickly followed by a spontaneous recovery of consciousness and the ability to resume the initial upright position. Syncope does not include other conditions of altered consciousness such as seizure or shock, but can be difficult to distinguish from them. Syncope is very common and is responsible for 1% to 5% of visits to emergency departments and approximately 5% of hospital admissions. This translates into almost a million syncope evaluations in the United States each year. The various etiologies of syncope can be divided into five broad categories including neurally mediated (i.e., vasovagal), orthostatic (most common), cardiac arrhythmia (both tachycardia and bradycardia), cardiac lesions obstructing outflow (i.e., aortic stenosis), and cerebrovascular ischemic attacks such as a vertebrobasilar attack (which is a rare cause of syncope) (Table 31-1). The dilemma is to differentiate benign neurally mediated syncope (NMS) from less common but more harmful etiologies.

These various etiologies all cause inadequate cerebral perfusion that ultimately results in syncope. After a careful history and physical examination and ECG, further diagnostic tests are often warranted to rule out the various causes. Regardless of the diagnosis, however, the treatment for syncope is always directed toward the underlying cause.

ETIOLOGY AND PATHOGENESIS

Neurally Mediated Syncope

NMS, also referred to as "vasovagal syncope," is the most common cause of syncope. Typical fainting is not a pathologic cardiac condition, but most likely a remnant defense mechanism in response to stress that dates back to the origins of humans and is also seen in other vertebrate animals in response to stress. Several types of situational syncope are also neurally mediated, such as micturition, postprandial, and post-exercise syncope. The pathophysiology of NMS remains to be fully elucidated. Several theories involve baroreceptor reflex abnormalities that cause disconnection between the autonomic nervous system and the cardiovascular system. Another theory is that venous pooling that occurs with the upright position leads to reduced cardiac filling, which then leads to activating mechanoreceptors that cause a paradoxical withdrawal of sympathetic tone (Fig. 31-1). The triad of apnea, bradycardia, and hypotension was first termed the *Bezold-Jarisch reflex* in the 1940s when it was appreciated that afferent and efferent pathways in the vagus nerve control heart rate and vasomotor tone by increasing or decreasing parasympathetic discharge to the heart. Several cardiac receptors are part of the intricate network including various baroreceptors and chemoreceptors.

In truth there probably is no single unifying syndrome that occurs in all NMS patients. In general, there seems to be an initial trigger that increases sympathetic activity followed by a withdrawal of sympathetic outflow and an increase in vagal activity. This results in tachycardia and vasoconstriction followed by bradycardia and vasodilation, which result in hypotension and ultimately unconsciousness.

Orthostatic Hypotension

Orthostatic hypotension is a common cause of syncope, particularly in elderly individuals or in individuals with decreased intravascular volume status from any of a number of causes. The American Autonomic Society defines orthostatic hypotension as a drop of at least 20 mm Hg of systolic pressure or at least 10 mm Hg of diastolic pressure within 3 minutes of standing. Some primary disorders of the autonomic nervous system cause orthostatic hypotension such as Parkinson's disease and Shy-Drager syndrome, and some disorders secondarily affect the autonomic system such as diabetes mellitus or a paraneoplastic process (Fig. 31-2). Also, many medications cause or exacerbate orthostatic hypotension, which disproportionately affect the elderly and are a frequent cause of falls and syncope.

Cardiac Arrhythmia

Both bradyarrhythmias and tachyarrhythmias can cause syncope. Bradycardia or asystole due to sinus node dysfunction is often abrupt in onset, which distinguishes it from neurally mediated bradycardia, which tends to be more gradual. Atrioventricular (AV) block also tends to be sudden in onset and typically occurs in the setting of AV conduction disease such as a bundle branch block or other infranodal conduction disease.

Both supraventricular and ventricular tachycardias can cause similar symptoms such as palpitations, shortness of breath, and dizziness, and both entities can lead to syncope. The rate of tachycardia (i.e., >170 bpm) is probably more predictive of causing syncope than the mechanism of the arrhythmia.

In patients with either an ischemic or dilated cardiomyopathy, ventricular tachycardia (VT) should be at the top of the differential until proven otherwise. Also, other structural abnormalities, such as hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, predispose individuals to ventricular arrhythmias. Inherited ion channel disorders, namely long QT syndrome, Brugada syndrome, short QT syndrome, and polymorphic VT, can cause spontaneous ventricular arrhythmias despite a structurally normal heart.

Cardiac Outflow Obstruction

Mechanical outflow obstruction of the left ventricle is a relatively uncommon cause of syncope. Some of these etiologies include aortic stenosis, hypertrophic cardiomyopathy, and cardiac myxoma. Most causes of cardiac obstruction have a murmur on physical examination, and the diagnosis is made by echocardiography, which reveals the mechanical obstruction.

Table 31-1 Etiologies of Syncope

Etiology	Typical Findings	Typical Symptoms	Age Range of Patient
Neurocardiogenic			
Classic vasovagal	Normal physical examination	Prodrome with diaphoresis	Young and old
Situational Cough Micturition	History details inciting event	Recovery within minutes	Young and old
Carotid sinus hypersensitivity		Occurs with head turning	Old
Orthostatic Hypotension			
Medications Antihypertensives, vasodilators, diuretics Autonomic dysfunction	Orthostatic on examination	Dizzy, unsteady with upright position	Old
Cardiac Arrhythmia			
Bradyarrhythmia Heart block Sinus block	ECG shows sinus bradycardia Bundle branch block Bifascicular block	Sudden onset Minimal prodrome	Old
Tachyarrhythmia SVT WPW (atrial fibrillation) RV dysplasia (VT) LQTS (torsades de pointes) Brugada (VT, VF) VT (coronary obstruction due to atherosclerosis or anomalous coronaries)	No structural heart disease (SVT) Structural heart disease or abnormal ECG (VT)	Rapid recovery	Young and old
Cardiac Outflow Obstruction			
Hypertrophic cardiomyopathy Aortic stenosis Tumor, myxoma Pulmonary hypertension	Murmur	Possibly exertional intolerance, heart failure symptoms	Old
Cerebrovascular			
Vertebrobasilar stroke Bilateral severe carotid stenosis	Neurologic findings Bruits	Neurologic symptoms Visual disturbances	Old

ECG, electrocardiogram; LQTS, long QT syndrome; RV, right ventricular; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

Cerebrovascular Disorders

Many neurologic disorders actually cause syncope by inducing orthostatic hypotension. Transient ischemic attacks and strokes in general do not cause syncope. Carotid sinus hypersensitivity is a common finding in older persons, even in those without a strong history of syncope. One hypothesis suggests that reduced carotid sinus compliance in patients with diffuse atherosclerosis leads to baroreflex hypersensitivity, causing hypotension and bradycardia when stimulated with massage or neck turning.

CLINICAL PRESENTATION

The symptoms that surround a syncopal event can often aid in determining the underlying etiology (Box 31-1).The quality and duration of symptoms preceding the loss of consciousness can vary considerably depending on the etiology. Observations of witnesses are also very important and can help recreate the events and timeline from prodrome to duration of unconsciousness and mental status upon arousal. Typically, NMS patients have a prodrome before losing consciousness that lasts from several seconds to minutes. The prodrome may consist of nausea, diaphoresis, anxiety, or palpitations. These symptoms are followed by a very brief period of unconsciousness (usually less than 1 minute) and then a rapid recovery within a few minutes. After the event, the patient may feel fatigued but should be oriented and coherent. These episodes generally occur when the person is in the upright position, similar to orthostatic hypotension events. Occasionally, patients will have little or no warning before passing out. A lack of prodrome is more frequently associated with an arrhythmic etiology. Traditionally, Stokes-Adams syndrome has been used to describe this abrupt loss of consciousness due to a marked decrease in heart

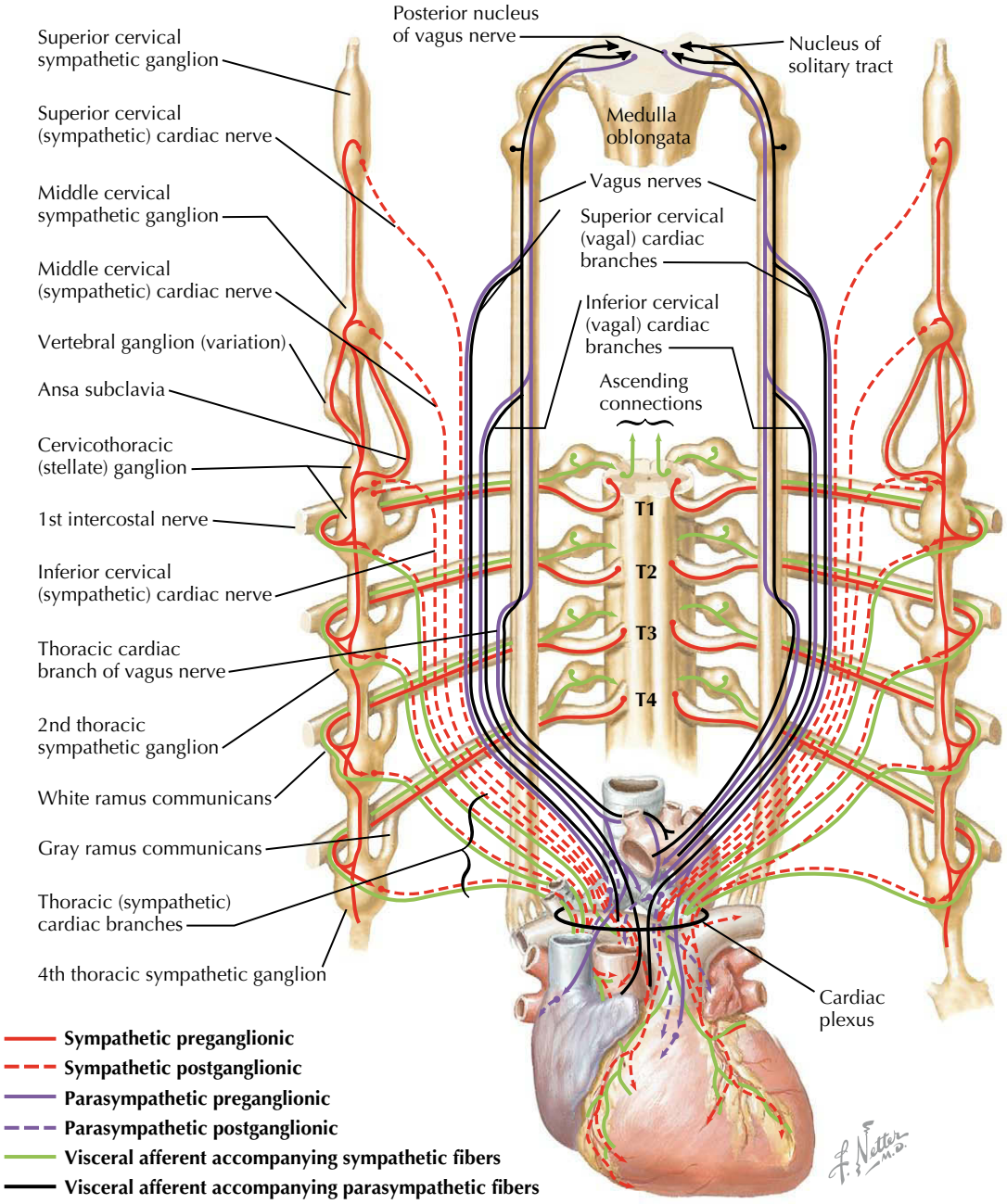


Figure 31-1 *Innervation of the heart.*

rate, although it has come to represent abrupt loss of consciousness from both tachyarrhythmias and bradyarrhythmias. If syncope occurs during exertion it is imperative that cardiac etiologies be considered. Chest pain may also accompany a tachycardic arrhythmia such as VT due to coronary disease.

It is important to note that tonic-clonic movements can be seen in both syncope and seizure activity, and it is often difficult to distinguish the two. Confusion present after arousal is more consistent with seizure activity. Strokes rarely cause syncope but can do so when either severe bilateral carotid artery disease or basilar artery insufficiency is present. Syncope due to these neurovascular causes are often in conjunction with focal neurologic findings.

DIFFERENTIAL DIAGNOSIS

Determining the event's etiology is often frustrating and elusive. A careful history of the event is the first step in trying to elucidate the etiology and establish if the event was truly syncopal. Knowing what activities preceded the event, the person's body position just before falling, and the person's affect after the event can be instrumental. Then, a detailed past medical history

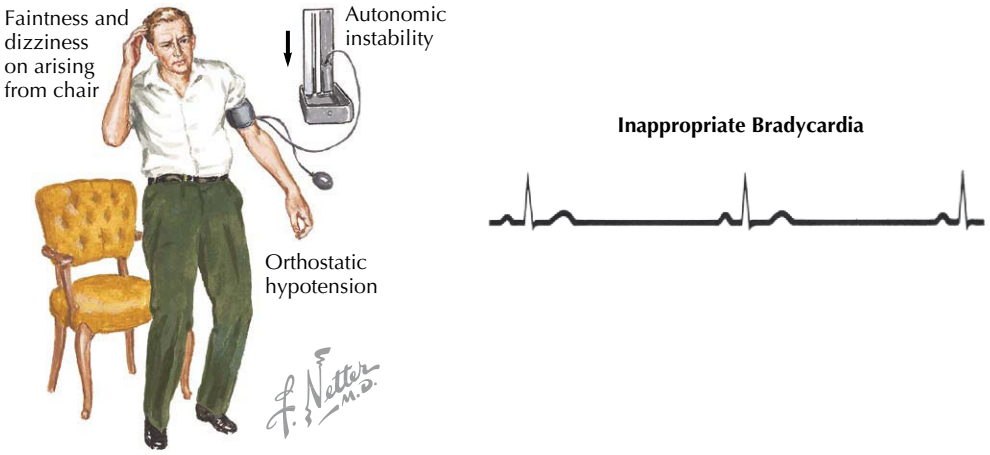


Figure 31-2 *Autonomic dysfunction causes hemodynamic abnormalities.*

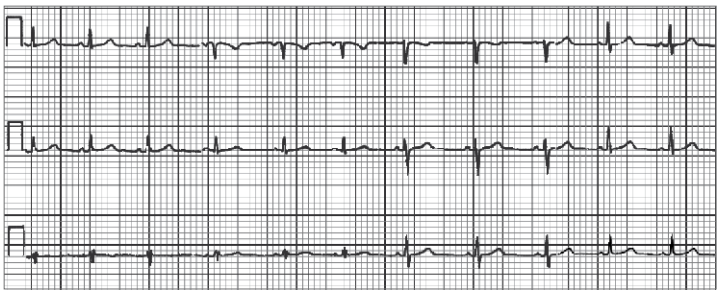
and family history can also help determine if the patient is at "high risk" for arrhythmic syncope. For example, cardiac syncope due to an arrhythmia is more likely in a person with a history of left ventricular dysfunction or an abnormal ECG. Ventricular arrhythmias should be considered, particularly if the ECG shows evidence of a prior myocardial infarction, of QT prolongation, or of numerous other cardiovascular abnormalities (see below). Recent changes in medication should be investigated. A syncopal event and a family history of sudden death in a patient warrants immediate attention, and further testing should probably be done on an inpatient basis (see also Chapters 27, 29, and 30).

DIAGNOSTIC APPROACH

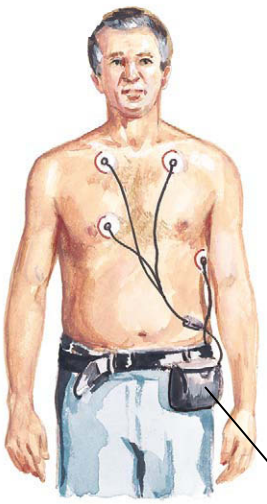
The physical examination should include blood pressure and pulse measurements in both arms and in the lying, sitting, and standing positions. Often the results of the examination are normal except in the rare cases of an outflow obstruction (as in individuals with hypertrophic cardiomyopathy), in whom a loud murmur may be present, or in patients with cardiomyopathy in which left ventricular enlargement and dysfunction can be diagnosed by physical examination. Carotid sinus massage can be performed to elicit carotid sinus hypersensitivity, which is a profound asystole due to baroreceptor stimulation. Baroreceptor function declines with advancing age, and carotid sinus hypersensitivity typically affects older patients, particularly males. It is not recommended to perform carotid massage on older patients with carotid bruits or suspected carotid vascular disease. Many processes can also masquerade as syncope, such as seizures, pseudoseizures or psychogenic seizures, and disorders of autonomic function. Often, the history, physical, and ECG are suggestive but insufficient to make the diagnosis, and further testing is required (Fig. 31-3).

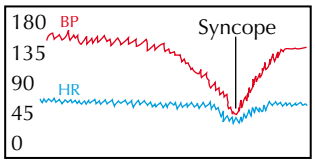
Box 31-1 Key Questions for the Patient with a History of Syncope

- Activities performed when the episode began
  - Exercise
  - Position changes
  - Postmicturition
  - Defecation
  - Cough
- Time of day
- Medications
  - Insulin
  - Other prescription medications
  - Over-the-counter medications
  - Illicit drugs
  - Alcohol
  - Time interval after taking medications/insulin
  - New medications or changes in dosing of medications/insulin
- Any recent febrile illness
- Vomiting or diarrhea
- Anemia
- Recent fractures
- Recent air travel
- Recent trauma
- Near-drowning
- Sight of blood
- Looking upward
- Family history of sudden unexplained death even in remote cousins
- Information about the episode
  - Presence of pallor, clamminess, or sweating
  - Tonic-clonic activity
  - Duration of the episode
  - Time until patient awoke (from a witness)
  - From witnesses: the time it took the patient to become fully alert and oriented
- Pulse rate
- Symptoms following the episode
  - Palpitations
  - Nausea
  - Vomiting
  - Chest pain
  - Shortness of breath
  - Sweating
- Pain related to injuries resulting from the syncopal episode

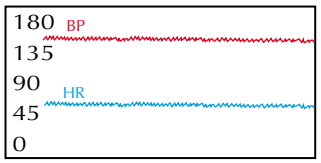


All patients with syncope should have an ECG done. Often, the ECG is normal.



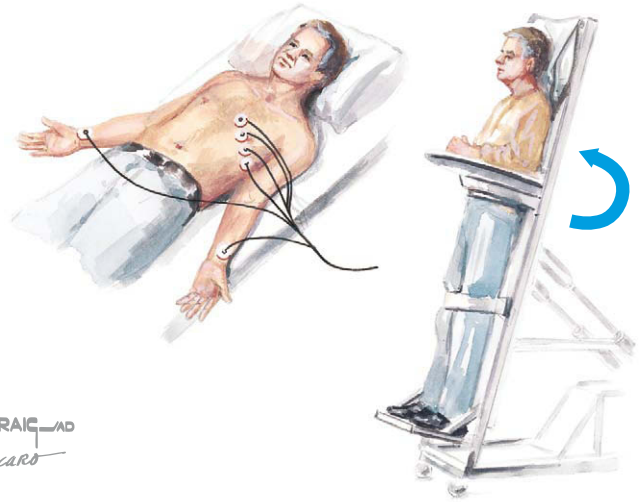


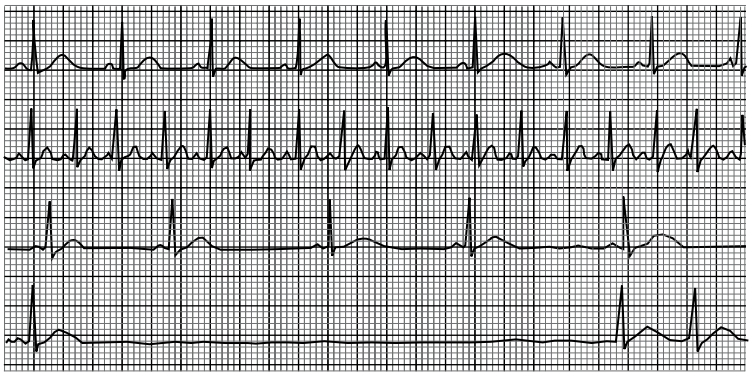
Positive neurocardiogenic tilt-table test shows drop in BP and HR.



Normal tilt-table test shows maintenance of normal BP and HR.

Holter monitor





A positive tilt-table test often show brief sinus tachycardia followed by sinus bradycardia and pauses.

Figure 31-3 *Syncope: diagnostic evaluation.* BP, blood pressure; ECG, electrocardiogram; HR, heart rate.

Electrocardiogram

ECG is part of any history and physical in patients presenting with syncope (Fig. 31-4). Although it is often normal, any evidence of AV block, bundle branch block, or pacemaker malfunction suggests bradycardia as a possible cause. Severe left ventricular hypertrophy can be seen with hypertrophic cardiomyopathy. The QT interval must be closely inspected, since QT prolongation can be a subtle finding and can be missed by the automated ECG computer interpretation algorithm. Brugada syndrome typically has a coved ST segment elevation and incomplete right bundle branch block pattern in leads V_1 to V_3. Arrhythmogenic right ventricular cardiomyopathy may show a distinguishing epsilon wave at the QRS complex's terminal portion or T-wave inversions in leads V_1 to V_3.

Blood Tests

Hematocrit and urinalysis can be helpful to determine volume status. Blood glucose can be checked acutely if hypoglycemia is suspected.

Echocardiography

If left ventricular dysfunction is suspected or abnormal cardiac findings are present on physical examination, an echocardiogram can assess if there is ventricular dysfunction, hypertrophy, or an obstructive process. Ventricular function is closely linked to the overall prognosis in syncope patients, with low systolic function portending a poor prognosis, presumably because of the increased incidence of cardiac arrhythmias in this group. In patients with syncope and a depressed ejection fraction, VT should be considered the cause of syncope until proven otherwise (see Chapters 29 and 30).

ECG Monitoring (Holter Monitors, Event Monitors, and Loop Recorders)

The goal of all monitors and recorders is to correlate an arrhythmia to symptoms. A Holter monitor is typically worn for 24 to 48 hours and continuously records the cardiac rhythm. The patient can record the time of day if symptoms occur. This is an effective method for symptoms that occur frequently or can be reproducibly recreated. The majority of patients with syncope or pre-syncope have a much lower frequency of symptoms, and the occurrence of these symptoms is unpredictable. Event monitors may be worn for 1 to 3 months. When symptoms occur, the patient activates the monitor, which captures the cardiac rhythm before and after the event. In some circumstances, it is necessary to obtain much longer term recordings. Loop recorders implanted under the skin can remain in place for up to 3

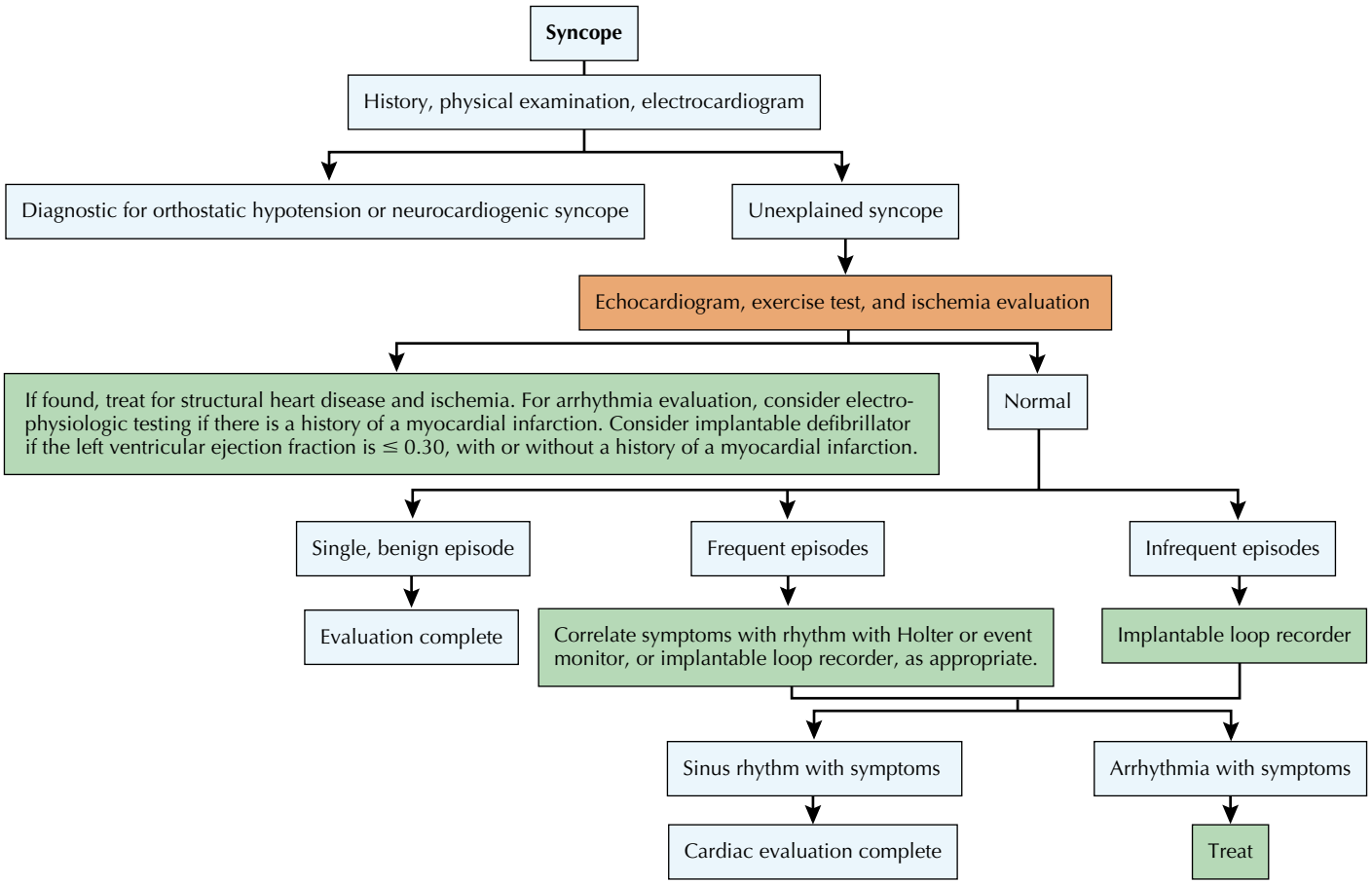


Figure 31-4 *Flow chart for the diagnostic approach to the patient with syncope.* From Strickberger SA, Benson DW, Biaggioni I, et al. AHA/ACCF Scientific Statement on the Evaluation of Syncope. From the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation In Collaboration With the Heart Rhythm Society. *J Am Coll Cardiol.* 2006;47:473–484.

years. Although both event monitors and implantable loop records have detection algorithms that automatically record for bradycardia and tachycardia, the highest yield is obtained when the patient activates the recorder based on symptoms.

Head-up Tilt-Table Test

A head-up tilt-table test is designed to keep patients in the upright position while continuously recording their blood pressure and heart rate. Occasionally, a head-up tilt-table test can be used to aid in the diagnosis of NMS. Isoproterenol or nitroglycerin can be administered to help reproduce symptoms or achieve a positive test result. If a patient has NMS during the test, it can be confirmed by the hemodynamic changes seen. The majority of patients with NMS do not require a tilt test, particularly if the history and physical indicate the diagnosis alone. In addition, the sensitivity of the head-up tilt-table test is variable and may not even be reproducible in the same patient. Nonetheless, it can be a useful test if the cardiac evaluation is normal and the history is suggestive of, but not "classic" for, an episode of vasovagal syncope.

Electrophysiology Study

An electrophysiology study (EPS) involves the placement of transvenous catheters within the heart to test sinus node function, AV conduction, and susceptibility to supraventricular and ventricular arrhythmias. The yield of an EPS is low in someone with a negative physical examination and cardiac evaluation including monitoring and an echocardiogram. In addition, the sensitivity of an EPS for detecting bradyarrhythmias and heart block is very low. Therefore, EPS is not routinely performed in most syncope patients. In patients with a history of myocardial infarction, an EPS can help risk-stratify those who are at higher risk for ventricular arrhythmias and should be considered. If ischemia is suspected, an ischemia evaluation with a stress test or heart catheterization should be performed before EPS. The EPS is less helpful in risk-stratifying patients with nonischemic cardiomyopathies for malignant tachyarrhythmias. If the ejection fraction is less than 35% (irrespective of etiology), these patients may qualify for an implantable cardioverter defibrillator regardless of the EPS results (see Chapter 32). If Brugada syndrome is suspected, a procainamide challenge

Table 31-2 Risk Assessment Scores Used in the Emergency Department to Select High-Risk Syncope Patients

Protocol	History, Presentation, and Exam Findings	Scoring
San Francisco Syncope Rule	History of CHF Hct <30 Either a new finding on ECG or a non-sinus rhythm Shortness of breath SBP <90 mm Hg	Any single feature present indicates "high risk."
OESIL	Age >65 years History of cardiovascular disease Syncope without prodrome Abnormal ECG	No features present indicates a mortality risk of 0% at 1 year.
EGSYS	Abnormal ECG Structural heart disease Palpitations before syncope Syncope during effort or supine position Absence of autonomic prodrome (diaphoresis, etc.) Absence of predisposing factor	Scoring: +4 to −1 per variable A score of >3 indicates cardiac syncope.

CHF, congestive heart failure; ECG, electrocardiogram; EGSYS, Evaluation of Guidelines in Syncope Study; Hct, hematocrit; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; SBP, systolic blood pressure.

can be performed. Unlike the standard EPS, which tests for inducible VT, a procainamide infusion tests for morphologic changes in the ECG, particularly in leads V_1 to V_3. If catecholaminergic VT is suspected, an epinephrine infusion can be given. A positive result consists of polymorphic VT or nonsustained VT.

T-Wave Alternans

This noninvasive method measures changes in the T wave on a beat-to-beat basis and is typically done on a treadmill, although some studies use Holter monitoring as well. Though a newer technology, it has consistently had a strong negative predictive value for sudden death and therefore is emerging as a useful tool to risk-stratify syncope patients with an otherwise negative workup for an arrhythmic etiology.

Risk Assessment

It is often difficult to distinguish a high-risk syncopal event or a high-risk patient from a low-risk one. Therefore, assessment scores have been created and validated for emergency department use to help triage adult patients in terms of admission to the hospital (Table 31-2). The simple scoring methods do not supplant a detailed history but can help as an adjunct when deciding whether to perform studies on an inpatient or outpatient basis.

MANAGEMENT AND THERAPY

Optimum Treatment

Prescribing appropriate treatment depends on making the correct diagnosis. If a bradyarrhythmia is the culprit, then the patient's condition probably warrants a pacemaker for rate support. If a malignant tachyarrhythmia is detected, the patient should receive a defibrillator for protection from sudden death. Treatment for NMS has evolved considerably and includes nonpharmacologic as well as pharmacologic aspects.

NONPHARMACOLOGIC TREATMENT FOR NMS

Many patients respond well to lifestyle modification training and maneuvers alone, so these should be tried as a first step. Many have significant anxiety about syncopal episodes, because they occur unpredictably and are often misinterpreted as a heart attack or stroke. Reassurance about the excellent prognosis of NMS is essential, because it is often a diagnosis that patients learn to live with rather than be cured of indefinitely. Education about pre-syncopal warning signs allows patients to use the prodrome to their advantage by using the symptoms as a signal to either lie down or sit down, if possible, rather than try to "walk it off." This can abort the loss of consciousness if done quickly and prevent any physical harm that may occur from the fall. For those who cannot or do not want to lie down, various isometric exercises such as leg crossing, hand-grip exercises, and tensing the muscles in the legs or arms are effective. These counterpressure maneuvers increase systemic blood pressure and decrease venous pooling, which abort the impending syncopal event. Squatting also effectively increases venous pressure and prevents syncope.

To prevent episodes from initially occurring, volume expansion with adequate fluid intake (1–2 L per morning depending on body size) and liberal salt intake are helpful and well tolerated. Compression stockings help avoid venous pooling in the lower extremities and are useful, particularly for those who stand for long periods. Tilt training is another safe and easy tool, wherein patients are instructed to stand against a wall for 30 minutes or until symptoms appear on a routine, daily basis. However, this approach is not generally well accepted by patients, and the results of studies on tilt training have been inconsistent.

There had been hope for pacemaker therapy, because bradycardia and even asystole are common aspects of vasovagal

episodes. However, the five trials looking at the utility of pacemakers to prevent syncopal episodes in this patient population have had mixed results. Although exceptions are certainly made for patients with a marked cardioinhibitory response, in general, pacemaker therapy is not considered an established treatment option in these patients.

PHARMACOLOGIC TREATMENT FOR NMS

Pharmacotherapy should be limited to those patients with vasovagal syncope who do not respond to conservative measures. Studies on drug therapy have had conflicting results, making definitive treatment guidelines difficult. Once considered the mainstay of treatment, β-blocker therapy has been ineffective in randomized studies and is no longer the treatment of choice. Drugs such as fludrocortisone and midodrine are frequently used. These drugs boost blood pressure but have potential adverse side effects such as supine hypertension and require intermittent monitoring. In randomized studies, paroxetine and other serotonin reuptake inhibitors have significantly reduced syncopal episodes. Although the mechanism is not fully elucidated, activated serotonin receptors are known to directly affect vagal tone, blood pressure, and heart rate in animal models. Despite paroxetine's known side effects such as weight gain and insomnia, it tends to be relatively safe and well tolerated. Ultimately, each patient should be prescribed treatment on an individual basis. Many patients find effective treatment with small doses of a multidrug regimen rather than large doses of a single agent.

Avoiding Treatment Errors

The most common error made when evaluating syncope is ordering a battery of tests without taking a thorough history. The history and physical examination results should dictate which diagnostic tests are ordered. Not all patients with syncope require a brain MRI or an admission to the hospital for serial cardiac biomarker testing. Second, although it is important to determine the cause of the syncope, often this is impossible. Therefore, it is important to keep in mind that the purpose of the evaluation is not only to determine cause but to risk-stratify the patient. If the patient has been thoroughly evaluated and risk-stratified for dangerous arrhythmias or other life-threatening conditions, then the evaluation should be deemed worthwhile even if a definitive diagnosis was not obtained.

Special Patient Populations

PEDIATRIC PATIENTS

A careful personal and family history and ECG are essential elements that help distinguish benign vasovagal syncope from a potentially life-threatening etiology. Elements in the history that should serve as a warning include syncope due to a loud noise or fright, during exercise, or while supine, and a family history of sudden death in a young person. The rare but serious conditions include long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, anomalous coronary arteries, and Wolff-Parkinson-White syndrome with atrial fibrillation. The frequency of vasovagal episodes in this age group often leads to dismissal of symptoms, despite the recently heightened awareness of potentially dangerous causes of syncope in children.

ELDERLY PATIENTS

Falls in the elderly are a common occurrence, and many falls are due to syncope. The ability to make the diagnosis is complicated by poor patient recall of the event and the clinical overlap between mechanical falls, orthostatic intolerance, generalized dizziness, and vasovagal syncope. Both orthostatic hypotension and carotid sinus hypersensitivity are fairly common in the elderly. Syncope can also be the first manifestation of an autonomic disorder or central nervous system problem (see Fig. 31-2). The elderly are more prone to cardiac causes of syncope with an increased prevalence of underlying heart disease but also more prone to vasovagal syncope due to reduced fluid intake and an age-related decline in baroreceptor and autonomic function. It is particularly important to be cognizant of polypharmacy in this at-risk group. Finally, consideration should be given to restricting driving privileges, particularly if the syncopal events are profound and without much warning.

FUTURE DIRECTIONS

Treatment strategies for cardiac arrhythmic syncope including device therapy and revascularization are effective and proven. However, our understanding of the pathophysiology of NMS and autonomic function in general is still incomplete. Further study in this area will lead the way for more effective treatment strategies. In addition, although the guidelines and suggested protocols in the literature aid with a systematic approach to evaluation of syncope patients, there will probably be increased use of specialized syncope units to further promote a cohesive, structured-care pathway that is also efficient and cost-effective.

ADDITIONAL RESOURCES

Brignole M, Alboni P, Benditt DG, et al. Guidelines on Management (Diagnosis and Treatment) of Syncope—Update 2004 Executive Summary, The Task Force on Syncope, European Society of Cardiology. *Eur Heart J.* 2004;25:2054–2072.

An update from the European Task Force guidelines in 2001; details the evaluation, diagnostic workup, and treatment for syncope patients.

Grubb BP. Clinical practice. Neurocardiogenic syncope. *N Engl J Med.* 2005;352:1004–1010.

A comprehensive review of the evaluation and management of neurocardiogenic syncope. Syncope guidelines are reviewed as well.

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Participants in the Framingham Heart Study were evaluated for the incidence and etiology of syncopal episodes from 1971 to 1998. This study demonstrates that the prognosis over many years of follow-up is dependent on the etiology of the syncopal event.

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Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation: In Collaboration With the Heart Rhythm Society: Endorsed by the American Autonomic Society. *Circulation.* 2006;113:316–327.

Outlines the evaluation process and differential diagnosis in patients with syncope as defined by an expert committee assembled by the American Heart Association and American College of Cardiology.

EVIDENCE

Connolly ST, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol.* 1999;33:16–20.

A nonblinded controlled study that randomized patients to pacemaker implantation and pacemaker therapy versus no pacemaker. There was a marked treatment effect in the pacemaker group leading to early termination of the study. However, given the results of VPS II, this is now felt to be largely due to placebo effect.

Connolly ST, Sheldon R, Thorpe KE, et al. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA.* 2003;289:2224–2229.

A double-blinded controlled trial in which all subjects underwent pacemaker implantation, followed by randomization to either a pacing protocol or pacemaker inactivation for the duration of the study. Pacemaker therapy did not reduce the incidence of recurrent vasovagal therapy.

Del Rosso A, Ungar A, Maggi R, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. *Heart.* 2008;94:1620–1626.

A prospective cohort study used to devise the EGSYS scoring system for syncope patients. The scoring system was then validated with another prospective cohort. The scoring system was devised to better detect those patients with syncope due to a cardiac cause.

Kapoor WN. Is there an effective treatment for neurally mediated syncope? *JAMA.* 2003;289:2272–2275.

The accompanying editorial to the published VPS II results.

Raviele A, Giada F, Menozzi C, et al. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). *Eur Heart J.* 2004;25:1741–1748.

Twenty-nine patients underwent pacemaker implantation and were randomized to pacemaker treatment on versus off. There was no significant reduction in syncopal events in the pacemaker-on group.

Schladenhaufen R, Feilinger S, Pollack M, et al. Application of San Francisco Syncope Rule in elderly ED patients. *Am J Emerg Med.* 2008;26:773–778.

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Venugopal D, Jhanjee R, Benditt DG. Current management of syncope: focus on drug therapy. *Am J Cardiovasc Drugs.* 2007;7:399–411.

Comprehensive review discussing the various pharmacotherapies available for neurocardiogenic syncope.

Cardiac Pacemakers and Defibrillators

Anil K. Gehi and J. Paul Mounsey

32

Technological advances have improved the versatility and function of implantable devices used to treat bradyarrhythmias and tachyarrhythmias. Surgical placement of pacemakers and implantable cardioverter defibrillators (ICDs) can be performed on an outpatient basis, with low risk and minimal morbidity, allowing the majority of patients to return to full functional capacity quickly.

INDICATIONS FOR IMPLANTATION OF CARDIAC RHYTHM DEVICES

Pacemakers

Pacemakers are indicated primarily for patients with symptomatic bradycardia or impressive bradycardia without symptom correlation but associated with a high risk of progression to a symptomatic bradycardia. Precise indications are published in the American College of Cardiology/American Heart Association Guidelines for Pacemaker and ICD Implantation. Symptoms of bradycardia may be subtle (lightheadedness, fatigue) or dramatic (syncope or cardiac arrest). Bradycardia may be the result of dysfunction of the sinus node (referred to as *sick sinus syndrome*), the atrioventricular node, or the infranodal conduction system. Damage to the conduction system results most commonly from fibrosis or infarction but may be the result of numerous other etiologies, including infection, pharmacologic agents, electrolyte imbalance, or thyroid disease. It is imperative to rule out potentially reversible causes before committing a patient to device-based therapy (Fig. 32-1).

Biventricular Pacemakers

Based on the concept that "dyssynchronous" electrical activation of the left ventricle—as with bundle branch block or right ventricular pacing—translates to inefficiency of cardiac function, biventricular pacing has been developed as a therapeutic approach for patients with impaired cardiac function who would not otherwise have an indication for pacemaker therapy (Fig. 32-2). For instance, in patients with left bundle branch block, delayed electrical activation of the lateral wall of the left ventricle leads to delayed contraction of this same wall. In an individual with normal systolic function, delayed contraction of the lateral wall of the left ventricle may not result in any significant decrement in function. However, in an individual with markedly impaired left ventricular function, the disorganized ventricular contraction resulting from left bundle branch block can result in decreased pumping efficiency and increased mitral regurgitation. By positioning pacemaker leads in the right ventricle and in a lateral branch of the coronary sinus on the epicardium of the left ventricle, simultaneous pacing of both walls of the left ventricle improves ventricular synchrony. Biventricular pacing is indicated for treatment of patients with symptomatic heart failure (New York Heart Association class III or IV) despite optimal medical therapy, reduced left ventricular ejection fraction, and a widened QRS duration (either intrinsically or due to chronic need for pacing).

Implantable Cardioverter Defibrillators

ICDs are indicated for patients with structural heart disease at risk for malignant ventricular tachyarrhythmias (i.e., ventricular tachycardia or ventricular fibrillation). These indications include patients with a prior history of resuscitated cardiac arrest or ventricular tachycardia as well as patients at high risk for future cardiac arrest or ventricular tachyarrhythmia such as a patient with ischemic or nonischemic cardiomyopathy or hypertrophic cardiomyopathy. ICDs are also often indicated in patients with structurally normal hearts who are at high risk for ventricular tachyarrhythmias, such as those with inherited disorders of cardiac rhythm: long QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia. The indications for ICD implantation, particularly in patients with tachyarrhythmias, are discussed in detail in this chapter and summarized in Figure 32-3.

PACEMAKER TECHNOLOGY

A pacemaker consists of a pulse generator and endocardial leads capable of sensing and pacing. The pulse generator contains a microprocessor to control the analysis of sensed activity and a battery. Pacemakers can be configured as single-chamber, dual-chamber, or biventricular devices. To clarify pacemaker characteristics, a four-letter code describes features specific to each pacemaker. The first letter or category of the code indicates the chamber(s) paced, and the second describes the chamber(s) sensed. Options for these positions include O (none), A (atrium), V (ventricle), and D (dual = A + V). The code's third position indicates the response of the device to a sensed event; options include O (none), T (triggered), I (inhibited), and D (dual = triggered or inhibited). The fourth position indicates programmability of rate modulation. The letter R in this position indicates that the device has an active responsive sensor. A pacemaker programmed to VOO mode, for example, paces the ventricle at a specified rate and will ignore any signal sensed by the ventricular lead. A pacemaker programmed to VVI paces the ventricle at a specified rate but will inhibit pacing in the ventricle if an appropriate signal is sensed by the ventricular lead. A pacemaker programmed to DDD mode paces both the atrium and ventricle, unless it is inhibited by an appropriate signal in the atrium or ventricle. Ventricular pacing can also be triggered after atrial sensing or pacing. Turning on the rate sensor with any mode of pacing allows the specified rate to increase in response to exercise that is detected by a sensor contained in the pacemaker (most commonly an accelerometer or a respiration sensor). In a patient with chronotropic incompetence, the pacing rate can adjust as necessary to correspond with and compensate for the patient's activity.

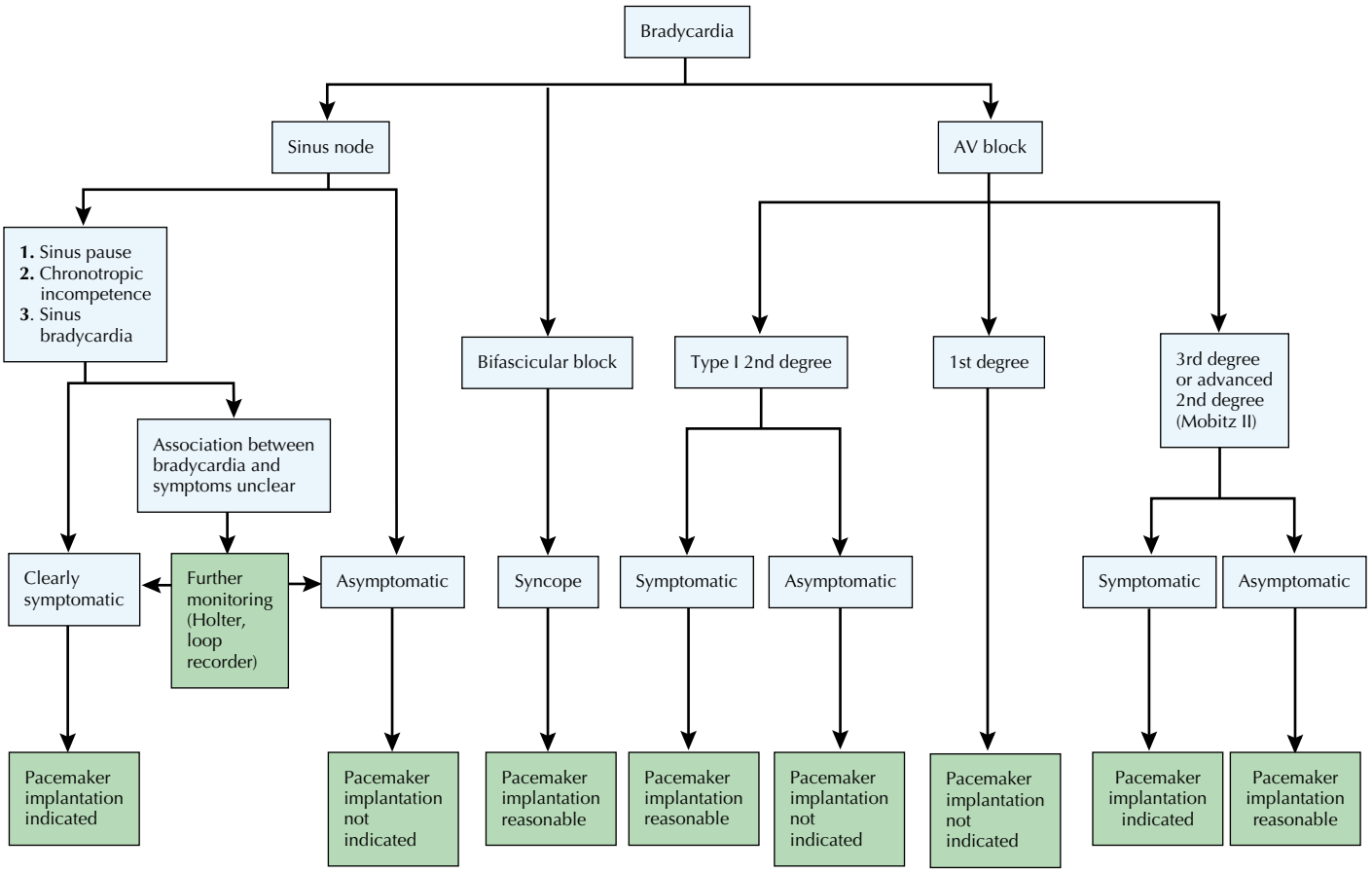


Figure 32-1 *Algorithm detailing evaluation of patients with bradycardia and indications for pacemaker implantation.* In general, pacemaker implantation is indicated for significant bradycardia associated with symptoms. AV, atrioventricular.

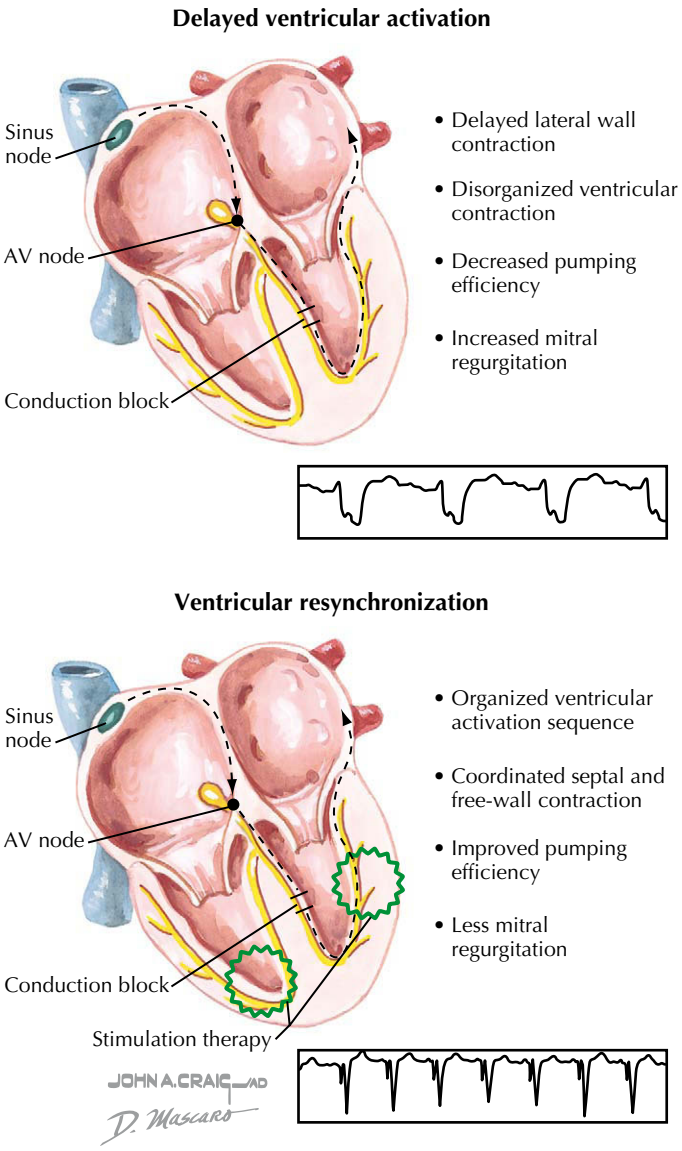
DEFIBRILLATOR TECHNOLOGY

As with a pacemaker, an ICD consists of a pulse generator and endocardial leads. In addition, an ICD requires high-voltage defibrillator coils, which are integrated into the right ventricular endocardial lead. An ICD pulse generator contains not only a microprocessor and a battery but also a high-voltage capacitor. Besides being capable of pacing for bradycardia when necessary, ICDs employ therapies for detected ventricular tachyarrhythmias. An ICD considers an episode of tachycardia as a potential malignant ventricular arrhythmia first based on a preprogrammed rate cutoff. Beyond this, an ICD can distinguish a tachyarrhythmia as ventricular in origin based on the associated activity in the atrium, the rapidity of onset (to distinguish from sinus tachycardia), the regularity of ventricular activity (to distinguish from atrial fibrillation with a rapid ventricular response), and the morphology of the ventricular signal. If diagnosed as a ventricular tachyarrhythmia, the ICD may employ therapies such as antitachyarrhythmic pacing, low-energy cardioversion, or high-energy defibrillation (Fig. 32-4). These therapies can be tailored to tachycardias in multiple rate tiers, allowing for different treatments for different types of tachycardia. This multi-tiered therapy helps reduce the need for high-energy defibrillation without compromising ICD efficacy.

DEVICE IMPLANTATION

Endocardial leads are introduced via access through the subclavian, axillary, or cephalic vein, typically on the left side. Epicardial lead placement may be required (if endocardial implantation is not feasible). Epicardial lead placement requires a more invasive surgical approach and is therefore used only when percutaneous endocardial lead placement is not possible or if a patient needing pacemaker or ICD placement is undergoing an open cardiac surgical procedure.

Endocardial leads are positioned and secured in the right atrium, right ventricle, and, in the case of biventricular pacing devices, a branch of the coronary sinus, using fluoroscopy. A pacemaker lead typically has two electrodes (bipolar) in contact with the atrial or ventricular myocardium (Fig. 32-5A). A biventricular pacemaker has an additional lead on the epicardium of the lateral left ventricle via the coronary sinus (Fig. 32-5B). Impulses delivered by the pulse generator through these electrodes pace the heart. An ICD lead's additional high-voltage coils act as shocking electrodes in conjunction with the ICD pulse generator itself (Fig. 32-6). Once positioned, the leads are inserted into the header of the pulse generator, which is implanted into the subcutaneous or submuscular region below the clavicle. The entire procedure can generally be



In patients with conduction block (e.g., left bundle branch block), there is delayed lateral wall electrical activation and mechanical contraction leading to decreased pumping efficiency. By simultaneously pacing the septal and lateral walls of the left ventricle with right ventricular and left ventricular leads (via the coronary sinus), the ventricular walls are "resynchronized," thereby improving pumping efficiency.

Figure 32-2 *Benefit of biventricular pacing.* AV, atrioventricular.

accomplished within 1 to 2 hours, depending on the complexity of the device, under conscious sedation or general anesthesia.

POSTPROCEDURE CARE AND LONG-TERM FOLLOW-UP

Postoperatively, patients are instructed to keep the surgical incision clean and dry for approximately 10 days and to notify their provider of any evidence of infection. They are asked to limit ipsilateral arm use to below shoulder level and to avoid heavy lifting for a few weeks to prevent lead dislodgment and promote wound healing. Driving restrictions are typically imposed for approximately 6 months in patients who have had an ICD placed for documented sustained ventricular tachycardia or ventricular fibrillation. Occasionally, it may be reasonable to shorten the driving restrictions. Patients who undergo ICD implantation for primary prevention are generally not restricted from driving. It is recommended that commercial driving be permanently prohibited. Pacemaker patients are followed trans-telephonically every 3 months, with clinic evaluations for complete battery voltage, and lead testing every 12 months. ICD patients may also be evaluated remotely with clinic evaluation approximately every 6 months for device testing and evaluation of electrograms recorded by the device during a tachyarrhythmia.

The management of a single ICD shock does not necessarily require an emergent office or emergency department visit. Although an ICD shock can be an anxiety-provoking experience, occasional shocks are to be expected. In the event of a single shock, a patient who is otherwise well should be reassured and referred for evaluation within the week. However, if the shock is associated with worrisome symptoms such as syncope, shortness of breath, persistent palpitations, or chest pain, or if a patient experiences multiple ICD shocks over a short period of time, an emergency department visit is required. In the event of an ICD shock, the appropriateness of ICD therapy should be determined by evaluation of stored recordings in the ICD. Any potentially reversible cause should be treated. Otherwise, management often requires optimization of ICD programming, the use of antiarrhythmic agents, or catheter ablation.

ELECTROMAGNETIC INTERFERENCE

Electromagnetic interference occurs when a source emits electromagnetic waves that interfere with the proper function of the device. It is important for individuals with pacemakers or ICDs to avoid any sources of electromagnetic interference. That said, with recent advances in pacemaker and ICD technology there are relatively few devices that interfere with their function. There is no restriction on the use of household items such as microwaves, televisions, radios, or electric blankets, since these are not sources of electromagnetic interference. Although passage through a metal detector will not harm ICD or pacemaker function, it is recommended that patients with these devices not be in close contact with handheld metal detectors or scanning "wands" containing magnets. Instead, patients are advised to present their device identification card to security personnel and request a hand search. Cellular telephone use is not prohibited, although patients are advised to use the phone on the contralateral ear (>10 cm from the device) and not to carry the phone in the breast pocket on top of the implanted device. Electronic article surveillance systems are not likely to cause a negative interaction with an implanted device as long as the patient is not standing close to the scanning system for a prolonged period of time. Patients are instructed to walk normally through such devices.

Medical sources of potential electromagnetic interference include MRI scanners, radiation therapy, transthoracic cardioversion, and electrocautery. The effect of a strong magnetic field differs for pacemakers and ICDs: pacemaker exposure to an electromagnetic field usually results in asynchronous pacing

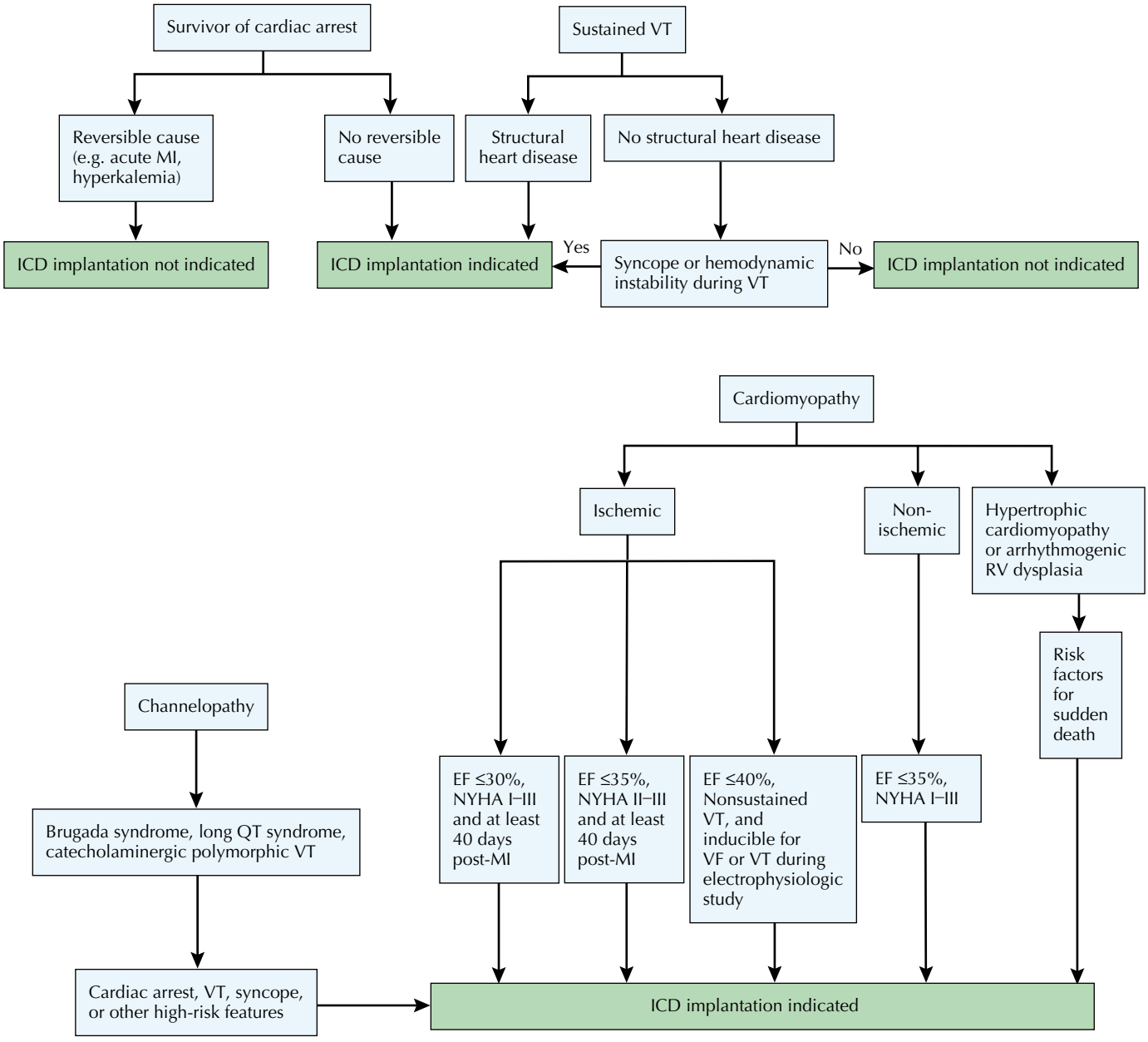
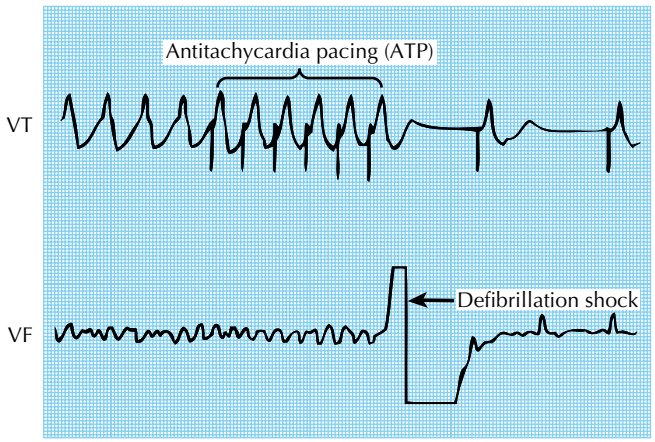


Figure 32-3 *Algorithm detailing evaluation of patients with sudden cardiac death and/or tachyarrhythmias and indications for implantable cardiac defibrillator (ICD) implantation.* In general, ICD implantation is indicated for secondary prophylaxis in survivors of cardiac arrest or hemodynamically significant sustained ventricular tachycardia (VT). ICD is indicated for primary prophylaxis in patients with cardiomyopathy or channelopathy of various etiologies and risk factors for sudden death. EF, ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association (class); RV, right ventricular; VF, ventricular fibrillation.



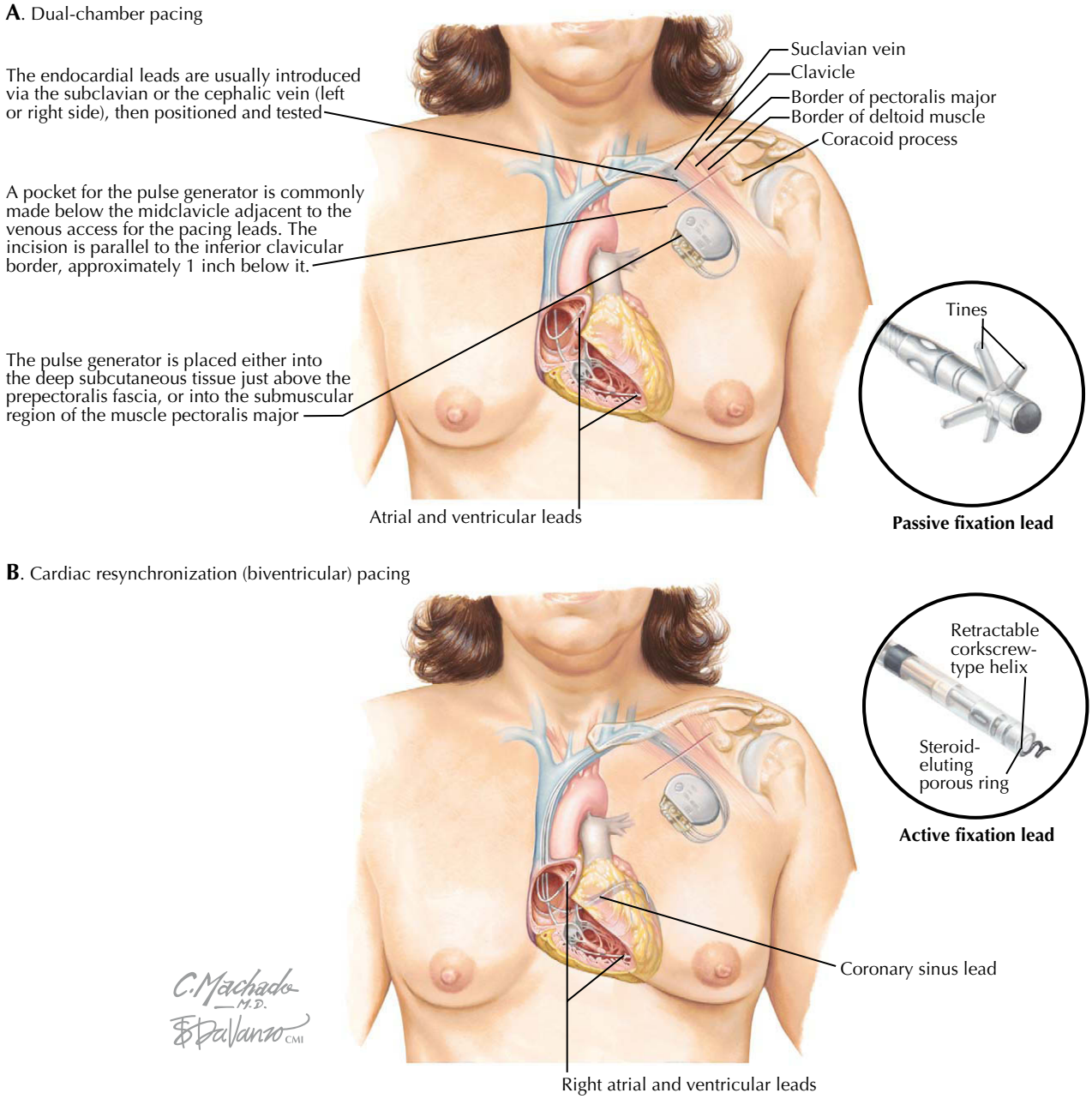
In the situation of VT, burst rapid ventricular pacing at a rate faster than the rate of the VT (known as antitachycardia pacing) will often terminate VT. In the situation of VF, a high-voltage defibrillation shock is delivered through defibrillation coils positioned on the right ventricular lead to terminate the arrhythmia.

Figure 32-4 *Therapy for ventricular tachycardia (VT).* VF, ventricular fibrillation.

(i.e., VOO); exposure of an ICD can result in "blinding" of the device, potentially resulting in inappropriate withholding of therapy for tachyarrhythmias. MRI scans are generally contraindicated in patients with implanted devices. Direct radiation (i.e., radiation therapy) that will be focused on the area where an implanted pacemaker or ICD is present is not recommended; if necessary, the device should be moved to the opposite side and shielded from the direct beam. Implanted ICDs and pacemakers should be evaluated before and after electrical cardioversion, and the external electrodes used for cardioversion (anterior-posterior position) should be positioned as far as possible (>5 cm) from the implanted device. Surgical electrocautery presents unique concerns for the ICD patient, because electrical output from the cautery can be mistakenly detected by the ICD, resulting in inappropriate delivery of therapy during a normal rhythm. Hence, the detection function of the ICD should be inactivated before any surgery or procedure during which electrocautery may be used. Electrocautery may also interfere with pacemaker sensing and inhibit output. In the pacemaker-dependent patient, the pacemaker should be programmed to asynchronous mode; otherwise, the anesthesiologist may need to apply a magnet to the pacemaker to provide asynchronous pacing. In addition, it is recommended that the rate-responsive feature be disabled. In a patient who is not pacemaker-dependent, no reprogramming aside from disabling the rate-responsive feature is necessary. Electrocautery in close proximity to an older pacemaker may render it nonoperational. It is recommended that postoperative ECGs, with and without magnet application, be performed after the use of electrocautery to confirm proper pacemaker function.

FUTURE DIRECTIONS

Advances in pacemaker and ICD technology have substantially improved survival and quality of life for patients with cardiac arrhythmias. In the future, indications for ICD therapy will probably expand as proper identification of those patients at risk for future ventricular tachyarrhythmic events improves (see Fig. 32-3). In addition, enhanced functionality is continuously being added to modern devices. Advanced patient monitoring—particularly when integrated into telemetric systems utilizing the Internet—will allow for greatly improved care of the cardiac patient.



The leads connecting the pulse generator to the endocardium can be different types: unipolar or bipolar and of active fixation or passive fixation. The unipolar system has a single electrode (cathode, negative pole) in contact with the endocardium, and the anode is the pulse generator itself. The bipolar system lead has both a cathode and an anode at the tip of the same lead. Passive fixation leads have tines, barbs that anchor the lead to the endocardial trabecular muscle of the chamber in which it is implanted. Active fixation leads have a corkscrew-type device or helix that is placed into the myocardium. Both types irritate the myocardium, causing inflammatory reaction and cellular growth around the lead. To minimize the inflammatory reaction, most leads have steroid-eluting tips. The coronary sinus lead allows for "resynchronization" of disorganized ventricular contraction in selected patients with impaired cardiac function and conduction block.

Figure 32-5 *Implantable cardiac pacemaker.*

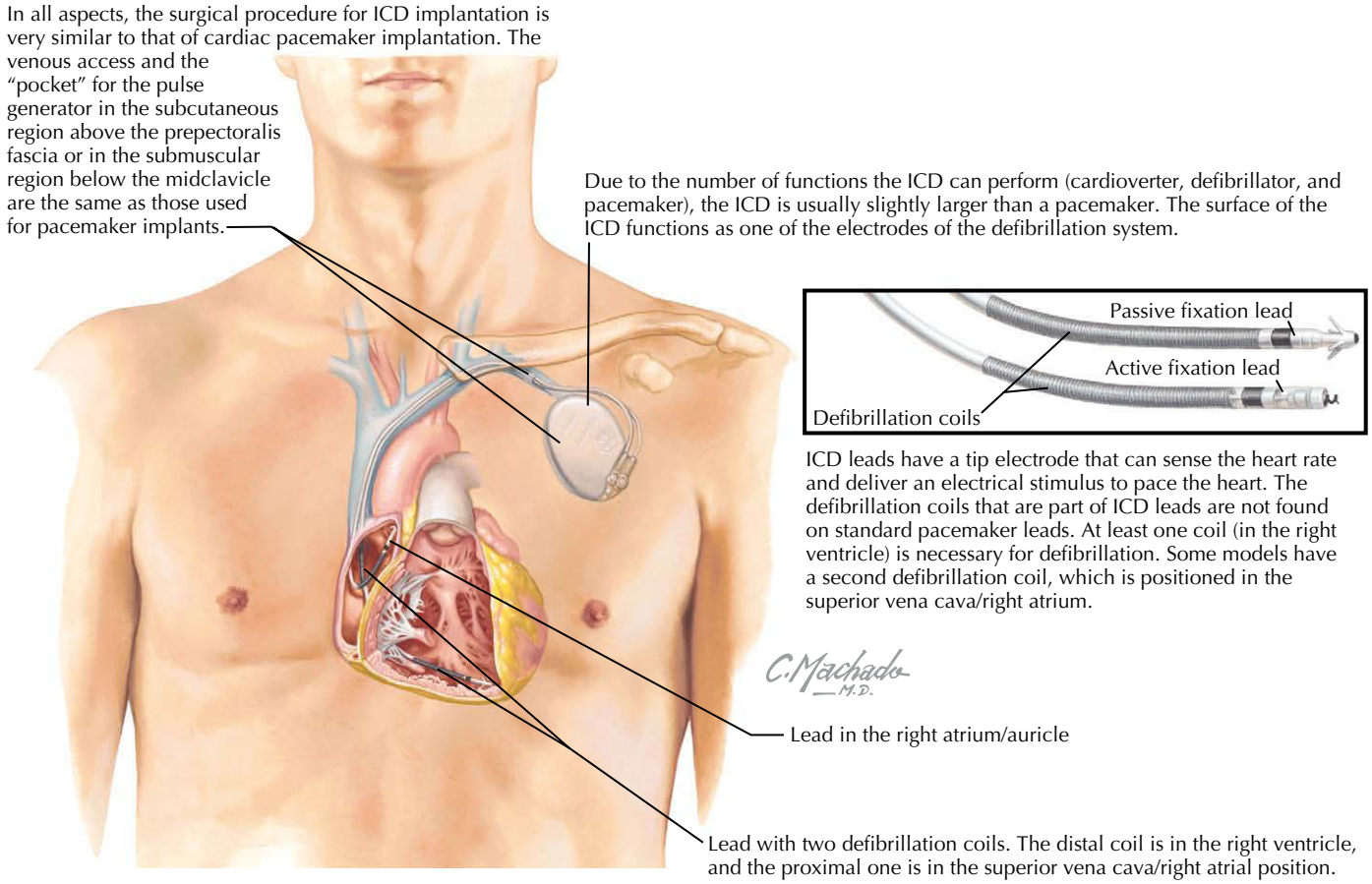


Figure 32-6 *Implantable cardiac defibrillator (ICD).*

EVIDENCE

Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med.* 2002;346:1845–1853.

One of the early seminal studies of cardiac resynchronization therapy demonstrating clinical improvement in patients with moderate-to-severe heart failure and intraventricular conduction delay.

AVID Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med.* 1997;337:1576–1583.

Demonstrates the clear benefit of implantable defibrillators in patients who had been successfully resuscitated from near-fatal ventricular arrhythmias.

Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol.* 2008;51:1–62.

A consensus statement of guidelines for device-based management of cardiac rhythm disturbances.

Gehi AK, Mehta D, Gomes JA. Evaluation and management of patients after implantable cardioverter-defibrillator shock. *JAMA.* 2006;296:2839–2847.

A review article discussing the evaluation and management of patients who receive a shock from their implantable defibrillator.

Kusumoto FM, Goldschlager N. Cardiac pacing. *N Engl J Med.* 1996;334:89–97.

A review article discussing indications, function, and management of cardiac pacemakers

Mangrum JM, DiMarco JP. The evaluation and management of bradycardia. *N Engl J Med.* 2000;342:703–709.

Review article describing the anatomy and pathology of the heart's conduction system.

Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877–883.

Seminal article demonstrating the benefit of implantable defibrillators for primary prophylaxis in patients with previous myocardial infarction who have a severely reduced ejection fraction.

Catheter Ablation of Cardiac Arrhythmias

33

Fong T. Leong and J. Paul Mounsey

One of the most important advances in cardiac electrophysiology over the last 30 years has been the introduction of fluoroscopically guided, catheter-based methods to cure or palliate arrhythmias. Symptomatic rhythm disturbances were formerly treated with potentially toxic drugs, open heart surgery, or a combination of the two. Catheter ablation has allowed the targeting and selective destruction of areas of the heart strategically important for the genesis or propagation of arrhythmias, using what is essentially a thin, flexible catheter inserted percutaneously and positioned under fluoroscopic guidance and electrophysiologic (EP) mapping. Today, this therapeutic modality has replaced cardiac surgery as the treatment of choice for almost all ventricular and supraventricular tachycardias (SVTs), particularly if antiarrhythmic drugs have been ineffective.

ENERGY SOURCES FOR CATHETER ABLATION

Initially, direct current (DC) shocks were delivered through the ablating catheter to achieve destruction of endocardial tissue. However, the effects of DC shock were often traumatic, unpredictable, and patchy. Blood surrounding the catheter tip could vaporize during the procedure and cause marked local injury to the myocardium. Not infrequently, the catheter tip also disintegrated. It then became apparent that radiofrequency (RF) energy, a type of alternating current (AC) already in use for electrocautery, could be modulated and applied through the catheter to create discrete and well-defined lesions. Subsequent experience showed that as long as tissue temperatures did not exceed 100°C, RF energy would not cause barotrauma. Furthermore, RF delivery is relatively painless and can be titrated to achieve the desired degree of tissue damage. Minimal muscle or nerve stimulation also meant that ablations could be performed without general anesthesia. Because of its safety and efficacy (Table 33-1), RF energy has become the preferred and most widely delivered form of energy for arrhythmia ablation.

In contrast to the household AC mains of 50 or 60 Hz, the RF current used for arrhythmia ablation alternates its polarity at between 300 and 1000 kHz, a frequency band high enough to prevent the induction of ventricular fibrillation when applied to the heart. Although RF energy works by thermal destruction of arrhythmogenic myocardium or abnormal conducting tissue, this heat does not arise from searing of the catheter tip. Rather, temperature builds up at the catheter tip–tissue interface, the point of highest resistance in the AC circuit. When resistive heating of cardiomyocytes in contact with the catheter tip exceeds 50°C for at least 10 seconds, coagulative necrosis occurs. Provided adequate tissue contact is maintained, the lesions created by RF energy are homogeneous and hemispheric in profile (roughly 3–5 mm in radius and 2–3 mm in depth). When cardiac tissue with intrinsic automaticity (e.g., a clump of cells driving an automatic tachycardia) is exposed to RF-induced heating, *acceleration* of the arrhythmia is seen. Conversely, RF treatment of a critical isthmus in a reentrant arrhythmia causes *slowing* or termination of the tachycardia.

Other types of transcatheter energy already in clinical use or currently under investigation include cryoablation (freezing), focused ultrasound, microwave, laser, and photocoagulation. RF ablation, rather than these less commonly used approaches, is the focus of this chapter.

RADIOFREQUENCY CATHETER ABLATION OF NODAL REENTRANT TACHYCARDIAS

Atrioventricular nodal reentrant tachycardia (AVNRT) is the most common type of paroxysmal SVT (Chapter 27). Although the exact nature of the tachycardia circuit remains uncertain, it is thought that the atrioventricular (AV) node and at least two discrete atrio-nodal tracts of different conduction velocities and refractoriness are involved in this arrhythmia. The most common type of AVNRT is referred to as slow-fast AVNRT. In individuals with slow-fast AVNRT, the "slow" atrio-nodal pathway, which is located in the inferior portion of the triangle of Koch (Fig. 33-1) between the coronary sinus (CS) ostium and tricuspid annulus, forms the antegrade limb of the tachycardia circuit, while the "fast" atrio-nodal pathway—located superior to and behind the tendon of Todaro, level with the apex of the triangle of Koch—conducts retrogradely to the atrium. Other forms of AVNRT have been described, such as fast-slow AVNRT, a type that propagates in a direction opposite to that just mentioned, and a third type that utilizes two slow pathways (slow-slow AVNRT).

The decision to use RF catheter ablation (RFCA) to treat AVNRT is a matter of clinical judgment and patient preference. If the tachycardia occurs frequently or is not well tolerated (either physically or psychologically), or if the patient is disinclined to try antiarrhythmic drugs, then RFCA may be recommended as first-line therapy, particularly given the improvements in RFCA in recent years. Enthusiasm for RFCA was initially limited, because early attempts to break the reentrant circuit by ablating the fast pathway—which lies in close proximity to the compact AV node and His bundle—were accompanied by an unacceptably high incidence of heart block (up to 20%). Following these early studies it was found that ablation or modification of the slow pathway (typically located further away from the AV node and His bundle) was equally effective and much safer. Mapping of the slow pathway is achieved by positioning the catheter within the inferior aspect of the triangle of Koch (see Fig. 33-1) and manipulating it until a delayed, multicomponent atrial potential (thought to represent slow-pathway

Table 33-1 Outcomes of Catheter-Delivered Radiofrequency Ablation

Type of Arrhythmia	Success Rate (%)	Complications (Rate)
AVNRT	>95	AV block (1%), pericarditis or cardiac tamponade (0.3%)
AVRT	>95 (left-sided AP) 80 (inferoseptal AP) >95 (right-sided AP) 85 (superoseptal AP)	AV block (<1%), cardiac tamponade (0.1% to 1.1%), pericarditis (0.2%), stroke (0.15%), coronary artery dissection (rare)
AV node ablation	98–100	Sudden death (rare)
Atrial flutter	85–95 (typical flutter) 80–90 (atypical flutter)	AV block (rare), stroke (rare)
Focal atrial tachycardia	86	AV block, cardiac tamponade, stroke, phrenic nerve damage (collectively 1%–2%)
Atrial fibrillation	65–95 (for paroxysmal AF)* 40–80 (for persistent AF)*	Stroke (0.1% to 5%), cardiac tamponade (1%), LA flutter (up to 30%), phrenic nerve damage (<0.5%), PV stenosis (uncommon), atrioesophageal fistula (rare)
Idiopathic VT	85–100	Cardiac tamponade (Rare)
Ischemic VT	54–81	MI, stroke, arterial complications, death (1%–2%)

AF, atrial fibrillation; AP, accessory pathway; AV, atrioventricular; AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; LA, left atrial; MI, myocardial infarction; PV, pulmonary vein; VT, ventricular tachycardia.
*Reported success rates vary widely, depending on definition of "success," number of repeat ablations, quality of postoperative surveillance, and so forth.

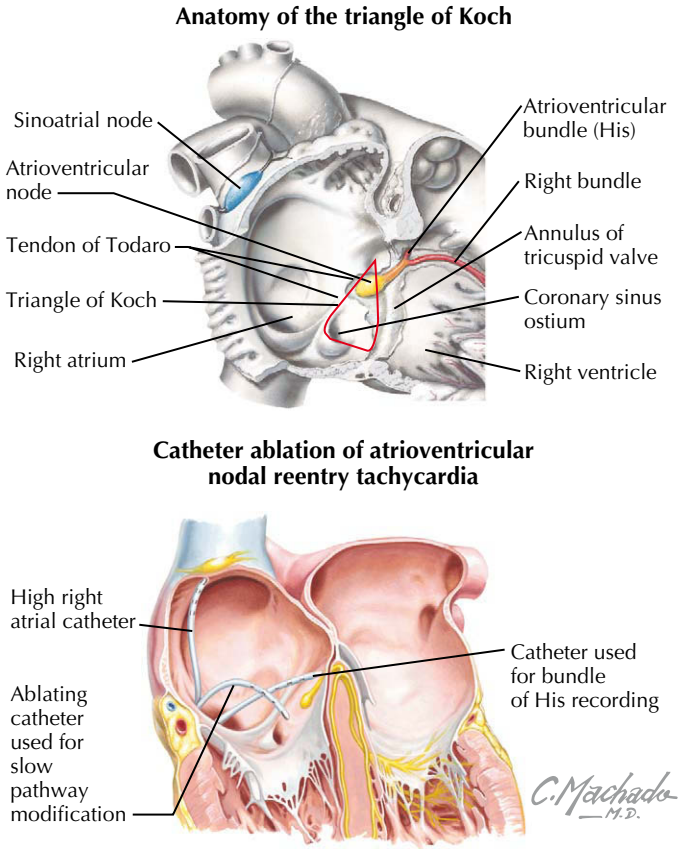


Figure 33-1 *Atrioventricular nodal reentry tachycardia.*

depolarization) is recorded at the catheter tip. Alternatively, fluoroscopy and anatomic landmarks can be used to localize a specific site where the local ventricular deflection is much larger than the atrial signal. RF energy is then applied to this site. The goal of this overall strategy is to initiate RF ablation at the more distal points in the slow pathway, allowing for subsequent RF applications further superiorly and proximally if the initial therapy is unsuccessful. When necessary, the two methods can be combined to locate more precisely sites amenable to RFCA. When RF energy is applied to the correct site, a transient, accelerated junctional tachycardia is nearly always observed. However, this finding is not specific. Up to 65% of therapeutically ineffective RF applications are also associated with junctional tachycardias. Nonetheless, the absence of a junctional response after 10 to 15 seconds of heating should prompt discontinuation of RF delivery and movement of the ablating catheter to a different location.

For typical AVNRT, slow-pathway modification delivers a cure rate of more than 95% (see Table 33-1). There remains a small but finite risk of inadvertent AV node damage during the procedure, a complication that may require treatment with permanent cardiac pacing.

CATHETER ABLATION OF ATRIOVENTRICULAR BYPASS TRACTS

The electrophysiology of atrioventricular reentrant tachycardia (AVRT) is described in Chapter 27. For this discussion, it is worth recalling that sustenance of this type of SVT depends upon an endocardially located extranodal bypass tract, composed of a tiny band of myocardial tissue connecting the atrium to the ventricle. If this accessory pathway (AP) is capable of high-rate antegrade conduction, then the coincidental development of atrial fibrillation (AF) in these patients may lead to

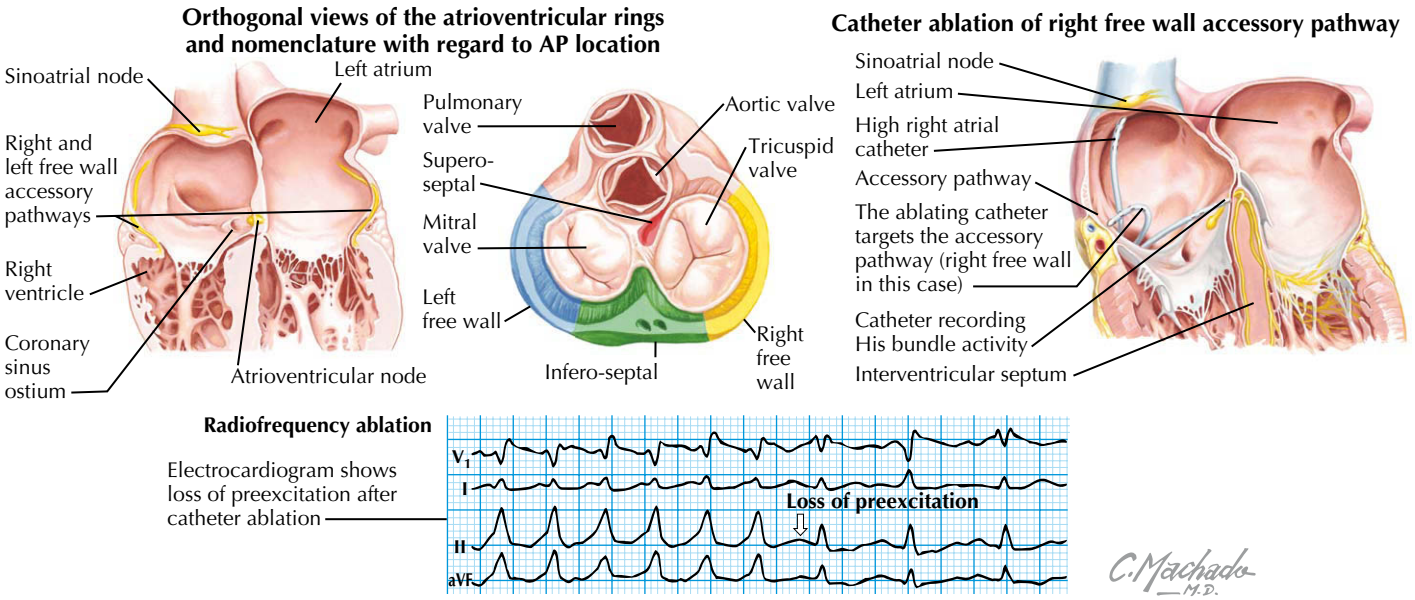


Figure 33-2 *Accessory pathways (APs) and atrioventricular reentrant tachycardia.*

very fast ventricular rates followed by ventricular tachycardia–ventricular fibrillation and sudden death. Overall, this risk is very small (0.05% to 0.5% per annum), even though AF occurs in one third of the patient population with Wolff-Parkinson-White (WPW) syndrome. Nevertheless, for patients with WPW syndrome, drug-refractory AVRT, or those wanting definitive therapy, RFCA, which is safe and potentially curative in this situation, should be considered first-line treatment. Whether asymptomatic WPW should be routinely ablated remains controversial. It should be noted that some individuals, especially those with Ebstein's anomaly, have multiple accessory pathways. Others have bypass tracts that are either epicardial in location (e.g., connecting the atrial appendage to the ventricle) or have uncommon connections (e.g. Mahaim fibers, fasciculoventricular tracts). For a description of RFCA in these situations the reader is referred to more comprehensive texts.

Although the typical AVRT circuit consists of the atria, AV node, His-Purkinje system, ventricles, and the AP, it is the latter that is sought and destroyed during RFCA. Between 50% and 60% of AV APs are located in the free wall or nonseptal aspect of the mitral annulus. The remainder are distributed in the inferoseptal space (20% to 30%), along the free wall of the tricuspid annulus (15% to 20%), and in the superior and midseptal area, close to the AV node (<10%) (Fig. 33-2). The AP location may be deduced with surprising accuracy from the morphology of preexcited QRS complexes on the 12-lead ECG. Definitive localization of the AP, however, requires the use of intracardiac catheters. With electrodes positioned in the right ventricle, CS, His bundle, and high right atrium, it is possible to define the tachycardia mechanism, establish the relevance of the AP to that tachycardia, determine its location, study its electrophysiologic properties, and then come to a decision as to whether the AP should be eradicated. An AP with slow conduction located close to the His bundle in a young patient with asymptomatic WPW syndrome, for example, can be safely left alone.

Left-sided APs may be reached either retrogradely (by extending the mapping-ablating catheter from a femoral artery up the aorta, down the aortic valve, and into the left ventricle), or with a transseptal puncture (crossing the fossa ovalis from the right atrium and then into the left ventricle). Once in the appropriate chamber, the AP's precise location can be mapped by a variety of means, depending on whether the AP is overt (i.e., conducts antegradely and has manifest delta waves during sinus rhythm) or concealed (i.e., is only capable of retrograde conduction). In the former scenario, the aim is to find a spot on the AV groove where the local ventricular potential precedes the onset of the delta wave by the greatest possible length of time, either during maximally preexcited sinus rhythm or with atrial pacing. Often this spot is also where the shortest annular AV time is observed. In the latter situation, the location of the concealed AP is demarcated by the shortest local ventriculoatrial time (usually ≤60 milliseconds) during orthodromic tachycardia, or during ventricular pacing. Sometimes a sharp AP potential may be recorded during sinus rhythm, indicating an appropriate site for ablation. During RF application, successful extirpation of the AP may be inferred from (1) disappearance of the delta wave (see Fig. 33-2), (2) termination of AVRT during RF energy delivery, or (3) the sudden appearance of crisp concentric-nodal conduction.

The acute success rates for RFCA of APs exceed 95% overall, with some variation depending on the insertion site of the bypass tract (see Table 33-1). Clinical recurrences necessitating repeat ablation occur in 5% to 10% of cases. The overall complication rate is approximately 4.4%.

CATHETER ABLATION OF MACROREENTRANT AND FOCAL ATRIAL TACHYCARDIAS

From a mechanistic standpoint, atrial tachycardias (ATs) may be segregated into those that are due to macroreentry ("atrial flutter") and those that are driven by one or more rapidly discharging foci ("focal AT"). Atrial flutters are in turn classified into those that use the cavotricuspid isthmus (CTI) as an obligate part of the tachycardia circuit and those that do not. The typical CTI-dependent counterclockwise atrial flutter (the direction of clocking describes the pattern of right atrial activation when the heart is viewed from its apex, looking up at the tricuspid valve) has a characteristic ECG (Fig. 33-3). Although this arrhythmia is exquisitely sensitive to external DC shocks, antiarrhythmic drugs are generally ineffective in preventing recurrence of CTI-dependent counterclockwise atrial flutter. Consequently, many regard RFCA as first-line treatment for this arrhythmia. The clockwise CTI-dependent atrial flutter is seen nine times less frequently than its counterclockwise cousin. It can be ablated using the same method. Of patients with typical atrial flutter, approximately 30% have concomitant AF. Ablation of the atrial flutter does not cure the AF.

In the second type of atrial flutter (also called atypical atrial flutter), the reentrant circuit is usually anatomically related to some atrial scar, the latter either arising de novo or as a residuum of previous cardiac surgery or AF ablation. In this situation the ECG may not have the typical sawtooth pattern, and the CTI is usually not essential for the maintenance of the arrhythmia. Some of these atypical atrial flutters are confined to the left atrium or interatrial septum, or even course in a figure-of-eight pattern.

Focal ATs occur whether or not structural atrial abnormalities exist. Unlike atypical atrial flutter, in which the ECG has limited resolution for circuit localization, the arrhythmogenic locus in focal AT can be inferred with reasonable accuracy from an analysis of the surface P wave. Furthermore, these automatic foci are distributed in a characteristic fashion. In the right atrium, for example, the "hot spots" tend to cluster around the crista terminalis and tricuspid annulus; in the left atrium, the pulmonary veins (PVs) are the centers of electrical unrest.

Regardless of the underlying mechanism, all types of AT are amenable to catheter ablation.

RFCA of Typical Atrial Flutter

When ECG documentation of typical atrial flutter is available, laboratory confirmation of CTI involvement can be obtained either from entrainment pacing during tachycardia or by demonstrating isthmus conduction during sinus rhythm. The ablation strategy with this arrhythmia is to create a complete line of RF lesions across the CTI and so achieve bidirectional conduction block across that corridor of tissue. In experienced centers, RFCA of typical atrial flutter is associated with an acute success rate exceeding 90%. During the first year after RFCA, approximately 10% of patients with initially verified bidirectional isthmus block experience recurrent atrial flutter, and in 95% of these patients a second ablation is successful. With a single procedure, 73% of patients will remain free of typical atrial flutter at 5 years. Procedure-related complications are rare.

RFCA of Atypical Atrial Flutter

Targets for ablation in atypical macroreentrant atrial flutter were formerly identified using pacing maneuvers only. Although reliable, this method had drawbacks, being time-consuming and prone to cause termination of tachycardia. Newly available three-dimensional electroanatomic mapping systems now facilitate the study and treatment of these SVTs. In fact, these systems work equally well for focal AT (see below). Briefly, for an atypical atrial flutter, the aim is to identify, during tachycardia, the part of the atrium that has slow activation during mid-diastole, and then confirm the relevance of that location to the tachycardia by entrainment pacing. This site represents the critical isthmus of the flutter circuit, and the local potentials recorded in this zone are often broad and fractionated. To prevent far-field "noise" (T waves and QRS complexes) from interfering with signal analysis, adenosine or verapamil is sometimes given to produce AV block (and a clean train of flutter waves). The slow isthmus is then destroyed with RF energy. Often it is necessary to create a supplementary line or lines of RF lesions to transect this and other parts of the atria that are critical or potentially critical for tachycardia conduction. Such lines are usually extended from an area of scarring to another electrically inert region. Initial success rates with RFCA are high (see Table 33-1), but recurrences are observed in up to 20% of cases, mainly because these patients have extensive atrial disease with islands of scar tissue that can facilitate further reentry. Those who relapse are either palliated with antiarrhythmic drugs or treated with a further ablation attempt.

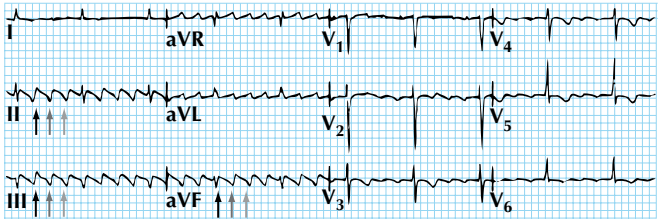
RFCA of Focal Atrial Tachycardia

Focal ATs are usually mapped during tachycardia, with attention initially directed at the anatomic location indicated by the P-wave morphology of the tachycardia. The means by which these arrhythmogenic foci are identified has evolved from single- or dual-catheter methods (probing different parts of the atria with multipolar electrodes) to the use of complex noncontact mapping systems. Regardless of technique, the aim remains the same: to pinpoint, during tachycardia or atrial ectopy, a site where local activation precedes the onset of the surface P wave by the greatest possible length of time (typically 30–100 milliseconds). This spot is then destroyed by RFCA. As with atypical atrial flutter, success rates for catheter ablation of focal AT are high; potential complications are listed in Table 33-1.

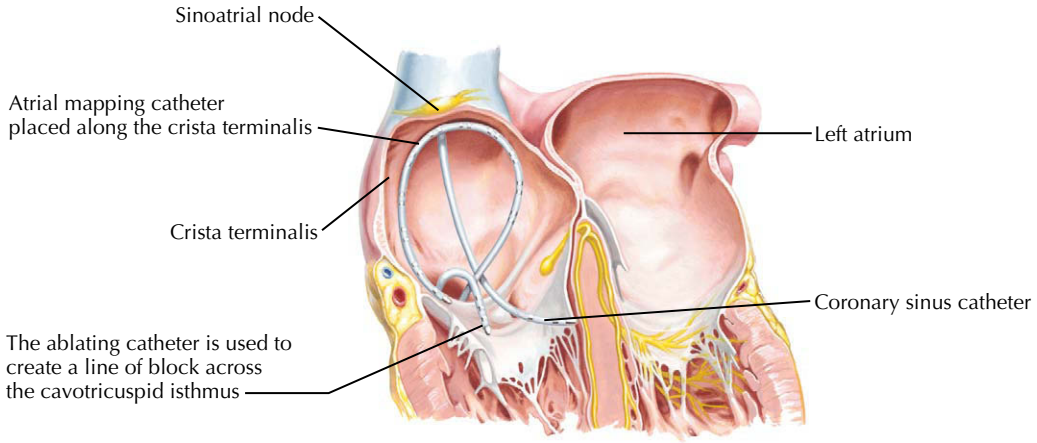
CATHETER ABLATION OF ATRIAL FIBRILLATION

There is agreement that recurrent symptomatic, drug-refractory AF (whether paroxysmal or persistent) is an indication for catheter ablation. In symptomatic patients with little or no left atrial (LA) enlargement, catheter ablation is also a reasonable alternative to medication to prevent recurrent AF. Nonetheless, there remains much uncertainty on how

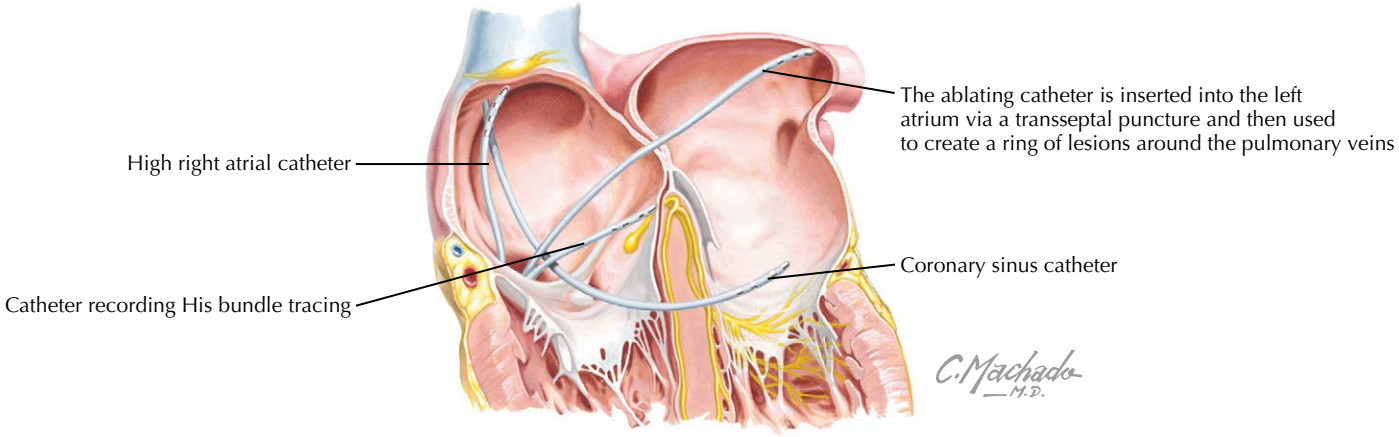
ECG of typical counterclockwise atrial flutter (note "sawtooth" pattern in inferior leads)

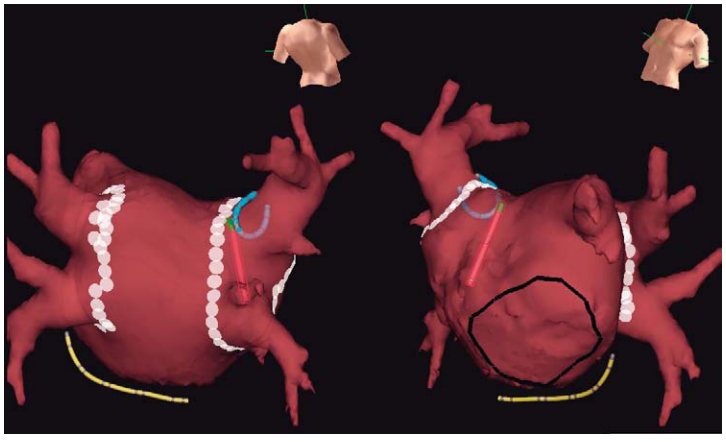


Catheter ablation of CTI-dependent atrial flutter



Catheter ablation of atrial fibrillation





The PVs have been isolated in pairs, using wide circumferential antral RF lesions applied in a point-by-point fashion. Note the circular (lasso) catheter in the right upper PV, to record electrical activity in that vein. The yellow catheter is seated in the coronary sinus, and the black circle on the right image indicates the location of the mitral annulus.

Figure 33-3 *Atrial flutter, atrial tachycardia, and atrial fibrillation.* CTI, cavotricuspid isthmus; ECG, electrocardiogram; PV, pulmonary vein; RF, radiofrequency.

best to ablate this arrhythmia. Because this is a rapidly expanding and complicated field, the discussion that follows is necessarily limited to key observations from this arena of electrophysiology.

In general terms, the number and configuration of RF lesions delivered to the atria vary according to the type of AF (Chapter 28). In paroxysmal AF, complete electrical isolation of all PVs is usually sufficient to achieve clinical success. Many studies have shown that the most common sites of origin of AF involve cells and tissue in the proximal portion of the PVs. This is particularly the case in patients with paroxysmal AF. In persistent AF, PV isolation is often combined with (1) the ablation of sites bearing complex fractionated atrial electrograms and (2) the application of additional atrial lesion lines. The latter may include any combination of the following: a "roofline" to connect the two upper PVs, a line to transect the mitral isthmus, linear lesions to isolate the other thoracic veins (namely, the CS, the vein of Marshall—a tributary of the CS—and the superior vena cava), and a conventional CTI line. Some groups also advocate destroying the ganglionated plexus (part of the cardiac autonomic nervous system) that are embedded in periatrial fat pads outside the heart (this destruction achieved through transmural RF heating). The foundation of any AF ablation technique, PV isolation is described briefly.

Electrical Isolation of the PVs by RFCA

The goal of PV isolation is to eradicate or dissociate PV potentials from LA activation, thereby eliminating an important fibrillatory trigger (see Chapter 28). For this operation, access to the LA is gained via transseptal puncture, with full systemic anticoagulation applied beyond (and sometimes before) that point. In the "conventional" approach, the thin muscular sleeves extending from the LA into the PVs are destroyed at the LA-PV junction using RFCA. Because of the risk of PV stenosis if too much RF energy is delivered inside a vein, there is now a move to place wide encircling RF lesions on the PV antrum, a short distance (0.5–1 cm) *away* from the ostia of those vessels (see Fig. 33-3). Limited data suggest that taking the antral approach may also beneficially modulate arrhythmogenic autonomic inputs into the LA, since the ganglia-containing fat pads are often superficial to the PV antra. Commonly, a separate deflectable circular mapping catheter is used to interrogate or record PV activity, and "touch-up" ablations are applied to spots where PV potentials persist after completion of the lesion lines. Note that these lesion lines are applied in a point-by-point fashion and not by continuous dragging of the ablator tip.

Success and Complications of AF Ablation

Depending on the duration of follow-up, thoroughness of rhythm monitoring, and whether antiarrhythmic drugs are used during the postoperative period, success rates for RFCA of paroxysmal AF range from 65% to 95%. For persistent AF the corresponding figures are 40% to 80% (the results from the higher end of this range are usually obtained after two separate attempts at RFCA). Robust data on the long-term outcomes of AF ablation are not yet available, and it remains uncertain if apparently "cured" AF may yet relapse years later. Even with meticulous anticoagulation, the risk of procedure-related cerebral embolism is approximately 2%. The other notable complications associated with RFCA of AF are cardiac perforation, LA flutter (with reentry arising from gaps in a lesion line), PV stenosis (typically presents with exertional dyspnea 3 months after PV isolation), and atrioesophageal fistulation (presents with multiple gaseous/septic emboli and signs of endocarditis 3 to 5 days after ablation; mortality for this complication exceeds 70%).

AV Node Ablation for Rate Control in Patients with Refractory AF

An entirely different approach for treatment of patients with AF who have very rapid ventricular rates is to perform catheter ablation of the AV node, coupled with permanent pacemaker placement. This approach is a dependable method for achieving rate control of AF (and other ATs), especially if DC conversion or rate-slowing medication has been ineffective or not well tolerated and if the patient is not a candidate for AF ablation for medical or preference reasons. AV node ablation palliates symptoms of tachycardia but does not address the underlying rhythm disturbance (i.e., the AF or other atrial tachyarrhythmias). Because complete heart block is the desired end point of the procedure, permanent ventricular pacing is necessary in these patients. Since the AF has not been eliminated, most of these patients require long-term anticoagulation.

CATHETER ABLATION OF VENTRICULAR TACHYCARDIA

VTs can be segregated into three general categories: (1) those that are "focal" in mechanism and have arrhythmogenic substrates near or above the ventricular valves (e.g., right or left ventricular outflow tract tachycardia); (2) those that are reentrant in nature, utilizing the native conduction system as part of the tachycardia circuit (e.g., bundle-branch reentry and fascicular VT); and (3) those that are scar-related, occurring in patients with structural or ischemic heart disease. In groups 1 and 2—sometimes referred to as "idiopathic" VTs—RFCA is potentially curative and is indicated in symptomatic patients in whom antiarrhythmic drugs have been tried and failed (because of toxicity, lack of efficacy, or both) and/or for whom an implantable cardiac defibrillator is not an optimal option. RFCA is also indicated in patients who prefer not to be on medication. In group 3, catheter ablation is often palliative rather than curative and is usually done when all possible combinations of drug treatment have been exhausted. At one end of this spectrum is the outpatient with monomorphic VT who is experiencing frequent appropriate therapy from his or her implantable cardiac defibrillator despite optimal device programming and medication. At the other end of the spectrum is the patient who is transferred to the tertiary center in a hemodynamically tenuous state with VT storm despite aggressive intravenous antiarrhythmic medication. Before considering RFCA it is relevant to ask if the underlying cause of the VT is fixed or reversible. VTs arising from electrolyte disturbance or myocarditis should not be subjected to RFCA. Sometimes simply restoring coronary flow to an ischemic myocardial territory may remedy or control an

otherwise troublesome ventricular arrhythmia. As with SVTs, a properly recorded 12-lead ECG not only establishes the diagnosis of VT but often provides useful information about its exit site (i.e., septal, right or left ventricle, cardiac apex or outflow tract, epicardial or endocardial).

Catheter Ablation of Idiopathic VTs

Potential ablation sites for idiopathic VTs may be identified by pace mapping, activation mapping, or by more advanced methods such as electromagnetic or noncontact mapping. Where relevant, entrainment of the tachycardia is done to validate the importance of a chosen location. Pace mapping (done during sinus rhythm) involves the stimulation of various ventricular sites with the aim of evoking a QRS configuration that is identical to the clinical arrhythmia. The exit site of that arrhythmia is localized and targeted for RFCA. In activation mapping (done during tachycardia), the aim is to identify a spot within the ventricles where the sampled local electrogram precedes the surface QRS by the greatest possible length of time. In fascicular VT, low-amplitude, presystolic Purkinje potentials demarcate optimal ablation sites. With newer mapping methods, the activation pattern of the VT is superimposed on a three-dimensional image of the local cardiac geometry, allowing visualization of the tachycardia circuit and identification of early activation or breakout points. Once suitable mapping and studies are complete, RF energy is applied to the chosen locations to terminate the arrhythmia.

Catheter Ablation of Macroreentrant VTs

The approach to mapping this type of arrhythmia is similar to that of atrial flutter (see previous discussion). Here the aim is to identify, during VT, critical parts of the reentrant circuit that are "protected" by electrically inert zones such as scars and valvular structures, and then to target these areas for RFCA. If the VT cannot be induced or if it is not tolerated hemodynamically when induced, substrate-based voltage or potential-guided mapping may be used to direct ablation efforts. With the latter methods, areas of low electrical voltage or those from which delayed or fractionated potentials are recorded during sinus rhythm are chosen for ablation. Pace mapping is often done simultaneously, with attention focused at the stimulation to QRS time (the longer this interval, the more likely it is for that area to harbor a diastolic conduction pathway). The intricacies of these mapping methods are complex; the interested reader is directed to texts devoted to EP mapping and RFCA. Note that in some cases, especially in patients with nonischemic cardiomyopathy, successful control of the VT can only be achieved by ablating the epicardial surface of the heart, using catheters inserted percutaneously into the pericardial space.

Due to extensive scarring and the inaccessibility of certain parts of the heart (e.g., midmyocardial and intraseptal areas), VTs arising in the context of ischemic heart disease have a tendency to recur, often taking on a different rate and configuration. Consequently, the success rate of RFCA for these sorts of arrhythmias lags behind that of AVNRT or AVRT (Table 33-1).

AVOIDING TREATMENT ERRORS

Because the decision to undertake RFCA is based on clinical judgment and an on-table diagnosis of the arrhythmia, treatment errors relating to RFCA may be avoided by careful assessment of the patient's symptoms, accurate ECG interpretation, adequate positioning and deployment of recording electrodes, and correct reading of intracardiac signals. Often, diagnostic pacing maneuvers are used to identify an arrhythmia mechanism or to map out its circuit. Finally, appropriate attention to the location and the manner in which RF energy is delivered will also reduce complications.

FUTURE DIRECTIONS

Remarkable advances have been made in RFCA since the 1990s. Better cardiac imaging, mapping software capable of greater signal resolution, catheters with differently configured tips or novel modes of energy delivery, and remotely operated robotic catheter steering systems are some recent developments that have potential to revolutionize the ablation of cardiac arrhythmias. With these technical advances it is anticipated that the length of time required for complex procedures such as AF ablation can be decreased considerably, making this approach more feasible for both patients and cardiac electrophysiologists.

ADDITIONAL RESOURCES

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EVIDENCE

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Aortic Stenosis

Timothy A. Mixon and Gregory J. Dehmer

34

The outflow of blood from the left ventricle can become limited because of abnormalities of the aortic valve or narrowing of the aortic outflow tract either below or above the aortic valve. The leaflets of the aortic valve form three pocket-like cusps of approximately equal size that separate the left ventricle from the aorta. The normal aortic valve opens completely during systole, allowing unimpaired ejection of blood from the left ventricle. Closure of the aortic valve prevents retrograde blood flow from the aorta into the left ventricle and allows the left ventricle to fill solely from the left atrium in preparation for the next cardiac cycle. The most common cause of aortic outflow obstruction is valvular aortic stenosis; that is, an abnormality within the valve apparatus that obstructs flow by impairing valve mobility and opening.

Nonvalvular obstruction of left ventricular (LV) outflow usually results from a congenital abnormality, such as a membrane, that may exist above or below the valve. Hypertrophic obstructive cardiomyopathy (HOCM), formerly called *idiopathic hypertrophic subaortic stenosis*, produces a dynamic subaortic obstruction and is the focus of Chapter 19.

ETIOLOGY AND PATHOGENESIS

The etiology of valvular aortic stenosis varies with the patient's age at presentation. In childhood, valvular congenital abnormalities are the usual cause. The aortic valve may be unicuspid, bicuspid, tricuspid, or, rarely, even quadricuspid (Fig. 34-1). Unicuspid valves usually are severely narrowed at birth and produce symptoms in infancy. Bicuspid and malformed tricuspid valves rarely cause symptoms during childhood. More frequently, the abnormal architecture of bicuspid and malformed tricuspid valves alters flow patterns across the valve, slowly traumatizing the leaflets, leading to progressive fibrosis, calcification, and stenosis between ages 40 and 70 years.

Acquired abnormalities from senile, calcific degeneration of a previously normal valve predominate in patients diagnosed after age 70 years, with a prevalence of 3% to 5% in patients over 75 years old (Fig. 34-2). The pathophysiology of degenerative, calcific aortic stenosis is an area of ongoing investigation. Although it shares some features and risk factors with atherosclerosis (accumulation of atherogenic lipoproteins, evidence of low-density lipoprotein oxidation, inflammation, and microscopic calcification), there are important differences. These include the presence of osteochondrogenic differentiation markers on the surface of valvular endothelial cells, essentially leading to "bone formation" in the valve, as well as a correlation between aortic stenosis and low serum levels of fetuin-A, a serum-based inhibitor of calcification.

Rheumatic involvement of the aortic valve, less prevalent today in the United States than a generation ago, typically results in a combination of stenosis and regurgitation, usually with concomitant mitral valve disease. The rheumatic valve is characterized by commissural fusion and calcification, whereas the more common degenerative aortic stenosis shows calcification progressing from the base of the cusps toward the leaflets, generally sparing the commissures (see Fig. 34-2). Rheumatic aortic stenosis generally presents between ages 30 and 50. Less common causes of aortic stenosis include obstructive vegetations from endocarditis, history of radiation therapy, and rheumatoid involvement with severe nodular thickening of the valve leaflets. Aortic stenosis may also be associated with systemic diseases including Paget's disease, Fabry's disease, ochronosis, and end-stage renal disease.

Bicuspid aortic valve disease merits special consideration given its prevalence (approximately 1% in the general population) and the frequent association of bicuspid aortic valve disease with genetic disorders that lead to enhanced elastolysis of the aortic wall and accelerated apoptosis of smooth muscle cells of the aortic media. This abnormality leads to a reduced aortic elasticity and dilatation of the annulus, aortic root, and ascending aorta with an increased risk of aortic dissection. Because of this defect at the arterial wall level, many experienced centers now approach patients with bicuspid aortic valve and aortic dilatation similarly to patients with Marfan's syndrome, considering elective repair when the aortic diameter approaches 4.5 to 5.0 cm, instead of the traditional threshold size of 5.5 cm.

CLINICAL PRESENTATION

Valvular aortic stenosis is often asymptomatic for years. Progressive and ultimately severe pressure overload imposed by the valve stenosis results in the development of concentric LV hypertrophy (LVH). This compensatory adaptation lowers wall stress and maintains forward flow but also leads to detrimental effects, including an abnormal diastolic filling pattern and subendocardial ischemia.

Classic symptoms of aortic stenosis are angina, syncope, and dyspnea, the latter being a manifestation of congestive heart failure (CHF). The average survival without valve replacement is 5 and 3 years in patients who present with angina or syncope, respectively. The most concerning presentation is CHF, because those patients have an average survival without valve replacement of less than 2 years.

Angina occurs in two thirds of patients with severe aortic stenosis, and approximately half of these have significant coronary obstructions. In the absence of important coronary obstructions, angina is caused by subendocardial ischemia induced by increased wall thickness with a relatively decreased capillary density, prolonged ejection time, and increased LV end-diastolic pressure, which reduces the diastolic transmyocardial perfusion gradient.

Syncope in patients with important aortic stenosis typically occurs during physical exertion. Exertion reduces systemic vascular resistance, while the necessary increase in cardiac output is blunted by the fixed valve obstruction. This combination results in cerebral and cardiac hypoperfusion. Moreover, the

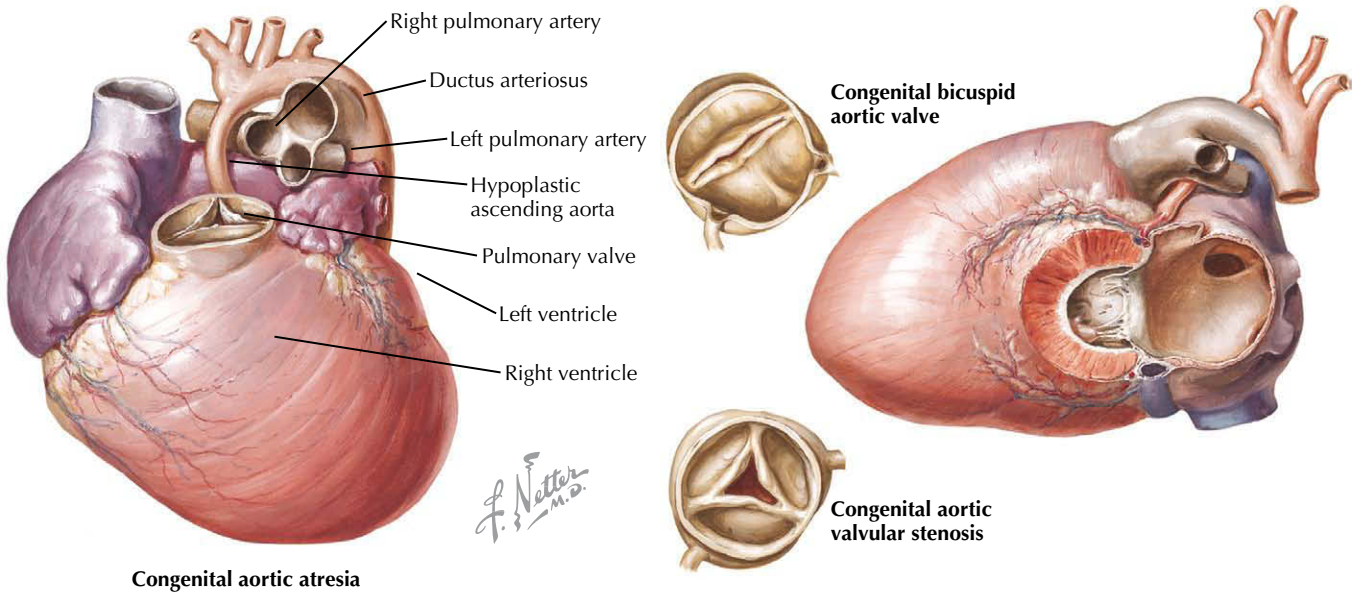


Figure 34-1 *Anomalies of the left ventricular outflow tract.*

greatly increased LV systolic pressure during exertion activates ventricular baroreceptors that may cause an exaggerated vasodepressor response, further reducing cerebral perfusion. Common arrhythmias such as atrial fibrillation or atrioventricular conduction abnormalities may reduce LV filling and cardiac output, resulting in syncope. Life-threatening arrhythmias, such as ventricular tachycardia or fibrillation, though uncommon, may occur in patients with aortic stenosis and result in syncope occurring at rest or with exertion and the potential for sudden cardiac death.

CHF can develop because of diastolic dysfunction, related to severe LVH with delayed ventricular relaxation and decreased compliance. Systolic dysfunction with progressive ventricular dilatation may occur late in the disease course. To compensate for the LV pressure load, the left atrium hypertrophies and develops vigorous contractions that allow adequate LV filling despite increased LV end-diastolic pressure. However, as the disease progresses or with physical activity, left atrial pressure increases further, leading to higher pulmonary venous pressures and eventually to pulmonary congestion and edema. Pulmonary

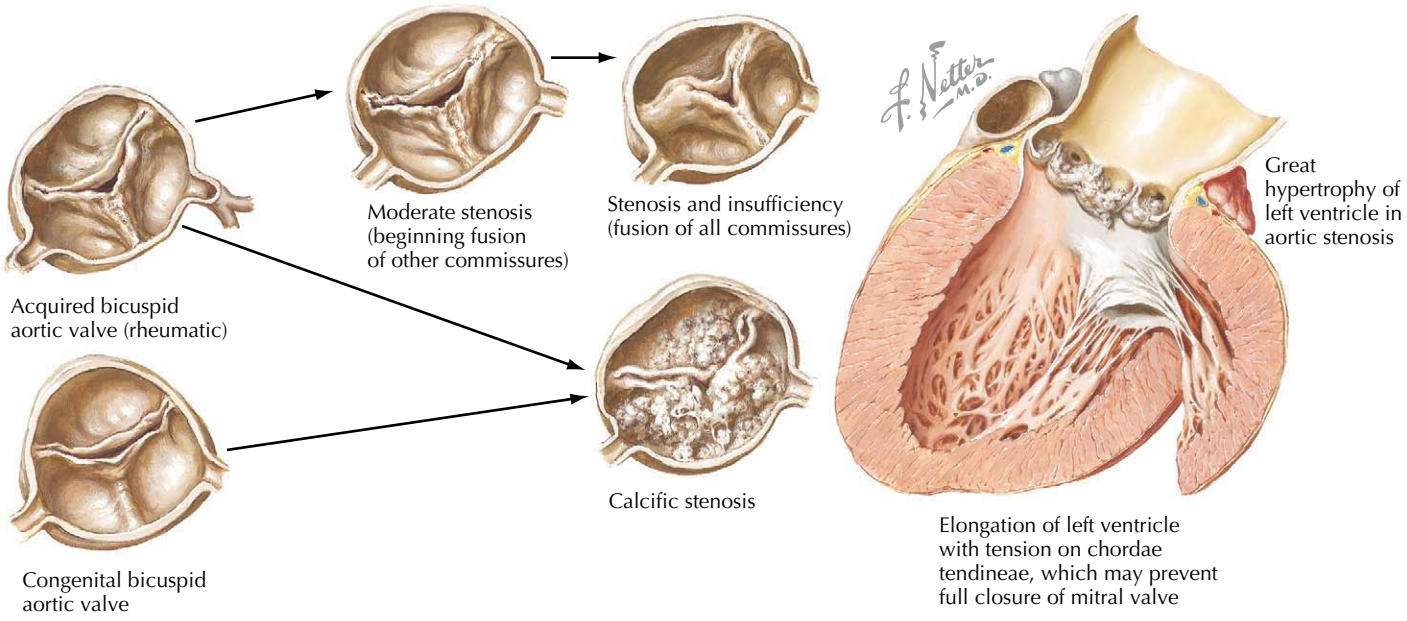


Figure 34-2 *Rheumatic and nonrheumatic causes of aortic stenosis.*

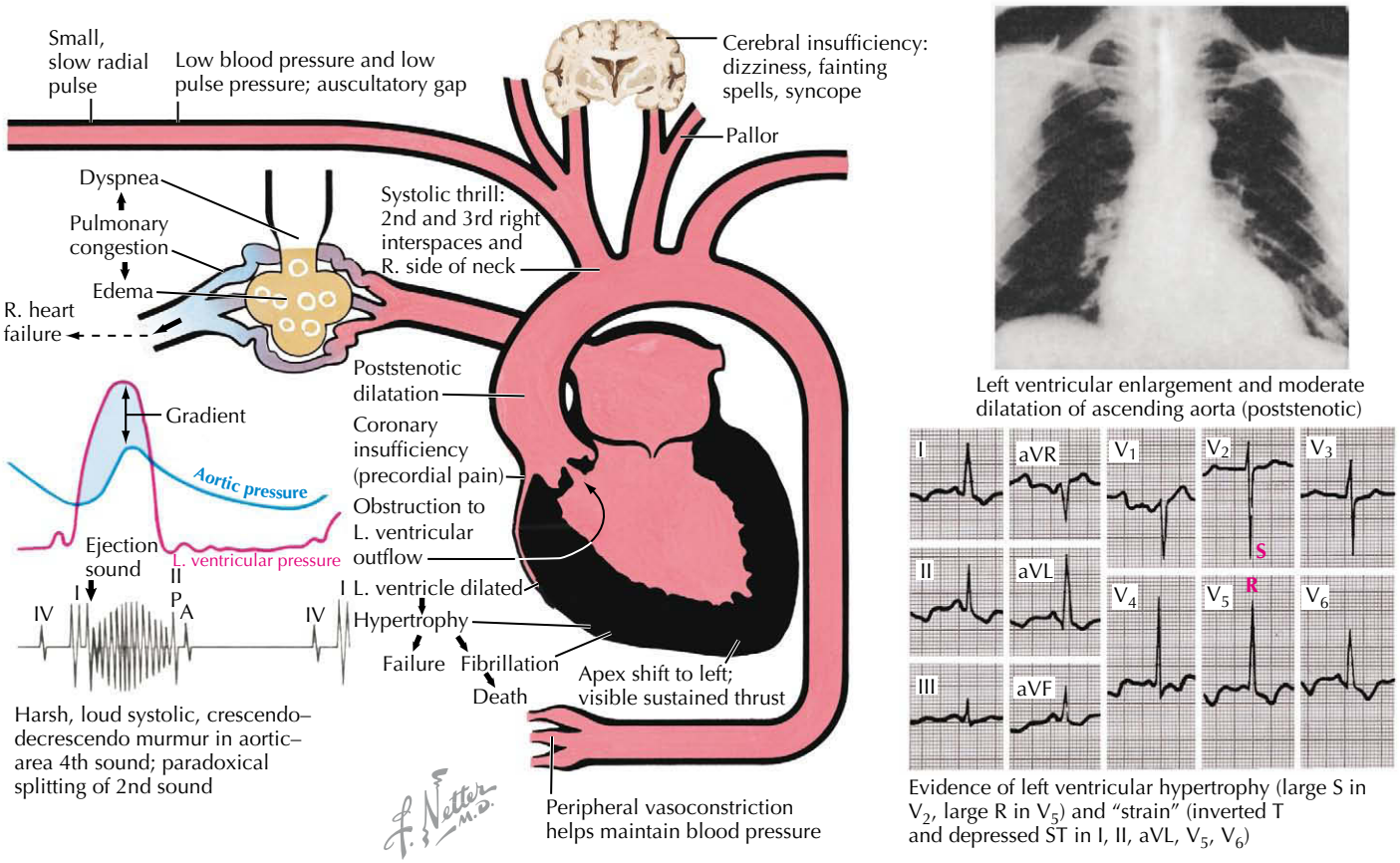


Figure 34-3 *Aortic stenosis.*

edema may develop abruptly during activity or with the loss of atrial function, as in atrial fibrillation.

Aortic stenosis may be associated with gastrointestinal bleeding from angiodysplasia (so called Heyde's syndrome, which is associated with a mild form of acquired von Willebrand's disease), or embolic events from detachment of small calcium deposits. Infective endocarditis is also a risk in patients with aortic stenosis and can have many morbid complications.

Physical Examination

Although noninvasive imaging provides an excellent tool for evaluation of patients with aortic stenosis, this condition can be assessed by a careful physical examination. One of the most notable findings in severe aortic stenosis is a decreased pulsation of the carotid arteries and a slowed arterial upstroke (pulsus parvus et tardus), with the maximum carotid upstroke noticeably delayed after the apical impulse (Fig. 34-3). A marked vibration or shudder may also be felt in the carotid artery. The jugular venous pressure is not elevated unless CHF is present. In mild aortic stenosis the jugular venous pulsations may be unremarkable, whereas late in the disease a prominent "v" wave may occur from tricuspid insufficiency caused by pulmonary hypertension and bulging of the hypertrophied septum into the right ventricle. As the degree of valve stenosis progresses, the LV apical impulse becomes displaced inferiorly and laterally, with a palpable presystolic pulsation (palpable S_4). If the apical impulse is hyperdynamic, concomitant aortic or mitral insufficiency should be considered.

The first heart sound is usually normal, but the second heart sound may have a reduced aortic closure sound or be single because of the absence of the aortic component from immobile aortic leaflets; it may also be paradoxically split from a marked delay of LV ejection. There is often a fourth heart sound (S_4), reflecting the reduced LV compliance during atrial contraction, and a third heart sound (S_3) if CHF has developed. The murmur of aortic stenosis may be preceded by an early systolic ejection click, heard more frequently with a bicuspid valve or congenital form of aortic stenosis in which the leaflets have preserved pliability. The murmur is characteristically described as crescendo-decrescendo and harsh in quality, most prominent at the upper sternal border, with transmission into the carotids. High-frequency resonations may be heard at the apex (Gallavardin phenomenon) and can be misinterpreted as mitral regurgitation. In the early stages of aortic stenosis, the murmur is confined to midsystole, but as the stenosis worsens, the murmur becomes longer, enveloping all of systole, and peaks later during systole, reflecting the delayed LV ejection. With aging the aortic valve leaflets can become thickened and calcified with slightly reduced mobility, but not truly stenotic, a condition termed *aortic sclerosis*. The murmur of aortic sclerosis is similar to that in aortic stenosis but tends to be an early-peaking murmur with normal

carotid pulsations. Aortic sclerosis, while not directly leading to serious sequelae, has been associated with a higher prevalance of coronary artery disease and cardiovascular mortality.

The murmur of mitral regurgitation is usually easily distinguished from that of aortic stenosis. It is pansystolic, with a more musical quality and constant intensity despite variations in cardiac cycle length. In contrast, the murmur of aortic stenosis is accentuated after pauses such as those associated with post-extrasystolic beats or long cycles in atrial fibrillation. The murmur associated with HOCM can be similar in character but responds to provocative maneuvers in a characteristic manner and has increased intensity after post-extrasystolic beats. The murmur of valvular aortic stenosis *increases with increased flow* across the valve resulting from squatting or maneuvers to increase preload and decreases in intensity with a Valsalva maneuver. The murmur of HOCM becomes *more prominent with decreasing preload*, such as the straining phase of the Valsalva maneuver or standing upright. Furthermore, the carotid upstroke in HOCM is rapid and has a bisferious quality.

DIFFERENTIAL DIAGNOSIS

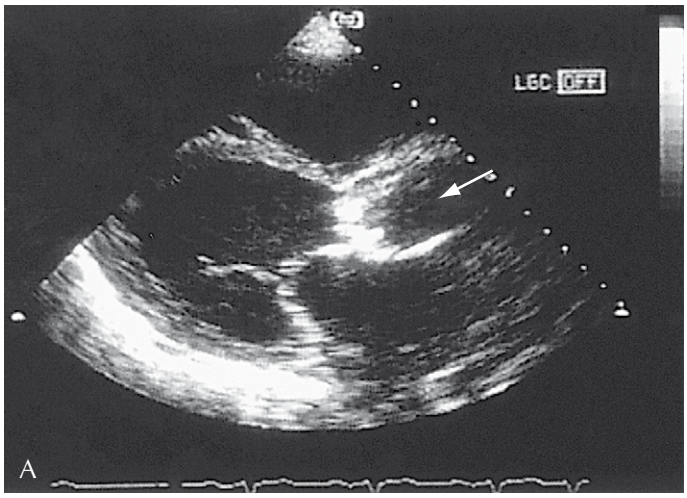
Differentiation of valvular aortic stenosis from other causes of LV outflow tract obstruction is important, because treatment and prognosis differ depending on the etiology. Subvalvular outflow tract obstruction may be due to a discrete subaortic membrane, a fibromuscular deformity (tunnel defect), or disproportionate muscular hypertrophy of the intraventricular septum with dynamic obstruction of the outflow tract. Supravalvular outflow tract obstruction is much less common than other varieties. It occurs in three forms: a circumferential hourglass narrowing of the aorta above the valve, a discrete fibromembranous ring, or a hypoplastic variety with diffuse narrowing of the ascending aorta (see Fig. 34-1).

DIAGNOSTIC APPROACH

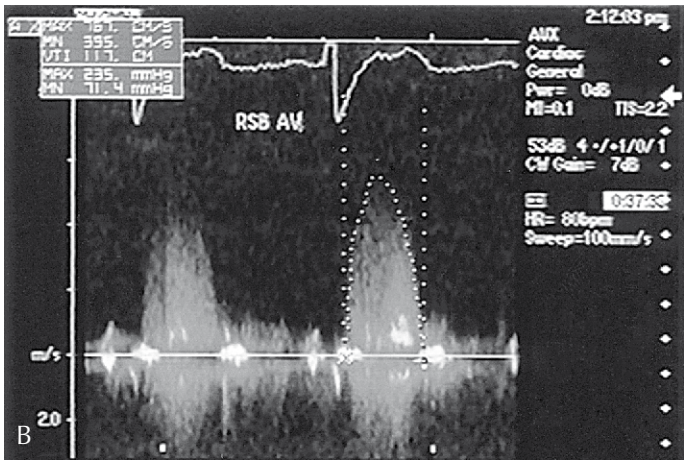
In patients with aortic stenosis, the ECG most commonly shows sinus rhythm until late in the disease course. The most common ECG findings are LVH (>80%) and left atrial (LA) abnormality manifested by a negative terminal deflection of the P wave in lead V_1, corresponding to LA hypertrophy. Less common findings are ST-segment depression in leads V_4 through V_6 (the LV "strain pattern") and conduction system disease from calcification of the specialized conduction tissue, manifested as atrioventricular block, left anterior fascicular block, or a nonspecific intraventricular conduction delay.

A chest x-ray usually shows a normal-sized cardiac silhouette, since the LV may be hypertrophied but is usually not grossly dilated unless end-stage CHF is present. LA enlargement and signs of pulmonary venous congestion may be present. It is uncommon to see calcification of the aortic valve leaflets on a standard chest x-ray, but some calcium near the aortic and mitral valve annuli is common, and poststenotic dilatation of the ascending aorta may be present. However, calcified aortic valve leaflets can often be visualized by cardiac fluoroscopy.

Two-dimensional echocardiography with Doppler is the most useful test for evaluating suspected aortic stenosis. A complete transthoracic echocardiogram can identify the location of the aortic outflow obstruction, estimate the severity of valvular obstruction, and provide supplemental information such as LV function, the degree of LVH, LA size, and the presence or absence of associated valvular abnormalities, most notably mitral regurgitation or aortic insufficiency (Fig. 34-4). Doppler interrogation of the flow across the aortic valve can estimate the transvalvular mean and peak pressure gradients (Table 34-1). The transvalvular gradient depends on the severity of the stenosis and the flow volume across the valve. With valvular aortic stenosis the valve area is fixed, but flow across the valve, and hence the pressure gradient, varies depending on many factors, including exercise, anxiety, anemia, hypovolemia, concomitant aortic insufficiency and the LV systolic function. Transvalvular gradients are reported as a mean value or a peak instantaneous



Parasternal long-axis two-dimensional echocardiogram showing an immobile, heavily calcified aortic valve (*arrow*).



Continuous wave Doppler echocardiograph shows the velocity profile across the aortic valve. Standard on-line software assists in determining the peak velocity and time velocity integral, which are used to determine the valve area based on the the continuity equation. It is essential to interrogate the jet from multiple transducer positions to obtain the true maximal jet, which is found when the transducer is parallel to the direction of flow.

Figure 34-4 *Two-dimensional echocardiography and Doppler analysis in a patient with aortic stenosis.*

Table 34-1 Echocardiographic Assessment of the Severity of Aortic Valve Stenosis

Degree of Stenosis*	Aortic Valve Area	Mean Pressure Gradient	Aortic Jet Velocity
Mild	≥1.5 cm^2	<25 mm Hg	<3.0 m/s
Moderate	1.0–1.5 cm^2	25–40 mm Hg	3.0–4.0 m/s
Severe	<1.0 cm^2	>40 mm Hg	>4.0 m/s

*Instead of relying on one single value, assessment of aortic stenosis is best viewed as a continuum, with integration of multiple measurements necessary to accurately characterize severity.

gradient. Although these measures are directionally related, neither corresponds exactly to the peak-to-peak gradient frequently reported from simultaneous invasive measurements made with catheters. In general, a peak transvalvular gradient greater than 64 mm Hg or a mean transvalvular gradient greater than 40 mm Hg is consistent with severe aortic stenosis. Aortic valve areas can be calculated via the continuity equation or estimated directly by planimetry. Because the pressure gradient can vary considerably under different conditions, the calculated aortic valve area is generally thought to be a more reliable measure of severity than the pressure gradient alone. A calculated aortic valve area smaller than 1.0 cm^2 or 0.6 cm^2/m^2 is consistent with severe aortic stenosis. One pitfall in echocardiography is relying solely on Doppler-derived "valve areas" without visualization of the valve for calcification and altered mobility. An increased outflow tract gradient actually due to HOCM can be mistaken for valvular aortic stenosis and lead to an inappropriate referral for aortic valve replacement (AVR). In patients with poor acoustic windows, a transesophageal echocardiogram may provide better visualization of the valve leaflets and allow more precise determination of valve area by planimetry.

Because of the relationship of flow and pressure across the valve, some patients with low cardiac output secondary to left-sided heart failure have a low transvalvular pressure gradient (<30 mm Hg) despite having significant aortic stenosis. Valve area calculations in this circumstance may be misleading; thus, it is often helpful to increase the cardiac output with an intravenous inotropic drug or exercise and use the new data to recalculate the valve area. If the increase in cardiac output causes a substantial increase in the calculated valve area with no change in transvalvular gradient, the clinical problem is likely to be a primary cardiomyopathy, rather than aortic stenosis ("pseudo-aortic stenosis"). In contrast, if the increase in cardiac output leads to a substantial increase in the gradient with an unchanged (or slightly decreased) calculated valve area, the primary problem is likely to be "true" aortic stenosis. Formerly, the degree of stenosis was commonly confirmed with invasive hemodynamic measurements. However, it is now acceptable to forgo such invasive evaluation unless historic, physical, and echocardiographic findings are discordant. Indeed, studies utilizing very sensitive measures such as MRI have identified the frequent presence of cerebral emboli with left heart catheterization in patients with aortic stenosis, even though the emboli may be subclinical. However, in the setting of discordant information, right- and left-sided heart catheterizations are indicated to directly obtain pressure gradients and measure cardiac output. Valve resistance can also be calculated and is less dependent on flow across the stenotic valve orifice.

Although not widely used in clinical practice, if echocardiographic images are nondiagnostic, some investigators have promoted cardiac CT or MRI as alternatives for diagnosing aortic stenosis severity. Planimetered valve areas by these techniques have good correlation compared with Doppler echocardiography and invasive catheterization in relatively small cohorts. Multiple studies have suggested that an anatomic planimeter of the valve by whatever imaging technique often yields a slightly higher valve area than one derived from a Doppler/pressure calculation, which probably better represents the functional valve area.

Before AVR, coronary angiography is indicated for all patients older than 35 years or who have two or more risk factors for coronary artery disease. It is estimated that up to 50% to 60% of patients with severe calcific aortic stenosis have serious obstructive coronary artery disease and 16% have carotid artery stenosis.

MANAGEMENT AND THERAPY

Optimum Treatment

In adults with severe and symptomatic aortic stenosis, AVR is indicated. Medical therapy for valvular aortic stenosis is usually limited to treatment of complications, such as CHF, rhythm disturbances, and infective endocarditis. Heart failure from LV systolic dysfunction is treated with judicious use of angiotensin-converting enzyme inhibitors, diuretics, and occasionally digoxin. Systemic hypertension should be controlled with medications, but excessive lowering of blood pressure should be avoided. Because the ability of cardiac output to increase is limited in severe aortic stenosis, lowering the systemic pressure can increase the transvalvular gradient and worsen symptoms.

Investigations have not shown a role for specific agents including β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers in slowing the progression of aortic stenosis. Some retrospective studies imply that statins may retard aortic stenosis progression; however, two prospective randomized controlled trials failed to demonstrate any benefit.

Atrial fibrillation may occur late in the disease course and can lead to significant hemodynamic deterioration due to these patients' dependence on a vigorous atrial contraction to adequately fill the LV and support a normal stroke volume. Atrial fibrillation is treated in the usual manner, with emphasis on the maintenance of sinus rhythm, if symptomatic, and anticoagulation as indicated based on the usual assessment of risk factors for thrombotic events. If serious LVH is present, amiodarone is the safest agent for maintenance of sinus rhythm. In patients presenting with atrial fibrillation and hemodynamic compromise, urgent electrical cardioversion is indicated.

Infective endocarditis occurs more frequently with congenital valvular abnormalities and is less common with senile, calcific aortic stenosis. Patients with moderate to severe degrees of outflow tract obstruction should not engage in vigorous, unsupervised exercise.

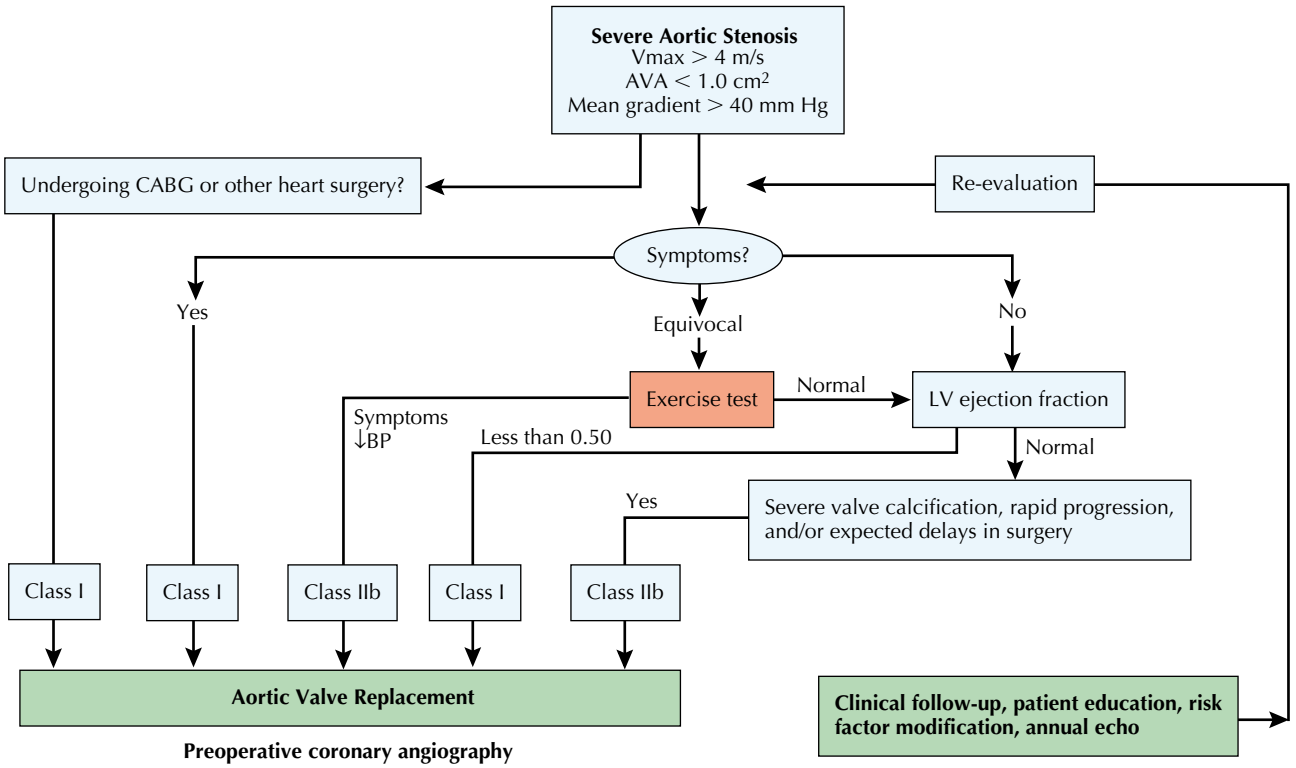


Figure 34-5 *Algorithm for clinical approach to severe aortic stenosis.* AVA, aortic valve area; BP, blood pressure; CABG, coronary artery bypass surgery; echo, echocardiography; LV, left ventricular; V_{max}, maximal velocity across aortic valve by Doppler echocardiography. From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *J Am Coll Cardiol;* 2008:52(13);e1–e142.

Aortic Valve Replacement

AVR is indicated for the treatment of *symptomatic* aortic stenosis. Although expert opinion varies at different medical centers, in general AVR can be safely delayed (even in patients with severe aortic stenosis) until symptoms develop. Mechanical, bioprosthetic, and homograft valves all provide excellent symptom relief and improve the mortality rate, with the expected survival rate approaching that of the unaffected population. Asymptomatic patients with severe aortic stenosis generally have an acceptable course and prognosis without valve replacement, with a rate of sudden death less than 1% per year, lower than formerly feared. However, these patients require close clinical follow-up, since less than half are free of cardiac symptoms at 5 years without AVR. Therefore, because the average perioperative mortality for AVR alone is 3% to 4% (5.5% to 6.8% for concomitant AVR plus coronary artery bypass), and there are additional risks from prosthetic valves (valve dysfunction, prosthetic valve endocarditis, bleeding from anticoagulant therapy), valve replacement is not recommended for most asymptomatic individuals.

Surgery should also be considered for asymptomatic patients who have LV dysfunction, an abnormal response to exercise (development of symptoms or exercise-induced hypotension), a high likelihood of rapid progression, or very severe aortic stenosis (valve area <0.6 cm^2) (Fig. 34-5). Patients with symptomatic aortic stenosis and impaired LV systolic function generally benefit from AVR, although the immediate risk of surgery is higher than in individuals with aortic stenosis and normal LV systolic function before surgery. After valve replacement, LV systolic function returns to normal in many patients. A frequent clinical dilemma is whether to refer an octogenarian with symptomatic aortic stenosis for AVR. Although there is no substitute for sound clinical judgment and careful consideration of comorbidities, several studies have demonstrated outcomes in operated octogenarians to be equal to normal, age-matched controls, thereby suggesting a survival benefit to AVR, even in this patient cohort. Patients undergoing AVR are frequently considered for a mechanical prosthesis if they are younger than 65 years of age (because of the significant risk of valve deterioration and the need for repeat surgery if a bioprosthesis is utilized), whereas patients older than 65 years of age can often be treated with a bioprosthesis (with its lower risk of thromboembolism and reduced need for anticoagulation) without ever experiencing valve degeneration in their lifetime.

Balloon valvotomy is useful in young patients for the palliation of congenital aortic stenosis, but late restenosis and a need for valve replacement often occur. In older patients with calcific aortic stenosis, balloon valvotomy is indicated (if at all) only as a bridge to AVR in critically ill patients, in patients who require urgent noncardiac surgery, or as palliation for terminal patients with a limited life expectancy. Percutaneous approaches for implantation of artificial valves (see below) are an approach currently under evaluation.

Avoiding Treatment Errors

Volume depletion must be avoided, because it reduces LV filling pressures and may lead to severe hypotension. Volume depletion can develop with aggressive diuresis but can also occur during or after noncardiac surgery from the effects of anesthesia or bleeding. Occasionally, the severity of aortic stenosis is underappreciated before surgery but manifests clinically as severe hypotension and a low cardiac output postoperatively. Aggressive volume and blood replacement is necessary to reverse the clinical deterioration. The inappropriate use of arterial vasodilators and venodilators such as nitroglycerin can also cause excessive hypotension.

When deciding whether to perform valve replacement in patients with poor LV function and low cardiac output, it is critical to determine if the primary problem is (1) severe aortic stenosis leading to LV failure and thus a low cardiac output and transvalvular pressure gradient or (2) primary LV systolic failure and thus a low cardiac output and transvalvular pressure gradient across what is really a minimally stenotic valve. In this circumstance, an accurate assessment of the valve area requires administration of an inotropic drug as described. Failure to perform this assessment can lead to an inappropriate valve replacement and a poor clinical outcome.

FUTURE DIRECTIONS

Minimally invasive AVR surgery via a right parasternal incision is often replacing the traditional approach of a median sternotomy when valve replacement is an isolated procedure. Completely percutaneous alternatives to surgical valve replacement are also being developed and tested in patients (see Chapter 40). Ongoing investigations will define the optimal candidates, further refine the devices available, and determine the success rates, survivability, and development of late complications. Hybrid approaches are being explored, including a limited anterolateral thoracotomy with a transapical, catheter-delivered valve implantation guided by fluoroscopy. Others have suggested that a lower periprocedural mortality rate in select patients with severe coronary disease and aortic stenosis can be achieved through a strategy of percutaneous coronary stent implantation followed within days by AVR, rather than a combined surgical procedure.

ADDITIONAL RESOURCES

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The dobutamine challenge aids in the identification of patients with aortic stenosis who can benefit from valve replacement.

Otto CM. Valvular aortic stenosis: disease severity and timing of intervention. *J Am Coll Cardiol.* 2006;47:2141–2151.

Review article on the pathogenesis, clinical spectrum, and treatment of calcific aortic stenosis in adults.

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Describes long-term outcome of hemodynamically significant asymptomatic aortic stenosis in adults.

EVIDENCE

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Outlines the evaluation and management of patients with aortic stenosis and other valve diseases as defined by an expert committee assembled by the American College of Cardiology and the American Heart Association.

Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol* 2008;52: e1–e142. Also available online at: <http://content.onlinejacc.org/cgi/content/full/52/13/e1> Accessed 6.01.2010.

Update of the 2006 guidelines listed above.

Aortic Regurgitation

Timothy A. Mixon and Gregory J. Dehmer

35

Aortic valve regurgitation results in impaired cardiac output and volume overload of the left ventricle. The distinction between acute and chronic forms of aortic regurgitation is important, since this affects the possible etiologies, associated diseases, prognosis, and treatment.

ETIOLOGY AND PATHOGENESIS

Etiologies of chronic aortic regurgitation may be broadly categorized based on one of two structural defects—those involving the *valve leaflets* and cusp, or those involving the *aortic root*—although in late stages of the disease both structural defects may coexist.

Common causes of acute aortic regurgitation include ascending aortic dissection with distortion of the normal valve architecture, infective endocarditis with destruction of a valve leaflet, traumatic disruption, and spontaneous rupture or prolapse of a valve cusp secondary to degenerative diseases of the valve. Acute aortic regurgitation also may occur with sudden dehiscence of the sewing ring of a prosthetic valve and after operative or balloon valvuloplasty.

Aortic Valve Leaflet Pathology

Causes of valve leaflet disease include rheumatic heart disease, congenital abnormalities of the aortic valve (especially bicuspid valves), calcific degenerative valve disease, myxomatous degeneration, or infective endocarditis. Rheumatic disease is characterized by shortening and scarring of the cusps and is frequently accompanied by mitral valve involvement (Fig. 35-1). Congenitally bicuspid valves are found in 1% to 2% of the population, with a 3:1 male predominance. There is a growing appreciation that the presence of a bicuspid valve is linked to a connective tissue disorder that leads to loss of elastic tissue within the proximal aorta, ultimately predisposing to aortic root dilatation and an increased propensity to dissection. While a bicuspid valve often presents as aortic stenosis or a mixed stenosis-regurgitation lesion, 10% of individuals with bicuspid aortic valves have pure regurgitation, occurring as a result of altered cusp architecture or an abnormal aortic root related to annular dilatation or dissection. Infective endocarditis may cause aortic regurgitation by several mechanisms, including (1) perforation of a single leaflet or a flail leaflet and (2) weakening of the cusp and valve annulus as a result of an expanding aortic root abscess.

Aortic Root Diseases

Aortic root disease is responsible for approximately one half of all clinically significant cases of aortic regurgitation. Common aortic root problems causing aortic regurgitation include connective tissue disorders (such as Marfan's syndrome, Loeys-Dietz syndrome, and type IV Ehler-Danlos) that may lead to annuloaortic ectasia or ascending aortic dissection and resulting distortion of valve structure and/or undermined support of the aortic valve leaflets (Fig. 35-2). In long-standing systemic hypertension, aortic regurgitation may occur from dilatation of the ascending aorta with distortion of the valve and chronic damage to the valve leaflets.

Less common causes of aortic regurgitation include syphilitic aortitis, ankylosing spondylitis, osteogenesis imperfecta, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, Behçet's syndrome, ulcerative colitis, discrete subaortic stenosis, and ventricular septal defect with prolapse of an aortic cusp (Fig. 35-3).

Natural History

The natural history of chronic aortic regurgitation is incompletely known. Data from the presurgical era indicate that patients with chronic, severe aortic regurgitation who have angina or heart failure have a prognosis similar to those with severe aortic stenosis, with mortality rates of at least 10% to 20% per year. Asymptomatic patients with normal left ventricular (LV) function develop symptoms of LV dysfunction at a rate of approximately 4% annually, but the occurrence of sudden death is rare (<0.2% per year). It is important to note, however, that 25% of patients who die or progress to LV dysfunction do so before manifesting symptoms, emphasizing the importance of serial quantitative assessments of LV function. Asymptomatic patients who develop LV dysfunction have higher event rates, with more than 25% developing symptoms annually.

In contrast, the natural history of acute aortic regurgitation—especially if severe—is dire, with morbid complications such as pulmonary edema and cardiogenic shock that can persist despite intensive medical therapy. In such cases, early mortality is high even with urgent surgical repair of the underlying problem.

CLINICAL PRESENTATION

Clinical presentation of aortic regurgitation varies with the onset (acute or chronic) and the degree to which compensatory changes have occurred within the left ventricle in response to volume overload (Table 35-1). In acute aortic regurgitation the presentation is usually dramatic. LV compensatory dilatation has not yet developed, so LV compliance is normal and remains so despite the sudden regurgitation. The acute volume overload is poorly tolerated, because the left ventricle is abruptly and markedly distended, resulting in impaired systolic function (based on the Frank-Starling mechanism). As a result, the left ventricle functions on the steep portion of the pressure-volume curve, leading to a considerably increased LV diastolic pressure, which in turn causes a severe increase in left atrial and pulmonary capillary wedge pressures, with resultant pulmonary edema. Forward cardiac output is reduced, and sinus tachycardia

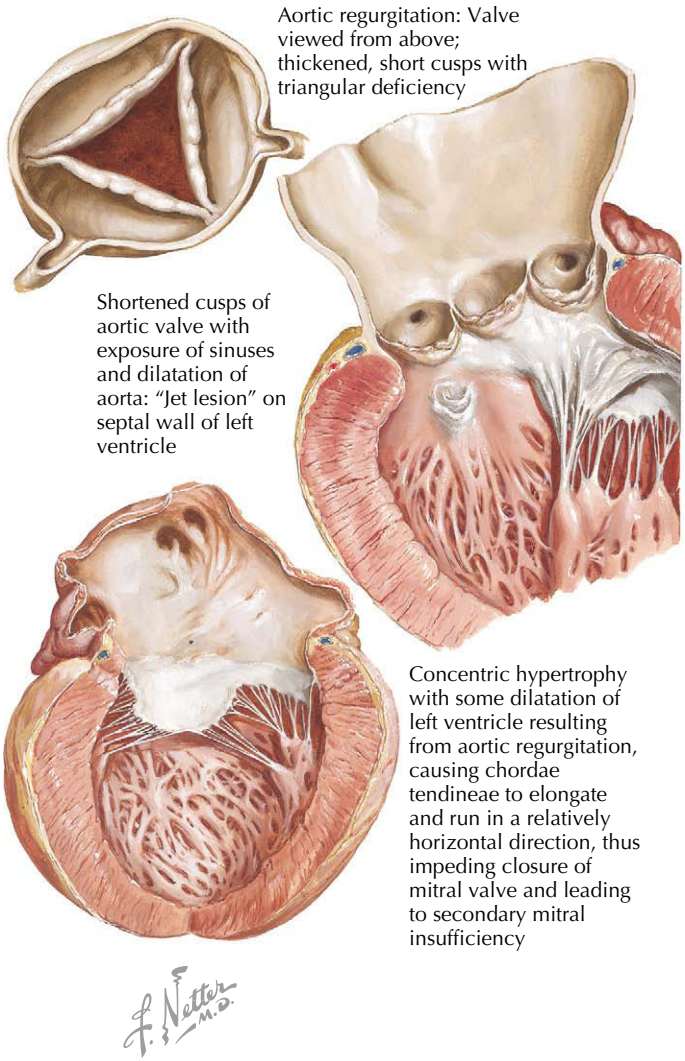


Figure 35-1 *Aortic regurgitation: Rheumatic heart disease.*

develops in an attempt to augment cardiac output. The regurgitation causes premature mitral valve closure with occasional diastolic mitral regurgitation. Because of these changes, the patient with acute aortic regurgitation usually appears severely ill, manifesting tachycardia, hypotension, peripheral vasoconstriction, and pulmonary edema, but lacks many of the physical signs of chronic regurgitation. Fatigue, apathy, agitation, or a decline in mental function may develop as a manifestation of the decrease in forward cardiac output. Finally, patients may develop signs and symptoms of myocardial ischemia due to the combination of a lower aortic diastolic blood pressure and increased LV end-diastolic pressure resulting in a reduced transmyocardial pressure gradient to support coronary blood flow.

Chronic aortic regurgitation may be asymptomatic for years. When symptoms develop, they are usually indolent, reflecting the disease's slow, progressive nature. Frequent complaints include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and palpitations. Angina pectoris may occur if there is significant coronary artery disease or because of reduced coronary blood flow in the setting of LV hypertrophy. As in acute aortic regurgitation, a reduced transmyocardial perfusion pressure exists that reduces coronary blood flow. This is further worsened by the degree of LV hypertrophy, which increases myocardial oxygen demand. As aortic regurgitation develops, the left ventricle slowly enlarges primarily with eccentric hypertrophy, although concentric hypertrophy also occurs from increased afterload (Fig. 35-4). As the regurgitation progresses, the left ventricle slowly dilates with an increase in end-diastolic volume and chamber compliance. Accordingly, in the early phases of LV dilation before the onset of systolic dysfunction, the increased end-diastolic volume is not associated with major increases in end-diastolic pressure. The resulting increased stroke volume maintains a normal forward cardiac output, usually without substantial increases in heart rate. The augmented stroke volume leads to many of the classic findings of chronic aortic regurgitation (Table 35-2; see Fig. 35-4). Occasionally, patients may experience an unpleasant awareness of each contraction, especially if irregular beats lead to a diastolic pause with a larger stroke volume in the subsequent beat. The augmented aortic systolic pressure from the increased stroke volume plus the lower aortic diastolic pressure from regurgitation into the left ventricle results in a wide pulse pressure. During exercise, systemic vascular resistance and diastolic filling period decrease, resulting in less regurgitation per cardiac cycle. This increases forward cardiac output without substantial increases in LV end-diastolic pressure. With time and worsening aortic regurgitation, the ability of the left ventricle to compensate for the chronic volume overload eventually is exceeded, and LV systolic failure develops. As the LV ejection fraction decreases, the ventricle dilates further, initiating a vicious cycle eventually leading to the typical symptoms of congestive heart failure. Throughout this process, myocardial fibrosis contributes to the gradual development of irreversible LV dysfunction.

Physical Examination

ACUTE AORTIC REGURGITATION

In acute severe aortic regurgitation, systolic blood pressure is normal or decreased, and diastolic blood pressure is slightly elevated—resulting in a pulse pressure that is normal or slightly narrowed. Although a tachycardia is usually present, the precordium is relatively quiet. The first heart sound is soft because of premature closure of the mitral valve and may be absent in severe acute regurgitation. The second heart sound is also soft, and a third heart sound is frequently present due to rapid early diastolic filling of the left ventricle. A fourth heart sound is uncommon. In contrast to chronic aortic regurgitation, the diastolic murmur of acute regurgitation is often short, ending well before the end of diastole, and soft in intensity or even absent in very severe cases. This occurs because diastolic flow across the valve stops when the aortic diastolic pressure equalizes with the rapidly rising LV diastolic pressure. A systolic murmur may also be present but is usually not particularly loud because of the reduced forward output. A second diastolic murmur, the Austin Flint murmur, is a mid-diastolic rumble similar to mitral stenosis best heard at the apex. Possible mechanisms of this murmur include relative mitral stenosis from the regurgitant jet

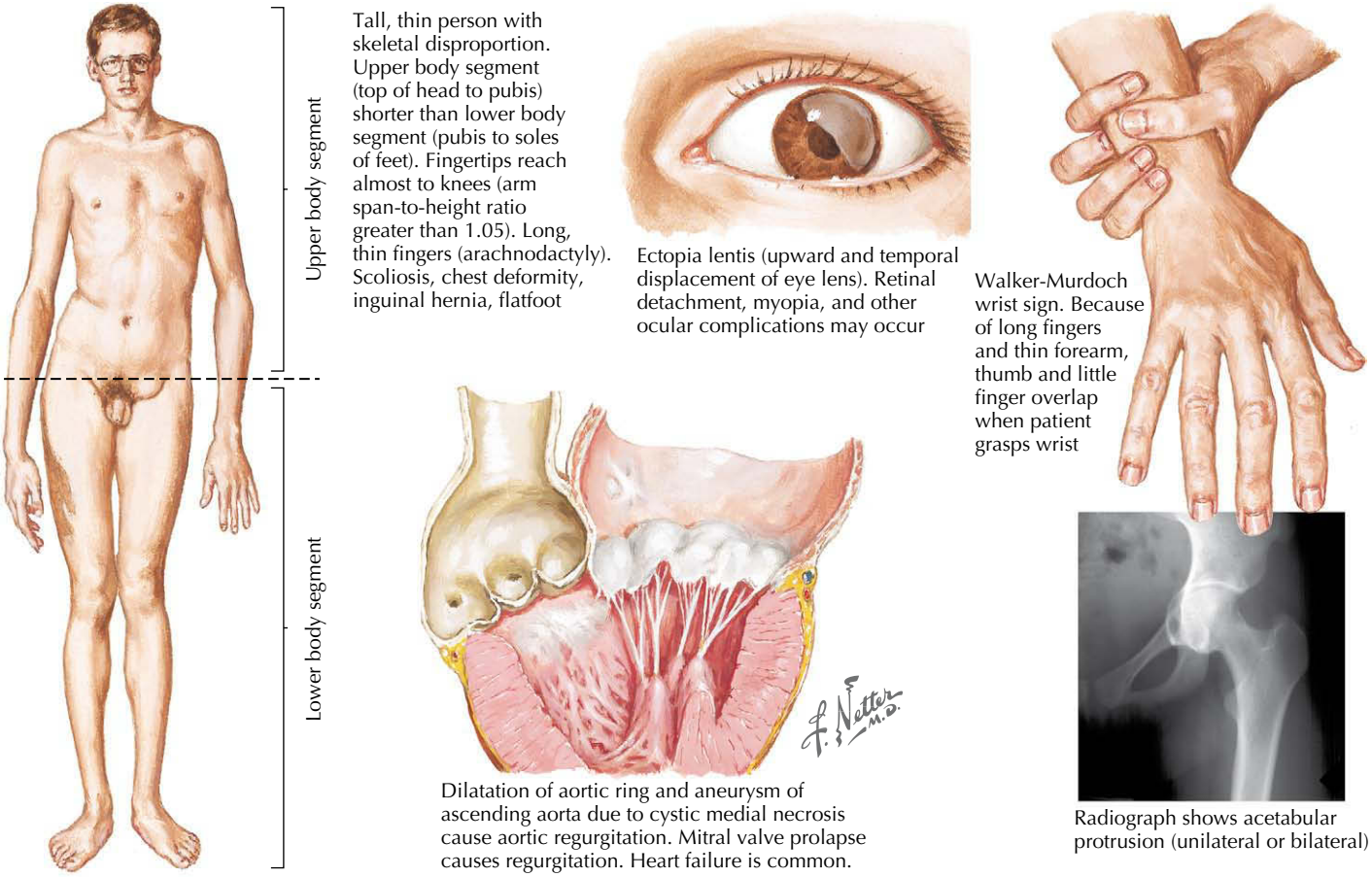


Figure 35-2 *Aortic regurgitation in Marfan's syndrome.*

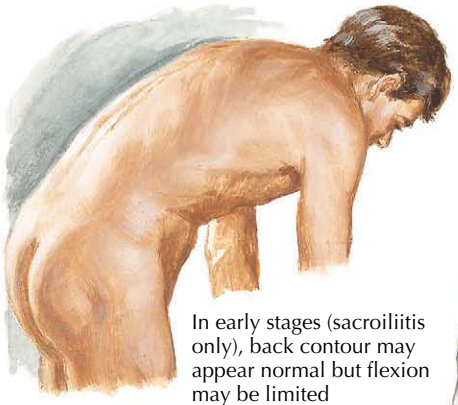
displacing the anterior mitral leaflet, impedance of left atrial outflow, or vibrations of the anterior mitral valve leaflet induced by the regurgitant jet.

CHRONIC AORTIC REGURGITATION

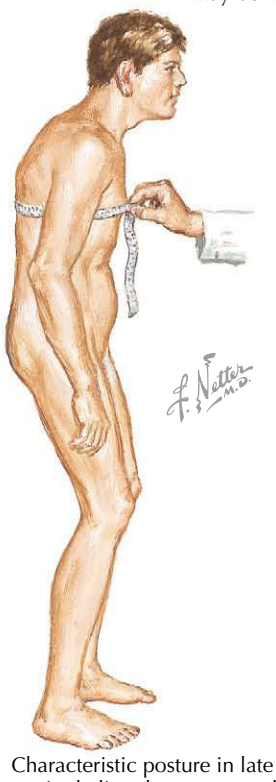
In chronic, compensated aortic regurgitation, increased carotid pulse volumes may be accompanied by a bruit or transmitted systolic murmur. Peripheral pulses are bounding as a result of the wide pulse pressure, with systolic hypertension and a low diastolic blood pressure. The LV apical impulse is enlarged and forceful and is displaced inferiorly and laterally. The first heart sound is normal or soft, and the second heart sound may be normal, single, or paradoxically split. Ejection clicks may be heard, especially in patients with a dilated aortic root. A fourth heart sound can be detected as LV hypertrophy develops, and a third heart sound occurs later in the clinical course of aortic regurgitation when the left ventricle decompensates. The diastolic murmur of chronic aortic regurgitation is best heard at the base of the heart along the left sternal edge or in the second right intercostal space. It is best detected with the diaphragm of the stethoscope while the patient is leaning forward during held expiration. The etiology of the regurgitation is more likely to be valvular if the murmur is louder to the left of the sternum, whereas aortic root disease may be the cause if the murmur is louder to the right of the sternum. The diastolic murmur begins at the second heart sound and continues for a variable portion of diastole. Severity of the regurgitation is better correlated with the length of the murmur than with its intensity. However, when the left ventricle begins to fail and end-diastolic pressure increases, the murmur shortens again. A systolic murmur may be present from increased forward flow across the aortic valve or concomitant aortic stenosis. An Austin Flint murmur, if present, indicates severe aortic regurgitation.

DIFFERENTIAL DIAGNOSIS

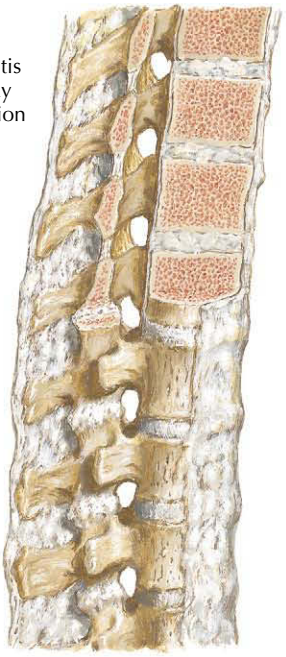
The hallmarks of chronic aortic regurgitation are an increased pulse pressure and diastolic decrescendo murmur heard at the upper sternal border. Several other conditions can mimic aortic regurgitation and should be considered in the differential diagnosis. First, patients with pulmonic regurgitation have a blowing diastolic decrescendo murmur but would not usually have a wide pulse pressure or bounding carotid pulse. The murmur of pulmonic regurgitation should increase with inspiration; the pulmonic valve closure sound is often increased in intensity, and a right ventricular (RV) heave may be present. The ECG would show signs of RV strain or hypertrophy rather than left-sided abnormalities, and chest radiography would show signs of RV enlargement. In adults there is usually a comorbid condition



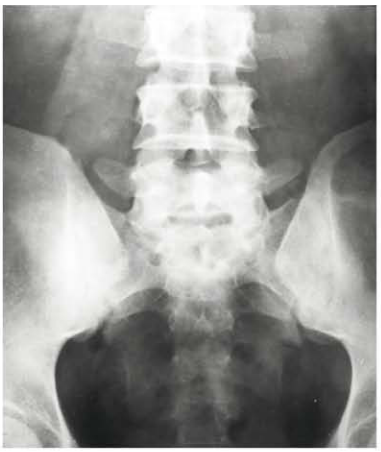
In early stages (sacroiliitis only), back contour may appear normal but flexion may be limited



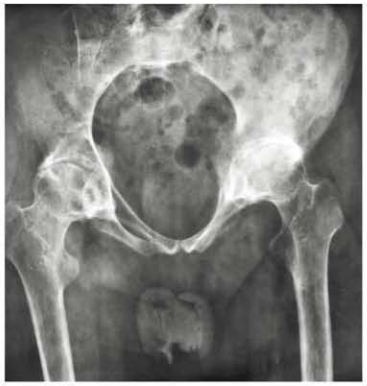
Characteristic posture in late stage of disease. Measurement at nipple line demonstrates diminished chest expansion



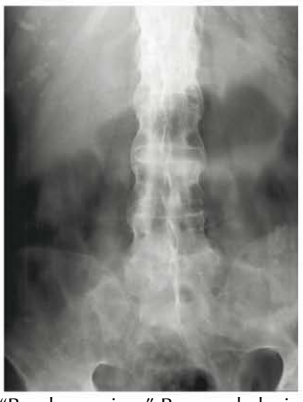
Ossification of annulus fibrosus of intervertebral discs, apophyseal joints, and anterior longitudinal and interspinal ligaments



Bilateral sacroiliitis is early radiographic sign. Thinning of cartilage and bone condensation on both sides of sacroiliac joints

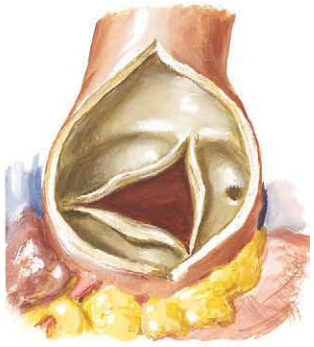


Radiograph shows complete bony ankylosis of both sacroiliac joints in late stage of disease



"Bamboo spine." Bony ankylosis of joints of lumbar spine. Ossification exaggerates bulges of intervertebral disks

Complications



Dilatation of aortic ring with valvular regurgitation

Iridocyclitis with irregular pupil due to synechiae

Figure 35-3 *Aortic regurgitation in ankylosing spondylitis.*

causing pulmonary hypertension and thus the pulmonary regurgitation. Second, in those presenting at a younger age, the diagnosis of patent ductus arteriosus should be considered. It causes a wide pulse pressure, as seen in aortic regurgitation, but the murmur is continuous with a low-pitched diastolic component. The ECG in this condition would be normal or show signs of LV hypertrophy, and chest radiography would show increased flow in the pulmonary vasculature. Third, if symptoms of dyspnea and chest pain begin suddenly, a ruptured sinus of Valsalva aneurysm should be considered. The pulse pressure is usually increased, but the murmur is continuous instead of only diastolic. Chest radiography would show signs of increased flow in the pulmonary vasculature. Finally and rarely, a coronary arteriovenous fistula may present with a murmur that can be confused with aortic regurgitation. The murmur should be continuous, but occasionally the diastolic component can dominate, mimicking aortic regurgitation. Echocardiography and, if necessary, cardiac catheterization can be performed to distinguish all of these conditions from aortic regurgitation.

DIAGNOSTIC APPROACH

With chronic aortic regurgitation, the ECG frequently shows left-axis deviation and LV hypertrophy. Other findings are nonspecific and may include intraventricular conduction defects, nonspecific ST-segment and T-wave changes, and PR-interval prolongation, especially if the etiology is inflammatory. None of these findings is an accurate predictor of regurgitation severity.

Chest radiography in chronic aortic regurgitation shows LV dilatation that may be massive ("cor bovinum"). An enlarged

Table 35-1 Hemodynamic Features of the Stages of Severe Aortic Regurgitation

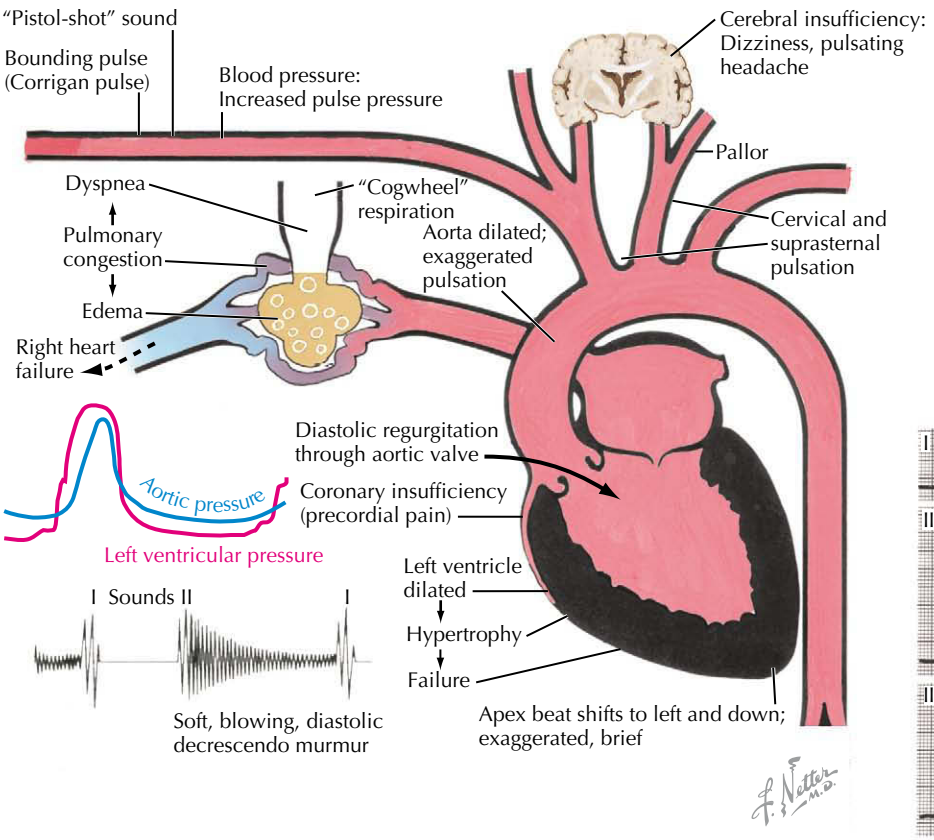
	Acute Severe Regurgitation	Chronic, Severe Regurgitation (Compensated)	Chronic, Severe Regurgitation (Late Decompensation)
LV compliance*	Not increased	Increased	No longer increased
LVEDP	↑↑↑	Normal	↑↑↑
LV dimensions	Normal	↑↑	↑↑
Aortic SBP	Normal or low	↑	Normal or low
Aortic DBP	Normal	↓↓	Normal
Pulse pressure	Normal to ↓	↑↑↑	Normal
LVEF	Normal	Normal to ↑	↓ to ↓↓↓
Total stroke volume	↑	↑↑↑	↑
Heart rate	↑↑↑	Normal	↑↑
Regurgitant volume	Large	Very large	Large
Effective cardiac output	↓↓	Normal	↓
Arterial pulse volume	Normal to ↑	↑↑↑	Normal

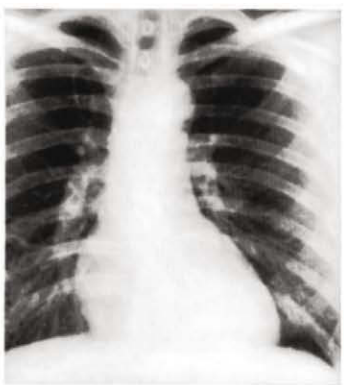
↑, slight increase; ↑↑, moderate increase; ↑↑↑, severe increase; ↓, slight decrease; ↓↓, moderate decrease; ↓↓↓, severe decrease; DBP, diastolic blood pressure; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

*Arrows are not used in the first row, because the changes in LV compliance are complex. In acute severe regurgitation, compliance is not really normal but is not increased. In the right-hand column, compliance is not really normal but is reduced compared with the state described in the middle column.

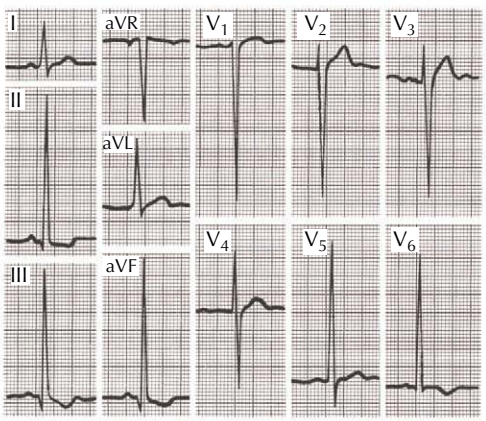
aortic root size suggests this as the etiology of the regurgitation. Pulmonary vasculature may be engorged during a decompensated state. With acute severe aortic regurgitation, there is minimal cardiac enlargement, with florid pulmonary edema the only finding.

Echocardiography is valuable for the initial assessment of acute and chronic aortic regurgitation and for serial follow-up examinations. Echocardiography provides information about the etiology and severity of aortic regurgitation, the presence of concomitant valve disorders, and the state of LV compensation





Left ventricular enlargement



Left ventricular hypertrophy and dilatation: Increased voltage of QRS in all leads; inverted T in several leads

Figure 35-4 *Manifestations of aortic regurgitation.*

Table 35-2 Physical Examination Findings with Severe Aortic Regurgitation

Finding	Description
De Musset's sign	Head bob with each systolic pulsation
Corrigan's pulse	Bounding pulse, alternatively named "water-hammer pulse"
Traube's sign	Booming systolic and diastolic sounds ("pistol shots") over the femoral arteries
Müller's sign	Systolic pulsation of the uvula
Duroziez's sign	Systolic murmur over the femoral artery when compressed proximally, diastolic murmur when compressed distally
Quincke's sign	Capillary pulsations noted in the nail beds or fingertips with each cardiac cycle
Hill's sign	Popliteal systolic pressure exceeding brachial pressure by 30–60 mm Hg

as assessed by chamber size, function, and wall thickness. The severity of regurgitation can be estimated semiquantitatively by measuring the width or cross-sectional area of the regurgitant jet in relation to the LV outflow tract cross-sectional area, by the finding of holodiastolic flow reversal in the descending aorta, or by measuring the pressure half-time of the regurgitant jet. Severity can be determined quantitatively by the continuity equation that yields the regurgitant volume and fraction. Additional information from echocardiography, notably LV ejection fraction and chamber dimensions, can be followed serially to determine the timing of surgical intervention.

Aortic regurgitation can also be evaluated by cardiac catheterization. Hemodynamic tracings in severe aortic regurgitation show a wide pulse pressure and an elevated LV end-diastolic pressure (Fig. 35-5). Aortic root angiography provides a semiquantitative assessment of severity, based on the speed and completeness of LV opacification. Quantitatively, regurgitant volume and regurgitant fraction are calculated using the stroke volume from LV angiography and forward cardiac output obtained by the thermodilution or Fick method.

MANAGEMENT AND THERAPY

Optimum Treatment

ACUTE AORTIC REGURGITATION

Regardless of the etiology, acute aortic regurgitation requires rapid diagnosis, with aggressive medical and surgical therapy, if feasible. Definitive therapy is surgical repair or (more commonly) valvular replacement. Occasionally, a brief period of medical stabilization is possible and desirable. Medical stabilization includes afterload-reducing agents to augment forward cardiac output, but worsening hypotension may preclude optimal use of this therapy. Intraaortic balloon counterpulsation is contraindicated, because it increases regurgitation. Slowing the heart rate is not recommended, because it prolongs the diastolic filling period and thus lengthens the time during which regurgitation can occur. However, if acute aortic dissection is the etiology of the regurgitation, β-blockers may reduce the force of LV ejection, and aggressive lowering of the blood pressure is appropriate.

With acute aortic dissection, the clinical picture may be dominated by other sequelae, including myocardial infarction from compromise of a coronary artery (most commonly the right coronary artery), hemopericardium with tamponade, hemorrhagic shock, or stroke due to involvement of a great vessel, all of which may alter treatment approach. When aortic regurgitation occurs as a result of infective endocarditis, surgery occasionally can be delayed a few days to allow further antibiotic therapy but should not be postponed if there is significant hemodynamic instability or heart failure.

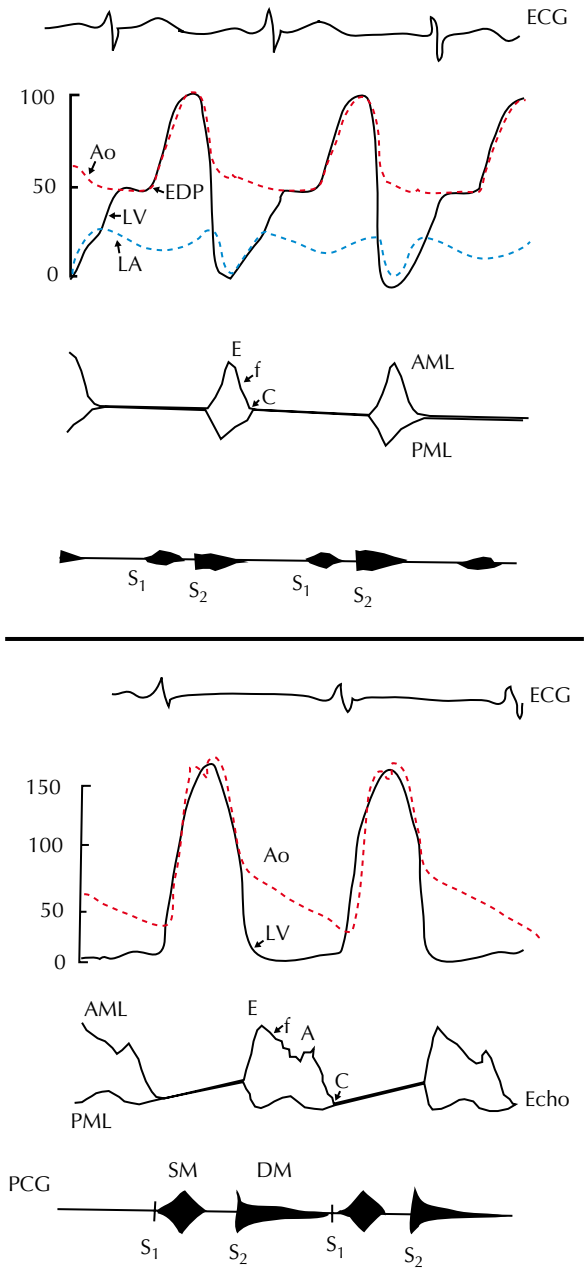
CHRONIC AORTIC REGURGITATION

Medical Therapy

Vasodilator therapy can reduce the degree of regurgitation, increase forward cardiac output, and delay the necessity of valve replacement. Vasodilator therapy may be considered for asymptomatic patients with severe aortic regurgitation who have normal systolic function with LV dilatation. It is important to carefully and frequently monitor patients treated with vasodilator therapy to assure their efficacy and to confirm that aortic regurgitation has not worsened. Vasodilators may also be useful in treating patients with severe, symptomatic aortic regurgitation who are not surgical candidates, or in preparation for surgery in patients with severe, decompensated congestive heart failure. Long-term administration of β-blockers is important for patients with Marfan's syndrome, because it slows the rate of aortic dilatation and progression to aortic complications.

Surgical Therapy

Valve replacement should be considered for most patients with symptomatic severe aortic regurgitation, unless comorbid conditions preclude surgery. Preoperative LV systolic performance is the major determinant of postoperative prognosis as assessed by LV function, persistent symptoms of heart failure, and survival rate. In general, symptomatic patients with abnormal LV systolic function who undergo valve replacement have reduced postoperative survival rates, as compared with those with preserved LV systolic function who have an excellent prognosis. However, patients with reduced LV systolic function on the basis of increased afterload (in distinction from patients with systolic dysfunction on the basis of depressed myocardial contractility) may show substantial improvement in LV function after valve replacement. In this subgroup, improvement in LV function results from elimination of valve regurgitation and LV volume overload. This begins to reverse the imbalance of



ECG, pressure tracings, M-mode echo, and PCG from a patient with acute severe (**top**) and chronic severe (**bottom**) aortic regurgitation.

Figure 35-5 *Hemodynamics and heart sounds in patients with acute and chronic severe aortic regurgitation.* AML, anterior mitral leaflet; Ao, aortic; ECG, electrocardiogram; Echo, echocardiogram; EDP, end-diastolic pressure; LA, left atrial; LV, left ventricular; PCG, phonocardiogram; PML, posterior mitral leaflet. (With permission from Morganroth J, Perloff JK, Zeldis SM, Dunkman WB. Acute severe regurgitation: pathophysiology, clinical recognition, and management. *Ann Intern Med.* 1977;87:223–232.)

opposing factors ("afterload mismatch") that initially led to the development of LV dysfunction.

To derive an improvement in LV function and prognosis after surgery, it is critical to identify patients with minimal or no symptoms yet of early signs of LV dysfunction and perform valve replacement before severe symptoms or LV dysfunction develop. Patients with preoperative LV dysfunction or excessive chamber dilatation have worse postoperative prognoses than do patients who have normal preoperative systolic function. Such patients may have no improvement or only a mild improvement after valve replacement, but surgery often will delay the course of further deterioration. Although less encouraging, the outcome with surgery in such patients is usually still better than with medical therapy alone but at a higher risk of perioperative complications.

There is controversy, however, about the timing of surgery in asymptomatic patients with severe regurgitation. If a patient's routine activity level is low, exercise testing may be considered with reclassification of patients as "symptomatic" if functional capacity is quite low, symptoms are elicited, or an abnormal hemodynamic response is encountered. Augmentation of post-exercise systolic function may be abnormal but is not prognostically or diagnostically predictive of outcomes. Surgery is strongly recommended in asymptomatic patients with severe aortic regurgitation who have a depressed LV ejection fraction (<50%). Surgery may be considered in asymptomatic patients with severe ventricular dilatation (LV end-systolic dimension >55 mm or end-diastolic dimension >75 mm, by echocardiography) or in patients who are undergoing surgery on a different valve, the aorta, or coronary arteries, but the evidence supporting this is not well-established.

The most common surgical procedure is valve replacement, but alternative approaches include use of the patient's pulmonary valve (Ross procedure) or valve repair (see Chapter 41). Valve repair should be performed only in experienced centers that can achieve equivalent outcomes with valve replacement. Indications for surgery are unchanged regardless of the technique anticipated. Concomitant aortic root reconstruction is often necessary in aortic dissection and Marfan's syndrome.

Avoiding Treatment Errors

If acute aortic regurgitation is suspected, early echocardiography leading to early, accurate diagnosis is essential, since delays in definitive surgical therapy can lead to poorer outcomes. This is critically important in that the physical findings in acute severe aortic regurgitation, especially with shock, can be very subtle.

Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that among asymptomatic patients with chronic aortic regurgitation who do not meet indications for surgery, vasodilators are not recommended in those with mild to moderate regurgitation or those with severe regurgitation in whom the LV systolic function and cardiac volumes are normal. Vasodilators are also not indicated as a substitute for surgical therapy in patients with LV dysfunction who are otherwise candidates for valve replacement, regardless of their symptom status.

FUTURE DIRECTIONS

Minimally invasive aortic valve replacement surgery is becoming more common as surgical techniques are improved. Aortic valve replacement can be performed through a small incision to the right of the sternum rather than the traditional median sternotomy. This approach seems to shorten length of stay and recovery periods before returning to normal activity, but it is unclear whether there are any long-term advantages or hazards. Percutaneous aortic valve replacement is also being developed but requires further refinement of devices and techniques.

ADDITIONAL RESOURCES

Enriquez-Sarano M, Tajik AJ. Clinical practice. Aortic regurgitation. *N Engl J Med.* 2004;351:1539–1546.

Concise review of the diagnosis and management of aortic regurgitation.

Evangelista A, Tornos P, Sambola A, et al. Long-term vasodilator therapy in patients with severe aortic regurgitation. *N Engl J Med.* 2005;353:1342–1349.

Long-term vasodilator therapy with nifedipine or enalapril did not reduce or delay the need for aortic valve replacement in patients with asymptomatic severe aortic regurgitation and normal LV systolic function.

Nitenberg A, Foult JM, Antony I, et al. Coronary flow and resistance reserve in patients with chronic aortic regurgitation, angina pectoris and normal coronary arteries. *J Am Coll Cardiol.* 1988;11:478–486.

In patients with chronic aortic regurgitation, LV hypertrophy, and normal coronaries, coronary flow reserve is severely reduced and may be the cause of exertional angina.

Ross Jr J. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy. *J Am Coll Cardiol.* 1985;5:811–826.

Classic article explaining the changes in LV function occurring in aortic and mitral regurgitation in terms of afterload mismatch.

Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med.* 1994;330:1335–1341.

Prophylactic β-adrenergic blockade slowed the rate of aortic dilatation and reduced development of aortic complications in some patients with Marfan's syndrome.

Tornos P, Sambola A, Permanyer-Miralda G, et al. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. *J Am Coll Cardiol.* 2006;47:1012–1017.

Provides further support for the recommendations of the ACC/AHA guidelines on the timing of aortic valve replacement.

EVIDENCE

Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol.* 2006;48:e1–e148.

Outlines evaluation and management of patients with aortic regurgitation and other valve diseases as defined by an expert committee assembled by the ACC and the AHA.

Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol.* 2008;52:e1-e142. Also available online at: <http://content.onlinejacc.org/cgi/content/full/52/13/e1> Accessed 09.01.10.

Update of the 2006 guidelines listed above.

Mitral Valve Disease

Thomas R. Griggs

36

Mitral valve leaflets consist of thin, pliable, fibrous material. The two leaflets—anterior and posterior—open by unfolding against the ventricular wall and close by apposition when the pressure in the left ventricle becomes greater than that in the left atrium. Mitral stenosis occurs when the mitral valve leaflets become stiffened, calcified, and unable to open completely during diastole. This process often involves the chordae tendineae in addition to the mitral valve leaflets. Mitral valve regurgitation occurs when the leaflets are unable to close completely in systole. In the United States, more than 20,000 patients annually require surgery for manifestations of mitral stenosis and mitral regurgitation, and thousands more require monitoring and treatment.

ETIOLOGY AND PATHOGENESIS

Mitral Stenosis

Rheumatic fever is responsible for a majority of cases of mitral stenosis. The initial infection and its sequelae result in thickened valve leaflets and fusion of the commissure between the leaflets. Chordae tendineae are also affected and become thickened, fused, and shortened. Most valves that are affected by rheumatic fever show abnormalities of all these structures. Few patients with rheumatic mitral valve disease have pure mitral stenosis; most have a combination of stenosis and regurgitation, and many have aortic and tricuspid involvement. Approximately two thirds of mitral stenosis cases in the United States occur in women.

The normal mitral valve cross-sectional area in diastole is 4 to 6 cm^2. Blood flow is impaired when the valve orifice is narrowed to less than 2 cm^2, creating a pressure gradient with exertion. A valve area smaller than 1 cm^2 is considered critical mitral stenosis and results in a significant pressure gradient across the valve at rest with chronically increased left atrial (LA) pressures (Fig. 36-1).

Chronically increased LA pressures associated with mitral stenosis, along with ongoing rheumatic inflammation, result in LA enlargement and a predisposition for atrial fibrillation. Valves affected by mitral stenosis are also vulnerable to recurrent thrombosis and implantation of bacteria that lead to infective endocarditis.

The hemodynamic effects of chronic mitral stenosis include pulmonary venous and arterial hypertension; right ventricular (RV) hypertrophy, dilation, and failure; peripheral edema; tricuspid regurgitation; ascites; and hepatic injury with cirrhosis (Fig. 36-2).

Mitral Regurgitation

Numerous etiologies contribute to mitral regurgitation, including mitral valve prolapse, rheumatic heart disease, bacterial or fungal endocarditis, and certain collagen-vascular diseases. Dysfunction of any component of the mitral apparatus can cause mitral regurgitation. Mitral regurgitation also frequently occurs in the absence of primary mitral valve disease in patients with cardiomyopathy and ventricular dilation. When the cause of mitral regurgitation is primarily a valve defect, valve repair or replacement can correct the mitral regurgitation and improve long-term prognosis. When the valve leaks because the ventricle is dysfunctional and dilated, mitral repair or replacement may have little or no effect on symptoms or prognosis.

With mitral regurgitation, blood is discharged during systole into the left atrium in addition to traveling its usual route through the aortic valve and into the aorta. If the regurgitant volume is large, LA remodeling occurs with dilation to accommodate increased volumes without intolerable LA hypertension (Fig. 36-3). Over time, as an increasing fraction of ventricular volume is regurgitant, the "forward" ventricular output is reduced, and symptoms and other findings of mitral regurgitation become obvious (Fig. 36-4). Patients are generally clinically well if the regurgitant fraction (regurgitant volume/total ejection volume) is less than 0.4. Patients with regurgitant fractions greater than 0.5 predictably develop left ventricular (LV) failure and have high morbidity and mortality. Any evidence of LV failure (LV ejection fraction <60%) is also a critical marker of poor prognosis.

Infectious endocarditis, spontaneous rupture of chordae tendineae, or ischemic injury of a papillary muscle may cause acute loss of mitral valve integrity and acute mitral regurgitation. In these cases of abruptly increased regurgitant flow, because there is no adaptation of the left atrium or pulmonary vasculature to the increased regurgitant volumes, acute pulmonary edema may suddenly occur. Aggressive use of vasodilators is the emergent treatment, but survival usually depends on emergency repair or replacement of the valve.

CLINICAL PRESENTATION

Mitral Stenosis

Patients notice the effects of moderate (valve area = 1–2 cm^2) mitral stenosis with activity. With severe stenosis, dyspnea with minimal exertion and paroxysmal nocturnal dyspnea may occur. In some cases a sudden, dramatic onset of atrial fibrillation produces the first symptoms, occasionally resulting in fatal pulmonary edema. When the development of atrial fibrillation is clinically silent, the initial event may be a stroke or other thromboembolic event. The classic presentation of severe cor pulmonale with ascites and edema is rarely seen today except in medically underserved populations. Mitral valve disease increases the risk for bacterial endocarditis, which should always be considered when symptoms worsen in a previously stable patient with mitral valve disease.

Auscultatory findings in a patient with mitral stenosis include a loud first heart sound, an opening snap after the second heart

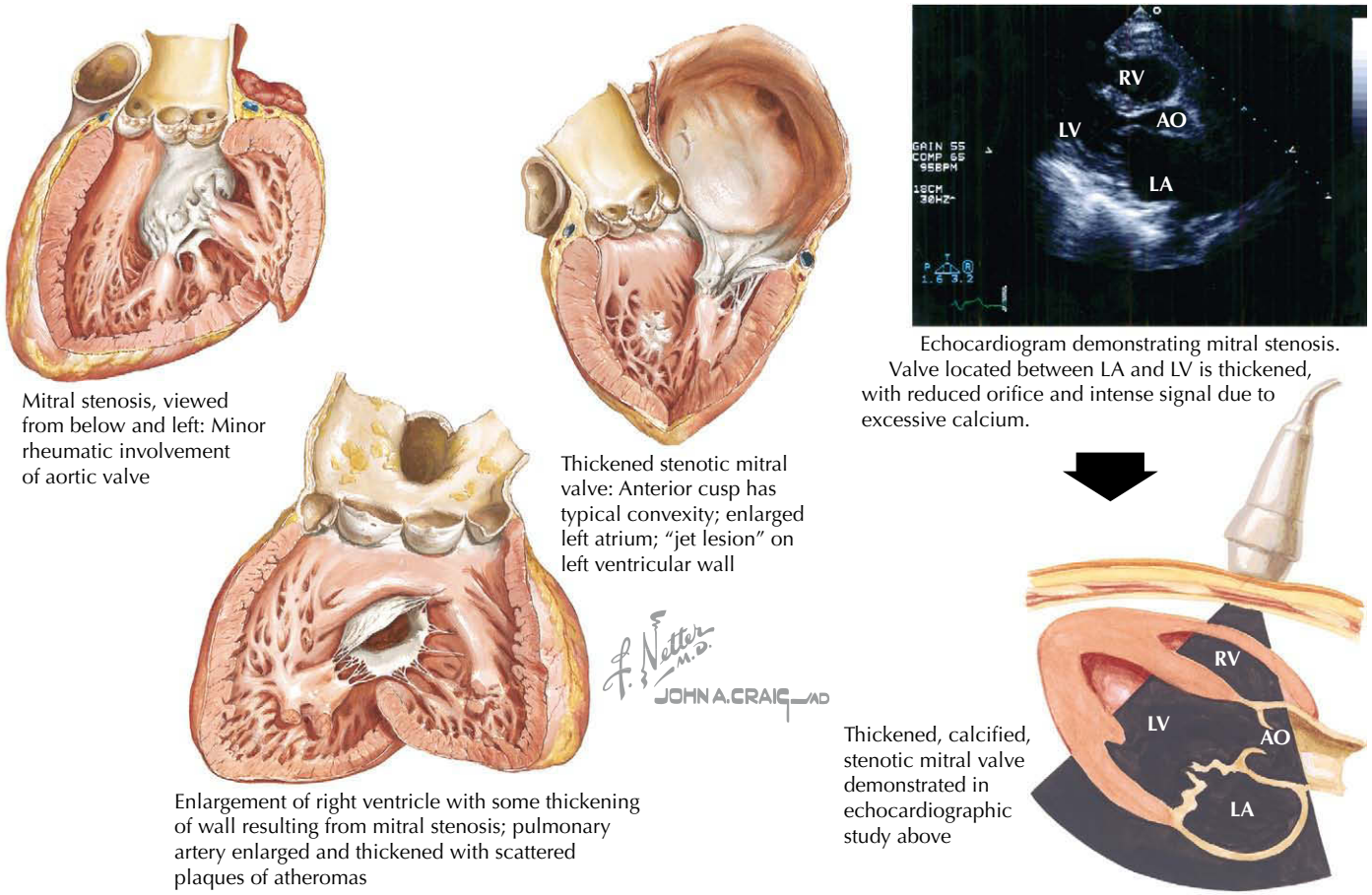


Figure 36-1 *Mitral stenosis.* AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

sound, and a low-pitched diastolic murmur with presystolic accentuation if the patient is in sinus rhythm. The opening snap is the sound generated by sudden full opening of the mitral valve. It reflects the severity of the pressure gradient across the mitral valve, because greater LA pressures generate earlier opening than do lesser ones. Therefore, the shorter the interval from second heart sound to opening snap, the greater the pressure gradient, and the more severe the stenosis.

The characteristic diastolic, low-frequency "rumble" or murmur associated with mitral stenosis is best heard at the apex with the patient in the left lateral decubitus position and the bell over the point of maximal ventricular intensity. The rumble occurs throughout diastole, with accentuation in late diastole (presystole) in patients who have preserved normal sinus rhythm. This murmur can be difficult to hear, and is soft and brief when the stenosis is minor. Therefore, heightened awareness of possible mitral stenosis is necessary. If the murmur is inaudible, it can be accentuated by having the patient exercise before auscultation or perform maneuvers such as isometric handgrip. This murmur sequence—loud first sound, opening snap, and diastolic rumble—is specific for mitral stenosis. Murmurs that mimic mitral stenosis include the Austin Flint murmur with aortic regurgitation, mitral diastolic murmurs in patients with large intracardiac shunts, and occasionally murmurs that are caused by an LA myxoma. However, none have all three components of classic mitral stenosis.

Electrocardiographic changes in mitral stenosis may range from minor ST-segment and T-wave abnormalities to electrocardiographic evidence of severe pulmonary hypertension and RV enlargement. The ECG pattern of LA and RV enlargement is a classic indicator. Atrial fibrillation is common.

Mitral Regurgitation

Mitral regurgitation following sudden catastrophic failure of the valve apparatus is almost always immediately and severely symptomatic. In this situation, the regurgitant volume competes for systemic blood flow and is simultaneously filling a small, noncompliant left atrium. This results in pulmonary edema often coupled with hypotension or shock. The physical examination will reflect the respiratory distress and evidence of poor systemic perfusion such as tachycardia, cool extremities, and diaphoresis. Importantly, however, the cardiac examination may not be helpful. Any systolic murmur may be difficult to hear or be absent. Emergent diagnosis usually requires echocardiography.

Conversely, even severe chronic mitral regurgitation may be tolerated without symptoms for years. Many cases of chronic mitral regurgitation are discovered during routine examinations

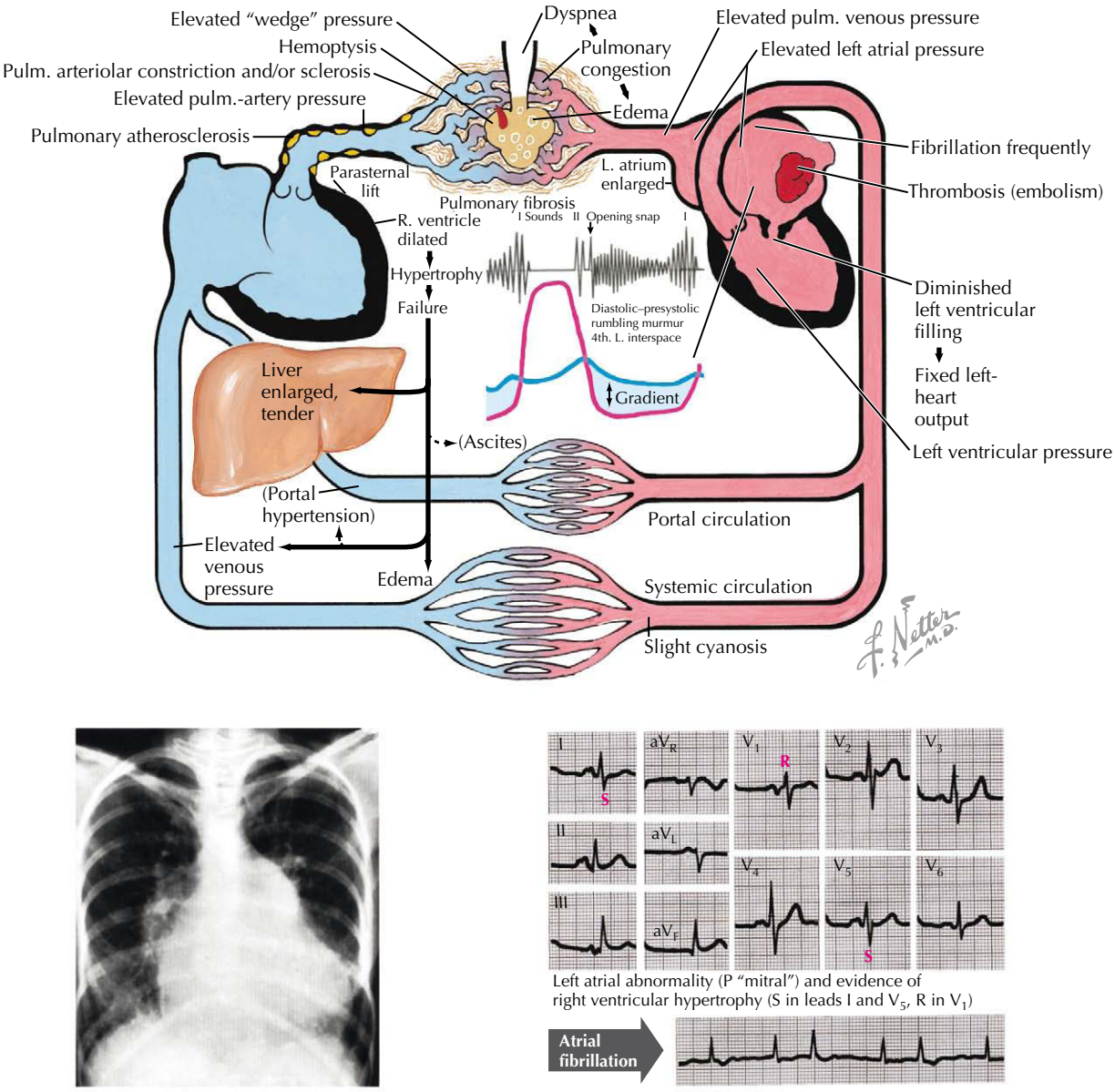


Figure 36-2 *Pathophysiology and clinical aspects of mitral stenosis.*

when the characteristic holosystolic murmur is noticed. Symptoms usually begin as dyspnea on exertion. Patients may also present with acute pulmonary edema or evidence of RV failure. Sudden decompensation can occur with the onset of atrial fibrillation or the development of bacterial endocarditis.

With chronic mitral regurgitation, the precordial cardiac impulse may be normal or may show a displaced, sustained LV impulse with a rapid filling wave. On auscultation the most prominent feature is a holosystolic murmur that classically radiates to the axilla. The intensity may not correlate with the severity of the mitral regurgitation; even severe mitral regurgitation can be associated with virtually no murmur. ECG changes in mitral regurgitation are nonspecific and are primarily changes of LV hypertrophy and strain; atrial fibrillation is common.

DIFFERENTIAL DIAGNOSIS

Primary pulmonary diseases (pneumonia, tuberculosis, chronic obstructive lung disease, and pulmonary thromboembolism) may present similarly to mitral valve disease, with dyspnea on exertion or pulmonary edema. Dyspnea may also be present in chronic interstitial pulmonary diseases, pulmonary hypertension, and malignancies that involve the chest. Other cardiovascular conditions that present similarly include ischemic heart disease, congenital heart disease, dilated cardiomyopathy, and hypertrophic cardiomyopathy. Chronic pericardial disease with restriction can cause RV failure that mimics the pulmonary hypertension associated with mitral valve disease.

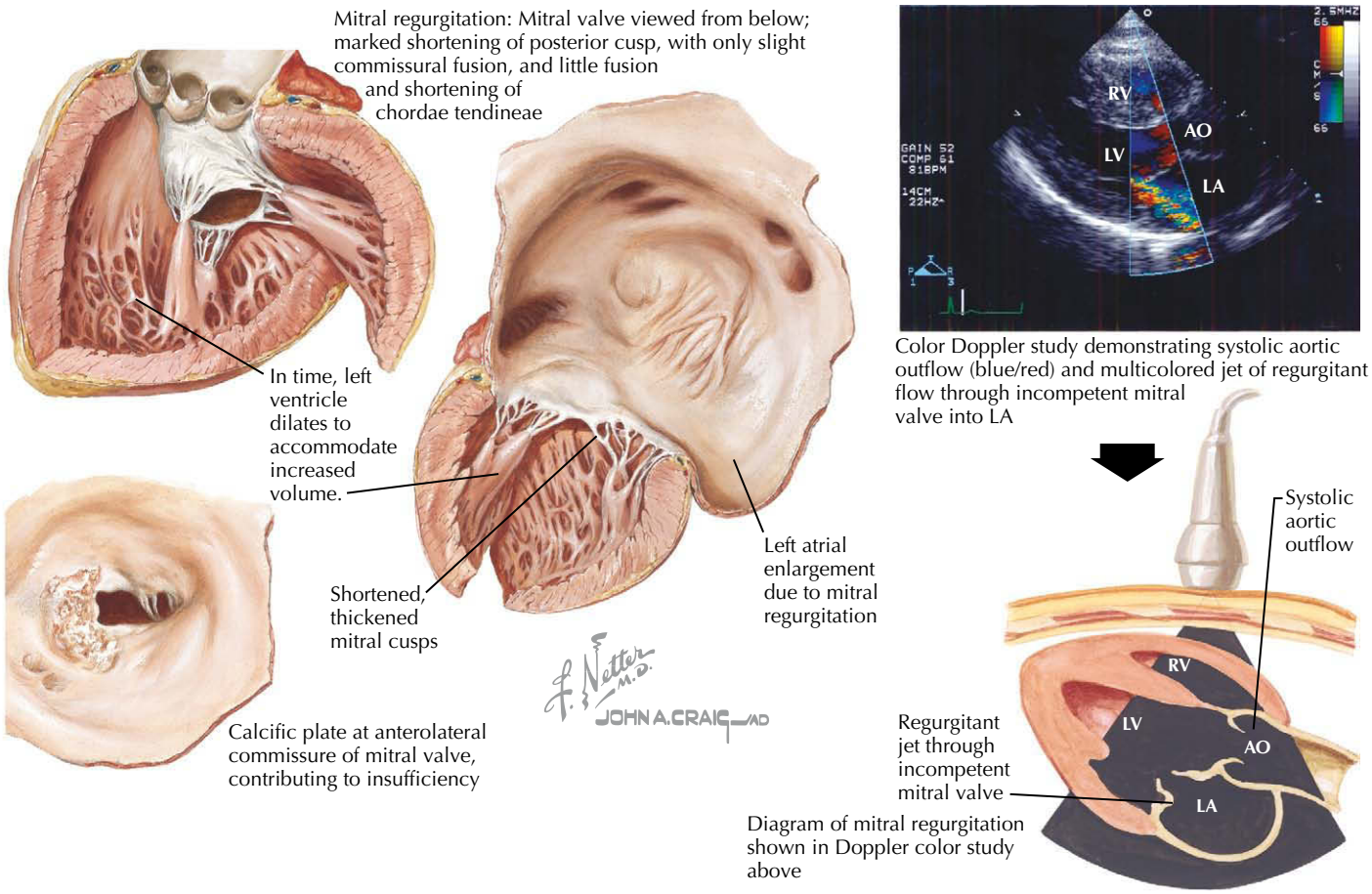


Figure 36-3 *Mitral regurgitation.* AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

DIAGNOSTIC APPROACH

Many pulmonary diseases can be differentiated from mitral valve disease by means of chest imaging, including both radiography and CT scanning. When an initial evaluation has focused the differential diagnosis on mitral valve disease, the most helpful clinical tool is echocardiography (see also Chapter 6).

In rheumatic mitral valve disease, echocardiography can demonstrate thickening, calcification, poor valve mobility, and thickening of subvalvular structures. The degree of valvular stenosis or regurgitation can be estimated using Doppler ultrasonography. When necessary, the anatomy of the valve and subvalvular apparatus can be further defined by transesophageal echocardiography. The goals of echocardiography are to evaluate the severity of the stenosis or regurgitation, the mobility of the valve, the involvement of subvalvular structures, and the degree of calcification, as well as to detect intracardiac thrombi. Echocardiography provides information about LV contractile function and an accurate estimation of pulmonary artery pressure and RV function. It can also identify bacterial and fungal vegetations, intracardiac masses (especially LA myxoma), and intraventricular septal defects, conditions that can complicate diagnosis of mitral valve disease.

Cardiac catheterization is indicated when there is a questionable diagnosis, when clinical and echocardiographic findings are inconsistent, and in many patients for whom surgical treatment is contemplated. Catheterization is performed to quantify the mitral valve area, to document key elements of hemodynamics such as cardiac output and systemic resistance, to define the degree of pulmonary hypertension, and to determine whether coronary artery disease is also present.

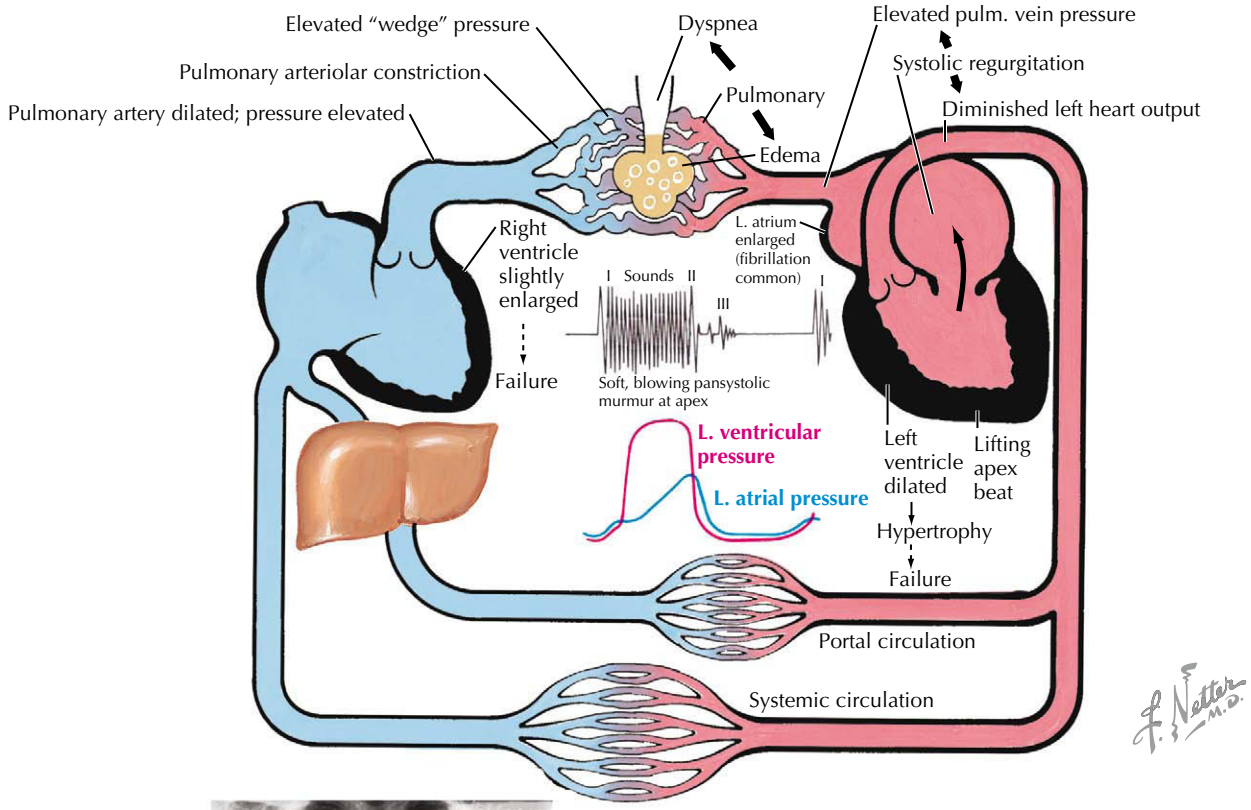
MANAGEMENT AND THERAPY

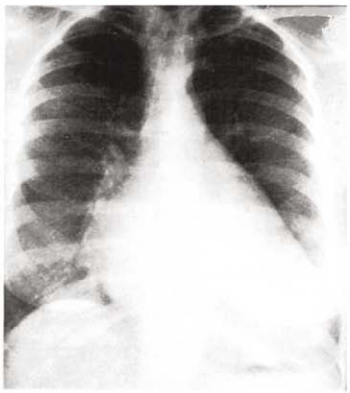
Mitral Stenosis

Asymptomatic patients in normal sinus rhythm with mild, uncomplicated mitral stenosis require only periodic monitoring for symptoms and prophylaxis against rheumatic fever. In symptomatic patients, diuretics can help reduce pulmonary congestion. With mitral stenosis, ventricular filling time is critically important; the heart rate should be maintained as low as is practical with a β-blocker or a rate-affecting calcium channel blocker. Patients with atrial fibrillation must be treated with warfarin anticoagulation, unless it is contraindicated.

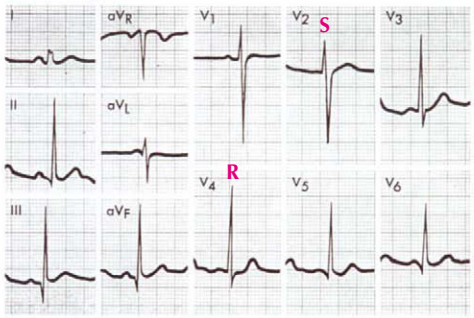
OPTIMUM TREATMENT

Symptomatic mitral stenosis can be improved by percutaneous mitral balloon valvotomy (PMBV), surgical valvotomy, or





Left and right ventricular enlargement



Electrocardiographic evidence of L. ventricular hypertrophy (large S in V_1, large R in V_4) and minor atrial abnormality (broad P)

Figure 36-4 *Pathophysiology and clinical aspects of mitral regurgitation.*

surgical replacement of the mitral valve. PMBV is the treatment of choice in selected patients in whom there is little valvular calcification, little involvement of the subvalvular apparatus, and minimal or no mitral valve regurgitation. It is essential to exclude LA thrombi by transesophageal echocardiography in patients being considered for PMBV. The results of PMBV depend in great part on operator experience. Longitudinal studies in expert centers have documented event-free survival to be greater than 70% at 7 years.

Open valvotomy is a repair procedure that involves direct visualization of the valve by the surgeon and facilitates debridement of valve structure and reconstruction of subvalvular apparatus. This approach also permits valve replacement per the surgeon's judgment. Mitral valve replacement is indicated for patients with severe mitral stenosis who are not candidates for percutaneous commissurotomy or surgical repair (Tables 36-1, 36-2, and 36-3) (see Chapter 41).

AVOIDING TREATMENT ERRORS

Many patients unknowingly minimize mitral stenosis symptoms by adopting a sedentary lifestyle. This situation may be suspected following a careful history and documented with exercise testing. These patients may benefit greatly from PMBV. Alternatively, patients may report severe symptoms despite echocardiographic data suggesting mild mitral stenosis. Exercise testing with simultaneous echocardiography or catheterization is indicated in this situation and may disclose dramatic worsening of atrial and pulmonary hypertension and the need for intervention.

Table 36-1 Management Approach for Patients with Asymptomatic Mitral Stenosis

	Yearly Follow-up	Consider Percutaneous Mitral Balloon Valvotomy
Asymptomatic	Mild stenosis (MVA >1.5 cm^2) *or* MVA <1.5 cm^2 but valve morphology not favorable for PMBV	Moderate or severe stenosis (MVA <1.5 cm^2) *and* Pulmonary artery systolic pressure >50 mm Hg *or* Exercise test results: Pulmonary artery pressure >60 mm Hg Pulmonary artery wedge pressure >25 mm Hg *or* New-onset atrial fibrillation *and* No LA thrombus or significant mitral regurgitation (3+ or 4+)

LA, left atrial; MVA, mitral valve area; PMBV, percutaneous mitral balloon valvotomy.
Recommendations are from Bonow RO, Carabello B, Chatterjee K, et al. Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. *2008;52:1–142.*

Rheumatic fever can affect all heart valves. Therefore, multiple valve disease must be considered in all patients. Special attention should be given to the possibility that echocardiography can underestimate the degree of aortic regurgitation in patients with severe mitral stenosis. Tricuspid stenosis may be similarly underestimated or even undetected and may complicate the immediate postoperative recovery after mitral valve repair or replacement.

Atrial fibrillation is a frequent cause of decompensation in patients with mitral stenosis and must be anticipated and

Table 36-2 Management Approach for Patients with Symptomatic Mitral Stenosis

	Periodic Follow-up	Consider PMBV	Consider Open Valvotomy or Mitral Valve Replacement
Mildly symptomatic (NYHA class II)	Mild stenosis (MVA >1.5 cm^2) *and* Exercise test results: PASP <60 mm Hg PAWP <25 mm Hg MVG <15 mm Hg *or* Valve morphology not favorable for PMBV	Mild stenosis (MVA >1.5 cm^2) *and* Exercise test results: PASP >60 mm Hg PAWP >25 mm Hg MVG >15 mm Hg *and* Valve morphology favorable for PMBV *and* No LA thrombus or significant mitral regurgitation (3+ to 4+)	Moderate or severe stenosis (MVA <1.5 cm^2) *and* Valve morphology not favorable for PMBV *and* Pulmonary pressure >60–80 mm Hg
	Moderate or severe stenosis (MVA <1.5 cm^2) *and* Valve morphology not favorable for PMBV *and* Pulmonary pressure <60 mm Hg	Moderate or severe stenosis (MVA <1.5 cm^2) *and* Valve morphology favorable for PMBV *and* No LA thrombus or significant mitral regurgitation (3+ to 4+)	
Moderately to severely symptomatic (NYHA class III–IV)	Mild stenosis (MVA >1.5 cm^2) *and* Exercise test results: PASP <60 mm Hg PAWP <25 mm Hg MVG <15 mm Hg	Moderate or severe stenosis (MVA <1.5 cm^2) *and* Valve morphology favorable for PMBV *or* High-risk surgical candidate with less than favorable morphology for PMBV *and* No LA thrombus or significant mitral regurgitation (3+ to 4+)	Moderate or severe stenosis (MVA <1.5 cm^2) *and* Valve morphology not favorable for PMBV *and* Acceptable surgical risk

LA, left atrial; MVA, mitral valve area; MVG, mitral valve gradient; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PMBV, percutaneous mitral balloon valvotomy.
Recommendations are from Bonow RO, Carabello B, Chatterjee K, et al. Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. *2008;52:1–142.*

Table 36-3 Management Approach for Patients with Chronic Severe Mitral Regurgitation

	Follow-up with Echo Every 6 Months or Medical Therapy	Mitral Valve Repair	Mitral Valve Replacement
No subjective symptoms and no suggestion of symptoms by exercise testing	Normal LV function (EF >60% and ESD <40 mm) *and* No new-onset atrial fibrillation *and* No pulmonary hypertension *and* Mitral valve repair unlikely*	LV dysfunction (EF <60%, ESD >40 mm) *or* Pulmonary hypertension *or* New-onset atrial fibrillation	LV dysfunction (EF <60%, ESD >40 mm) *and* Mitral valve repair not possible
Symptoms	Severe LV dysfunction (EF <30% and/or ESD >55 mm) *and* Chordal preservation not likely	EF >30% ESD <55 mm	Intervention indicated but mitral valve repair not possible

EF, ejection fraction; ESD, end-systolic dimension of the left ventricular chamber; LV, left ventricular.
*Mitral valve repair may be an option for asymptomatic patients with normal LV function in an experienced center.
Recommendations are from Bonow RO, Carabello B, Chatterjee K, et al. Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. *2008;52:1–142.*

managed aggressively. Similarly, pregnancy increases requirements for cardiac output and requires special planning and management. In women with rheumatic or congenital mitral stenosis, initial symptoms often manifest with pregnancy. Bacterial endocarditis should be considered whenever symptoms worsen in patients with mitral stenosis.

Mitral Regurgitation

Primary mitral regurgitation is a structural problem causing valve incompetency that can only be corrected adequately by valve repair or replacement. Therefore, the physician's primary role is to monitor patients with mitral regurgitation for development of symptoms and evidence of LV dysfunction, events that portend the need for intervention. The most promising medical therapies for chronic mitral regurgitation, vasodilators and β-blockers, have not been adequately documented to delay the need for surgery and thus are not recommended for this purpose alone. Aggressive treatment of hypertension is useful in patients with chronic mitral regurgitation.

OPTIMUM TREATMENT

The timing of surgical intervention for patients with chronic mitral regurgitation is critical. In most cases, mitral regurgitation is well tolerated, and patients are asymptomatic for many years. Delaying surgery as long as possible avoids the trauma, expense, and risk of surgery. However, every effort must be made to proceed with surgery before ventricular function has degenerated. LV systolic function is estimated using one of several methods for determining the LV ejection fraction. The unique accommodating effects of ventricular dilation and myocardial remodeling with chronic mitral regurgitation allow the ejection fraction to be preserved late into the disease course; therefore, any decrement in ejection fraction may represent a considerable decrease in myocardial functional reserve. In general, mitral valve surgery should be considered in patients with known moderate to severe mitral regurgitation when they are symptomatic or there is objective evidence of decreased LV function (LV ejection fraction <60%).

Valve repair for severe mitral regurgitation lessens mortality and decreases the frequency of complications. Valves must be relatively free of calcification and have pliable leaflets with chordae tendineae that can be separated, reinforced, or reattached as needed. Placement of a reinforcing mitral ring is frequently included in the repair. Valve repair, as opposed to replacement, preserves functional subvalvular components, including the papillary muscles, and significantly improves postoperative LV function. Additionally, natural valves are resistant to thrombus formation, obviating the need for long-term anticoagulation.

AVOIDING TREATMENT ERRORS

Mitral regurgitation resulting from dilated cardiomyopathy is caused by dilation of the mitral ring and ventricles with anatomic deformity of the spatial and functional relationship of the papillary muscles and chordae tendineae to the mitral valve leaflets. In severe LV dysfunction, mitral valve repair or replacement may fail to improve symptoms and is associated with a high risk of operative death. New surgical and percutaneous approaches for correction of mitral regurgitation in this circumstance are in clinical trials to determine safety and efficacy.

Coronary heart disease can cause mitral regurgitation by several mechanisms. The mitral valve is tethered to papillary muscles that depend on myocardial blood flow. Acute ischemia of the papillary muscles can cause temporary mitral regurgitation and be corrected with coronary vascular interventions, either surgical or percutaneous. Acute myocardial infarction that involves a papillary muscle frequently causes acute, life-threatening mitral regurgitation, with mortality rates near 30%. These are managed, usually surgically, with both repair of the valve and subvalvular apparatus and simultaneous revascularization. In some circumstances, an infarction results in rupture of the tip of the papillary muscle with acute mitral regurgitation. This is almost always fatal unless surgically corrected.

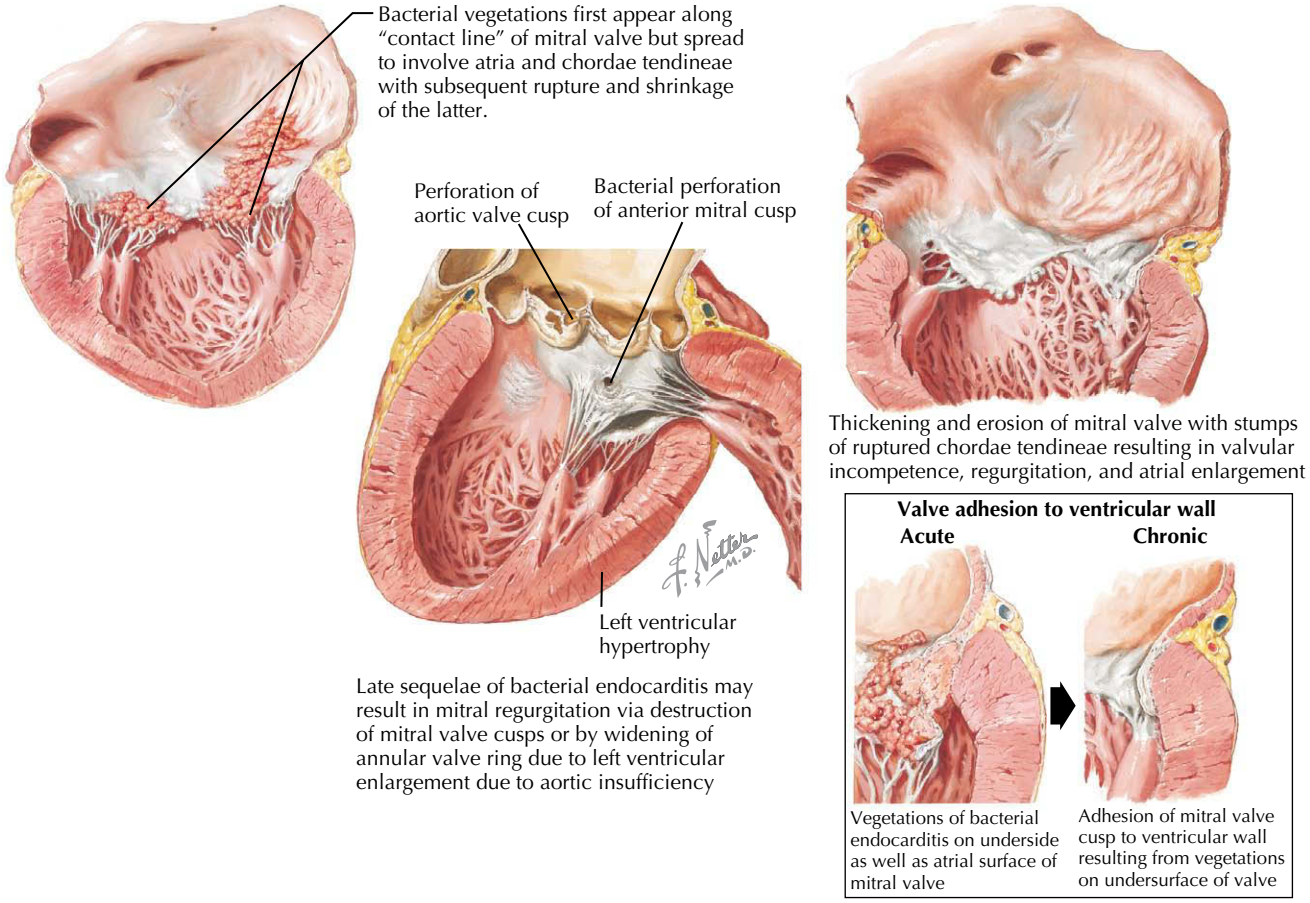


Figure 36-5 *Bacterial endocarditis in mitral valvular disease.*

Any structural abnormality of the valve can result in flow aberrations that promote deposition of microthrombi. These can be the nidus for a bacterial or fungal infection resulting in further damage from endocarditis (Fig. 36-5). Endocarditis can affect valve competency because of interference in valve function by vegetations or by destruction or fenestration of the valve leaflets. Although endocarditis is usually managed with antibiotics, the damage effected by the bacteria is permanent, as is the resultant mitral regurgitation. Indications for surgery after cured bacterial endocarditis are identical to those for other causes for mitral regurgitation. In addition, acute surgical care is indicated for extremely large vegetations, when heart failure is otherwise unmanageable, when a myocardial abscess is documented, and for patients with persistent bacteremia.

FUTURE DIRECTIONS

Improving worldwide morbidity and mortality associated with rheumatic heart disease necessitates better systems of hygiene and improved prophylactic treatment of streptococcal infection, especially the current drug-resistant strains. Mitral regurgitation's prevalence will increase as the population ages, spurring improvements in several areas: imaging with more accurate estimates of ventricular reserve, surgical technology with early repair of severely regurgitant valves, balloon valvotomy with improved patient selection and equipment, and minimally invasive surgical techniques with reduced recovery time and morbidity. Better treatment for atrial fibrillation and improved therapies for prevention of thrombosis will greatly improve the quality of life for patients with mitral valve disease and valve prostheses.

ADDITIONAL RESOURCES

Carabello BA. Modern management of mitral stenosis. *Circulation.* 2005; 112:432–437.

Carabello BA. The current therapy for mitral regurgitation. *J Am Coll Cardiol.* 2008;52:319–326.

State-of-the-art reviews by a noted expert.

EVIDENCE

Bonow RO, Carabello B, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol.* 2008;52:1–142.

In this recently updated report from a panel of experts assembled by the ACC and AHA, the authors cite more than 1000 articles and provide a comprehensive review of the diagnosis and management of valvular heart disease. Tables and algorithms provide easy access to the practical aspects of patient care.

Mitral Valve Prolapse

Lee R. Goldberg and Park W. Willis IV

37

Mitral valve prolapse (MVP) is the most common form of congenital heart disease in adults, affecting 4% to 5% of the U.S. population. MVP refers to the superior and posterior displacement of one or both mitral leaflets into the left atrium during systole. Although MVP is usually benign, important complications, including infective endocarditis and severe mitral regurgitation, can occur.

MVP can be classified as primary, secondary, or functional. Primary MVP occurs in the absence of connective tissue disease. Myxomatous degeneration of the tricuspid valve may be present, and the aortic and pulmonic valves are sometimes involved. Primary MVP can be associated with skeletal abnormalities, von Willebrand's disease, and hypomastia. Secondary MVP occurs in the presence of a known connective tissue disorder, such as Marfan's syndrome, Ehlers-Danlos syndrome, adult polycystic kidney disease, osteogenesis imperfecta, and pseudoxanthoma elasticum. The pathologic changes of the mitral valve apparatus are identical to those found in primary MVP. In functional MVP the mitral valve is anatomically normal, but both superior and posterior displacement of the valve can occur secondary to other cardiac conditions. Causes of functional MVP include a dilated mitral annulus and ischemic papillary muscle dysfunction. In hypertrophic cardiomyopathy, the left ventricular (LV) cavity may be too small to accommodate the mitral valve, causing functional MVP. In atrial septal defect, left-to-right shunting and right ventricular chamber dilation secondary to volume overload can result in a small left ventricle and functional MVP.

ETIOLOGY AND PATHOGENESIS

The etiology of MVP is unknown. There is a familial form of MVP in which transmission occurs in an autosomal-dominant fashion, with variable penetrance. However, there is no single, or group of, genetic abnormalities thought to be responsible for MVP. Pathologic findings in primary and secondary MVP often involve the mitral leaflets and the chordae tendineae. Typical gross pathologic findings include thickened, redundant mitral leaflets and elongated chordae tendineae.

Although both the anterior and posterior mitral leaflets may be affected, the middle scallop of the posterior leaflet is most commonly involved in the myxomatous process. Histologic examination of the mitral valve leaflets reveals interruption of collagen bundles and an accumulation of acid mucopolysaccharides within the spongiosa layer.

CLINICAL PRESENTATION

The clinical presentation of MVP is highly variable. Most patients with MVP are asymptomatic. The most common complaint is atypical chest pain. Other nonspecific symptoms associated with MVP include palpitations, dizziness, dyspnea, anxiety, numbness, and tingling. There is ongoing controversy about whether these complaints are caused by MVP, as was initially reported, or are a coincidental finding. It is quite possible that the original descriptions of MVP were probably influenced by selection bias. Several subsequent studies have not shown a truly increased frequency of symptoms such as chest pain, dyspnea, or dizziness.

MVP is usually discovered incidentally on routine physical examination, and cardiac auscultation is the key to making the clinical diagnosis. One or more nonejection systolic clicks in midsystole or late systole with or without a late systolic murmur are characteristic of MVP. The systolic click, or clicks, heard in MVP are thought to originate from the chordae tendineae snapping as the mitral leaflets bow into the left atrium. Multiple systolic clicks can cause a scratching sound occasionally likened to a pericardial friction rub. Mitral regurgitation at the time of leaflet prolapse results in late systolic murmur. This murmur typically has a crescendo contour and envelops the second heart sound (S_2). It is commonly preceded by a nonejection click but may occur alone. A late systolic murmur usually indicates mild mitral regurgitation; with more significant mitral regurgitation, the murmur can be pansystolic and a click may not be audible. Although late systolic accentuation is often preserved, the murmur can become indistinguishable from the murmur related to mitral regurgitation from other causes. In the case of posterior leaflet prolapse, the mitral regurgitant flow is commonly directed anteriorly toward the aortic root and the murmur may be transmitted along the left sternal border and to the aortic area. With anterior leaflet prolapse, the murmur radiates to the left axilla and back.

MVP is a dynamic, load-dependent phenomenon, and the most sensitive and specific physical diagnostic criteria are based on characteristic postural changes in auscultatory findings. A complete examination with the patient in the supine, standing, and sitting positions is required to alter hemodynamics and ventricular loading conditions and thus detect the characteristic findings with the highest degree of accuracy. The postural auscultatory changes are related primarily to changes in LV volume, augmented by alterations in heart rate and myocardial contractility. Generally, measures that decrease LV volume produce earlier and more prominent systolic prolapse of the mitral leaflets, causing the systolic click and murmur to move closer to the first heart sound (S_1) (Fig. 37-1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a nonejection systolic click includes ejection sounds arising from the aortic and pulmonic valves, splitting of S_1 or S_2, and clicks arising from nonvalvular structures such as an atrial septal aneurysm, pericardial sounds, and clicks heard in patients with a pneumothorax. Aortic and pulmonic ejection sounds are high-frequency sounds that occur in early systole. An aortic ejection sound is best heard with the diaphragm of the stethoscope and simulates wide splitting of S_1.

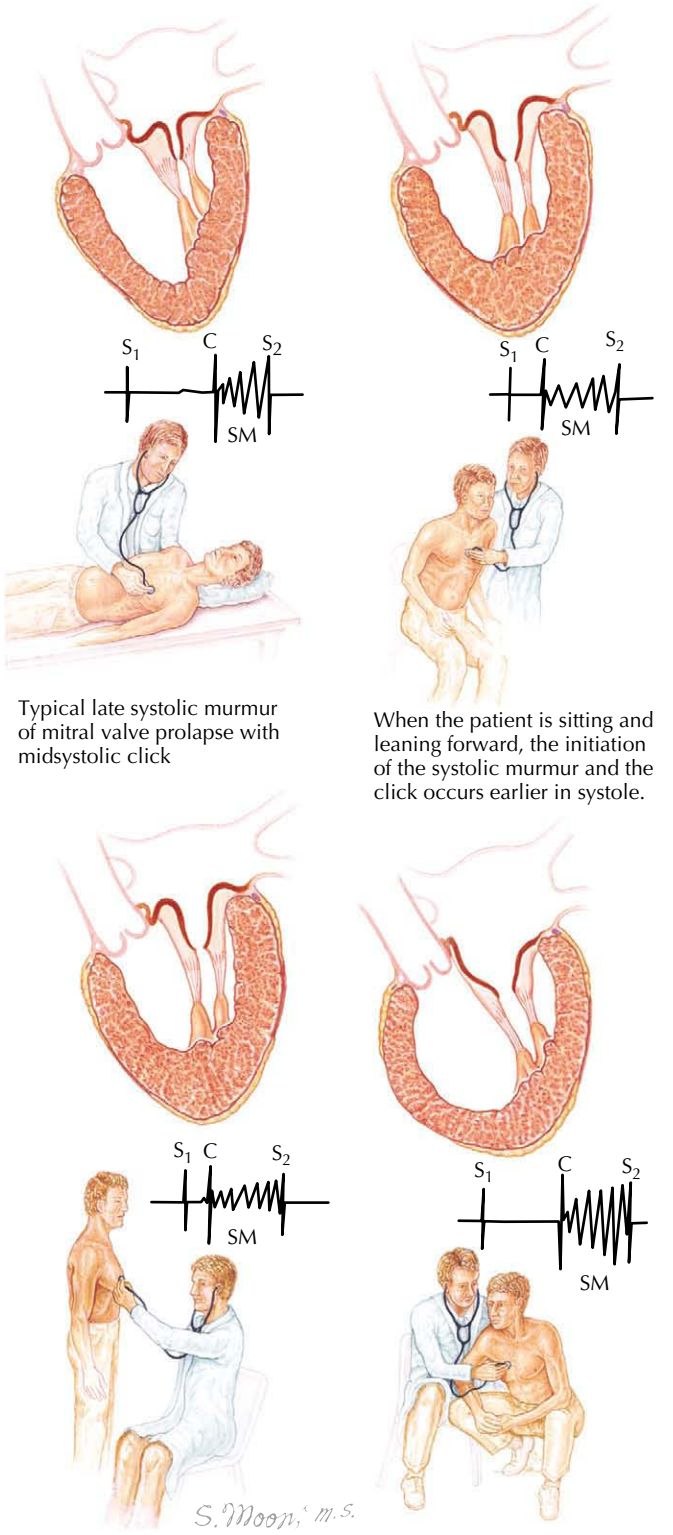


Figure 37-1 *Auscultation in mitral valve prolapse.* C, click; SM, systolic murmur.

Though audible over the entire precordium, these sounds are usually loudest at the mitral area, where the S_1–ejection click sequence is commonly mistaken for a fourth heart sound followed by S_1. Pulmonary ejection sounds can be difficult to differentiate from the splitting of S_1, but the characteristic loud and "clicky" quality of these sounds, exaggerated in the expiratory phase of respiration and disappearing on inspiration, is a reliable diagnostic feature. Ejection clicks are not perceptibly affected by altering preload with postural changes. Because the ejection clicks occur as the semilunar valve opens, they precede the carotid upstroke, whereas the nonejection clicks of MVP occur afterward. A midsystolic click can occur with an atrial septal aneurysm. In this circumstance there is no associated late systolic murmur. Clicking pneumothorax can mimic MVP, but extra sounds do not show a consistent relationship to the cardiac cycle and can also occur in diastole. For this reason, a prolonged period of continuous cardiac auscultation is useful in diagnosis.

DIAGNOSTIC APPROACH

When the diagnosis of MVP is made by cardiac auscultation, transthoracic echocardiography can be useful to confirm the physical findings. Both two-dimensional and M-mode techniques are sensitive in detecting MVP. Echocardiography provides additional information, including the degree of leaflet prolapse, the severity of the mitral regurgitation, and the thickness of the mitral leaflets (Fig. 37-2). The improvement in echocardiographic methods and technology and changing diagnostic criteria have resulted in a degree of variability in the clinical interpretation of the information generated. Today, far fewer patients are diagnosed as having MVP than were diagnosed 20 years ago. However, the load-dependent nature of MVP does make its diagnosis more difficult, because patients routinely are studied in a supine position.

The originally described M-mode criteria for MVP required displacement of the mitral leaflet echo beyond the CD segment in systole. Either 3 mm of holosystolic displacement or 2 mm of late systolic displacement were sufficient to meet M-mode criteria for MVP. Because of the saddle shape of the mitral annulus, the diagnosis of MVP by two-dimensional echo is limited to parasternal long-axis views. Prolapse in the parasternal long axis is defined by the bowing of mitral leaflets beyond an imaginary line that connects the anterior and posterior annular hinge points. Prolapse greater than 2 mm beyond this line is diagnostic of MVP. "Classic" MVP is present in patients with at least 2 mm of leaflet displacement and a leaflet thickness of at least 5 mm. Close correlation of echocardiographic features with clinical findings, and recognition that important complications such as mitral regurgitation, infective endocarditis, and the need for surgery have been associated with leaflet redundancy and thickening, have led to concentration on the echocardiographic valvular morphology and the degree of displacement. Today, the echocardiographic diagnosis of MVP relies on a combination of all of these methods.

ECG abnormalities reported in MVP include atrial and ventricular arrhythmias, prolonged QT interval, nonspecific ST-segment and T-wave changes, and T-wave inversion in the inferior frontal plane leads. However, several studies have failed

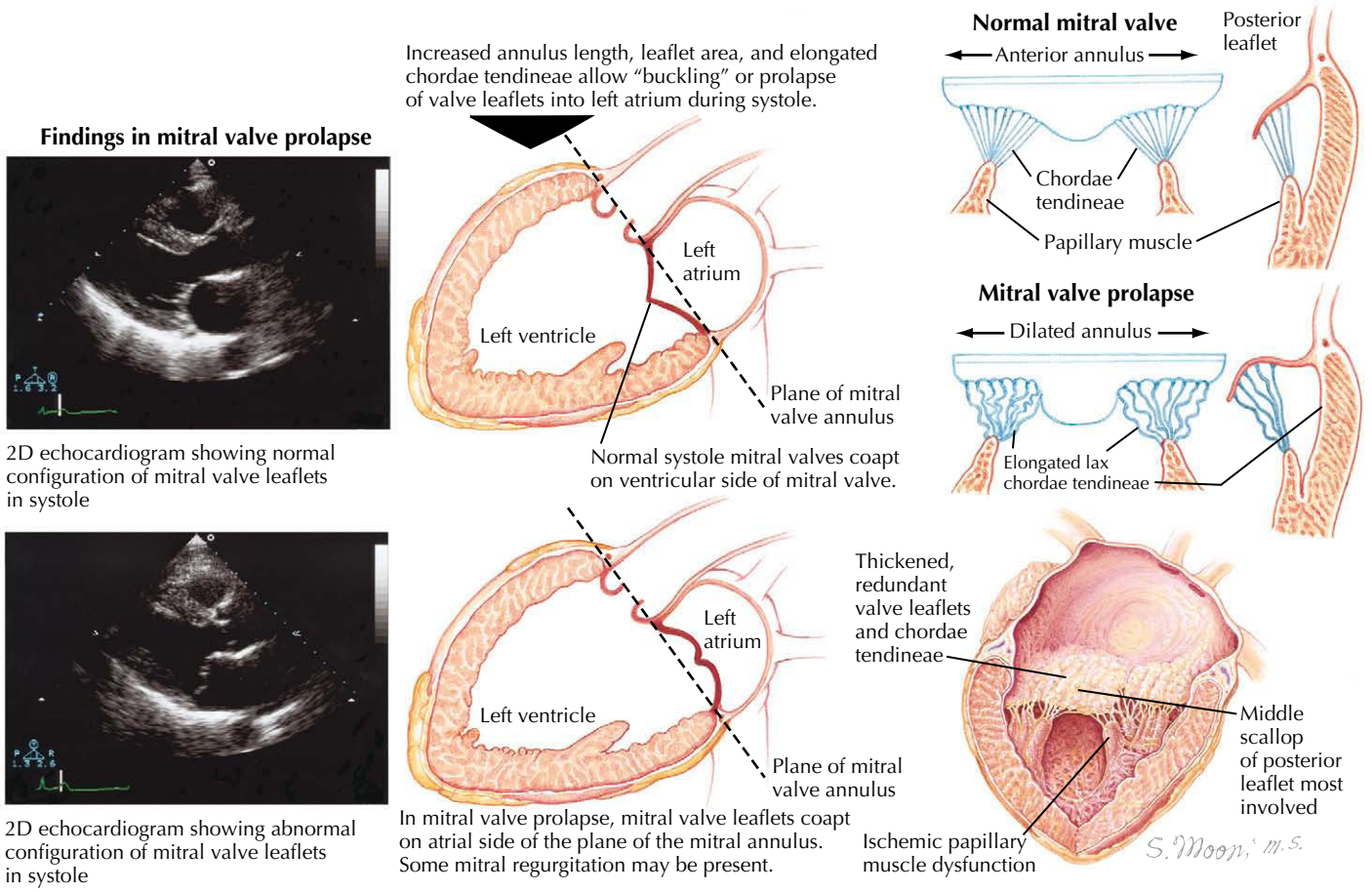


Figure 37-2 *Diagnosis of mitral valve prolapse.*

to show consistent diagnostic or clinically useful ECG abnormalities in patients with MVP, and for this reason, the ECG is not useful in diagnosing this entity. Ambulatory ECG recording (Holter monitoring) can document arrhythmias in patients who present with symptoms of palpitation. It is important to temporally correlate symptoms with arrhythmias on Holter. Chest radiography is of little use in diagnosing MVP, but with hemodynamically important mitral regurgitation there may be radiographic evidence of left atrial and LV chamber dilation and pulmonary venous congestion.

COMPLICATIONS

The clinical course and the prognosis are favorable for most patients with MVP. The survival rate in patients with MVP is similar to the survival rate in an age- and sex-matched population without MVP. The risk of serious cardiac complications is approximately 1% per year. Rarely, patients with MVP may present with a cardiac arrhythmia, infective endocarditis, or severe mitral regurgitation and subsequent congestive heart failure. The most important risk factors for the development of complications are age older than 45 years, male sex, a pansystolic murmur of mitral regurgitation, and dilation of the left-sided heart chambers. Echocardiographic predictors of an increased risk of complications include mitral leaflet redundancy and thickening and significant mitral regurgitation.

The link between MVP and the development of arrhythmias is controversial. Nevertheless, symptoms of palpitations commonly prompt otherwise healthy patients to seek medical attention. This can lead to coincidental diagnosis of MVP based on physical or echocardiographic findings. Although many studies have suggested that patients with MVP are at increased risk for premature atrial beats, supraventricular tachycardia, and premature ventricular beats, these reports were probably influenced by selection bias. The association between MVP and the development of arrhythmias is probably related most directly to the presence of severe mitral regurgitation. Patients with significant mitral regurgitation have an increased risk of ventricular arrhythmias, ventricular tachycardia, and sudden cardiac death. The risk is approximately the same whether MVP is the etiology of the severe mitral regurgitation or the mitral regurgitation is from another cause. There is no convincing evidence that patients with MVP, but without severe mitral regurgitation, have a higher incidence of arrhythmias than the general population. Atrial fibrillation is usually a complication of progressive and severe mitral regurgitation, but it occasionally complicates the clinical course in patients with lesser degrees of hemodynamic disturbance.

It has been reported that patients with MVP have a fivefold greater risk for the development of infective endocarditis as compared with normal controls. However, the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines on infective endocarditis do not recommend antibiotic prophylaxis for either asymptomatic or symptomatic patients with MVP.

By virtue of its prevalence in the general population, MVP is probably the most common cardiac condition predisposing to infective endocarditis. In patients with MVP, a holosystolic murmur of mitral regurgitation is the strongest risk factor for the development of infective endocarditis. Mitral leaflet thickening of 5 mm or more, measured in diastole when the mitral valve is not under extreme tension, has also been associated with an increased risk. Additional risk factors for this complication include older age and male sex. For many years these factors led to the recommendation that patients with MVP receive antibiotic prophylaxis for certain procedures. However, the absolute risk for this complication continues to be low. Assuming that 4% of the population is affected with MVP, only an estimated 1 in 5700 patients with MVP develops infective endocarditis each year. The presence of mitral regurgitation substantially increases the risk for the development of infective endocarditis to 1 in 1900 patients. In the absence of a murmur of mitral regurgitation, the incidence of infective endocarditis is no greater in patients with MVP than it is in the general population.

Mitral regurgitation is a frequent finding in patients with MVP because leaflet prolapse results in inadequate coaptation and secondary mitral regurgitation. Most patients have only trace or mild regurgitation. However, an estimated 2% to 7% of MVP patients have hemodynamically significant mitral regurgitation. Prospective studies show that the risk for the development of severe mitral regurgitation requiring mitral valve repair or replacement is less than 1% per year. The estimated cumulative risk is 4% for men and 1% for women by age 70 years. Systemic arterial hypertension can accelerate degenerative change in the mitral apparatus, increasing the risk for the development of severe mitral regurgitation requiring surgery. Patients with poorly controlled blood pressure may be at risk for acute or subacute progression of mitral regurgitation from rupture of the chordae tendineae. Because of the high prevalence of MVP in the population, even a small percentage of patients with significant mitral regurgitation constitutes a relatively large number of cases of mitral regurgitation. In fact, MVP is the most common cause of operative mitral valve repair or replacement for isolated mitral regurgitation in the United States.

MANAGEMENT AND THERAPY

Optimum Treatment

The management of mitral regurgitation secondary to MVP depends on the magnitude of the hemodynamic derangement. Patients with mild mitral regurgitation can be followed with an annual physical examination. Repeat echocardiography is indicated only if symptoms develop or if physical findings change. Asymptomatic patients with moderate to severe mitral regurgitation should undergo annual physical examination and echocardiography for assessment of ventricular contractile performance. The development of resting LV dysfunction (ejection fraction ≤60%) or LV end-systolic dimension greater than or equal to 45 mm should prompt referral for valve repair or replacement. Patients with severe mitral regurgitation and symptoms of congestive heart failure are best treated with surgical intervention. However, in patients with severe mitral regurgitation and LV dysfunction, surgery can be contraindicated because the left ventricle may be unable to function once mitral regurgitation is eliminated.

In 2008, the AHA altered recommendations with respect to MVP and infective endocarditis prophylaxis. Although patients with MVP and coexistent mitral regurgitation do have an increased risk for developing infective endocarditis, the actual number of MVP patients who develop infective endocarditis remains very low. Furthermore, the prognosis of patients with MVP and infective endocarditis is favorable when compared with patients with congenital heart disease, prosthetic heart valves, and other conditions in which infective endocarditis prophylaxis is now recommended. Finally, the risk of a serious reaction from antibiotic use is not trivial, and the emergence of drug-resistant bacterial strains is a reason to curtail unnecessary antibiotic use. For the previous reasons, infective endocarditis prophylaxis is no longer recommended in patients with MVP, even in the presence of significant mitral regurgitation.

The management of patients with MVP consists largely of reassurance about the generally benign course of the disease. A transthoracic echocardiographic examination is indicated at initial diagnosis to assess the valvular morphology, the degree of mitral regurgitation, the LV contractile performance, and the associated structural cardiac disease. Asymptomatic patients without mitral regurgitation may be followed at 2- to 3-year intervals by physical examination. The development of a new murmur or symptom is an indication for repeat echocardiography. Serial echocardiographic studies are indicated to assess LV contractile performance and the degree of hemodynamic derangement in patients with moderate or severe mitral regurgitation.

Avoiding Treatment Errors

The high incidence of chest pain and palpitations in patients with MVP poses a common diagnostic and therapeutic challenge. In general, the evaluation and treatment of chest pain in individuals with MVP should not be different from that utilized in other patients. Clinicians should avoid attributing symptoms of atypical noncardiac chest pain to the presence of MVP. Palpitations in patients with MVP are most commonly the result of premature atrial and ventricular contractions. A standard ECG may be sufficient to establish the diagnosis when a patient is experiencing palpitations at the time of a clinical evaluation. Less frequent symptoms can be investigated with ambulatory electrocardiographic monitoring techniques; these relatively simple and inexpensive methods usually provide reassuring information, and further studies are rarely necessary. Abstinence from alcohol and caffeine can reduce the frequency of palpitations, and some studies of MVP patients suggest that symptoms improve after the initiation of a regular exercise program.

Because the majority of patients can be managed effectively with simple reassurance about their benign condition, premature initiation of pharmacologic therapy should be avoided. However, low-dose β-blocker therapy can be helpful for patients with refractory symptoms. The presence of an important arrhythmia discovered on ambulatory monitoring may be an indication for an electrophysiology study or antiarrhythmic therapy.

FUTURE DIRECTIONS

MVP is a common clinical condition. As detection continues to increase through heightened awareness, improved physical diagnostic skills, and wider application of modern cardiac imaging techniques, primary care physicians will have opportunities to risk-stratify patients and to educate them in the prevention of complications related to MVP. As a result of accumulated surgical experience and innovative techniques, the threshold for operative repair is decreasing for patients with severe mitral regurgitation. The development of more sophisticated imaging methods will help cardiologists and cardiac surgeons to identify more precisely the best type of repair and the optimal timing of operative intervention.

ADDITIONAL RESOURCES

Avierinos J-F, Gersh BJ, Melton III LJ, et al. Natural history of asymptomatic mitral valve prolapse in the community. *Circulation.* 2002;106:1355–1361.

From their community-based study of 833 patients who were first diagnosed with asymptomatic MVP between 1989 and 1998, the authors concluded that the natural history is widely heterogeneous, ranging from normal life expectancy with little morbidity in half the patients to high morbidity, and even excess mortality, in those with mitral regurgitation. The most frequent primary risk factors for cardiovascular mortality were moderate to severe mitral regurgitation and a LV ejection fraction <50%.

Devereux RB, Kramer-Fox R, Shear K, et al. Diagnosis and classification of severity of mitral prolapse: methodologic, biologic and prognostic considerations. *Am Heart J.* 1987;113:1265–1280.

This comprehensive review presents a critical analysis of the accuracy of current methods for the diagnosis of MVP, an assessment of biologic and methodologic factors influencing the variability of diagnostic findings, and recommendations for classification of severity for clinical and research purposes.

Fontana ME, Pence HL, Leighton RF, Wooley CF. The varying clinical spectrum of the systolic click–late systolic murmur syndrome: a postural auscultatory phenomenon. *Circulation.* 1970;41:807–816.

This systematic study of auscultatory findings in 30 patients with MVP, documented by phonocardiography, emphasized variations associated with change in posture; the investigators concluded that unless auscultation is performed in at least four body positions (supine, left lateral, sitting, standing), the correct diagnosis may be missed.

Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med.* 1999;341:1–7.

This large community-based study of the offspring cohort of the Framingham Heart Study applied strict two-dimensional echocardiographic diagnostic criteria and determined that the prevalence of MVP in the general population was lower than previously reported. Of the 1845 women and 1646 men examined, 2.4% had MVP; the prevalence of adverse sequelae commonly associated with MVP was low.

EVIDENCE

Bonow RW, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2006;48:e1–e148.

A comprehensive evidence-based guideline statement detailing current recommendations for the diagnosis and management of patients with known or suspected valvular heart disease.

Nishimura RA, Carabello BA, Faxon DP, et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis. *Circulation.* 2008;118:887–896.

This update modifies the previously published guidelines (see Wilson et al., below), which reflected a significant departure from prior recommendations, resulting in consternation among both patients and clinicians. The authors recommend that clinicians determine that the risks associated with antibiotics are low before continuing prophylaxis in patients with bicuspid aortic valve or coarctation of the aorta, severe MVP, or hypertrophic cardiomyopathy.

Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation.* 2007;116:1736–1754.

This document reflected a major change in the recommended approach to antibiotic prophylaxis for infective endocarditis. Based largely on the committee's conclusion that, even if 100% effective, antibiotic therapy might prevent only a very small number of cases, the expert panel advised against prophylaxis based solely on an increased lifetime risk. Antibiotic prophylaxis is recommended only for those patients with the highest risk for adverse outcomes from infective endocarditis.

Tricuspid and Pulmonic Valve Disease

David A. Tate

38

Acquired disease of the right-sided cardiac valves is much less common than disease of the left-sided valves, possibly because of the relatively lower pressures and hemodynamic stress to which the right-sided valves are subjected. Indeed, right-sided valvular dysfunction is usually seen when morphologically normal valves are subjected to abnormal hemodynamic stresses, such as pulmonary hypertension. Tricuspid and pulmonic valvular abnormalities are also part of numerous congenital syndromes (discussed in Section VIII). This chapter focuses on acquired abnormalities of the right-sided cardiac valves, and, because it is frequently diagnosed in adults, pulmonic stenosis.

TRICUSPID STENOSIS

Etiology, Pathogenesis, and Differential Diagnosis

Tricuspid stenosis is uncommon. Most cases are due to rheumatic heart disease. When rheumatic tricuspid stenosis is present, it is generally associated with mitral stenosis, which usually accounts for most of the presenting signs and symptoms. Carcinoid heart disease may also cause tricuspid stenosis, and the signs and symptoms may be mimicked by tumors (myxoma or metastasis), or vegetations that obstruct right ventricular (RV) inflow, particularly those associated with pacemaker leads (Box 38-1).

Clinical Presentation

The symptoms of tricuspid stenosis are mainly due to increased systemic venous pressure that results from a hemodynamically significant tricuspid valve lesion (Fig. 38-1). Peripheral edema, ascites, hepatic enlargement, and right upper quadrant discomfort may develop with chronic tricuspid stenosis or regurgitation. Decreased cardiac output may cause pronounced fatigue, and an occasional patient will complain of the appearance or sensation of the prominent *a* wave in the jugular veins, which results from increased jugular venous pressure due to impaired RV filling during atrial systole. The murmur of tricuspid stenosis is a low-pitched diastolic murmur at the lower left sternal edge. However, this is often obscured by or difficult to differentiate from the usually associated mitral stenosis murmur. The physical examination, however, may demonstrate the presence of tricuspid stenosis in patients with mitral stenosis, including when there is accentuation of the diastolic murmur during inspiration (as is the case for most right-sided murmurs), a prominent *a* wave in the jugular venous pulse, or both. An opening snap is occasionally appreciated but may be difficult to distinguish from that of coexistent mitral stenosis. When appreciated, it is usually heard following and more medial to the mitral opening snap.

Diagnostic Approach

Useful diagnostic studies include chest radiography, ECG, and echocardiography with Doppler evaluation. Right atrial (RA) enlargement is frequently evident on radiographs and is manifest on the ECG as a large peaked P wave in lead II (Fig. 38-2). Because of the increased RA pressure, atrial fibrillation is often present.

Echocardiography typically reveals thickened tricuspid leaflets, decreased mobility, scarred chordae, and sometimes doming, if the tricuspid valve leaflets remain pliable. Carcinoid heart disease is associated with a distinctive morphology of a thickened tricuspid valve that is narrowed and fixed in the open position. Doppler evaluation allows estimation of the diastolic pressure gradient by the modified Bernoulli equation. Cardiac catheterization is generally not necessary for the diagnosis of tricuspid stenosis, but when performed it calls for separate, simultaneous catheters in the right atrium and ventricle. If cardiac output is low, tricuspid gradients may also be low and are not adequately evaluated with use of a catheter pullback. Clinically significant tricuspid stenosis is usually associated with a valve area 1.5 cm^2 or less.

Management and Therapy

Initial treatment of tricuspid stenosis includes diuretics and nitrates to relieve venous congestion. Refractory cases have traditionally required open tricuspid valve repair or replacement, and concomitant mitral valve disease has primarily determined the indication and timing for surgery. A surgical approach may also be indicated for debulking of obstructive tumors or myxoma. However, while no randomized trials are available given the relatively low prevalence of this condition, published studies do suggest that percutaneous techniques are effective and safe, either as therapy for isolated tricuspid stenosis or for combined mitral and tricuspid disease, and referral to experienced centers should be considered. Percutaneous therapy should generally not be undertaken, however, if there is more than mild associated tricuspid regurgitation, as is often the case.

TRICUSPID REGURGITATION

Etiology and Pathogenesis

Tricuspid regurgitation may be due to primary disease of the valve apparatus or diseases causing pulmonary hypertension with secondary annular dilatation. Secondary tricuspid regurgitation is seen in any condition associated with increased pulmonary artery pressures, and is the predominant cause of tricuspid regurgitation. The most common secondary causes are left ventricular failure, mitral regurgitation, mitral stenosis, primary pulmonary disease, and primary pulmonary hypertension. The

Box 38-1 Differential Diagnosis of Acquired Tricuspid Stenosis

RA myxoma causing RV inflow obstruction
Metastatic disease causing RV inflow obstruction
Bacterial endocarditis of pacemaker leads or prosthetic valves
Congenital stenosis or atresia

RA, right atrial; RV, right ventricular.

rare causes of primary tricuspid regurgitation include rheumatic heart disease, myxomatous disease (prolapse), infective or marantic endocarditis, carcinoid heart disease, iatrogenic injury during endomyocardial biopsy or placement of pacemaker or defibrillator leads, and trauma.

Clinical Presentation

Symptoms are often due to associated left-sided heart disease or pulmonary disease. Prominent signs and symptoms of right-sided heart failure suggest tricuspid regurgitation as a component. A patient will occasionally present with a pulsatile sensation in the neck. Endocarditis or carcinoid syndrome may be associated with characteristic systemic symptoms.

Jugular venous pressure is usually increased, and there is a prominent *cv* wave produced by regurgitant flow into the right atrium. The typical murmur is holosystolic and located at the left sternal edge or subxiphoid area. The murmur is generally of very low intensity, and indeed may be absent even in the presence of severe regurgitation. Augmentation of the murmur with inspiration (due to increased venous return) helps distinguish tricuspid from mitral regurgitation. When severe RV enlargement is present, a right-sided S_3 may be appreciated, which will also be accentuated with inspiration.

Diagnostic Approach

Chest radiography often reveals RV enlargement manifested as filling of the retrosternal space. Dilation of the right ventricle often causes incomplete or complete right bundle branch block, seen on the ECG.

Doppler echocardiography is helpful in evaluating tricuspid regurgitation. Two-dimensional echocardiography evaluates the structure of the valvular apparatus and size of the right atrium and ventricle. Pulse-wave or color flow Doppler reveals the presence, direction, and magnitude of the regurgitant jet.

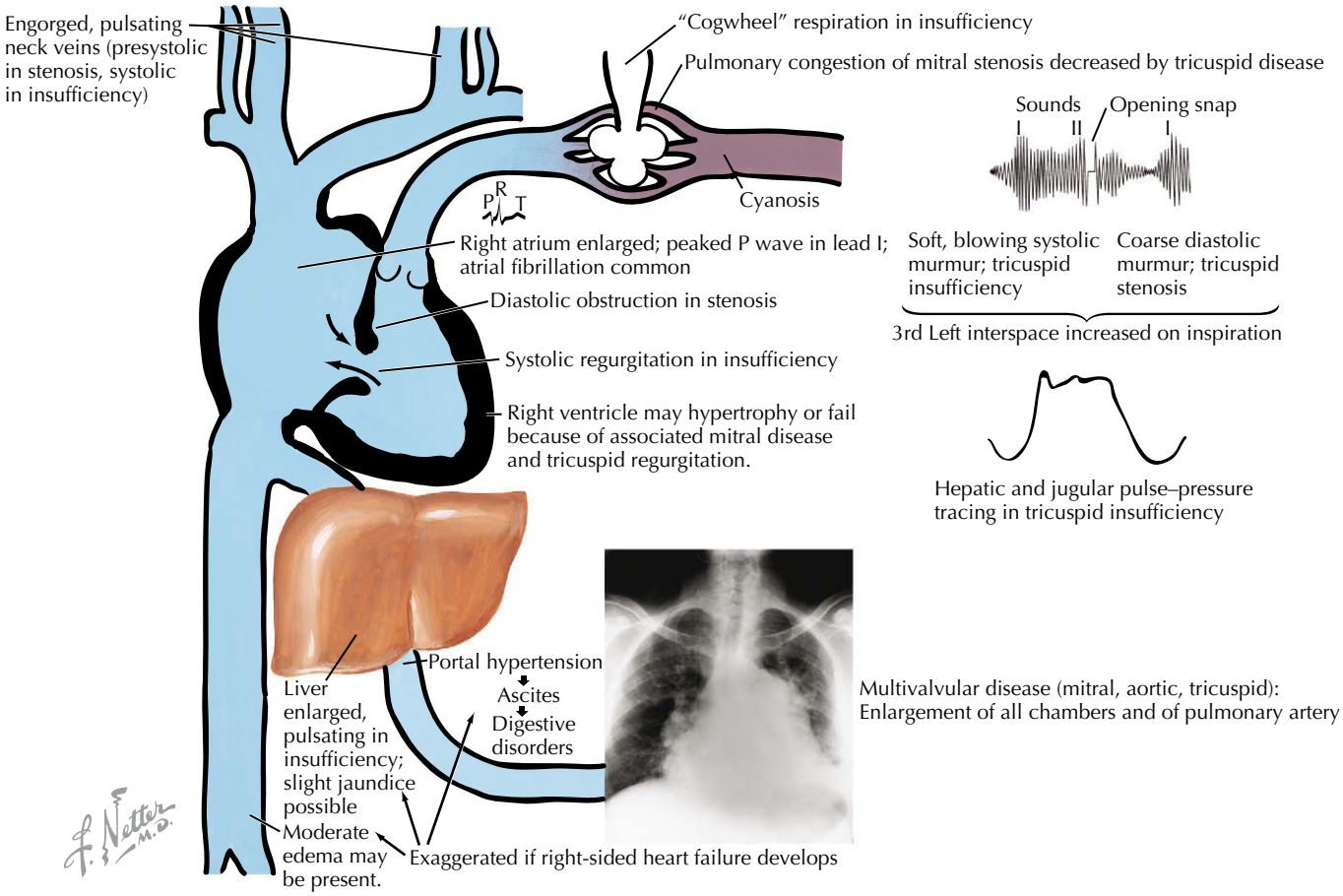


Figure 38-1 *Tricuspid stenosis and/or insufficiency.*

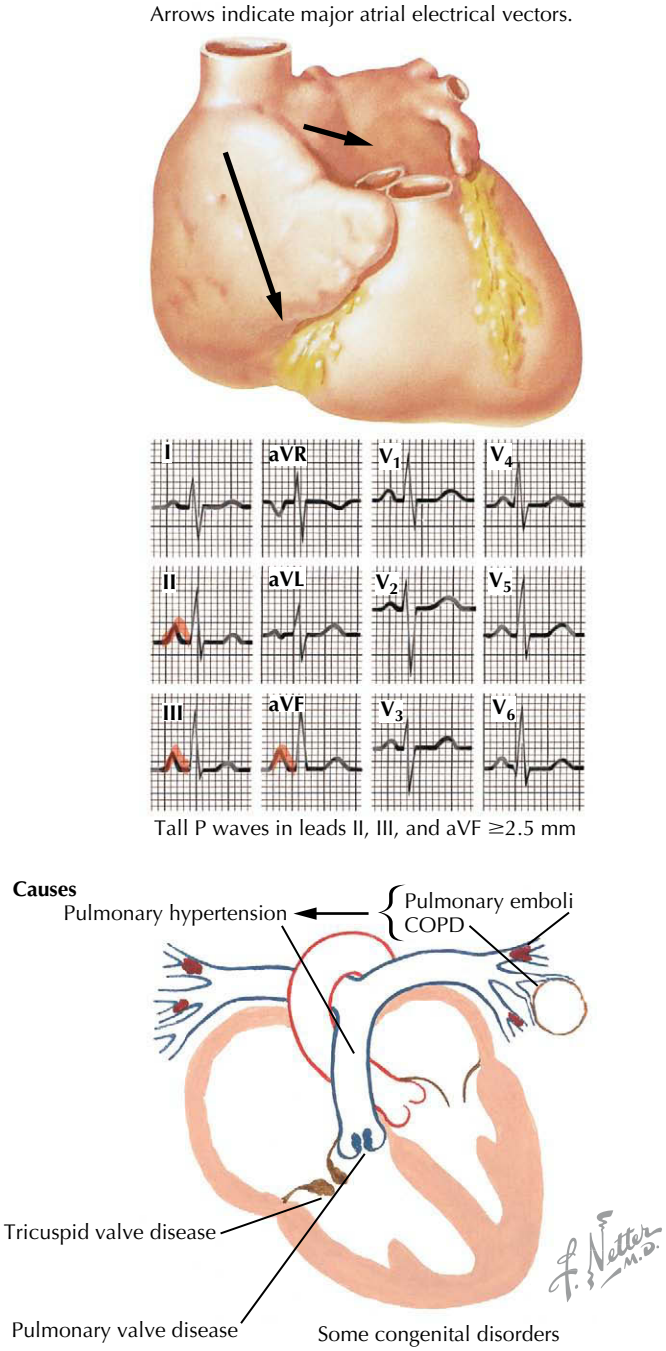


Figure 38-2 *Right atrial enlargement.* COPD, chronic obstructive pulmonary disease.

Severe regurgitation is generally associated with systolic flow reversal in the hepatic veins and a vena contracta width (the narrowest portion of the regurgitant jet) greater than 0.7 cm. Finally, continuous-wave Doppler and the modified Bernoulli equation can be used to estimate the RV and pulmonary artery systolic pressures. In tricuspid regurgitation, the gradient between the right ventricle and the right atrium during systole equals four times the square of the velocity. This gradient is then added to the estimated RA pressure (the jugular venous pressure) to estimate RV systolic pressure. In the absence of pulmonic stenosis, this also equals pulmonary systolic pressure. It is important to recognize that this calculation estimates the severity of the pulmonary hypertension, not the volumetric severity of the tricuspid regurgitation itself.

Management and Therapy

The mainstay of therapy for tricuspid regurgitation is treatment of the condition causing pulmonary hypertension. Diuretics may be useful for refractory fluid retention. Tricuspid annuloplasty, generally including placement of a semirigid prosthetic valvuloplasty ring, is occasionally necessary for patients whose condition is refractory to medical therapy. More commonly it is performed at the time of operation for concurrent left-sided valvular disease. In this circumstance, tricuspid annuloplasty should be performed in patients with severe tricuspid regurgitation. If the left-sided disease is mitral valve prolapse, however, even mild tricuspid regurgitation should be repaired, because myxomatous involvement often leads to progressive regurgitation. Rarely, tricuspid valve replacement is necessary, and in this circumstance bioprostheses are favored because the tricuspid valve may be relatively prone to thrombosis.

PULMONIC STENOSIS

Etiology and Pathogenesis

RV outflow obstruction may be subvalvular, valvular, or supravalvular (Fig. 38-3). Both the subvalvular and the supravalvular forms of RV outflow obstruction are usually associated with other congenital heart disease, as discussed in Section VIII. True valvular pulmonic stenosis, however, usually occurs as an isolated congenital defect. In addition, it may occur as the sole cardiac abnormality in patients with Noonan's syndrome. Rarely, pulmonic stenosis is due to rheumatic disease, endocarditis, or carcinoid syndrome.

Clinical Presentation

Patients with pulmonic stenosis are often asymptomatic. Patients may reach the fourth through sixth decades of life with significant pressure gradients across the pulmonic valve but with no symptoms and no evidence of right-sided heart failure. If right-sided heart failure does develop, abdominal swelling, peripheral edema, abdominal discomfort, and fatigue may be present. Patients seldom present with chest pain or exertional syncope.

The physical examination typically reveals a mid systolic crescendo-decrescendo murmur at the left sternal edge. Often, an associated ejection click, which usually decreases with inspiration, is present. P_2 is soft and delayed, producing a widely split S_2, but one that does narrow with appropriate physiologic changes (unlike the fixed, widely split S_2 present in patients with an atrial septal defect). Occasionally, a right-sided S_4 is appreciated at the left sternal border. An RV lift may also be present. If RV failure is present, there may be peripheral edema, hepatomegaly, abdominal swelling, and jugular venous distention with a prominent *a* wave.

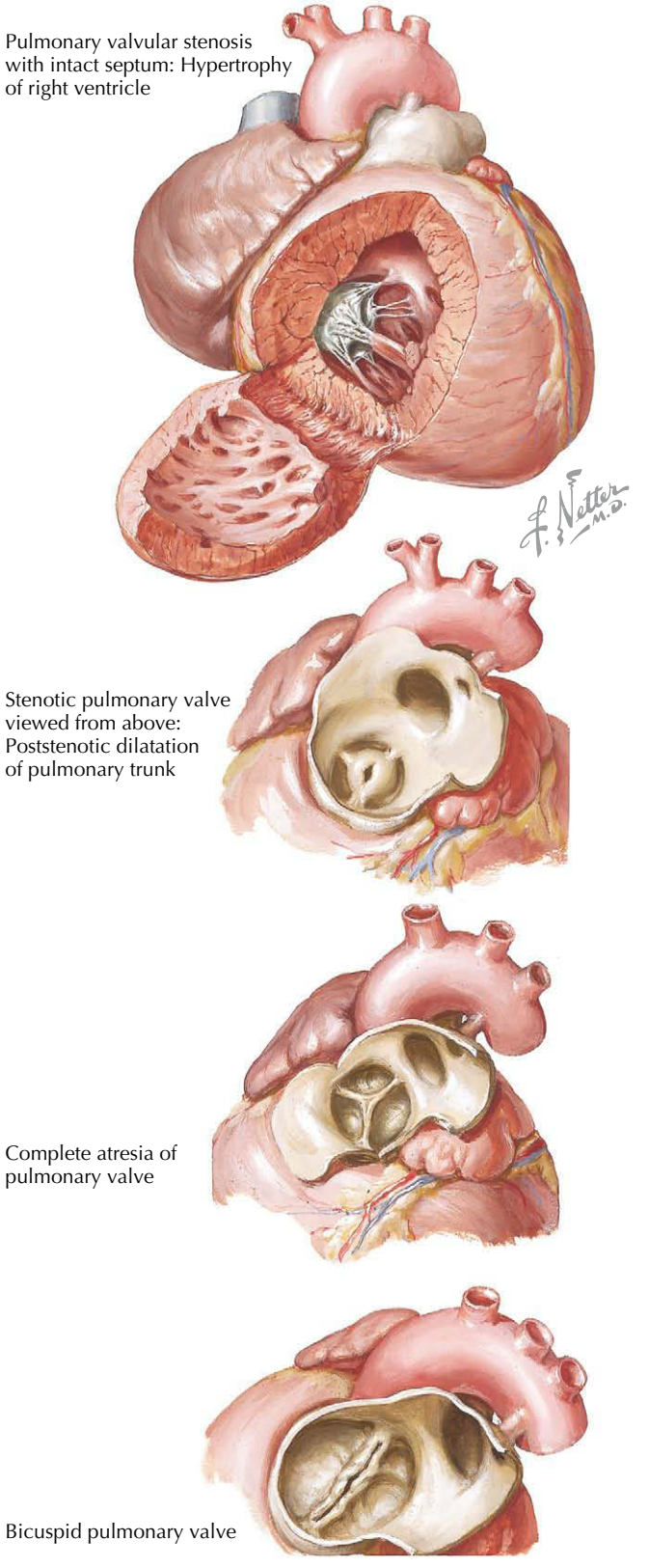


Figure 38-3 *Pulmonary valvular stenosis and atresia.*

Diagnostic Approach

Electrocardiography may be normal with mild-to-moderate stenosis, but in more severe cases will often reveal right-axis deviation, RA enlargement, and RV hypertrophy. A complete or incomplete right bundle branch block is sometimes present, although patients with Noonan's syndrome characteristically have a left bundle branch block. Chest radiography reveals poststenotic dilatation of the pulmonary artery but diminished peripheral pulmonary vascular markings. RV hypertrophy and enlargement are highly variable.

Echocardiography with Doppler evaluation is useful for establishing the diagnosis and assessing therapy. Morphologic assessment is best performed with the parasternal short-axis and subcostal views and will generally reveal thickened but pliable leaflets with restricted motion and doming. Occasionally, patients will have more severe thickening with severely dysplastic valves. This is important to recognize, because such patients are not well-suited to percutaneous valvuloplasty. Transesophageal echocardiography is not usually necessary but can be performed if a transthoracic study fails to provide an adequate assessment. The right ventricle may be normal, particularly in childhood, but stenosis of long duration, greater severity, or both is usually associated with RV hypertrophy and enlargement. Paradoxical motion of the interventricular septum is often present. Continuous-wave Doppler evaluation is highly reliable in establishing the gradient across the pulmonic valve. Cardiac catheterization is usually not necessary but may be performed if Doppler studies are suboptimal or immediately before (and after) planned balloon valvuloplasty.

Management and Therapy

Adult patients with mild pulmonic stenosis generally do well and require no intervention. More severe disease is appropriately treated with balloon valvuloplasty, which is highly effective. The 2006 American College of Cardiology/American Heart Association guidelines recommend percutaneous valvuloplasty in symptomatic young adults with a systolic gradient greater than 30 mm Hg and asymptomatic patients with a systolic gradient greater than 40 mm Hg.

PULMONIC REGURGITATION

Etiology and Pathogenesis

A minor degree of pulmonic valve regurgitation evident by Doppler echocardiography is an essentially normal finding present in many healthy individuals. Moderate or severe regurgitation is usually secondary to severe pulmonary hypertension (either primary or secondary), pulmonary artery dilatation, or both. Rarely, it is secondary to endocarditis, carcinoid syndrome, rheumatic heart disease, trauma, Marfan's syndrome, or congenital valvular abnormalities.

Clinical Presentation

Accordingly, the dominant symptoms in pulmonic regurgitation are usually those of the underlying disease process. Patients

without severe underlying disease are often asymptomatic. However, patients with severe pulmonic regurgitation may ultimately have typical symptoms and signs of right-sided heart failure.

The characteristic physical finding is a decrescendo diastolic murmur, loudest at the left third and fourth intercostal spaces, which increases with inspiration. S_2 is usually widely split with an accentuated pulmonic component if there is significant pulmonary hypertension. In the absence of pulmonary hypertension, the murmur is low-pitched. The more common high-pitched murmur associated with a prominent P_2 in the presence of severe pulmonary hypertension is the classic Graham Steell murmur. There is occasionally an associated crescendo-decrescendo systolic murmur from increased flow across the valve, or a holosystolic murmur due to coincident tricuspid regurgitation. Jugular venous distention and signs of right-sided heart failure may be apparent.

Diagnostic Approach

The findings on ECG and chest radiography are generally those of the underlying disease and of RV hypertrophy and dilatation. Echocardiography with Doppler can identify and grossly quantitate pulmonic regurgitation and assess the size and contractility of the right ventricle. Regurgitation is considered severe when the color Doppler jet fills the RV outflow tract and there is a dense continuous-wave Doppler signal associated with rapid deceleration.

Management and Therapy

Treatment is generally directed at the underlying disease process. Rarely, valve surgery will be necessary for severe regurgitation and progressive right heart failure. Occasionally, valve surgery will be necessary when the valve is damaged at the time of other surgery on the RV outflow tract, as in tetralogy of Fallot. In the absence of other indications, pulmonic regurgitation does not require endocarditis prophylaxis for dental procedures.

FUTURE DIRECTIONS

The treatment of pulmonic and tricuspid valve disease will continue to benefit from the steady evolution of percutaneous techniques. Pulmonic valvuloplasty was introduced in the early 1980s. Follow-up studies confirm the continued long-term effectiveness of a percutaneous approach. It is clear that most patients have a subsequent further decrease in the RV outflow gradient due in part to resolution of infundibular hypertrophy. This success has led to a generally lower threshold for intervention with each iteration of guidelines. With respect to tricuspid stenosis, valvuloplasty techniques that use multiple balloons or the newer Inoue balloon appear promising.

ADDITIONAL RESOURCES

American Heart Association [home page on the Internet]. <http://www.americanheart.org>; Accessed 05.03.10.

Provides access to the most recent guidelines for the management of valvular heart disease, including those developed jointly with the American College of Cardiology. From the home page, select "For Healthcare Professionals," then "Statements, Guidelines, and Clinical Updates."

American Society of Echocardiography [home page on the Internet]. <http://www.asecho.org>; Accessed 05.03.10.

Given the importance of echocardiographic and Doppler techniques in the assessment of valvular disease, this site is helpful in providing expert consensus guidelines on the optimal evaluation of lesion severity.

European Society of Cardiology [home page on the Internet]. <http://escardio.org>; Accessed 05.03.10.

Provides the latest guidelines from a consensus of European authorities.

EVIDENCE

Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2006;48:e1–148.

This joint American College of Cardiology/American Heart Association report outlines the appropriate diagnosis and management of valvular heart disease according to an assembled panel of experts. It is thoroughly referenced, and the level of evidence is cited for the recommendations.

Rao PS. Percutaneous balloon pulmonary valvuloplasty: state of the art. *Catheter Cardiovasc Interv.* 2007;69:747–763.

This review article illustrates the ongoing technical advances in balloon valvuloplasty that have led to recommendations for lower thresholds for intervention.

Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the task force on the management of valvular heart disease of the European Society of Cardiology. *Eur Heart J.* 2007;28:230–268.

Provides a similar consensus guideline for the management of valvular heart disease from a European perspective.

Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.

Provides a critical review of echocardiographic and Doppler techniques used to evaluate the severity of regurgitant valvular lesions.

Infective Endocarditis

Kristine B. Patterson and Cam Patterson

39

Infective endocarditis (IE) is an infection typically of one of the cardiac valves or elsewhere on the endocardial surface of the heart and implies the presence of microorganisms in the lesion. Despite advances in medical and surgical interventions, IE continues to be associated with high morbidity and mortality, especially given the evolution of antimicrobial resistance. Early diagnosis, prompt and appropriate antimicrobial therapy, echocardiographic evaluation, and timely surgical intervention are cornerstones of successful management.

ETIOLOGY AND PATHOGENESIS

The three main bacterial causes of IE are streptococci, staphylococci, and enterococci. *Staphylococcus aureus* has now replaced viridans group streptococci as the leading cause as a result of the increased frequency of oxacillin-resistant *S. aureus* in tertiary care centers and community-acquired infections. IE most often occurs in the setting of an already damaged valve surface or on artificial valves. This provides a suitable site for bacterial colonization and adherence, allowing replication to a critical mass, which allows a mature infected vegetation to form.

CLINICAL PRESENTATION

Any organ system can be involved in patients with IE, and thus the clinical presentation is highly variable. Four processes contribute to IE's clinical manifestations: (1) the infectious process on the valve causing local intracardiac complications (e.g., perivalvular abscess, incompetent valve, conduction disturbances, congestive heart failure [CHF]) (Fig. 39-1); (2) vascular phenomena (e.g., septic pulmonary or arterial emboli, mycotic aneurysm, intracranial hemorrhage); (3) bacteremic seeding of remote sites (e.g., osteomyelitis, psoas or perirenal abscess) (Fig. 39-2); and (4) immunologic phenomena (e.g., glomerulonephritis, Osler's nodes, Roth's spots, positive rheumatoid factor, and antinuclear antibodies).

The presentation of IE is straightforward when the classic signs and symptoms are present: fever, bacteremia or fungemia, valvular incompetence, peripheral emboli, and immune-mediated vasculitis as is seen in subacute IE. However, acute IE may evolve too quickly for immunologic phenomena to develop, and patients may present only with fever or severe manifestations such as those related to valve incompetency. In both acute and subacute IE, fever is the most common presenting symptom.

Frequently the diagnosis can be made clinically if a careful physical examination is performed. Attention should be given to the conjunctiva (hemorrhages), dilated fundoscopic exam (Roth's spots), complete cardiovascular examination (new or changing murmur, especially aortic, mitral or tricuspid regurgitation, and signs of CHF), splenomegaly, and extremities (splinter hemorrhages, septic emboli, Janeway's or Osler's nodes) (Fig. 39-3). The comprehensive physical examination can be complemented by several nonspecific, yet suggestive laboratory studies. Findings in IE include (but are not limited to) anemia, thrombocytopenia, leukocytosis, active urinary sediment, elevated sedimentation rate, hypergammaglobulinemia, positive rheumatoid factor, antinuclear antibodies, hypocomplementemia, and false-positive Venereal Disease Research Laboratory and Lyme disease serology.

DIFFERENTIAL DIAGNOSIS

Almost any disseminated, severe bacterial, fungal, mycobacterial, viral, parasitic, or spirochete infection can manifest some features of IE. Several connective tissue or autoimmune diseases and hematologic malignancies can also mimic IE. By utilizing the expertise of the microbiologist and the cardiologist early in the process, a definitive positive diagnosis alerts the clinician to any potential complications and therapeutic interventions. Conversely, a negative echocardiogram allows alternative diagnoses to be explored more rapidly.

DIAGNOSTIC APPROACH

Since 1994, the "Duke criteria" has been the diagnostic strategy most consistently used in stratifying patients suspected of having IE into "definite," "possible" or "rejected" categories. These criteria have been modified to include newer diagnostic methods. Although the modified Duke criteria can provide a primary diagnostic schema, they should not replace clinical judgment.

Microbiology

The first definitive test should be at least three sets of routine blood cultures during the first 24 hours of observation. More cultures may be necessary if the patient received antibiotics in the preceding weeks. Almost 50% of culture-negative IE can be attributed to antibiotic use before obtaining cultures. Organisms such as the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) and *Brucella* are slow growing and require extended incubation of cultures (4 weeks). Special culture techniques or media may be required for some organisms (e.g., *Legionella*). Genetic sequencing is being used more frequently for organisms that have been difficult to identify through traditional microbiologic methods. Blood culture results are negative in more than 50% of fungal endocarditis cases. Serologic studies are frequently necessary to diagnose Q fever, brucellosis, legionellosis, and psittacosis and are now included as a surrogate marker in lieu of positive blood cultures for diagnosis.

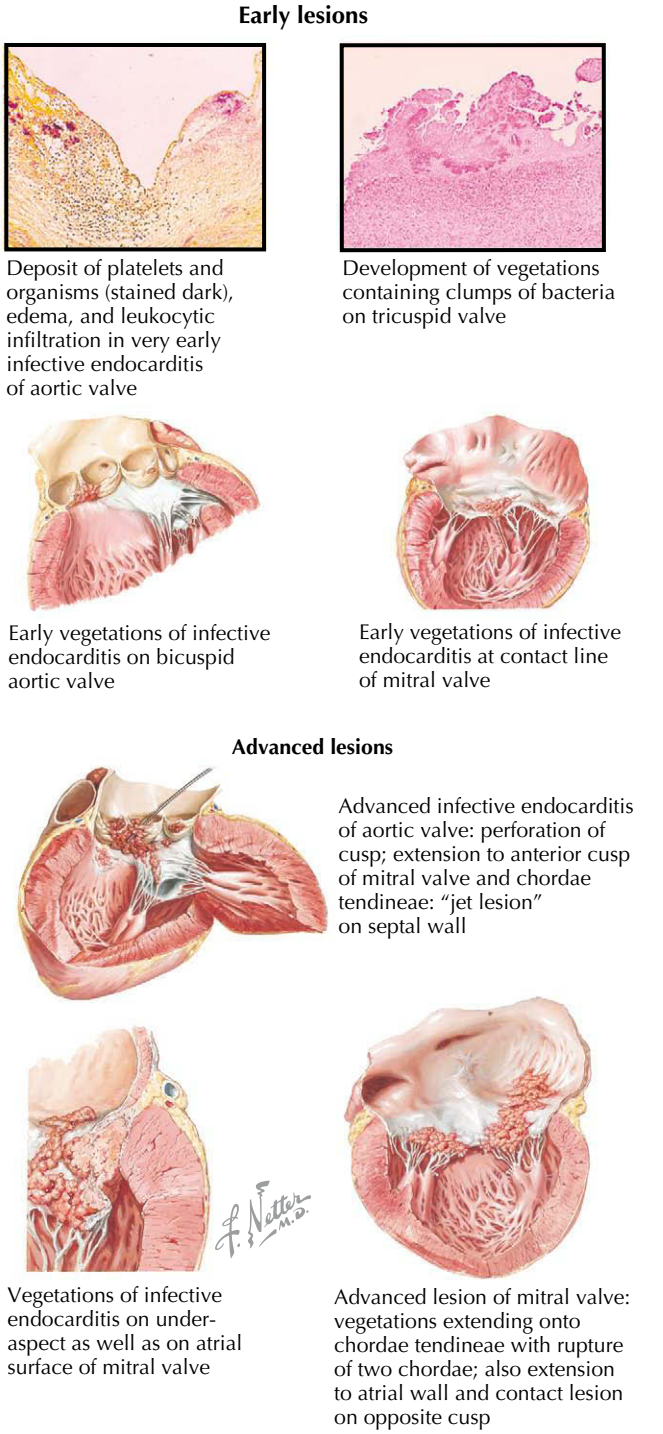


Figure 39-1 *Infective endocarditis.*

Specific Pathogens

STAPHYLOCOCCAL ENDOCARDITIS

Staphylococci are now the most common cause of IE, especially *S. aureus* native valve IE. Increasing rates of infection with methicillin-resistant *S. aureus* are being reported. The course of *S. aureus* infection is typically fulminant with myocardial and valve-ring abscesses and widespread metastatic infection common. Thirty percent of patients experience neurologic manifestations. IE caused by oxacillin-resistant *S. aureus* is particularly common in injection drug users or patients with nosocomial infection. Coagulase-negative staphylococci are an important cause of prosthetic valve endocarditis (PVE). Right-sided IE is more commonly seen in injection drug users and may be either sensitive or resistant to oxacillin.

STREPTOCOCCAL ENDOCARDITIS

Streptococci are now the second most common causative agents of IE, with the viridans group streptococci the most common subgroup. The cure rate exceeds 90%, but complications occur in approximately 30% of cases.

Streptococcus pneumoniae IE is rare and usually involves the aortic valve. It frequently has a fulminant course and is often

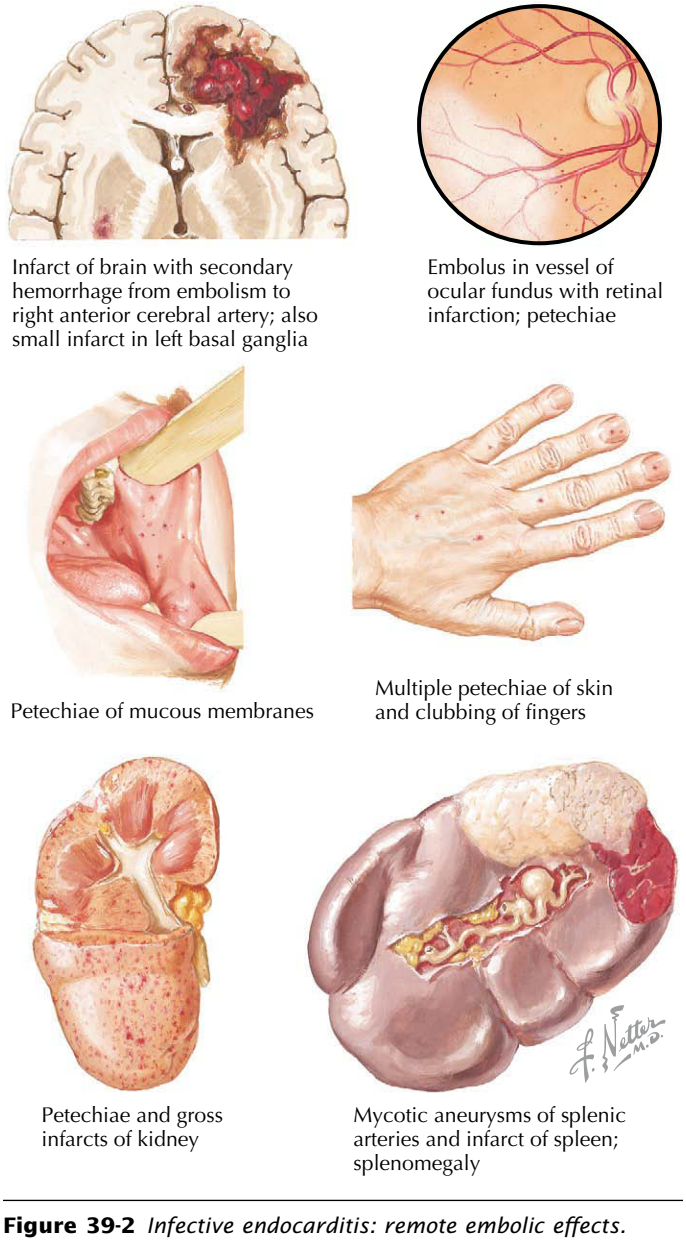


Figure 39-2 *Infective endocarditis: remote embolic effects.*

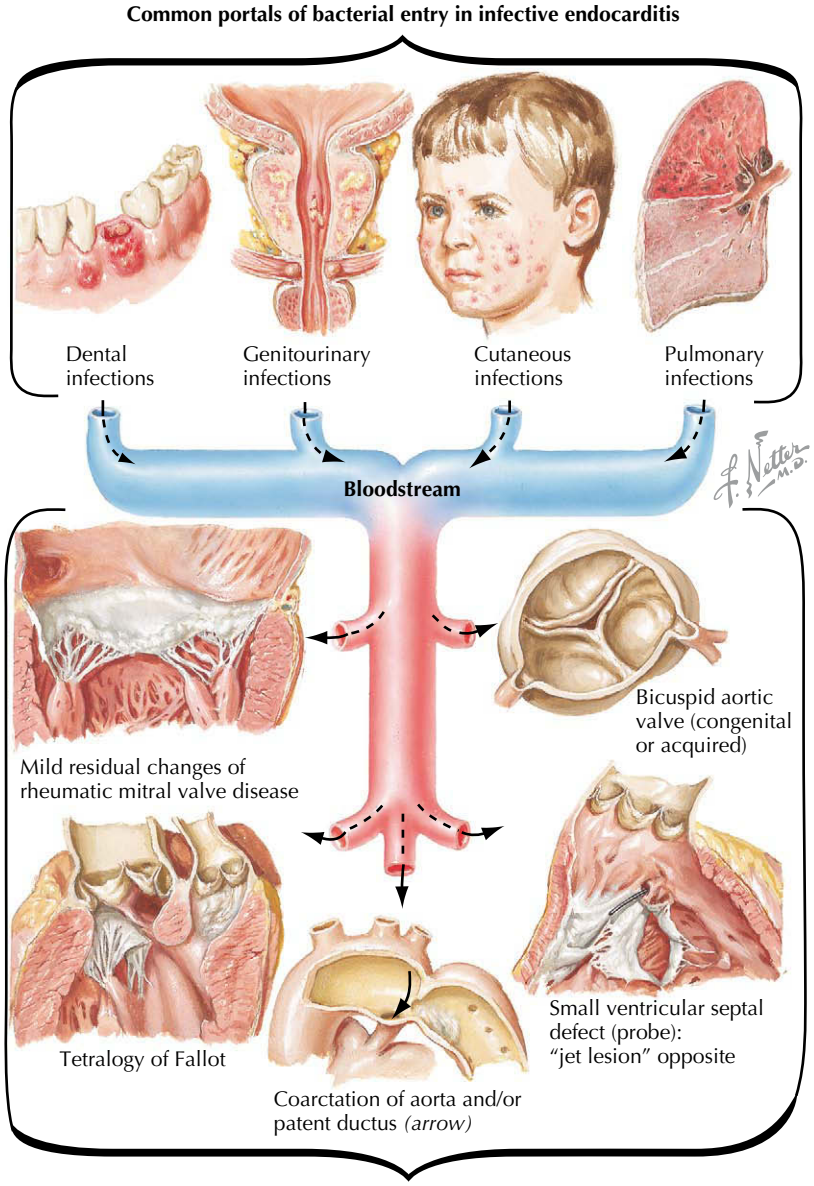


Figure 39-3 *Most frequent origins of infective endocarditis in nonimmunocompromised individuals.*

associated with perivalvular abscess, pericarditis, and concurrent meningitis. Penicillin resistance is increasing. Valve replacement may be beneficial in preventing early death.

S. anginosus has a predilection to disseminate and form abscesses, and may require a longer course of therapy compared with other α-hemolytic streptococci. *S. bovis* IE should prompt a colon malignancy evaluation.

IE due to nutritionally variant streptococci typically is indolent in onset and associated with previous heart disease. Special media are required for microbiologic identification. Therapy is difficult because of systemic embolization and frequent relapse.

ENTEROCOCCAL ENDOCARDITIS

Enterococcus faecalis and *E. faecium* IE usually affects older men after genitourinary tract manipulation or younger women after an obstetric procedure. Classic peripheral manifestations are uncommon. The rate of penicillin-resistant enterococcal infection in tertiary-care centers is rapidly increasing.

GRAM-NEGATIVE ENDOCARDITIS

Persons using injection drugs, prosthetic valve recipients, and patients with cirrhosis are at increased risk for gram-negative endocarditis. CHF is common.

Salmonella IE usually involves abnormal valves and is associated with significant valvular destruction, atrial thrombi, myocarditis, and pericarditis. Valve replacement after 7 to 10 days of antimicrobial therapy is typically required.

Pseudomonas IE is almost exclusively seen in injection drug users and often affects normal valves. Embolic phenomena, inability to sterilize valves, neurologic complications, ring and

annular abscesses, splenic abscesses, bacteremic relapses, and progressive heart failure are common. Early surgical intervention is recommended for left-sided involvement.

Neisseria gonorrhoeae rarely causes IE and typically follows an indolent course, with aortic valve involvement, large vegetations, valve-ring abscesses, CHF, and nephritis.

HACEK ENDOCARDITIS

The gram-negative bacilli of the HACEK group account for 5% to 10% of cases of native valve IE. All are fastidious and may require 3 weeks or longer for primary isolation. HACEK endocarditis is more common in patients who have dental infections or injection drug users who contaminate the injection with saliva.

FUNGAL ENDOCARDITIS

Candida and *Aspergillus* species are the most common cause of fungal IE. *Candida* species are more common in persons with central venous catheters or receiving parenteral nutrition. Both can be seen following prosthetic valve insertion. Other *Candida* species, *C. parapsilosis* and *C. tropicalis*, predominate in injection drug users. Blood culture results are usually negative in *Aspergillus* IE. Surgical intervention is almost always required, especially with prosthetic valves, following a course of antifungal agents. Lifelong antifungal suppressive therapy is frequently considered.

CULTURE-NEGATIVE ENDOCARDITIS

Culture-negative IE is common. Causes include recent administration of antimicrobial agents; slow growth of fastidious organisms, such as the HACEK group; fungal endocarditis; *Coxiella* species; intracellular parasites such as *Bartonella* or *Chlamydia* species; and noninfectious endocarditis.

PROSTHETIC VALVE ENDOCARDITIS

PVE occurs in up to 10% of patients during the lifetime of the prosthesis. Early PVE (within 60 days after implantation) usually results from valve contamination during the perioperative period. Late PVE (after 60 days) results from transient bacteremia. Clinical manifestations are similar to those of native valve IE; however, new or changing murmurs are more common. Persistently positive blood culture results and valvular dysfunction by echocardiography are the hallmarks. Transesophageal echocardiography (TEE) is recommended for diagnosis and assessment of complications such as perivalvular abscess and regurgitation. Coagulase-negative staphylococci are the dominant cause of PVE in the first year. After 1 year, the causative organisms are similar to those of native valve IE. Therapy is by necessity aggressive. Rifampin and gentamicin can be added to nafcillin or oxacillin for methicillin-sensitive *S. aureus* or to vancomycin for methicillin-resistant *S. aureus*. For culture-negative PVE, vancomycin and gentamicin should be used to provide broad bactericidal coverage.

Echocardiography

Echocardiography is an essential tool in the diagnosis and management of patients with IE and should be performed in all patients with suspected and confirmed IE (Fig. 39-4). An oscillating vegetation or mass, annular abscess, prosthetic valve dehiscence, and new regurgitation are all major Duke criteria and, as such, confirm IE. Transthoracic echocardiography (TTE) is rapid, noninvasive, and has excellent specificity for vegetations (98%); however, sensitivity is less than 60%. TTE should be performed initially when the suspicion is low. TEE allows imaging of very small vegetations and is the procedure of choice for assessing the pulmonic valve, prosthetic valves, and perivalvular areas for abscesses. TEE has a substantially higher sensitivity (76% to 100%) and specificity (94%) than TTE for perivalvular extension of infection. TEE should be obtained initially when clinical suspicion is high, especially when PVE is suspected or when images obtained by TTE will be poor (i.e., severe pulmonary disease or obesity). If clinical suspicion of IE persists after an initially negative TEE, a repeat study is warranted within 7 to 10 days. The combination of a negative TEE and a negative TTE confers a 95% negative predictive value.

MANAGEMENT AND THERAPY

Optimum Treatment

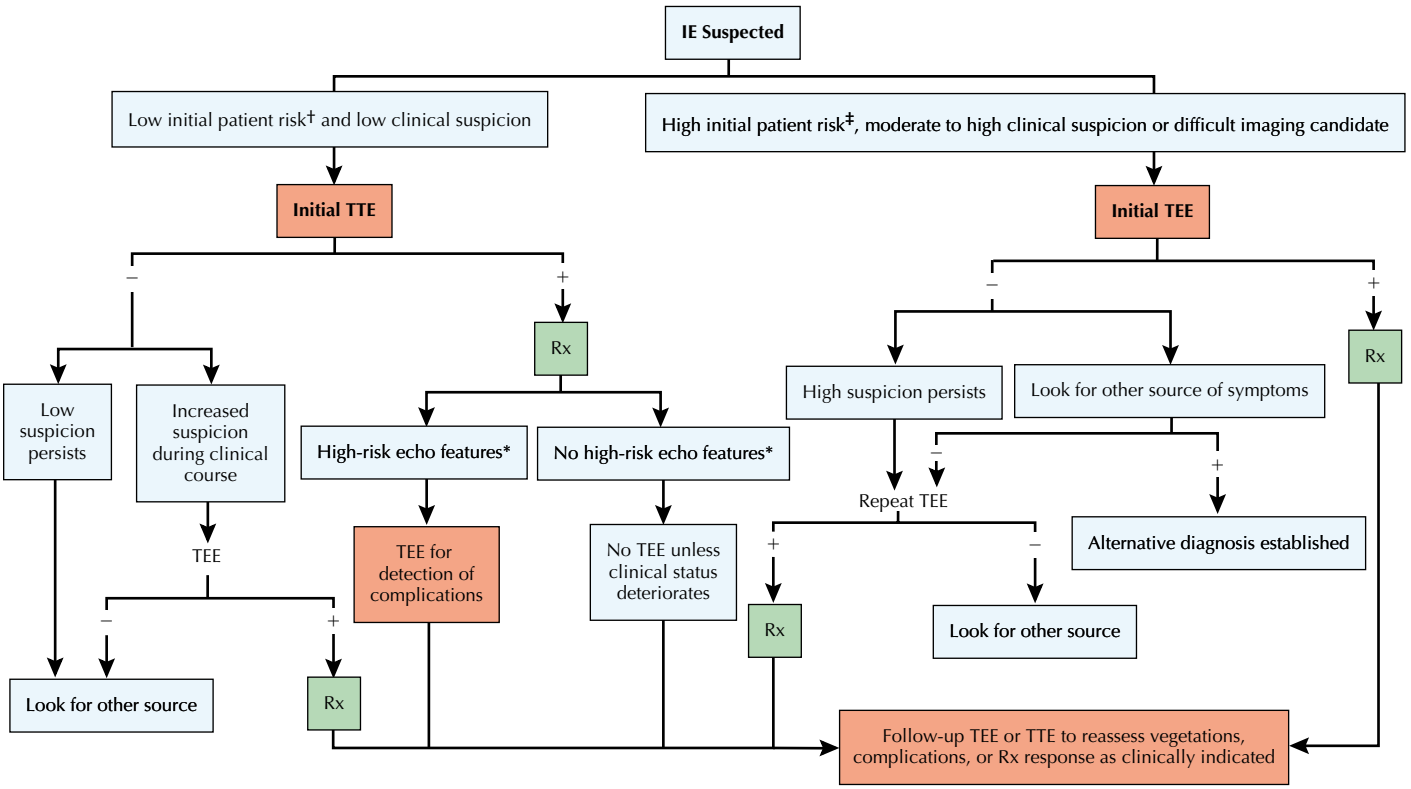
ANTIMICROBIAL THERAPY

After initial empiric therapy, antimicrobial agents should be selected based on susceptibility testing of the isolated causative microbe (Table 39-1). Prolonged administration of antimicrobial agents is required, almost always via the parenteral route. Bactericidal agents or antibiotic combinations that produce synergistic, rapidly bactericidal effects are the agents of choice. Although serum antibiotic levels are broadly useful, in particular if aminoglycosides are part of the therapeutic regimen, it is important to monitor serum concentrations carefully to avoid toxicity. Blood culture specimens should be obtained early in therapy to ensure eradication of the bacteremia, and throughout therapy when persistent or recurrent fever is present. Patients with IE complicated by cardiac arrhythmias and CHF require close observation in an intensive care unit. Anticoagulation is contraindicated in patients with native valve IE.

Many of the newer antimicrobial agents may not have been specifically evaluated in IE patients. Daptomycin, a cyclic lipopeptide antibiotic, is bactericidal in vitro against most gram-positive bacteria, especially oxacillin-sensitive and -resistant *S. aureus*. Recently, daptomycin was shown to be equivalent to standard therapy for bacteremia and right-sided IE. However, there were too few subjects with left-sided IE to definitively determine superiority.

ECHOCARDIOGRAPHY

After the initial diagnosis, echocardiography is useful in managing individuals, identifying those at high risk for complications and assessing the need for surgery. Findings that indicate



*High-risk echocardiographic features include large and/or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction.
†For example, a patient with fever and a previously known heart murmur and no other stigmata of IE.
‡High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis.

Figure 39-4 *Echocardiography in the diagnosis and management of infective endocarditis (IE).* Rx, antibiotic treatment for endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. From Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation.* 1998;98:2936–2948.

increased risk of complications and/or the need for surgical intervention include:

- Persistent vegetation after embolization
- Vegetations larger than 10 mm, especially those on the anterior mitral leaflet (greater risk for embolization)
- Vegetations that increase in size while on therapy
- Acute aortic or mitral insufficiency with CHF
- CHF unresponsive to therapy
- Valve perforation or rupture
- Large abscess or abscess unresponsive to therapy
- New heart block
- Valvular dehiscence

CARDIAC SURGERY

Appropriate, timely surgical intervention can reduce morbidity and mortality substantially. Relatively substantiated indications for surgical intervention include:

- Refractory CHF
- More than one serious systemic embolic episode
- Fungal IE, especially involving a prosthetic valve
- IE with antibiotic-resistant bacteria or ineffective antimicrobial therapy
- Persistent positive blood cultures following 1 week of antibiotic therapy
- Left-sided IE with *Pseudomonas* or *Salmonella* species
- Prosthetic valve IE 12 months or less after initial replacement
- Echocardiographic findings listed above

Avoiding Treatment Errors

Effective treatment of IE requires a multidisciplinary approach with input from infectious disease specialists, cardiologists, and cardiothoracic surgeons. Although guidelines and criteria such as the Duke criteria have been established, treatment should be individualized based on clinical judgment.

After a person is put on appropriate antimicrobial therapy, it is imperative to ensure that repeat blood cultures are negative. If not it is essential to reevaluate therapy and consider the possibility of a remote abscess or other complication. Blood cultures should be repeated near the end of antimicrobial therapy and shortly after completing therapy to ensure

Table 39-1 Antimicrobial Therapy for Infective Endocarditis

Etiology	Antimicrobial Therapy*,†,‡,‖,¶
Viridans streptococci and *S. bovis* penicillin-susceptible (MIC <0.1 μg/mL)	Penicillin G 12–18 million U/24 hr either continuously or q4h for 4 wk *or* Ceftriaxone 2 g IV once daily for 4 wk, *or* Penicillin G 12–18 million U/24 hr IV in six doses for 2 wk *with* gentamicin 1 mg/kg q8h for 2 wk, *or* Vancomycin 30 mg/kg/24 hr IV in two divided doses for 4 wk (recommended only for patients allergic to β-lactams)
Viridans streptococci and *S. bovis* relatively resistant to penicillin (MIC 0.1–0.5 μg/mL)	Penicillin G 24 million U/24 hr either continuously or q4h for 4 wk *with* gentamicin 1 mg/kg q8h for 2 wk (ceftriaxone 2 g IV once daily may be substituted for penicillin in patients with penicillin hypersensitivity not of the immediate type), *or* Vancomycin 30 mg/kg/24 hr IV in two divided doses for 4 wk (only recommended for patients allergic to β-lactams)
Enterococci (and viridans streptococci with penicillin MIC >0.5 μg/mL, nutrient variant viridans streptococci)§	Penicillin G 18–30 million U/24 hr either continuously or q4h *with* gentamicin 1 mg/kg IV q8h† for 4–6 wk, *or* Ampicillin 12 g/24 hr in six divided doses *with* gentamicin 1 mg/kg IV q8h for 4–6 wk, *or* Vancomycin 30 mg/kg/24 hr IV in two divided doses for 4–6 wk *with* gentamicin 1 mg/kg IV q8h for 4–6 wk (only recommended for patients allergic to β-lactams; cephalosporins are not acceptable alternatives for patients allergic to penicillins)
Staphylococci (penicillin-susceptible with MIC ≤1 μg/mL)	Penicillin G 24 million U/24 hr IV in six doses for 6 wk
Staphylococci (methicillin-susceptible, penicillin-resistant)	Nafcillin or oxacillin 2 g IV q4h for 6 wk *with* gentamicin 1 mg/kg IV q8h for 3–5 days,† *or* Cefazolin (or other first-generation cephalosporin) 2 g IV q8h for 6 wk *with* gentamicin 1 mg/kg IV q8h for 3–5 days
Staphylococci (methicillin-resistant)	Vancomycin 30 mg/kg/24 hr IV in two divided doses for 6 wk
HACEK microorganisms	Ceftriaxone 2 g IV once daily IV for 4 wk *or* Ampicillin-sulbactam 12 g/24 hr IV in four doses for 4 wk
Culture-negative (native valve)	Ampicillin-sulbactam 12 g/24 hr IV in four doses for 4–6 wk *plus* gentamicin 1 mg/kg q8h for 4–6 wk *or* Vancomycin 30 mg/kg IV in two doses for 4–6 wk *plus* gentamicin 1 mg/kg IV in three doses for 4–6 wk *plus* ciprofloxicin 1000 mg/24 hr PO in two divided doses or 800 mg/24 hr in two doses IV for 4–6 wk
Prosthetic valve endocarditis	Refer to 2005 American College of Cardiology/American Heart Association endocarditis guidelines

MIC, minimum inhibitory concentration.

*Antimicrobial doses are for adult patients with normal renal and hepatic function.

†Aminoglycosides are used for synergy for gram-positive infections.

‡When gentamicin is administered in multiple daily doses, the dose should be adjusted according to the patient's renal function to achieve a peak concentration of approximately 3 mg/L and a trough concentration of <1 mg/L.

‖Vancomycin doses should be adjusted according to the patient's renal function to achieve a peak concentration of 30 to 45 mg/L and a trough concentration of 10 to 15 mg/L.

¶Dosing of penicillin, nafcillin, and oxacillin is frequent and often problematic for home therapy patients. Because these drugs are stable for 24 hours at room temperature, they may be given via a pump that remains with the patient, requiring adjustment only once every 24 hours.

§Test infecting strain of *Enterococcus* for resistance to aminoglycosides. High-level resistance means loss of synergy, and thus aminoglycosides should not be used in these instances. Therapy should be prolonged to 8 to 12 weeks.

Adapted from Wilson WR, Karchmer AW, Dajani AS, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA. 1995;274:1706–1713, copyrighted 1995 American Medical Association; and Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy and management of complications. American Heart Association. Circulation. *2005;111:e394–e434.*

resolution, and a new baseline echocardiogram should be obtained. It is imperative to educate patients regarding signs of symptoms of IE. Often overlooked are the need for thorough dental evaluation and treatment for substance abuse.

PROPHYLAXIS

Antimicrobial prophylaxis is recommended for patients with increased risk of endocarditis due to underlying cardiac conditions who are undergoing invasive procedures likely to generate bacteremia. Detailed prophylaxis recommendations are available on the American Heart Association website.

FUTURE DIRECTIONS

Some clinicians believe that the size of the vegetation and other echocardiographic characteristics predict which patients are at risk for poor outcome and need early surgery. However, specific echocardiographic criteria have not been demonstrated. Future studies will help to determine whether echocardiographic

findings other than perivalvular or myocardial abscesses are added to the current list of indications for surgery.

ADDITIONAL RESOURCES

American Heart Association [home page on the Internet]. <http://www.americanheart.org>; Accessed 16.02.10.

Provides guidance in the management of other cardiac-related diseases.

Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation.* 1998;98:2936–2948.

Clearly outlines the global management of IE.

European Society of Cardiology. European Society for Cardiologist guidelines for infective endocarditis. <http://www.escardio.org/knowledge/guidelines/Guidelines_list.htm>; 2004 Accessed 16.02.10.

Reviews European guidelines, which differ from the Infectious Disease Society of America and AHA guidelines.

Schlant RC, Alexander RW, O'Rourke RA, et al. eds. *Hurst's the Heart.* 10th ed. New York: McGraw-Hill Inc; 2001.

Comprehensively reviews the management of IE from a cardiologist's perspective.

EVIDENCE

Fowler Jr VG, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med.* 2006;355:653–665.

Describes use of a newer generation antibiotic in resistant bacterial infections.

Infectious Diseases Society of America. American Heart Association infective endocarditis guidelines. <http://www.idsociety.org/Content.aspx?id=9088>; Accessed 16.02.10.

Publishes updated guidelines for the management of IE, an essential tool in managing these complicated patients.

Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 6th ed. New York: Churchill Livingstone; 2005.

Provides more specific guidance in the diagnosis and treatment of suspected and/or confirmed IE. Less common pathogens and complicated IE are comprehensively reviewed.

Percutaneous Catheter-based Therapy for Valvular Heart Disease

40

Thomas M. Bashore

Charles Dotter is credited with noting that the stenotic severity of a high-grade iliac lesion was lessened when a diagnostic catheter was passed through it. Early vascular efforts used progressively larger catheters to open the lesions by blunt dilatation. Eventually, this approach using progressively larger bougies was replaced by the use of elastic balloon-tipped catheters, first for peripheral vascular disease, then for coronary angioplasty. Reports from the National Heart, Lung, and Blood Institute (NHLBI) Registry, the Mansfield Balloon Catheter Registry, and large institutional experiences subsequently shaped the development of percutaneous balloon procedures for stenotic valvular lesions. Percutaneous valvuloplasty (or valvotomy) has now become the standard of care for the treatment of certain patients with congenital pulmonary valve and aortic valve stenosis and for a subset with rheumatic mitral stenosis. Recently, percutaneous valve replacement or repair has been proposed as a feasible advance in percutaneous therapies applicable to both stenotic and regurgitant valve lesions. It is anticipated that selected patients will be candidates for these novel approaches in the near future. This chapter is meant to provide an overview of all of these percutaneous therapeutic approaches to valvular heart disease.

PULMONARY VALVE STENOSIS

Pathophysiology

Pulmonary valve stenosis results from fusion of the valve cusps during mid- to late fetal development. The most common form of isolated right ventricular (RV) obstruction, pulmonary valvular stenosis, occurs in approximately 7% of individuals with congenital heart disease (see also Chapters 50 and 52). Pulmonary valve stenosis may be associated with significant RV hypertrophy and infundibular narrowing. The fusion of the valvular cusps produces a classic systolic "doming" appearance angiographically (Fig. 40-1). Tissue pads within the valve sinuses may exist and result in a thickened, rigid valve that is considered dysplastic (a common finding in Noonan's syndrome). Excessive thickening in dysplastic valves renders the valve unsuitable for percutaneous valvuloplasty, although attempts have occasionally been successful. Similarly, narrowing of the RV outflow tract limits the efficacy of percutaneous balloon techniques. Acquired forms of stenosis are rare (i.e., carcinoid).

Percutaneous Balloon Pulmonary Valvuloplasty

Figure 40-2 demonstrates the gradient between the right ventricle and the pulmonary artery (PA) before and after successful percutaneous balloon valvuloplasty. The RV outflow tract may have considerable muscular subpulmonic stenosis, which may be masked when valvular obstruction is present. The sudden removal of the valvular stenosis after the procedure may result in acute decompensation from marked RV infundibular obstruction, sometimes called the "suicide RV." Fluid loading, calcium channel blockers, and β-blockers can be used for emergent treatment. After pulmonary valvuloplasty, the subpulmonic hypertrophy may regress considerably over the next several months.

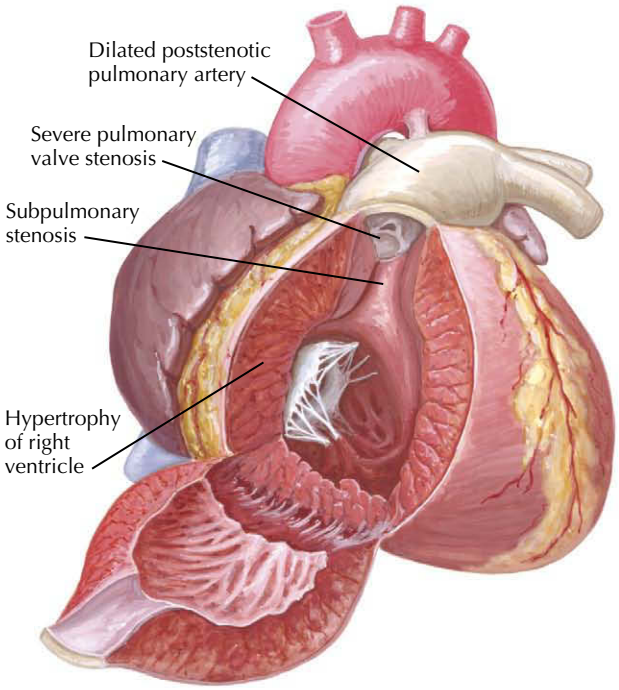
INDICATIONS

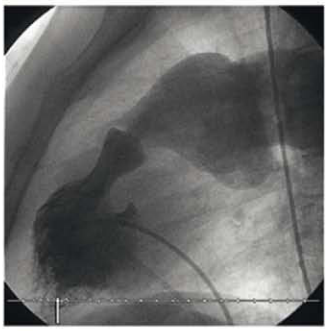
Valvular regurgitation is generally graded from 1+ (mild) to 4+ (severe). In patients with less than 2+ pulmonic regurgitation and a doming pulmonic valve, American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggest that a peak pulmonary valve gradient of greater than 60 mm Hg or a mean gradient of greater than 40 mm Hg by echo-Doppler warrants balloon valvuloplasty, even without symptoms. Any evidence of RV dysfunction or associated RV failure and tricuspid regurgitation should also prompt intervention if the mean gradient is greater than 30 mm Hg. Procedural success is much lower in patients with pulmonary valve dysplasia and may have only limited value when there is carcinoid plaque involvement of the pulmonic valve. The procedure is effective in reducing the RV outflow tract gradient in the presence of RV conduit obstruction from prosthetic valve dysfunction, although the patient generally experiences an increase in pulmonic regurgitation in these situations.

TECHNIQUE

Before the procedure, RV angiography in the cranial right anterior oblique and straight lateral views is performed. Pulmonary angiography assesses preprocedural pulmonic regurgitation. Severe pulmonic regurgitation (3+ or more) is a contraindication to valvuloplasty; severe regurgitation as a result of the procedure represents an adverse outcome. Baseline annular size is determined by echocardiography, MRI, or contrast angiography. In the cardiac catheterization laboratory, a catheter (with radiopaque markers a known distance apart) may be used for angiography at the valve level to determine appropriate balloon size. Quantitative angiographic methods may be similarly applied.

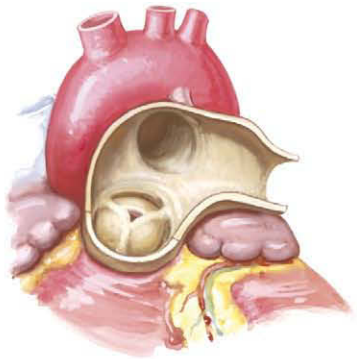
The dilating balloon or balloons are percutaneously inserted into the femoral vein without a sheath. The maximum inflation of the balloon(s) should be equal to 1.2 to 1.4 times the estimated annular size (see Fig. 40-2). In contrast to the aortic valve (see "Aortic Valve Stenosis"), the pulmonic valve is elastic and often requires oversizing for adequate results. The goal of the procedure is a final peak-to-peak valvular gradient less than 30 mm Hg by cardiac catheterization. Recurrence rates are much lower if that threshold is reached. A single balloon, often



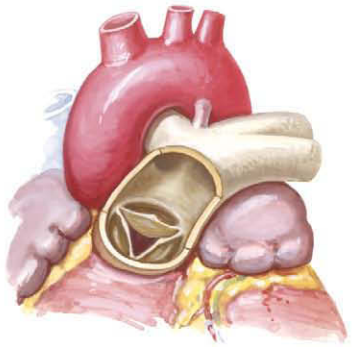


Classic pulmonary valvular stenosis. The figure reveals the doming stenotic pulmonary valve evident during right ventricular angiography. Note the dilated poststenotic pulmonary artery.

K. Carter



Open stenotic pulmonary valve with fused commissures creating the classic domed shape



Open normal pulmonary valve

Figure 40-1 *Pulmonary stenosis.*

23 mm in diameter in adults, may be used, although two balloons side by side may be necessary in patients with a large annulus. In some laboratories, trefoil or bifoil balloon catheters are available and preferred. The Inoue mitral valvuloplasty balloon (Toray Industries, Inc., Tokyo, Japan) has increasingly been used for pulmonary valvuloplasty because of its stability during inflation.

Careful measurement of postprocedural gradients allows differentiation of infundibular stenosis from residual valvular stenosis. Postprocedural PA angiography evaluates the severity of pulmonic regurgitation as a result of the procedure, while postprocedural RV angiography addresses the presence and significance of infundibular stenosis.

SHORT-TERM RESULTS AND COMPLICATIONS

Numerous groups have reported excellent short-term results in children and adults, as exemplified by a report of 66 infants and children in whom the peak gradient across the pulmonic valve fell from 92 ± 43 mm Hg to 29 ± 20 mm Hg with no change in cardiac output. The NHLBI Adult Registry included 37 adult patients with successful completion of the procedure in 97%, and a reduction in the average peak gradient from 46 to 18 mm Hg. Larger balloon sizes, up to 30% to 50% larger than the annulus, resulted in greater reductions in the valvular gradient without increasing complications.

Minimal complications in the acute setting include vagal symptoms and ventricular ectopy from catheters in the right ventricle. Pulmonary edema, presumably from increasing pulmonary flow to formerly underperfused lungs, perforation of a cardiac chamber, high-grade atrioventricular nodal block, and transient RV outflow obstruction (as noted earlier) have also been reported. Pulmonary valve regurgitation occurs in approximately two thirds of the patients after the procedure, but it is rarely clinically significant.

LONG-TERM RESULTS

Long-term data are available for over 10 years after percutaneous balloon valvuloplasty of the pulmonary valve. In one representative study, 62 children undergoing this procedure, with an average balloon-to-pulmonary annulus ratio of 1.4, were followed for a mean of 6.4 ± 3.4 years. Persistent pulmonary valve regurgitation was found in 39% of the patients, there was evidence of a progressive resolution of infundibular hypertrophy, and the restenosis (>35 mm Hg gradient) rate was only 4.8%. Restenosis was more common in patients with dysplastic valves. If restenosis occurred, repeat valvulo-

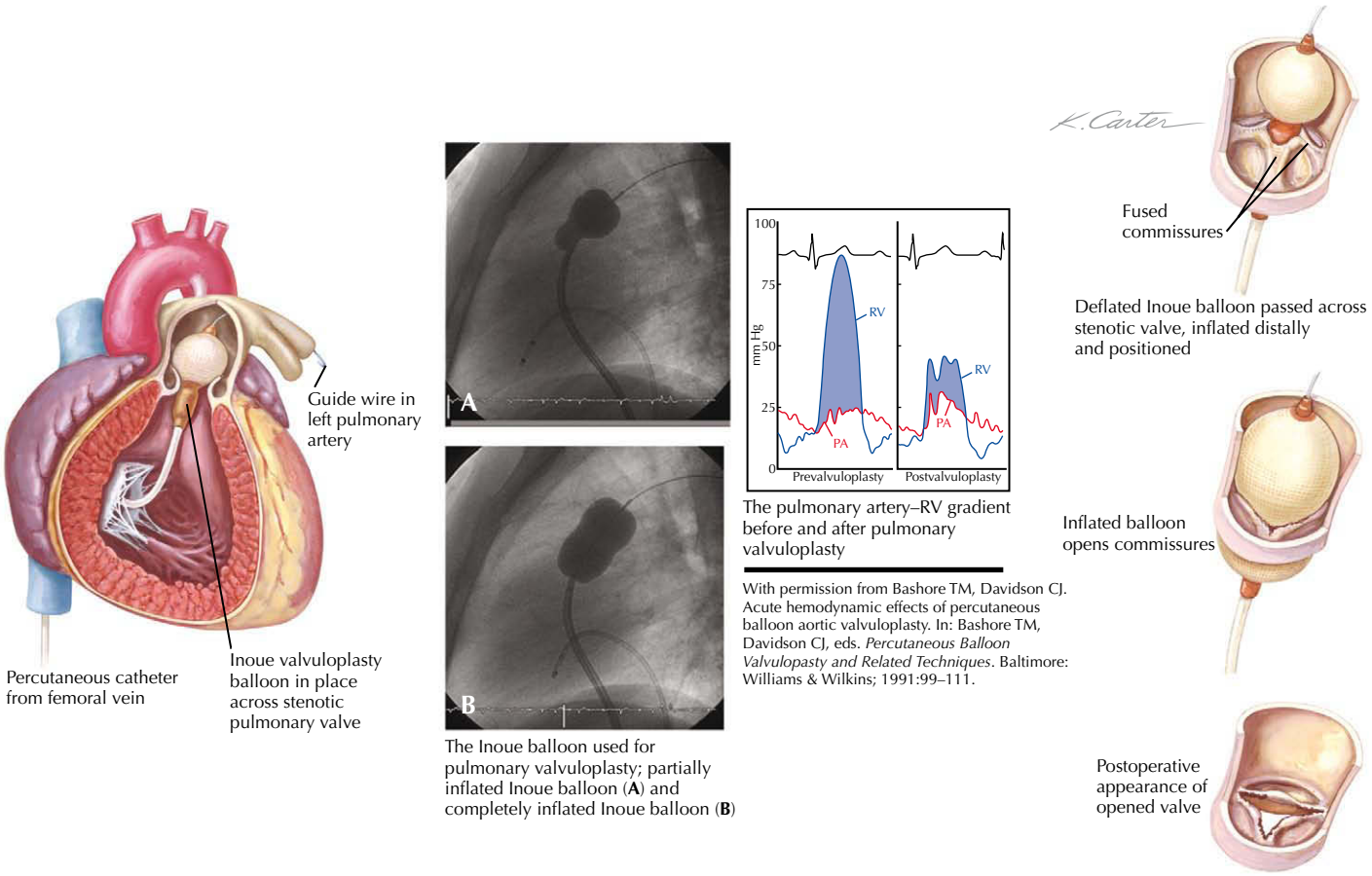


Figure 40-2 *Pulmonary balloon valvuloplasty.* PA, pulmonary artery; RV, right ventricular.

plasty seemed to be effective in patients without dysplastic pulmonary valves.

These data compare favorably with the outcomes of surgical valvotomy. One large study of surgical valvotomy in children reported a surgical mortality rate of 3%, with poor surgical results (residual gradient >50 mm Hg) in 4%. Restenosis rates after surgery were 14% to 33% at up to 34 months of follow-up. Thus, percutaneous balloon valvuloplasty for valvular, nondysplastic, pulmonic stenosis is the treatment of choice and provides excellent short- and long-term relief from pulmonary valvular obstruction.

Percutaneous Pulmonary Valve Replacement

In 1992, the first percutaneous catheter-mounted pulmonary heart valve procedure using a stented porcine bioprosthetic valve was implanted in an animal model. In 2000, Bonhoeffer and colleagues were the first to treat a human with a percutaneous pulmonary valve implanting of a stent-mounted bovine jugular vein valve in an RV-to-PA conduit of a 12-year-old. The remarkable success of the index case led quickly to its application in eight additional cases, with major hemodynamic improvement in both stenosis and regurgitation seen in five of the eight. The procedure has now been applied to a wider group of patients with available follow-up at a median of 3 years. The overall results remain encouraging.

INDICATIONS

Whereas congenital pulmonary valve stenosis often responds well to percutaneous balloon techniques alone, as described above, pulmonary outflow tract stenosis and/or regurgitation is the expected consequence following the use of pulmonary valve replacement or homograft repair in a variety of disease states, notably late repair of tetralogy of Fallot or following the Ross procedure (transfer of the pulmonary valve to the aortic position and replacement of the pulmonary valve and root with a pulmonary homograft in aortic stenosis). Indeed, any surgically placed RV outflow valved conduit can be expected to become stenotic, regurgitant, or both over time. These situations currently require valve replacement, since the anatomy does not lend itself to percutaneous balloon valvuloplasty. Most commonly the valve is implanted surgically; however, these individuals may be candidates for nonsurgical repair utilizing percutaneous pulmonary valve replacement.

TECHNIQUE

Currently there are two models of percutaneous valves being investigated for use in the pulmonary position. The Melody Pulmonary Valve (Medtronic, Inc., Minneapolis, MN) uses a stented bovine jugular vein valve and has been deployed in humans. Initial experience with the Edwards SAPIEN percutaneous stent aortic valve (using bovine pericardium) (Edwards Lifesciences, Irwin, CA) was in a sheep model. A self-expanding stented valve is also under investigation. The basic techniques are similar to percutaneous balloon valvuloplasty except the delivery catheter has a crimped stented valve on the balloon. Under general anesthesia, a stiff guide wire is placed from the femoral vein or rarely the right internal jugular vein to the PA. The valve assembly is then positioned over the wire. The assembly is composed of the valved stent within a long sheath. Once in position, the sheath is withdrawn and the balloon subsequently inflated within the obstructed conduit. At times, a manual inflation of the same size balloon is performed in the RV outflow tract before insertion for sizing as an outflow larger than 22 mm in diameter is considered an exclusion with currently available devices. This size restriction currently prevents the application of this technique in many patients with native pulmonary valve stenosis because of concerns regarding stent apposition to the walls of a dilated main PA.

COMPLICATIONS AND EARLY RESULTS

Recently published data on the first 155 patients who have undergone the procedure suggests there is a steep learning curve and complications occur much less frequently once this is overcome. In the first 50 patients, seven major complications were noted including homograft rupture, right coronary compression, device dislodgement, and embolization to the right PA. Five of the seven required surgical device removal. The incidence of complications was 6% in the first 50 patients and 2.9% in the next 105.

INTERMEDIATE-TERM RESULTS

Follow-up is now available at a median of 28.5 months. Among the 155 patients, 4 have died, with survival at 83 months of 96.6%. Freedom from transcatheter reintervention is 95% at 10 months and 73% at 70 months. Reintervention includes placing a stented valve within the first stented valve and/or repeat ballooning of the stented valve. Reasons for reintervention include stent fracture, residual gradient, and restenosis. Pulmonary regurgitation is generally not a major issue.

Stent fracture remains an unresolved issue, occurring in 21% of the series reported. Stent fracture is more common if the stent is implanted in the contractile RV outflow tract, or when there is no calcium in the conduit, or when there is evidence for recoil of the implanted valve immediately after deployment.

There are as yet no long-term data on the durability of the bovine pericardium valves in this situation, but it is likely these will suffer degenerative processes similar to those of all surgically implanted valves.

AORTIC VALVE STENOSIS

Pathophysiology

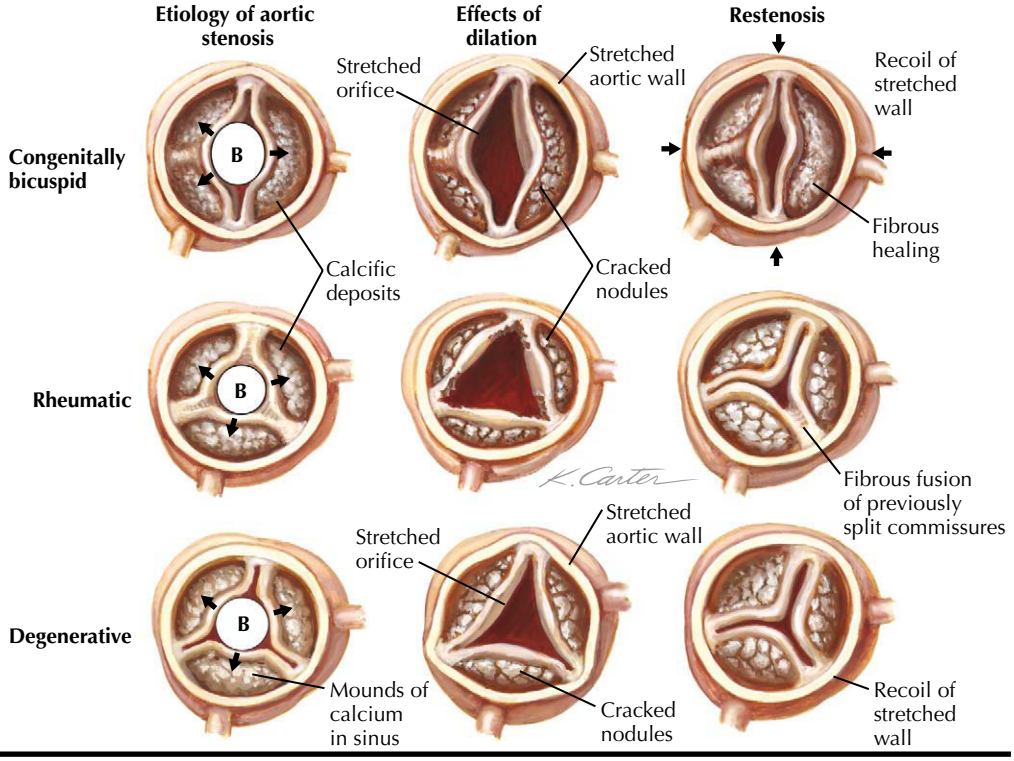
The normal aortic valve has thin, flexible cusps composed of three tissue layers sandwiched between layers of endothelium on both sides of the valve. The layers include a fibrosa with collagen fibers oriented parallel to the leaflet that support the major leaflet, a ventricularis layer composed of elastic fibers oriented perpendicularly to the leaflet edge that provide flexibility, and a spongiosa layer of loose connective tissue in the basal third of each leaflet.

Congenitally deformed aortic valves have fused commissures and can generally be described as either unicuspid or bicuspid. Unicuspid valves are inherently stenotic at birth and cause symptoms early in life. Unicuspid aortic valves account for approximately 10% of all cases of isolated aortic valve stenosis in adulthood, whereas bicuspid aortic valves account for approximately 60% of isolated aortic valve stenosis in patients aged 15 to 65 years of age. Bicuspid aortic valves generally have two cusps of nearly equal size with a false commissure (raphe). Over time, progressive valvular fibrosis and calcium deposition occur, worsening the functional stenosis. Some commissural fusion between the functioning leaflets may occur, but the major limitation is often valvular rigidity from calcium buildup and scarring. High serum lipids may contribute to the degeneration of these valves similarly to those patients with calcific aortic stenosis.

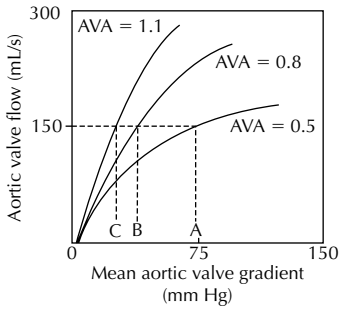
Aortic valve stenosis in elderly persons generally involves a trileaflet valve and probably represents a continuum, from benign aortic valvular sclerosis to severe aortic valvular stenosis. The prevalence of aortic valve sclerosis has been reported to be 25% in individuals older than 65 years of age, with severe aortic valve stenosis evident in 1% to 2% of the population. There is growing evidence that the mechanism of calcific aortic valve stenosis in the elderly is related to atherosclerosis and not to what has commonly been referred to as a "degenerative" process. Little commissural fusion exists; large accretions of calcium can be present in the sinuses of Valsalva. The leaflets gradually lose their flexibility as a result of these calcium deposits. In calcific aortic valve stenosis, the minimal reduction in the gradient that can be obtained by balloon procedures has generally been attributed to cracks in the calcific nodules, cuspal tears, and aortic wall expansion (Fig. 40-3).

When left ventricular (LV) outflow is obstructed at the valvular level, a gradient develops between the left ventricle and the aorta (see Fig. 40-3). The relationship between the gradient and the aortic valve area (AVA) is complex, however, and depends on the severity of the lesion as measured by the AVA and on the cardiac output or the aortic flow. After aortic valvuloplasty, aortic flow may increase because of an improvement in the cardiac output or the development of aortic regurgitation. Either result could increase the gradient, even if the actual AVA also increases. Alternatively, the cardiac output may fall, and the gradient may appear lower even if the AVA has increased. Thus, the short-term postprocedural valvular gradient change may not always reflect the actual change in the AVA.

Using just the change in the AVA can also be problematic for other reasons. For instance, if the baseline AVA is severe, an

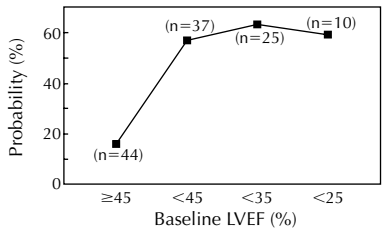


With permission from Waller BF, van Tassel JW, McKay C. Anatomic basis for and morphologic changes produced by catheter balloon valvuloplasty. In: Bashore TM, Davidson CJ, eds. *Percutaneous Balloon Valvuloplasty and Related Techniques*. Baltimore: Williams & Wilkins; 1991:34.



The relation between the aortic valve area and aortic flow (cardiac output). Note the curvilinear relation. The more flat the curves at the smaller aortic valve areas, the greater the gradient at any particular aortic flow. Because of this relation, a change in the aortic valve of 0.3 cm^2 has a much greater impact on the gradient going from 0.5 cm^2 to 0.8 cm^2 (A to B) than the same incremental change going from 0.8 cm^2 to 1.1 cm^2 (B to C).

With permission from Bashore TM, David CJ. *Acute Hemodynamics Effects of Percutaneous Balloon Aortic Valvuloplasty and Related Techniques*. Baltimore: Williams & Wilkins; 1991:105.



The relation between the baseline EF and the probability of recurrent symptoms at the 1-year outcome in elderly patients undergoing percutaneous balloon aortic valvuloplasty. Only those with an EF >45% experienced acceptable results.

With permission from Davidson CJ, Harrison JK, Pieper KS, et al. Determinants of one-year outcome from balloon aortic vavuloplasty. *Am J Cardiol* 1991;68:79.

Figure 40-3 *Effect of valvuloplasty on aortic valve area (AVA).* The position and size of the aortic valvuloplasty balloon is shown (B). EF, ejection fraction; LVEF, left ventricular ejection fraction.

improvement in the AVA of 0.3 cm^2 from baseline has a dramatic effect on the peak LV systolic pressure (e.g., when the AVA increases from 0.5 to 0.8 cm^2), but if the baseline AVA is less severe, the same incremental change may have much less consequence (e.g., when the AVA increases from 0.8 to 1.1 cm^2). Hence, either an improvement in the gradient or an improvement in both the gradient and the final valve area can be used to define a successful result (i.e., a final valve gradient of <50 mm Hg, a 50% improvement in the AVA, or both).

Indications for Intervention

The decision whether to intervene in aortic valve stenosis usually depends on the presence of symptoms of congestion, angina, or exertional syncope and an assessment of the likelihood of improvement in AVA. Serial measurements of transvalvular pressure gradients by Doppler echocardiography can be helpful. When the maximum Doppler velocity exceeds 4 m/s (estimated gradient of 64 mm Hg), symptoms emerge relatively

quickly. A change in the Doppler gradient of more than 0.3 m/s within 1 year also portends symptoms. Thus, recent guidelines suggest that severe aortic stenosis is present when the Doppler estimated peak instantaneous gradient is greater than 64 mm Hg, the mean gradient is greater than 40 mm Hg and/or the estimated AVA is less than 1.0 cm^2. Because of the variable means for measuring valvular gradients and the dependence of the valve gradient on the aortic valvular flow and the effective orifice area, the use of a specific AVA to make a decision on the need for an operation is always tenuous. This may be particularly true in patients with a low cardiac output and low gradient, but severe aortic stenosis by calculated AVA. In this situation, the use of an inotropic agent or nitroprusside to augment aortic flow may help determine whether the low output (and the subsequently low gradient) is a consequence of the valvular stenosis or is attributable to poor ventricular function. A very high brain natriuretic protein level may suggest a poor prognosis in this group, even if aortic valve replacement (AVR) is performed.

In neonates and very young children, the initial success rates for percutaneous intervention are not encouraging, although older children and young adults may benefit and should be considered for the procedure as a temporizing measure. In older adults, surgical intervention has consistently proven superior to percutaneous balloon valvuloplasty. The use of percutaneous balloon valvuloplasty in adults with either bicuspid or calcific aortic stenosis should be restricted to situations in which the risk of surgical intervention is very high (e.g., in a pregnant patient or in an elderly patient with cardiogenic shock), because of the generally poor results. In these circumstances, percutaneous balloon valvuloplasty may serve as a bridge to eventual AVR. Also, in the rare elderly adult with preserved LV systolic function and severe aortic valve stenosis who is not a candidate for surgical AVR because of comorbid conditions, valvuloplasty can provide short-term symptomatic benefit or be used as a bridge to eventual AVR.

Technique of Percutaneous Balloon Aortic Valvuloplasty

In contrast to pulmonary valvuloplasty, the balloon catheter used for aortic valvuloplasty should have a maximum inflated diameter slightly smaller than the measured size of the aortic annulus. In adults, a 20-mm-diameter balloon is usually used, although a 23-mm balloon may be required for larger patients. Brief, rapid RV pacing during positioning and inflation of the aortic balloon across the stenotic valve lowers cardiac output transiently and allows for more stable positioning. The balloon catheter is placed in the middle of the valve plane and manually inflated, using dilute (25%) radiographic contrast in saline (Fig. 40-4). Inflation pressures do not seem to influence the outcome significantly, and these pressures are no longer measured. Usually one to three separate 15- to 20-second inflations are adequate.

Whether the approach is percutaneous (via the femoral artery, with or without a sheath), cut-down (using the brachial artery), or transseptal (using an antegrade approach to the aortic valve via the right femoral vein), similar results are obtained. The transseptal approach is particularly useful in patients with significant aorto-iliac atherosclerosis, a common problem in elderly individuals. Following the transseptal puncture, a 0.038-inch wire is navigated through the left atrium and the left ventricle, across the aortic valve, and down the descending aorta for stability. The intra-atrial septum is predilated using an 8-mm balloon catheter before insertion of the aortic valvuloplasty balloon catheter. The remainder of the procedure is similar to the retrograde approach.

ACUTE RESULTS AND COMPLICATIONS

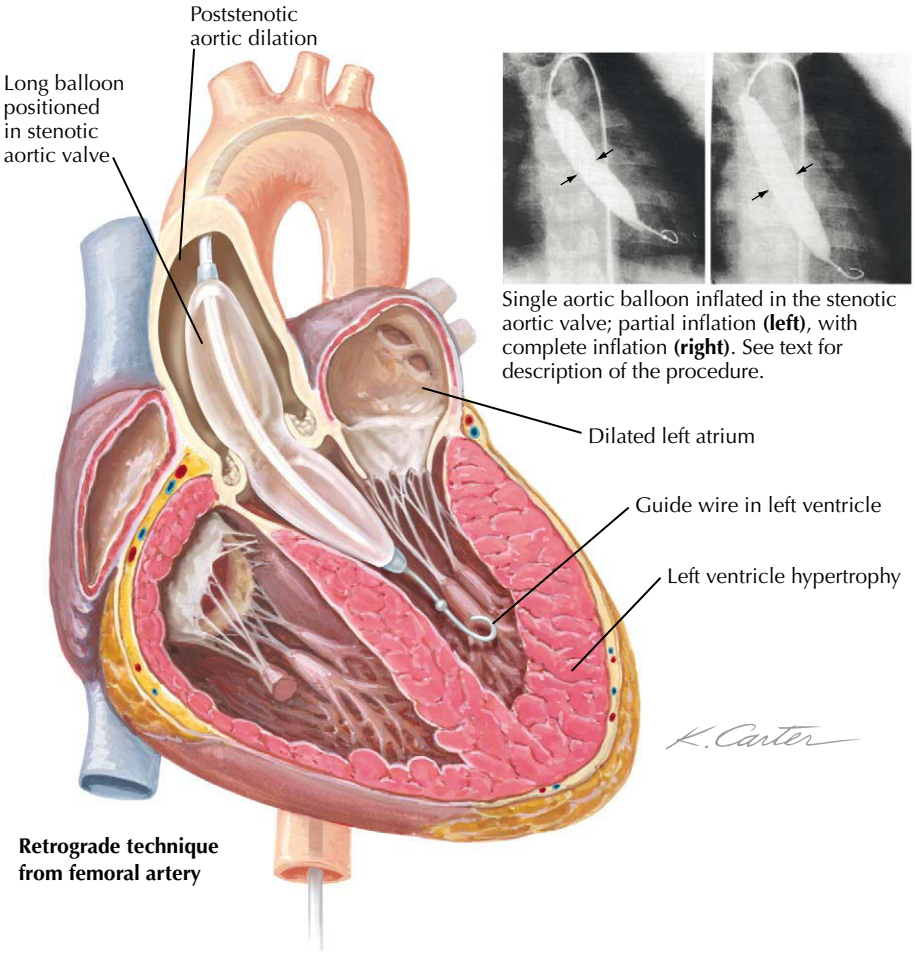
The mean aortic gradient can be expected to fall from about 55 to 29 mm Hg acutely, with the AVA increasing from 0.5 to 0.8 cm^2 with no measurable change in cardiac output.

In those patients for whom pressure-volume data were derived before and immediately after the procedure, systolic function was largely unchanged, with the ejection fraction (EF) rising only slightly, the peak positive dP/dt falling slightly, and stroke volume and peak and end-systolic wall stress all modestly reduced. A negative impact was noted acutely on diastolic measures of ventricular function, including a significant decrease in peak negative dP/dt and a prolongation of tau (a measure of active diastolic relaxation). Transient mild ischemia during the procedure was considered responsible for some of the acute changes.

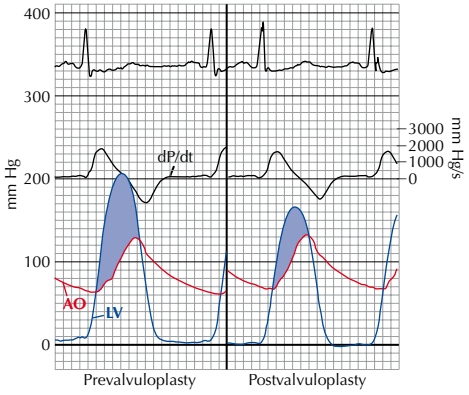
Results in children and neonates vary broadly depending on the patient's clinical status and associated cardiac anomalies. Many neonates with critical aortic valve stenosis have severe LV hypoplasia or endocardial fibroelastosis and do poorly with either percutaneous aortic valvuloplasty or surgery. After the neonatal period, the results from valvuloplasty improve. Data from 232 patients with a mean age of approximately 9 years showed the aortic gradients decreased approximately 60% from about 75 mm Hg to 30 mm Hg after percutaneous balloon valvuloplasty. The procedure seems often to work reasonably well in the adolescent age group, offering an important opportunity to delay surgery until the individual has reached full adult size. It should be noted that, even with an excellent initial outcome, restenosis will occur over time.

The rate of serious life-threatening complications from aortic valvuloplasty is remarkably low given the elderly population in whom it is usually applied. Almost all protocols for calcific aortic stenosis require patients to be noncandidates for surgical intervention. In a review of 791 such patients, in-hospital mortality rates were 5.4% with a risk of serious morbidity (cerebrovascular accident, cardiac perforation, myocardial infarction, or serious aortic regurgitation) of up to 1.5%. Vascular complications were overwhelmingly the greatest complicating feature, with a 10.6% incidence. The common practice today of using vascular occlusion devices after the procedure has virtually eliminated major vascular injury as a concern.

In the NHLBI Registry of 671 patients, complications were considerable. At least one complication was reported in 25% of the patients within 24 hours, and 31% had some complication before hospital discharge. The most common complication was the need for transfusion (23%), followed by the need for vascular surgery (7%), cerebrovascular accident (3%), systemic embolization (2%), or myocardial infarction (2%). All-cause mortality was 3%, with death usually related to multiorgan failure and poor preprocedural LV function. In patients who



Single aortic balloon inflated in the stenotic aortic valve; partial inflation **(left)**, with complete inflation **(right)**. See text for description of the procedure.



Representative hemodynamic changes

Representative pressure changes before and after percutaneous balloon aortic valvuloplasty. High-fidelity simultaneous LV and aortic pressures are shown with the accompanying dP/dt before and after the valvuloplasty procedure. The aortic gradient before and after is shaded.

With permission from Bashore TM, Davidson CJ. *Acute Hemodynamics Effects of Percutaneous Balloon Aortic Valvuloplasty and Related Techniques*. Baltimore: Williams & Wilkins; 1991:105.

Figure 40-4 *Aortic balloon valvuloplasty.* Ao, aortic; dP/dt, delta pressure/delta time; LV, left ventricular.

survived to 30 days, 75% had improved by at least one NYHA functional class.

LONG-TERM RESULTS

In adolescents with a bicuspid valve, good results are often seen for up to 5 to 10 years, with aortic regurgitation a common problem during that time period. In calcific aortic stenosis, short-term studies reveal an initial increase in the aortic valve gradient as early as 2 days after the procedure, undoubtedly related to aortic recoil. There may also be some early improvement in cardiac output that contributes to the increase in aortic valve gradient seen early after the valvuloplasty. By 6 months, most patients have evidence of significant restenosis, although symptoms are related more to diastolic dysfunction than to the AVA gradient; if LV remodeling has occurred, symptoms may not directly correlate with the measured valve area.

In one study, the probability of recurrent symptoms at 1-year follow-up could also be predicted by the baseline EF before the procedure. Only those patients with a baseline EF over 45% seemed to benefit (see Fig. 40-3). This implies that patients with poor LV systolic function are rarely good candidates for percutaneous balloon aortic valvuloplasty as a final procedure. Because most patients with preserved LV systolic function would clearly be candidates for AVR surgery, this limits the value of the procedure in the older adult patient.

Percutaneous Aortic Valve Replacement

There is a great interest in percutaneous replacement of the aortic valve. The procedure involves a stent-mounted aortic valve that can be delivered through a catheter and positioned directly within the diseased aortic valve. Figure 40-5 illustrates the two most common stent-mounted valves under investigation and their method of deployment. The Edwards SAPIEN device is made of bovine pericardium and is positioned in the diseased valve via balloon inflation similar to percutaneous pulmonary valve replacement. The device can also be delivered in the operating room via an LV puncture, thus avoiding cross-clamping of the aorta in the situation of a heavily calcified aorta (porcelain aorta). A second device, the CoreValve ReValving System (Medtronic, Inc.) is made of a self-expanding nitinol frame with a porcine pericardial prosthesis implanted. The frame has three distinct functional levels with different radial and hoop strengths. It figuratively "hangs" from the ascending aorta with the valve device positioned in the aortic valve plane. The valve cage is

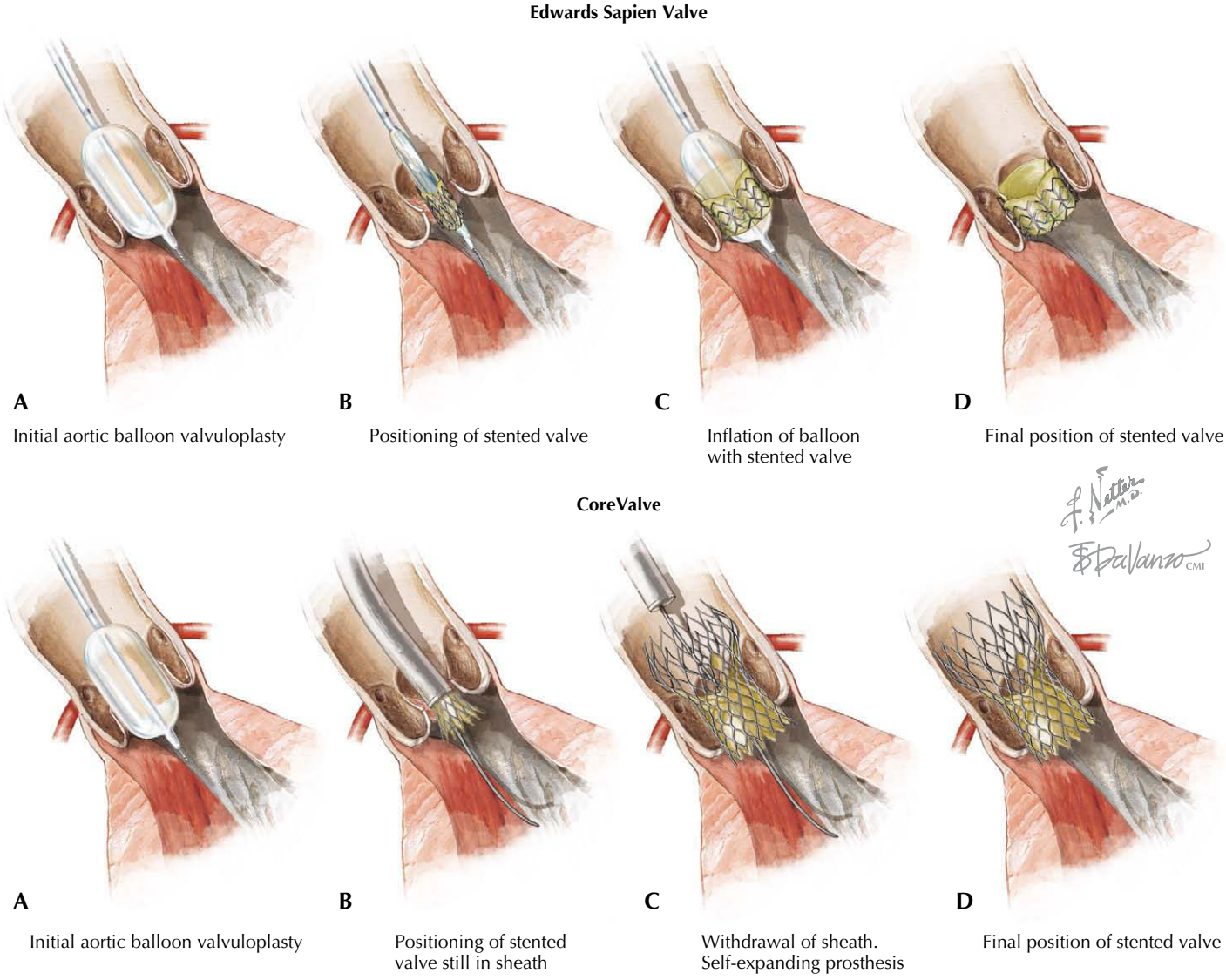


Figure 40-5 *Percutaneous aortic valve (Edwards Sapien and CoreValve) replacement.*

constrained just above the aortic valve plane to avoid interference with the coronary ostia. Early data suggest the cage does not interfere with subsequent coronary angiography or intervention should it be required. Other stented-valve designs are also under investigation at this time, and four are currently undergoing first-in-human implantations. These newer designs are being promoted as allowing smaller arteriotomies, improving repositioning of the prosthesis during deployment, and resulting in less aortic regurgitation. The stented aortic valve has also been used in isolated patients to improve stenosis or regurgitation of a degenerative bioprosthesis.

INDICATIONS

Current indications for percutaneous AVR are quite limited. Similar to aortic balloon valvuloplasty in the elderly, most patients must have significant aortic stenosis with surgical intervention felt to be prohibitive or of exceptionally high risk. Only those with the potential for functional clinical improvement should be considered. The major anatomic features that complicate the placement are size, degree of tortuosity, and amount of calcium in the aorta and iliac and femoral vessels. The current catheters in use are generally 22French (F) and 24F for the Edwards SAPIEN valve and 18F for the CoreValve. Basal septal hypertrophy may also interfere with the valve positioning. At this time, bicuspid valves are not considered appropriate because of their elliptical orifice. The use of the transcatheter AVR in low-gradient, low-output aortic stenosis is still under investigation. A randomized trial comparing surgical to percutaneous valve replacement or medical therapy is ongoing (PARTNER [Placement of AoRTic TraNscathetER Valve] Trial).

TECHNIQUES

Under general anesthesia, all patients initially undergo percutaneous balloon valvuloplasty before implantation. The selected

percutaneous valve must be slightly larger than the aortic annulus to ensure anchoring and minimal postprocedural aortic regurgitation. Unfortunately, the available percutaneous valves are limited to 23 and 26 mm for the Edwards SAPIEN valve; the patient's annulus diameter must therefore be between 18 and 21 mm for the smaller and between 21 and 24 mm for the larger valve. The CoreValve uses a 26-mm valve for an aortic annulus between 20 and 23 mm and a 29-mm valve for one between 23 and 27 mm. Both valves are positioned during rapid ventricular pacing to transiently reduce the cardiac output. The Edwards SAPIEN system can be placed either retrograde across the valve (see Fig. 40-5) or antegrade across the aortic valve, via either an atrial transseptal approach or via a transapical approach in the operating room. The antegrade approach has the advantage of venous instead of arterial access for these large devices, and allows placement in patients with significant iliac and femoral artery disease. Because the CoreValve device is a self-expanding stent that positions itself in the ascending aorta, it can only be delivered retrograde (see Fig. 40-5). The self-centering nature of the CoreValve system does allow for partial repositioning.

COMPLICATIONS AND EARLY RESULTS

Because patients currently undergoing these procedures are at high risk, complications have been common, although both aortic valve pressure gradients and calculated AVA have demonstrated remarkable improvement. Recent studies suggest the AVA increases from approximately 0.6 cm^2 to 1.5 cm^2. Mean gradients fall from approximately 40 mm Hg to 8 mm Hg. Cardiac output remains unchanged or slightly improves. In all of the current series, the average patient age is from 81 to 83 years. Some aortic regurgitation is common, but severe aortic regurgitation is not. In the early series, 30-day mortality has been very high, from 13.6% to 17.5%, with a stroke risk of 3% to 5%. Other common complications include conversion to AVR (2.5% to 7.1%), myocardial infarction (1.2% to 17%), bleeding (~5%), pacemaker therapy (~6%), and aortic dissection (0.8%). Procedural complications have been somewhat less in the CoreValve series as compared with the Edwards SAPIEN, although the data are still preliminary. Newer sheath systems are being developed to prevent scraping of the aortic arch as the device is delivered. Procedural success is initially reported as 75% in the Edwards SAPIEN series and 88% using the CoreValve. Recent studies using both types of valve have shown a steady reduction in periprocedural mortality (as low as 1.5%) and an overall improvement in procedural success (as high as 97%). There are as yet no intermediate- or long-term studies to help define the durability of these devices.

MITRAL VALVE STENOSIS

Pathophysiology

Obstruction to LV inflow through the mitral valve is usually attributed to rheumatic heart disease. Congenital mitral valve stenosis may also occur, generally from chordal fusion or abnormal papillary muscle positioning. The anterolateral and posteromedial LV papillary muscles may be so close that a single papillary muscle is evident (the parachute mitral valve). Rarely, a mitral web on the atrial side of the mitral leaflet can obstruct flow. In the elderly, mitral valve annular calcification may result in leaflet stiffening and mitral stenosis, in which calcium invades from the annulus toward the center of the valve. There is frequently associated mitral regurgitation. Other causes of mitral stenosis are rare: carcinoid (usually in association with a patent foramen ovale or an atrial septal defect), systemic lupus erythematosus, rheumatoid arthritis, Fabry's disease, and amyloidosis. Rheumatic involvement predominates as a cause for mitral stenosis, and when it is present, the aortic valve is often involved as well.

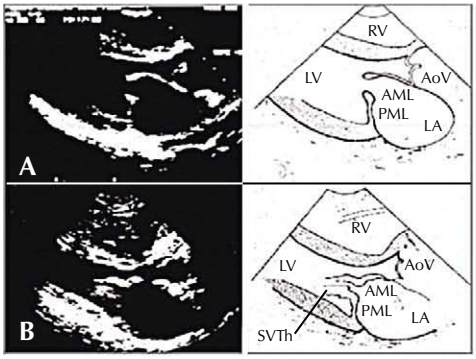
The interval between an episode of acute rheumatic fever and symptomatic mitral stenosis averages approximately 16 years. Most patients do not recall the acute event when they ultimately present with symptomatic mitral stenosis. Fusion of the commissures between the anterior and posterior leaflets is the most characteristic feature of rheumatic mitral stenosis. Fusion, thickening, and retraction of the chordae; thickening of the valvular leaflets; and calcium deposition contribute to the obstructive process. The severity of these features has led to an echocardiographic qualitative scoring system in which numbers are assigned to each characteristic. The mobility of the anterior mitral valve leaflet, the presence of valvular thickening, the degree of submitral scarring, and the amount of valvular calcification by echocardiography are weighted from 1 to 4, helping to define which valves are suitable for a percutaneous approach. Figure 40-6 represents the spectrum of involvement from transthoracic two-dimensional echocardiography.

The location of the commissural fusion also helps predict success of balloon dilation. Because the balloon valvuloplasty procedure works by tearing the commissural fibrosis that causes leaflet fusion, the presence of minimal commissural fusion suggests the gradient may be in the chordae and that the procedure will be ineffective. If there is eccentric commissural fusion on only one side of the leaflet, the inflated balloon(s) may be forced to the nonfused side of the leaflet, increasing the risk of valvular or ventricular trauma. The area of the mitral valve measured by planimetry usually correlates well with the Doppler-derived valve area. When the planimetric area seems much larger than the Doppler-derived area, this dichotomy may signal the presence of a significant submitral gradient.

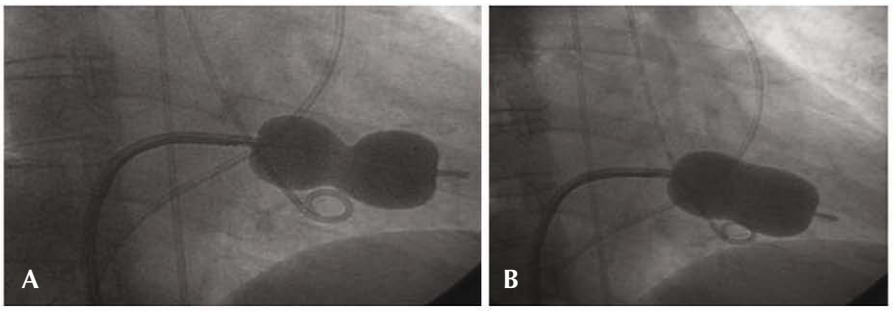
Indications for Intervention

Mitral valve stenosis results in obstruction to LV inflow and an elevated left atrial (LA) pressure. Any activity that increases flow (e.g., exercise) or shortens diastolic time (e.g., the onset of a rapid tachycardia, such as atrial flutter or fibrillation) increases the mitral gradient. When the pressure gradient across the mitral valve is increased, symptoms of dyspnea and pulmonary congestion emerge. The decision to intervene in mitral stenosis is based primarily on exertional symptoms or evidence for pulmonary hypertension.

Pulmonary hypertension that is greater than would be expected from the magnitude of the LA pressure alone (secondary stenosis at the pulmonary capillary level) may be



Echocardiographic scoring of mitral valve stenosis severity
Representative 2D echocardiograms from a patient with mitral stenosis with a mobile mitral valve and a low echo score (**A**) and from a patient with a high echo score (**B**)



Inoue balloon mitral valvuloplasty. The Inoue balloon is seen partially inflated in the stenotic mitral stenosis orifice on the left **(A)** and fully inflated on the right **(B)**. See text for description of the procedure.

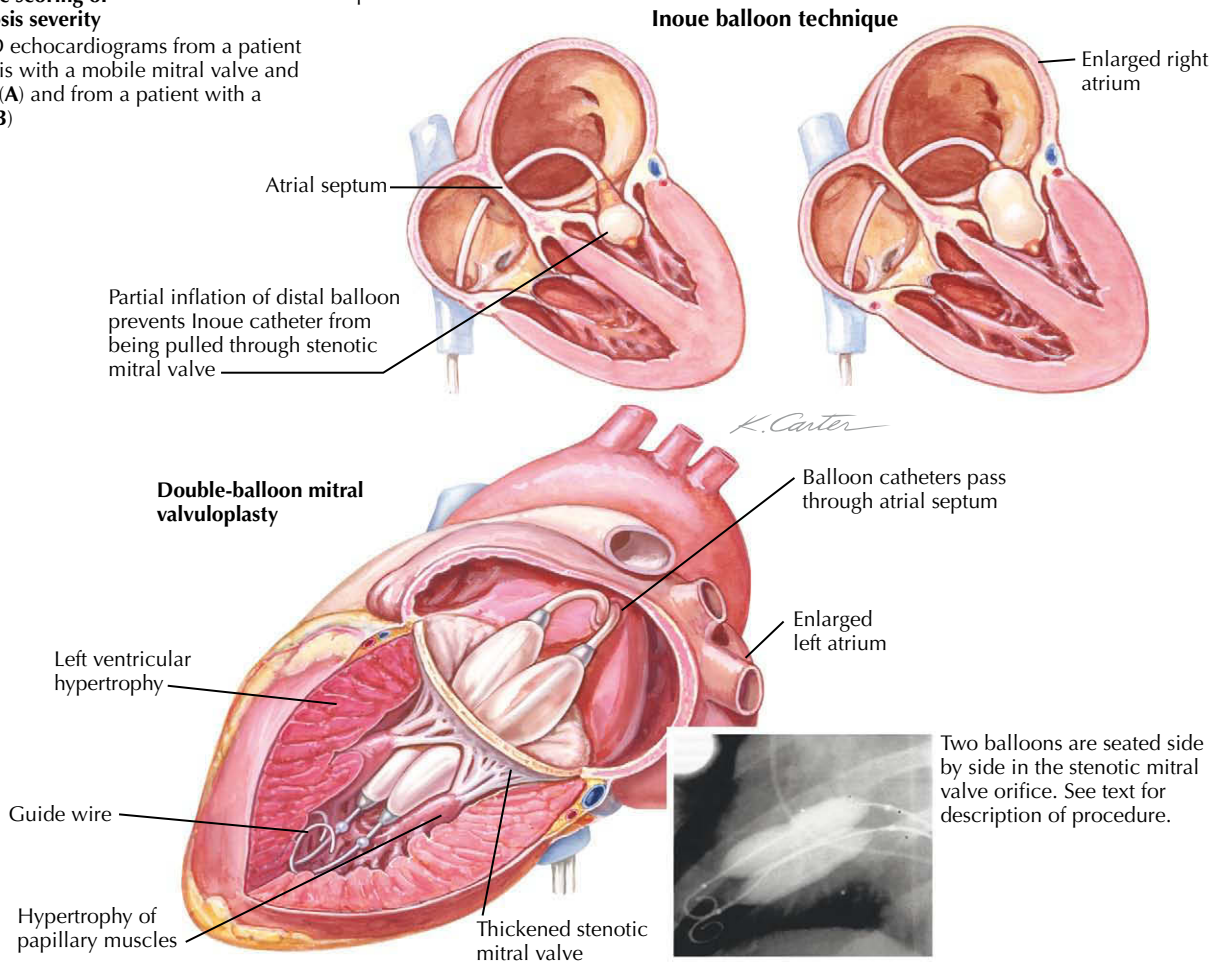


Figure 40-6 *Mitral balloon valvuloplasty.* AML, anterior mitral leaflet; AoV, aortic valve; LA, left atrium; LV, left ventricle; PML, posterior mitral leaflet; RV, right ventricle; SVTh, subvalvular thickening.

present. Although the trigger for the excessive elevation in the pulmonary vascular resistance is unknown, endothelin and adrenomedullin, both potent pulmonary vasoconstrictors, may be involved. Because pulmonary hypertension in this situation may regress following balloon valvuloplasty or valve replacement, evidence for pulmonary hypertension or right-sided heart failure, even without congestive symptoms, is an indication for intervention in mitral stenosis.

Whether to proceed with valve replacement or valvuloplasty depends on the morphology of the stenosed mitral valve. Several echocardiographic scoring systems have been suggested, the most popular being the Massachusetts General Hospital System, in which each of four characteristics is graded 1 to 4, with 1 being minimal involvement (Table 40-1). The higher the score, the less likely it is that a satisfactory result will be obtained by percutaneous balloon dilation and the more likely that

Table 40-1 Anatomic Classification of the Stenotic Mitral Valve: The Massachusetts General Hospital System

Measurement	Valve Score
A. Leaflet mobility	1. Highly mobile valve with only leaflet tip restriction 2. Midportion and base of leaflets with reduced mobility 3. Valve leaflets move forward in diastole mainly at the base 4. No or minimal forward movement of the leaflets in diastole
B. Valvular thickening	1. Leaflets minimally thickened (4–5 mm) 2. Midleaflet thickening, pronounced thickening of the margins 3. Thickening extends through the entire leaflets (5–6 mm) 4. Pronounced thickening of all leaflet tissue (>8 mm)
C. Subvalvular thickening	1. Minimal thickening of chordal structures just below the valve 2. Thickening of the chordae extending up to one third of the chordal length 3. Thickening extending to the distal third of the chordae 4. Extensive thickening and shortening of all chordae extending down to the papillary muscles
D. Valvular calcification	1. A single area of increased echo brightness 2. Scattered areas of brightness confined to the leaflet margins 3. Brightness extending to the midportion of the leaflets 4. Extensive brightness through most of the leaflet tissue
Assessment	A "0" score implies normal valve morphology. A total valve score of ≤8 implies a mobile valve amenable to percutaneous valvuloplasty. Progressively higher total valve scores result in less favorable outcomes, both acutely and in the long term.

With permission from Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J. *1988;60:299–308.*

treatment should be by valve replacement. The scoring system has successfully predicted acute results in many studies; a score greater than 8 is more likely to be associated with a suboptimal result.

Before the procedure, patients undergo transesophageal echocardiography to ensure that no atrial thrombus is present and to provide an additional assessment of the valvular morphology. Patient age or a history of surgical commissurotomy does not significantly influence the acute results of the procedure, provided the valvular morphology is favorable. In general, a symptomatic patient with a reasonably low morphology score and less than 2+ mitral regurgitation is a candidate for percutaneous mitral valvuloplasty. Essentially all patients with symptoms related to mitral stenosis have a calculated mitral valve area (MVA) of less than 1.5 cm^2.

Technique

Early experience and suboptimal results with single-balloon techniques initially prompted the development of double-balloon techniques to further expand the mitral orifice. Since then, a unique single-balloon technique using the Inoue balloon has become the most popular method. Most laboratories use an antegrade approach that requires transseptal catheterization. Right-sided heart catheterization and ventriculography initially determine the degree of mitral regurgitation, cardiac output, pulmonary pressure, the valve gradient, and the MVA. Some interventionalists use a right atrial angiogram with LA levophase filling to guide transseptal needle placement.

Transseptal catheterization is performed using a hollow Brockenbrough needle within an 8F Mullins sheath. Continuous pressure monitoring alerts the operator if the needle punctures the aorta or enters the pericardium. Once the sheath has been advanced into the left atrium, the needle is removed, the mitral gradient remeasured, and MVA calculated.

Double-balloon techniques are more complex than the Inoue balloon method. Some operators favor using double balloons that are positioned side by side using two guide wires. Other systems are available that use two balloons on a single catheter (the bifoil system) or two balloons on a single guide wire (the Multi-Track System). In any approach, the dilating balloons are then positioned side by side across the mitral valve and simultaneously inflated one to four times with dilute contrast (see Fig. 40-6). When the procedure is completed, the mitral gradient is remeasured and the left ventriculogram repeated to assess any residual mitral regurgitation.

The Inoue balloon method simplifies the procedure. The 12F balloon catheter is designed so the distal end of the balloon inflates before the proximal end, allowing balloon positioning across the mitral valve, inflation of the distal end, and pulling of the remaining balloon into the mitral orifice before inflation of the entire balloon. With double balloons, the maximum diameter is predetermined and dependent on the inflated maximum balloon diameter(s). With the Inoue system the diameter depends on the amount of contrast used to inflate the balloon. This feature allows for graded increases in the diameter of the balloon during the procedure without replacing the entire balloon catheter. The balloon size can be determined from echocardiographic measurements of the mitral annulus or by the

patient's height. The most commonly used sizes are maximum diameters of 26 mm and 28 mm.

Once in the left ventricle, the balloon is sequentially inflated in the mitral valve orifice in increments of 1 to 2 mm. The LA pressure and the mitral gradient are reevaluated after each balloon inflation. Echocardiography of the chest wall between each inflation increment allows observation of any change in the mitral valve and any Doppler evidence of mitral regurgitation. If mitral regurgitation is present or if the valvular gradient has been satisfactorily reduced, the procedure is completed.

Acute Results and Complications

Immediate improvement in the hemodynamic and clinical outcomes has been found in virtually all studies. A 50% to 70% decrease in the transmitral gradient with an accompanying 50% to 100% increase in the MVA is a reasonable expectation on the basis of these studies. A median preprocedural MVA of 0.9 cm^2 can be expected to improve to a postprocedural MVA of 1.9 cm^2. Similarly, the preprocedural mitral gradient of approximately 14 mm Hg generally is approximately 6 mm Hg following valvuloplasty. Cardiac output tends to remain unchanged acutely. The postprocedural valve areas are similar with the double-balloon method or the Inoue system. About 8% to 10% of valve areas will not improve to a final valve area of greater than 1.0 cm^2.

Pulmonary pressures fall immediately, consistent with the change in LA pressure. In patients with severe pulmonary hypertension, the pulmonary pressures drop further by 24 hours and continue to decline during the ensuing months.

The issues involved in the relationship between the valve area and valve flow discussed in the assessment of the results of aortic valvuloplasty also pertain to mitral valvuloplasty. A successful procedure is generally defined as a 50% improvement in the MVA or a final MVA of more than 1.5 cm^2 plus no more than 2+ mitral regurgitation. An acute success rate of approximately 90% can be expected, depending on the valvular morphology. The major factors identified as predictive of success are a low valvular score by whatever method and the absence of significant baseline mitral regurgitation.

Complications from percutaneous mitral valvuloplasty have declined as the learning curve of the procedure has improved, and the procedure has largely been restricted to the relatively few centers that perform the procedure frequently. Table 40-2 summarizes figures for acute complications from several reviews. With the routine use of transesophageal echocardiography before the procedure, the risk of embolic events has virtually disappeared. Major complications are related to the transseptal technique and the development of significant mitral regurgitation from injury to the mitral valve apparatus. The use of serial echocardiography following each balloon dilation has increased awareness of any developing mitral regurgitation, allowing the procedure to be aborted before serious mitral regurgitation develops. Careful attention to the change in the LA *v* wave during the procedure is also important, with an increase predictive of acutely worsening mitral regurgitation.

Table 40-2 Contemporary Complications Associated with Percutaneous Mitral Valvuloplasty

Complication	Estimates (%)
Emergency cardiac surgery	1–4
Cardiac perforation-tamponade	0.5–4
Significant mitral regurgitation	2–3
Cerebrovascular accident–embolic events	0.5–1.5
Death	0–1

Long-Term Results

Ten-year survival rates have been reported at 85% to 97%, with event-free survival rates of 61% to 72%. Event-free survival seems to be dependent on optimal valve morphology, the presence of sinus rhythm, lower LA pressures, and no more than 2+ mitral regurgitation following the procedure. Survival (82% vs. 57%) and event-free survival (38% vs. 22%) rates at 12-year follow-up are better in patients with an echocardiography score of 8 or below than in those with scores above 8. Atrial fibrillation and valvular calcium have a negative effect on event-free survival.

Essentially all studies emphasize the impressive improvement in patients' symptoms after percutaneous balloon mitral valvuloplasty. Serial hemodynamic studies suggest that clinical restenosis may not correlate well with anatomic restenosis. One report of serial echocardiographic restenosis data in 310 patients with high baseline echocardiography scores assessed restenosis, defined as an MVA of less than 1.5 cm^2 and/or at least 50% loss of the initial MVA increase. Acute procedural success (a final valve area >1.5 cm^2) occurred in 66% of patients. The cumulative restenosis rate was approximately 40% at 6 years after successful valvuloplasty. The only independent predictor of restenosis was the echocardiographic score (the probability of restenosis at 5 years was 20% for scores <8 vs. 61% for scores ≥8). The decline in MVA and the occurrence of restenosis were gradual and progressive during follow-up.

Clinical restenosis data are more impressive. Mitral valve anatomy always seems to predict the symptomatic outcome. The clinical restenosis rate has been reported at 20% to 39% at 7 years after valvuloplasty. A 10-year clinical restenosis rate of 23% was found for those with an echocardiography score of 8 or lower, 55% for those with an echocardiography score of 9 to 11, and 50% for those with a score of 12 or higher.

COMPARATIVE DATA WITH SURGICAL COMMISSUROTOMY

Studies comparing surgery and balloon valvuloplasty have shown similar initial results. In 60 patients with favorable anatomy randomized to valvuloplasty (using the double-balloon technique) or open surgical commissurotomy, excellent early results were reported with both techniques. However, at 3 years the MVAs of the balloon valvuloplasty patients were actually better than those of the surgical group (2.4 cm^2 vs. 1.8 cm^2), and 72% of the valvuloplasty patients were in NYHA functional class I as compared with 57% of the surgical group.

In another study, 90 patients were randomized to valvuloplasty, open commissurotomy, or closed commissurotomy and

followed for 7 years. Little difference existed between the valvuloplasty patients and the open-commissurotomy patients at the conclusion of the study. The valvuloplasty and open surgical procedure groups had less clinical restenosis than the closed-commissurotomy group (0% for the valvuloplasty and open-commissurotomy groups, 27% for the closed surgical group). At 7 years, 87% of the valvuloplasty patients and 90% of the open-commissurotomy patients were in NYHA functional class I, as compared with 33% of the closed surgical commissurotomy patients.

It appears that balloon valvuloplasty is equivalent or superior to surgical commissurotomy for symptomatic mitral stenosis, at least through the first 7 years after the procedure, so long as the preprocedural valve score falls within an acceptable range. Hence, the percutaneous approach is advocated in those with appropriate valve morphology.

MITRAL VALVE REGURGITATION

Pathophysiology

Mitral regurgitation can result from any abnormality of the mitral valve apparatus. The mitral valve apparatus includes the mitral annulus, the valve leaflets, the chordae, the papillary muscles, and the supporting myocardium. Clinically, mitral regurgitation is considered either primarily valvular (mitral valve prolapse, rheumatic disease, endocarditis, annular calcium, systolic anterior motion from hypertrophic cardiomyopathy, ruptured chordae or papillary muscle, aberrant chordal attachments, cleft leaflets, etc.) or primarily functional (dilated annulus, displacement of the papillary muscles in a dilated cardiomyopathy, post infarction, LV aneurysm, etc.).

There are fundamentally four main categories of percutaneous approaches to reducing mitral regurgitation severity. One approach takes advantage of the proximity of the mitral annulus to the coronary sinus and attempts to remodel the mitral annulus by crimping it with an implanted coronary device. Three systems have been studied that use this approach: (1) the percutaneous transvenous mitral annuloplasty (PTMA) approach (Viacor PTMA [Viacor, Wilmington, MA]), (2) the Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA), and (3) the Monarch system (Edwards Lifesciences). A second approach utilizes the concept of creating a double-orifice mitral valve with a transvalvular clip (the eValve MitraClip [Evalve, Inc., Menlo Park, CA]) or stitch (the Mobius device, Edwards Lifesciences). A third concept under investigation includes attempts to remodel the mitral valve complex and annulus using a transventricular suture-based method (Percutaneous Suture Annuloplasty [Mitralign, Inc., Tewksburg, MA], and AccuCinch [Guided Delivery Systems, Santa Clara, CA]), or even a radiofrequency application (Quantum-Cor Endovascular Device [Quantum-Cor, San Clemente, CA]). Finally, systems have been developed to reduce the mitral annular septal-to-lateral-wall dimension by tugging on it from the atrial septum (Percutaneous Septal Sinus Shortening or PS3 System [Ample Medical, Foster City, CA]) or by pinching it between the epicardial surfaces (iCoapsys [Myocor, Inc., Maple Grove, MN]). A percutaneous mitral cerclage method wherein the entire mitral annulus is reduced with an encircling string has been proposed as well.

Indications for Intervention

In patients with chronic mitral regurgitation, current guidelines suggest that intervention should be performed for symptoms, for pulmonary hypertension, or if detrimental effects on the LV from chronic volume overload are apparent. In accordance with recent guidelines, mitral valve replacement or mitral repair is generally recommended when the LV EF is less than 60% or the LV end-systolic dimension is greater than 4.0 cm by echocardiography in the face of severe mitral regurgitation. A variety of noninvasive and invasive hemodynamic parameters may be used to estimate mitral regurgitation severity. Mitral regurgitation is common, with approximately 9% to 10% of the population over 75 years of age exhibiting some degree, including 15% to 20% of those with heart failure.

Percutaneous Mitral Edge-to-Edge Repair

THE MITRACLIP

As shown in Figure 40-7, the Mitraclip device is placed within the mitral orifice via a transseptal catheter approach using a 24F guide catheter that tapers to a 22F at its distal end. The system delivers a two-armed polyester clip that grabs up to 8 mm of mitral tissue on each side. Once delivered, a double-orifice mitral valve is created and the clip device remains attached to the mitral leaflets.

This procedure has the greatest amount of available clinical data for percutaneous mitral regurgitation reduction. The EVEREST I (Endovascular Valve Edge-to-Edge Repair) Study confirmed its clinical safety, and the EVEREST II Study is ongoing. This latter phase II study randomizes patients 2:1 (Mitraclip vs. surgery). Of the initial 102 patients in the two trials, 79% have degenerative mitral valve disease and the rest have functional mitral regurgitation. Acute procedural success (clip placement and ≤2+ mitral regurgitation) has been demonstrated in 84%. At 30 days, 91% were free of adverse major events; 9% had partial clip detachment. At 1 year, approximately 70% have improved, and a similar number have avoided further surgery. Those who have improved have now maintained that improvement out to 24 months. A total of approximately 400 patients have undergone percutaneous mitral repair. Initial results suggest that the percutaneous method remains inferior to surgical repair. The procedure appears well tolerated and does not interfere with eventual surgical repair if needed. Its role still remains to be defined.

MOBIUS STITCH REPAIR

The Mobius Leaflet Repair System is similar to the MitraClip device, except an actual percutaneous stitch sutures the leaflets together. A 10F catheter is used, and a transseptal approach is required. The therapy catheter vacuums, captures, and delivers a 4-0 suture to the free edges of the mitral valve, and a 7F catheter deploys a nitinol suture clip and cuts the excess suture. It is possible to remove the suture before deploying the clip. Early results in the first 15 patients were unsatisfactory, and the device is undergoing further refinement before additional studies are contemplated.

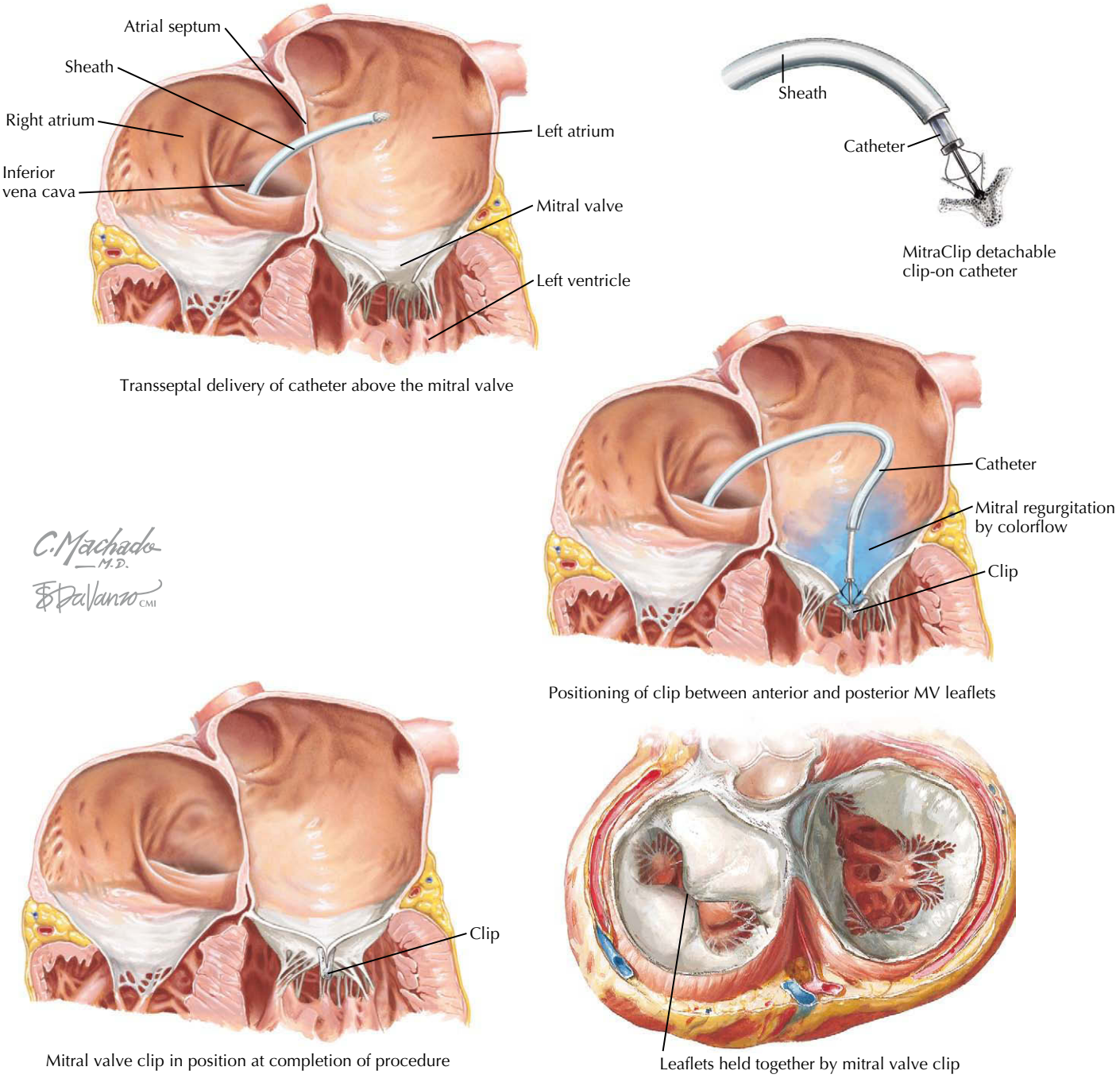


Figure 40-7 *Mitral clip procedure for mitral regurgitation.* MV, mitral valve.

Transcatheter Coronary Sinus Techniques

Transcatheter coronary sinus techniques attempt to reshape the mitral annulus and to reduce the septal-lateral LV wall dimension. In the majority of patients, the coronary sinus is superior to the mitral annulus and in direct contact with it. The coronary sinus is closest to the mitral annulus at its proximal end and farthest at its distal ends. The left circumflex coronary artery also lies in this plane and crosses over the coronary sinus in approximately 75% of patients. The coronary sinus also has variable branching points that alter its relationship with the mitral annulus. All of these anatomic issues come into play when attempts at reducing the septal-lateral annulus dimension are to be made using coronary sinus catheters.

VIACOR PTMA CORONARY SINUS DEVICE

The Viacor PTMA device is a 7F multilumen catheter. Up to three rods of varying stiffness and length can be inserted within the catheter to alter the stiffness. The concept is to exert an

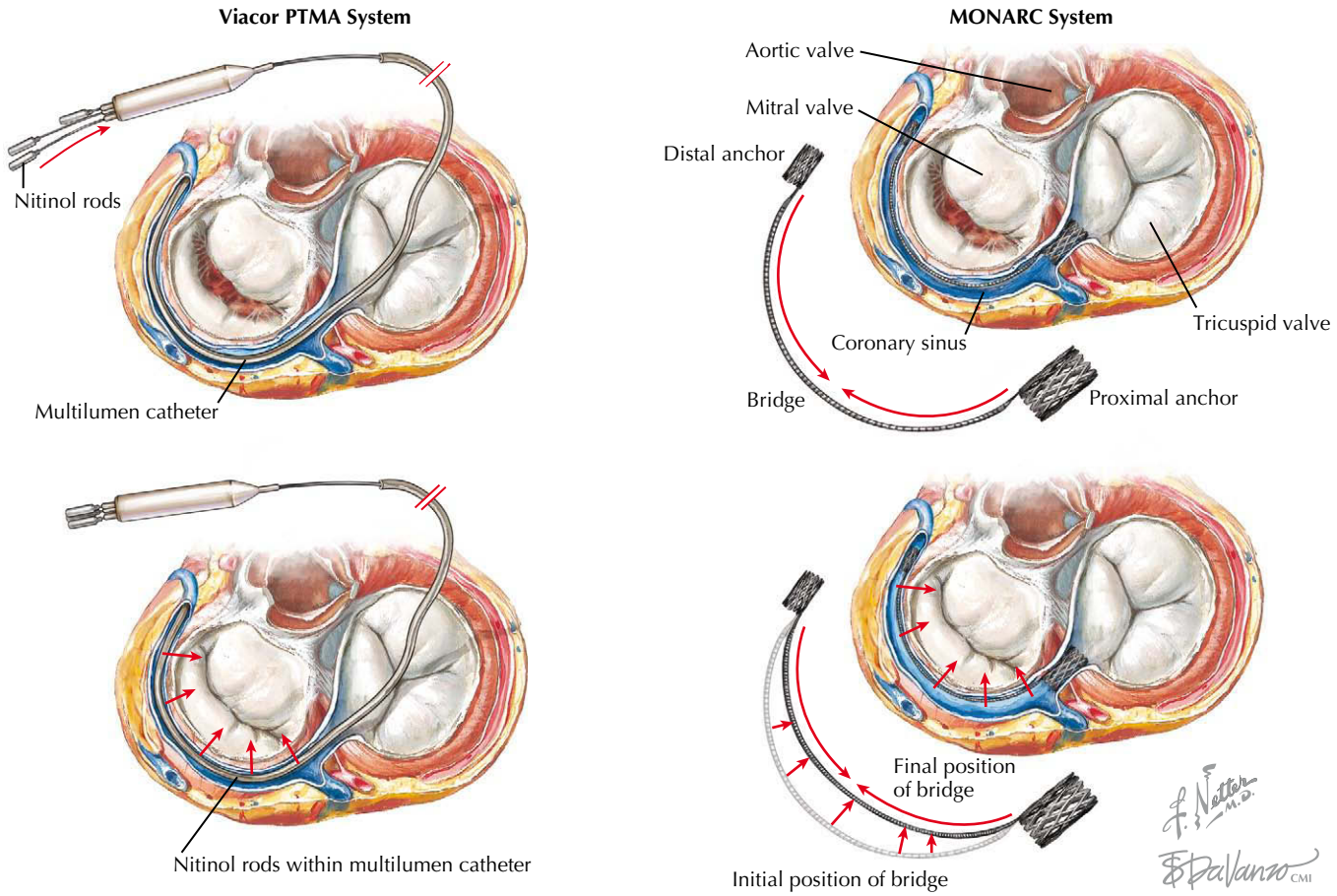


Figure 40-8 *Coronary sinus devices for mitral regurgitation.* PTMA, percutaneous transvenous mitral annuloplasty.

outward force at the proximal and distal segments and to create anterior displacement of the P2 segment of the mitral valve due to the decrease in septal-lateral dimension of the mitral annulus (Fig. 40-8).

After initial animal studies were promising, the device has been tested in a phase I trial, PTOLEMY I (Percutaneous TransvenOus Mitral AnnuloplastY), in Europe and Canada. In the initial 27 patients, 8 had unsuitable anatomy. Subsequently, 13 of 19 patients with successful device delivery had a reduction in the severity of mitral regurgitation. In 4, however, the device had to be removed early (1 due to fracture and 3 due to device migration). PTOLEMY II is currently underway after some device modifications. It will evaluate the device in patients with symptoms and LV dysfunction.

CARILLON MITRAL CONTOUR SYSTEM

The Carillon Mitral Contour System (Cardiac Dimensions) is a curved nitinol bridge that is anchored on both ends by helical nitinol loops. It is delivered via the right internal jugular vein in a 9F sheath. After deploying the distal anchor in the great cardiac vein, tension is applied by virtually pulling on the system and then deploying the proximal anchor. The device is capable of being repositioned if necessary.

After animal studies suggested a fourfold reduction in mitral regurgitation-LA area, a European trial was begun that was called AMADEUS I (Carrilon Mitral Annuloplasty Device European Union Study). The device was successfully deployed in 30 of 43 (70%), and 80% had at least one grade reduction in the mitral regurgitation. Coronary artery compromise was noted in 6 (14%). Major adverse events noted at 30 days included one death, two myocardial infarctions, one dissection, two coronary sinus perforations, and one anchor displacement. All unsuccessful implants were able to be recaptured without complications.

CORONARY SINUS DEVICES FOR MITRAL REGURGITATION

Another novel approach to reducing the mitral annular size via the coronary sinus is the Edwards MONARC device (Edwards Lifesciences) (see Fig. 40-8). The catheter is inserted into the coronary sinus and anchored with stents on each end. Between the stents is a springlike nitinol bridging segment that contains a biodegradable substance. The device is first implanted; then the biodegradable substance resorbs over time and the nitinol spring re-forms to its original curved shape, bringing the proximal and distal ends closer together. This displaces the posterior

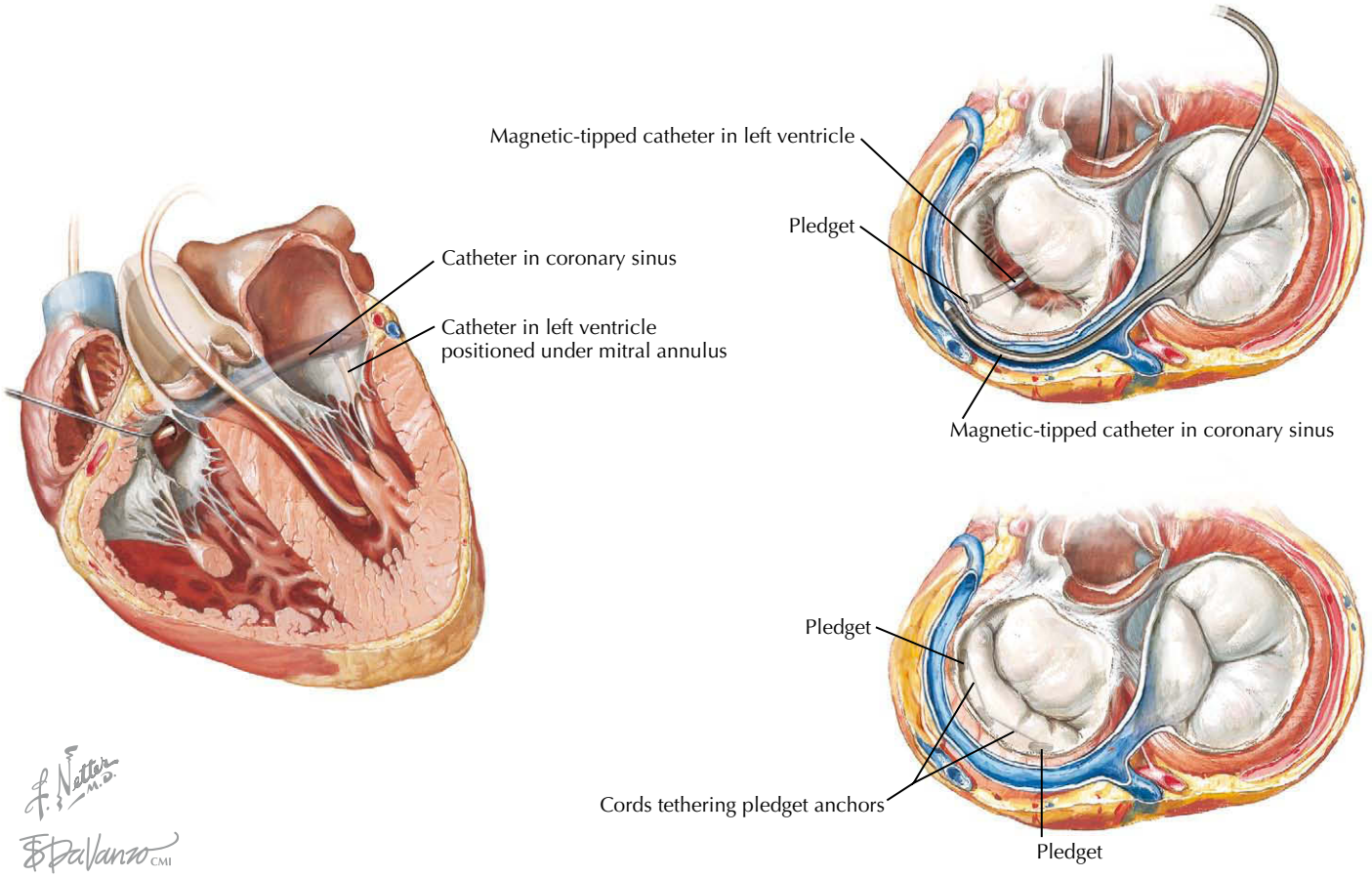


Figure 40-9 *Mitral annuloplasty with the Mitralign System.*

mitral annulus anteriorly and reduces the septal-lateral valve annulus dimension. This reforming of the device occurs over several days to weeks, so the actual impact on the mitral annulus is unknown until after implantation.

The initial human experience with the Viking System (Viking Systems, La Jolla, California) suggested an improvement in mitral regurgitation, although separation of the nitinol bridge segment was a common problem. This has led to a phase I trial (EVOLUTION) in patients with functional mitral regurgitation wherein the success rate for implantation was 59 out of 72 (82%). Freedom from major adverse events was 91% at 30 days and 86% at 90 days. Notably, coronary compression was angiographically noted in 15 of 50 patients at follow-up (30%). A nonrandomized phase II trial is under way.

Direct and Indirect Annuloplasty Approaches

Directly reducing the mitral annular size in the septal-lateral position by only 20% has been shown to considerably reduce the severity of mitral regurgitation. Instead of cinching the mitral annulus via the coronary sinus, there are several direct and indirect percutaneous annuloplasty techniques under investigation. None have enough patients enrolled in their first-phase trials to determine whether the methods will be useful in the future, so only a brief mention is made here.

MITRALIGN SYSTEM

The Mitralign System attempts to replicate a surgical suture annuloplasty. Via the femoral artery, a 14F catheter is inserted across the aortic valve and, using a deflector tip, the catheter is pointed toward the mitral annulus. Pledgets are then anchored across the mitral annulus from the left ventricle to the left atrium in several positions along the mitral annulus (Fig. 40-9). These anchors are then tethered, and tension between them decreases the septal-lateral annulus diameter. Phase I trials are under way in Europe.

ACCUCINCH

The AccuCinch System (Guided Delivery Systems) also is a catheter system that allows retrograde access to the subannular space under the mitral valve. As with the Mitralign System, pledget anchors are delivered across the mitral annulus and a cinching cable is used to reduce the septal-lateral dimension.

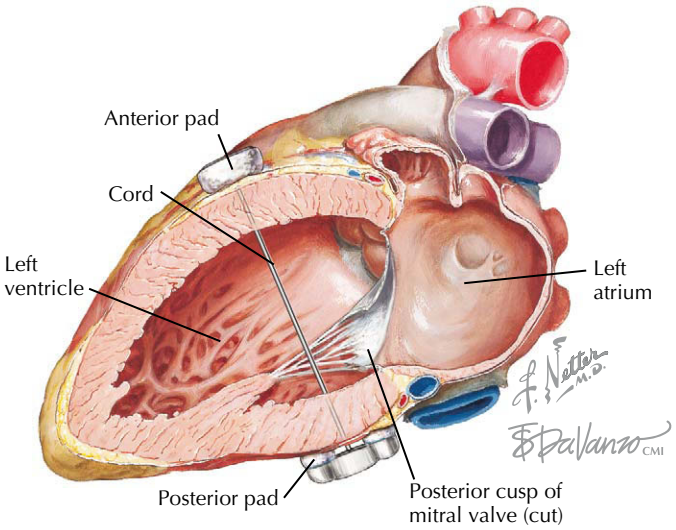


Figure 40-10 *Coapsys device.* Modified from Pedersen WR, Block PC, Feldmen TE, et al. The iCoapsys repair system for percutaneous treatment of functional mitral insufficiency. *Eurointervention.* 2007;1:A44-A48.

The device has been surgically tested with percutaneous phase I trials set to begin.

COAPSYS AND ICOAPSYS

An external approach to implanting anchors on the outside of the heart with the cinching cable crossing the left ventricle intraventricularly has been investigated. The surgically placed approach (Coapsys, Myocor, Inc.) results in a reduction in the septal-lateral mitral annulus and displaces the papillary muscles toward a more superior position, both helpful in functional mitral regurgitation (Fig. 40-10). Two trials have been completed, the latter (RESTOR-MV, or Randomized Evaluation of a Surgical Treatment for Off-pump Repair of the Mitral Valve) randomized 138 patients with acceptable initial results, including the acute reduction in mitral regurgitation from 3+ to 1+ in most patients.

The iCoapsys method is a subxiphoid pericardial approach wherein a needle punctures the left ventricle and a transventricular cord is passed and exteriorized. The sizing cord is then pulled to reduce the LV geometry. A prospective, nonrandomized study on its feasibility, the VIVID (Valvular and Ventricular Improvement via iCoapsys Delivery) Study, has been launched.

PERCUTANEOUS SEPTAL SINUS SHORTENING (P3 SYSTEM)

Following coronary sinus and transseptal puncture, magnetically tipped catheters are used to place a T-bar into the coronary sinus from the LA side. A cord attached to the T-bar traverses the left atrium and is pulled back through the transseptal puncture site. Here it is attached to an atrial-septal occluder, and tension is then applied pulling the T-bar (and the mitral annulus) toward the atrial septum. Animal studies have been completed, and the initial patients studied have shown a reduction in mitral regurgitation and up to a 31% change in the septal-lateral mitral annular dimension. Phase I trials are being developed.

QUANTUMCOR RADIOFREQUENCY ABLATION (QUANTUMCOR)

Using a catheter with a ring at its end creating a 40-mm-diameter loop, 7 electrodes with 14 thermocouples spaced along the middle third of the loop has been developed. The catheter is placed with the loop resting on the mitral annulus. Radiofrequency energy is then emitted between the electrodes, and the heat generated results in shrinkage of the mitral annulus. Animal models suggest about a 20% reduction in annular septal-lateral dimension. Studies in humans are planned.

In summary, there remains a wide variety of percutaneous approaches attempting to reduce mitral regurgitation. None have yet emerged as applicable to the large patient population that would benefit. All remain in various stages of technical development.

TRICUSPID VALVE STENOSIS

Pathophysiology

Tricuspid valve anatomy is more variable than mitral anatomy. The three leaflets of the tricuspid valve are of unequal size; the septal leaflet is the smallest, the anterior leaflet the largest. Although some chordae attach to distinct papillary muscles in the right ventricle, they also attach directly to the RV endocardium. Therefore, tricuspid regurgitation is a frequent occurrence when the right ventricle dilates from any cause. The orifice of the tricuspid valve is considerably larger than the mitral orifice, the normal tricuspid valve area being approximately 10 cm^2. Considerable valve stenosis must be present to obstruct the RV inflow. Although a mean gradient of 2 mm Hg establishes the diagnosis, most consider a mean gradient of at least 5 mm Hg or a calculated valve area of less than 2.0 cm^2 to indicate significant tricuspid valve stenosis.

Tricuspid valve stenosis is decidedly uncommon and essentially never an isolated lesion. Rheumatic disease accounts for 90% of tricuspid stenosis cases. Of patients with rheumatic mitral valve disease, approximately 3% to 5% have associated tricuspid stenosis. Commissural fusion is present, but the fibrosis and/or fusion of the chordae is seen less often than is observed in rheumatic mitral stenosis. Leaflet calcium is uncommon.

In the United States, the second most common cause of tricuspid stenosis is carcinoid syndrome. Carcinoid plaque thickens the leaflets and the chordae, and commissural fusion is unusual. The valves often appear virtually frozen in position, resulting in both tricuspid stenosis and tricuspid regurgitation. Congenital forms of tricuspid stenosis exist and are generally

due to abnormalities in the leaflets (absent or decreased number), in the chordae (absent, reduced number, or shortened), and/or in the papillary muscles (reduced number). Tricuspid repair to reduce functional tricuspid regurgitation is commonplace during mitral valve replacement, and the associated reduction in the tricuspid annulus can lead to tricuspid stenosis when the annulus is undersized.

Open surgical commissurotomy on the tricuspid valve is rarely performed because of the high risk of tricuspid regurgitation. It is particularly inadvisable to open the commissure between the anterior and posterior leaflets, although surgical commissurotomy may succeed if fusion is relieved between the anterior and septal or the posterior and septal leaflets. On the basis of surgical experience, the use of balloon valvuloplasty is limited in all of the conditions that cause tricuspid stenosis.

Indications

Patients with tricuspid stenosis usually present with low cardiac output, fatigue, anasarca, and abdominal swelling from hepatomegaly and ascites. Giant *a* waves may be visible in the neck and even felt by the patient. Symptomatic tricuspid stenosis is an acceptable reason to consider intervention. The limiting factor is usually associated tricuspid regurgitation. Balloon valvuloplasty could be considered in the unlikely circumstance that a patient was not a surgical candidate and had limited tricuspid regurgitation or would clinically benefit from conversion from tricuspid stenosis to tricuspid regurgitation.

Procedure and Results

There are few data on the use of percutaneous balloon tricuspid valvuloplasty. The technical aspects are similar to percutaneous mitral valvuloplasty except that no transseptal procedure is required. In the NHLBI Balloon Valvuloplasty Registry, only three patients underwent the procedure on a native valve.

Most tricuspid valvuloplasty procedures have been performed in patients who had both mitral and tricuspid valvuloplasty at the same setting. Results of these procedures also include data on the treatment of tricuspid stenosis from carcinoid syndrome. No long-term reports exist about the efficacy of tricuspid valvuloplasty in any setting.

PERCUTANEOUS TRICUSPID VALVE REPLACEMENT

A novel percutaneous tricuspid valve has been placed in an animal model. The device is a prototype nitinol stent with two large disks separated by a thin cylinder. Within the cylinder is mounted an 18-mm bovine jugular vein. No human experience has yet been reported.

BIOPROSTHETIC VALVE STENOSIS

Pathophysiology

Porcine or bovine pericardial prosthetic valves may be implanted in any valvular position. All of these valves have a limited life span because of eventual mineralization and collagen degeneration. Cuspal tears, fibrin deposition, disruption of the fibrocollagenous structure, perforation, fibrosis, and calcium infiltration appear after a few years; by 10 years, tissue valve failure occurs in approximately 30% of patients. By 15 years, more than 50% of the valves have failed. The degenerative structural changes occur earlier in valves in the mitral compared with the aortic position, because of greater hemodynamic stress on the mitral valve. Patients on dialysis seem to be particularly susceptible to early valve failure. Other identified factors associated with valve failure include younger age, pregnancy, and hypercalcemia.

Commissural fusion is uncommon in these valves, the major problem being leaflet immobility. At times these valves become relatively stenotic immediately after surgery from undersizing (patient-prosthetic mismatch). From an anatomic standpoint, the use of percutaneous balloon valvuloplasty procedures seems problematic given the lack of commissural fusion.

Prosthetic Valvuloplasty and Percutaneous Valve Replacement

Limited data exist about the use of balloon procedures in prosthetic valve stenosis. Success in two patients with porcine tricuspid stenosis has been described, although little follow-up data were available and "restenosis" quickly occurred in one patient. The NHLBI Balloon Valvuloplasty Registry reported four successful procedures with no follow-up. In every instance of our investigations of explanted porcine valves, considerable trauma occurred to the explanted valve, and balloon techniques did not seem to be a viable option. No prospective studies have addressed the safety and efficacy of this procedure, and on the basis of the evidence available, it is not recommended. In the future, bioprosthetic valve degeneration may be treated by use of the percutaneous valve replacement techniques discussed earlier. Already isolated case reports have suggested that this is a potentially viable option.

EVIDENCE

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Ben Farhat M, Ayari M, Maatouk F, et al. Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. *Circulation.* 1998;97:245–250.

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Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 practice guidelines for the management of patients with valvular disease. *J Am Coll Cardiol.* 2006;48:e1–e148.

Most recent update from the ACC and AHA on standards of care in treating valvular heart disease.

Boudjemline V, Agnoletti G, Bonnet D, et al. Steps toward the percutaneous replacement of atrioventricular valves: an experimental study. *J Am Coll Cardiol.* 2005;46:360–365.

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Dotter CT, Judkins MP. Transluminal treatment of atherosclerotic obstruction: description of a new technique and a preliminary report of its application. *Circulation.* 1964;30:654–670.

Landmark study showing percutaneous dilation of iliac artery stenosis.

Grube E, Schuler G, Buellesfeld L, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high risk patients using the second and current third generation self-expanding CoreValve prosthesis. *J Am Coll Cardiol.* 2007;50:69–76.

Showed that treatment of severe aortic valve stenosis in high-risk patients with percutaneous implantation of the CoreValve prosthesis was feasible and associated with a lower mortality rate than predicted by risk algorithms.

Harrison JK, Wilson JS, Hearne SE, Bashore TM. Complications related to percutaneous transvenous mitral commissurotomy. *Cathet Cardiovasc Diagn.* 1994;2(Suppl):52–60.

Describes incidence of complications of mitral valvuloplasty including cardiac perforation, embolic stroke, and severe mitral regurgitation.

Lurz P, Coats L, Khabadkone S, et al. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. *Circulation.* 2008:117:1964–1972.

Data demonstrating that percutaneous pulmonary valve implantation resulted in the ability to avoid surgical RV outflow tract revision in the majority of cases.

Multicenter experience with balloon mitral commissurotomy. NHLBI Balloon Valvuloplasty Registry Report on immediate and 30-day follow-up results. The National Heart, Lung, and Blood Institute Balloon Valvuloplasty Registry Participants. *Circulation.* 1992;85:448–461.

Reported that balloon mitral commissurotomy, as practiced in a broad range of experienced centers, produced significant short-term hemodynamic and clinical improvement.

Percutaneous balloon aortic valvuloplasty: acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry. *Circulation.* 1991;84:2383–2397.

Showed that in patients with reasonably preserved LV function who are otherwise inappropriate surgical candidates because of comorbid factors, survival and early improvement in symptomatic status are frequently observed after percutaneous aortic valvuloplasty.

Piazza N, Asgar A, Ibrahim R, Bonan R. Transcatheter mitral and pulmonary valve therapy. *J Am Coll Cardiol.* 2009;53:1837–1851.

Provides an update on the clinical status, applicability, and limitations of transcatheter mitral and pulmonary valve therapies.

Reyes VP, Raju BS, Wynne J, et al. Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. *N Engl J Med.* 1994;331:961–967.

Reported that in the treatment of mitral stenosis, balloon valvuloplasty and open surgical commissurotomy have comparable initial results and low rates of restenosis, and both produce good functional capacity for at least 3 years.

Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary. *J Am Coll Cardiol.* 2008;52:1890.

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Webb JG, Pasupati S, Humphries K, et al. Percutaneous aortic valve replacement in selected high risk patients with aortic stenosis. *Circulation.* 2007;116:755–763.

Demonstrated feasibility of percutaneous aortic valve replacement in high-risk patients with severe symptomatic aortic stenosis.

Zajarias A, Cribier AG. Outcomes and safety of percutaneous aortic valve replacement. *J Am Coll Cardiol.* 2009;53:1829–1836.

Midterm follow-up showed no evidence of restenosis or prosthetic valve dysfunction in 4000 cases worldwide treated with transcatheter aortic valve replacement for symptomatic aortic stenosis.

Surgical Treatment of Valvular Heart Disease

41

Michael E. Bowdish, Michael R. Mill, and Brett C. Sheridan

Competency of the atrioventricular valves allows blood to enter the ventricles, where pressure is generated. When adequate systolic blood pressure is generated, the aortic and pulmonary valves open, allowing blood to enter the arterial system. The atrioventricular valves close, preventing the flow of blood into the atria. During diastole, the aortic and pulmonary valves close, the atrioventricular valves open, and the ventricles fill and ultimately begin the cycle of pulsatile blood flow through the systemic and pulmonary vascular tree.

Malfunction of any of the cardiac valves results in a less efficient circulatory system. Valvular dysfunction causes work overload in one or both ventricles. In extreme cases, resultant congestive heart failure can cause death. More information about etiology, pathogenesis, differential diagnoses, and diagnostic approaches used for evaluation of valvular diseases can be found in Chapters 34 to 40.

Rheumatic heart disease was commonplace before the discovery of penicillin. Astute physicians recognized that mitral valve stenosis frequently occurred many years after an episode of rheumatic fever. As mitral valve "stenosis" progressed, medications provided symptomatic relief but did not interrupt the stenotic process, and a need to relieve the obstruction surgically was apparent. The first successful attempt at surgical treatment involved incising the left atrial appendage, placing a finger through the incision into the left atrium, feeling the stenotic mitral valve, and relieving the obstruction by simple finger pressure. Soon after these initial therapeutic approaches, special knives and dilators were developed to relieve mitral valve stenosis. In the early days of cardiovascular surgery these procedures were all performed on the beating heart.

The use of the anticoagulant heparin allowed blood to circulate outside a patient's vasculature without clotting and led to the development of cardiac and pulmonary bypass machines in the 1950s. It was then possible to keep the patient alive while stopping the heart for surgical repair. The ability to stop the heart, examine valve pathology, and attempt repair stimulated surgeons' collaboration with mechanical engineers to develop prosthetic valves to replace those that were too diseased to repair.

FIRST-GENERATION PROSTHETIC VALVES

Initial attempts to duplicate valve leaflets with flexible, nonbiologic materials failed. The leaflets of these valves were too stiff in comparison with normal valve leaflets. Efforts at using nonflexible leaflets by constructing hinged-valve leaflets resulted in hinge thrombosis and malfunction. Design engineers then focused on free-floating occluders, such as disks or balls retained in a cagelike housing. This general valve design produced the first clinically useful valves, including the Hufnagel, Starr-Edwards, Smeloff-Cutter, and Beall valves (Fig. 41-1). In 1958, the Starr-Edwards valve was used in the first clinically successful valve replacement.

Although these early designs functioned as intended, the first caged-ball valves had major shortcomings: (1) they were bulky in design and did not fit well into a small ventricle or aorta; (2) they had a small internal orifice, making them relatively stenotic; and (3) they stimulated thrombus formation, which precipitated thromboembolic events, necessitating long-term anticoagulation therapy.

SECOND-GENERATION PROSTHETIC VALVES

The disadvantages of early prosthetic valves led to the development of two divergent lines of valve design using synthetic materials (mechanical valves) or biologic tissue (bioprosthetic valves). The caged-ball valves were modified, and pivoting hingeless disk valves, such as the Lillehei-Kaster, Medtronic-Hall, and Björk-Shiley valves, were developed. The St. Jude and Carbomedics valves were the first successful hinged-leaflet valves (Fig. 41-2, top).

Homograft valves harvested at autopsy and preserved in antibiotic solution or frozen were the first nonsynthetic valves to be implanted successfully. Their limited availability prompted the use of porcine valves procured from slaughterhouses. Porcine valves were preserved with glutaraldehyde and mounted on modified nylon-covered plastic or metal stents. Valves made of pericardium were also developed and used successfully (Fig. 41-2, bottom). Porcine and bovine pericardial valves are commonly used bioprosthetic valves today, whereas the hinged-leaflet valves are the commonly used mechanical valves.

ETIOLOGY AND PATHOGENESIS

Cardiac valve pathology comprises two broad categories, congenital valve deformity and acquired valvular dysfunction. Congenital deformity can occur in one or more cardiac valves (see Section VIII). Patients with severe congenital valvular dysfunction can die if prompt surgical intervention is not undertaken. In patients with normally developed hearts, infection can cause valvular dysfunction at any age. Rheumatic heart disease secondary to untreated streptococcal infection and bacterial endocarditis can destroy a normal heart valve (Chapter 39). Generalized inflammatory illnesses, such as lupus erythematosus, rheumatoid arthritis, and eosinophilic endocarditis, as well as carcinoid disease, similarly can cause valvular dysfunction. Connective tissue diseases, such as Ehlers-Danlos syndrome and myxomatous degeneration, can cause valve deformity and dysfunction. Severe myocardial ischemia and injury can cause papillary muscle dysfunction, which can result in mitral valve

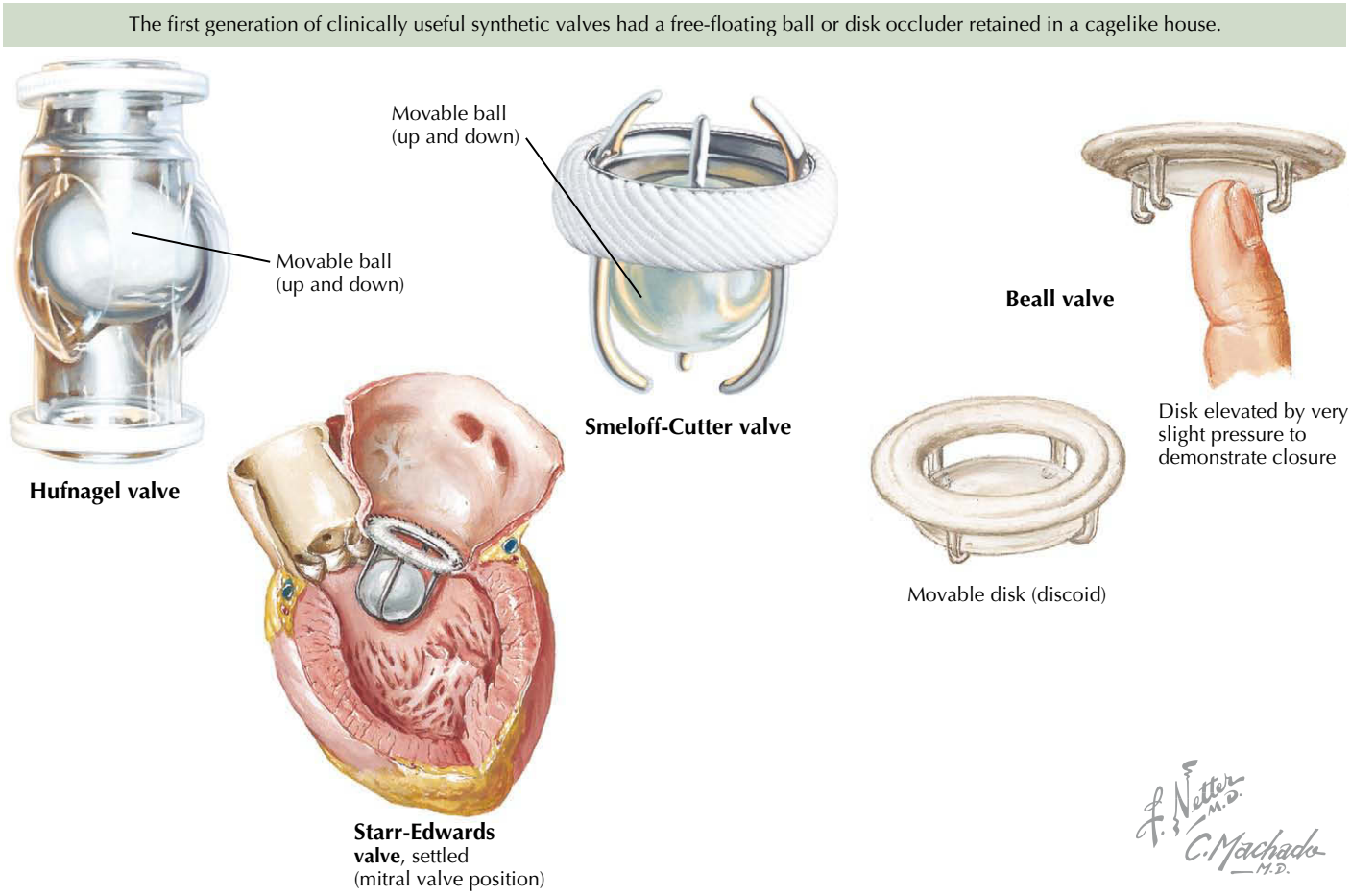


Figure 41-1 *First generation of synthetic prosthetic valves.*

insufficiency. Finally, just as aging often results in atherosclerotic changes and calcium deposition in arterial walls, so can it affect the aortic valves, sometimes with severe calcification of the leaflets (Chapter 34). The mitral valve annulus can also be severely calcified, with or without valvular dysfunction.

CLINICAL PRESENTATION

The presenting symptoms in patients with dysfunctional valves vary considerably, depending on the type and severity of dysfunction and the location of the affected valves. Diseased valves can become incompetent, stenotic, or both. Young patients with moderate aortic valve stenosis are often asymptomatic. Likewise, many patients with moderate mitral valve stenosis or insufficiency may be asymptomatic. In general, patients whose valve dysfunction progresses eventually experience dyspnea on exertion. Syncope or angina pectoris, alone or in association with dyspnea, can develop in patients with aortic stenosis.

DIFFERENTIAL DIAGNOSIS

In patients presenting with dyspnea and fatigue, noncardiac causes, such as anemia, hypertension, pulmonary pathology, and hypothyroidism, should be excluded. Primary cardiac myopathy (see Chapters 18–25) should be considered. Coronary artery disease must be ruled out if angina pectoris is a symptom.

DIAGNOSTIC APPROACH

Physical findings such as cardiac murmurs, wide pulse pressure, cardiomegaly, hepatomegaly, ascites, or pedal edema help to confirm abnormal circulatory conditions. Chest radiography and ECG offer supportive evidence of cardiac pathology. The most descriptive and definitive tests pinpointing cardiac valve anomalies are echocardiography in association with hemodynamic data from cardiac catheterization.

MANAGEMENT AND THERAPY

Optimum Treatment

SURGICAL THERAPY

A variety of procedures are available to treat cardiac valvular disease. Replacing diseased valves with prosthetic valves has become a routine procedure, and valve repair—particularly mitral and tricuspid valve repair—has evolved considerably. Techniques routinely used in the repair of mitral and tricuspid insufficiencies include ring annuloplasty, resection of prolapsing portions of leaflets not supported by chordae, shortening or

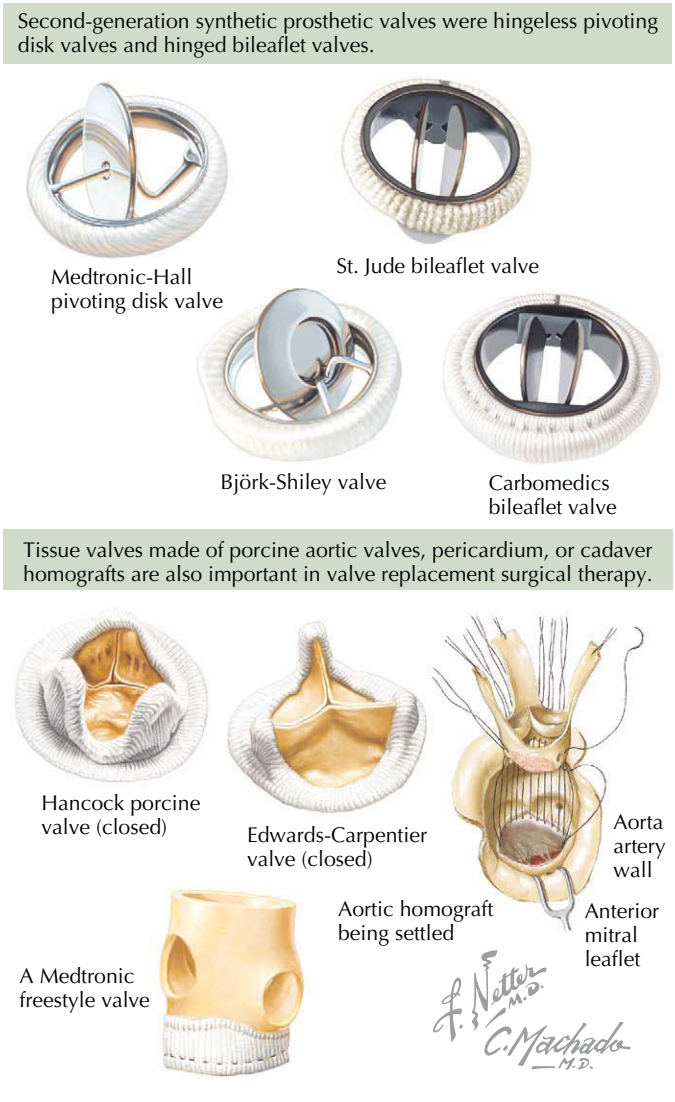


Figure 41-2 *Second generation of synthetic prosthetic valves and biologic valves.*

using artificial chordae, and increasing or decreasing the leaflet area by sliding annuloplasty (Fig. 41-3). In patients who need aortic valve replacement, some surgeons advocate aortic valve repair and resuspension if possible to preserve the native valve. An alternative to replacement is the Ross procedure, which entails transplanting a patient's pulmonary valve into the aortic position. This provides the patient with a living, durable, nonthrombogenic, and hemodynamically superior valve. The pulmonary valve is then reconstructed using a tissue homograft valve. The choice of procedure depends on many factors, including the patient's valve pathology, age, and ability to tolerate and comply with long-term anticoagulation.

MITRAL AND TRICUSPID VALVES

Patients with mitral and tricuspid valve pathology should be considered for valve repair rather than replacement, because the operative mortality associated with repair of these valves is lower than that associated with their replacement.

Conditions precluding satisfactory repair of the mitral and tricuspid valves include severe scarring and deformation by a disease process such as advanced rheumatic heart disease or advanced lupus, or another inflammatory process involving the valve leaflets and destruction of valve leaflets and annuli by endocarditis. Under these circumstances, the valve should be replaced (Fig. 41-4). Mitral valve replacement should include preservation of a portion of the subvalvular chordae and papillary muscles to aid in preserving normal ventricular contractility.

AORTIC VALVES

Adult patients with aortic valve pathology are seldom candidates for valve repair, and thus valve replacement is usually the preferred treatment for significant aortic stenosis or regurgitation. The patient's age, lifestyle and preferences, and the preferences of the surgeon dictate the type of prosthetic valve replacement (see Fig. 41-4B).

Avoiding Treatment Errors

ISSUES WITH PROSTHETIC VALVE REPLACEMENT

Patients with bioprosthetic valves have a lower incidence of bleeding, because long-term anticoagulation is not required in patients in sinus rhythm. Unfortunately, all bioprosthetic tissue valves eventually deteriorate and become insufficient. Deterioration of tissue valves occurs at an accelerated rate in younger patients and in patients with end-stage renal disease on hemodialysis. For older patients, particularly those with a risk of falling, a bioprosthetic valve may be the most appropriate choice, because long-term anticoagulation is not required for bioprosthetic aortic valves. Younger patients, with a natural life expectancy exceeding 15 to 20 years, should have prosthetic valves made of durable synthetic materials, such as pyrolytic carbon, titanium, stainless steel, or a combination of these. Use of mechanical valves necessitates indefinite anticoagulation.

Mechanical valves must have an appropriate sewing ring sutured to the annulus of the patient's valve after the leaflets are excised. Sewing rings are usually circular and rigid and vary in thickness. The rigid sewing rings change the natural shape of the valve annulus and, depending on thickness, decrease the size of the internal orifice of the prosthetic valve. Implanting a valve with a circular sewing ring into a noncircular annulus can generate unnatural tension between the valve annulus and sewing ring, which can lead to paravalvular leaks; the surgical approach in these instances must take this possibility into account.

The use of rigid circular sewing rings is unnecessary in bioprosthetic valves implanted in the aortic position. Freehand suturing is used to insert autograft pulmonary valves into the aortic position (the Ross procedure). It is also used in homograft cadaver valve implantation and with nonstented freestyle porcine valves.

MINIMALLY INVASIVE TECHNIQUES

Minimally invasive coronary artery revascularization surgery uses small incisions and therefore is performed on a beating

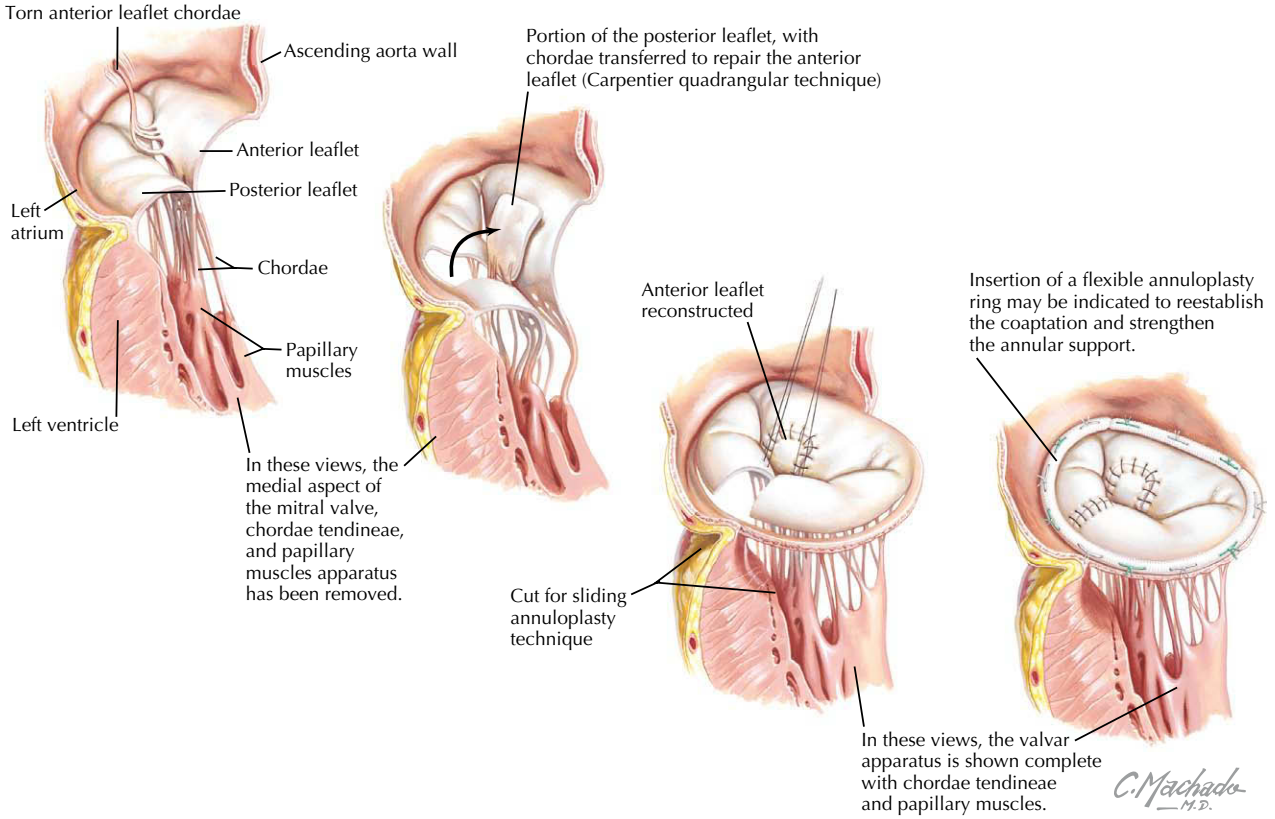


Figure 41-3 *Chordal transfer, sliding annuloplasty, and ring annuloplasty.*

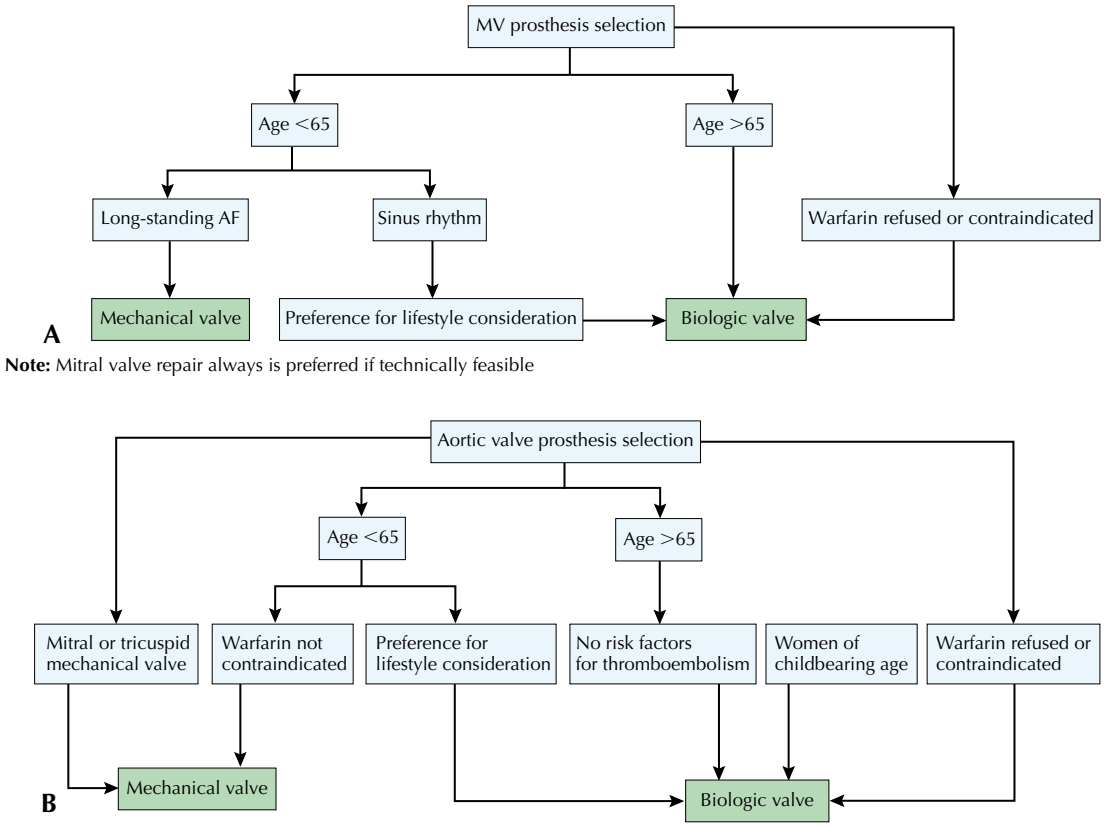


Figure 41-4 *Algorithm for prosthesis selection in valvular heart disease.* **A**, mitral valve (MV) prosthesis selection. **B**, aortic valve prosthesis selection. AF, atrial fibrillation. Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Valvular Heart Disease). *Circulation.* 2006;114:e84–e213.

Exposing the mitral valve through the interatrial septum and an extension of the incision through the roof of the left atrium is common. This surgical exposure allows excellent visualization of the mitral and tricuspid valves and can be performed through a standard sternotomy, as well as through a variety of partial sternotomy and right thoracotomy incisions.

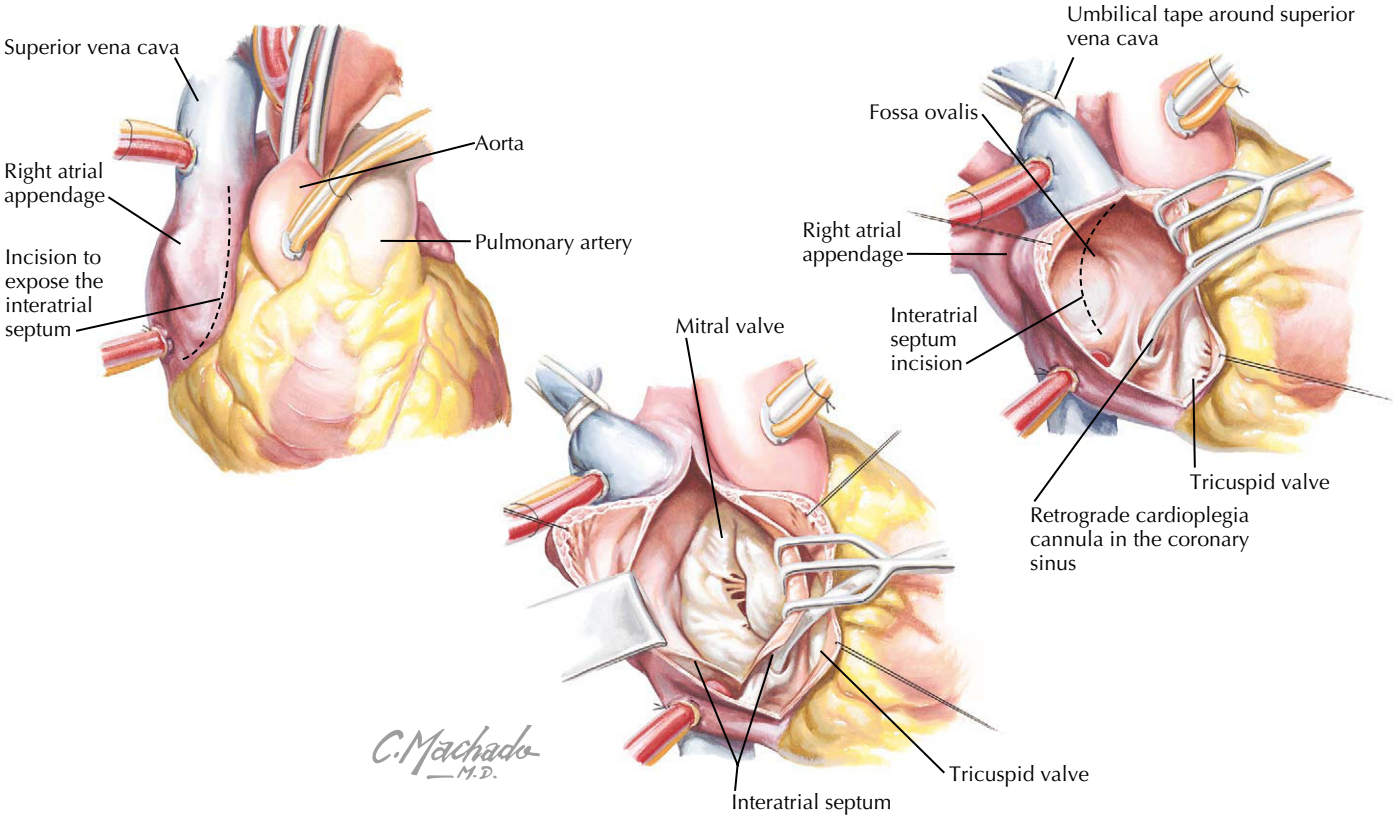


Figure 41-5 *Exposing the mitral valve through the interatrial septum.*

heart, obviating the use of cardiopulmonary bypass. In valve repair and replacement procedures, the use of smaller incisions is possible, but eliminating cardiopulmonary bypass is not feasible with current techniques and prosthetic valves.

Good visualization of the operative field is a prerequisite for proper valve repair or replacement. Smaller incisions limit visualization, although the use of miniature video cameras improves the view of the operative field. The mitral valve is generally the most difficult to visualize, so many surgeons approach it through the interatrial septum, sometimes extending the incision to the roof of the left atrium (Fig. 41-5).

FUTURE DIRECTIONS

Refinements in manufacturing mechanical prosthetic valves and their sewing rings will continue to decrease thromboembolic complications while improving their hemodynamic characteristics. Better chemical preservation of bioprosthetic valves will improve their longevity and resistance to deterioration and make bioprosthetic valves a more attractive choice for younger patients.

The teaching of valve repair techniques to surgical trainees is already becoming more standardized. The appropriate surgical repair technique will be more predictable from the preoperative evaluation including echocardiographic and hemodynamic data. Freehand valve implantation techniques will find increased use in selected patients, particularly for patients in whom the annulus is small and the valve sewing rings make the prosthetic valves too stenotic. Finally, with clinical acceptance of genetic engineering, farms of genetically altered pigs and baboons might provide viable biologic leaflets, valves, and entire hearts for implantation.

ADDITIONAL RESOURCE

Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Valvular Heart Disease). *Circulation.* 2006;114:e84–e213.

ACC/AHA guidelines regarding the management of patients with valvular heart disease. Essential reading for clinicians caring for patients with valvular heart disease.

EVIDENCE

Moon MR, Pasque MK, Munfakh NA, et al. Prosthesis-patient mismatch after aortic valve replacement: impact of age and body size on late survival. *Ann Thorac Surg.* 2006;81:481–489.

Important contribution regarding patient size and valve size in aortic valve replacement.

Carpentier A. Cardiac valve surgery: The "French connection." *J Thorac Cardiovasc Surg.* 1983;86:323–337.

Important contribution to mitral valve repair surgery.

David TE, Ivanov J, Armstrong S, Rakowski H. Late outcomes of mitral valve repair for floppy valves: implications for asymptomatic patients. *J Thorac Cardiovasc Surg.* 2003;125:1143–1152.

Outcomes for mitral valve repair from a leading center for patients with myxomatous disease.

David TE, Feindel CM, Webb GD, et al. Long-term results of aortic valve-sparing operations for aortic root aneurysm. *J Thorac Cardiovasc Surg.* 2006;132:347–354.

Important contribution regarding aortic valve repair.

Pericardial Disease: Clinical Features and Treatment

42

Christopher D. Chiles and George A. Stouffer

The pericardium is a two-layered sac that encircles the heart (Fig. 42-1). The visceral pericardium is a mesothelial monolayer that adheres to the epicardium. It is reflected back on itself at the level of the great vessels, where it joins the parietal pericardium, the tough fibrous outer layer. Under normal conditions, a small amount of fluid (approximately 5–50 mL) separates the two layers and decreases friction between them.

The normal pericardium serves three primary functions: fixing the heart within the mediastinum, limiting cardiac distension during sudden increases in intracardiac volume, and limiting the spread of infection from the adjacent lungs. However, the importance of these functions has been questioned because of the benign prognosis associated with congenital absence of the pericardium.

This chapter discusses the clinical features and treatment of four pathologic conditions involving the pericardium: acute pericarditis, chronic pericarditis, constrictive pericarditis, and pericardial effusions. The hemodynamic effects of pericardial pathology are discussed in Chapter 43.

ACUTE PERICARDITIS

Etiology and Pathogenesis

The most common presentation of a pericardial abnormality is acute pericarditis, inflammation of the pericardium (Fig. 42-2). In general, this is a self-limited disease that is responsive to oral anti-inflammatory medication. Acute pericarditis infrequently necessitates hospital admission. It is more common in men than in women and more common in adults than in children. The two most common causes of acute pericarditis in the United States are viral and idiopathic. Other causes include uremia, pericardiectomy associated with cardiac surgery, pulmonary embolism, collagen-vascular diseases, Dressler's syndrome, malignancy, tuberculosis, fungus (e.g., histoplasmosis), parasites (e.g., ameba), myxedema, radiation, acute rheumatic fever, and trauma (Fig. 42-3).

Clinical Presentation

The clinical presentation of pericarditis most often is dominated by chest pain, which is generally sharp, pleuritic, and positional in nature. Classically, the pain is increased by lying supine and improved by leaning forward. Symptoms may include dyspnea, palpitations, coughing, and fever, and the patient may have a history of a viral prodrome. On physical examination a pericardial friction rub is generally the most remarkable finding. The classic description is of a scratchy sound heard best along the lower left sternal border. It typically has three components (when the patient is in sinus rhythm), which correspond to atrial systole, ventricular systole, and rapid ventricular filling during early diastole. The component corresponding to rapid ventricular filling (atrial systole) may be absent, resulting in a two-component friction rub. In one series of 100 patients with acute pericarditis, a three-component friction rub was detected in approximately 50% of the patients, whereas any friction rub (one component, two components, or three components) was present in almost all cases.

Differential Diagnosis

The differential diagnosis of acute pericarditis includes other pathologies involving the chest and heart, with two of the most common being myocardial ischemia and pulmonary embolus. Features that distinguish the discomfort of myocardial ischemia from acute pericarditis include previous exertional symptoms, lack of variation with respiration or position, associated symptoms of nausea or diaphoresis, and/or dyspnea. In addition, the discomfort of pericarditis is often described as "sharp" or "stabbing," whereas the pain of myocardial infarction is pressure-like. ECG changes of ST elevation can be seen in both pericarditis and myocardial ischemia (infarction); however, the ST elevation present with myocardial ischemia or infarction is generally localized to a vascular bed and is accompanied by reciprocal ST depression in myocardial infarction. PR depression is common in acute pericarditis and exceedingly rare in myocardial infarction (it would imply atrial infarction in this setting). Cardiac biomarkers can be elevated in both conditions.

The pain associated with pulmonary embolus can mimic acute pericarditis in that it is pleuritic in nature, but associated symptoms and diagnostic evaluation including arterial blood gas and ECG can help differentiate these conditions. Other conditions that can mimic acute pericarditis include disease states that involve inflammation of structures in close proximity to the pericardium including cholecystitis, pancreatitis, and pneumonia.

Diagnostic Approach

The diagnosis of acute pericarditis is based on clinical criteria, but the ECG can make an important contribution. The lack of ECG changes cannot exclude the diagnosis of pericarditis. That said, most patients progress through one or more of the four stages of ECG changes commonly associated with the evolution of acute pericarditis (see Fig. 42-2 (ECG); Fig. 42-4). Stage I changes accompany the onset of chest pain and include the classic ECG changes associated with acute pericarditis: diffuse concave ST elevation with PR depression (see Chapter 4). Stage II occurs several days later and is represented by the return of ST segments to baseline and T-wave flattening. In stage III, T-wave inversion is seen in most leads. The ECG in stage IV shows the return of T waves to an upright position. The

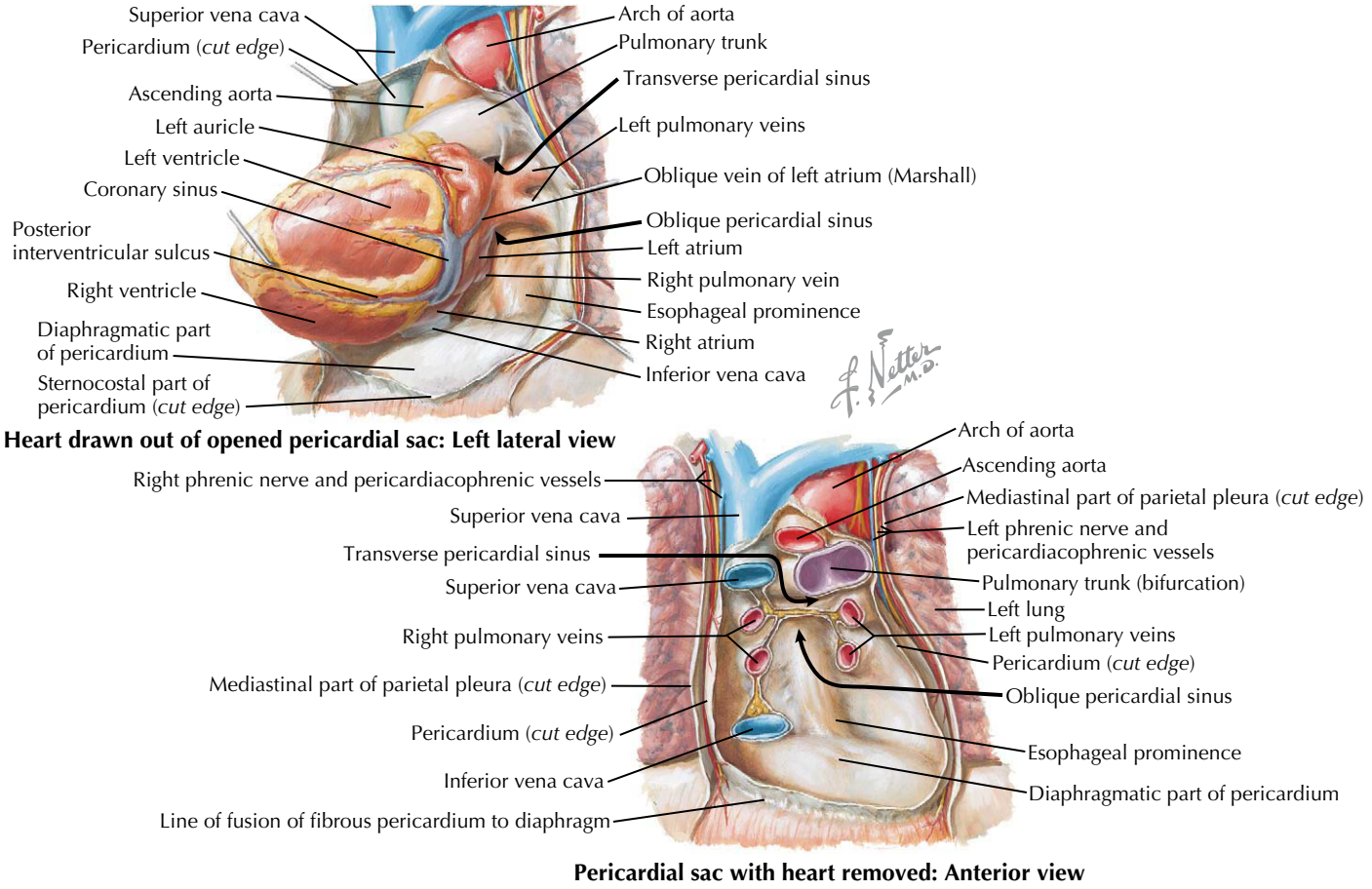


Figure 42-1 *The anatomy of the pericardium.*

approximate time frame for passage through all four stages of ECG changes in most cases of acute pericarditis is 2 weeks.

Electrocardiographic abnormalities are present in approximately 90% of patients with acute pericarditis, but only about 50% of patients show all four stages. Other ECG presentations include isolated PR depression, absence of one or more stages, and persistence of T-wave inversion. Atrial arrhythmias are seen in 5% to 10% of cases.

Laboratory studies are nondiagnostic in acute pericarditis. Nonspecific markers of inflammation may be present, including an elevated white blood cell count. If concurrent myocarditis is present, serum levels of cardiac biomarkers (creatine kinase and troponin) may be elevated. An echocardiogram may or may not show a pericardial effusion.

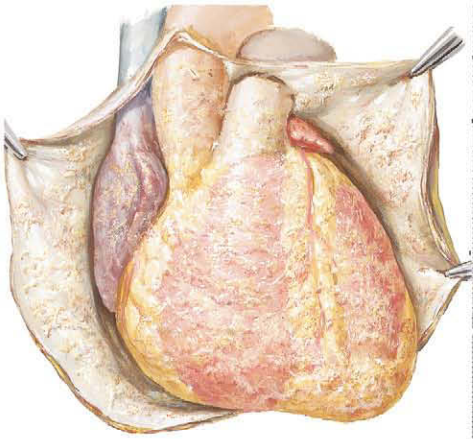
Management and Therapy

OPTIMUM TREATMENT

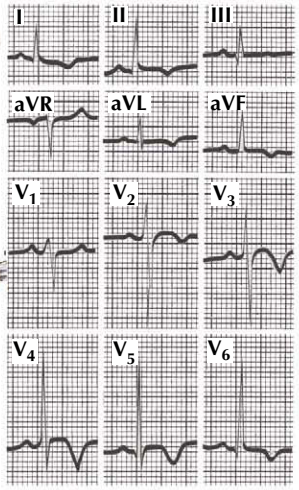
Most cases of acute pericarditis are self-limited, although symptoms can persist for weeks. The goals of acute pericarditis management include pain relief, identification and treatment of the underlying cause, and observation for evidence that a pericardial effusion is developing with or without pericardial tamponade. Nonsteroidal anti-inflammatory agents are generally first-line therapy for pain relief, but steroids may be used if pain does not improve within 48 hours. Therapy with colchicine has also been shown to provide more rapid relief of symptoms than aspirin and reduces the rate of recurrent symptoms. Tamponade has been reported in up to 15% of patients with acute pericarditis. Transient constrictive physiology within the first 30 days after an acute episode of pericarditis is found in some patients—9% of patients with pericarditis in one study—but generally is self-limiting and abates within 3 months. Constrictive pericarditis develops in a small group of patients with acute pericarditis but generally is not clinically evident for many years (discussed in more detail later).

AVOIDING TREATMENT ERRORS

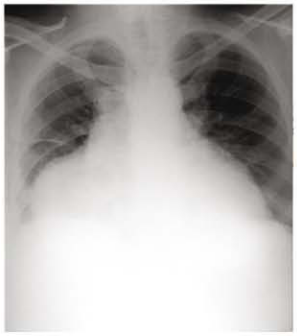
Acute pericarditis can be confused with several life-threatening disorders including myocardial ischemia and pulmonary embolus. A careful history and physical examination in combination with accurate ECG interpretation will often establish the diagnosis of acute pericarditis. It is also important to consider the pre-test probability of various disorders in a specific patient;



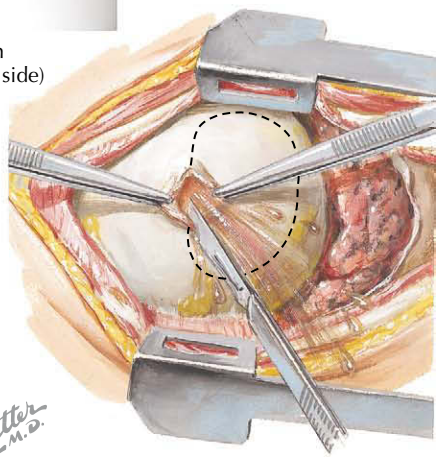
Mild fibrinous pericarditis



Characteristic ECG changes: T-wave inversion in all leads except aVR and V_1; isoelectric in lead III



Pericardial effusion (loculated on right side)



Pericardial effusion; pleuropericardial window being created and biopsy specimen taken via incision in the 5th left intercostal space

Figure 42-2 *Diseases of the pericardium: Presentation and treatment of pericarditis.* ECG, electrocardiographic.

the risk of myocardial infarction will be higher in older patients with coronary artery disease risk factors, the risk of pulmonary embolus is increased in individuals with prothrombotic disorders or recent immobilization, and the likelihood of acute pericarditis is increased in younger patients with an antecedent viral illness. In cases wherein the diagnosis remains in doubt, the patient should be admitted to the hospital for observation and undergo further evaluation.

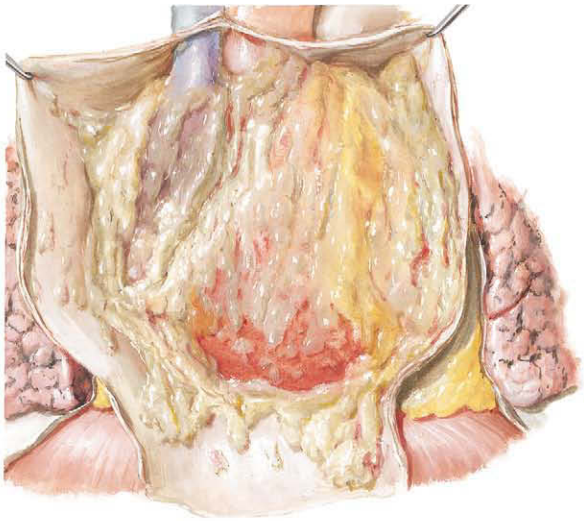
CHRONIC OR RECURRENT PERICARDITIS

Recurrent or chronic symptoms develop in approximately 25% of patients with acute pericarditis. The mechanism is unknown, although there is evidence that recurrent infection or autoimmune processes may have a contributory role in individual patients. Most cases of recurrent pericarditis are treated with reinstitution of nonsteroidal anti-inflammatory agents or steroids. There are data that colchicine reduces recurrent symptoms in comparison to aspirin. In severe cases, more potent immunosuppressive therapy and even pericardiectomy are occasionally necessary.

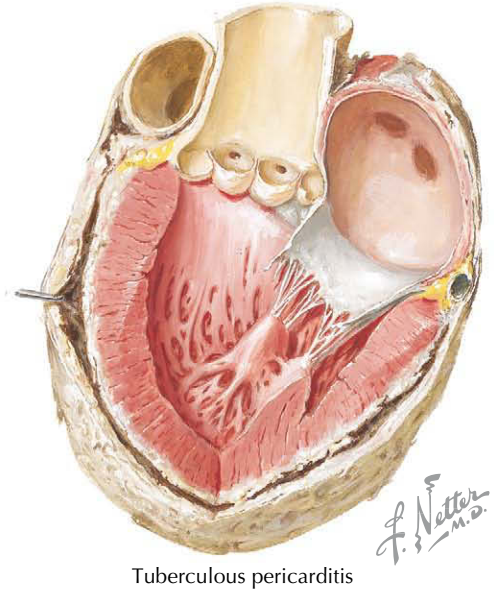
CONSTRICTIVE PERICARDITIS

Etiology and Pathogenesis

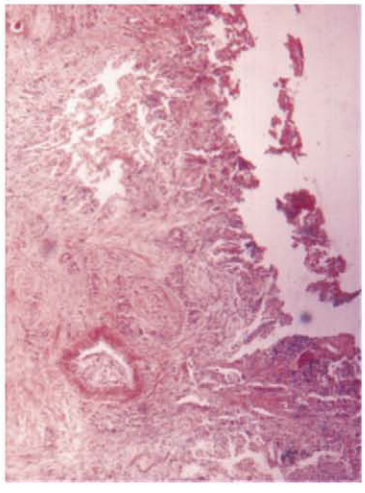
Constrictive pericarditis is characterized by a dense, fibrous thickening of the pericardium that adheres to and encases the myocardium, resulting in impaired diastolic ventricular filling (Fig. 42-5). The general paradigm is that constrictive pericarditis occurs over a period of years as a result of an acute injury (e.g., a viral infection) that elicits a chronic fibrosing reaction or as a result of a chronic injury that stimulates a persistent reaction (e.g., renal failure). Clinically, constrictive pericarditis generally is a chronic disease with symptom progression over a period of years. The presentation is that of right-sided heart failure and may resemble restrictive cardiomyopathy, cirrhosis, cor pulmonale, or other conditions. Because pericardial constriction is uncommon, patients occasionally are treated for an incorrect diagnosis (left- or right-sided heart failure, hepatic failure, or others) for years. Patients with pericardial constriction often have even been admitted to a hospital for symptoms attributed to other causes before a definitive diagnosis of constriction is made. Newer diagnostic technologies and a change in the predominant etiologies of constriction have increased the recognition of subacute presentations occurring over a period of months.



Purulent pericarditis



Tuberculous pericarditis



Biopsy specimen revealing carcinomatous infiltration of pericardium

Figure 42-3 *Diseases of the pericardium: Etiologies.*

The most common causes of constriction in industrialized countries are cardiac surgery, mediastinal radiation, pericarditis, and idiopathic etiologies (Table 42-1). Other causes include infection (e.g., fungal or tuberculosis), malignancies such as breast cancer or lymphoma, connective tissue disease (e.g., systemic lupus erythematosus or rheumatoid arthritis), trauma, and drugs.

Clinical Presentation

HISTORY

The symptoms and signs of constrictive pericarditis result from reduced cardiac output (CO), elevated systemic venous pressure, and pulmonary venous congestion. The typical history is progressively worsening dyspnea, edema, or other volume overload symptoms. Patients generally have features of right-sided heart failure with ascites and edema, but other features may include anorexia, nausea, fatigue, orthopnea, and, sometimes, cardiac tamponade, atrial arrhythmia, and frank liver disease. Chest pain typical of angina may be related to underperfusion of the coronary arteries or compression of an epicardial coronary artery by the thickened pericardium.

PHYSICAL EXAMINATION

The physical examination in constrictive pericarditis generally reveals increased jugular venous pressure, a prominent *y* descent in the jugular pulse, and an increase of jugular venous pressure on inspiration (Kussmaul's sign), resulting from the thickened pericardium's impairment of venous return to the right side of the heart. The pulse pressure may be reduced, and a pulsus paradoxus may be present in up to one third of patients. Tachycardia may develop to compensate for the diminished stroke volume. The apical impulse is reduced, and it is rarely displaced because the heart size is generally normal. The heart sounds may be distant, and the first heart sound is typically soft because the mitral and tricuspid valves are nearly closed at end diastole (because almost all ventricular filling occurs early in diastole). A pericardial knock (heard best along the left sternal border) often occurs shortly after the second heart sound as a result of a sudden deceleration of ventricular filling. A pericardial knock may be confused with an S_3 gallop, but knocks usually occur earlier in the cardiac cycle and have a higher acoustic frequency. Pericardial knocks can also be confused with the opening snap of mitral stenosis. Murmurs found at diagnosis are generally unrelated to pericarditis. Ascites, pleural effusions, and peripheral edema may be found. Additionally, hepatosplenomegaly and its clinical sequelae, such as protein-losing enteropathy from impaired lymphatic drainage from the gut, may occur. Because the most impressive physical findings are often the insidious development of hepatomegaly and ascites, patients with constrictive pericarditis may initially be mistakenly thought to have hepatic cirrhosis or an intra-abdominal tumor.

Differential Diagnosis

Constrictive pericarditis and restrictive cardiomyopathy are very different diseases sharing a similar hemodynamic profile.

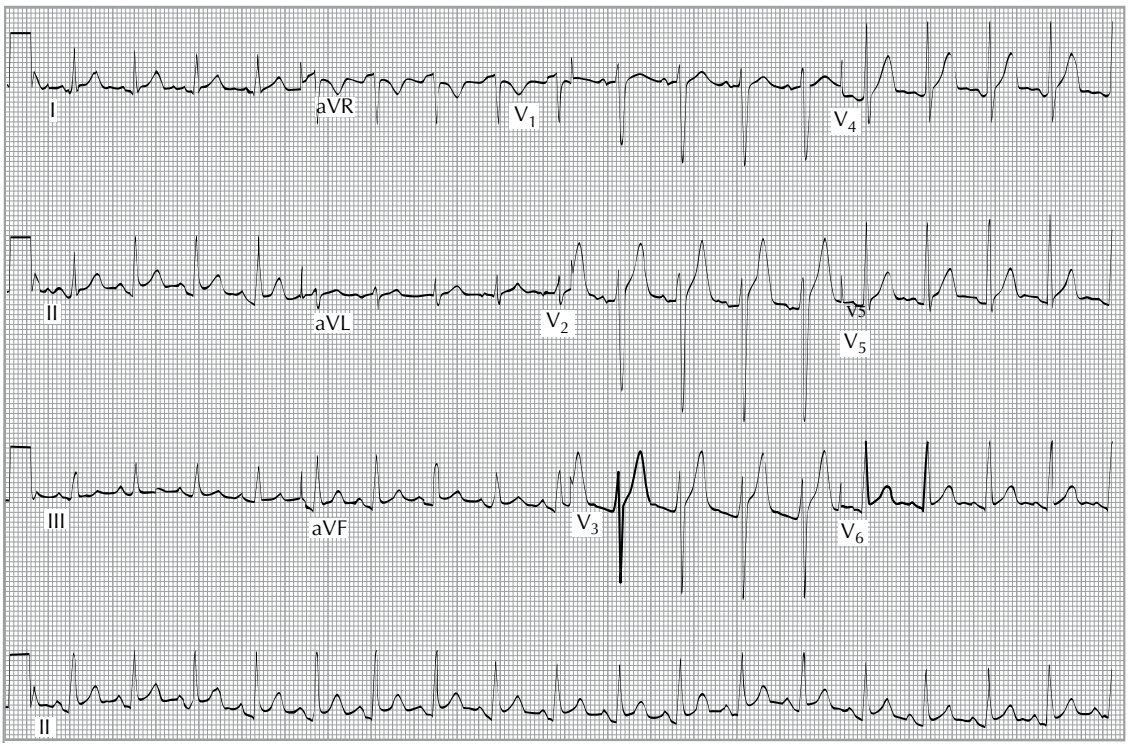


Figure 42-4 *Typical stage I electrocardiographic findings in a patient with acute pericarditis.* Note diffuse ST.

The primary hemodynamic abnormality in both conditions is impaired diastolic filling of the ventricles. In the case of constrictive pericarditis, the impediment to filling is caused by the thickened unyielding pericardium. In restrictive cardiomyopathy, the abnormality is a result of a poorly compliant myocardium that limits the ability of the ventricles to expand and accept the filling volume of the atria. Rarely, there is overlap, and both entities can coexist (e.g., radiation-induced myopericardial disease). The heart failure that develops is insidious in onset and predominantly right sided. These syndromes may mimic many other disease entities, and it is common for both conditions to go undiagnosed for years.

The differentiation of these two entities can be challenging to the clinician. Although various hemodynamic factors are helpful in differentiating constrictive pericarditis from restrictive cardiomyopathy, commonly it is not possible to arrive at a firm diagnosis of either condition based on hemodynamics alone. Plain chest x-ray has some value in chronic pericardial constriction as calcification of the pericardium can be seen in up to 25% of cases. Pericardial thickening can sometimes be

Table 42-1 Mayo Clinic Experience: Causes of Constrictive Pericarditis and Pericardial Effusions Requiring Pericardiocentesis in Different Cohorts

	CP		***PE***		
	1936–1982 (*n* = 231) %	**1985–1995 (*n* = 135) %**	**1979–1986 (*n* = 182) %**	**1986–1993 (*n* = 354) %**	**1993–2000 (*n* = 441) %**
Idiopathic	73	33	9	8	8
Infectious	6	3	7	4	7
After cardiac surgery	2	18	21	22	28
Connective tissue disease	2	7	6	3	4
Exposure to radiation	5	13	—	—	—
Acute pericarditis	10	16	—	—	—
Invasive procedure	—	—	4	9	14
Neoplastic	—	—	41	39	25

CP, constrictive pericarditis; PE, pericardial effusion requiring pericardiocentesis.
Adapted from Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. Circulation. *1999;100:1380–1386; and Tsang TS, Enriquez-Sarano M, Freeman WK, et al. Consecutive 1127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years.* Mayo Clin Proc. *2002:77:429–436.*

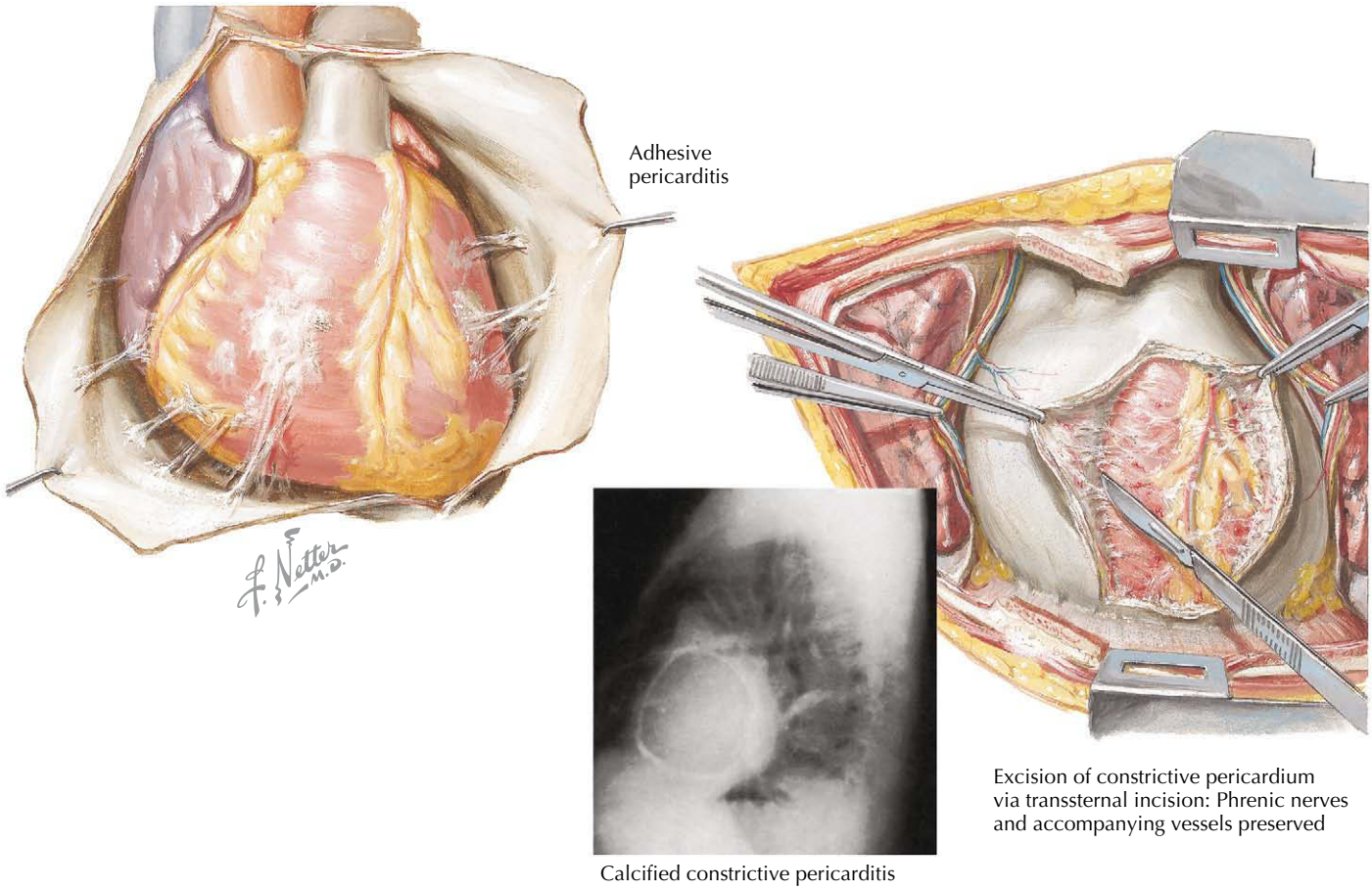


Figure 42-5 *Diseases of the pericardium: Constrictive pericarditis.*

visualized by echocardiography but must be distinguished from gain artifact or harmonics, and a lack of pericardial thickening on echocardiography does not rule out constrictive pericarditis. Pericardial effusions can be seen but are generally small. CT scanning and cardiac MRI are now widely used to visualize the pericardium in patients with suspected constrictive pericarditis. A pericardial thickness of greater than 3 mm is suggestive of pericardial constriction, but it is important to note that pericardial thickening is absent in 20% of cases. Similarly, not all patients with thickened pericardium will have constrictive pericarditis; however, a thickness of greater than 6 mm adds considerable specificity to the diagnosis.

Diagnostic Approach

Laboratory evaluation might show the result of congestive hepatopathy with an elevated bilirubin concentration, mild elevation of hepatic transaminase concentrations, a low albumin concentration, and an elevated prothrombin time.

Electrocardiographic results are rarely normal in constriction. They may reveal low-voltage QRS and diffuse flattening of the T waves. Low voltage can result from effusive constrictive disease or myocardial atrophy. Conduction abnormalities and other nonspecific abnormalities may be present. Atrial fibrillation occurs in approximately one third of patients.

When tuberculous pericarditis was common, chest radiography showed classic pericardial calcification in up to one third of chronic cases, but this finding is less common today (see Fig. 42-5). Indeed, the lack of pericardial calcification in constrictive pericarditis is now the rule rather than the exception. Alveolar edema and radiographic evidence of congestive heart failure are rarely present and should suggest consideration of alternative diagnoses. Cardiac size is generally normal.

The two-dimensional echocardiographic features of constriction include a thickened pericardium, abnormal ventricular septal motion, flattening of the left ventricular (LV) posterior wall during diastole, respiratory variation in ventricular size, and a dilated inferior vena cava. Doppler echocardiographic features include impaired diastolic filling and dissociation of intracardiac and intrathoracic pressures. The thickened pericardium acts as a buffer to the transmission of the usual intrathoracic pressure changes on the intrapericardial structures. This dissociation between the respiratory (intrathoracic) pressure variations is one feature of constriction but may also occur in tamponade. This may be seen as an inspiratory decrease in the mitral inflow velocity greater than 25%. A decrease in LV filling during inspiration allows more room for right ventricular (RV) filling as the interventricular septum moves to the left and hepatic diastolic flow velocities increase. During expiration, LV filling increases, with a concomitant decrease in right-sided heart filling and a decrease

in hepatic diastolic forward-flow velocity. In constriction, diastolic forward flow is usually greater than systolic forward flow. Additionally, hepatic diastolic flow reversal is increased, because the inflow across the tricuspid valve is interrupted by the pericardium and movement of the septum toward the right ventricle with expiration.

CT and MRI of the heart can be important in determining pericardial thickness. These modalities directly visualize the pericardium and can detect thickness greater than 2 mm. The finding of normal pericardial thickness does not exclude constrictive pericarditis, because up to 20% of patients with surgically confirmed disease have normal pericardial thickness on these imaging modalities. Recall that not all patients with a thickened pericardium have constrictive pericarditis, but a thickness greater than 6 mm adds considerable specificity to the diagnosis.

Left- and right-sided heart catheterization provides important information in evaluating potential constrictive pericarditis. There are three key features: elevation and equalization of the diastolic pressures in each cardiac chamber, an early diastolic "dip-and-plateau" configuration in the RV and LV tracings, and a prominent *y* descent on right atrial (RA) pressure tracings. (For a more detailed discussion of hemodynamics, see Chapter 43.)

Management and Therapy

OPTIMUM TREATMENT

Chronic constrictive pericarditis is a progressive disease without spontaneous reversal of pericardial abnormalities, symptoms, or hemodynamics. A minority of patients survive for years with modest jugular venous distention and peripheral edema controlled by the judicious use of diuretics and dietary restriction of sodium intake. Drugs that slow the heart rate (e.g., β-blockers and calcium channel blockers) should be avoided, because mild sinus tachycardia is a compensatory mechanism. The majority of patients become progressively more disabled and experience the complications of severe cardiac cachexia.

The mainstay of therapy is surgical removal of the pericardium. In cases with a firmly adherent pericardium, scoring of the pericardium may "loosen" it, but results are less than optimal in many cases. Pericardiectomy is associated with significant risk for morbidity and mortality, especially in elderly patients or those with significant preoperative symptoms, organ dysfunction, or coexisting coronary artery disease. Mortality with pericardiectomy has also been reported to range from 5.6% to 19% and to correlate with RA pressure. In one series, survival of individuals after pericardiectomy at 5 and 10 years was 78 ± 5% and 57 ± 8%, respectively, and was inferior to those of an age- and sex-matched U.S. population. In another single-center series, long-term survival after pericardiectomy was related to the etiology of the constrictive pericarditis, LV systolic function, renal function, serum sodium, and pulmonary artery systolic pressure. Idiopathic constrictive pericarditis had the best prognosis followed by postsurgical and postradiation. Pericardial calcification had no impact on survival.

Of patients who survive the pericardiectomy, 90% report symptomatic improvement, and approximately 50% become asymptomatic. Symptom resolution may be immediate but can take weeks to months. However, symptoms may recur.

AVOIDING TREATMENT ERRORS

A major difficulty in treating patients with constrictive pericarditis is that the diagnosis is often made many years after symptoms develop. As noted, pericardiectomy is associated with significant morbidity and mortality, and, in general, outcomes are better in patients with higher functional status before the operation.

PERICARDIAL EFFUSION

Etiology and Pathogenesis

Pericardial effusions are generally exudative and a response to pericardial injury. Exudative effusions occur secondary to inflammatory, infectious, malignant, or autoimmune processes within the pericardium. Transudative effusions are rare but can result from obstructed fluid drainage, which occurs through lymphatic channels. The hemodynamic effects of pericardial effusions occur on a spectrum with increasing pericardial pressure resulting in increased intracardiac diastolic pressures. Cardiac tamponade is a clinical syndrome caused by increased intrapericardial pressure due to the accumulation of exudative fluid, blood, pus, other fluid, or gas in the pericardial space. Cardiac tamponade can cause hemodynamic collapse by impairing venous return, which impairs diastolic ventricular filling and CO.

There are few data regarding etiologies of pericardial effusions in a community setting or in patients who do not require drainage. The most common etiologies requiring pericardiocentesis include malignancy, previous cardiac surgery, a complication during a percutaneous procedure (e.g., RV perforation during pacemaker lead placement), idiopathic etiologies, connective tissue disorder, and infection (Table 42-1). Other causes include acute pericarditis, renal failure, coagulopathy, hypothyroidism, trauma, previous radiation, human immunodeficiency virus infection, and myocardial infarction. Transudative effusions are rarely seen in congestive heart failure, cirrhosis, nephrosis, and pregnancy.

Pericardial effusions are common after cardiac surgery, occurring in more than 80% of cases. The maximal size is apparent by 10 days, and the effusions usually resolve spontaneously within 1 month after surgery.

Malignancy is one of the most common causes of pericardial effusions, reported in up to 20% of patients with cancer in autopsy series. The primary tumors most often associated with pericardial effusions are lung (40%), breast (23%), lymphoma (11%), and leukemia (5%). Pericardial effusions in patients with cancer are malignant approximately 50% of the time. Nonmalignant causes of pericardial effusions in patients with cancer include radiation-induced pericarditis and infections.

Clinical Presentation

Clinical manifestations of pericardial effusion depend on the intrapericardial pressure, which, in turn, depends on the

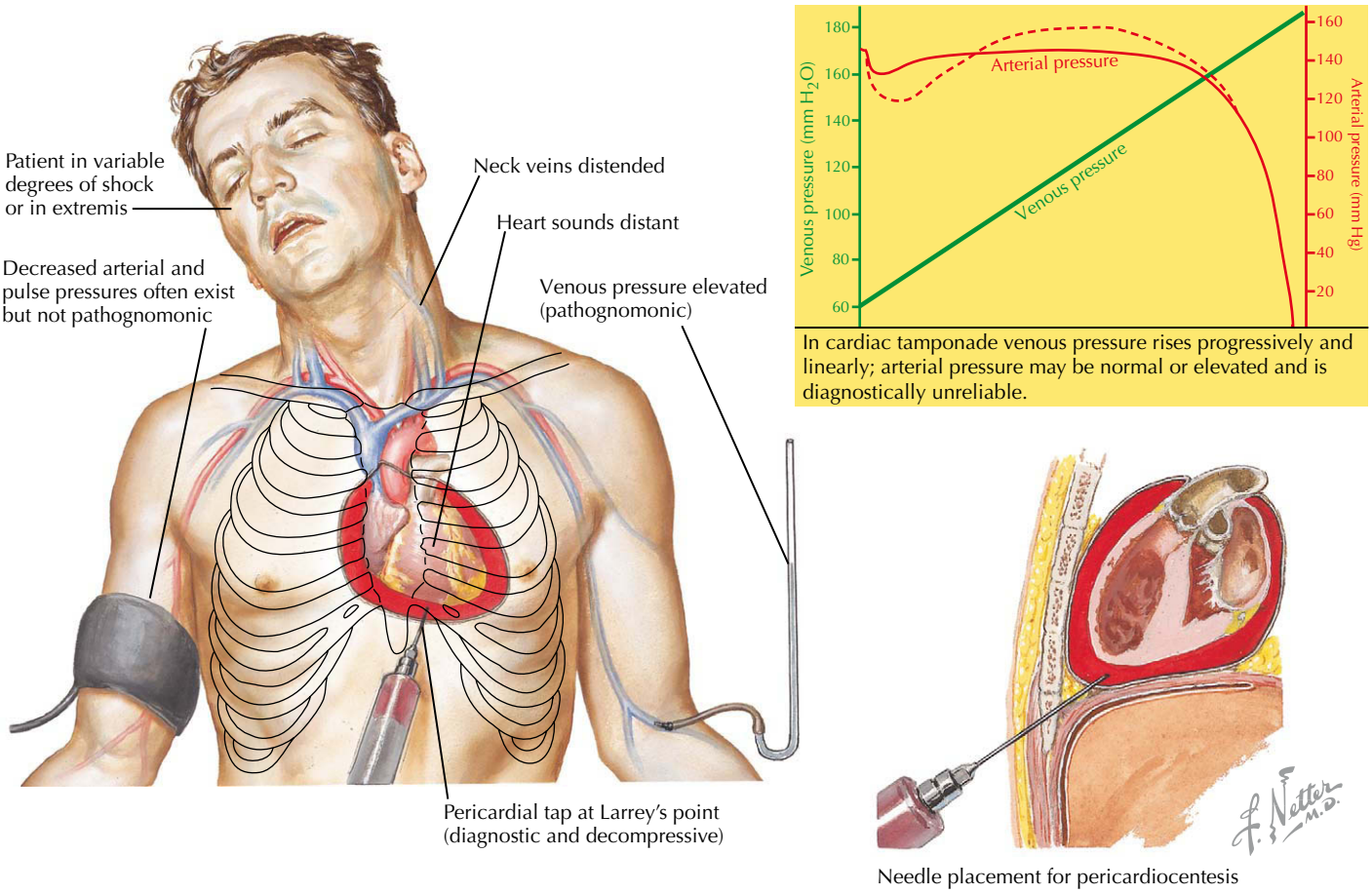


Figure 42-6 *Cardiac tamponade.*

amount and rate of fluid accumulation in the pericardial sac. As intrapericardial pressure increases, ventricular diastolic pressure increases. Atrial pressures increase to maintain forward flow across the tricuspid and mitral valves. Further increases in intrapericardial pressure cause ventricular filling to decrease, leading to impaired CO and hypotension. Rapid accumulation of pericardial fluid may elevate intrapericardial pressures with as little as 80 mL of fluid, whereas slowly progressing effusions can grow to 2 L without symptoms. When pericardial fluid accumulation is rapid or sustained, pericardial tamponade may result, the hemodynamics of which are discussed in detail in Chapter 43.

HISTORY AND PHYSICAL EXAMINATION

Most pericardial effusions are asymptomatic. Once symptoms occur, the most common complaints include dyspnea (85%), coughing (30%), orthopnea (25%), and chest pain (20%). The common signs of pericardial effusion are a paradoxic pulse (45%), tachypnea (45%), tachycardia (40%), hypotension (25%), and peripheral edema (20%), all of which raise the possibility that pericardial tamponade is present.

Small pericardial effusions are generally not detectable by physical examination. Large effusions result in muffled heart sounds and occasionally in Ewart's sign, dullness to percussion beneath the angle of the left scapula from compression of the left lung by pericardial fluid.

Patients with pericardial tamponade generally are tachycardic and tachypneic and appear ill (Fig. 42-6). Pericardial tamponade is a medical emergency that necessitates hospital admission and intervention to remove fluid to reduce pericardial pressure and thus relieve the associated hemodynamic abnormalities. Beck's description of pericardial tamponade included the classic triad of hypotension, muffled heart sounds, and jugular venous distention. Tamponade is generally associated with a pulsus paradoxus, a decrease in systolic blood pressure of more than 10 mm Hg with inspiration. Systolic blood pressure normally decreases during inspiration, but cardiac tamponade causes an exaggeration of physiologic respiratory variation in systemic blood pressure from decreasing CO during inspiration. However, pulsus paradoxus is neither sensitive nor specific for cardiac tamponade. It can also occur in constrictive pericarditis, obstructive lung disease, RV infarction, pulmonary embolus, or large pleural effusions.

Differential Diagnosis

The differential diagnosis of tachycardia and hypotension is broad and includes hypovolemia, cardiogenic shock (from either LV failure or RV infarction), neurogenic shock,

anaphylactic shock, adrenal insufficiency, massive pulmonary embolus, pneumothorax, and pericardial tamponade. Of these conditions, elevated RA pressure (jugular venous distention on examination) is seen in pericardial tamponade, cardiogenic shock, pulmonary embolus, or pneumothorax. The etiology of shock will often be suggested by the clinical presentation, physical examination, ECG findings, and chest x-ray. Echocardiography can be very useful in these patients and is the best modality for determining whether a pericardial effusion is present. In some patients, right heart catheterization may also be helpful.

Diagnostic Approach

ELECTROCARDIOGRAPHY

Typical findings include sinus tachycardia and low voltage. If associated pericarditis is present, PR-segment depression, diffuse ST elevation, and possibly atrial tachyarrhythmias may be apparent. Electrical alternans, in which R-wave voltage varies from beat to beat, is the most specific ECG finding but is rarely found and only in association with large pericardial effusions.

CHEST RADIOGRAPHY

An enlarged cardiac silhouette is seen after the accumulation of at least 200 mL of fluid. A large pericardial effusion results in a so-called water bottle appearance. One third to one half of patients have a coexisting pleural effusion, with left being more common than right. Separation of the epicardial fat pad from the outer border of the cardiac silhouette can occasionally be observed, especially in the lateral view.

ECHOCARDIOGRAPHY

Echocardiography is the gold standard test for evaluating pericardial effusions. Pericardial fluid appears as an echo-free space between the visceral and parietal pericardia. Effusions can be circumferential (completely surrounding the heart) or loculated. In pericardial tamponade, echocardiographic findings include diastolic collapse of the right atrium and ventricle. Doppler interrogation demonstrates marked respiratory variation in flow across the tricuspid and mitral valves. Echocardiography is a sensitive and specific test for pericardial effusions; however, false-positive results can occur in pleural effusions, pericardial thickening, increased pericardial fat (especially the anterior epicardial fat pad), atelectasis, and mediastinal lesions. Transthoracic echocardiography is generally diagnostic, and transesophageal echocardiography is rarely needed for the diagnosis of pericardial tamponade.

COMPUTED TOMOGRAPHY

A CT scan may detect as little as 50 mL of fluid. This modality is rarely used to evaluate patients with suspected effusions; more commonly, effusions are incidentally found in patients undergoing chest CT evaluation for other indications (e.g., lung cancer, unexplained dyspnea).

MAGNETIC RESONANCE IMAGING

MRI can detect as little as 30 mL of pericardial fluid and may be used to distinguish hemorrhagic and nonhemorrhagic effusions based on T_1 and T_2 signal intensities.

Management and Therapy

OPTIMUM TREATMENT

Most pericardial effusions resolve without drainage. In some patients, however, pericardiocentesis is needed as emergent treatment for tamponade (see Fig. 42-6) or for diagnostic purposes, including to evaluate the possibility of an infectious etiology. Pericardiocentesis can be performed percutaneously or surgically. Surgical procedures have several advantages, including complete drainage of loculated effusions and access to pericardial tissue for biopsy. However, percutaneous pericardiocentesis is simpler, more rapid, and associated with a quicker recovery.

A subxyphoid approach is generally used for percutaneous pericardiocentesis, although echocardiographically guided approaches via the chest wall are widely used. Needle insertion can be performed under electrocardiographic, echocardiographic, or radiographic guidance. Although pericardiocentesis usually leads to clinical improvement, pulmonary edema, hypotension, and acute ventricular dysfunction have been reported after the procedure. The safety and efficacy of this procedure is dependent on the operator's skill and the size of the effusion. Recurrence rates of 12% to 40% have been reported after successful drainage.

Malignant pericardial effusions tend to recur, and several approaches have been advocated to prevent the need for repeated pericardiocentesis. The literature consists primarily of small prospective or larger retrospective studies, and no consensus on the best approach has formed. Balloon pericardiotomy involves tearing a hole in the pericardium with a balloon placed in the pericardial space under fluoroscopy. This hole allows pericardial fluid to drain into the pleural space. Pericardial sclerosis involves application of a sclerosing agent (e.g., tetracycline, doxycycline, cisplatin, 5-fluorouracil, bleomycin) into the pericardial space to scar the visceral and parietal pericardia with elimination of the pericardial space. Success rates of as high as 91% are reported at 30 days, but potential complications include intense pain, atrial arrhythmias, fever, and infection. Another viable approach, surgical creation of a subxyphoid pericardial window, is associated with low morbidity, mortality, and recurrence rates, and can be performed under local anesthesia. However, this approach is not effective with loculated pericardial effusion. In some cases, a pleuropericardial window can be created via thoracotomy under general anesthesia.

AVOIDING TREATMENT ERRORS

Pericardial tamponade is a medical emergency and may lead to severe hypotension and death if untreated. The diagnosis is occasionally missed because the patient does not have any clues in the history to point to the presence of pericardial disease. Because the initial presentation of malignancy and other

disorders can be pericardial tamponade, the lack of prior history of pericardial disease or predisposing factors (e.g., chest radiation or cardiac surgery) does not exclude the diagnosis. In general, any patient with unexplained hypotension should undergo echocardiographic evaluation.

FUTURE DIRECTIONS

Diagnosis of pericardial diseases continues to become more accurate, resulting in improved therapies. Future challenges include development of more effective therapies for the more serious pericardial diseases, including refractory pericarditis, pericardial constriction, and pericardial tamponade. Little improvement in this area has occurred in the past decade, perhaps because of diagnostic inaccuracies. A renewed focus on a better understanding of pericardial response to injury and inflammation, combined with advances in diagnostic modalities and therapeutic options, provides a blueprint for development of improved treatments for pericardial disease.

ADDITIONAL RESOURCES

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Reviews pericardial disease including acute pericarditis, effusive constrictive pericarditis, cardiac tamponade, and constrictive pericarditis.

Spodick DH. Diagnostic electrocardiographic sequences in acute pericarditis: significance of PR segment and PR vector changes. *Circulation.* 1973;48:575–580.

A detailed study of the ECG changes seen in acute pericarditis.

Spodick DH. Pericardial rub: prospective, multiple observer investigation of pericardial friction rub in 100 patients. *Am J Cardiol.* 1975;35:357–362.

In this series of 100 patients with acute pericarditis, a three-component friction rub was detected in approximately 50% of the patients, whereas any friction rub (one component, two components, or three components) was present in almost all cases.

Troughton RW, Asher CR, Klein AL. Pericarditis. *Lancet.* 2004;363:717–727.

Reviews pericardial disease including acute pericarditis, effusive constrictive pericarditis, cardiac tamponade, and constrictive pericarditis.

EVIDENCE

Bilchick KC, Wise RA. Paradoxical physical findings described by Kussmaul: pulsus paradoxus and Kussmaul's sign. *Lancet.* 2002;359:1940–1942.

A brief description of the history and significance of Kussmaul's sign.

Sagristà-Sauleda J, Angel J, Sánchez A, et al. Effusive constrictive pericarditis. *N Engl J Med.* 2004;350:469–475.

The largest study of patients with effusive-constrictive pericarditis.

Nishimura RA. Constrictive pericarditis in the modern era: a diagnostic dilemma. *Heart.* 2001;86:619–623.

A review of the challenges in making the diagnosis of constrictive pericarditis.

Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis results of the CORE (COlchicine for REcurrent pericarditis) Trial. *Arch Intern Med.* 2005;165:1987–1991.

A prospective, randomized study of colchicine plus aspirin versus aspirin for the first episode of recurrent pericarditis in 84 patients. Treatment with colchicine significantly decreased the recurrence rate and symptom persistence at 72 hours.

Pericardial Disease: Diagnosis and Hemodynamics

43

Thomas M. Bashore

Pericardial pathology can present as an outpatient disease, in a setting requiring invasive diagnostic testing and surgery, or anywhere in between (see Chapter 42). This chapter focuses on the more significant presentations that result in hemodynamic compromise. In these cases, the common underlying physiologic abnormality, regardless of the specific pericardial pathology, is impaired diastolic filling of the heart. Significant constrictive pericarditis presents with evidence of right-sided heart failure, whereas pericardial tamponade presents with distinctive systemic hypotension. Diagnosis of these conditions is not always simple, since combinations of the disease processes can exist (effusive-constrictive pericarditis) and milder forms may require acute fluid loading to bring out characteristic hemodynamic findings (occult constrictive pericarditis). In addition, localized and transient forms of constrictive pericarditis have been described. The differential diagnosis between constrictive pericarditis and restrictive cardiomyopathy, addressed primarily in Chapter 20, can also be a challenge, because myocardial involvement may accompany the pericardial component and all three can indeed be present in the same patient. The hemodynamics can be further complicated if the patient has another disease altering the hemodynamics, such as pulmonary hypertension, an associated dilated cardiomyopathy, or significant valvular heart disease. Attention to details is mandatory in an attempt to sort out the presence of pericardial disease under these circumstances.

ETIOLOGY AND PATHOGENESIS

Normal Physiology

The pericardium can be conceptualized as a balloon with the heart pushed into it like a fist. The visceral pericardium adheres to the heart itself and is separated from the parietal pericardium by a space, the pericardial cavity. This space normally holds a small collection of fluid. The fluid within the pericardial space is in dynamic equilibrium with the blood serum. The normal amount of pericardial fluid is less than 50 mL and is transudative with a low protein content. Because there are many smaller sinuses and recesses in the pericardial space (around the atria, the superior vena cava, the great vessels, the pulmonary veins [PVs], and the inferior vena cava), a minimum of about 250 mL of fluid forms the normal pericardial reserve volume before tamponade physiology becomes evident. As noted below, the volume of pericardial fluid required for tamponade physiology depends upon the rate at which it accumulates; the faster the fluid accumulates, the less is required to achieve pericardial tamponade.

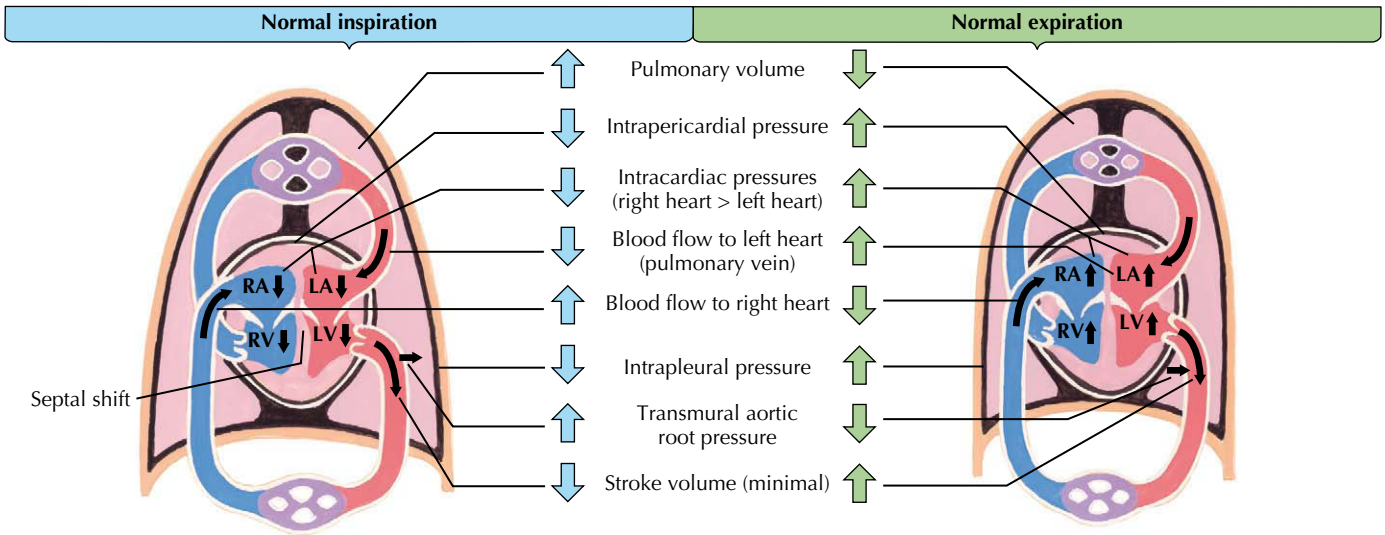
The pericardium provides a thin tissue barrier between the heart and the surrounding structures and exerts constant pressure on the heart, affecting thin structures (the atria and the right ventricle) more than the thicker-walled left ventricle. Resting diastolic pressures within the heart are directly affected by this pericardial constraint (for instance, pericardial removal results in greater dilatation of the right ventricle than of the left ventricle).

Normal intrapericardial pressures range from −6 to −3 mm Hg, directly reflecting intrapleural pressures. The pressure differential between the pericardium and the cardiac chambers (transmural pressure) is about 3 mm Hg. The pericardium is much stiffer than cardiac muscle, and once the pericardial reserve volume is exceeded, the pressure-volume curve of the normal pericardium rises steeply. The pericardium has little effect on ventricular systole; however, interactions between the right- and left-sided cardiac chambers are enhanced by the pericardium, because atrial and ventricular septal movements are independent of pericardial constraint.

Intracardiac pressures are a reflection of the contraction and relaxation of individual cardiac structures and the changes imparted to them by the pleural and pericardial pressures (Fig. 43-1). Changes in pleural or pericardial pressure affect the intracardiac diastolic pressure. With inspiration, the intrapleural pressures drop and the abdominal cavity pressure increases. Blood flow to the right side of the heart increases, whereas blood return to the left side of the heart decreases slightly. The fall in the intrapleural pressures also causes an increase in the transmural aortic root pressure, slightly increasing impedance to left ventricular (LV) ejection. The reverse occurs during expiration. In the normal setting, the respiratory changes are reflected in the intrapericardial and intracardiac pressures, with inspiration lowering the measured right atrial (RA) pressures and the systolic right ventricular (RV) pressure more than the left-sided heart pressures.

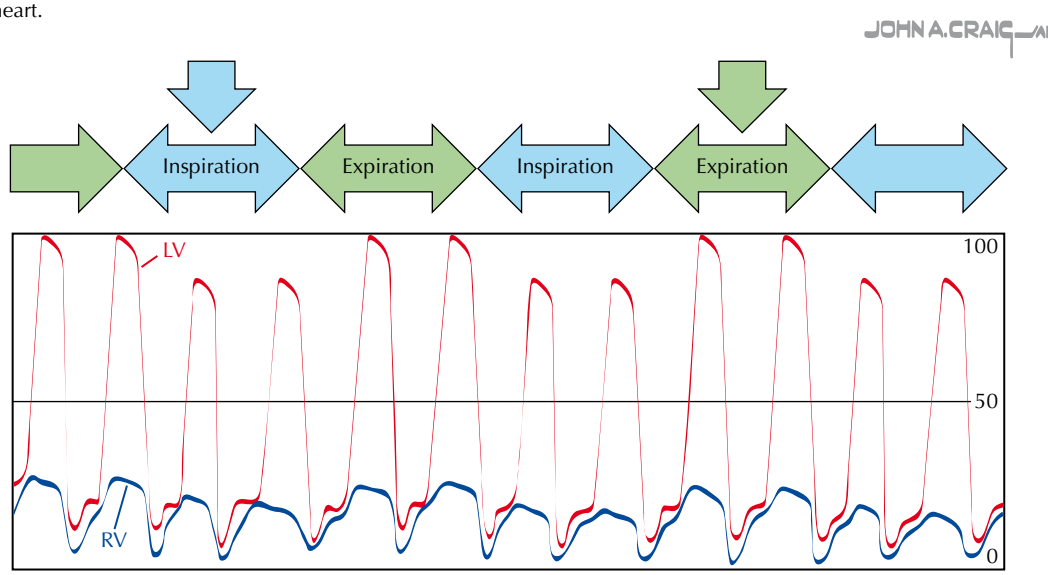
The slight reduction in LV filling and the slightly increased impedance to LV ejection with inspiration produce a modest decline in the LV stroke volume and slightly lower systolic aortic pulse pressures with inspiration. Marked swings in the intrapleural pressures from very negative during inspiration to very positive during expiration (as occur in asthma or severe chronic obstructive lung disease) exaggerate these changes in LV filling and may produce a paradoxical pulse (>10 mm Hg decline in the aortic systolic pressure) purely from the pleural pressure swings. Such a paradoxical pulse related to marked swings in the intrapleural pressure must be differentiated from a similar phenomenon due to pericardial tamponade.

The normal atrial and ventricular waveforms are shown in Figure 43-2. With atrial contraction, the atrial pressures rise (*a* wave). With the onset of ventricular contraction, the atrioventricular (AV) valves bulge toward the atria and a small *c* wave results (the *c* wave is evident on hemodynamic tracings but usually is not visible to the examiner observing the jugular venous pulsations). As ventricular contraction continues, the AV



On inspiration, intrapleural pressure drops and abdominal pressure increases with increased blood flow to right heart and slight decrease in flow to left heart. Increased aortic root transmural pressure adds a minor amount of increased LV afterload. Conceptually, one can visualize inspiration pulling blood through the right heart with a slight decrease in blood to the right heart.

On expiration, intrapleural pressure increases and abdominal pressure decreases with decreased blood flow to right heart and increase in flow to left heart. Conceptually, one can visualize expiration pushing blood toward the left heart and reducing blood flow to the right heart.



Simultaneous measurement of RV and LV systolic pressure reveals a concordant decrease in pressure in both chambers during inspiration, with a similar concordant increase in pressure in both ventricles during expiration.

Figure 43-1 *Normal cardiac blood flow during inspiration and expiration.* LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular.

annulus is pulled into the ventricular cavity and the atria begin diastole, enlarging the atria and decreasing the atrial pressure (represented by the *x* descent). Passive filling of the atria during ventricular systole produces a slow rise in the atrial pressure (the *v* wave) until the AV valves reopen at the peak of the *v* wave; the pressure then falls rapidly as the ventricles begin active relaxation. Passive filling of the ventricles then follows until atrial contraction recurs, and the cycle repeats. Ventricular diastole can be conceptually divided into an initial active phase (a brief period when the ventricle fills about halfway) and a later passive filling phase. The nadir, or lowest, diastolic pressure during ventricular diastole occurs during the early active relaxation phase (suction effect).

Hemodynamics of Pericardial Constriction and Pericardial Tamponade

Constrictive pericarditis and pericardial tamponade alter the normal intracardiac pressures in several ways. Some of the hemodynamic abnormalities, such as ventricular interdependence, are seen in both processes, whereas others, such as the magnitude of the *y* descent, are unique to each (see Fig. 43-2).

PERICARDIAL CONSTRICTION

Pressure Measurements

Constrictive pericarditis was recognized at autopsy in the 19th century and described as a "chronic fibrous callous thickening

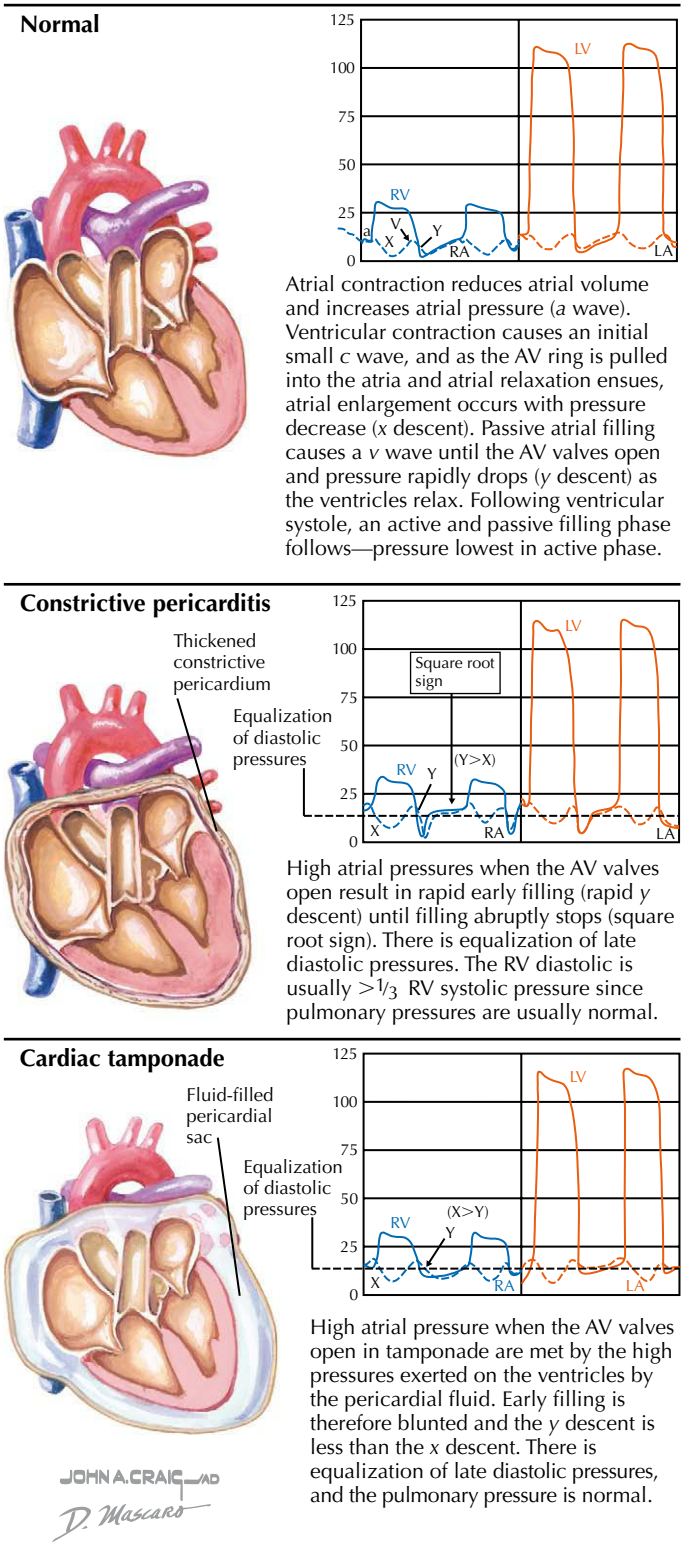


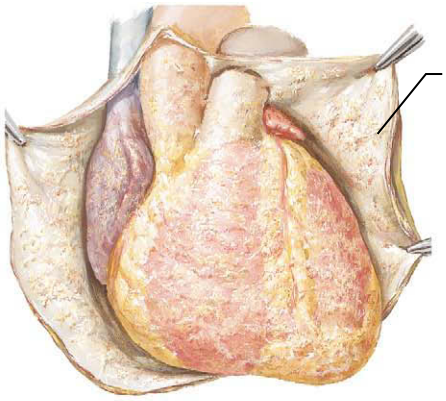
Figure 43-2 *Comparison of normal and pathologic intracardiac pressures.* AV, atrioventricular; LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular.

of the wall of the pericardial sac that is so contracted that the normal diastolic filling of the heart is prevented" (Fig. 43-3). The variable severity of the constrictive process results in a spectrum of hemodynamic change. Table 43-1 outlines the major features of the subacute (elastic) and the more chronic (rigid shell) forms of pericardial constriction.

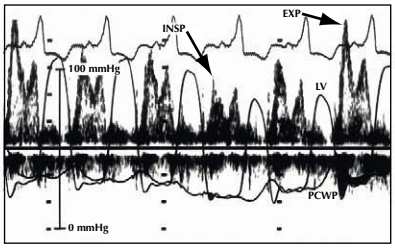
The difference between the subacute and the more chronic forms of constrictive pericarditis probably relates to whether only the visceral pericardium is fused to the epicardium of the heart (subacute) or both the visceral and the parietal pericardial layers are fused together (chronic). In both instances, the diastolic pressures in the atria are elevated due to the restriction of ventricular diastolic inflow. In constriction, the elevated atrial pressures and the normal early LV filling result in a rapid decrease in atrial pressure after the AV valves open and are responsible for the rapid *y* descent seen (see Fig. 43-2). However, the constraint imposed by the pericardium as the ventricle fills results in the sudden halting of this rapid early filling and an abrupt rise in pressure producing the "square root sign" or "dip and plateau" in the pressure tracings. The *x* descent is generally minimally affected; thus, the atrial *y* descent is greater than the *x* descent in constrictive pericardial disease. RV and pulmonary pressures are usually normal or only mildly elevated, with the result that the RV end-diastolic pressure (EDP) tends to be greater than one third the RV systolic pressure. At the end of ventricular diastole, both the right and left ventricles are confined by the pericardium, and there is equalization of the RV and LV EDPs.

The normal respiratory changes in cardiac flow are altered in constriction. The normal inspiratory fall in the RA pressures may not occur or may even rise (Kussmaul's sign). Also reflecting the loss of normal RV filling, the inferior vena cava diameter may not collapse with inspiration as expected. The precise mechanisms responsible for these losses of respiratory effects on cardiac flow are the subject of some debate. It is possible that the rigid pericardium in constrictive pericarditis acts to disassociate the usually related intrathoracic and intracardiac pressures described earlier. In constriction, the right side of the heart is forced to fill to more than its capacity, and the right heart pressures rise rather than fall with inspiration. In addition, there is an inspiratory drop in the diaphragm that may pull the pericardium downward and actually further reduce the overall cardiac volumes. Kussmaul's sign is not specific for pericardial constriction since it also can be seen in acute or chronic RV failure, RV infarction, RV volume overload, and restrictive cardiomyopathy. In most of these conditions, the constrictive physiology is due more to RV volume overload (reaching the limit of RV capacity) than to constriction from the pericardium.

Because the atrial and ventricular septa are unaffected by the pericardial process, changes in atrial and ventricular filling on the right side of the heart can affect left-sided filling (ventricular interdependence). Demonstration of ventricular interdependence is generally accepted as a fundamental requirement for diagnosing constrictive pericarditis. In constriction, as the negative intrapleural pressure draws blood through the RV with inspiration, the increase in RV filling into the confined right ventricle results in a rise in the RV systolic pressure while the normal fall in the LV systolic pressure occurs. This

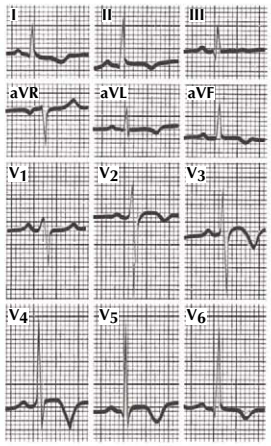


Mild fibrinous pericarditis

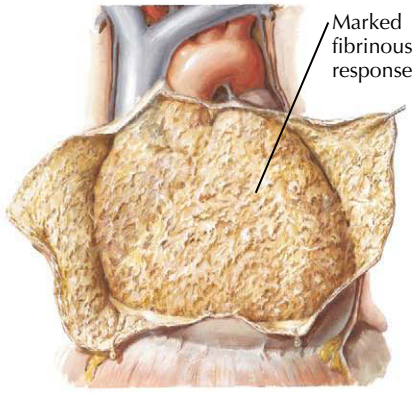


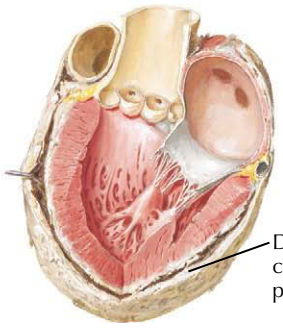
Doppler flow in constrictive pericarditis during peak inspiration and expiration. There is a decrease in initial gradient between LV diastolic pressure and PCWP. This results in initial decrease in E velocity. The transmitral gradient is reestablished in expiration with an ↑ in E velocity and transmitted flow velocity.

With permission from Nishimura RA. Constrictive pericarditis in the modern era: A diagnostic dilemma. *Heart* 2001;86:619–623.



Characteristic electrocardiographic changes in pericarditis: T-wave inversion in all leads except aVR and V_1, isoelectric in lead III





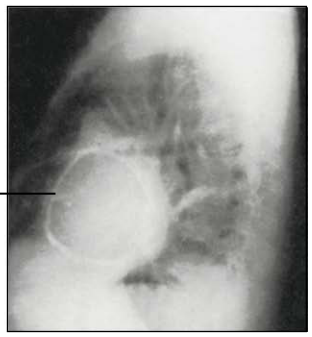


Figure 43-3 *Constrictive pericarditis.* Figure of mitral inflow Doppler reveals an inspiratory (INSP) decrease in gradient between the pulmonary wedge pressure and the left ventricular end-diastolic pressure and an increase in this gradient with expiration (EXP). LV, left ventricular; PCWP, pulmonary capillary wedge pressure.

phenomenon is illustrated in Figure 43-2. An additional finding is that the width and area of the RV pressure tracing also increase with inspiration. Since LV filling falls with inspiration, the systolic areas of the RV and LV pressure-time tracing can be determined and the ratio of the RV systolic area to the LV systolic area determined during each respiratory phase. If constriction is present, the ratio of the RV systolic area to the LV systolic area is expected to be greater than 1.1. This ratio remains constant in restrictive disease and increases in constrictive pericarditis as the RV systolic pressure and area rise while the LV systolic pressure and area fall (discordance). In a review from the Mayo Clinic of this index, the average ratio in a group of 59 patients with constriction was 1.4 as compared with 0.92 for a group of 41 without constriction. The sensitivity of a systolic area index greater than 1.1 was 97% with a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 95%. In addition, reduced LV filling results in a lower pulmonary capillary wedge pressure to LV diastolic gradient in inspiration and a greater gradient in expiration (see Fig. 43-3).

Echo-Doppler Measurements

Normally, with inspiration, the LV minimal pressure and the left atrial (LA) pressures fall equally, and no change is noted in the Doppler mitral inflow velocities. In constriction, the high LA pressures inhibit filling from the pulmonary venous bed. The reduced initial flow into the left ventricle during inspiration

Table 43-1 Comparison of Features Characteristic of Subacute (Elastic) and Chronic (Rigid Shell) Constrictive Pericarditis

Subacute (Elastic)	Chronic (Rigid Shell)
Paradoxical pulse usually present. Signs of ventricular interdependence prominent	Paradoxical pulse usually minimal or absent Ventricular interdependence less prominent
Prominent *x* and *y* descents ("M" or "W" waveform in the JVP)	Prominent *y* descent; *x* descent sometimes minimal
Dip and plateau pattern less obvious	Conspicuous dip and plateau pattern
Early diastolic nadir may not approach zero.	Early diastolic nadir approaches zero
Calcification of pericardium rare	Calcification of pericardium more likely
Pericardial effusion may be present.	Pericardial effusion absent
Constriction primarily due to visceral pericardium	Constriction due to fusion of visceral and parietal pericardium and with epicardium of the heart
ECG "P" waves usually normal	ECG "P" waves wide, notched, and low amplitude
Atrial fibrillation or flutter uncommon	Atrial fibrillation or flutter common

ECG, electrocardiogram; JVP, jugular venous pressure.
With permission from Hancock EW. Differential diagnosis of restrictive cardiomyopathy and constrictive pericarditis. Heart. *2001;86:343–349.*

can be observed in the transmitral Doppler flow pattern by noting a greater than 25% decrease in the already described high initial driving force across the mitral valve (decreased E velocity) during inspiration (see Fig. 43-3). Mitral E deceleration time is usually short (<160 ms) as well. The ventricular interdependence can be further documented by examining the hepatic vein (or superior vena cava), the tricuspid and mitral inflows, and the PV inflow patterns with expiration and inspiration (Fig. 43-5). With *inspiration*, the hepatic systolic (S) and diastolic (D) waves along with the tricuspid inflow E and A waves increase while the mitral E and A waves decrease along with the pulmonary S and D waves. A "w" pattern is seen in the hepatic flow. A septal shift (and often septal "bounce") can be seen on the chest wall echocardiogram as the left ventricle underfills with the expanding right ventricle. With *expiration*, the mitral and PV inflow waveforms all increase while the tricuspid E and A waves decline, and there is also an abrupt interruption in the systolic wave and diastolic flow reversal in the hepatic venous velocity waveform. These findings can be helpful to confirm constriction in situations that are not "classical" from other hemodynamic standpoints. Otherwise, they are confirmatory.

Up to one in five patients with constriction may not reveal classic interdependence on echo-Doppler, and maneuvers to decrease preload (e.g., sitting or head-up tilt) may unmask the changes. Transesophageal echocardiography may provide better images for evaluating the pericardium and can often demonstrate the PV flow variations with respiration better than the transmitral flow pattern variations.

Tissue Doppler echocardiography measures actual myocardial motion. Since myocardial relaxation is preserved in constrictive pericarditis, the early relaxation observed on tissue Doppler velocity patterns (Ea) is normal. If it is abnormal, then a primary myocardial problem is more likely. For example, if the Ea is greater than 8 cm/sec, then that is consistent with constriction, while less than 8 cm/sec is more indicative of myocardial restriction.

A method of speckle tracking of B-mode echoes allows for global assessment of stress and strain (deformation) of the myocardium. When speckle tracking has been performed, constrictive pericarditis appears to have constrained circumferential deformation while restrictive pericarditis has constrained longitudinal deformation.

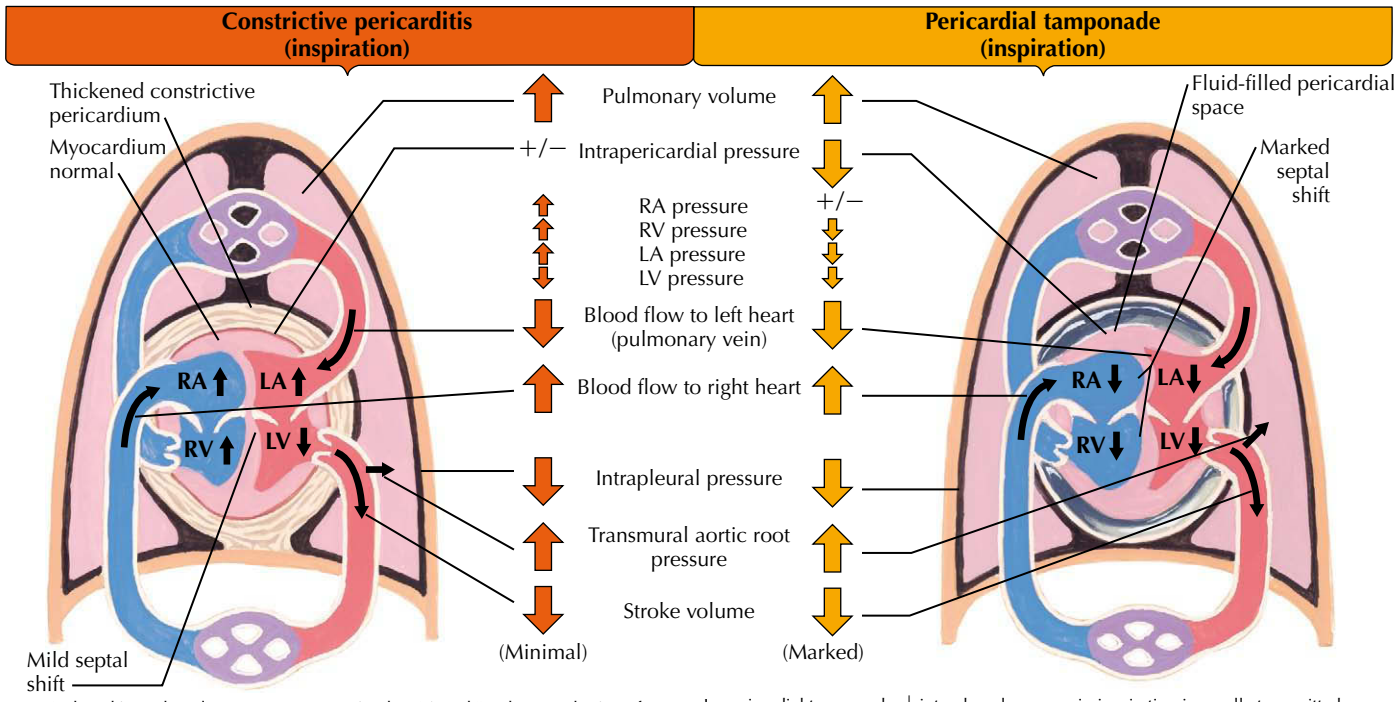
PERICARDIAL TAMPONADE

Pericardial tamponade occurs when pericardial fluid exceeds pericardial reserve volume. The result is cardiac compression and restricted diastolic filling of all the cardiac chambers (Fig. 43-6). The amount of pericardial fluid required for tamponade depends on the parietal pericardial compliance and the rate of fluid accumulation. Acute tamponade can result with even a small increase in pericardial fluid because of the normally steep pericardial pressure-volume relationship. When fluid accumulates slowly, as in patients with metastatic cancer or chronic uremia, the parietal pericardium adapts and stretches. Tamponade occurs only after the accumulation of a large amount (sometimes >1 L) of fluid in these chronic situations. Therefore, the rate of fluid accumulation determines the clinical presentation.

Pressure Measurements

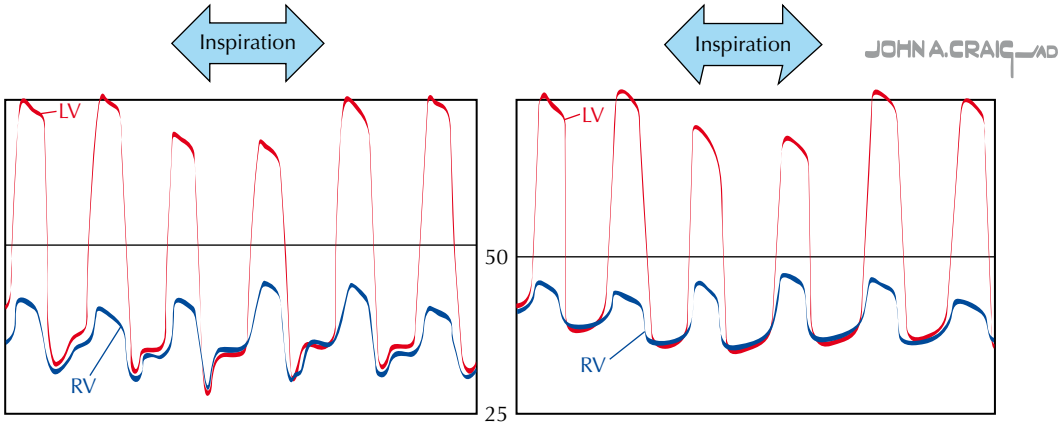
As fluid accumulates in the pericardium, the thinnest walled chambers (the right atrium and the right ventricle) are affected first. Right-sided diastolic pressures are normally lower than left-sided diastolic pressures, and collapse of the right atrium and the right ventricle in diastole is observed early in tamponade (often before a paradoxical pulse, for instance). With cardiac contraction, the heart is also less full, and there is literally more room in the pericardial space for the left and right ventricles. The high intrapericardial pressures are thus transmitted to the early diastolic atrial and ventricular pressures. When the AV valves open, the diastolic pressure is already elevated, as reflected in the reduced *y* descent and loss of rapid ventricular filling (see Fig. 43-2). These high diastolic pressures may also cause premature closure of the AV valves before systole initiates. As the ventricles contract to eject blood, the pericardial space is actually increased and the atria can fill in atrial diastole (preserving the *x* descent). The *x* descent is therefore greater than the *y* descent in pericardial tamponade. Increasing intrapericardial pressures progressively affect the RA diastolic pressure, then the RV diastolic pressure (especially in the thinner RV outflow tract), and eventually the left-sided heart diastolic pressure. This finally results in the equalization of diastolic pressures throughout the heart.

As in constriction, the increased filling of the right side of the heart, mandated by the negative intrathoracic pressure during inspiration, increases the early filling of the right heart



Reduced intrapleural pressure not transmitted to RA and RV due to tethering of pericardium to descending diaphragm. The negative intrapleural pressure and expanding lung bring blood into lungs, and pressures may rise in the right heart (Kussmaul's). The ↑ in RV systolic pressure contrasts with ↓ in LV systolic pressure since ↑ LA pressure further reduces the normal modest ↓ in pulmonary venous flow. (This reduction is generally inadequate to cause paradoxical pulse.)

In pericardial tamponade, ↓ intrapleural pressure in inspiration is usually transmitted to right heart structures, so no Kussmaul's is noted. ↑ flow to right heart expands RA and RV at the expense of LA and LV. The normal ↓ in pulmonary venous flow is further reduced by smaller left heart chamber sizes and ↑ filling pressures. A substantial ↓ in stroke volume occurs, creating paradoxical pulse.



Simultaneous measurement of RV and LV systolic pressures in constrictive pericarditis shows a discordance during inspiration, with decrease in LV systolic pressure, while RV systolic pressure increases. Note square root sign in diastole due to rapid *y* descent.

Simultaneous measurement of RV and LV pressures in pericardial tamponade. There is loss of rapid early filling of ventricles. Inspiration results in blood being drawn into RV, with RV systolic pressure rising. Increased RV volumes result in marked septal shifting and LV volumes decline (ventricular interdependence). Subsequent decrease in LV stroke volume results in paradoxical pulse.

Figure 43-4 *Comparison of blood flow in constrictive pericarditis and pericardial tamponade.* LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular.

structures and reduces filling of the left. Because there is a fixed space for the heart chambers in tamponade, a leftward shift in the atrial and ventricular septa takes place. This reduces LV chamber compliance and further impairs LV filling during inspiration. Atrial reservoir function increases in importance during pericardial tamponade; the left atrium may fill only during expiration, with subsequent emptying only during atrial systole. The reduced LV filling also reduces LV preload and contractile function, further lowering the stroke volume. The paradoxical pulse in pericardial tamponade results from this dramatic inspiratory reduction in LV filling. In the most extreme cases of tamponade, the aortic valve may open only during expiration. A paradoxical pulse from tamponade may not occur in the presence of extreme hypotension, in patients with severe aortic insufficiency, in the presence of an atrial septal defect or a single ventricle, or in some cases of acute LV infarction. Table 43-2 outlines the major hemodynamic differences between constrictive pericarditis and pericardial tamponade.

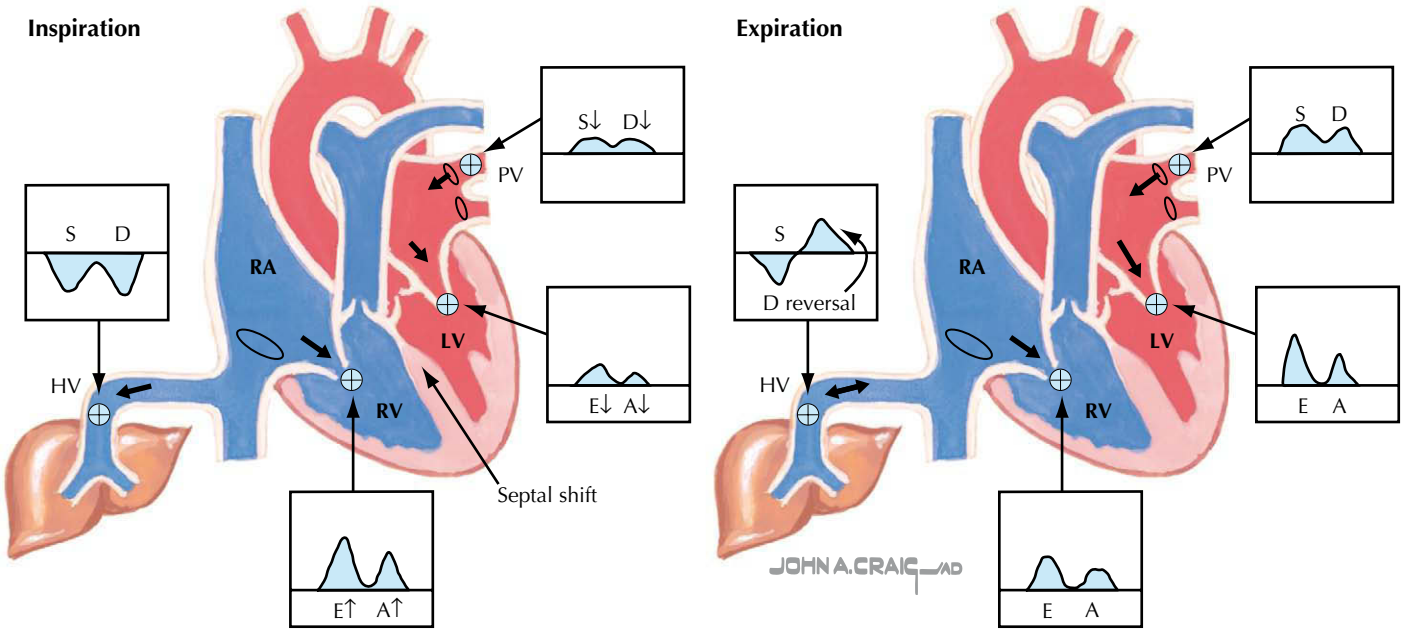


Figure 43-5 *Echo-Doppler patterns in pericardial disease. With inspiration*, blood is "pulled" through the right heart and there is reduced filling of the left heart. Increased right heart filling increases systolic and diastolic flow in the hepatic veins and flow across the tricuspid valve. Flow in the PV and across the mitral valve decreases. The septal shifts toward the LV. *With expiration*, there is a reduction in flow through the right heart, flow is only systolic in the hepatic veins, and flow across the tricuspid valve is reduced. Expiration increases flow through the PVs and through the mitral valve. D, diastolic; HV, hepatic vein; LA, left atrial; LV, left ventricular; PV, pulmonary vein; RA, right atrial; RV, right ventricular; S, systolic.

Echo-Doppler Measurements

Two-dimensional echocardiography is critical in the diagnosis of a pericardial effusion and helpful in deciding whether tamponade is present. An echo-free space must be demonstrated and differentiated from epicardial fat. In large effusions, the heart may swing within the pericardial fluid, correlating with electrical alternans on the surface ECG. Systolic LV function is preserved. During inspiration, the aortic valve may demonstrate early closure, and the LV ejection time may decrease with the inspiratory reduction in the LV stroke volume. With tamponade, there is evidence of a smaller RV diameter (usually <7 mm) and early diastolic RV collapse. RV collapse is most marked in expiration, as the LV fills and RV filling is reduced. The duration of RV diastolic collapse is directly related to the pericardial pressure. RV collapse is a more sensitive and specific marker of tamponade physiology than RA collapse. The RA free wall may show late diastolic collapse lasting at least one third of the cardiac cycle. Occasionally, the LA free wall is also indented. The superior and inferior vena cavae diameters are enlarged and usually greater than 2.2 cm, and these diameters collapse less than 50% with inspiration or during a brief sniff (the patient is asked to sniff to increase negative inspiratory pressure). The inspiratory increase in the RV size, the septal shift, the reduced LV size, the delayed mitral valve opening, and the decreased mitral E-F slope all reflect the hemodynamic changes that characterize pericardial tamponade.

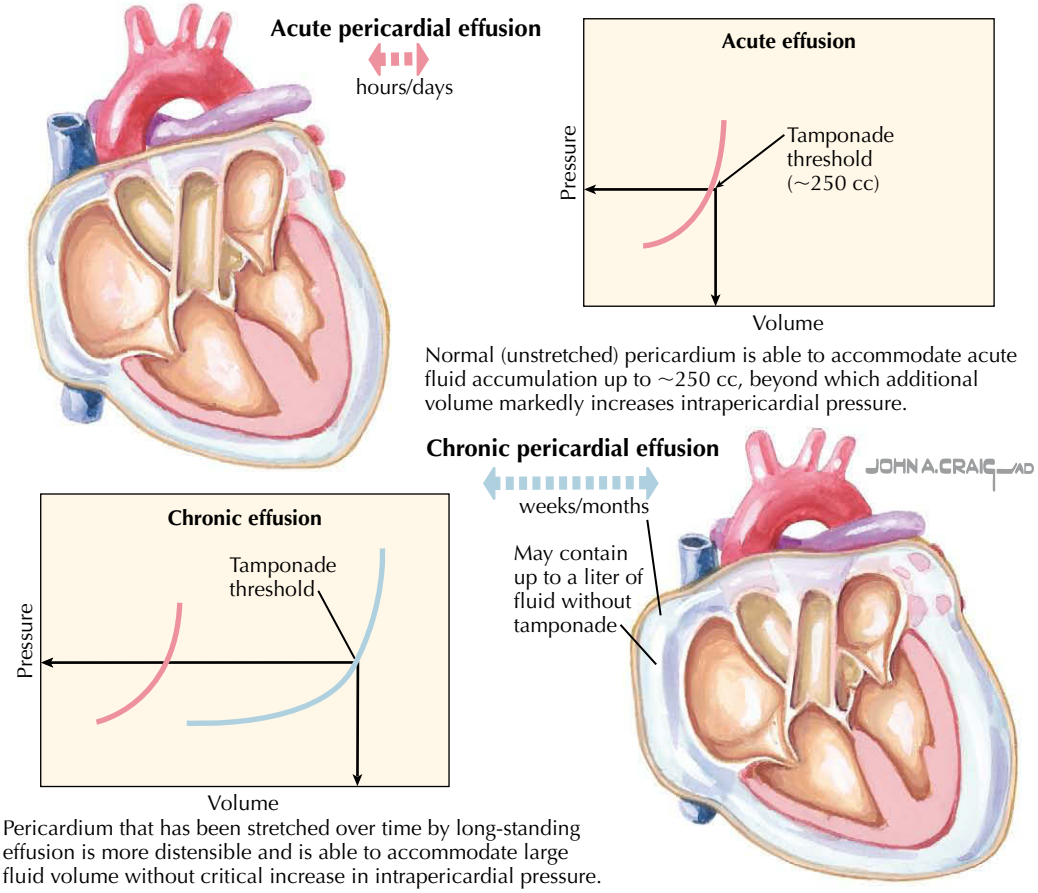
Doppler studies similarly reflect the flow variation that occurs with respiration. Many of these changes in flow are similar to those seen in constrictive pericarditis, including a greater than 25% variation in the mitral peak E wave with inspiration. As a result of the loss of early ventricular filling due to the compression of the heart, most of the systemic and pulmonary venous flow occurs during ventricular systole. These reciprocal changes with respiration are also present in the respective pulmonary venous flow or mitral annular movements (tissue Doppler) and in the hepatic venous flows. The hepatic venous flow may also demonstrate marked atrial reversal of diastolic flow with expiration. These Doppler changes are outlined in Figure 43-5. The LV ejection time may decrease and the RV ejection time may increase during inspiration, again documenting the expected respiratory changes between the ventricles.

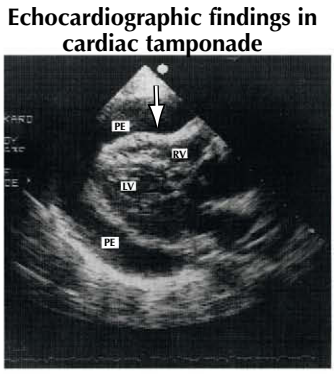
CLINICAL PRESENTATION

The classic findings of pericardial constriction and tamponade are presented in Chapter 42. This chapter reviews the key findings with an emphasis on understanding the underlying hemodynamics that they represent and how these findings are helpful in some cases (and not in others) for distinguishing pericardial constriction from pericardial tamponade.

Pericardial Constriction

Pericardial constriction may be subtle, while significant constriction presents as primarily right-sided heart failure with





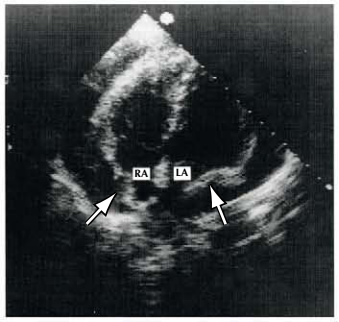


Figure 43-6 *Pressure-volume relationship of pericardium.* LA, left atrial; LV, left ventricular; PE, pulmonary embolism; RA, right atrial; RV, right ventricular. (With permission from Spodick DH. Pericardial diseases. In: Braunwald E, Zipes DP, Libby P, eds. *Heart Disease.* Philadelphia: WB Saunders; 2001:1842–1843.)

normal LV systolic function. A history of antecedent pericarditis, pericarditis-inducing drug use, uremia, cardiac surgery, or thoracic radiation (which may also be a contributing factor in restriction) may be a clue. There is usually evidence of venous congestion, pedal edema, ascites (often out of proportion to peripheral edema), fatigue, dyspnea, and low cardiac output. Most patients compensate with tachycardia. Atrial arrhythmias are common. The retinal veins are often engorged. Jugular venous distention is universal, and a positive Kussmaul's response is expected. The sharp, rapid *x* and *y* descents are often seen in the jugular venous pulsations at bedside. Because the jugular veins may be so distended as to not be visible when the patient is reclining, patients should be examined in an upright position. To time the pulse waveforms, one should feel the opposite

Table 43-2 Major Hemodynamic Differences between Constrictive Pericarditis and Pericardial Tamponade

Constrictive Pericarditis	Pericardial Tamponade
Atrial pressures elevated with rapid *y* descent	Atrial pressures elevated with blunted *y* descent
y descent greater than *x* descent	*x* descent greater than *y* descent
Kussmaul's sign often present	Kussmaul's sign occasionally present
Square root sign in diastole	Blunted early filling in diastole
Nadir of early ventricular pressure near zero	Elevated early ventricular diastolic pressure
Paradoxical pulse uncommon	Paradoxical pulse common
Normal heart size on chest radiograph	Water-bottle cardiac enlargement
Calcification of the pericardium occasionally present	Calcification rarely seen
Atria normal in size and shape on echo	Right atrial, right ventricular, and occasional left atrial diastolic collapse
No or trivial pericardial effusion on echo, CT, or MRI	Pericardial effusion present
Often, thickened pericardium seen on CT or MRI	Normal or minimally thickened pericardium seen on CT or MRI

carotid pulse: the *x* descent occurs during ventricular systole. Precordial palpation may be normal, or the apex may even retract with systole. The rapid filling of the ventricles may produce a loud filling sound (pericardial knock) on auscultation. The liver is often enlarged, and ascites is often the prominent examination feature. A paradoxical pulse is not usually demonstrated unless associated lung disease or concurrent pericardial tamponade exists.

Pericardial Tamponade

Pericardial tamponade symptoms are generally more related to low output than to right-sided heart failure. The setting for acute tamponade often includes chest trauma, recent cardiac surgery, recent (but generally not acute) myocardial infarction, or evidence of aortic dissection. Chronic tamponade is generally related to malignancy, uremia, or other causes of inflammatory pericarditis. Tachypnea and dyspnea are common findings in pericardial tamponade. Orthopnea from pulmonary interstitial edema, which increases lung stiffness, is also common. Cough, dysphagia, and presyncope or frank syncope are often seen, along with fatigue, weakness, and anorexia. Anemia, common in uremia and malignancies, exacerbates the symptoms. Eventually, shock, with accompanying renal and hepatic failure and mesenteric ischemia, may be seen.

The physical examination may be deceptive when hypotension and shock predominate. Tachycardia is the rule (although the heart rate may be lower in patients with hypothyroidism or in some patients with uremia). The jugular venous pressure (JVP) is usually elevated (in the absence of hypovolemia), and Kussmaul's sign is usually not evident unless there is associated constrictive physiology. At times, the JVP elevation may be striking and may result in venous distention of the scalp, the forehead, and the ocular veins. The jugular venous waveforms reveal a normal or even diminished *y* descent (as opposed to the rapid *y* descent seen in constriction), with preservation of the *x* descent during ventricular systole (timed at bedside by palpation of the opposite carotid). A paradoxical pulse is usually present unless there is marked hypotension and/or hypovolemia (which then leads to hypotension), and its presence should be aggressively sought. Pericardial rubs are variable and may exist even in the presence of large pericardial effusions. At times, very large pericardial effusions produce dullness and bronchial breathing between the left scapula and the spine (Bamberger-Pins-Ewart's sign). The cardiac impulse may not be palpable. Evidence of chronic right-sided heart failure, such as ascites, is usually absent.

Table 43-3 outlines the differences in the physical examination of patients with pericardial constriction and patients with pericardial tamponade.

Table 43-3 Differences in the Physical Examination of Patients with Constrictive Pericarditis versus Patients with Pericardial Tamponade

Constrictive Pericarditis	Pericardial Tamponade
Clear lung fields	Clear lung fields, with occasional Ewart's sign in large pericardial effusions
Ascites often present; peripheral edema occasionally present	Ascites and peripheral edema rare
Evidence of pleural effusions common	Pleural effusions uncommon
JVP markedly elevated; rapid *x* and *y* descents	JVP moderately elevated; loss of *y* descent evident
Pericardial rub rare	Pericardial rub common
Apical pulse localized and may retract with systole	Apical pulse large and diffuse
Loud filling sound ("knock") occasionally present with normal S_1 and S_2	Heart sounds often diminished

JVP, jugular venous pressure.

DIAGNOSTIC APPROACH

ECG and Chest X-ray

As discussed in Chapter 42, while often helpful, the ECG and chest radiograph should not be relied on to make the diagnosis of either pericardial constriction or pericardial tamponade, or to distinguish the two. In pericardial constriction, the ECG is frequently abnormal, with low voltage being common. Interatrial block demonstrated by a wide P wave is common. An RV strain pattern may present with right-axis deviation. In chronic pericardial constriction, myocardial calcification and fibrosis can affect coronary perfusion and the conduction system. Stress tests in patients with pericardial constriction can produce a "false-positive" result, with ECG changes due to myocardial calcification and fibrosis rather than typical coronary artery disease. Atrial arrhythmias, especially fibrillation, are common. In pericardial tamponade, nonspecific findings such as P-R depression, ST-segment elevation, and low voltage may be seen. When the pericardial effusion is large, the heart may swing within the pericardium, producing an electrical alternans that primarily affects the QRS and not the T waves. Atrial arrhythmias are common.

In pericardial constriction, chest x-ray findings may reveal a normal or only modestly enlarged cardiac silhouette. However, in pericardial tamponade (particularly when a large effusion is present), chest radiography can be very useful, demonstrating clear lung fields with evidence of a markedly enlarged cardiac silhouette (water-bottle heart). Identification of the cardiac fat pad may reveal that the cardiac enlargement is from an increase in the extracardiac space. The superior vena cava and the azygous veins may be dilated as well.

Echo-Doppler

PERICARDIAL CONSTRICTION

The major echo-Doppler findings in constrictive pericarditis were described previously and in Figures 43-2, 43-3, 43-4, and 43-5 and Table 43-4. Distinguishing features between constrictive pericarditis and a restrictive cardiomyopathy can be found in Chapter 20. It is important to note that echocardiography is an insensitive method for measuring pericardial thickness.

Table 43-4 Comparison of the Echo-Doppler Findings in Constrictive Pericarditis versus Pericardial Tamponade

Constrictive Pericarditis	Pericardial Tamponade
Pericardial effusion small or not present	Pericardial effusion evident and often large
Atria normal in size	Atria demonstrate free wall collapse
Right ventricle is normal in size. Septal shift is occasionally noted with inspiration.	Right ventricle (especially outflow) may demonstrate free wall collapse. Septal shift with inspiration common
Distinct interventricular septal bounce in early ventricular diastole	No interventricular septal bounce
Mitral valve motion usually normal	Delayed mitral valve opening and reduced E-F slope of mitral opening are evident. Aortic valve may close prematurely with inspiration.
With inspiration, LVET normal or slightly shortened and RVET prolonged	With inspiration, LVET shortened and RVET prolonged
Mitral valve E wave initially high with short deceleration and reduced "A" wave	Mitral valve E wave height usually blunted
With inspiration or sniff, IVC does not decrease >50% in diameter.	Similarly, with inspiration or sniff, IVC does not decrease >50% in diameter.
With inspiration, >25% decline in mitral valve E-wave height	Similarly, with inspiration, >25% decline in mitral valve E-wave height
With inspiration, RV pressure may rise (as noted on tricuspid regurgitation jet, if present).	With inspiration, RV systolic pressure may fall normally or rise modestly.
With inspiration, tricuspid valve E wave increases >40% and mitral valve E wave decreases.	Similarly, with inspiration, tricuspid valve E wave increases >40% and mitral valve E wave decreases.
With inspiration, hepatic vein flow increases and pulmonary vein flow decreases.	Similarly, with inspiration, hepatic vein flow increases and pulmonary vein flow decreases.

IVC, inferior vena cava; LVET, left ventricular ejection time; RV, right ventricular; RVET, right ventricular ejection time.

PERICARDIAL TAMPONADE

The major echo-Doppler findings in tamponade are outlined above and described in Figures 43-2, 43-4, and 43-5 and Table 43-4. Pericardial effusions are common and do not result in hemodynamic compromise unless evidence of tamponade is present.

Computed Tomography and Magnetic Resonance Imaging

PERICARDIAL CONSTRICTION

Thickening of the pericardium may help confirm pericardial disease and constriction, but constrictive physiology can clearly be present with minimal changes on CT or MRI. To detect pericardial thickening by CT or MRI, pericardial thickness must be greater than 3 mm. Focal areas of thickening can also be identified by CT, MRI, or both. Around 20% of patients with surgically documented pericardial constriction do not have pericardial thickening by CT or MRI, so the absence of pericardial thickening by CT or MRI should not rule out constriction if other compelling findings are present. Neither modality can as yet reliably identify respiratory differences, although the use of gadolinium bolus observation with MRI can sometimes elucidate the presence or absence of interventricular interaction in gated studies. The studies are hampered by the need for temporal averaging of the images and for breath holding to acquire the highest quality imaging. Calcification, present in about 25% of cases, is useful but not a sensitive measure of constriction. Electron beam and multislice CT are more sensitive to pericardial calcium than chest radiography or standard CT methods and can identify very small amounts. The presence of calcium does not necessarily imply that constriction is present, however.

PERICARDIAL TAMPONADE

Neither chest CT nor cardiac MRI provides additional information that is not available from Doppler echocardiography for the diagnosis of pericardial tamponade. Both studies can confirm the presence of an effusion. From an etiologic standpoint, both studies provide additional information about the involvement of contiguous structures, enlarged lymph nodes, lung lesions, evidence of pleural involvement, and other factors that may help determine the cause of the pericardial effusion.

Cardiac Catheterization

PERICARDIAL CONSTRICTION

The hemodynamics of constrictive pericarditis were described earlier in this chapter (see Tables 43-2 and 43-4 and Figs. 43-2, 43-3, and 43-4). It is important to track all right-sided heart pressures in relation to the left-sided heart pressures and to note any respiratory changes in systolic and diastolic pressures. Right-sided heart catheterization by itself is usually inadequate for diagnosing pericardial disease. Observations to be made at cardiac catheterization include nearly equal levels of EDP in all chambers, relatively normal or only slightly elevated pulmonary pressures with a normal pulmonary vascular resistance, a discrepancy of less than 5 mm Hg between the LV EDP and the RV EDP, a positive Kussmaul's sign in the right atrium, and the classic square root (dip and plateau) pattern in the atrial and diastolic ventricular waveforms.

The role of cardiac catheterization should be to demonstrate ventricular interdependence. Critical to confirming ventricular interdependence is the demonstration of discordant peak systolic RV and LV pressures or an increased RV/LV pressure time-to-area ratio greater than 1.1 with inspiration compared to

expiration, or both. The RV EDP is usually greater than one third the RV systolic pressure. A paradoxical pulse is unusual. In significant constriction, the nadir of the ventricular pressures usually approaches zero. At times, rapid fluid loading is required to reveal the constrictive physiology in patients with hypovolemia. If the patient is in atrial fibrillation, it may be impossible to sort out the subtle changes between the LV and RV pressures without using a temporary RV pacemaker to pace at a higher than baseline rate and establish a regular rhythm. High-fidelity catheters improve the quality of the data but are rarely used anymore. In addition, an RA angiogram in the anteroposterior view may reveal a cardiac "peel" or thickening at the interface of the RA free wall and the lung fields. Similarly, contrast angiography of the coronary arteries may reveal a "peel" or a radiographic shadow between the coronary arteries and the lung fields. Portions of the coronaries may also appear frozen in the pericardium during cardiac motion.

PERICARDIAL TAMPONADE

As noted earlier, in pericardial tamponade, the expected findings include marked elevation in the atrial and ventricular diastolic pressures, loss of the *y* descent in the atrial tracings, no Kussmaul's sign (in general), blunting of the early diastolic filling pressures in the ventricles, normal pulmonary pressure and pulmonary resistance, equalization of the diastolic pressures, and a paradoxical pulse. As with constriction, a normal rhythm is needed and ventricular pacing may be required if the patient is in atrial fibrillation. On fluoroscopy, the heart may be observed to swing within the pericardial sac. When the issue of mixed disease (i.e., effusive-constrictive disease) is present, pericardiocentesis may remove the tamponade component and reveal the underlying constrictive physiology. To help analyze effusive-constrictive disease, it may be useful to remeasure the intracardiac pressures once the pericardial fluid has been tapped. Classic tamponade physiology may change to constrictive physiology if both are contributory.

FUTURE DIRECTIONS

Despite improvements in the diagnosis and treatment of pericardial disease, opportunities for advances still exist—particularly with respect to pericardial constriction. Further diagnostic improvement will probably come with more advanced CT and MRI technologies. Additionally, improved imaging combined with hemodynamic assessment will offer more definition of those individuals who will benefit from pericardiectomy. At present, pericardiectomy generally requires open-chest surgical approaches. With the continued advances in laparoscopic technology, enhanced minimally invasive pericardiectomy could be developed. This could result in reductions in the morbidity and mortality risks of pericardiectomy and would be of significant benefit for those with pericardial constrictive disease.

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Sengupta PP, Krishnamoorthy VK, Abhayavata WP, et al. Disparate patterns of left ventricular mechanics differentiate constrictive pericarditis from restrictive cardiomyopathy. *J Am Coll Cardiol Img.* 2008;1:29–38.

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Angiogenesis and Atherosclerosis

Cam Patterson

44

Revascularization via coronary artery bypass surgery and percutaneous coronary interventions remains the definitive therapy for patients with refractory ischemic heart disease, particularly when accompanied by left ventricular (LV) dysfunction. Bypass surgery in particular reduces mortality in patients with multivessel coronary artery disease and LV dysfunction. However, the surgery itself is invasive and is associated with significant mortality and morbidity. In addition, many patients are poor candidates for bypass based on their coronary anatomy, coexisting conditions, or the severity of their heart failure. Likewise, anatomic complications may make percutaneous coronary interventions such as balloon angioplasty and stent implantation a poor choice for many of these patients. Thus, there is a need for an alternative means of revascularization. The identification of endogenous pathways that regulate angiogenesis—the growth of new blood vessels from existing vessels—has fostered the intriguing hypothesis that if angiogenesis could be promoted in a controlled manner, recently elucidated, endogenous pathways could be stimulated to augment blood vessel formation and revascularize tissues in myocardial ischemic zones.

MECHANISMS OF ANGIOGENESIS

Angiogenesis occurs by the budding of new blood vessels from existing vessels (Fig. 44-1). Inflammation and hypoxia are the two major stimuli for new vessel growth. Hypoxia regulates angiogenesis predominantly by activating a transcription factor, hypoxia-inducible factor-1, which in turn activates the angiogenesis gene expression cascade. Inflammation stimulates angiogenesis mainly by the secretion of inflammatory cytokines derived primarily from macrophages. In either event, the result is production of vascular endothelial growth factor (VEGF) and other potent angiogenic peptides. VEGF interacts with specific receptors on endothelial cells that, in turn, activate pathways to break down the extracellular matrix and stimulate proliferation and migration toward an angiogenic stimulus and recruitment of pericytes and smooth muscle cells to establish the three-dimensional structure of a blood vessel. After making appropriate connections with the vascular system, the newly formed vessel is capable of maintaining blood flow and providing oxygen to the tissue in need.

Angiogenesis occurs in numerous circumstances, some of which are necessary for normal development and organ function. In other circumstances, angiogenesis is a maladaptive response to local injury or stress. During development, the formation of every organ system is dependent on angiogenic events; in fact, the cardiovascular system is the first organ system to function during embryogenesis. In adult females, the menstrual cycle is dependent on cyclic angiogenesis that is stimulated in part by reproductive hormones. Beyond this, however, most angiogenesis in adults occurs in pathologic conditions or as a response to injury. Tumor growth and metastasis, diabetic vascular disease (including retinopathy), inflammatory arthritides, and wound healing are some of the processes that depend on angiogenesis. In addition, the invasion of ischemic tissues with new capillaries and the development of a collateral circulation to supply occluded vessels, as may occur in chronic obstructive coronary disease, are angiogenic processes.

ANGIOGENESIS AND ATHEROSCLEROSIS

The response to ischemia in organs such as the heart involves angiogenic events that increase perfusion to the compromised tissue. Thus, it is ironic that atherosclerosis (the most common cause of myocardial ischemia) is itself an angiogenesis-dependent process. The media of blood vessels remains avascular until a critical width is achieved, beyond which vascularization is necessary for medial nutrition. Increased blood flow within atherosclerotic lesions is due to new growth of medial vessels and not to dilation of existing vessels. New vessels in atherosclerotic lesions form primarily by branching from the adventitial vasa vasorum. The possibility that neovascularization contributes to the pathophysiology of atherosclerosis surfaced when cinefluorography demonstrated the presence of rich networks of vessels surrounding human atherosclerotic plaques.

Neovascularization may contribute to the clinical consequences of atherosclerosis by several mechanisms. Neovascularization provides a source of nutrients, growth factors, and vasoactive molecules to cells within the media and the neointima, which is evident from the association between neovascularization of atherosclerotic lesions and proliferation of adjacent smooth muscle cells. Intimal hemorrhage, associated with plaque instability, is due to rupture of the rich network of friable new capillaries surrounding lesions. Regulation of blood flow through plaque microvessels may contribute to the pathophysiology of vasospasm in advanced lesions. Vascular wall remodeling also seems to be related to neovascularization. Finally, neovascularization within human atherosclerotic lesions is associated with expression of adhesion molecules, which is strongly related to neointimal inflammatory cell recruitment.

ANGIOGENESIS AND ISCHEMIC HEART DISEASE

Refractory coronary ischemia, particularly in patients with decreased LV function who may not be candidates for revascularization, remains a difficult clinical problem. Recognition of angiogenesis as an endogenous mechanism for perfusion of ischemic tissues raises the possibility that angiogenic factors or cells that produce them might be therapeutic tools for patients with refractory ischemia. Angiogenesis seems to be amenable to gene therapy approaches. Although gene therapy may induce angiogenesis and improve perfusion in a wide spectrum of animal models of ischemia, thus far the utility of these approaches in humans has been limited. New vessel growth is a process that

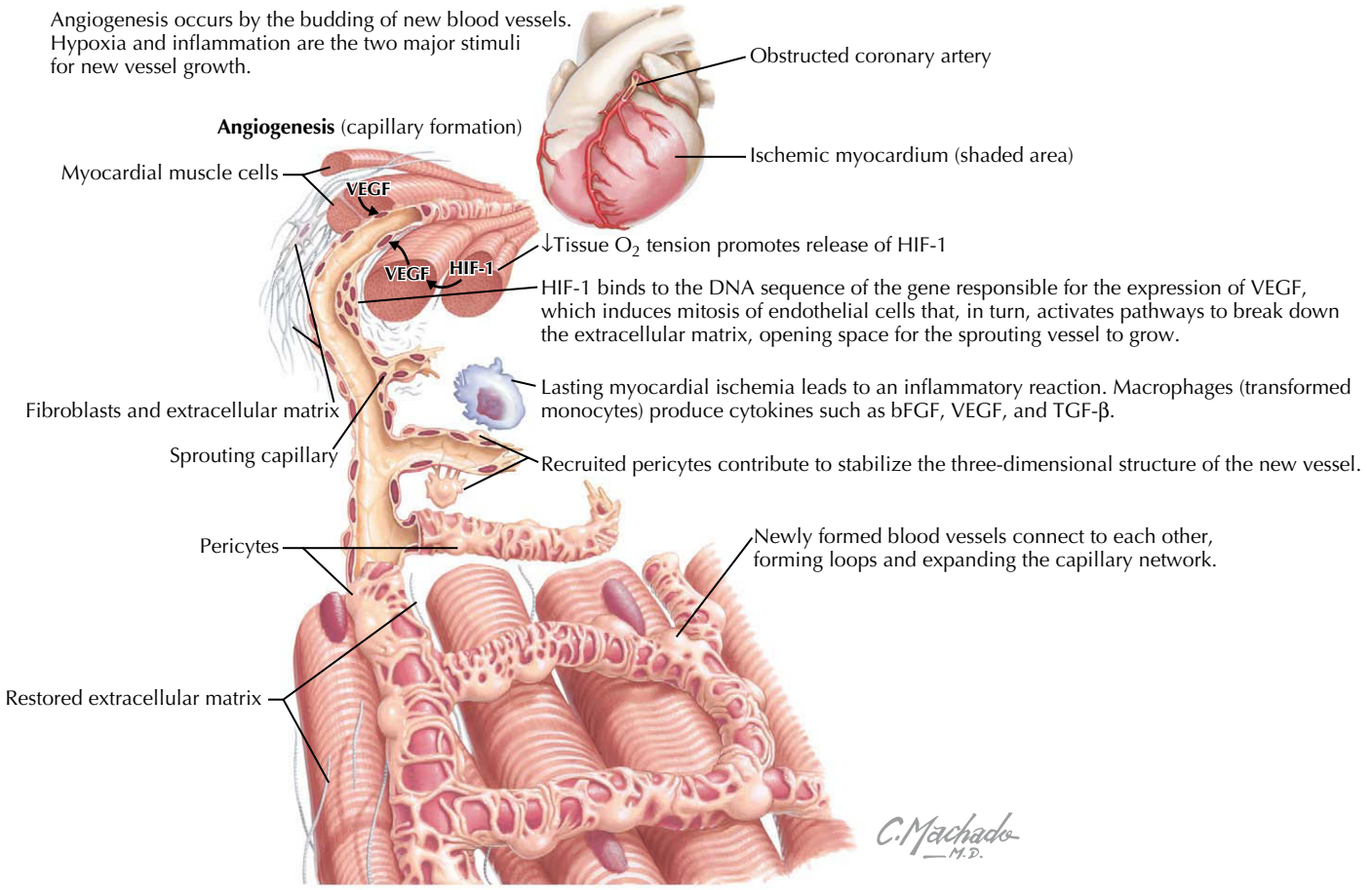

Figure 44-1 *Mechanisms of angiogenesis.* bFGF, basic fibroblast growth factor; HIF-1, hypoxia inducible factor; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor.

occurs over weeks to months (precluding single-dose therapies). However, after new vessels form, they are not likely to regress if they are conduit vessels; therefore, long-term therapy may not be necessary. Gene delivery by plasmids and adenoviruses can be directed to occur within this "angiogenic window," raising hope for angiogenic gene therapies in chronic ischemic syndromes.

Gene therapy approaches to deliver VEGF in patients with ischemic coronary and peripheral vascular diseases have progressed, albeit not at the rates hoped for based on initial investigations in the 1990s. The use of angiogenic gene therapy still has tremendous potential for patients with refractory ischemic heart disease who otherwise have no options. Because angiogenesis is a new mechanism for treating this disease, it should be additive to the effects of pharmacologic agents (β-blockers, aspirin, and nitrates). The possibility of the creation of new, long-lived conduit vessels offers the potential for a "cure," because these new vessels should provide relief long after the effects of VEGF or other angiogenic factors have dissipated.

However, it is not yet clear that angiogenesis, which predominantly involves the formation of new capillaries, creates vessels with the capacity to significantly increase blood flow to ischemic tissues. Uncontrolled capillary growth may cause hemangioma formation, which would not be beneficial and might well be deleterious. Few data are available that allow prediction of the appropriate dose, location, and duration of angiogenic gene therapy. In therapy for myocardial ischemia, required invasive approaches are associated with appreciable morbidity. Despite predictions of side effects based on diseases with known angiogenic components, little is known about side effects of angiogenic therapies in humans. Of greatest concern is the possibility that angiogenic therapies will accelerate or unmask occult tumors or metastases, since it is well known that tumor growth is an angiogenesis-dependent process. Worsening diabetic neovascular complications, especially diabetic retinopathy, are also a concern, given the prevalence of diabetes in patients with severe atherosclerotic disease.

Early clinical trials in angiogenesis have produced results that are variably interpreted, depending on the views of those reviewing these studies. Small, but statistically significant, improvements in pain-free exercise duration have been demonstrated in angiogenesis trials involving the coronary vasculature (with chest pain as the limiting symptom) as well as the peripheral vasculature (in patients with limiting claudication). These data support the concept of clinical angiogenesis. An opposing view is that because the improvements are modest, these studies fall short of demonstrating an important clinical benefit; moreover,

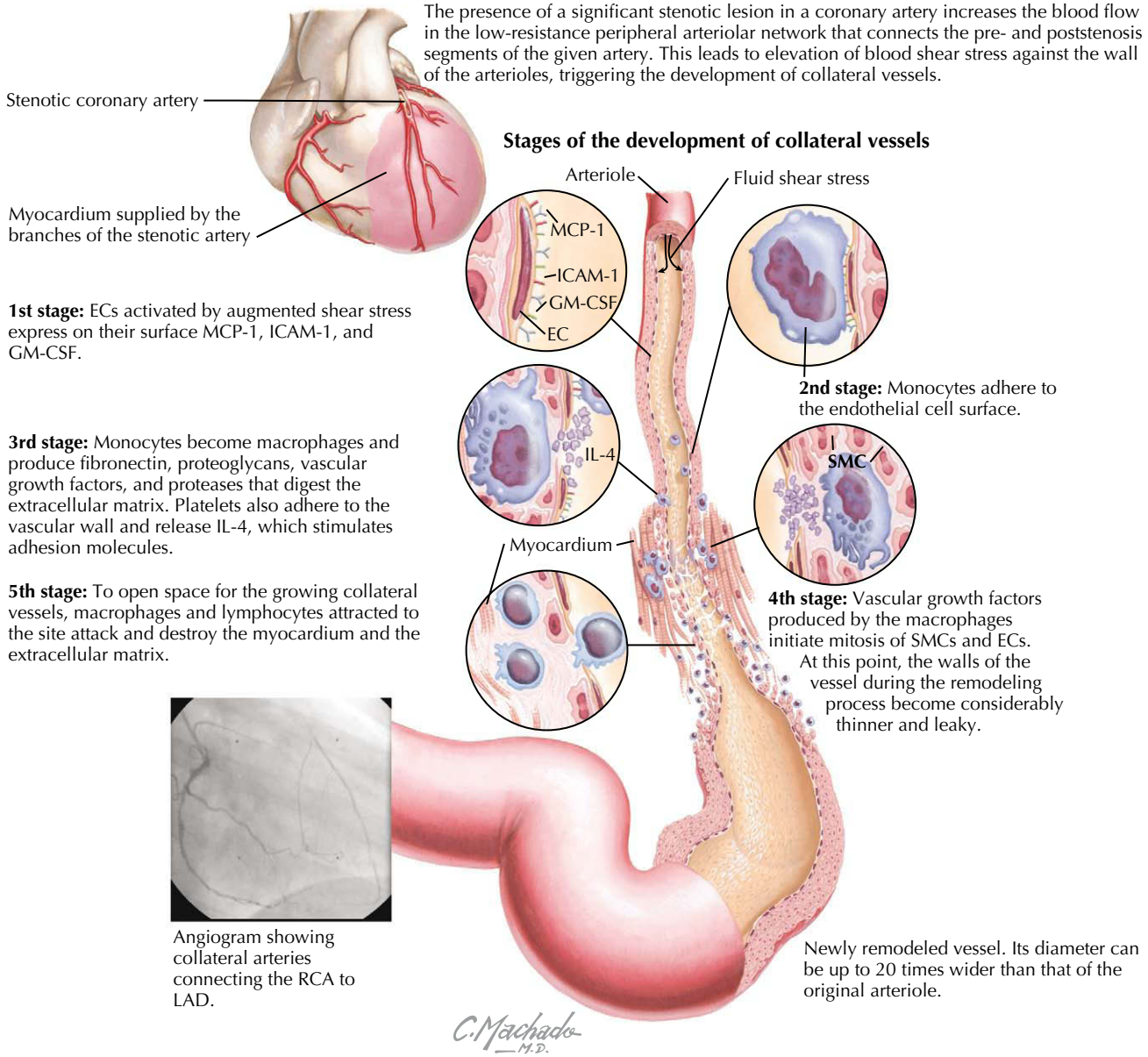

Figure 44-2 *Mechanisms of arteriogenesis and development of collateral vessels.* ECs, endothelial cells; GM-CSF, granulocyte macrophage colony-stimulating factor; ICAM-1, intercellular adhesion molecule 1; IL-4, interleukin-4; LAD, left anterior descending artery; MCP-1, monocyte chemotactic protein 1; RCA, right coronary artery; SMCs, smooth muscle cells.

thus far no studies have shown an effect on mortality or major morbidity.

Still under investigation are whether this is an effective approach, how and when to apply angiogenic agents, and the possible side effects of angiogenic stimulants. Long-term studies are necessary to definitively exclude adverse consequences such as tumor promotion.

VASCULOGENESIS AND ARTERIOGENESIS: ALTERNATIVES TO ANGIOGENESIS

New vessel growth in chronic ischemic syndromes is an attractive idea. Fortunately, more than one mechanism exists to create new blood vessels. Angiogenesis is the creation of blood vessels from sprouts off existing vessels. In contrast, vasculogenesis is the creation of blood vessels de novo by differentiation of new blood cells. Endothelial cell precursors in the bone marrow and circulating in the bloodstream can incorporate into developing vessels and contribute to vessel growth in a manner very similar to the vasculogenesis of embryonic development. The therapeutic potential of these cells has not been tested, but they can be recruited from bone marrow and may be a means to accelerate endogenous revascularization in patients with ischemia.

In contrast to angiogenesis, arteriogenesis is the recruitment of existing vessels to increase their capacity and consequent blood flow to ischemic tissue (Fig. 44-2). In a sense, arteriogenesis represents the maturation of vessels that exist but may not

contribute significantly to regional blood flow until properly stimulated. Most collateral vessels visualized by arteriography are probably vessels that have undergone arteriogenesis instead of angiogenesis. Because arteriogenesis creates capacitance vessels, this process is more likely to increase blood supply in a way that substantially affects tissue perfusion. Interestingly, the proteins that affect arteriogenesis are distinct from those that regulate angiogenesis; VEGF does not seem to be important for arteriogenesis, whereas macrophage-derived factors are necessary. The therapeutic potential of arteriogenesis has not been tested, but given the role of arteriogenesis in collateral formation in patients with chronic myocardial ischemia, this represents another potential therapeutic tool for the creation of new blood vessels in patients with refractory angina.

FUTURE DIRECTIONS

Despite the range of therapies for patients with coronary atherosclerosis, there is still a large population that is not adequately treated. Many of these patients have severe LV dysfunction from ischemic disease and, either because of coronary anatomy or because of other comorbidities, are not good candidates for revascularization. The creation of new blood vessels to increase tissue perfusion is one way to alleviate myocardial ischemia. The challenge is to determine the best way to increase tissue perfusion with minimal side effects. Angiogenic agents such as VEGF have the lead in drug development, although their overall benefit remains unproven. It is likely that other therapies designed to stimulate vasculogenesis and arteriogenesis will be evaluated for this patient population. Treatments designed to enhance blood vessel growth are being tested on patients with otherwise refractory disease, but eventually these approaches could be applied to any patient with ischemic heart disease and could even obviate the need for revascularization procedures in a significant cohort of patients.

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Diagnostic Techniques in Vascular Disease

45

Joseph Stavas

Peripheral vascular disease (PVD) encompasses a broad spectrum of arterial diseases that reduce or alter tissue perfusion. Morphologic changes that narrow the vessel lumen (stenosis) or abnormally enlarge its diameter (aneurysms) cause alterations in flow patterns, thereby leading to ischemic symptoms. Evaluation of PVD always involves advanced imaging. The imaging method of choice depends upon the vessels in question and the end organs and tissue that are affected. Noninvasive imaging techniques include Doppler ultrasound, multidetector CT angiography, and magnetic resonance angiography (MRA). Digital subtraction angiography (DSA) can be utilized to confirm the results of a noninvasive examination and to guide catheter-based therapies. This chapter summarizes the various diagnostic techniques available to evaluate the most commonly encountered occlusive and aneurysmal clinical disorders of the aorta and renal, carotid, and lower and upper extremity arteries.

ETIOLOGY AND PATHOGENESIS

A large number of pathologic processes result in arterial occlusive and aneurysm diseases. By far the most common etiology is atherosclerotic plaque formation in the vessel wall leading to luminal narrowing, wall calcification, plaque destabilization and hemorrhage with rupture, thrombosis, and end-organ damage or showering of emboli distally with resulting tissue damage and necrosis. In other circumstances, atherosclerosis leads to weakening of the vessel lumen leading to true aneurysms, defined as a vessel diameter greater than 1.5 times its normal diameter involving all layers. Genetic abnormalities and environmental exposures are almost always contributory in individuals with advanced vascular pathology. Specific genetic abnormalities have been elucidated in Marfan's syndrome (fibrillin-1), Ehlers-Danlos syndrome, William's syndrome (hypercalcemia), Loeys-Dietz syndrome (transforming growth factor-β receptor), and homocysteinuria. Thromboangiitis obliterans (Buerger's disease), which is usually associated with heavy nicotine use, is also seen with PVD. Other risk factors for atherosclerosis (e.g., hypertension, diabetes, lipid abnormalities) all accelerate disease progression and may lead to a need for surgical or percutaneous intervention. Extrinsic mass effects or vessel encasement in the case of popliteal artery entrapment by the gastrocnemius muscle, celiac artery by the diaphragmatic crus (median arcuate ligament syndrome), or renal artery by neurofibromatosis may lead to similar occlusive symptoms. Clinical manifestations depend on the location and severity of the vessel disease and presence of collateral circulation (see Chapter 44 for additional information on the pathogenesis of atherosclerosis).

LOWER EXTREMITY PERIPHERAL VASCULAR DISEASE

Clinical Presentation

Population studies suggest that approximately 15% of the general population older than 55 years have lower extremity PVD. In individuals with a genetic predisposition, diabetes, hypercholesterolemia, or a history of significant cigarette smoking, the prevalence of PVD is higher. Symptoms range from mild, intermittent claudication (pain or discomfort that develops during exercise and is relieved with rest) to constant, severe rest pain. The level of the occlusion typically correlates with the level of pain. Distal aortic (Leriche's syndrome) and iliac disease cause gluteal, thigh, lower extremity, and occasional back pain and impotence. In these individuals, the femoral artery pulses are usually abnormal, diminished, or absent. Superficial femoral and popliteal artery stenoses result in foot and calf symptoms. Less than 20% of patients with PVD progress to critical limb ischemia that jeopardizes the tissue viability of the extremity. The presence of PVD is evidence of systemic atherosclerosis and is associated with a threefold increase in cardiovascular mortality. Cross referral between cardiology and vascular surgery–interventional radiology services is vital to identify patients at risk for treatable coronary disease.

Diagnostic Approach

Examinations used to evaluate the lower extremity arteries are designed to establish the presence and location of disease, quantify severity, and determine temporal progression.

ANKLE-BRACHIAL INDEX AND SEGMENTAL PRESSURE MEASUREMENTS

The ankle-brachial index (ABI) is the simplest baseline examination used for PVD screening. This examination has a high positive predictive value except in diabetics with noncompressible calcified vessels. As an arterial stenosis increases, there is a progressive decrease in the systolic blood pressure (SBP) distal to the stenosis. The decreased blood pressure can be quantified and localized using pneumatic cuffs and either continuous Doppler or plethysmographic sensors. The ABI is determined by measuring SBP in the tibial and brachial arteries. Normally, SBP is amplified in the distal limb by pulse-wave reflection, and the ABI is greater than 1. An ABI of 0.80 to 0.90 is considered to be mildly diminished; 0.50 to 0.80, moderately diminished; and less than 0.50, severely diminished. These values reflect the degree of proximal PVD.

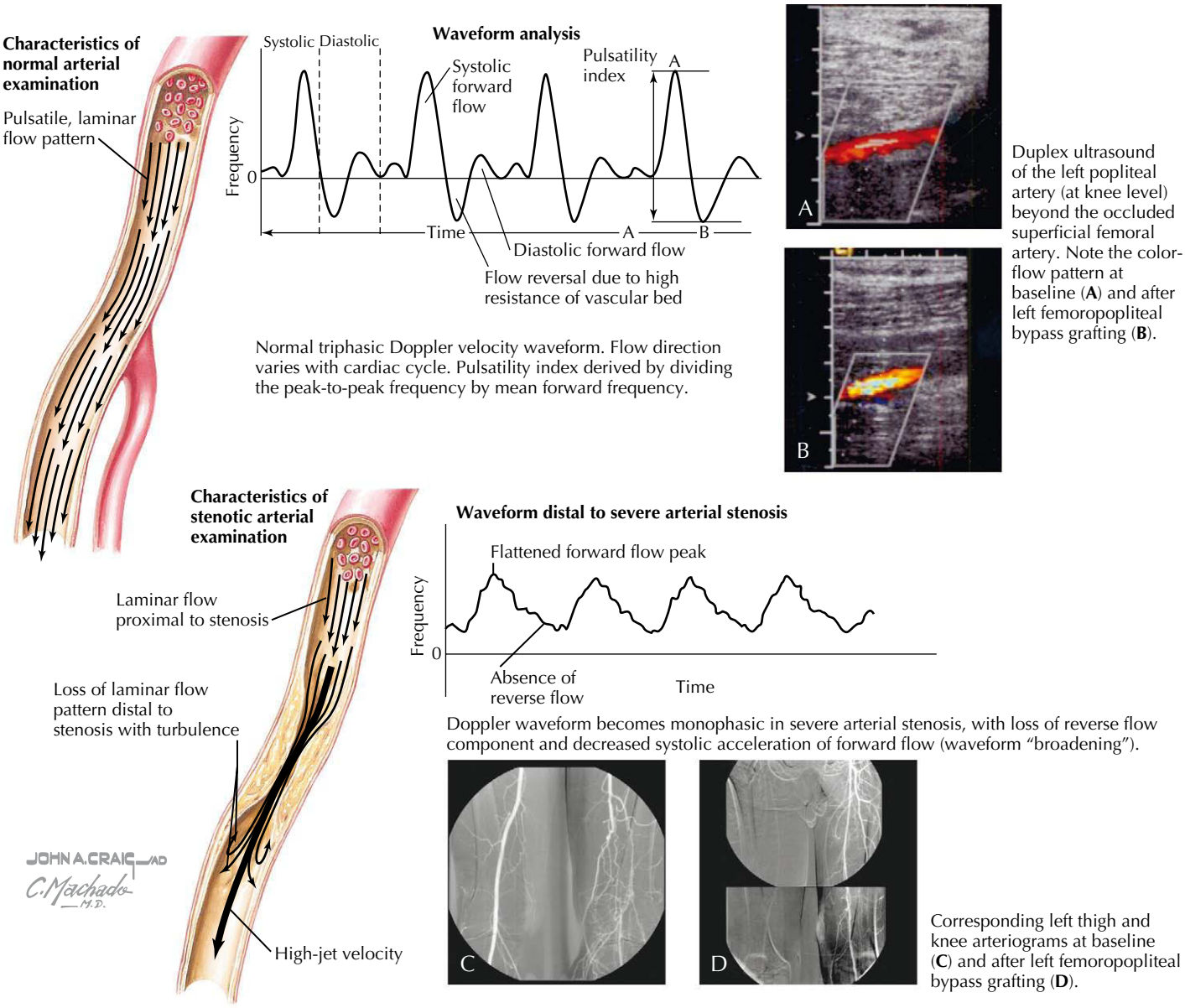


Figure 45-1 *Types of arterial noninvasive tests.*

The ABI is simple and inexpensive to use and is an excellent office-based screening tool to identify individuals at risk for limb ischemia who may warrant further investigation if results are abnormal. Pressure measurements at multiple levels along the leg can estimate the location of an arterial occlusion. Blood pressure cuffs are placed on the upper and lower thighs and calves, and a gradient of greater than 10 to 15 mm Hg between adjacent sites suggests a physiologically significant stenosis. Measurements after treadmill exercise may disclose a hemodynamically significant lesion that is unapparent at rest.

DUPLEX ULTRASONOGRAPHY

Doppler waveform analysis is an accurate method for defining arterial lesion location and severity (Fig. 45-1). Significant arterial stenoses alter the pattern of flow velocity, as assessed by continuous-wave Doppler analysis. A change in the flow velocity waveform—an increase in peak systolic velocity at the site of the lesion, turbulence, loss of the reverse flow component, or a decrease in pulse velocity distal to the lesion—is diagnostic of a flow-limiting arterial lesion. Color Doppler imaging is able to identify the vessel(s) of interest. A critical stenosis (>50%) is characterized by poststenotic turbulence on color imaging (see Fig. 45-1) and a doubling of the peak systolic velocity on continuous-wave Doppler.

COMPUTED TOMOGRAPHY ANGIOGRAPHY AND MAGNETIC RESONANCE ANGIOGRAPHY

Current multidetector or dual-source CT scans with power-injected intravenous contrast provide rapid high-resolution axial scans with imaging of the major vessels throughout the entire

cardiovascular system. The temporal spatial and contrast resolution of these scanners to 0.3 mm has allowed improved diagnosis of the location and severity of occlusive and aneurysmal disease, and also can provide information on whether plaques are calcific and whether a thrombus is present. Three-dimensional (3D) curved multiplanar reconstruction, rotational imaging, and postprocessing techniques, such as volume-rendering imaging and stenosis quantification, allow for a thorough analysis of a specific lesion or aneurysm. These outpatient studies have replaced diagnostic angiography in many situations and are completely adequate for targeting interventions, thereby reducing the volume of contrast required and length of examination. CT angiography (CTA) is widely available. The major contraindications to its use are an allergy to iodine (and intravenous contrast) and renal insufficiency. Patients with known or potential dye allergies can be pretreated to reduce allergic reactions, and depending on the degree of renal insufficiency, it is often possible to reduce the risk of worsening renal failure by hydration before and after the procedure. The incidental diagnosis of additional unrecognized disease occurs frequently during the PVD CT scan. Asymptomatic lung, renal, bladder, and other cancers, more common in a population using nicotine, are often discovered during diagnostic CTA. The use of CTA must be weighed against the above complications and the significant radiation exposure dose, especially for younger patients.

High-field (1.5 Tesla or greater) MRA is nonionizing and can be used in patients with iodine allergies or renal insufficiency. Newer gradient coils, software, and hardware have improved the spatial resolution of MRA, and for some diseases it approaches CTA and conventional angiography for diagnostic accuracy. Contraindications to MRI-MRA are cardiac pacemakers or defibrillators and decreased creatinine clearance, since gadolinium contrast agents have been implicated in the development of nephrogenic systemic fibrosis. There may be impaired imaging due to artifacts from endovascular stents, grafts, and coils, and imaging sequences may be limited by the need for specific table and coil requirements. Some patients may also require anxiolytics because of the increased length of examinations and/or claustrophobia. Data from both CTA and MRA are enhanced with 3D laboratory capabilities (Fig. 45-2).

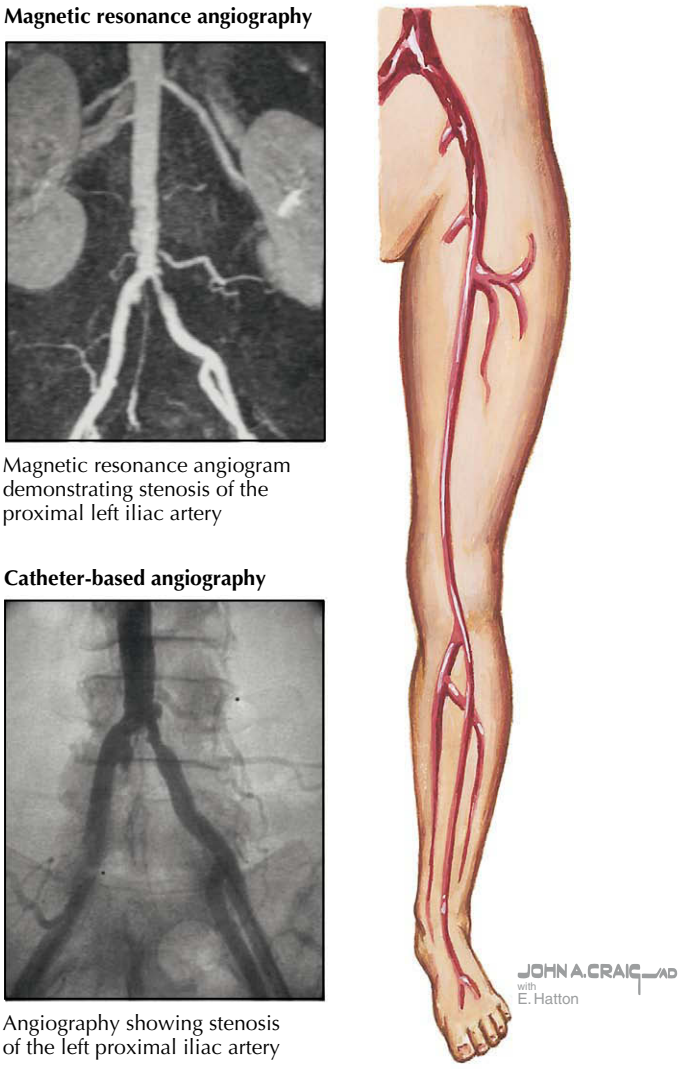


Figure 45-2 *Diagnostic techniques in vascular disease.*

ABDOMINAL, PELVIC, AND LOWER EXTREMITY ANGIOGRAPHY

Angiography is an invasive examination with some risk, albeit small, due to arterial puncture site and catheter manipulation complications. These are typically groin hematoma and pseudoaneurysm formation, and less commonly vessel wall dissection. Despite these potential complications, diagnostic and frequently therapeutic angiography examinations are performed in outpatient settings. Image quality and diagnostic accuracy are superb with high-resolution flat panel DSA equipment. Small-vessel anatomy, especially in the foot and ankle region, is clearly defined, better than by either CTA or MRA. Visualization of distal upper and lower extremity anatomy is crucial for distal bypass graft surgery. Diagnostic angiography is indicated when ultrasound, CTA, or MRA is unable to answer the clinical question, or when intervention is planned at the same setting. The examination typically requires conscious sedation, postprocedure observation space, and an adequate inventory of catheters, wires, and sheaths. Initial and ongoing capital costs are required to maintain an angiography suite.

CAROTID ARTERY DISEASE

Clinical Presentation

Close to 700,000 new or recurrent strokes occur each year in the United States, and approximately 4.6 million stroke survivors are alive today. Stroke is a leading cause of disability, with nearly one of every five victims requiring institutional rehabilitation care. An important cause of preventable stroke is large-vessel or carotid atherosclerosis, which may account for 15% to 20% of ischemic strokes.

Patients with cerebrovascular disease may present with an asymptomatic bruit, a transient ischemic attack, weakness, paralysis, or a variety of vague symptoms. The risk of stroke increases with greater degrees of carotid plaque burden, particularly for those with recent ischemic neurologic events. The 5-year stroke risk in these patients can be as high as 35%.

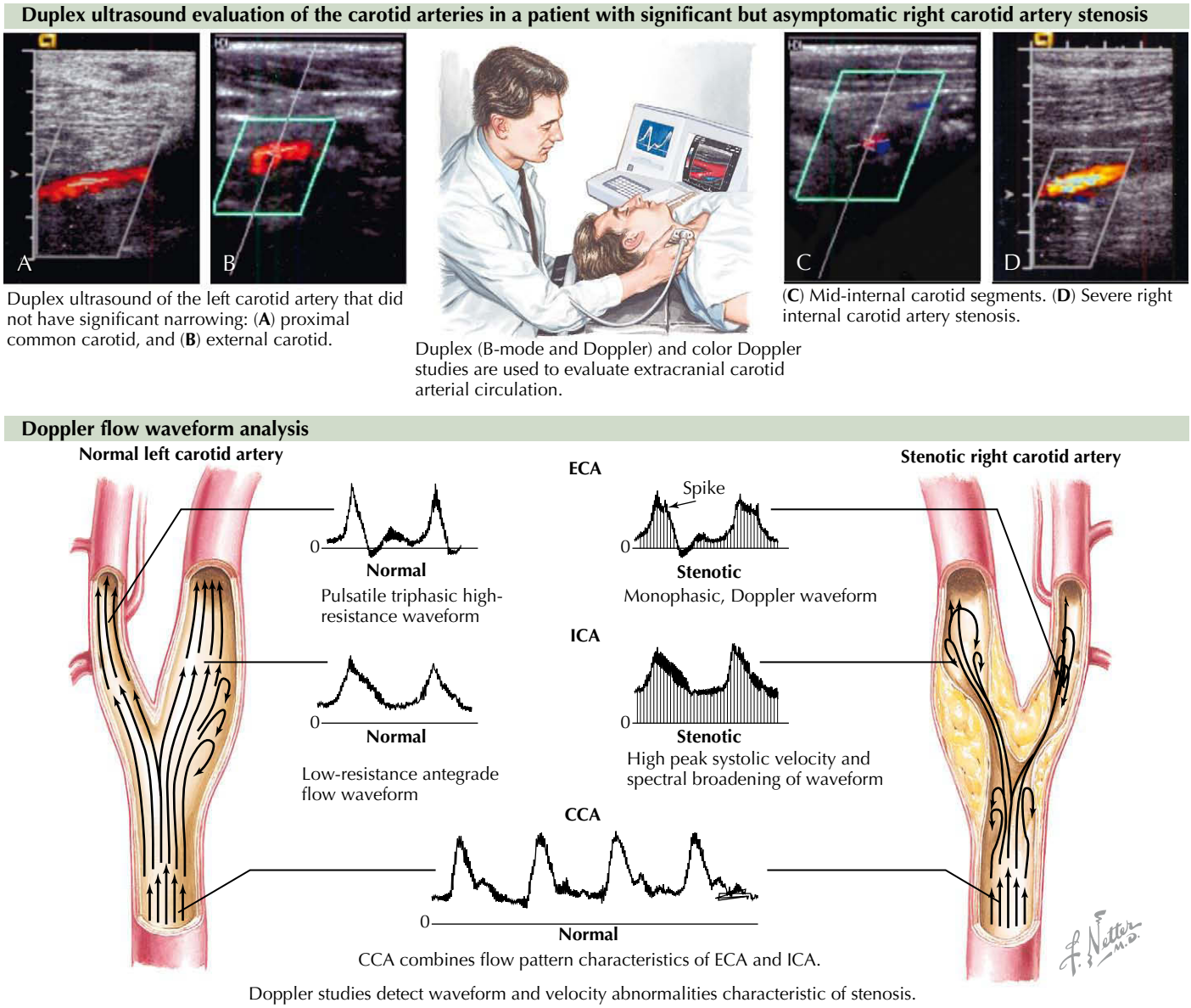


Figure 45-3 *Noninvasive evaluation of carotid arteries.* CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery.

Despite the availability of multiple natural history studies of asymptomatic carotid lesions, it is still difficult to predict which patients will have a neurologic event, whether or not they receive antiplatelet therapy.

Diagnostic Approach

The goal of evaluation of the carotid arteries is to define the location, laterality, and extent of carotid disease.

DUPLEX ULTRASONOGRAPHY

The mainstay of noninvasive evaluation of carotid disease is duplex ultrasonography (Fig. 45-3). The combination of two-dimensional ultrasound imaging and Doppler assessment is an inexpensive, noninvasive, safe, convenient, and accurate means of localizing and determining the hemodynamic significance of carotid lesions. Surgical carotid endarterectomy (CEA) can be performed on the basis of the duplex findings.

The sensitivity and specificity of this approach are lessened in patients with increased carotid wall calcification and/or subocclusive stenoses (string sign of near-complete occlusion), and in the hands of less-experienced operators. Laboratory certification offers standardization of imaging quality.

COMPUTED TOMOGRAPHY ANGIOGRAPHY AND MAGNETIC RESONANCE ANGIOGRAPHY

Advantages of these noninvasive imaging techniques include the capacity to visualize the aortic arch, as well as the brachio-

cephalic trunks and intracranial arteries (see "Lower Extremity Peripheral Vascular Disease"). Duplex correlation with CTA or MRA is sometimes necessary in patients with recurrent symptoms and postoperative CEA, those who had prior head and neck surgery, and in technically difficult duplex examinations. CTA requires iodinated contrast administration, and MRA can be degraded by motion artifact from breathing and swallowing, signal voids due to surgical clips, extensive calcification, and metallic dental fillings and implants.

FOUR-VESSEL CEREBRAL ARTERIOGRAPHY

This invasive procedure can provide additional details to influence the decision to proceed with surgery. The two groups of patients that derive greatest benefit from CEA (compared with medical therapy)—those with either ulcerative lesions or synchronous intracranial artery stenoses—are best identified by angiography. Both of these circumstances occur in 20% to 50% of patients with extracranial carotid disease.

Another important limitation of noninvasive diagnostic imaging methods is the difficulty in distinguishing between subtotal and total occlusion. Patients who have even a small channel of flow through the internal carotid artery (string sign) are still candidates for surgical or endovascular therapy, whereas complete occlusions are best treated medically (see Chapter 48). Finally, angiography provides superb delineation of collateral blood flow, particularly in the setting of occlusive disease. Catheter-related risks include puncture site and catheter-related complications, such as vessel dissection and stroke. Iodine-related contrast allergies can be pretreated with steroids, antihistamines, and histamine-2 inhibitors.

RENAL ARTERY STENOSIS

Clinical Presentation

See Chapter 47 for a discussion of the clinical presentation of renal artery stenosis.

Diagnostic Approach

The objectives of noninvasive evaluation of renovascular disease are to determine the location and severity of renal arterial lesions and to assess the functional significance of these stenoses. Four methods of noninvasive imaging can provide useful information in evaluating the renal arteries: (1) the nuclear medicine captopril renal scan, (2) Doppler ultrasound imaging, (3) MRA, and (4) CTA. Each method varies in the degree of specificity and sensitivity. DSA is an invasive technique and carries the same risk as other forms of angiography. Angiography is generally required only if revascularization is being considered.

Evaluation for renal artery stenosis should be based on the clinical index of suspicion of disease, as outlined in Figure 45-4.

CAPTOPRIL RENAL SCAN

In patients with functionally significant renal artery stenosis, high levels of angiotensin II maintain glomerular filtration and renal blood flow. Administration of captopril causes an abrupt decrease in filtration pressure in the ischemic kidney, resulting in reduced uptake of ^{99m}Tc-DTPA or delayed secretion of ^{131}I-hippurate or ^{99m}Tc-MAG$_3$. Captopril renography is an accurate diagnostic technique in patients with a moderate likelihood of renovascular hypertension and normal renal function, with sensitivities and specificities approaching 90%. It is less reliable, however, in patients with a creatinine concentration greater than 2.0 mg/dL or in patients with bilateral renal artery stenosis (Fig. 45-5). Often a non-captopril study is performed initially. The oral administration of captopril adds to the length of the examination.

DOPPLER ULTRASONOGRAPHY

In selected centers, Doppler ultrasonography is the preferred method of detection of changes in renal arterial flow characteristics and detection of significant renal arterial stenoses. Doppler ultrasonography is a highly sensitive and specific technique. Doppler indices of structural alterations of the renal microvasculature (resistive index and pulsatility index) are, in addition, predictors of the blood pressure response to revascularization. Although technical advances have significantly enhanced the diagnostic accuracy of this technique, it remains operator-dependent and is not sensitive in detecting disease in accessory renal arteries.

MAGNETIC RESONANCE ANGIOGRAPHY

Contrast-enhanced MRA provides excellent images of the main renal arteries, perirenal aorta, and mesenteric vasculature; however, evaluation of smaller accessory renal arteries is less accurate. It is a useful technique in patients with mild renal insufficiency in whom iodinated contrast is contraindicated or for follow-up to reduce the amount of radiation exposure. The examination is operator- and software-sensitive, since spatial resolution may be limited. Stents (from prior treatment of renal artery stenosis or aneurysm) result in significant imaging artifacts, essentially precluding the use of this technique.

COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Multidetector CTA visualizes the main and segmental renal arteries and accessory vessels in three dimensions and is highly accurate in detecting anatomic stenoses. The examination requires iodinated contrast medium and is contraindicated in patients with impaired renal function. Of the four examinations listed, CTA offers the most reproducible method of determining renal artery anatomy and is readily available to most clinicians.

DIGITAL SUBTRACTION ANGIOGRAPHY

DSA is reserved for situations of inconclusive noninvasive examinations and when intervention is being considered. Flat-panel DSA provides high-resolution imaging of the main and accessory renal arteries and of the adjacent aorta and mesenteric arteries. An examination can be performed with limited contrast volume and in an outpatient setting.

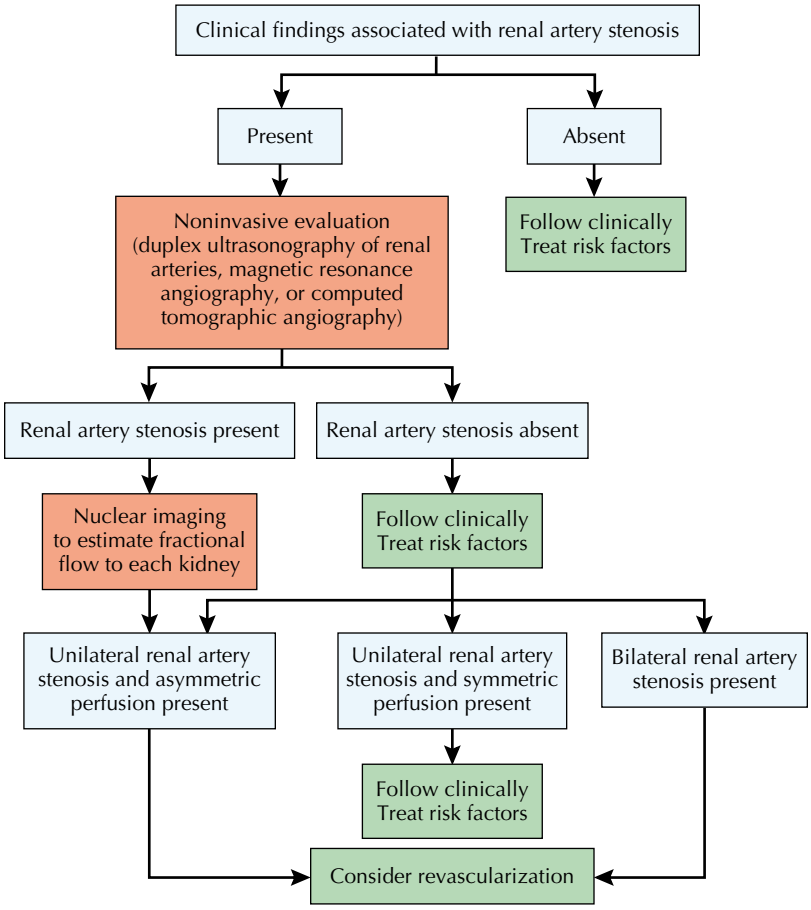
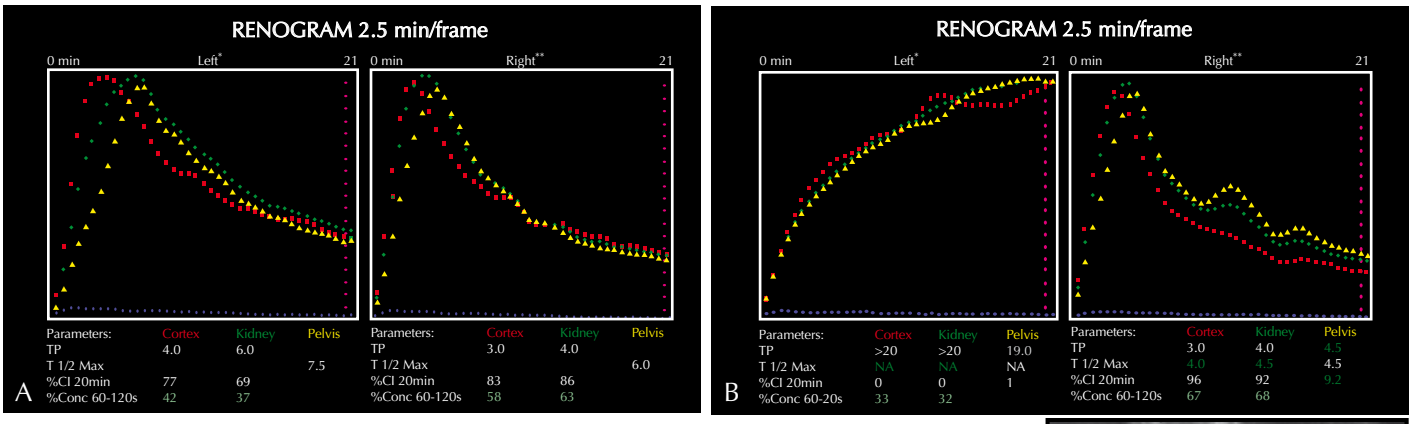


Figure 45-4 *Algorithm for evaluating patients in whom renal artery stenosis is suspected.* (From Safian RD, Textor SC. Medical progress: Renal-artery stenosis. *N Engl J Med.* 2001;344:431–442.)



Uptake and excretion of ^{99}Tc-MAG$_3$, given IV, by the left and right kidney before (**A**) and after (**B**) oral administration of 50 mg of captopril. Slow uptake and no excretion of the radiopharmaceutical, suggesting functionally significant stenosis of the left renal artery is shown in **B**. A high-grade atherosclerotic stenosis of the left renal artery with poststenotic dilation in the same patient is shown in **C**. The right renal artery is normal. Note the atherosclerotic changes of the abdominal aorta.

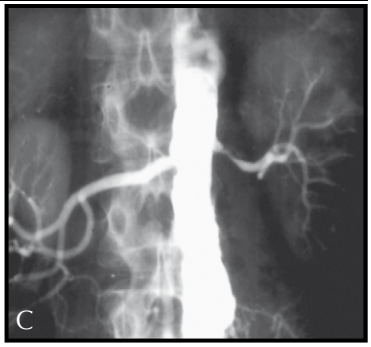
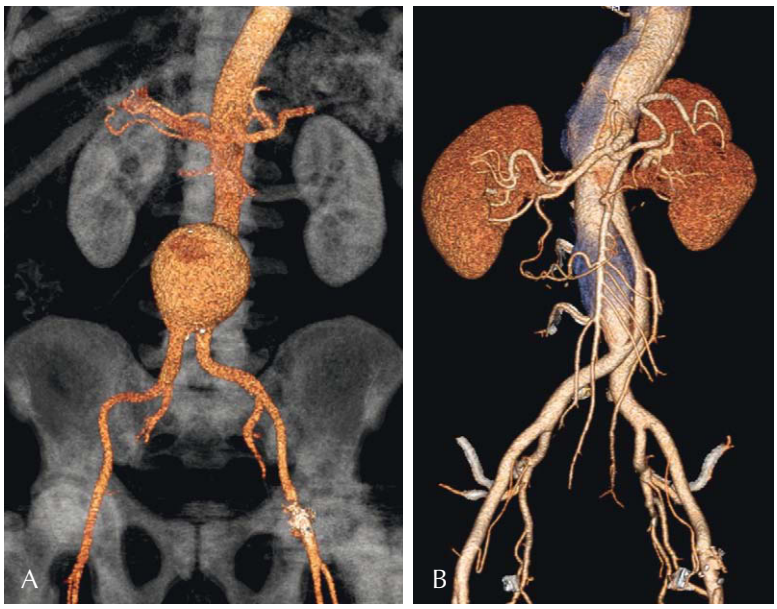


Figure 45-5 *Abnormal captopril renal scan and angiogram in a patient with renal artery stenosis.* *Left kidney; **right kidney.



(**A**) 3D CT volumetric reconstruction: Saccular infrarenal AAA extending to the bifurcation. (**B**) Volumetric reconstruction of abdominal aorta. AAA with dissection involving the superior mesenteric artery and right common iliac artery.

Figure 45-6 *Three-dimensional (3D) CT volumetric reconstruction.* AAA, abdominal aortic aneurysm.

ABDOMINAL AORTIC ANEURYSMS

Clinical Presentation

Abdominal aortic aneurysm (AAA) rupture is an important cause of unheralded deaths in individuals above the age of 55 years. Although atherosclerotic changes accompany almost all AAAs, classic coronary risk factors seem to be less predictive for this disease, and abnormal collagen, elastin, matrix metalloproteinases, and inflammatory changes causing vessel wall weakness seem to have important contributory roles.

Diagnostic Approach

The best independent predictor of rupture rate is maximal aneurysm diameter. Elective surgical or endovascular treatment is therefore contingent on accurate measurements and is recommended for AAAs 5 cm or greater in diameter, or for aneurysms greater than 4 cm that are enlarging at a rate of 0.5 cm or more per year.

ULTRASONOGRAPHY

Two-dimensional ultrasonography allows detection (>95% sensitivity) of a suspected AAA. The broad availability and reproducibility of ultrasonography make it an ideal method for serial follow-up. Obesity, excessive bowel gas, and recent abdominal surgery can limit examinations. The superior (thoracic) and inferior (iliac) extension of the AAA and concomitant involvement of visceral or renal arteries are difficult to determine via ultrasound, and thus diagnosis may require alternative imaging.

COMPUTED TOMOGRAPHY ANGIOGRAPHY AND MAGNETIC RESONANCE ANGIOGRAPHY

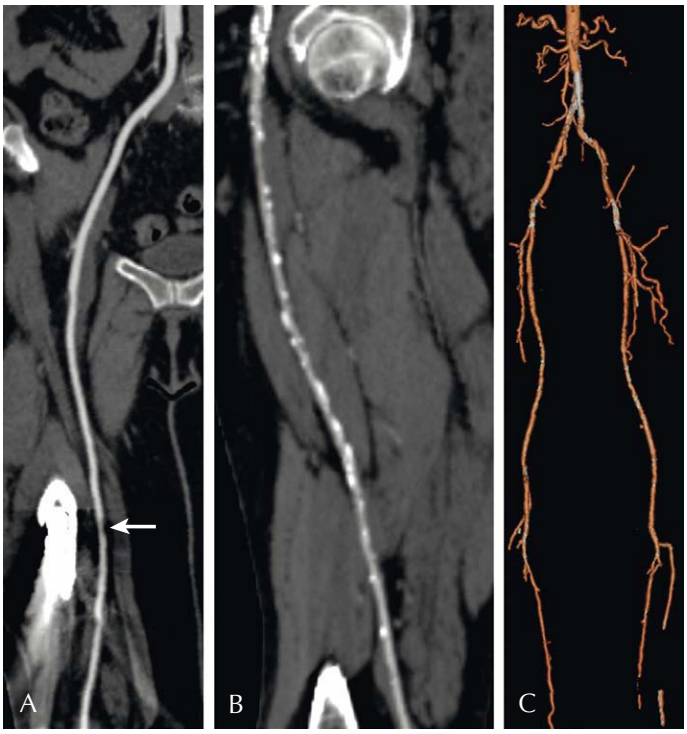
CTA and MRA provide information about the aortic wall and luminal diameter and delineate the presence and quantity of thrombi. They both provide detail about surrounding abdominal structures and their relation to the AAA. The occasional finding of perianeurysmal fibrosis, venous anomalies (e.g., retroaortic left renal vein, circumaortic venous collar), or horseshoe kidney is important for surgical planning. Furthermore, aortic neck length, aneurysm angulation, superior and inferior extension, and involvement of the adjacent visceral and renal arteries offer additional information. Volumetric data following AAA repair can be performed with 3D software (Figs. 45-6 and 45-7).

ANGIOGRAPHY

DSA provides high spatial resolution of the lumen of the aorta and other vessels and defines anomalies and aberrant vessels. It is a poor method for assessing AAA size (because laminated flow or mural thrombus may give the false arteriographic impression of normal luminal diameter) and is unable to image the outer diameter of the aorta. Angiography is important, however, if mesenteric or renal artery stenosis is suspected and if pre-endograft vessel embolization or stent placement is necessary.

FUTURE DIRECTIONS

Dramatic developments in noninvasive imaging techniques have revolutionized the evaluation of patients with PVD, and



Rotational CT reconstruction. (**A**) Oblique in-line reconstruction of external iliac and proximal SFA. Noncalcified vessel with mild proximal SFA stenosis (*arrow*). (**B**) Diffuse SFA calcified plaque. (**C**) 3D volumetric reconstruction of the lower extremities: occluded bilateral anterior and posterior tibial arteries.

Figure 45-7 *Rotational CT reconstruction.* 3D, three-dimensional; SFA, superficial femoral artery.

angiography is generally not necessary unless an intervention is anticipated. Technical advances in CTA, MRA, and other methods will undoubtedly further improve image quality, and clinical research will better define the roles of these techniques in patient evaluation. CTA scanners with 128 or more detectors and MRI scanners functioning at 7 Tesla or greater will redefine noninvasive imaging capabilities. Noninvasive methods and devices have been developed to evaluate global, regional, or local indices of vessel wall stiffness. Most use one of three methods: measurement of pulse transit time, analysis of the arterial pulse contour, or direct measurements of vascular diameter change and distending pressure. High-frequency B-mode ultrasound can identify the lumen-intima and media-adventitia interfaces of arteries, permitting quantification of the thickness of the intima and the media, the two layers of the arterial wall involved in atherosclerosis. Methodologies that provide not only anatomic information but also assessments of the functional significance of vascular lesions, such as MR spectroscopy, will be valuable in guiding therapy. Finally, techniques to refine the risk stratification provided by evaluation of traditional PVD risk factors may help to identify patients most likely to benefit from aggressive therapies.

ADDITIONAL RESOURCES

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Hypertension

Alan L. Hinderliter and Romulo E. Colindres

46

Hypertension is a major risk factor for atherosclerotic cardiovascular disease (Box 46-1). Despite advances in the understanding of the pathophysiology, epidemiology, and natural history of hypertension, as well as improvements in therapy, many patients with hypertension are undiagnosed or inadequately treated. Hypertension, or high blood pressure (BP), remains an important contributor to coronary events, heart failure, stroke, and end-stage kidney disease.

BP is a continuous variable, and any BP level chosen to define hypertension is arbitrary. Nevertheless, an operational definition of hypertension has been advocated as a treatment guideline. The Seventh Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended the classification of BP for adults shown in Table 46-1.

Approximately 50 million people in the United States have hypertension, and BP is controlled in only about one third. The percentage of patients with controlled hypertension is even lower in some other Western countries (i.e., Canada and England) and is less than 10% in developing countries—a disappointing figure given the available medications and education of the public and physicians about the risks of high BP. Because hypertension is a worldwide problem and a major cardiovascular risk factor, its prevention and treatment should be high public health priorities.

ETIOLOGY AND PATHOGENESIS

Hypertension is a disorder of BP regulation that results from an increase in cardiac output or, most often, an increase in total peripheral vascular resistance. Cardiac output is usually normal in essential hypertension, although increased cardiac output plays an etiologic role. The phenomenon of autoregulation explains that an increase in cardiac output causes persistently elevated peripheral vascular resistance, with a resulting return of cardiac output to normal. Figure 46-1 shows mechanisms that can cause hypertension. Inappropriate activation of the renin-angiotensin system, decreased renal sodium excretion, and increased sympathetic nervous system activity, individually or in combination, are probably involved in the pathogenesis of all types of hypertension. Hypertension also has genetic and environmental causes, the latter including excess sodium intake, obesity, and stress. The inability of the kidney to optimally excrete sodium, and thus regulate plasma volume, leads to a persistent increase in BP whatever the etiology.

Many elderly patients with elevated BP have isolated systolic hypertension—a systolic pressure that exceeds 140 mm Hg with a normal diastolic pressure. Stiffening of large arteries and increased systolic pulse wave velocity elevate systolic BP, increase myocardial work, and decrease coronary perfusion.

CLINICAL PRESENTATION

Most patients with early hypertension have no symptoms attributable to high BP. However, long-term BP elevation often leads to hypertensive heart disease, atherosclerosis of the aorta and peripheral vessels, cerebrovascular disease, and chronic kidney disease.

Left ventricular hypertrophy (LVH) is the principal cardiac manifestation of hypertension. Increased left ventricular (LV) mass can be identified by echocardiography in nearly 30% of unselected hypertensive adults and in the majority of patients with long-standing, severe hypertension. LVH is more prevalent in males and more common in black individuals than in white individuals with similar BP values. Increasing age, obesity, high dietary sodium intake, and diabetes are also associated with cardiac hypertrophy.

Increased ventricular afterload resulting from elevated peripheral vascular resistance and arterial stiffness is considered the principal determinant of myocardial hypertrophy in patients with hypertension. Hemodynamic overload stimulates increases in myocyte size and the synthesis of contractile elements. Fibroblast proliferation and deposition of extracellular collagen accompany these cellular changes and contribute to ventricular stiffness and myocardial ischemia. A growing body of evidence suggests that angiotensin II and aldosterone, independent of pressure overload, stimulate this interstitial fibrosis (Fig. 46-2).

Clinical consequences of hypertensive heart disease include heart failure and coronary heart disease (CHD). More than 90% of patients with heart failure have hypertension, and data from the Framingham Heart Study suggest that high BP accounts for almost half of the population burden of this disorder. Treating hypertension reduces the risk of heart failure by nearly 50%. Heart failure develops because of the myocyte hypertrophy and ventricular fibrosis that characterize hypertensive LVH. As illustrated in Figure 46-3, the early functional manifestations of LVH include impaired LV relaxation and decreased LV compliance. Although the ejection fraction is preserved initially, diastolic dysfunction often results in increased filling pressures, leading to pulmonary congestion. This mechanism accounts for the symptoms observed in approximately 40% of hypertensive patients with heart failure. If excessive BP levels persist, myocyte loss and fibrosis contribute to ventricular remodeling and contractile dysfunction. Compensatory mechanisms, including remodeling of the peripheral vasculature and activation of the sympathetic nervous and renin-angiotensin systems, accelerate the deterioration in myocardial contractility. Ultimately, decompensated cardiomyopathy and heart failure from systolic dysfunction develop (Fig. 46-4).

CHD is approximately twice as prevalent in hypertensive as in normotensive persons of the same age. CHD risk increases in a continuous and graded fashion with both systolic BP and diastolic BP. A reduction in diastolic BP of 5 mm Hg with drug

Box 46-1 Hypertension as a Risk Factor for Cardiovascular Disease

- High BP accelerates atherogenesis and increases the risk of cardiovascular events by two- to threefold.
- Levels of SBP and DBP are associated with cardiovascular events in a continuous, graded, and apparently independent fashion. This relation is closer for SBP than for DBP.
- Every 20-mm Hg increase in SBP above 115 mm Hg results in a doubling of mortality from CHD and stroke.
- Hypertension often occurs in association with other atherogenic risk factors, including dyslipidemia, glucose intolerance, and obesity.
- The association of hypertension with other cardiovascular risk factors increases the risk of cardiovascular events in a multiplicative rather than an additive fashion.

BP, blood pressure; CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 46-1 Classification of Blood Pressure for Adults Aged 18 Years and Older

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Normal	<120	<80
Pre-hypertension	120–139	80–89
Hypertension		
Stage 1	140–159	90–99
Stage 2	≥160	≥100

With permission from Chobanian VA, Bakris GL, Black AR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA. *2003;289:2560–2572.*

therapy decreases the incidence of myocardial infarction (MI) by approximately 20%. Multiple factors contribute to the enhanced risk of CHD associated with high BP: atherosclerotic narrowing of epicardial coronary arteries is accelerated; coronary arteriolar hypertrophy, reduced myocardial vascularity (rarefaction), and perivascular fibrosis limit coronary arterial flow reserve and predispose the left ventricle to ischemia; and impaired coronary endothelial function increases coronary tone. MI and chronic ischemia contribute to LV dysfunction, increasing the risk of heart failure and cardiovascular death.

DIFFERENTIAL DIAGNOSIS

Approximately 95% of patients with elevated arterial pressure have hypertension of unknown etiology, known as *essential hypertension*. The remaining 5% have an identifiable cause of secondary hypertension (Box 46-2). Although relatively few patients have secondary hypertension, identification of these patients is important, because the hypertension can often be cured or significantly ameliorated by an interventional procedure, a specific drug therapy, or stopping a culprit drug.

Identifiable causes of hypertension should be sought in the initial history, physical examination, and laboratory studies. Further diagnostic evaluation for secondary hypertension causes is pursued when the presentation is atypical for essential hypertension or when the initial evaluation suggests an identifiable cause (Box 46-3).

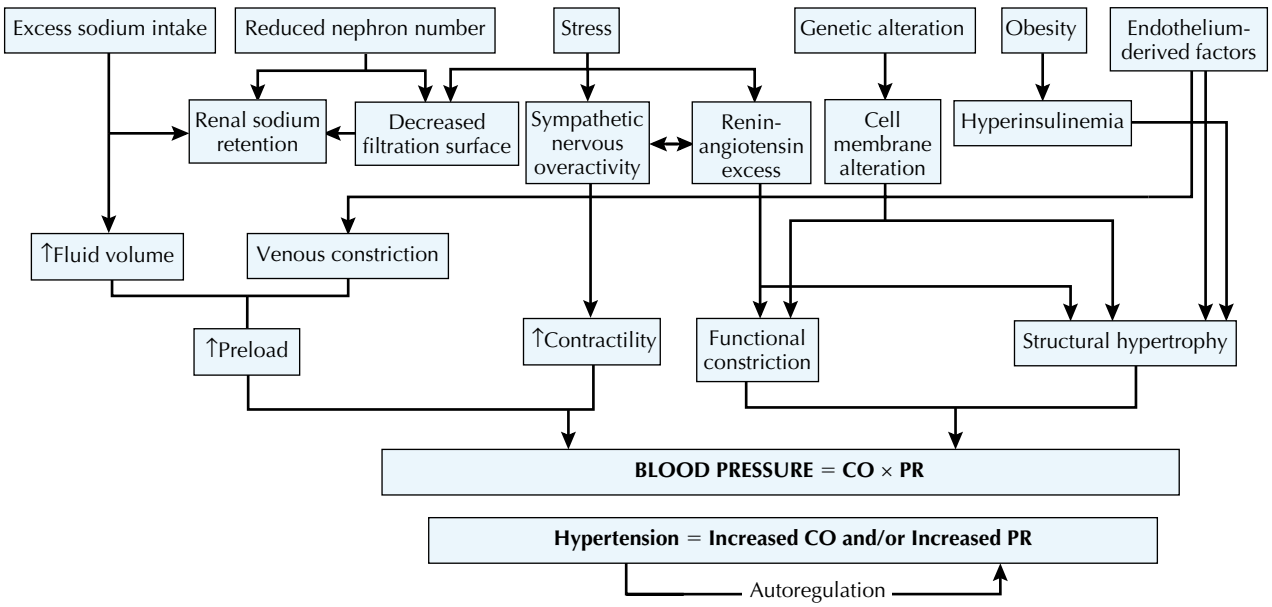


Figure 46-1 *Factors involved in the control of blood pressure.* CO, cardiac output; PR, peripheral resistance. With permission from Kaplan NM. *Kaplan's Clinical Hypertension.* 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2002.

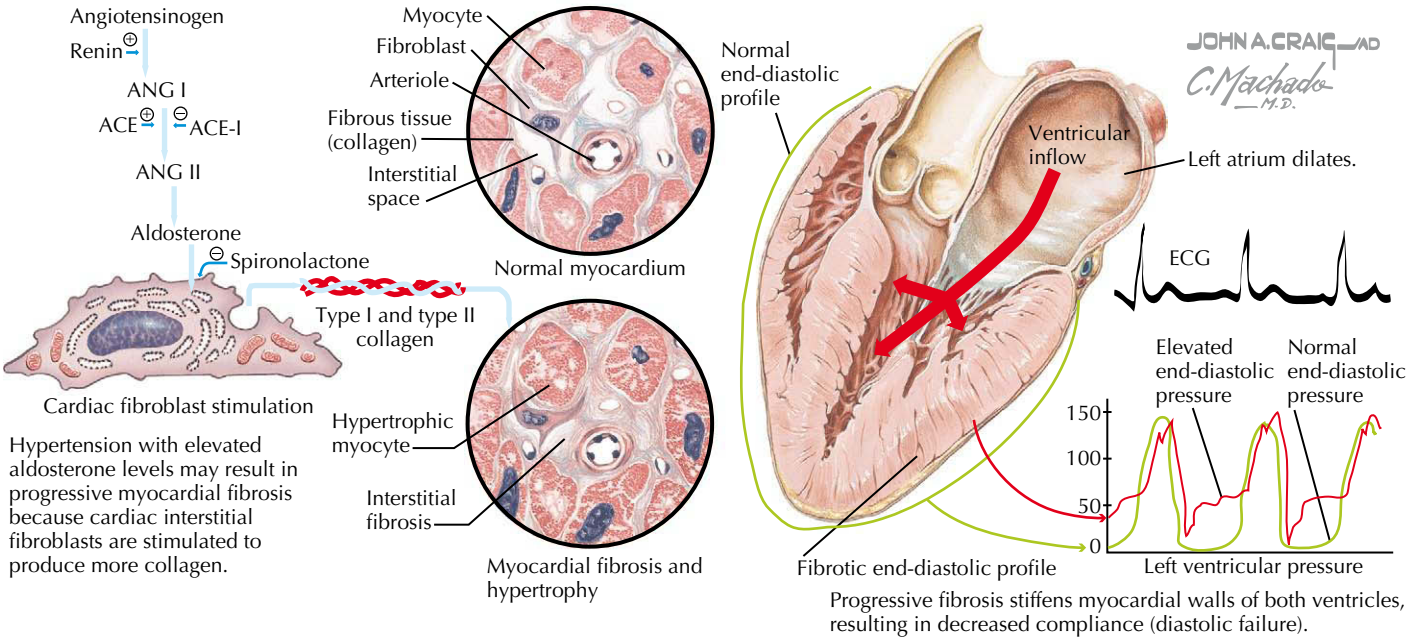


Figure 46-2 *Myocardial fibrosis.* ACE, angiotensin-converting enzyme; ACE-I, angiotensin-converting enzyme inhibitor; ANG I, angiotensin I; ANG II, angiotensin II.

Box 46-2 Identifiable Causes of Hypertension

- Renal
  - Renal parenchymal disease
  - Renal vascular disease
- Endocrine
  - Hypo- or hyperthyroidism
  - Adrenal disorders
  - Primary hyperaldosteronism
  - Cushing's syndrome
  - Pheochromocytoma
- Exogenous hormones
  - Glucocorticoids
  - Mineralocorticoids
  - Sympathomimetic agents
  - Erythropoietin
- Coarctation of the aorta
- Sleep apnea
- Neurologic disorders
  - Elevated intracranial pressure
  - Quadriplegia
- Acute stress
  - Perioperative
  - Hypoglycemia
  - Alcohol withdrawal
- Drugs and medications
  - Alcohol
  - Cocaine
  - Nicotine
  - Nonsteroidal anti-inflammatory agents
  - Immunosuppressive agents (cyclosporine, tacrolimus)

DIAGNOSTIC APPROACH

Objectives of the initial evaluation of a hypertensive patient include confirmation of the presence of hypertension, evaluation of the presence and extent of target organ disease, identification of cardiovascular risk factors and coexisting conditions that influence prognosis and therapy, and exclusion or detection of identifiable causes of elevated BP. These goals can usually be achieved with a comprehensive history, a thorough physical examination, and selected laboratory studies (Box 46-4).

Detection and diagnosis of hypertension begin with the accurate measurement of BP. Measurements should be acquired at each encounter, with follow-up determinations at intervals based on the initial level. Accurate equipment and proper

Box 46-3 Indications for Considering Testing for Identifiable Causes of Hypertension

- Onset of hypertension at age younger than 20 years or onset of diastolic hypertension at age older than 50 years
- Target organ damage at presentation
  - Serum creatinine concentration >1.5 mg/dL
  - LV hypertrophy determined by electrocardiography
- Presence of features indicative of secondary causes
  - Hypokalemia
  - Abdominal bruit
  - Labile pressures with tachycardia, sweating, and tremor
  - Family history of kidney disease
- Poor response to generally effective therapy

LV, left ventricular.

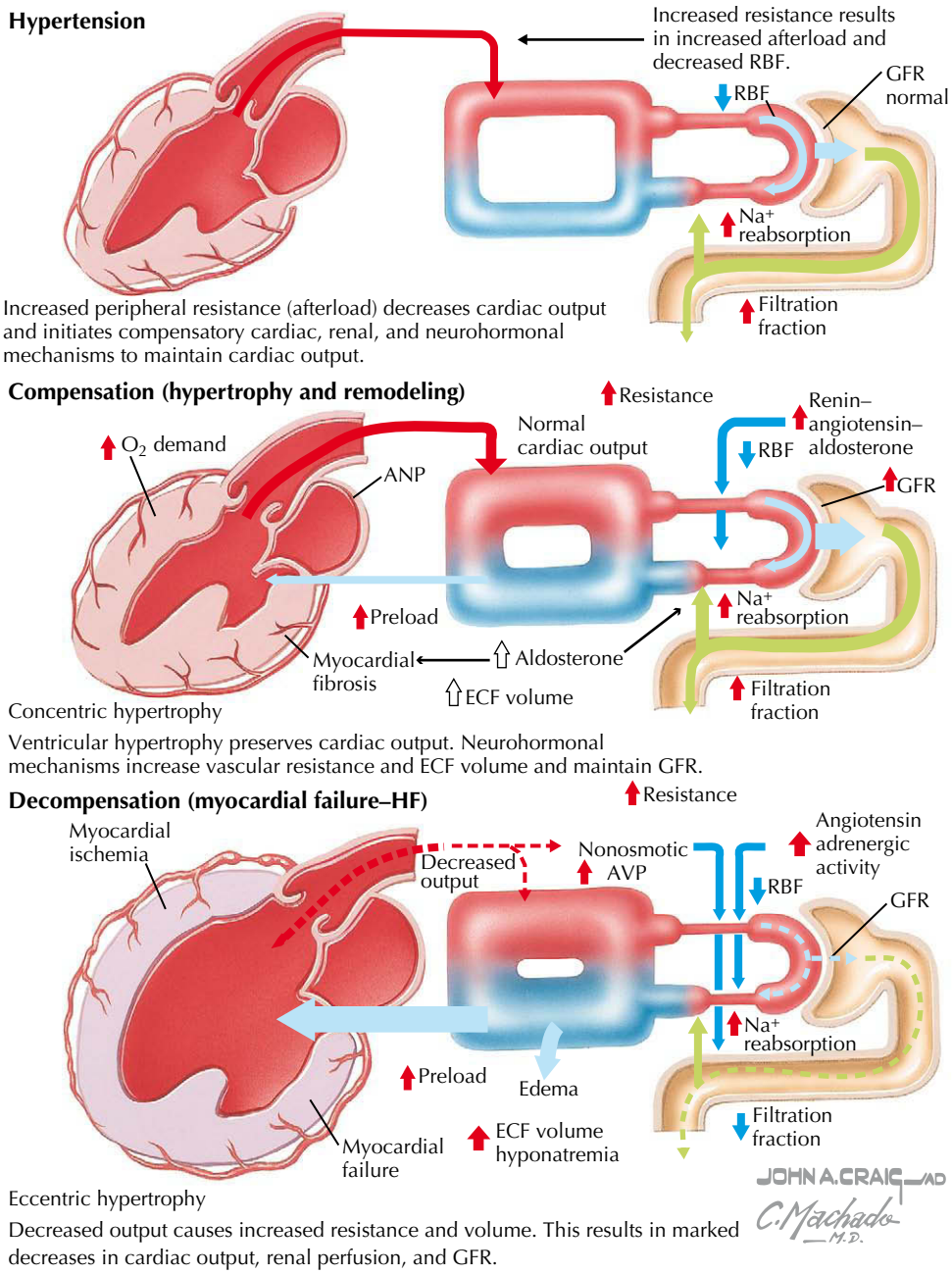


Figure 46-3 *Hypertension and heart failure (HF).* ANP, atrial natriuretic peptide; AVP, arginine vasopressin; ECF, extracellular fluid; GFR, glomerular filtration rate; RBF, renal blood flow.

technique, as described in Box 46-5, are critical. In many patients, measurement of BP outside the clinic is helpful in establishing a diagnosis of hypertension and in assessing the response to therapy. The availability of reliable and relatively inexpensive oscillometric monitors has made it possible for patients to regularly check their BPs at home. Home readings acquired in a standardized fashion (Box 46-6) are more reproducible, correlate more closely with target organ damage, and are more predictive of cardiovascular events than office BP measurements. In selected patients, 24-hour ambulatory BP monitoring is useful, especially in those with large differences between office and home measurements, those with home BP measurements that are equivocal, and those with marked BP lability.

MANAGEMENT AND THERAPY

Optimum Treatment

The principal goal of hypertension treatment is to reduce the risk of cardiovascular morbidity and death. The treatment approach is determined by the absolute risk of a cardiovascular event based on the presence of major cardiovascular risk

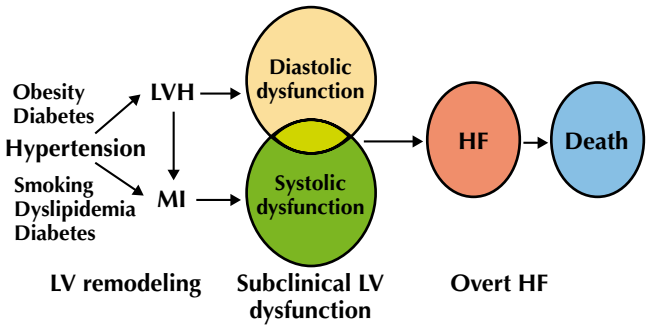


Figure 46-4 *The development of heart failure (HF) in patients with hypertension.* LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction. Adapted from Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. *Arch Intern Med,* 1996:156:1789–1796.

factors, clinical cardiovascular disease, and target organ damage. In patients at highest risk—especially those with diabetes or chronic kidney disease—pharmacologic therapy should be considered when BP is mildly elevated or in the upper prehypertension range, with a goal value of less than 130/80 mm Hg. Lower-risk patients may benefit from a period of observation and lifestyle modification, using medical therapy if the average systolic BP (SBP) exceeds 140 mm Hg or if the diastolic BP (DBP) exceeds 90 mm Hg over months of monitoring.

Lifestyle modifications are an important component of therapy for high BP. All patients with hypertension, high-normal BP, or a strong family history of hypertension should be encouraged to adopt the measures outlined in Box 46-7. These lifestyle changes are proven to lower BP and may reduce the need for drug therapy, enhance the effectiveness of antihypertensive drugs, and favorably influence other cardiovascular risk factors. Other measures, including smoking cessation and reduced intake of saturated fats, may further reduce cardiovascular risk.

Pharmacologic treatment of hypertension reduces the incidence of heart failure, stroke, and MI and decreases mortality rate from cardiovascular causes in middle-aged and older adults. Drug therapy is indicated if lifestyle modifications do not bring BP into the desired range within a reasonable period of time. Thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and calcium antagonists are appropriate first-line agents. β-adrenergic receptor blockers are less effective in preventing strokes and more likely to exacerbate the tendency of an individual to develop new-onset diabetes than alternative agents; they are no longer preferred for initial therapy of uncomplicated hypertension in the elderly. In many patients, the choice of a drug is influenced by comorbid conditions. Table 46-2 lists agents that are preferred or relatively contraindicated in specific circumstances.

Many patients with hypertension have established cardiovascular disease, and their treatment regimen should include medications that control symptoms, retard disease progression, and prevent cardiovascular events. Treatment strategies for patients with ischemic heart disease or heart failure are addressed in Chapters 12 and 23. In brief, β-blockers and ACE inhibitors mitigate symptoms and prolong survival in patients with CHD or LV dysfunction. ARBs are an effective alternative in patients with heart failure who cannot tolerate ACE inhibitors. Aldosterone antagonists are beneficial in patients with LV systolic dysfunction or a history of MI. Calcium antagonists are useful adjuncts in patients with angina or hypertension that cannot be controlled by β-blockers and ACE inhibitors. The optimal therapy for patients with heart failure but a normal ejection fraction is not well established and is under investigation; agents that treat LV systolic dysfunction seem to be useful. Lowering BP with any of the first-line therapy drugs leads to LVH regression.

Box 46-4 Appropriate History, Physical Examination, and Laboratory Tests

Comprehensive History

- Assessment of the duration and severity of elevated BP and the results of prior medication trials
- Evaluation for the presence of diabetes, hypercholesterolemia, tobacco use, and other cardiovascular risk factors
- Identification of a history or symptoms of target organ disease, including CHD and heart failure, cerebrovascular disease, peripheral vascular disease, and renal disease
- Assessment of symptoms indicating identifiable causes of hypertension
- Identification of the use of drugs or substances that may raise BP
- Evaluation of lifestyle factors (such as diet, leisure-time physical activity, and weight gain) that may influence BP control
- Assessment of psychosocial and environmental factors, such as family support, income, and educational level, that influence the efficacy of antihypertensive therapy
- Identification of family history of hypertension or CVD

Physical Examination

- Careful measurement of BP
- Measurement of height and weight
- Funduscopic examination for hypertensive retinopathy
- Examination of the neck for carotid bruits, elevated jugular venous pressure, and thyromegaly
- Examination of the heart for abnormalities of the apical impulse or the presence of extra heart sounds or murmurs
- Examination of the abdomen for bruits, enlarged kidneys, and other masses
- Examination of the extremities for diminished arterial pulsations or peripheral edema

Laboratory Studies

- Complete blood count
- Serum concentrations of potassium, calcium, creatinine, thyroid-stimulating hormone, fasting glucose, triglycerides, total cholesterol, HDL-C, and total LDL-C
- Urinalysis for blood, protein, glucose, and microscopic examination
- Electrocardiography

BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Aliskiren, the first representative of a new class of drugs, the direct renin inhibitors, was recently approved for clinical use. This agent is well tolerated and effective in lowering BP. Whether it offers unique benefits in target organ protection will be evaluated in future clinical trials.

The optimal target BP in patients with isolated systolic hypertension and chronic ischemic heart disease is controversial. In general, lower values of systolic BP are associated with better outcomes. Myocardial perfusion occurs almost exclusively in diastole, however, and excessive lowering of diastolic BP in patients with obstructive coronary disease could theoretically result in ischemia and increase the risk of coronary events. Several studies have suggested a J-shaped relationship between DBP and coronary risk, with an increase in events as DBP is lowered below 80 mm Hg. These observations have led some experts to caution against aggressive BP lowering in patients with isolated systolic hypertension and ischemic heart disease.

In general, therapy should be initiated at low doses to minimize side effects. Based on patient response, the dose of the initial agent can be slowly titrated upward, or a small dose of a second agent can be added. Most patients with hypertension require multiple drugs for optimal BP control. Effective drug combinations use medications from different classes and result in additive BP-lowering effects, while minimizing dose-dependent adverse effects. Thiazide diuretics potentiate the effect of β-blockers, ACE inhibitors, and ARBs. Other useful combinations include dihydropyridine calcium antagonists and β-blockers, and calcium antagonists and ACE inhibitors. Long-acting formulations with 24-hour efficacy are preferred over shorter-acting agents because of greater patient adherence to once-daily dosing regimens and more consistent BP control throughout the day.

Prevention of cardiovascular morbidity and death is usually achieved with slow, gradual reduction of BP, maintained over many years. Urgent reduction of BP with intravenous medications, however, is necessary in patients with malignant hypertension (Table 46-3).

Box 46-5 Measurement of Blood Pressure in the Clinic

- Measurements should be made by a trained provider with a mercury sphygmomanometer, a calibrated aneroid sphygmomanometer, or a validated oscillometric device with an appropriately sized cuff.
- The patient should be seated for 5 minutes with the feet on the floor and the arm at heart level.
- Caffeine, exercise, and smoking should be avoided for at least 30 minutes.
- The cuff should be inflated to 20 to 30 mm Hg above SBP and deflated at a rate of approximately 2 mm Hg per second.
- The onset of phase 1 and phase 5 Korotkoff sounds should be used to define SBP and DBP.
- At least two measurements should be made and the results averaged.
- Standing BP should be measured in older patients and in patients with postural symptoms.

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Box 46-6 Home Blood Pressure Monitoring

- Validated oscillometric monitors that measure BP in the upper arm with a cuff of the appropriate size should be used for home monitoring.
- Two to three readings should be taken after resting in the seated position for longer than 5 minutes, both in the morning and in the evening, over the course of a week.
- At least 12 readings should be acquired for making clinical decisions; average systolic and diastolic BPs should be calculated.
- The target average home BP is <135/85 mm Hg in uncomplicated hypertension and <130/80 mm Hg in high-risk patients.
- Ambulatory BP monitoring may be helpful if there are large differences between office and home measurements, if home BP measurements are equivocal, or if BP is markedly labile.

BP, blood pressure.

Lowering blood pressure is but one mechanism by which cardiovascular risk can be reduced in hypertensive patients. Irrespective of baseline cholesterol levels, statin therapy is effective in reducing the incidence of MI and stroke. Low-dose aspirin also reduces the risk of cardiovascular events.

Avoiding Treatment Errors

- Institute lifestyle modifications as the first step for the treatment of hypertension, and continue these measures if drug therapy is ultimately required.
- Include a thiazide diuretic in the medication regimens of patients requiring a combination of antihypertensive drugs.
- Monitor for the metabolic effects of antihypertensive medications.
- Look for an orthostatic fall in BP in older patients and in those suspected of having autonomic dysfunction, such as subjects with long-standing diabetes mellitus; titrate antihypertensive medication to avoid an excessive fall in BP in the standing position.

Box 46-7 Lifestyle Modifications for Prevention and Treatment of Hypertension

- Weight loss if overweight. All overweight hypertensive patients should be enrolled in a monitored weight reduction program.
- Moderation of alcohol intake. Patients with high blood pressure who drink alcohol should be counseled to limit their daily intake to 1 oz alcohol for men and 0.5 oz for women.
- Regular aerobic physical activity. Sedentary individuals should be encouraged to engage in regular aerobic exercise.
- Dietary restrictions. Adequate intake of potassium (>90 mmol/day) from fruits and vegetables and of calcium from low-fat dairy products and moderate reduction in sodium intake (<100 mmol [2.5 g]/day) are recommended.

Table 46-2 Choice of Antihypertensive Agent Based on Coexistent Illness

	Specific Drugs
Indications	
Diabetes mellitus	ACE-I or ARB
Heart failure	ACE-I or ARB, β-blocker, diuretic, aldosterone antagonist
Myocardial infarction	ACE-I or ARB, β-blocker, aldosterone antagonist
Chronic coronary heart disease	ACE-I or ARB, β-blocker
Chronic kidney disease	ACE-I or ARB
Contraindications	
Pregnancy	ACE-I, ARB, direct renin inhibitor
Chronic kidney disease*	Potassium-sparing agent
Peripheral vascular disease*	β-blocker
Gout*	Thiazide diuretic
Depression*	β-blocker, central α–agonist
Reactive airway disease*	β-blocker
Second- or third-degree heart block	β-blocker, non-dihydropyridine calcium antagonist
Hepatic insufficiency	Labetalol, methyldopa

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.
*Relative contraindication.

- Avoid sudden withdrawal of certain antihypertensive medications such as β-blockers and clonidine to prevent acute coronary syndromes or rebound hypertension.
- Avoid ACE inhibitors, ARBs, and renin inhibitors in pregnant women.

Table 46-3 Agents Used for Intravenous Drug Therapy of Hypertensive Emergencies

Agent	Use
Nitroprusside	Preferred agent in most instances except acute coronary syndromes or pregnancy. Should be combined with a β-blocker in some instances, such as acute aortic dissection.
Nitroglycerin	Use in combination with a β-blocker for acute coronary syndromes.
Labetalol	Use as adjunctive therapy with nitroprusside or nitroglycerin. Use alone in less intensely monitored situation or treatment of postoperative hypertension.
Enalaprilat	Use for sclerodermal crisis or as adjunctive therapy in some high-renin states.
Hydralazine	May use for treatment of preeclampsia and eclampsia
Fenoldopam	Same indication as for nitroprusside. Useful in postoperative or postprocedure hypertension in closely monitored situations.
Esmolol	Use in case of need for immediate, very short-acting β-blocker effect. Use for supraventricular tachycardia.

- Avoid overtreatment of subjects with the "white coat" effect and undertreatment of patients with "masked hypertension" by utilizing home BP monitoring to assess the adequacy of therapy.

FUTURE DIRECTIONS

Future research and public health initiatives should more accurately define treatment thresholds and optimal target BP in patients at high risk of cardiovascular events, including elderly individuals, patients with diabetes mellitus, and patients with ischemic heart disease; determine the agents most useful in alleviating symptoms and improving longevity in patients with hypertension and heart failure with preserved LV systolic function; develop more effective drugs for treating elderly individuals with isolated systolic hypertension; and provide better strategies to improve patient awareness and compliance with lifestyle modifications and medication regimens.

ADDITIONAL RESOURCES

British Hypertension Society [home page on the Internet]. Available at: <http://www.bhsoc.org>; Accessed 05.03.10.

Through this website the British Hypertension Society provides a medical and scientific research forum to permit sharing of clinical information on hypertension management. Included is information regarding cutting-edge research in the field, ongoing clinical trials, and important recent publications. Also reviews recent guidelines, such as the partial update of the U.K. National Institute of Clinical Excellence and British Hypertension Society's Guidelines for Management of Hypertension in Adults published in June 2006. Reviews the most recent clinical trials of hypertension treatment in a brief but comprehensive manner.

Kaplan NM. *Kaplan's Clinical Hypertension.* 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.

This thorough, detailed, yet succinct, eminently readable textbook on clinical hypertension reflects the vast clinical experience and wisdom of the author and offers current references on all topics.

U.S. Department of Health and Human Services, National Heart, Lung and Blood Institute. National High Blood Pressure Education Program. Available at: <http://www.nhlbi.nih.gov./about/nhbpep/index.htm>; Accessed 05.03.10.

The National High Blood Pressure Education Program provides valuable educational information on hypertension for health care providers and the public. All of the reports, guidelines, and publications sponsored by the program are available. Educational materials such as slides, tables, and graphs can be downloaded. Some materials are available in Spanish.

EVIDENCE

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA.* 2002; 288:2981–2997.

This is the largest double-blind trial undertaken in hypertensive patients and strongly influenced the recommendations of JNC 7. The trial compared treatment with amlodipine or lisinopril with a reference drug chlorthalidone and found no advantage of newer drugs over a thiazide-type diuretic in preventing fatal CHD or nonfatal MI.

Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular

events: results of prospectively-designed overviews of randomized trials. *Lancet.* 2003;362:1527–1535.

This set of prospectively designed overviews with data from 29 randomized trials examines the comparative effects of different BP-lowering regimens and the benefits of targeting lower BP goals on the risk of major cardiovascular events and death. The overall conclusion is that treatment with any commonly used regimen reduces the risk of major cardiovascular events, and that larger reductions in BP produce larger reductions in risk.

Chobanian AV, Bakris GL, Black HR, et al, and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: JNC 7—Complete Version. *Hypertension.* 2003;42:1206–1252.

Provides a comprehensive guideline for hypertension prevention and management and is a "must read" for all physicians who treat patients with high BP. Differences from previous reports include an emphasis on SBP as a cardiovascular disease risk factor and introduction of the classification "pre-hypertension." Thiazide-type diuretics are recommended for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes.

Dahlof B, Sever PS, Poulter NR, et al, for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* 2005;366:895–906.

This large European study found an advantage of newer drugs (amlodipine ± perindopril, as required) over conventional BP-lowering therapy (atenolol ± bendroflumethiazide, as required) in reducing cardiovascular mortality. These results reinforced data from previous studies suggesting that β-blocker–based therapy is less effective than other first-line drugs in reducing cardiovascular events in older patients.

Pickering TG, Miller NH, Ogedegbe G, et al. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension.* 2008;52:10–29.

Position paper strongly advocating the use of home BP monitoring in the majority of patients with known or suspected hypertension. Provides useful advice on how to acquire and interpret home BP data.

Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation.* 2007;115:2761–2788.

Provides a comprehensive review of the epidemiology of hypertension and coronary artery disease and of the mechanisms by which hypertension contributes to the development of atherosclerosis. Includes recommendations for primary prevention of coronary disease in patients with hypertension and for management of hypertension in patients with chronic ischemic heart disease, acute coronary syndromes, and heart failure.

Sever PS, Dahlöf B, Poulter NR, et al, for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;361:1149–1158.

Demonstrates the value of a statin in reducing the risk of CHD and stroke in patients with hypertension.

Williams B, Poulter NR, Brown MJ, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV: British Hypertension Society Guidelines. *J Hum Hypertens.* 2004;18:139–185.

This comprehensive guideline differs from the JNC 7 report in several important respects. It recommends a more individualized threshold BP for treatment with medications, based on the presence of target organ damage, cardiovascular complications, diabetes, and estimated 10-year risk of cardiovascular disease. It recommends basing the choice of an initial BP-lowering drug on the age and ethnicity of the patient. ACE inhibitors, angiotensin receptor blockers, or perhaps β-blockers are recommended for young, non-black patients without compelling indications, while calcium antagonists or thiazide-like diuretics are recommended as first-line therapy for older or black patients.

Renal Artery Stenosis

George A. Stouffer and Walter A. Tan

47

Obstructive disease in the renal arteries can decrease blood flow to the kidneys, which can result in activation of the renin-angiotensin system, hypertension, ischemic nephropathy, and other pathologic changes. Technologic advances, including intra-arterial stenting, have generated enthusiasm for revascularization as a treatment for hypertension and progressive renal dysfunction caused by renal artery stenosis (RAS). However, measurable beneficial outcomes (e.g., blood pressure improvement or stabilization of renal function) occur in only approximately 50% to 70% of patients who undergo successful revascularization, underlining the limited understanding of this disease and the importance of careful patient selection.

ETIOLOGY AND PATHOGENESIS

The predominant cause of obstructive RAS is atherosclerosis (Fig. 47-1). The atherosclerotic process can involve the renal artery or the aorta, with disease of the latter affecting the ostium of the renal artery. Rarely, obstructive RAS is caused by fibromuscular dysplasia (FMD; <10% of cases of RAS).

FMD is a collection of vascular diseases characterized by intimal or medial hyperplasia. It is commonly bilateral and affects women more often than men. The middle and distal portions of the vessel are the most commonly involved sites, with a typical angiographic appearance of "beads on a string" (see Fig. 47-1). FMD can cause hypertension but rarely leads to major loss of renal function, although progressive renal impairment has been described in smokers with FMD.

Regardless of its underlying pathologic cause, decreased renal perfusion results in compensatory activation of the renin-angiotensin system (Fig. 47-2), which can cause systemic hypertension, salt retention, and activation of the neurohormonal system. RAS also causes ischemic changes within the kidney (ischemic nephropathy) and increased systemic markers of oxidative stress. Other pathologic effects have been postulated but not proven to result from RAS.

Natural History

Hemodynamically significant RAS is associated with an increased incidence of major adverse cardiovascular events including cardiac death, myocardial infarction, and stroke. In the Cardiovascular Health Study, a prospective, multicenter cohort study of Americans older than 65 years, the presence of renovascular disease as determined by duplex ultrasonography increased the risk of short-term adverse cardiovascular outcomes by approximately twofold. This risk persisted after controlling for coronary artery disease risk factors and existing cardiovascular disease and was not dependent on the effects of increased blood pressure (BP). In other studies, 4-year survival was 57% in patients with severe RAS discovered incidentally at the time of cardiac catheterization and 74% in a multicenter study of patients undergoing percutaneous renal revascularization. In a single-center study of 748 patients with severe renal artery disease requiring percutaneous revascularization, 10-year survival was only 41%.

RAS is a progressive disease in which the rate of progression is a function of the disease severity and BP. Studies of patients with documented RAS have shown that progression of atherosclerotic disease in renal arteries occurs in approximately 25% of patients at 1 year, 35% at 3 years, and 50% at 5 years. The rate of progression to total occlusion at 5 years has been reported to be approximately 10% in arteries with lesions less than 60% occlusion. In another study, in which the average stenosis at the time of enrollment was 72%, 16% of the patients randomly assigned to receive medical treatment had total occlusion at 1 year.

CLINICAL PRESENTATION

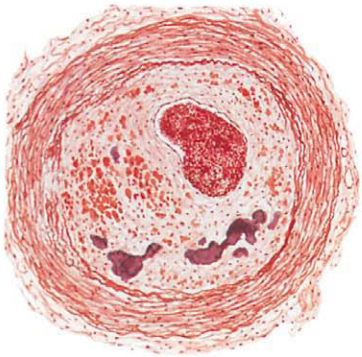
The vast majority of patients with hypertension have essential hypertension. Overall, renovascular disease is the etiology in 0.5% to 2% of patients with hypertension (Fig. 47-3), but it is more common in patients who present with new-onset, severe hypertension. RAS is more common in white than in black individuals, and the prevalence increases with age. Clinical factors that increase the likelihood of RAS include age, recent onset or sudden worsening of hypertension, and the presence of an abdominal bruit. The prevalence of RAS is also higher in patients with atherosclerosis in other vascular beds. Hemodynamically significant RAS is found in 6% to 23% of patients with hypertension who are undergoing cardiac catheterization. Significant RAS has been found in 10.4% of patients at autopsy after a cerebrovascular accident.

Atherosclerotic renovascular disease has been estimated to cause renal failure in 5% to 10% of Medicare patients starting dialysis for end-stage renal disease. The mortality in individuals with RAS and end-stage renal disease is staggering; survival rates reported at 2, 5, and 10 years are 56%, 18%, and 5%, respectively.

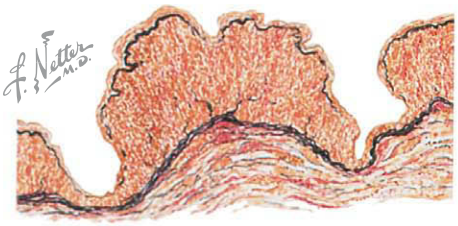
The American Heart Association Working Group for RAS has proposed that a grading classification for patients with RAS be used to facilitate trial design and reporting. Grade 1 is RAS plus no clinical manifestations (normal BP and renal function). Grade II is RAS plus medically controlled hypertension and normal renal function. Grade III is RAS plus uncontrolled BP, abnormal renal function, and/or evidence of volume overload.

DIFFERENTIAL DIAGNOSIS

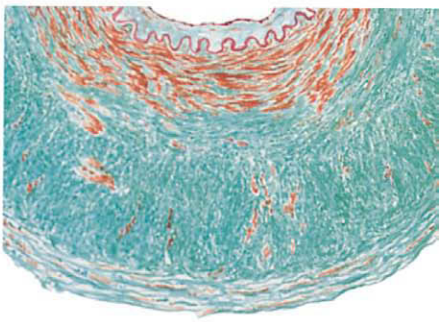
The primary entity in the differential diagnosis is essential hypertension (Chapter 46), although several other less common causes of hypertension must also be considered (see Fig. 47-3). The point at which renal artery atherosclerosis becomes



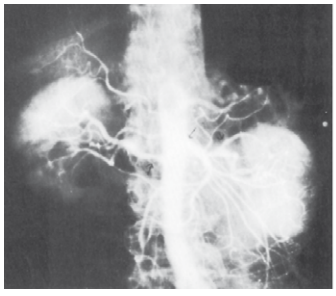
Severe concentric atherosclerosis with lipid deposition and calcification complicated by thrombosis (composite, ×12)



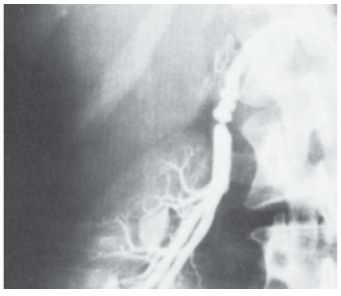
Medial fibroplasia (longitudinal section) with variation in mural thickness, chiefly of media, and aneurysmal evaginations (Verhoeff-Van Gieson stain, ×20)



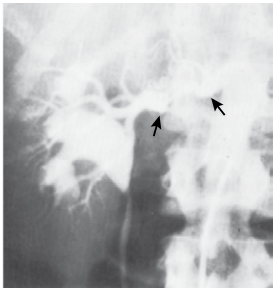
Subadventitial fibroplasia with concentric ring of dense collagen between media and adventitia (Masson's trichrome stain, ×80)



Aortorenogram showing atherosclerotic narrowing and poststenotic dilatation of both renal arteries



Renal arteriogram showing characteristic beaded appearance caused by alternate stenoses and aneurysmal dilatations



Arteriogram showing extensive, varied stenosis of right renal artery

Figure 47-1 *Etiologies of renal artery disease likely to cause hypertension.*

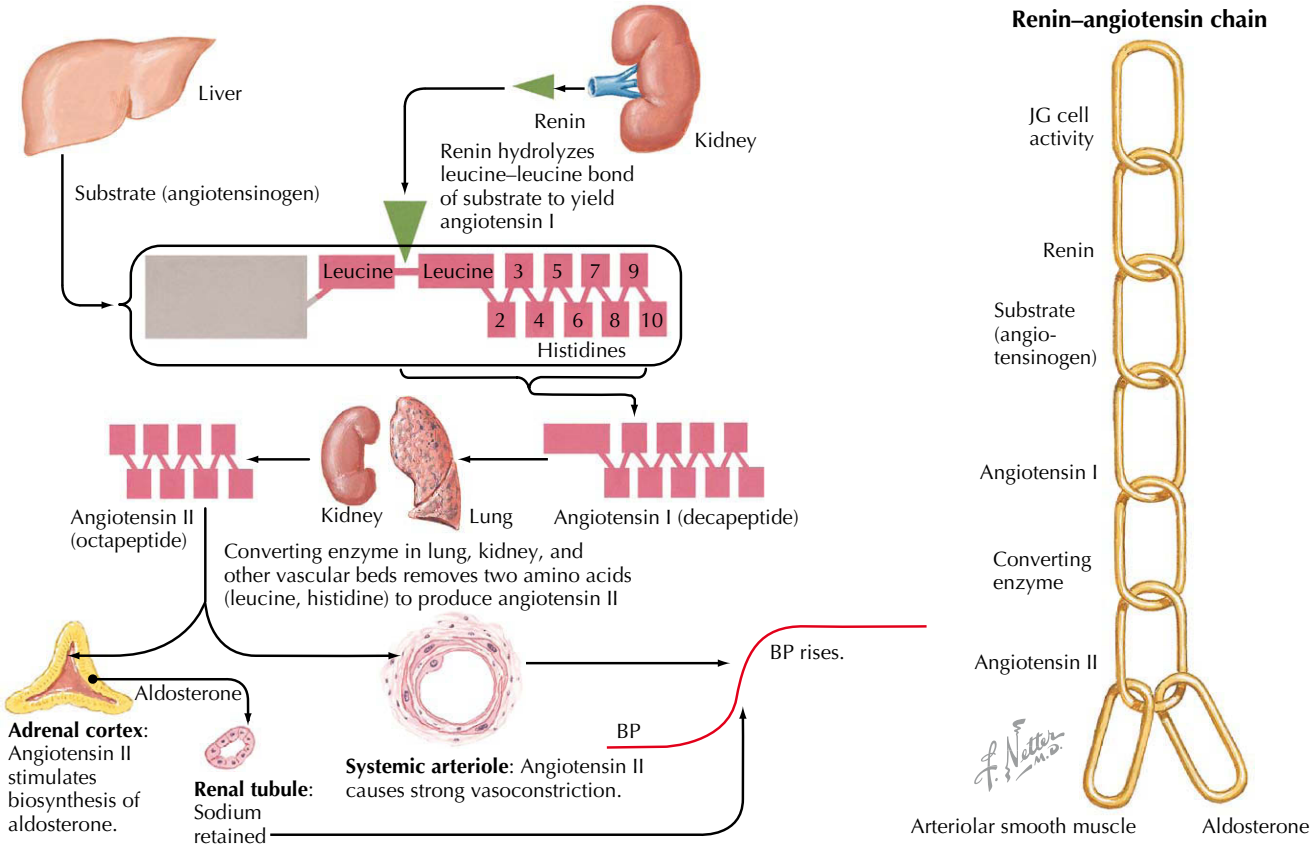


Figure 47-2 *Renin-angiotensin system.* BP, blood pressure. JG, juxtaglomerular.

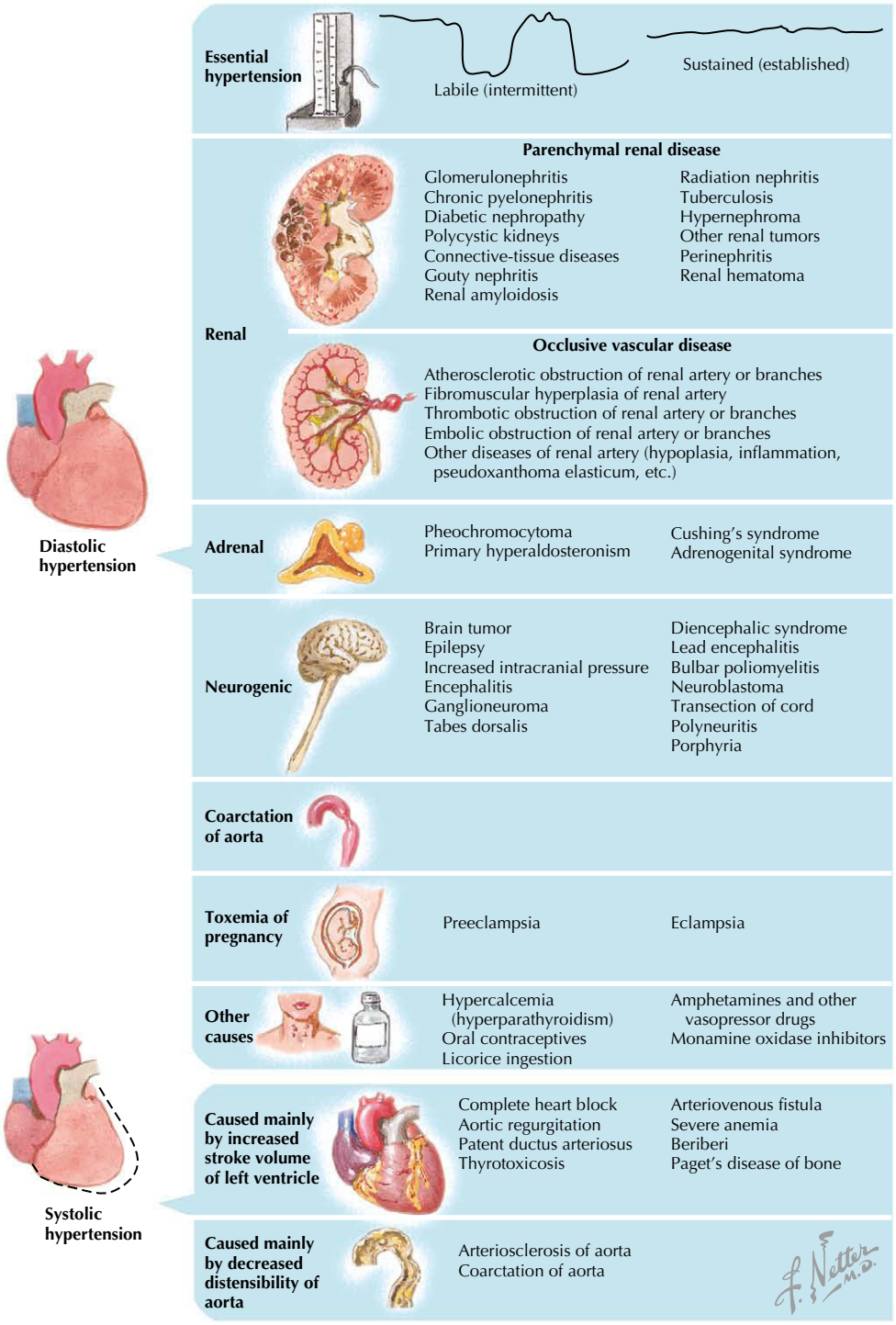


Figure 47-3 *Etiology of hypertension.*

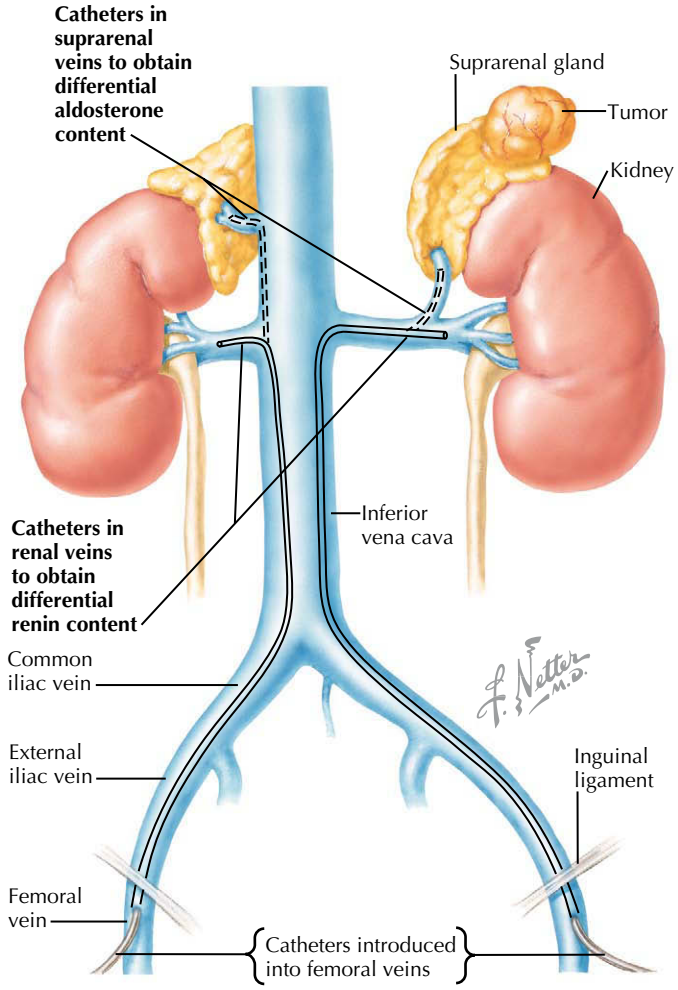


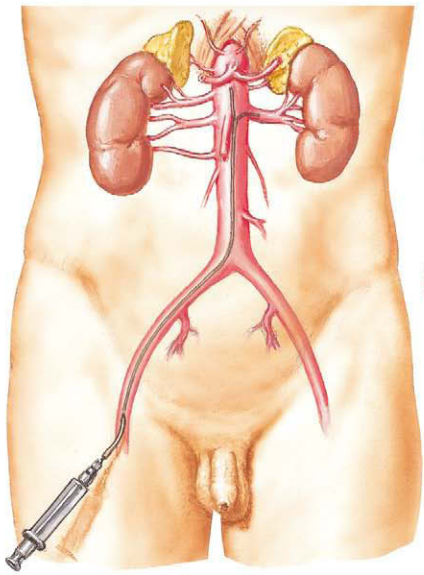
Figure 47-4 *Differential renin/aldosterone concentrations.*

physiologically significant and leads to increased BP and ischemic nephropathy is incompletely understood. Recognition of lesions that compromise blood flow to the kidney is essential to identify patients whose conditions will improve with renal revascularization. This is especially important, because there is also a high rate of essential hypertension in patients with RAS.

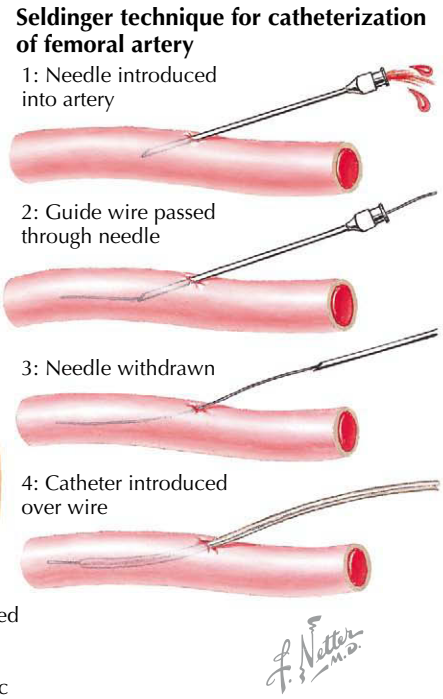
There is as yet no consensus on how to identify significant RAS. In part this reflects that there is not a one-to-one correlation with stenosis severity and favorable outcomes after the stenosis has been reduced by percutaneous interventions. Although many surrogates have been proposed, one well-controlled study found that the only clinical factors that predicted a beneficial BP response to renal artery revascularization were a preprocedure mean arterial pressure greater than 110 mm Hg and bilateral RAS. Other studies have indicated that measurement of split-vein renin levels may be a means to determine who will benefit from renal artery revascularization (Fig. 47-4). A renal vein renin ratio of 1.5:1 correlates with BP improvement in some studies. Likewise, using captopril as a provocative agent coupled with nuclear imaging (scintigraphy) may be of value in identifying patients who will benefit from renal artery revascularization, with a sensitivity of approximately 75% and a specificity of 90%.

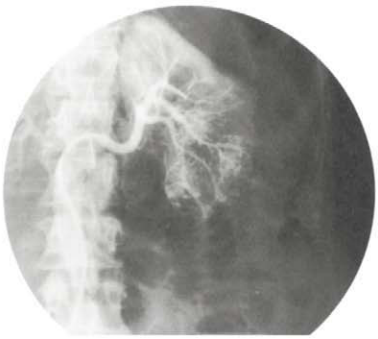
Doppler ultrasonography, although technologically demanding, is a promising technique. The measurement of a resistance index by Doppler can be used as a predictive tool. Patients with resistance index values greater than 80 show much poorer results (no improvement in BP, worsening renal function) after revascularization than do patients whose values are less than 80. Recently, brain natriuretic peptide (BNP) has been investigated as a marker for predicting outcomes as well. In a study of 27 patients undergoing renal artery intervention, there was a correlation between baseline BNP levels and BP response to renal intervention. Initial BNP concentrations of less than 80 pg/mL predicted nonresponders (response defined as BP improvement to <140/90 mm Hg on same or less medications), with a negative predictive value of 100%.

There is general agreement that lesions ≥70% by angiography are hemodynamically significant, whereas lesions ≤50% have no hemodynamic effect. The significance of lesions between 50% and 70% varies, leading some experts to advocate a measurement of translesional pressure gradients in these

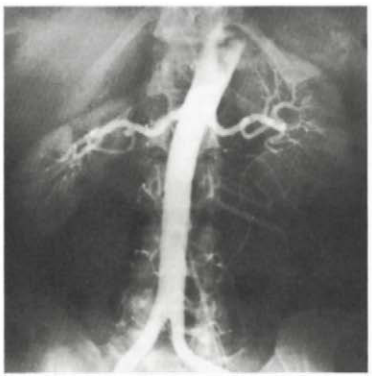


Catheter introduced via femoral artery to desired level of aorta and contrast medium injected, which then flows into normal and accessory renal arteries and possibly also into other aortic branches (aortorenal angiography), or catheter may be made to enter renal arteries for direct injection (selective renal angiography)





Selective left renal arteriogram. Multiple tumor vessels in lower pole of left kidney suggestive of highly vascular tumor (hypernephroma)



Aortorenal angiogram. Beaded appearance of left renal artery is evidence of fibromuscular hyperplasia; aneurysm at bifurcation of right renal artery

Figure 47-5 *Aortorenal and selective renal angiography (transfemoral approach).*

patients to determine hemodynamic significance. There are limited data correlating translesional gradients to clinical outcomes, and there is no consensus on whether absolute systolic, peak systolic, or mean pressure should be used; whether the pressure should be measured during a resting or hyperemic state; and what level constitutes a lesion that would benefit from revascularization. Although not validated in large clinical studies or included in current guidelines, early work on renal fractional flow reserve (rFFR) has been promising in that it appears to have good predictive value relative to patient outcomes. rFFR is a proportional determinant of the severity of a stenosis by comparing the pressure distal to a stenosis with aortic pressure during hyperemia.

DIAGNOSTIC APPROACH

The renal arteries can be visualized with arteriography, magnetic resonance angiography (MRA), and spiral CT. Arteriography, the direct injection of contrast dye into the renal artery, remains the gold standard for identifying and quantifying obstructive lesions (Fig. 47-5). MRA and spiral CT are noninvasive methods with excellent sensitivity and good, but not optimal, specificity for identifying RAS.

MANAGEMENT AND THERAPY

Optimum Treatment

RENAL ARTERY REVASCULARIZATION

Renal artery obstructive disease can be treated by either surgical or percutaneous approaches. Surgical renal artery revascularization generally involves aortorenal bypass (with use of a hypogastric artery, a saphenous vein, or polytetrafluoroethylene grafts), ileorenal, splenorenal (for left RAS), or hepatorenal (for right RAS) approaches (Fig. 47-6). Results of surgical renal artery revascularization show operative mortality rates of 2% to 6%, with improvement of hypertension observed in 79% to 95% of patients. With advances in percutaneous revascularization, surgical renal artery revascularization is rarely used and mainly reserved for patients with severe aortic disease that requires treatment.

Percutaneous balloon angioplasty for RAS, first reported by Gruentzig and colleagues in 1978, has resulted in varying rates of improvement in hypertension (36% to 100% of patients in uncontrolled studies) (Fig. 47-7). Success rates with balloon angioplasty are better for nonostial as opposed to ostial stenoses. Restenosis has been reported in 10% to 47% of cases.

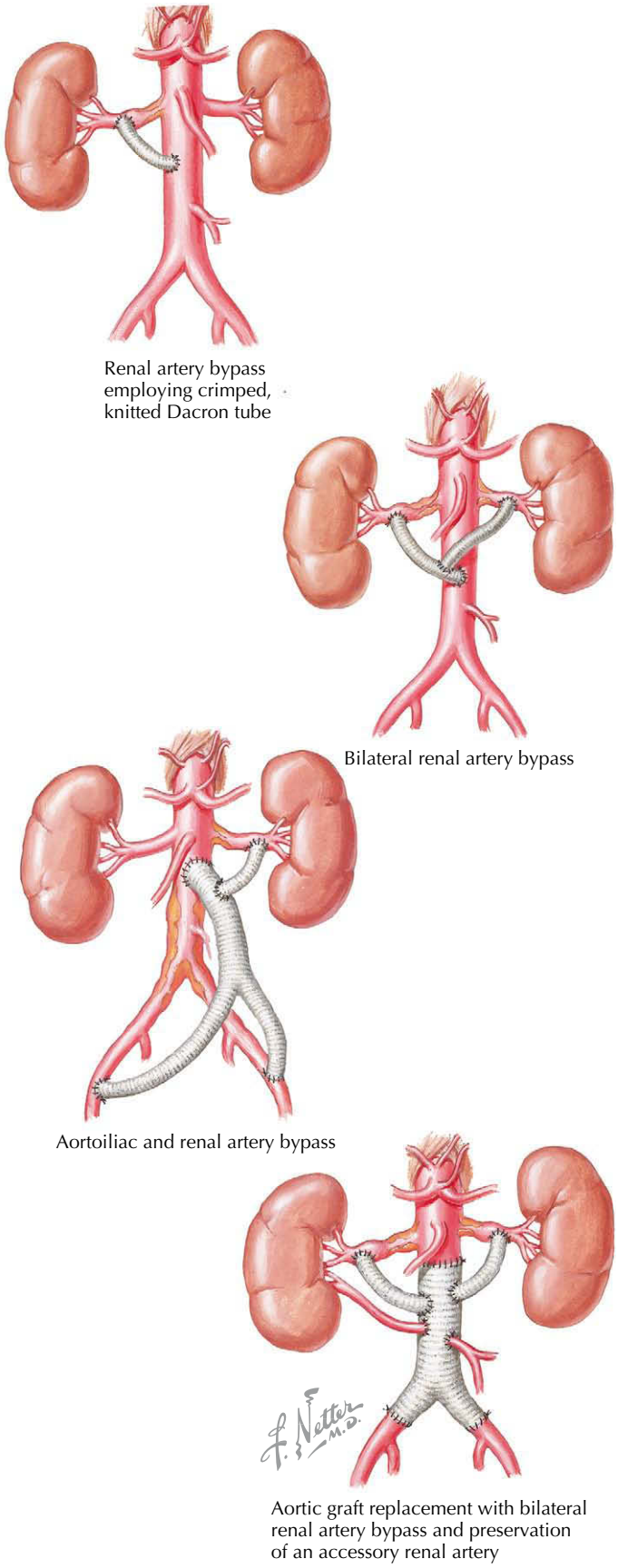


Figure 47-6 *Renal revascularization.*

Careful assessment of the significance of a renal artery lesion is key to obtaining reductions in BP. One study often cited in this regard randomized 106 patients with hypertension and a renal artery lesion of 50% stenosis or greater; there were no significant differences in average BP between patients treated with medical therapy and patients treated with balloon angioplasty at 1 year in an intention-to-treat analysis. Criticism of this study included the lack of physiologic evaluation of the significance of the RAS, the high crossover rate from the medical group to the balloon angioplasty group (>40%), and the conclusion that the treatments had equal efficacy, even though 68% of the angioplasty group had reduced BP as opposed to 38% of the medical therapy group.

Percutaneous intervention is generally preferred over medical management in patients with FMD, because it reduces hypertension in approximately 75% of patients. Balloon angioplasty is successful in 82% to 100% of patients, with restenosis in 10% to 11%.

Stenting has been advocated as the preferred percutaneous treatment for RAS, especially when the lesion is ostial (Fig. 47-8). The use of stenting, as opposed to balloon angioplasty, is associated with higher rates of technical success and lower rates of restenosis. Procedural success rates are generally greater than 95%, with long-term angiographic patency rates of 86% to 92%. Major complications occur in approximately 2% of patients and include parenchymal perforation, cholesterol emboli, embolized stents, and aortic dissection.

INDICATIONS FOR REVASCULARIZATION IN ATHEROSCLEROTIC RAS

Hypertension

The most common indication for renal artery revascularization is to improve BP control. Improvement occurs in the majority of patients, but complete resolution of hypertension is uncommon. Factors that predict improvement include pretreatment BP (mean arterial pressure >110 mm Hg) and the presence of bilateral RAS. Because renovascular and nonrenovascular hypertension often coexist in an elderly population with atherosclerotic disease, patient selection is critical in deciding whether to undertake renal artery revascularization.

Several randomized prospective clinical trials have compared angioplasty with or without stenting to medical therapy. None of these studies have shown a consistent benefit to revascularization; however, these studies all contain serious flaws. Among the factors that limit interpretation of the data are enrollment of patients with hemodynamically insignificant RAS (patients with mild stenoses in the 50% to 70% range were included), the high crossover rate in the medically treated group (for example, in the Dutch RAS Intervention Cooperative [DRASTIC] Study, approximately 40% of subjects in the medically treated group underwent angioplasty within the first 3 months), and that the medical regimen of antihypertensives was not specified, which confounded the interpretation.

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) Trial examined whether revascularization together with medical therapy improved renal function and other

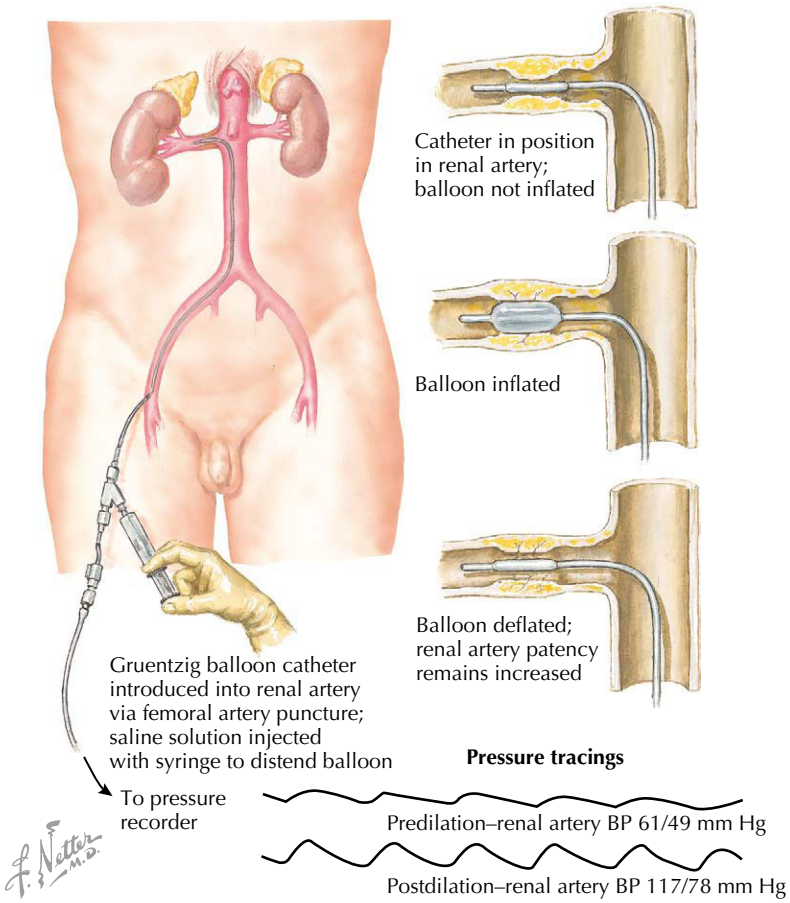


Figure 47-7 *Transluminal renal angioplasty, as pioneered by Gruentzig.* BP, blood pressure.

outcomes, as compared with medical therapy alone, in patients with atherosclerotic renal artery stenosis in cases where the patient's physician was uncertain that the patient would definitely have a worthwhile clinical benefit from revascularization. This randomized, unblinded trial included 806 patients with a median follow-up of 34 months. The two study groups had similar rates of renal events, major cardiovascular events, and death.

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) is an ongoing, National Institutes of Health–sponsored, large, multicenter, randomized, prospective trial that is enrolling all patients with RAS, a more inclusive population than addressed by the ASTRAL Trial. In this trial, all patients receive "optimal medical therapy" that includes treatment of hypertension to target levels (using angiotensin receptor blockers as first-line treatment), lipid management, treatment of diabetes, smoking cessation, and use of antiplatelet agents. By protocol, patients with more than 60% RAS are randomized to angioplasty with stenting (use of embolic protection is at the discretion of the operator) plus medical therapy or medical treatment alone. This trial is the largest and has the longest follow-up period of any trial of RAS. The primary end points are clinical outcomes. It is anticipated that the results of CORAL will have a major impact on choosing therapy for patients with RAS.

Renal Preservation

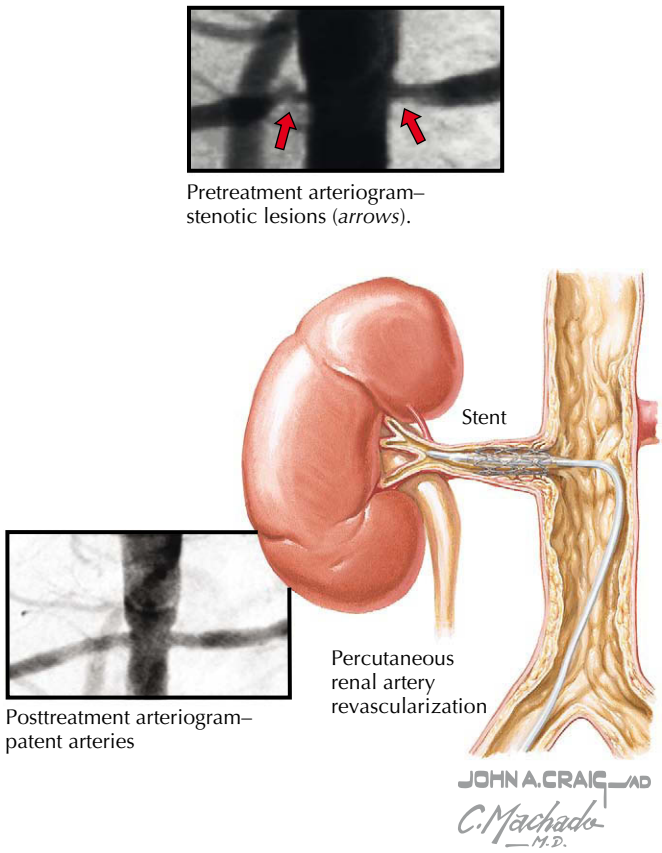
Renal artery revascularization can stabilize and even reverse progressive decreases in renal function in selected patients. In a meta-analysis of six studies, revascularization in patients with ischemic nephropathy resulted in an improvement in renal function in 46%, stabilization of renal function in 31%, and worsening of renal function in 22%. Unfortunately, there are still limited data regarding appropriate identification of patients with ischemic nephropathy who will improve with revascularization.

Pulmonary Edema

Acute pulmonary edema with respiratory failure and death can occur in patients with RAS, especially in patients with bilateral (but usually not unilateral) RAS. Successful revascularization can virtually eliminate recurrent episodes.

Avoiding Treatment Errors

One of the major difficulties in treating RAS is identifying patients who will benefit from revascularization. Clinical trials have found that measurable beneficial outcomes occur in only approximately 50% to 70% of patients who undergo successful



Patients with hypertension and atherosclerotic renal artery stenosis most likely to respond to balloon angioplasty percutaneous renal artery revascularization are those with onset of hypertension within the past 5 years, those without primary renal disease, and middle-aged men with atherosclerotic renal artery stenosis and malignant hypertension not caused by primary renal disease. A positive captopril renogram predicts cure or improvement of hypertension after revascularization.

Figure 47-8 *Percutaneous revascularization of stenotic renal arteries.*

renal artery revascularization. The possibility that clinical benefits independent of the traditional end points (primarily BP reduction and renal function preservation) occur with renal artery revascularization is being studied in the CORAL Trial. In addition, many techniques are being evaluated to assess the hemodynamic significance of renal artery lesions with the goal of better identifying patients who will improve following treatment of RAS.

FUTURE DIRECTIONS

Important areas of future study include identifying characteristics that predict which patients will benefit from renal artery intervention, determining whether RAS has deleterious effects independent of hypertension and ischemic nephropathy, and optimizing renal artery revascularization.

ADDITIONAL RESOURCES

The Agency for Healthcare Research and Quality (AHRQ) guidelines on renal artery stenosis. Available at: <http://www.guidelines.gov/summary/summary.aspx?ss=15&doc_id=11949&nbr=6133>; Accessed 01.03.10.

An evidence-based approach to treating patients with RAS.

CORAL [home page on the Internet]. Available at: <http://www.coralclinicaltrial.org/>; Accessed 01.03.10.

The website describing the Cardiovascular Outcomes in Renal Atherosclerotic Lesions Trial.

Hildreth CJ, Lynm C, Glass RM. JAMA patient page. Renal artery stenosis. *JAMA.* 2008;300:2084.

A description of RAS in language that a patient can understand.

Rocha-Singh KJ, Eisenhauer AC, Textor SC, Cooper CJ, et al. American Heart Association Writing Group 8. Atherosclerotic Peripheral Vascular Disease Symposium II: intervention for renal artery disease. *Circulation.* 2008;118:2873–2878.

A recent paper from a distinguished group of authors summarizing current data regarding RAS and benefits and risks of revascularization.

EVIDENCE

Cooper CJ, Murphy TP. Is renal artery stenting the correct treatment of renal artery stenosis? The case for renal artery stenting for treatment of renal artery stenosis. *Circulation.* 2007;115:263–269.

Part of a debate on the merits of renal artery revascularization.

Dworkin LD, Jamerson KA. Is renal artery stenting the correct treatment of renal artery stenosis? Case against angioplasty and stenting of atherosclerotic renal artery stenosis. *Circulation.* 2007;115:271–276.

Part of a debate on the merits of renal artery revascularization.

Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med.* 2001;344:431–442.

A good overview of RAS.

Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med.* 2004;350:1862–1871.

A good overview of FMD.

Todd J, Stouffer GA. Hemodynamics of renal artery stenosis. *Catheter Cardiovasc Interv.* 2008;72:121–124.

An overview of the hemodynamic changes in renal perfusion associated with RAS and the ways these changes are used in various diagnostic modalities to determine "hemodynamically significant" disease.

Interventional Approaches for Peripheral Arterial Disease

48

Robert Mendes and Matthew A. Mauro

Charles Dotter and Melvin Judkins first introduced catheter-based interventions in atherosclerotic disease in 1964. Major technological advances now make possible interventions for a vast array of conditions, benefiting millions of patients with coronary, cerebral, or peripheral arterial disease. Percutaneous interventions have greatly expanded therapeutic options, often complementing and occasionally replacing drugs or surgery. This chapter reviews the indications for endovascular therapy for relatively common extracardiac arterial diseases.

CEREBROVASCULAR AND CARDIOEMBOLIC DISEASE

Carotid Artery Stenosis

More than 600,000 strokes occur annually in the United States, and disability as a consequence of stroke is estimated to affect more than 1 million Americans. An important cause of preventable stroke is large-vessel or carotid atherosclerosis. The risks and therapies for carotid atherosclerosis have been examined in a number of clinical trials. The Asymptomatic Carotid Atherosclerosis Study reported a 5-year risk of stroke ipsilateral to an asymptomatic carotid artery stenosis (of 60% or greater) to be approximately 11%, despite aspirin therapy. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated a 2-year stroke risk of 26% in the presence of a previous transient ischemic attack (TIA) or stroke. Both trials reported significant reductions in stroke with carotid endarterectomy (CEA) (see Chapter 49). The perioperative death and stroke risks of CEA approximate 2% and 6% in asymptomatic and symptomatic carotid disease, respectively. However, the advancement of technology and the desire for developing a less morbid and minimally invasive approach to this disease have led to consideration of percutaneous approaches for the treatment of carotid artery stenosis.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first randomized trial to establish the general equivalency of endovascular therapy for carotid stenosis. The 3-year death and stroke rates in the predominantly balloon angioplasty group (only 24% received stents) were similar to those in the CEA group. The tradeoff was a higher rate of incidentally detected restenosis: 18% in the balloon angioplasty group compared with 5% for CEA. Since CAVATAS, improvements in the technology available for percutaneous carotid artery revascularization have reduced procedural risks and improved outcomes. In particular, the development and improvements in devices to protect against embolization represent an important step toward improving outcomes in carotid artery stenting (Fig. 48-1). The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Study demonstrated that carotid stenting in conjunction with cerebral emboli protection was comparable (using "noninferiority" as an end point) with CEA in high-risk patients. Indeed, at 30 days, the primary composite end point of death, stroke, or myocardial infarction was higher in the CEA group than in the stented group (12.6% vs. 5.8%, $P < 0.05$). The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), which has completed enrollment of 2500 patients, will be the largest randomized controlled study comparing stenting and CEA. The results of CREST will address a multitude of issues still being debated and, hopefully, will allow health care providers and patients to better inform their decisions on revascularization for carotid artery stenoses.

It is important to note that procedural experience is a critical determinant of outcome. Numerous studies have demonstrated that excessive complication rates occur with operators who have performed fewer than 10 carotid interventions. Although cerebral emboli protection devices generally increase the safety of catheter manipulations within the diseased aortic arch and brachiocephalic arteries, further study will be needed before broad application can be recommended.

At present, it is recommended that carotid artery stenting be considered for patients who would benefit from revascularization but are at increased risk of surgery because of medical comorbidities or unfavorable anatomic characteristics. These include symptomatic patients with more than 50% carotid stenosis and who have at least one high-risk feature: congestive heart failure, severe coronary artery disease, severe chronic obstructive pulmonary disease, previous CEA presenting with restenosis, previous radical neck surgery or radiation therapy, or a carotid lesion that is behind the jaw or within the thoracic cavity.

Cerebral Arterial Occlusive Disease

Although angioplasty and stenting of stenoses involving cerebral or vertebral arteries have been performed in patients who do not respond to standard therapy, few randomized data exist to aid in clinical decision making. However, several randomized controlled trials have assessed fibrinolytic therapy for the treatment of acute stroke. The time window for successful rescue of cerebral tissue is narrow. One trial sponsored by the National Institutes of Health used treatment with intravenous tissue plasminogen activator within 3 hours after the onset of ischemic stroke and reported improved clinical outcome (death and disability) at 3 months despite an increased incidence of in-hospital intracerebral hemorrhage. Several studies are underway comparing several different drug and device strategies for the treatment of acute stroke.

Cardioembolic Stroke

As many as 120,000 strokes per year are attributed to atrial fibrillation. In people 80 years of age and older, atrial fibrillation

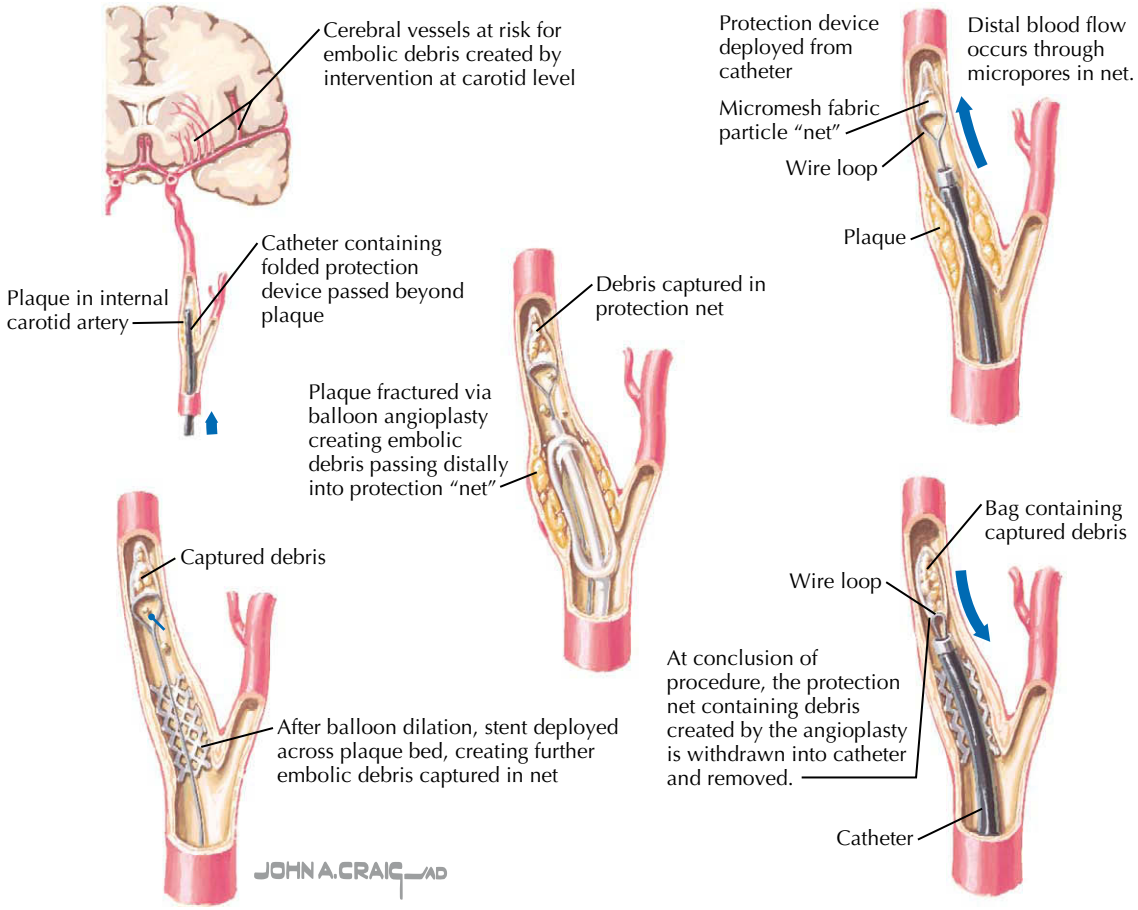


Figure 48-1 *Cerebrovascular emboli protection device.*

accounts for nearly 40% of strokes. Although the efficacy of long-term warfarin therapy is established for stroke prevention, a significant number of individuals have contraindications to or complications with anticoagulation or have breakthrough events despite therapeutic concentrations of warfarin. Emerging nonpharmacologic options have focused on maintaining sinus rhythm and include percutaneous ablation of arrhythmogenic atrial foci, implantable atrial defibrillators, and percutaneous left atrial appendage transcatheter occlusion (Fig. 48-2, upper).

In younger people (under 55 years of age), causes of stroke are more variable and approximately 40% of strokes are of undetermined origin. It has been proposed that venous-to-systemic (or paradoxical) embolization through a patent foramen ovale (PFO) may account for a significant number of these cryptogenic strokes. Evidence in support of this hypothesis includes the finding that the 4-year risk of idiopathic recurrent stroke or TIA in patients found to have a PFO is estimated to be 2% to 15%, even with anticoagulation therapy, whereas the risk is virtually none after surgical closure of the PFO. Features that predispose patients with PFO to neurologic events are concurrent atrial septal aneurysm, hypercoagulable states, fat or air embolism (e.g., during or following orthopedic surgery or at parturition), and conditions that increase right atrial pressures (e.g., chronic obstructive pulmonary disease, recurrent pulmonary embolism). Other high-risk markers for subsequent stroke include previous TIA or stroke, large PFO, and higher transatrial bubble counts on echocardiography. Low rates of stroke recurrence have been observed in relatively large case series with transvenous PFO closure devices (Fig. 48-2, lower), and randomized controlled trials comparing this strategy to anticoagulation therapy are in progress.

UPPER EXTREMITY DISEASE

The innominate and subclavian arteries supply blood flow to the arms and brain via the carotid and vertebral arteries. In patients who have undergone coronary artery bypass grafting using the internal thoracic (mammary) artery, coronary blood flow relies on the innominate and subclavian arteries. In addition to presenting with arm coolness and claudication, or embolization to the fingers, patients with lesions in the innominate and subclavian arteries can present with angina and with symptoms of cerebral hemispheric and vertebrobasilar insufficiency, depending on the specific location of occlusive disease.

The most recent studies on percutaneous transluminal angioplasty and stenting for brachiocephalic and subclavian stenosis show consistent relief of symptoms and resolution of blood pressure differences between the right and left arms. Complete

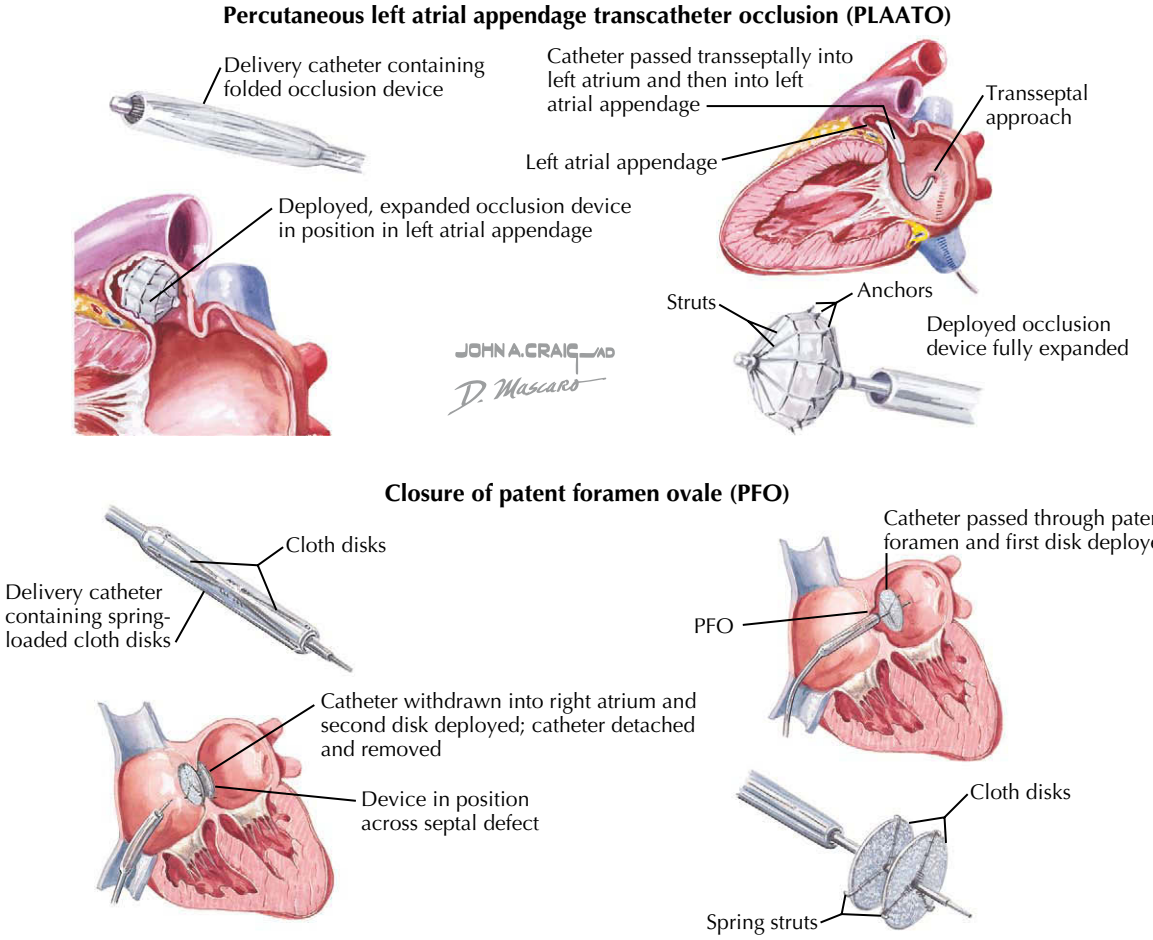


Figure 48-2 *Interventional approaches to peripheral arterial disease.*

occlusions are technically more difficult to revascularize, because more manipulations and force are needed for recanalization, resulting in a higher complication rate and variable clinical outcomes.

There are no available randomized comparisons of surgical and percutaneous revascularization for occlusive diseases involving the aortic arch vessels. Nevertheless, technical short-term success rates for both strategies approach 97%, and patency rates for percutaneous approaches have been reported as high as 97% with a mean follow-up of 20 months compared with patency rates of 84% to 88% at 51 months for surgery. Vascular access bleeding and stent embolization necessitating surgical retrieval are the most common complications of percutaneous approaches. Dissection, thrombosis, and embolization involving the cerebrovascular arteries, internal thoracic artery, and upper extremity territories have been reported but are rare.

Symptomatic extrinsic compression of the subclavian or axillary artery or vein as it crosses the thoracic outlet is a separate clinical entity. Associated anomalies include a cervical rib or fusion of the first and second ribs. Surgical revascularization is the preferred treatment in severe cases of thoracic outlet syndrome presenting as subclavian vein thrombosis (Paget-Schroetter's syndrome). While catheter-directed thrombolysis is an integral component in the therapy of Paget-Schroetter's syndrome, stents are relatively contraindicated because of the risk of kinked or crushed stents with subsequent rethrombosis secondary to extrinsic compression.

DISEASES OF THE VISCERAL ARTERIES

The classic presentation of chronic mesenteric ischemia is postprandial abdominal pain 30 to 60 minutes after a meal and weight loss from avoidance of food intake, or "food fear." Symptomatic chronic mesenteric ischemia is rare because multiple collateral pathways connect the three major intestinal branches of the abdominal aorta: the celiac artery, the superior mesenteric artery, and the inferior mesenteric artery. The differential diagnosis includes atherosclerosis, celiac artery compression from the median arcuate ligament, and nonocclusive etiologies, such as heart failure with low cardiac output and visceral artery vasospasm from cocaine, ergot, or vasopressors. See Chapter 47 for a discussion of renal artery stenosis.

Surgery for mesenteric ischemia is highly successful, with nearly a 100% short-term success rate and a primary patency rate of 89% at 6 years and a perioperative mortality rate of 3% to 4%. The short-term procedural success rates of visceral

artery percutaneous transluminal angioplasty (PTA) are reported to be approximately 79% to 95% and up to 92% to 100% when stents are used. The few procedural failures that occur are generally in the setting of either an occult malignancy (resulting in a prothrombotic state) or extrinsic arterial compression by the median arcuate ligament. Major complications can occur, however, and restenosis is not rare. A comparison of chronic mesenteric ischemia treated by percutaneous approaches to historic surgical controls in which the percutaneous group was significantly older (68 vs. 62 years) and had more coronary disease (68% vs. 33%) showed no statistically significant differences in death. In this report, two periprocedural deaths reported after PTA or stenting were related to bowel gangrene and subsequent multisystem organ failure. A third death resulted from myocardial infarction. There were more than twice as many systemic complications (cardiac, pulmonary, gastrointestinal, or renal) after surgery than after percutaneous revascularization (40% vs. 19%, $P = 0.034$). However, there was almost a threefold difference in cumulative symptom recurrence by 3 years: 34% after percutaneous revascularization and only 13% after surgery. Poor results are often seen with acute mesenteric ischemia associated with cardioembolism or acute aortic dissections primarily because of associated bowel infarction or necrosis, and exploratory laparotomy should be the main strategy.

LOWER EXTREMITY DISEASE

Peripheral arterial disease afflicts approximately 12% of the adult population in the United States. This population has a higher risk of death (three to four times that of age-matched controls), mostly attributed to associated cardiac and cerebrovascular diseases. Intermittent claudication presents in approximately 2% of the population over the age of 65, with a rate of progression to amputation of 1% per year. Surgical revascularization is primarily reserved for advanced disease (lower extremity ulcers or rest pain); however, endovascular therapies have increased the therapeutic options for claudication.

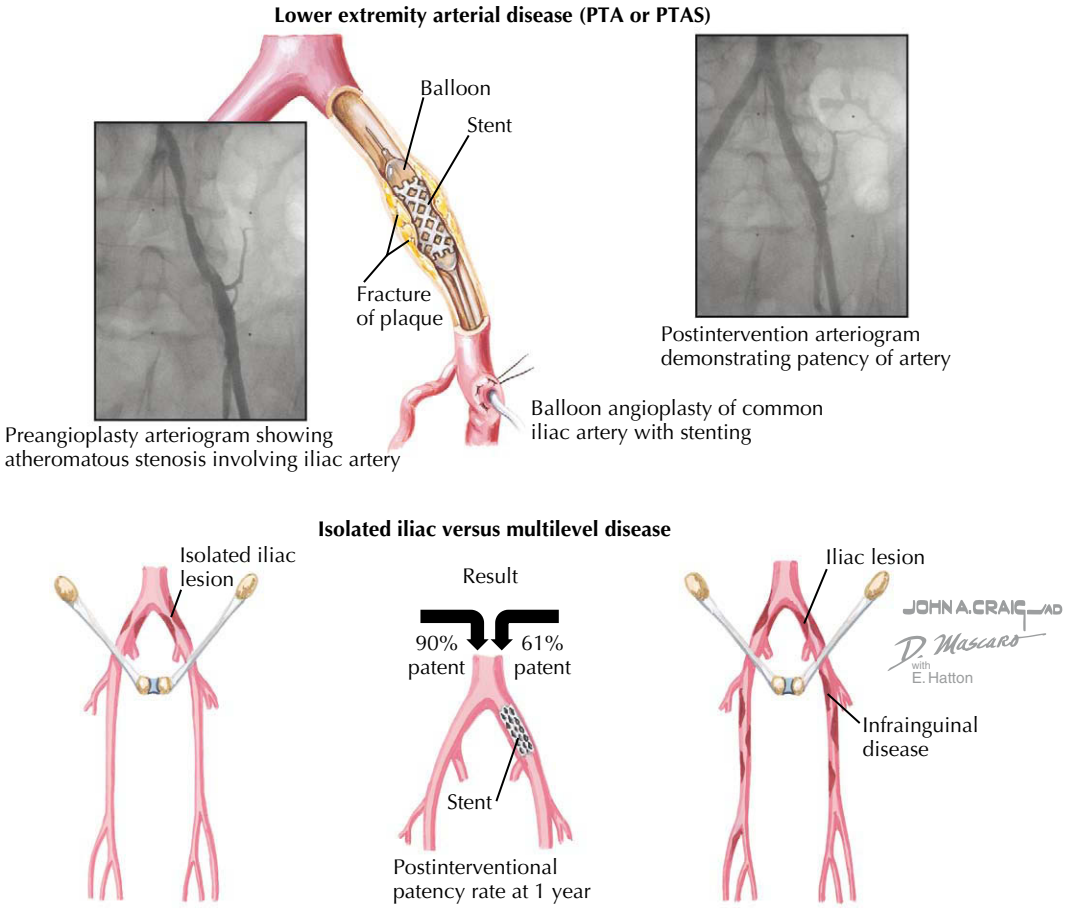
The Trans-Atlantic Inter-Society Consensus (TASC) on the Management of Peripheral Artery Disease, first published in 2000 and revised in 2007 (TASC II), was created to provide a guideline for the treatment of peripheral arterial disease. The document received multidisciplinary input from 16 societies and leading physicians who stressed the medical management of the disease, but it also evaluated the evidence of therapies based upon morphologic classification. Revised recommendations support endovascular therapies for lesions in the superficial femoral artery (SFA) less than 10 cm in length (TASC II type A) and surgical revascularization for occlusive lesions of the SFA longer than 20 cm in length (TASC II type D) (Fig. 48-3). For intermediate lesions (TASC II type B or C lesions), the patient's comorbidities and fully informed preference and the operator's experience and long-term outcomes must be considered.

Whyman and colleagues (1997) showed that a clear advantage exists with PTA after up to 6 months' follow-up in terms of improvement in ability to walk up to 1 km and the distance that could be traversed before claudication on a standard treadmill test. Moreover, twice as many patients had lower pain scores on the Nottingham Health Profile after undergoing PTA as compared with patients who received medical therapy alone. Unfortunately, these benefits were not maintained, and there was no statistically significant benefit in the PTA group compared with the control group after 2 years of follow-up. PTA and supervised exercise achieved different but complementary goals in one study. PTA resulted in statistically significant improvement in ankle-brachial pressure index scores immediately and up to 15 months after the procedure (mean increase of 0.21), but maximum walking distances improved only modestly. However, the maximum walking distance increased progressively for patients randomized to exercise. In the PTA group, the failure to double the walking distance was due to contralateral (untreated) claudication in five patients and angina or dyspnea in two patients. Although PTA definitely improves perfusion to the feet, which can confer protection for populations at higher risk for limb loss (e.g., diabetic patients), supervised exercise improves functional outcome and simultaneously enhances global cardiovascular conditioning and therefore should be the initial therapeutic approach.

The subset of patients with stenosis confined to the iliac arteries is one group that substantially benefits from PTA or stenting. In one study in which 37% of the randomized patients had iliac artery stenosis, the 1-year patency rate was 90% for the iliac subgroup but diminished to 61% when patients with infrainguinal disease were included. While surgical revascularization seems to confer better long-term patency, complication rates are higher, especially in patients with significant comorbidities.

Primary stenting of intermediate lesions (4–15 cm) involving the SFA was superior to PTA in a study performed by Schillinger and colleagues (2006). In the evaluation of self-expanding nitinol versus angioplasty, restenosis rates were found to be 24% versus 43%, respectively, at 6 months, and 37% versus 63%, respectively, at 12 months. Patients were also able to walk considerably greater distances on a treadmill in the primary stent group as compared with PTA at both the 6- and 12-month follow-up. The Randomized Study Comparing the Edwards Self-Expanding LifeStent vs. Angioplasty-Alone In LEsions INvolving The Superficial Femoral Artery and/or Proximal Popliteal Artery (RESILIENT) Trial is a randomized controlled study that has compared primary PTA with nitinol stenting to PTA alone in lesions averaging 6.5 cm in the SFA. The study was designed to follow patients for 36 months, but interim analysis at 12 months indicated a significant difference between the two groups with freedom from revascularization at 90% for the stent group versus 47% for the PTA arm of the study. Primary patency rate of the stented population was approximately 80% at 1 year. The study data proved convincing enough that the U.S. Food and Drug Administration approved the use of the Bard LifeStent (Bard, Tempe, AZ) in the SFA, the first bare-metal stent to obtain such an indication.

Many other modalities are being used in the lower extremities, including atherectomy devices, drug-eluting stents, absorbable metal stents, and a multitude of variations on the simple angioplasty balloon. Although data are lacking to support the routine use of any such device, unique situations exist wherein such devices may prove useful in experienced hands.



Clinical results of PTA are comparable to those of surgical bypass for above-knee (iliac or femoropopliteal) arterial disease that does not include multiple serial stenoses or long occlusions. The subset of patients with stenosis confined to iliac arteries benefits most from PTA or stenting.

Figure 48-3 *Interventional approaches to peripheral arterial disease.* PTA, percutaneous transluminal angioplasty; PTAS, percutaneous transluminal angioplasty with stenting.

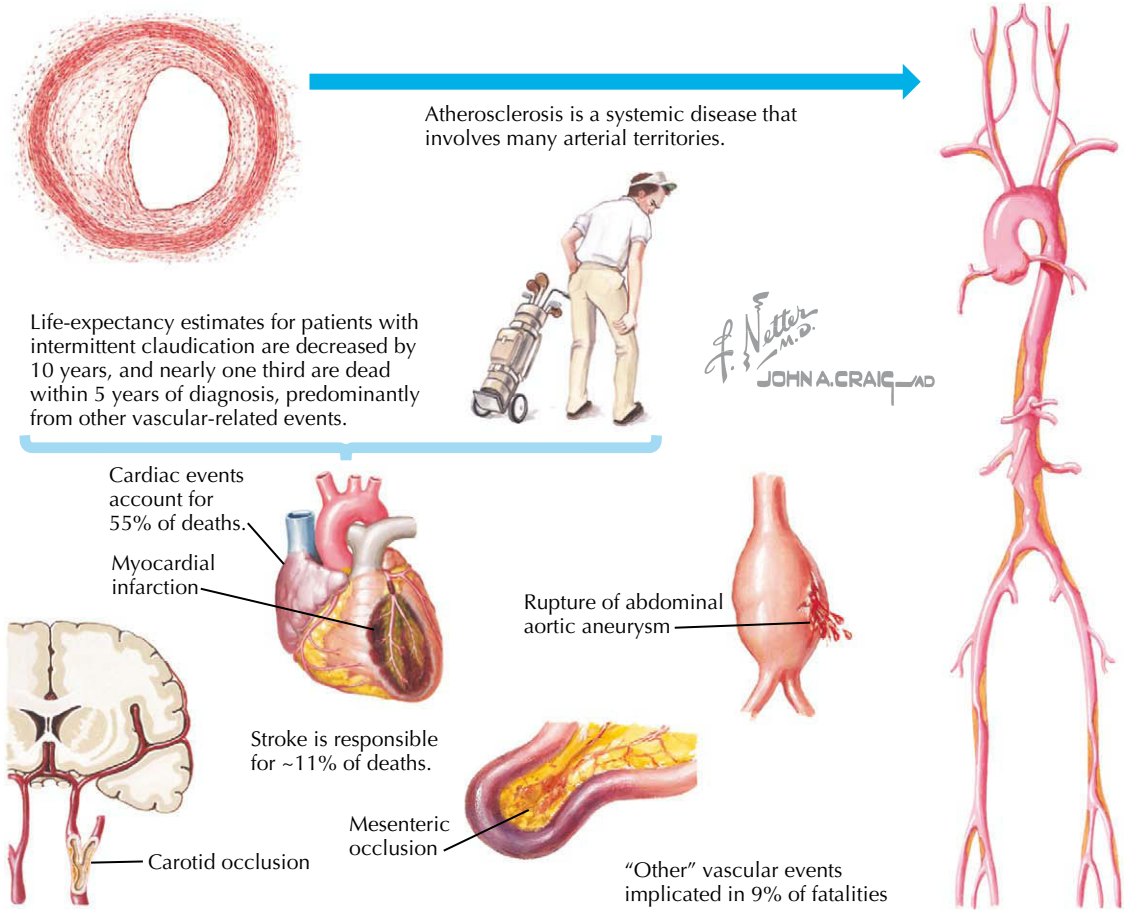


Figure 48-4 *Multiterritorial disease.*

FUTURE DIRECTIONS

Atherosclerosis is a systemic disease that involves many arterial territories (Fig. 48-4). Patients with this disease are at an increased risk for death, most likely from cardiac or cerebral events. These patients are also at increased risk for aortic aneurysms. Patients with diffuse atherosclerosis often have multiple comorbidities that require interspecialty communication and collaboration among primary care providers, geriatricians, cardiologists, interventional radiologists, endocrinologists, neurologists, surgeons, and other health care team members. Multidisciplinary care maximizes prevention, health maintenance, and optimal selection of patients and procedures (diagnostic and therapeutic). It is anticipated that continuation of technologic advances in peripheral vascular devices, adjunctive drug therapy, and the creation of more specialized vascular centers will result in enhanced quantity and quality of life.

ADDITIONAL RESOURCES

American Heart Association (AHA). 2002 Heart and Stroke Statistical Update. Dallas: AHA; 2001. p. 1–38. Available at: <http://www.americanheart.org/downloadable/heart/HS_State_02.pdf>; Accessed 31.03.10.

The AHA guide to heart and stroke statistics.

Norgrena L, Hiattb WR, Dormandy JA, et al, on behalf of the TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease. *J Vasc Surg.* 2007;45(Issue 1, Jan Suppl.):S5–S67.

The Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease was published in January 2007 as a result of cooperation among 14 medical and surgical vascular, cardiovascular, vascular radiology, and cardiology societies in Europe and North America.

EVIDENCE

Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1998;339:1415–1425.

NASCET randomized 2226 patients with a symptomatic internal carotid artery stenosis to medical care or carotid endarterectomy. Patients had either a transient ischemic attack or stroke within 4 months of enrollment and a 30% to 99% internal carotid artery stenosis. For patients with a stenosis greater than or equal to 70%, carotid endarterectomy reduced the risk of any ipsilateral stroke from 26% to 9% at 2 years ($P < 0.001$).

Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Available at: <http://clinicaltrials.gov/ct2/show/NCT00004732>; Accessed 31.03.10.

This study is complete and the data have been presented at a national meeting but have not been published yet. National Institute of Neurological Disorders and Stroke clinical trials identifier: NCT00004732.

CAVATAS investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet.* 2001;357:1729–1737. Available at: <http://www.cavatas.com/>.

CAVATAS is an international randomized trial of stroke prevention reviewing the safety and effectiveness of angioplasty compared with endarterectomy (surgery) or best medical treatment in patients with carotid or vertebral artery stenosis. CAVATAS stopped enrolling new patients in 1997 but followed patients enrolled in the trial until 2007.

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA.* 1995;273:1421–1428.

Patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy can be performed with less than 3% perioperative morbidity and mortality.

Hadjipetrou P, Cox S, Piemonte T, Eisenhauer A. Percutaneous revascularization of atherosclerotic obstruction of aortic arch vessels. *J Am Coll Cardiol.* 1999;33:1238–1245.

Subclavian and brachiocephalic artery obstruction can be effectively treated by primary stenting or surgery. Comparison of stenting and the surgical experience demonstrates equal effectiveness but fewer complications and suggests that stenting should be considered as first-line therapy for subclavian and brachiocephalic obstruction.

Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. *Ann Surg.* 1984;199:223–233.

In an attempt to reduce early and late mortality caused by myocardial infarction, coronary angiography was performed in 1000 patients (mean age, 64 years) under consideration for elective peripheral vascular reconstruction since 1978. Severe correctable coronary artery disease was identified in 25% of the entire series.

Katzen B, Laird J. Update on the RESILIENT trial. Cardiovascular and Interventional Radiology Society of Europe 2006, Rome, 9–13 September.

Preliminary finding from phase 1 demonstrated 90% patency and 0% stent fractures at 12 months.

Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med.* 2001;345:1740–1746.

Patients with both PFO and atrial septal aneurysm who have had a stroke constitute a subgroup at substantial risk for recurrent stroke, and preventive strategies other than aspirin should be considered.

MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet.* 2004;363:1491–1502.

In asymptomatic patients younger than 75 years of age with carotid diameter reduction of about 70% or more on ultrasound (many of whom were on aspirin, antihypertensive, and, in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard). Half this 5-year benefit involved reduction in disabling or fatal strokes. However, outside trials, inappropriate selection of patients, or poor surgery could obviate such benefits.

Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med.* 2006;354:1879–1888.

In the intermediate term, treatment of SFA disease by primary implantation of a self-expanding nitinol stent yielded results that were superior to those with the currently recommended approach of balloon angioplasty with optional secondary stenting.

Whyman MR, Fowkes FG, Kerracher EM, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. *J Vasc Surg.* 1997;26:551–557.

Two years after PTA, patients had less extensive disease than medically treated patients, but this did not translate into a significant advantage in terms of improved walking or quality of life. There are important implications for patient management and future clinical research.

Wilson SE, Wolf GL, Cross AP. Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis: report of a prospective randomized trial in a selected group of patients. *J Vasc Surg.* 1989;9:1–9.

A prospective, randomized comparison of PTA with surgery in the treatment of occlusive disease of the iliac, superficial femoral, or popliteal arteries began in 1983. Radiologists and vascular surgeons independently assessed index lesions on arteriograms to decide whether their respective treatments were appropriate.

Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med.* 2004;351:1493–1501.

Among patients with severe carotid artery stenosis and coexisting conditions, carotid stenting with the use of an emboli protection device is not inferior to carotid endarterectomy.

Surgery for Peripheral Vascular Diseases

49

Robert Mendes, Mark A. Farber, and Blair A. Keagy

Peripheral vascular disease (PVD) encompasses pathology of both the arterial and the venous circulations. Advanced disease of either system can be debilitating and disabling. The clinical presentation and therapeutic choices for patients with PVD vary widely depending upon the vascular distribution involved and the severity of the disease. This chapter focuses on the more common problems that require surgical intervention. Although PVD includes venous pathologies, these are less likely to result in serious morbidity and mortality, and thus this chapter focuses on arterial pathologies.

Aneurysmal disease usually involves large arteries, most commonly the infrarenal aorta and iliac arteries, and less often involves other major arteries, including the thoracic aorta and the femoral and popliteal arteries. Although small aneurysms have been reported to rupture, the risk of rupture is thought to rise exponentially with increasing diameter according to LaPlace's law—that the greater the radius of an artery, the greater the pressure on the arterial wall. Atherosclerosis is an important contributor to aneurysmal dilatation, but genetic and other factors are also important in aneurysm formation and rupture, as described below.

Atherosclerosis involving the infrarenal aorta and the iliac and infrainguinal arteries is also the most common cause of arterial insufficiency of the lower extremities. PVD can be subdivided into categories based on location: inflow (infrarenal aorta, iliac), outflow (femoral, popliteal), and runoff (tibial, peroneal) vessels. These categories help define the risks and benefits of intervention and treatment options.

A detailed history and physical examination can identify the anatomic distribution of vascular pathology. Invasive and noninvasive imaging augment clinical findings and aid decision making. Several open surgical and endovascular interventions, discussed later, provide significant benefits to patients with PVD.

Other important areas of the vascular system affected by occlusive disease include the carotid arteries and the visceral vessels. Surgical and other interventional approaches to treating atherosclerosis of the carotid and visceral arteries are also discussed in this chapter.

ETIOLOGY AND PATHOGENESIS

For many years the etiology of aneurysmal disease was believed to be primarily related to atherosclerosis, largely because aneurysmal disease occurs predominantly in elderly hypertensive individuals and is associated with tobacco use. The etiology is now thought to be multifactorial. Genetic predisposition may be involved in up to one third of patients with aneurysms. Microscopic analysis indicates that deficiencies in elastin, collagen, or both may be crucial factors. Collagen-degrading matrix metalloproteinases are probable culprits in aneurysm formation, and current research focuses on their role in the pathogenesis of aneurysmal disease. Elastin and collagen breakdown, which may be accelerated based on a genetic predisposition to produce matrix metalloproteinases, may precipitate an inflammatory reaction. This inflammatory reaction can then contribute to weakening of the arterial wall and eventual dilatation. The presence of several cytokines and systemic biomarkers has been shown to correlate with the presence and size of abdominal aortic aneurysms, and it is likely that a causative relationship exists. Embolic disease, thrombosis, or trauma may also cause arterial occlusion (Fig. 49-1). However, the most common cause of lower extremity arterial occlusion is atherosclerosis. The etiology and pathogenesis of atherosclerosis are discussed in Chapter 44.

ABDOMINAL AORTIC ANEURYSMS

Clinical Presentation

Each year approximately 9000 deaths occur from ruptured abdominal aortic aneurysms (rAAAs), and this disease is the thirteenth leading cause of death in the United States, despite advances in diagnostic imaging, screening programs, and heightened awareness. Abdominal pain may indicate rapid enlargement or impending rupture of an AAA. Other symptoms of an AAA include nausea, early satiety, and back pain from compression of adjacent structures; however, approximately 75% of patients are asymptomatic at presentation, and the presence of an AAA is detected by physical examination or screening of high-risk individuals.

Management and Therapy

OPTIMUM TREATMENT

Management guidelines center on evaluation of rupture risk. When the risk of rupture exceeds the risk of surgical repair, replacement of the artery's aneurysmal segment is indicated. For an asymptomatic AAA, the risk of rupture varies with the diameter of the aneurysm; an AAA of 5 cm has a 5% rupture risk per year, and an AAA of 6 cm has an estimated 10% to 15% rupture risk per year. Patients with saccular aneurysms, chronic obstructive pulmonary disease, or hypertension are thought to have a higher than average risk of aneurysm rupture. Treatment is indicated for aneurysms that are greater than twice the normal artery diameter, that are enlarging rapidly (>0.5 cm in 6 months), or that are symptomatic—the major symptoms being pain or evidence of distal emboli potentially related to the aneurysm.

The number of patients in the United States with the diagnosis of an rAAA has declined in recent years from 23.2 to 12.8 per 100,000 Medicare beneficiaries ($P < 0.0001$), as did repairs

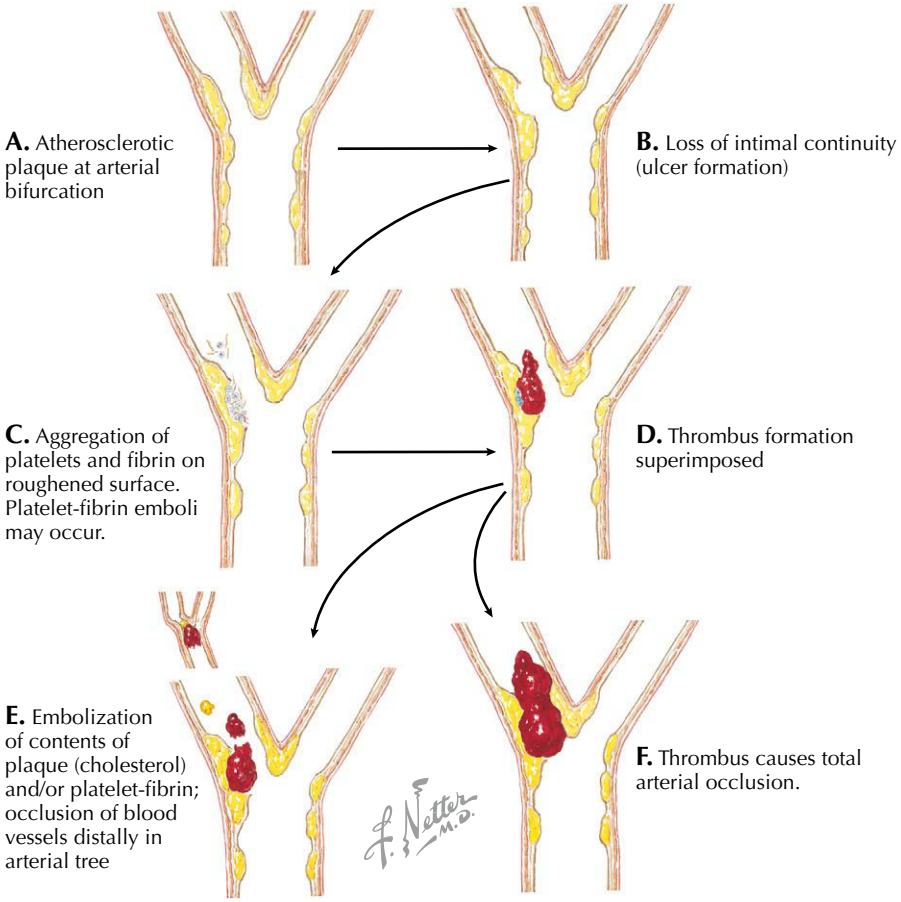


Figure 49-1 *Atherosclerosis, thrombosis, and embolism.*

of rAAAs (15.6 to 8.4 per 100,000; $P < 0.0001$). These data reflect increased surveillance for AAAs and the increased use of endovascular aneurysm repair. With the increasing number of endovascular aneurysm repairs (EVARs), the threshold for intervention based on size has become more controversial. Some evidence suggests that observation of AAAs smaller than 5.5 cm is the proper course, whereas other observers believe that EVAR should be offered to patients earlier in the course of their disease. This question is being addressed in a large randomized study that, when complete, should provide much-needed direction on when to intervene in patients with AAAs.

During the past 50 years the surgical technique for AAA repair has remained essentially unchanged, with outcome improvements resulting from advances in preoperative screening and risk stratification, improved anesthetic practice, and intensive care management. Notably, however, the use of more durable synthetic grafts in recent years (rather than using homografts for AAA repair; Fig. 49-2, upper) has also contributed to the improved long-term outcome following AAA repair. Aneurysmorrhaphy involves mobilization and exposure of the aneurysm and the normal artery above and below the diseased section. Blood flow through the artery is arrested for inline replacement of the diseased artery with an artificial one, resulting in major cardiovascular stress during the procedure and for several days after. The combination of cardiovascular stress and the advanced age and comorbid conditions of the patient increases the procedure-associated morbidity and mortality rates. Patients usually require 7 to 10 days of hospitalization and 6 to 8 weeks to recover. However, once patients fully recover from the procedure, long-term follow-up indicates that few patients need further intervention. When further intervention is needed, generally it is because progression of the disease has occurred in adjacent arteries. Ongoing research focuses on the identification of mechanisms to arrest the disease process to prevent spread and inhibit the inflammatory process.

As general medical care and nutrition have improved, the mean age in the United States and industrialized countries has increased, and with this there is an increasing number of individuals with AAAs. As the age and medical comorbidities of patients with an AAA increased, so did the interest in less-invasive procedures for treatment, resulting in the development of minimally invasive techniques for the treatment of aneurysmal disease. AAA endovascular repair techniques involve the insertion of a new lining into the diseased artery with the use of hooks or stents to secure the lining to the arterial wall. Four devices are approved by the U.S. Food and Drug Administration for the treatment of infrarenal AAAs. The indications for treatment with endovascular devices are identical to those for open surgical repair. The procedure can be performed under local, regional, or general anesthesia, and typically involves exposure

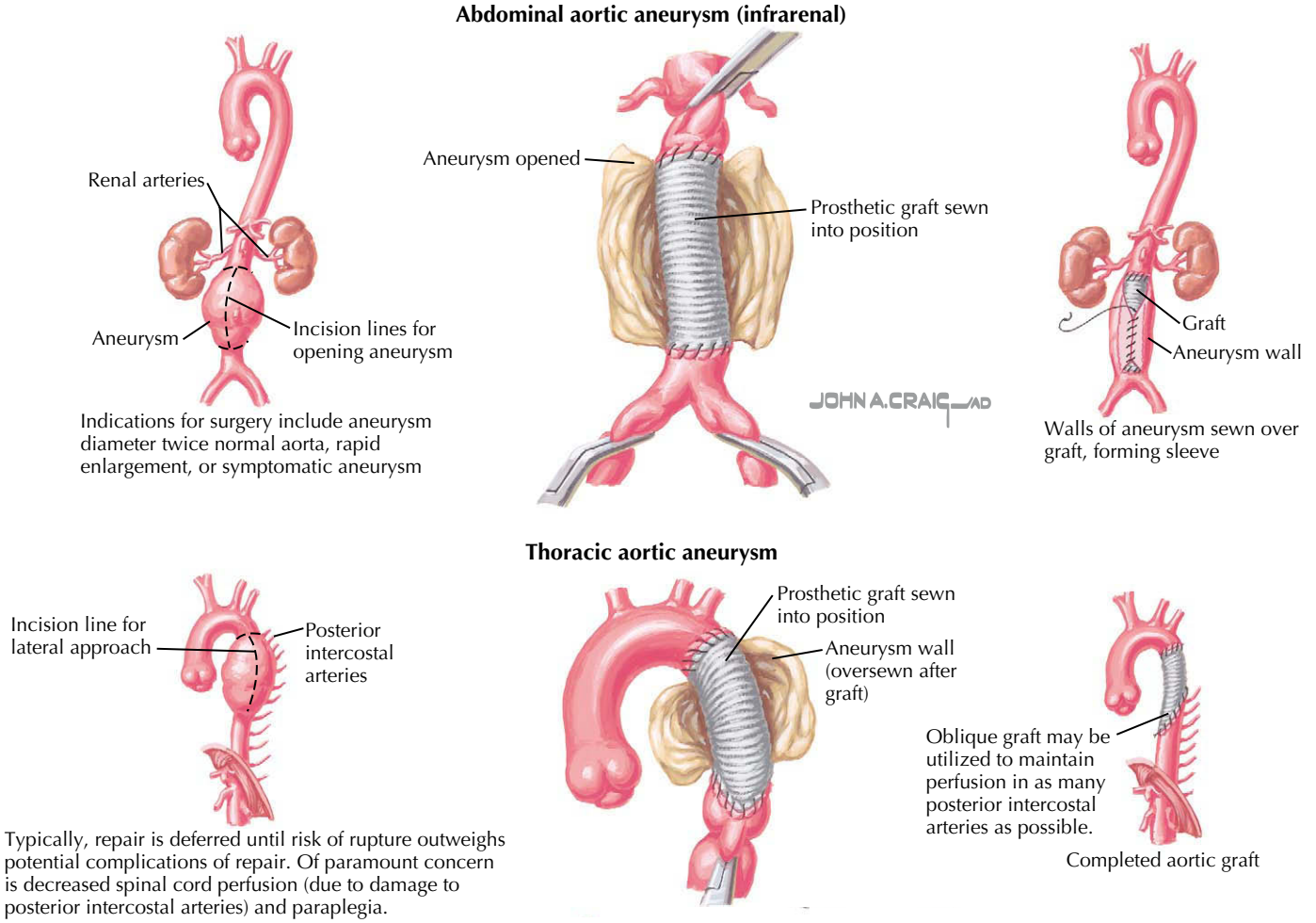


Figure 49-2 *Surgical management of aortic aneurysms.*

of the common femoral arteries for device insertion. Although insertion has been accomplished with percutaneous techniques, most devices are too large for insertion by routine percutaneous treatment methods. Once the aorta is accessed, imaging methods guide device implantation just below the renal arteries, where the aorta and its endothelium are the healthiest. Most patients are hospitalized for 1 day and are fully recovered from the procedure within 1 week. Successful implantation is accomplished in more than 98% of patients.

Patient selection is crucial to outcomes with EVAR. Seal failures (endoleak) are more likely to occur in patients with short, angled, or diseased proximal infrarenal arteries. During follow-up, complications associated with endoleaks or migration develop in 6% to 15% of patients. Many of these complications can be treated with secondary endovascular interventions and do not necessitate conversion to open repair and removal of the device. Iliac artery access issues (smaller or diseased arteries) may also create complications associated with implantation. Although new design techniques and lower profile devices have overcome many of these problems, complications occur in 1% to 2% of patients.

Prospective studies have not shown a reduction in the mortality rate associated with EVAR procedures compared to open surgery, but taken as a whole these studies show the rate of major morbidity is significantly lower (by ~50%) following EVAR. Blood loss and time required to return to an active lifestyle are also significantly reduced. Interim data also suggest that patient survival is greater after EVAR than after traditional open surgical treatment, and this has resulted in the increased use of this approach. Notably, a report from the Agency for Healthcare Research and Quality states that EVAR did not improve longer term overall survival or health status and was associated with greater complications, need for reintervention, long-term monitoring, and costs.

In 2008, approximately 50% of AAAs were treated with endovascular therapy. As branched designs and other innovations are incorporated and durability concerns are addressed, the use of EVAR technology will most likely increase.

AVOIDING TREATMENT ERRORS

With both the endovascular and open approaches, the anatomy of the aneurysm must be determined. This includes proximity to the renal arteries as well as the angulation of the neck of the aneurysm and the status of the inferior mesenteric artery. Failure to revascularize the inferior mesenteric artery may result in

postoperative visceral ischemia, whereas graft impingement on the renal arteries may result in renal failure. Placement of an endograft in a patient with a severely angulated neck can be associated with a type I endoleak.

THORACIC ANEURYSMS

Clinical Presentation

Thoracic aneurysms are less prevalent than AAAs. The clinical presentation of thoracic aneurysms is similar to that of AAAs, in that most patients are asymptomatic. The most common clinical presentation results from compression of adjacent structures, which can produce chest pain, hoarseness from recurrent laryngeal nerve injury, back pain, or pulmonary problems from compression of bronchial structures.

Management and Therapy

OPTIMUM TREATMENT

As is the case for surgical repair of infrarenal disease, surgical repair of thoracic aneurysms usually requires replacement of the diseased artery. However, the risks associated with surgical repair of thoracic and thoracoabdominal aneurysms are significantly higher than those of AAA repair. One major risk associated with thoracoabdominal aneurysm repair is paraplegia, because perfusion to the spinal cord must be interrupted during the repair. Several approaches have been developed to limit the amount of ischemia, including the use of barbiturates, hypothermia, and spinal cord drainage to increase perfusion pressure via collaterals. Even with these protective approaches, for extensive aneurysms involving the area from the left subclavian artery to the aortic bifurcation, the risk of paraplegia is as high as 25%. For small aneurysms involving a short section of the aorta, the risk of paraplegia is not negligible (2% to 8%). Because of the high risk, treatment is delayed until the risk of rupture is greater than the risk of repair, typically when an aneurysm is 6 cm in diameter (Fig. 49-2, lower). Individuals with Marfan's disease or other collagen vascular diseases represent an important subset in whom the risk of dissection and/or rupture is increased even at smaller aneurysm diameters, requiring earlier surgical intervention.

Recent treatment of thoracic aneurysms with endografts has lowered the risk associated with treating this problem and increased the number of patients who are candidates for treatment. The results of endovascular therapy trials being conducted for the treatment of thoracic diseases are promising. Although an association between endovascular therapy and paraplegia exists in patients with a concomitant or previous infrarenal repair, the association between length of the aneurysm and paraplegia as a complication of surgical repair is not present when the aorta is covered by the endograft. Other thoracic aortic pathologies being treated include aortic dissections, aortic transections, penetrating ulcers, and ruptured plaques, all with promising results.

In the past, repair of many extensive thoracoabdominal aneurysms involved the use of atriofemoral bypass. In patients with visceral ischemia, especially to the kidneys and liver, the potential for renal failure and serious coagulopathy was significant with conventional surgical repair. Fortunately, recent studies are demonstrating that visceral revascularization techniques performed in conjunction with placement of an endograft have decreased the morbidity associated with thoracic aortic cross-clamping.

AVOIDING TREATMENT ERRORS

There are few clinical manifestations associated with thoracic aneurysms. The diagnosis is by chest x-ray or CT scan in patients at high risk for systemic aneurysms.

FEMORAL AND POPLITEAL ANEURYSMS

Clinical Presentation

Popliteal aneurysms are often associated with thrombosis or embolization, or both. The risk of rupture is very low. Importantly, these aneurysms are bilateral in at least 50% of patients; it is therefore mandatory that a careful physical examination be performed in both popliteal fossae. A duplex scan is an easy and accurate way of evaluating the presence and size of popliteal aneurysms. Some patients with popliteal aneurysms may present with posterior knee complaints from compression of adjacent structures. As is the case with popliteal aneurysms, femoral aneurysms may also be associated with thrombosis and rupture. There is also an increased incidence of AAAs in patients with femoral and popliteal aneurysms, and all patients should be screened for AAAs at the time of their initial presentation.

Management and Therapy

OPTIMUM TREATMENT

Because of the superficial location and easy surgical access of femoral artery aneurysms, these aneurysms are treated with aneurysmorrhaphy and, if necessary, reconstruction of the femoral bifurcation. Complication rates are low, usually involving recurrence, intimal hyperplastic issues, or graft infection. Endovascular techniques are not necessary because of the aneurysm's location, the ease of repair, excellent outcome, and low morbidity with surgical intervention.

Surgical bypass with the use of a vein graft is generally employed for popliteal aneurysms, with aneurysm ligation to prevent further embolization. In the case of a large aneurysm, resection may be required because of associated compression of the popliteal vein. Endovascular therapy for popliteal aneurysms has been used but has been associated with graft thrombosis in some cases. This therapy should probably be used only with older and high-risk patients.

AVOIDING TREATMENT ERRORS

Femoral aneurysms are palpable and often noted by the patient. The majority of popliteal aneurysms are bilateral, so a high index of suspicion is indicated in patients who have presented with a popliteal aneurysm on one side.

LOWER EXTREMITY ATHEROSCLEROSIS

Clinical Presentation

With the tendency for development of collateral circulation in the lower extremities, patients with lower extremity atherosclerosis may be asymptomatic despite significant arterial insufficiency. Additionally, many of these patients have comorbid conditions, such as cardiac disease, that restrict their activity and preclude them from having symptoms until very advanced disease is present. For individuals who can ambulate, claudication—muscle "cramping" or discomfort after walking a specific distance, with relief of the pain upon resting—is often the chief complaint. This pain is reproducible and consistent with pathophysiology that limits muscular blood supply during exertion, causing lactic acid accumulation.

Claudication of the proximal muscles of the leg, buttock, or hip usually indicates inflow disease, commonly referred to as aortoiliac occlusive disease. In some patients with severe disease, Leriche's syndrome may develop. Patients with Leriche's syndrome exhibit the characteristic triad of sexual dysfunction, buttock claudication, and absent femoral pulses. The association between aortoiliac occlusive disease and proximal muscle complaints is variable, and some patients complain of calf claudication despite the presence of significant occlusion more proximally. Atheromatous embolization from aortoiliac lesions can lodge in the distal vessels, creating localized ischemia of the digits with resulting cyanosis. Because this is an embolic process, patients with the "blue toe syndrome" often have palpable distal pulses and may, depending on the degree of involvement, experience resolution of their clinical symptoms with time or medical therapy, or both.

Patients with atherosclerosis involving the femoropopliteal (outflow) vessels or with multilevel distribution of the disease can present with complaints ranging from claudication, the mildest presentation, to the most severe symptoms of rest pain and tissue loss. Often patients with mild complaints never seek medical attention because they attribute symptoms to arthritis or "old age." However, as the disease worsens and rest pain ensues, a persistent "burning" or "aching" sensation over the dorsum of the foot often prompts individuals to seek help. Although usually of little benefit, patients may keep the ischemic limb in a dependent position, in an attempt to have gravity aid blood flow. Other signs characteristic of severe ischemia include dependent rubor, muscle atrophy, skin changes, lower extremity alopecia, ulcerations, and the lack of palpable distal pulses. Although these symptoms and signs of severe ischemia occur in nondiabetic individuals, with the increasing prevalence of diabetes, a higher proportion of patients presenting with femoropopliteal disease are diabetic (Fig. 49-3).

Isolated lesions at a single level rarely result in lower extremity rest pain and nonhealing ulcerations. Patients who present with concomitant lower extremity infections and persistent ulcerations despite medical therapy should be thoroughly evaluated for significant arterial insufficiency. In many instances, these patients require lower extremity revascularization to salvage limbs.

Assessment by a noninvasive vascular laboratory can provide extensive information on the location and severity of lower

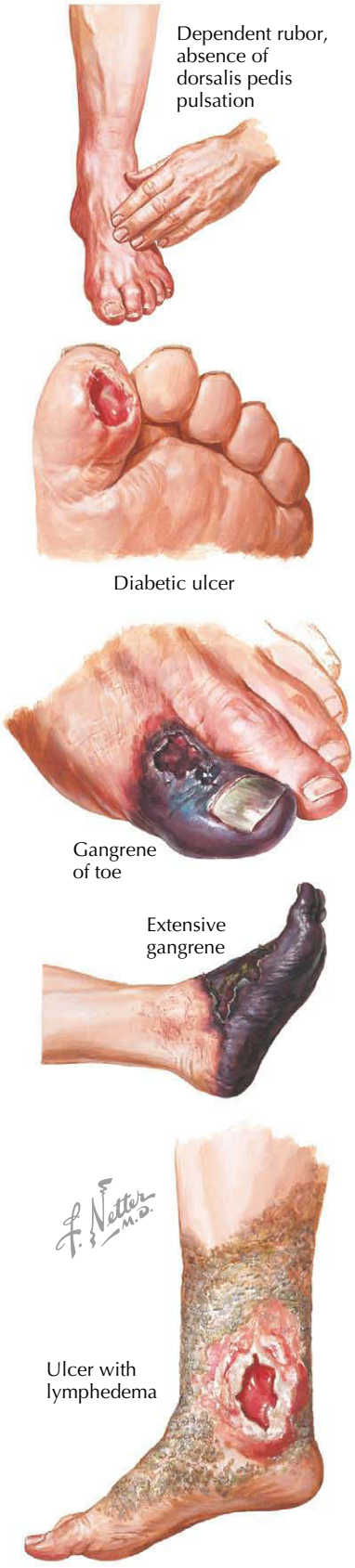


Figure 49-3 *Complications of diabetic vasculopathy and neuropathy.*

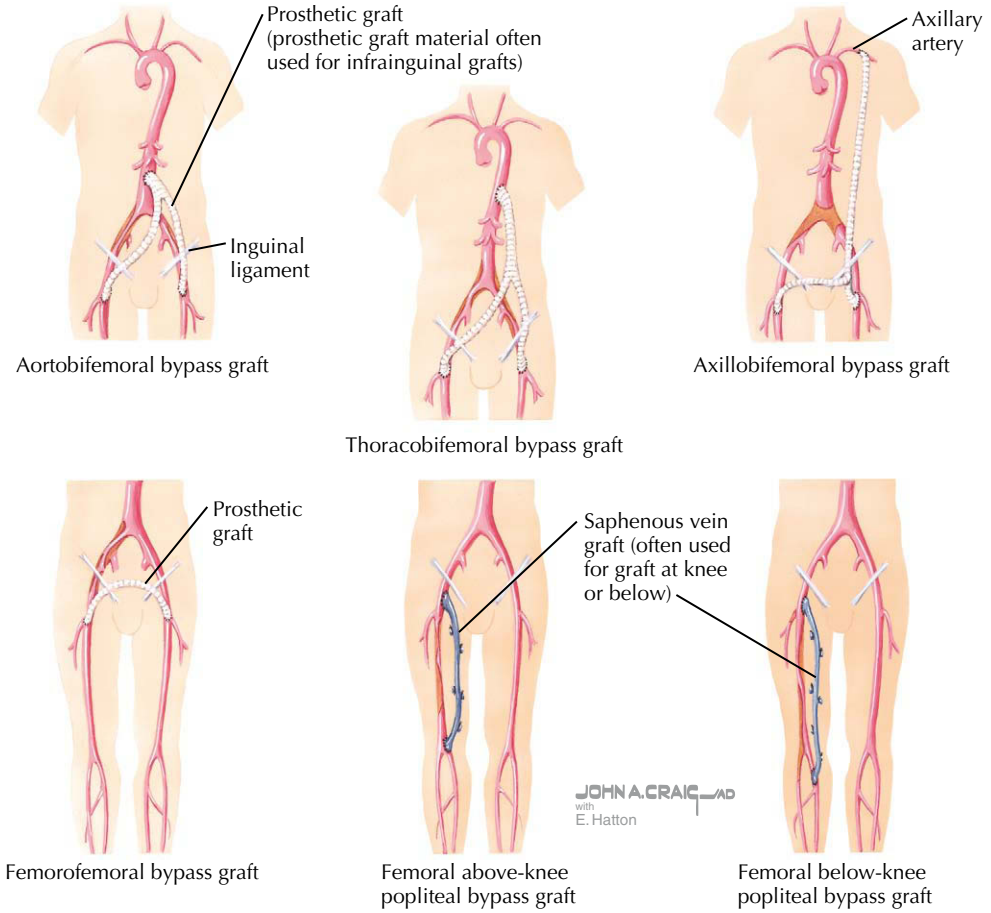


Figure 49-4 *Surgical management of peripheral arterial disease of the lower extremities.*

extremity arterial obstruction. The ankle-brachial index provides an overall estimate of limb perfusion pressure, while analysis of velocity waveforms in the arteries at the groin, knee, and ankle helps to classify the obstruction as inflow (aortoiliac), outflow (superficial femoral artery), or runoff (tibioperoneal vessels). Photoplethysmography waveforms in the toes as well as toe pressures help diagnose even more distal disease. Transcutaneous oxygen measurements aid in the quantification of tissue ischemia, and a promising new technology (hyperspectral imaging) may be used to analyze ischemia and predict wound healing.

Management and Therapy

OPTIMUM TREATMENT

All patients should undergo aggressive evaluation and treatment for hyperlipidemia and other genetic disorders associated with progressive atherosclerosis. Reducing risk factors, most importantly cessation of smoking, will slow disease progression. In addition, patients should integrate diet modification, exercise regimens that encourage collateral circulation, and prevention of lower extremity trauma and infection into their lifestyles. Drug therapy with an antiplatelet or hemorheologic agent such as pentoxifylline or cilostazol can provide symptomatic improvement in some patients.

Ischemic rest pain, ulceration, and gangrene of the digits are indications for arterial reconstruction if anatomically feasible. Decisions about operations for lifestyle-impairing claudication must be based on patient comorbidities and the anatomic distribution of the disease. The decision as to which operative approach is best for an individual (and whether a surgical approach is indicated) should be based on the natural history of the disease, the overall condition of the patient, and the risks and benefits specific to the procedure and individual (Fig. 49-4). The goal of the procedure (e.g., limb salvage, wound healing, relief of rest pain, exercise tolerance) must be determined before surgical intervention. Endovascular procedures increase the options for therapy and are discussed in detail in Chapter 48.

If inflow disease is present, it should be addressed first because surgical correction can relieve symptoms and obviate the need for the less successful infrainguinal bypass surgery. Patients with symptomatic inflow disease can be treated with endovascular therapies, inline arterial reconstructions, or extra-anatomic bypass. In making the decision about surgical therapy, consideration of both the patient's perioperative risk and the influence of his or her anatomy and comorbidities on graft survival is important. For instance, comorbidities may exclude one approach or another. Other issues, such as cigarette smoking, may also influence the therapeutic decision. Many vascular

surgeons will not perform reconstructive surgery on patients who are still smoking, because smoking lowers bypass patency rates dramatically.

Bilateral aortoiliac disease is best treated with aortobifemoral grafting, using a prosthetic graft. The patency of this graft is approximately 80% to 90% at 5 years and approximately 70% at 10 years. Mortality risks for this procedure are less than 5%. In patients with a history of abdominal infection, prior irradiation, abdominal stomas, or multiple abdominal operations (all of which increase operative morbidity rates), the descending thoracic aorta can be used as an alternative inflow source. The thoracobifemoral bypass achieves patency rates of 75% to 85% at 5 years, with perioperative mortality rates below 5% when the bypasses are performed by experienced vascular surgeons. Extra-anatomic bypasses (grafts that course through an anatomic pathway that is significantly different from the native arteries) should be performed in patients who would not tolerate major aortic reconstructive surgery because of comorbidities. The most common extra-anatomic procedures are axillobifemoral and femorofemoral bypass grafts. Axillobifemoral reconstruction, used for aortoiliac occlusive disease, has a 5-year patency rate of 50% to 60%. For patients with unilateral iliac disease not amenable to angioplasty, femorofemoral bypass has a 5-year patency rate of 50% to 80%.

Critical ischemia or tissue loss from infrainguinal occlusive disease is best treated with arterial reconstruction. With respect to patency and resistance to infections, autologous vein grafts are superior to other conduits, especially when reconstruction below the knee is necessary. Availability, quality, and length requirements may necessitate a search for alternate sites for veins, such as the arms (basilic, cephalic) or the posterior leg (lesser saphenous vein). If possible, an autologous graft rather than synthetic material should be used for infrainguinal bypasses. Prosthetic material in lower extremity bypass procedures is reserved mainly for patients without other conduit options. In some cases, prosthetic material may be used for reconstructions above the knee.

Comparison of the use of an autologous saphenous vein with polytetrafluoroethylene grafts in above-the-knee (femoropopliteal) and below-the-knee (distal femoropopliteal and femorodistal) bypass procedures showed equivalent 2-year patency rates in grafts to the same level, but patency diverged to a significant difference at 4 years. The differences at 4 years were significant for infrapopliteal bypasses but not for above-the-knee procedures. Of course, prosthetic graft material for distal bypasses is a better option than primary amputation in patients with suboptimal autologous vein options.

An excellent summary of the diagnosis and treatment of patients with lower extremity ischemia may be found in the American College of Cardiology/American Heart Association 2005 Practice Guidelines for the management of patients with peripheral arterial disease.

AVOIDING TREATMENT ERRORS

Patients often attribute calf or thigh pain to orthopedic conditions. Individuals with lower extremity pain associated with exercise should have a careful vascular evaluation.

CAROTID DISEASE

Clinical Presentation

Most patients with carotid artery stenosis are asymptomatic (see also Chapters 45 and 48). For patients with symptoms, complaints range from short-lived symptoms consistent with a transient ischemic attack—which may include contralateral extremity weakness, ipsilateral facial weakness, slurred speech, or temporary monocular blindness (amaurosis fugax)—to fully developed stroke deficits.

Management and Therapy

OPTIMUM TREATMENT

Carotid endarterectomy has been the mainstay of treatment of carotid artery disease for decades. Large multicenter trials, such as the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the North American Symptomatic Carotid Endarterectomy Trial, validated the safety and efficacy of carotid endarterectomy in treating and preventing strokes in patients with carotid artery stenosis. Surgical therapy involves exposure of the carotid bifurcation under general or regional anesthesia. After arresting flow and removing the intima and the media of the diseased section, the artery is closed. The procedural stroke rate is 1% to 2%. Adjacent nerve injuries and hematomas are the most common complications. With the use of routine carotid patch closure, long-term restenosis rates are significantly reduced. Patients recover quickly from this procedure (1 week), and hospitalizations are routinely less than 24 hours.

Carotid angioplasty with stenting is increasing in frequency. Although early studies showed an increased risk of stroke after carotid angioplasty, with the use of distal protective devices, the safety of carotid angioplasty–stenting has improved substantially. Most trials in this area are "noninferiority studies" to determine whether or not the outcomes of carotid artery angioplasty–stenting equal those with carotid endarterectomy. The results of these trials have been equivocal. There is not a consensus on whether any intervention (carotid endarterectomy or carotid artery stenting) is indicated with asymptomatic carotid stenosis. The results of the ACAS supported revascularization for asymptomatic individuals with significant carotid artery stenoses. It should be noted, however, that the ACAS was conducted in an era when aspirin therapy was considered optimal medical management. No similar study has been done with a combination of aspirin and one of the newer antiplatelet agents (such as clopidrigrel) in asymptomatic patients.

AVOIDING TREATMENT ERRORS

The optimum treatment for asymptomatic carotid stenosis remains somewhat controversial, as discussed previously. Careful consideration should be given to advocating an invasive procedure in asymptomatic patients.

VISCERAL DISEASE

Clinical Presentation

Patients with atherosclerotic lesions involving visceral arteries typically present with end-organ ischemia. Although abdominal

bruits are often detected, the disease's natural history indicates that patients rarely become symptomatic and that symptoms generally occur only when the disease is far advanced. There is considerable debate about whether (and how) asymptomatic stenoses of visceral arteries should be treated. Duplex scanning is being used more frequently to identify patients with significant visceral stenosis. The greatest challenge for clinicians in this regard involves decision making following the detection of renal artery stenosis either by noninvasive testing or at the time of aortography. These issues are discussed in detail in Chapter 47.

Management and Therapy

OPTIMUM TREATMENT

In patients with mesenteric ischemia, collateral flow can come from several vascular distributions, including the iliac arteries, the supraceliac aorta, and the thoracic aorta. Because of the disease's low prevalence, individual series are small and results difficult to compare. After surgical repair, long-term patency is difficult to assess without follow-up angiography. Based on relief of symptoms, surgical approaches are highly successful; symptom-free disease is experienced by 80% to 100% of patients. Because of the limited involvement of the thoracic aorta in atherosclerotic disease, many surgeons prefer that the bypass originate from the thoracic aorta. Graft failures are unusual with this approach in patients followed longitudinally by duplex ultrasonography. Surgical mortality and morbidity rates are also low. Bypass techniques for the renal arteries typically utilize a replacement aortic graft or, for inflow, the splenic or hepatic artery. However, with advances in endovascular therapies, fewer open surgical procedures are being performed on visceral arteries.

AVOIDING TREATMENT ERRORS

The major symptoms associated with superior mesenteric artery and celiac stenosis are postprandial pain and weight loss. If both these symptoms are present, strong consideration should be given to ultrasound or angiographic evaluation, or both.

AORTIC DISSECTIONS

Clinical Presentation

Aortic dissection of the thoracic aorta typically occurs in a younger subset of patients. Patients with aortic dissection typically are very symptomatic, presenting with back pain and uncontrollable hypertension. Management is based largely on the location of disease. The acute and long-term morbidity and mortality rates in patients with ascending aortic arch dissections are very high. Patients presenting with acute aortic regurgitation, cardiac tamponade, and coronary ischemia usually have ascending arch involvement. Fortunately, the majority of thoracic aortic dissections (80%) involve the descending thoracic aorta, have lower acute mortality and morbidity rates, and often do not require surgery.

Management and Therapy

OPTIMUM TREATMENT

Dissections involving the ascending arch require emergent repair to prevent or correct a rupture into the mediastinum or the pericardium and to prevent or correct coronary artery dissection. In many instances (and in virtually all patients with Marfan's disease and dissection of the ascending aorta), replacement of the ascending aortic arch and the aortic valve is necessary, with reimplantation of the coronary arteries from their normal ostia into the aortic graft.

Management of descending dissections has largely been medical, with blood pressure reduction and expectant management of ischemic complications involving the branch vessels (mesenteric, renal, spinal cord, and lower extremities). When malperfusion exists, reperfusion via bypass or endovascular techniques is necessary to reestablish flow. Improvement in endovascular techniques has decreased the use of open surgical treatment. When surgical intervention is required, it is associated with a mortality rate greater than 50%. In general, surgical correction is most successful for treating patients with descending aortic dissection when the major issue is lower extremity ischemia. In this case, the use of extra-anatomic bypasses, such as axillobifemoral or femorofemoral bypasses, is effective and reasonably safe. When necessary, fenestration with or without aortic stent grafts is used to improve hemodynamics. Stent grafts can exclude acute aortic ruptures resulting from dissections. Multimodality treatment including intravascular ultrasonography is critical for accurate assessment and for identifying the best intervention. Promising results with the use of endografts in aortic dissections may lead to the increased use of this approach in the future.

AVOIDING TREATMENT ERRORS

In patients presenting with back pain and severe hypertension, clinicians should obtain a CT angiogram to rule out the possibility of a dissection.

FUTURE DIRECTIONS

As the development of endovascular devices continues, more than 50% of traditional surgical vascular procedures will be replaced with minimally invasive procedures because of patient preference and outcomes. The minimally invasive techniques will include branched devices for aneurysmal disease and drug-eluting stents or other devices such as absorbable stents (analogous to those used in coronary artery disease; see Chapter 15) to inhibit intimal hyperplasia and arrest the aneurysmal disease process in adjacent arteries. Standard surgical management algorithms will center on endovascular therapies with combined open and endovascular treatments for patients with complex problems not amenable to solely endovascular approaches. Until treatment options involve only endovascular percutaneous therapies—with proven long-term success rates comparable to the success rates of surgical treatments—physicians trained to perform both endovascular and surgical treatments are best suited to provide care.

New drugs used in the treatment of cardiovascular disease are described elsewhere in this text, and it is likely that further implementation of preventative strategies will be increasingly important for patients at risk for PVD. In the future, medical treatment may be used to treat smaller aneurysms, stabilize plaques, prevent atherosclerosis, and revascularize ischemic chronic lower extremity ulcers.

EVIDENCE

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This AHRQ review analyzes the evidence in the literature with regard to the use of endovascular aneurysm repair.

An Approach to Children with Suspected Congenital Heart Disease

50

G. William Henry and Frédérique Bailliard

Birth defects occur in approximately 2% of all births. Congenital heart disease comprises almost half of such defects, occurring in approximately 8 in 1000 newborn infants. Many classifications exist for congenital heart disease, and two variations based on a simple physiologic approach follow.

Congenital heart defects can be classified into those that result in cyanosis and those that do not. Acyanotic defects include those with a left-to-right shunt and increased pulmonary blood flow and obstructive defects without associated shunting. Left-to-right shunts occur at various anatomic levels: atrial (e.g., atrial septal defect), ventricular (e.g., ventricular septal defect—part of the complex defect depicted in Fig. 50-1), or arterial (e.g., patent arterial duct). Obstructive lesions without any associated shunts include pulmonary stenosis, aortic stenosis, and coarctation of the aorta.

Cyanotic defects are generally characterized by a right-to-left shunt and may be classified into two broad categories. In the first group, with intracardiac defects and obstruction to pulmonary flow, cyanosis results from decreased pulmonary blood flow and the intracardiac mixing of oxygenated and desaturated blood. In the second group, cyanosis results from the admixture of pulmonary and systemic venous returns despite normal or increased pulmonary blood flow. In most cardiac malformations classified in this group, a single chamber receives the total systemic and pulmonary venous returns. The mixing of oxygenated and desaturated blood can occur at any level: venous (e.g., total anomalous pulmonary venous connection), atrial (e.g., single atrium), ventricular (e.g., single ventricle), and great vessel (e.g., persistent truncus arteriosus). In all these circumstances, near-uniform mixing of the venous returns usually occurs. Complete transposition of the great arteries (Fig. 50-2) can be included in this group, although only partial admixture of the two venous returns occurs, leading to severe hypoxemia.

CLINICAL INDICATIONS FOR MEDICAL OR SURGICAL INTERVENTION

The interdisciplinary approach that is needed clinically to optimally care for children with congenital heart disease includes accurate assessment of anatomic defects and their physiologic consequences and effective communication of these findings. Management of congenital heart disease revolves around manipulating abnormal pulmonary and systemic blood flows. The consequences of altered blood flow induced by congenital heart disease and the effects of therapeutic interventions invariably influence the pulmonary circulation by increasing pulmonary blood flow (e.g., left-to-right shunting through intracardiac septal defects), decreasing pulmonary blood flow (e.g., right-sided obstructive heart lesions, such as tetralogy of Fallot) (Fig. 50-3), altering the pathway of pulmonary blood flow (e.g., Fontan-Kreutzer repair), or altering the hemodynamics to which pulmonary blood flow (e.g., pulmonary hypertension) is subjected. The clinician must be able to manage such conditions in which there is increased pulmonary blood flow or a paucity of pulmonary blood flow and the associated repercussions as to how they relate to the systemic circulation. Obtaining the optimal balance between these two circulations, which are frequently not in series in the case of congenital heart disease, requires the ability to monitor pulmonary hemodynamics and assess pulmonary vascular impairment successfully. Critically important to an understanding of the physiologic consequences of these defects are the maturational differences that occur in cardiopulmonary function during a child's development. For example, cardiac function is subject to maturational changes occurring at the cellular level in a variety of processes, including those in the neurocardiac functional unit: changes in neurotransmitter content, the receptor system, innervation, the effector-transducer systems, and the cellular components that are affected by autonomic stimulation (Fig. 50-4). These changes affect the strategies that can be utilized to successfully manage the sequelae of congenital heart disease.

A second approach to children with suspected congenital heart disease is based on risk stratification. Regardless of the anatomic defects, the physiologic consequences necessitating medical intervention, surgical intervention, or both, fall into three broad categories: heart failure, hypoxemia-hypoxia, and risk of pulmonary vascular disease. Stratifying these risks is useful in predicting prognosis and for therapeutic decision making.

Heart failure is defined as the inability of the heart to supply an adequate cardiac output to meet the aerobic metabolic demands of the body, including those incurred by growth. An alteration in one or more physiologic determinants of ventricular function—preload, afterload, contractility, and heart rate or rhythm—can adversely affect cardiac performance beyond the compensatory mechanisms, particularly in fetuses or newborn infants, where cardiac function occurs much higher (and hence less efficiently) on the Frank-Starling curve because of maturational aspects. As a physiologic consequence, fetuses and infants are more dependent on mechanisms that increase heart rate rather than those that increase stroke volume to increase cardiac output in response to increased metabolic demands. Heart failure occurs in patients with significant left-to-right shunts. By increasing pulmonary blood flow, tachypnea ensues. Concomitantly, a decrease in systemic blood flow results, albeit undetectable by conventional physical examination or blood pressure measurements. Nonetheless, this decrease is sufficient to stimulate the sympathetic nervous system, resulting in an increase in heart rate. Infants with congestive heart failure due to congenital heart disease will invariably be tachypneic and tachycardic without a loss in ventricular function. However, these increases in respiratory and heart rates both increase the body's metabolic

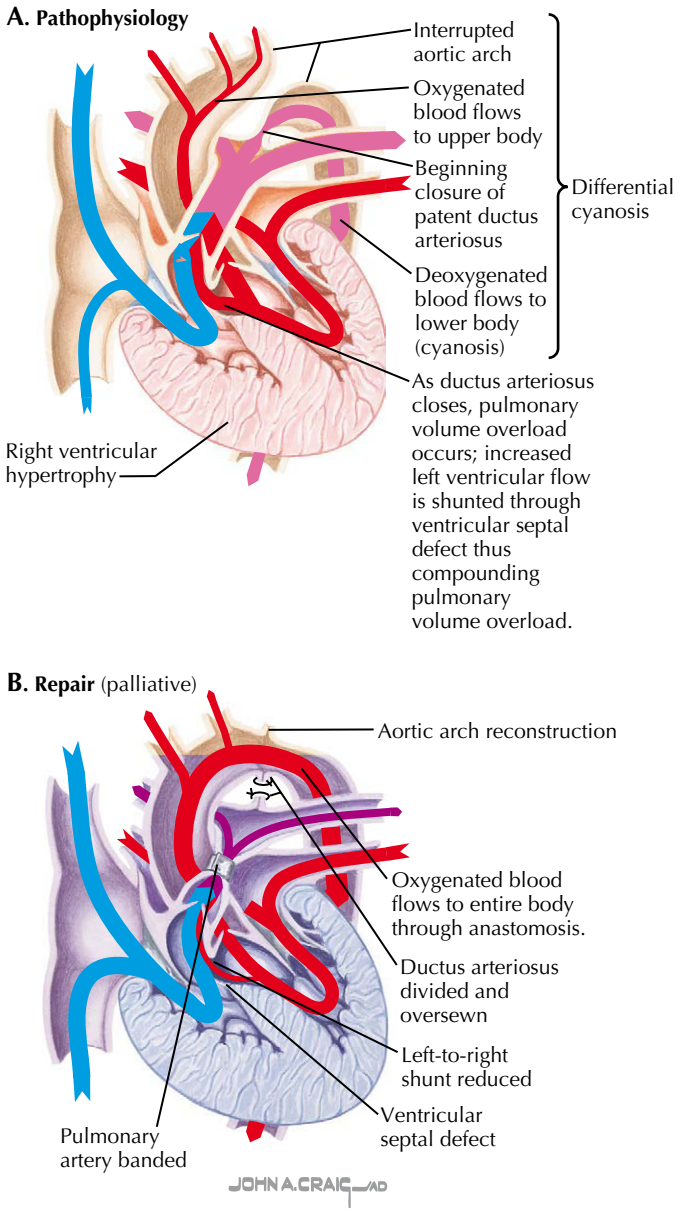


Figure 50-1 *Interrupted aortic arch.* **A**, Pathology. **B**, Surgical technique consisting of aortic arch reconstruction and pulmonary artery banding, demonstrating complex manipulation of hemodynamics, including pulmonary blood flow.

needs. An increased amount of energy, and thus a disproportionate proportion of the energy from caloric intake, is required to maintain these basic metabolic needs, and failure to thrive results. The etiology of hypoxemia (abnormal reduction in the arterial oxygen tension) must be established to determine whether therapeutic intervention is necessary immediately. Hypoxia (inadequate tissue perfusion) is always a medical emergency, because high morbidity and mortality are associated with uncorrected metabolic acidosis. Hypoxemia is most often associated with defects characterized by right-to-left intracardiac shunting in which effective pulmonary blood flow is reduced. Pulmonary blood flow may be entirely dependent on the patency

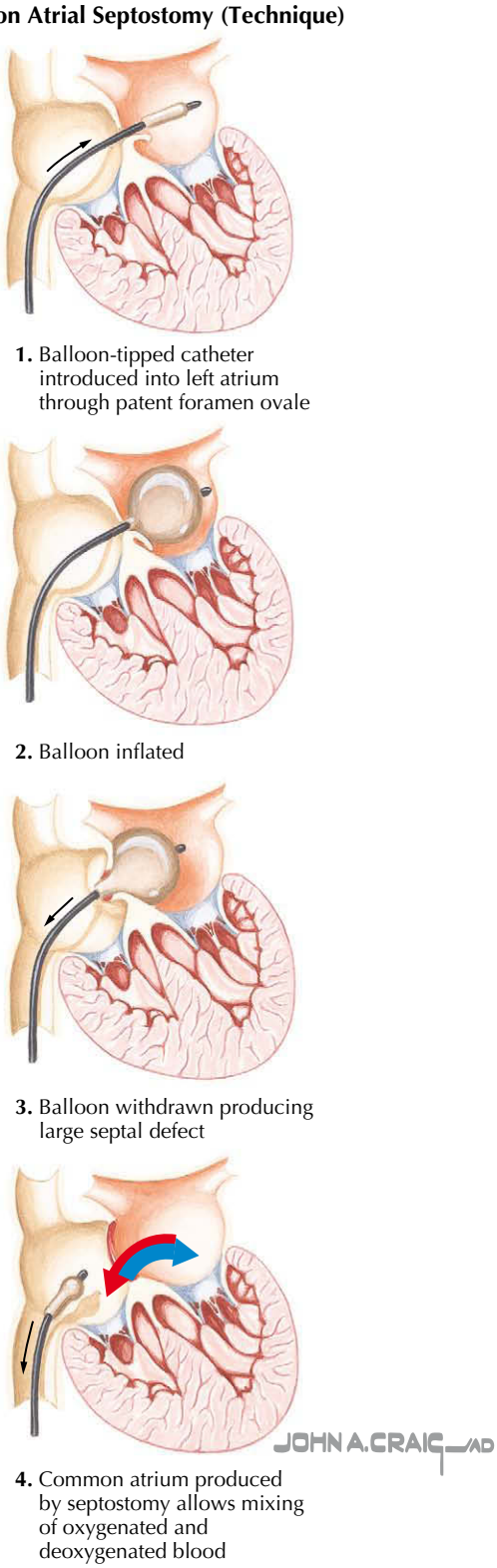


Figure 50-2 *Transposition of the great arteries; technique shown is used to promote venous mixing while awaiting surgical repair.*

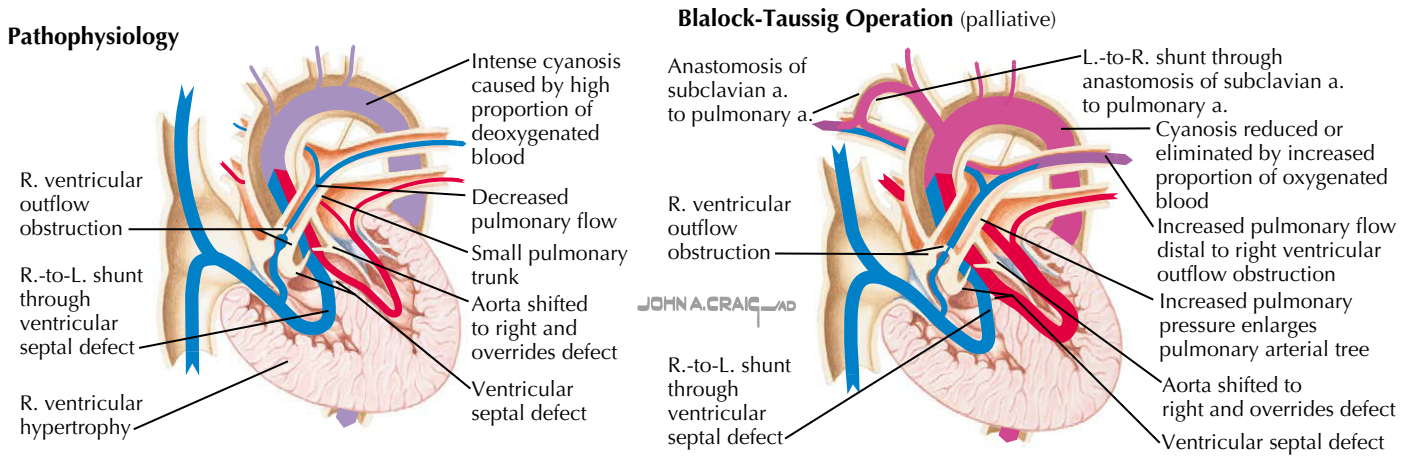


Figure 50-3 *Tetralogy of Fallot.* a, artery.

of the arterial duct. The arterial duct begins to close shortly after birth, at which time the hypoxemic (and hypoxic) consequences of ductal dependency manifest. Since the 1970s, pharmacologic manipulation of the arterial duct to maintain or reestablish patency by constant intravenous infusion of prostaglandin E_1 has dramatically improved the care of affected children by diminishing hypoxia during transport to a center where diagnostic and therapeutic interventions can more safely take place.

Defining the pathophysiology of pulmonary vascular disease remains an important area of research. The primary approaches used today involve therapeutic interventions to eliminate the risk factors for pulmonary vascular disease in all children identified at high risk. Three principal risk factors must be characterized in the assessment of congenital heart disease: increased pulmonary blood flow from left-to-right intracardiac or extracardiac shunting (e.g., septal defect, patent arterial duct, arteriovenous fistula, transposition of the great arteries) (Fig. 50-5); increased pulmonary artery pressure from a downstream increase in pulmonary venous pressure or inherent increased pulmonary vascular resistance; and hyperviscosity as a consequence of hypoxemia from decreased pulmonary blood flow in right-sided obstructive heart lesions (e.g., tetralogy of Fallot, tricuspid atresia, pulmonary atresia) or from inadequate mixing (e.g., transposition of the great arteries).

Increased pulmonary blood flow can occur as a result of independent or obligatory flow, where dependency is defined relative to pulmonary vascular resistance (or impedance). For example, in children with unrestricted ventricular septal defects, the magnitude of the left-to-right shunting, and therefore pulmonary blood flow, depends on the relative difference between pulmonary and systemic vascular resistances (or impedances). As physiologic influences change this relative difference, the ratio of pulmonary to systemic flow changes proportionally. Therefore, this type of shunting depends on the status of the pulmonary vascular bed. In contrast, in children with atrioventricular (AV) septal defects with unrestricted left ventricular (LV) to right atrial shunting via the abnormal left AV valve, a significant difference in the pressures determining this flow (e.g., LV systolic pressure compared with simultaneous right atrial pressure) always exists. Therefore, increased flow occurs across the tricuspid and pulmonary valves, independent of the pulmonary vascular resistance. The magnitude of this left-to-right shunt is modulated more by ventricular function than by systemic and pulmonary vascular resistances.

Decisions on the optimal timing for medical or surgical intervention depend on examining the actuarial consequences of three risk factors for pulmonary vascular disease: increased pulmonary blood flow, pulmonary vascular resistance, and hyperviscosity. Increased pulmonary blood flow alone contributes to the risk of development of pulmonary vascular disease, but the time course for irreversible pulmonary vascular changes is measured in years. Pulmonary hypertension due to increased pulmonary vascular resistance is a more significant risk, with irreversible changes observed in months to 1 or 2 years. Severe hyperviscosity states and pulmonary hypertension in children with cyanotic heart disease contribute to an extremely high risk of irreversible changes as early as 3 months of age. An optimal time for intervention to decrease the risk associated with the natural history can be determined by overlaying the risk of not intervening with the risks for specific medical and surgical interventions in that setting.

The severity of heart failure, hypoxemia, and the risk of irreversible pulmonary vascular disease therefore must be quantified and will determine the appropriate course of medical and surgical management of congenital heart disease.

INITIAL NONINVASIVE ASSESSMENT OF CHILDREN WITH CONGENITAL HEART DISEASE

History

The history is critically important for children with suspected congenital heart disease. Because congenital heart disease is most often diagnosed in early infancy, a chronologic approach is simple but effective. The history of pregnancy, labor, and

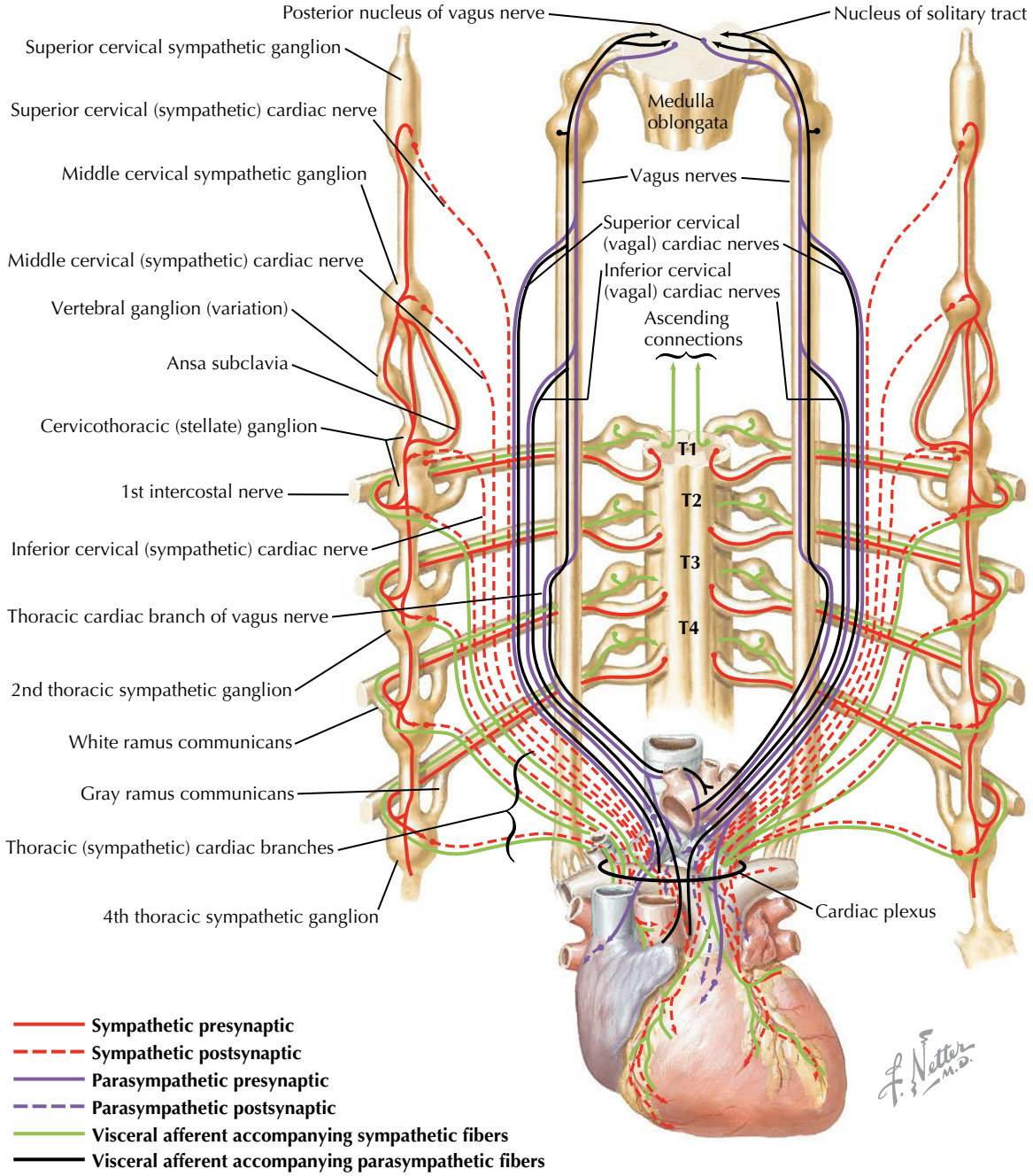


Figure 50-4 *Innervation of heart: Schema.*

delivery is often helpful (e.g., perinatal asphyxia) with age and developmentally appropriate attention to expected activity. For example, inquiry into the feeding history may be disproportionately important in infants, whereas inappropriate fatigue or exercise tolerance may be important in older children. One issue that cannot be overemphasized in the pediatric age group is growth. Growth is a cardiovascular stress, and absence of growth may be the only manifestation of heart failure and therefore of congenital heart disease.

The family history is often benign but may alert the clinician to relevant issues, such as the incidence of and the genetic predisposition to congenital heart disease. Children born with certain genetic syndromes such as trisomy 21 are at much greater risk of having congenital heart disease, and genetic syndromes therefore should compel clinicians to perform a thorough cardiac evaluation. Exposures to certain medications such as lithium have become less prevalent as their association has become known to increase the risk of congenital heart disease, and use has therefore decreased in women of childbearing age. Other exposures such as alcohol and certain infections such as rubella are also worthwhile noting, as these do result in a higher rate of cardiac abnormalities in a fetus.

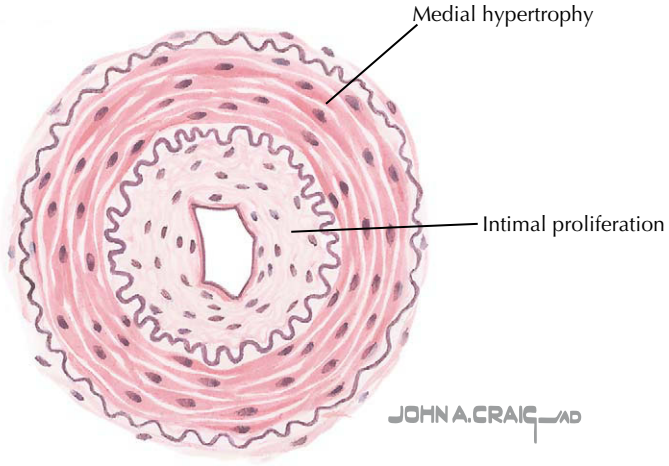


Figure 50-5 *Pulmonary vessel complications of left-to-right shunts.*

Physical Examination

The cardiac examination should begin with a global assessment of the patient's health. This should include a subjective assessment of the child's development, ease of breathing, and color. Cardiac situs (normal positioning of the heart with the point of maximum impulse at the midclavicular line in the fifth intercostal space, dextrocardia, or an intermediate location of the heart) should first be established by means of palpation. Palpation should also serve to determine the cardiac impulse location and strength, which will help determine the ventricular balance of the circulations. The first and second heart sounds must be carefully identified and characterized as single or split. The intensity of the heart sounds should be noted. Murmurs should be characterized by location on the chest, loudness, position in the cardiac cycle, and finally by quality of the sound. Upper and lower extremity pulses should be palpated and compared.

The complete cardiac examination includes lung and abdominal examination. Respiratory effort and rate should be noted. Bilateral breath sounds should be auscultated and compared. The liver and spleen should be palpated for size and firmness.

Children with decreased pulmonary blood flow secondary to congenital heart disease present clinically with cyanosis. Cyanosis necessitates approximately 5 g of circulating deoxygenated hemoglobin. In children with relative anemia, cyanosis may not be as obvious as expected, even in cyanotic congenital heart disease. Despite cyanosis, children with congenital heart disease often seem comfortable, without evidence of respiratory distress—an important distinction to differentiate hypoxemia as a consequence of a parenchymal disorder (leading to a ventilation-perfusion defect of perfused but underventilated portions of the lungs). Children with congenital heart disease who are cyanotic because of obstruction to pulmonary blood flow have alterations in the second heart sound with a diminished or absent pulmonary component resulting from diminished or absent flow across the pulmonary valve.

The physiologic features associated with altered pulmonary artery hemodynamics that are discernible by physical examination can be generally ascribed to features associated with pulmonary hypertension and decreased or increased pulmonary blood flow.

The physical diagnosis of pulmonary hypertension is rarely difficult. The cardiac examination predictably consists of a prominent right ventricular (RV) impulse that is either visible or easily palpable at the lower left sternal border or in the subxiphoid area (when present with normal cardiac situs). On auscultation, a single loud or narrowly split second heart sound with a loud pulmonary component is present. Pulmonary systolic ejection clicks are also common in severe pulmonary hypertension, arising from a dilated, hypertensive, proximal main pulmonary artery. Systolic murmurs at the lower left sternal border consistent with tricuspid insufficiency are sometimes present, although tricuspid insufficiency rarely results in a murmur that can be auscultated. In severe, long-standing pulmonary hypertension, a decrescendo, high-pitched, early diastolic murmur of pulmonary insufficiency may be present along the mid left sternal border. When pulmonary hypertension is accompanied by RV failure, findings of systemic venous engorgement are present, including hepatosplenomegaly and peripheral edema. Abnormal *v* and *a* waves may be found during examination of the neck veins.

Features associated with increased pulmonary artery flow are typically related to auscultatory findings from excessive flow crossing normal heart valves (Fig. 50-6) and pulmonary vascular engorgement. Because the semilunar valves have approximately

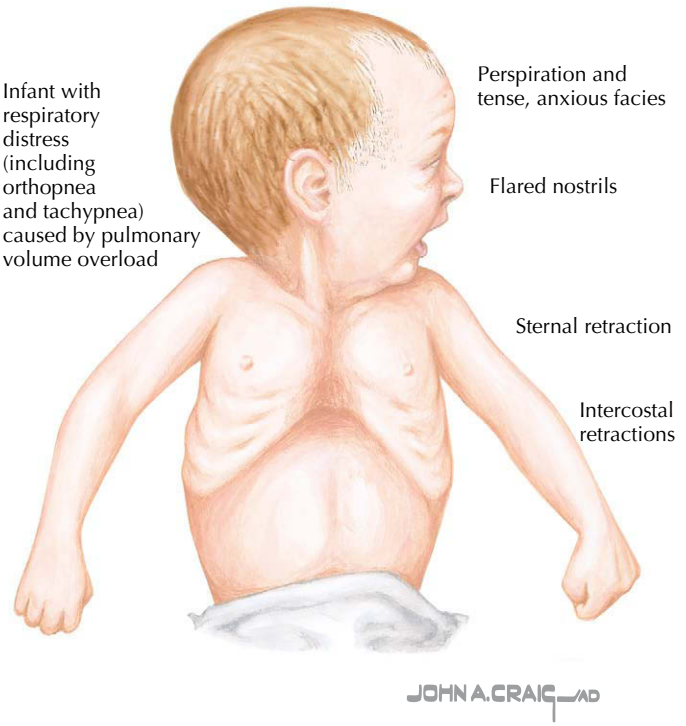


Figure 50-6 *Clinical characteristics of too much pulmonary flow (pulmonary volume overload).*

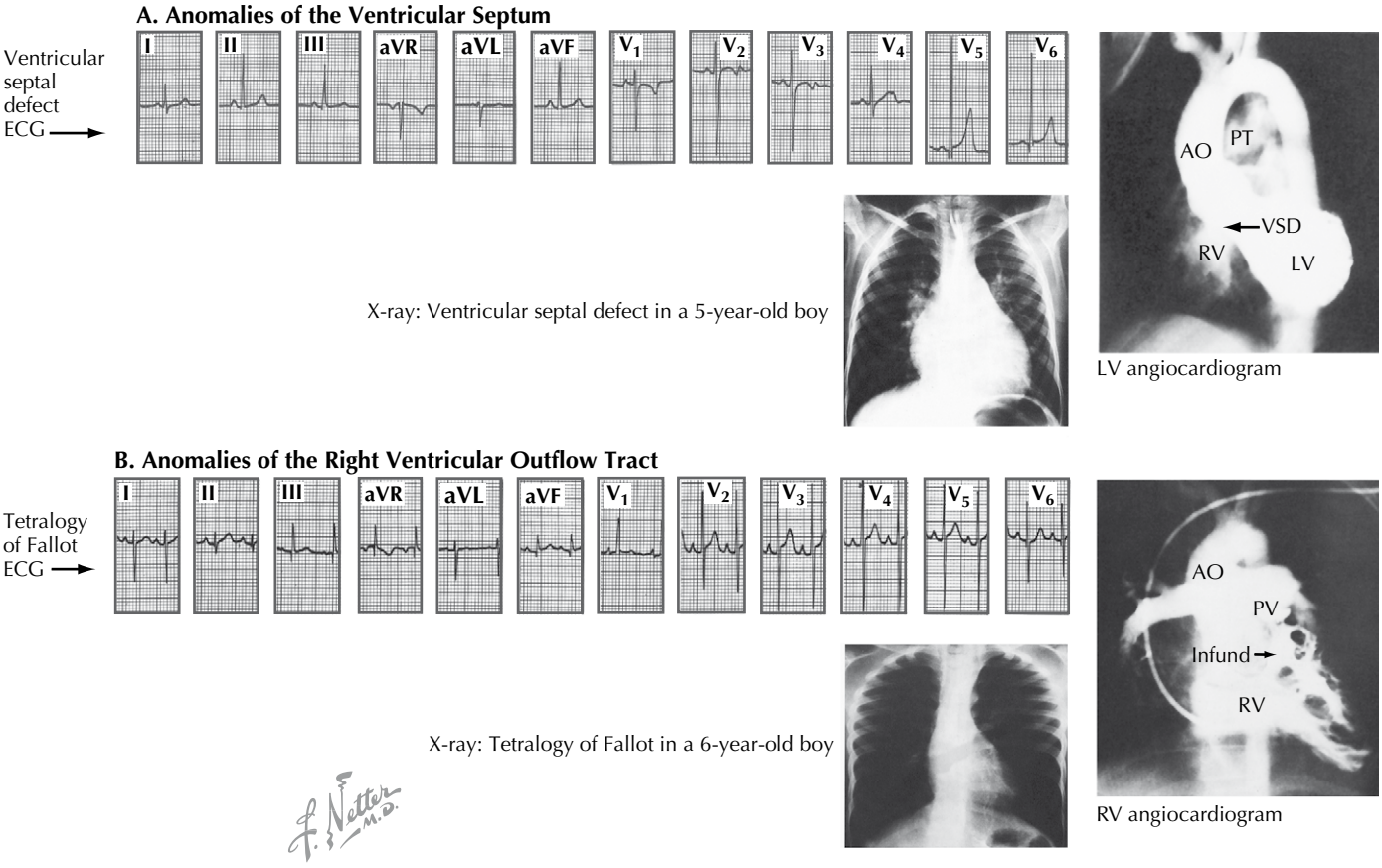


Figure 50-7 *Anomalies of the ventricular septum (**A**) and of the right ventricular outflow tract (**B**).* AO, aorta; ECG, electrocardiogram; Infund, infundibulum; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary valve; RV, right ventricle; VSD, ventricular septal defect.

one half the cross-sectional area of the AV valves, early diastolic murmurs associated with increased flow across the AV valves require more flow than midsystolic flow murmurs associated with flow across the semilunar valves. This point can be a distinguishing feature in quantifying a left-to-right shunt with normal ventricular function, because flow across the AV valves must be approximately doubled to auscultate such diastolic murmurs. Prominent third and fourth heart sounds (a gallop rhythm) may be audible from relatively enlarged ventricles due to recirculation of blood within the pulmonary circuit. Children with excessive pulmonary blood flow will have pulmonary findings of increased respiratory rate and effort. They may exhibit crackles on lung examination.

Despite the most astute clinical efforts, the diagnosis of specific congenital heart defects by means of physical examination is often inadequate. For this reason, the physical examination should be regarded as only an initial screening procedure.

Chest Radiography

Although more sophisticated imaging modalities exist to provide anatomic and physiologic information regarding the pulmonary circulation and the possibility of congenital heart disease, chest radiography is still used routinely as a screening method to determine the status of the pulmonary vasculature, pulmonary parenchyma, and cardiac situs, size, and morphology. Although its role in cardiopulmonary assessment when compared with echocardiography is often challenged, the availability, speed, and usefulness of a screening chest x-ray in providing information about pulmonary features mean that its future as an imaging modality remains secure.

Evaluation of pulmonary hemodynamics by chest radiography includes assessment of pulmonary ventilation and perfusion. Evaluation of perfusion by pulmonary vasculature assessment in chest radiographs is useful to distinguish the pathophysiology of altered pulmonary hemodynamics in children with congenital heart disease. For example, specific diagnostic entities can be considered by evaluating the pulmonary vascularity. Pulmonary vascularity on a posteroanterior chest radiograph can be classified as normal, increased (Fig. 50-7A), decreased (Fig. 50-7B), or abnormally redistributed, and for such classification each lung field must be compared with the other fields. For pulmonary arterial vasculature to be identified as increased by chest radiography, an increase in pulmonary blood flow of approximately 100% is required. This can help in the evaluation of children with left-to-right shunting and correlate physical examination findings. Pulmonary edema presents a distinctive pattern of haziness in the lung fields that warrants immediate

investigation about etiology, because this finding is associated with significantly increased morbidity and mortality.

Diminished pulmonary vasculature typically represents obstruction of blood flow to the lungs and is an ominous radiographic finding in newborns. Central dilation and peripheral pruning of pulmonary arterial vessels are noted in more advanced pulmonary vascular disease and are most often found with evidence for RV hypertrophy as defined by retrosternal filling on the lateral chest radiograph with the cardiac silhouette.

Specific assessment of the size of the main pulmonary artery is possible by means of the chest radiograph. Because the pulmonary artery is thin walled, it dilates readily when exposed to increased flow or pressure. Dilation of the main pulmonary artery is readily visible on the chest radiograph, and differentiating radiographic features are then sought to determine the physiologic etiology. Conversely, a concavity in the mediastinal silhouette may be reflective of a hypoplastic pulmonary artery, as seen in patients with tetralogy of Fallot. Evaluation of lung ventilation by assessment of conducting airways and lung parenchyma, including lobar and lung volumes, provides information about pulmonary physiology.

Evaluation of the cardiac situs and chamber enlargement by cardiac contour evaluation can greatly aid in the assessment of altered pulmonary hemodynamics. Because the right ventricle is affected by altered pulmonary hemodynamics, attention must be given to changes in shape and size. However, chest radiography is less sensitive and specific in defining changes in RV function than is evaluation of the amount of pulmonary perfusion.

Additional noninvasive assessment of children with congenital heart disease includes application of echocardiographic techniques (Chapter 51) and cardiac magnetic resonance imaging (CMR). Less frequently, an invasive approach involving cardiac catheterization is required (Chapter 52).

FUTURE DIRECTIONS

Today the clinical evaluation of children with suspected congenital heart disease focuses on optimizing diagnosis and treatment, and on including fetuses as patients. CMR, the most recent emerging imaging modality, is an important advance in the evaluation of children with congenital heart disease. As a noninvasive tool, CMR provides anatomic and physiologic information that echocardiography and catheterization alone do not provide. New techniques such as CMR-guided interventional catheterization procedures are being performed and have in many cases made traditional open heart surgery procedures unnecessary. In the future, the clinical focus will also include the prevention of congenital heart disease through a more complete understanding of the influence of cardiac development. Completion of the mapping phase of the human genome has resulted in accelerated investigations into the control and modulation of gene expression in the development of the human heart. This expanded understanding of cardiac development may allow interventions to augment specific structural and functional deficiencies and to prevent maldevelopment of the human heart.

ADDITIONAL RESOURCES

American Heart Association [home page on the Internet]. Available at: <http://www.americanheart.org/>; Accessed 17.02.10.

Official website of the American Heart Association. Has a useful section for physicians and parents devoted to cardiovascular issues affecting children.

Anderson RH, Baker EJ, Penny D, Redington A, et al, eds. *Paediatric Cardiology.* 3rd ed. London: Churchill Livingstone; 2009.

A comprehensive textbook of congenital heart disease that incorporates the international contributions to the standard of care.

Cardiology in the Young, Cambridge: Cambridge University Press.

Cardiology in the Young is a journal devoted to cardiovascular issues affecting the young and the older patient suffering the sequels of congenital heart disease or other cardiac diseases acquired in childhood. By design, it is international and multidisciplinary in its approach.

Rudolph AM. *Congenital Diseases of the Heart: Clinical-Physiological Considerations.* Hoboken, NJ: Wiley-Blackwell, 2001.

Classic reference initially published in 1974 that emphasizes the transitional changes in physiology from the fetal to postnatal states.

EVIDENCE

Bailliard F, Hughes ML, Taylor AM. Introduction to cardiac imaging in infants and children: techniques, potential, and role in the imaging work-up of various cardiac malformations and other pediatric heart conditions. *Eur J Radiol.* 2008;68:191–198.

Provides an overview of an important and expanding imaging modality for both morphologic and physiologic characterization of the patient with congenital heart disease.

Ha B, Henry W, Lucas C, et al. Pulmonary artery blood flow and hemodynamics. In: Howe TC, ed. *Advances in Hemodynamics and Hemorheology*. Vol 1. Greenwich, CT: Jai Press; 1996:230–324.

Provides an essential discussion regarding the geometric maturational changes and the derivative effects on physiology.

Hoffman JIE. Incidence, mortality and natural history. In: Anderson RH, Baker EJ, Macartney FJ, et al, eds. *Paediatric Cardiology.* 2nd ed. London: Churchill Livingstone; 2002:111–139.

An insightful overview of the relevant history of the natural history of congenital heart disease, an area of surprising paucity of longitudinal data.

Long WA, Henry GW, Llanos AJ. Autonomic and central neuroregulation of fetal cardiovascular function. In: Polin RA, Fox WW, eds. *Fetal and Neonatal Physiology.* 2nd ed. Philadelphia: WB Saunders; 1998: 943–961.

This chapter provides an overview of maturational changes that serve as the predicate for physiologic changes expressed in the transitional circulation from the fetal to postnatal state.

Echocardiography in Congenital Heart Disease

51

John L. Cotton

Multipleplane cardiac imaging by echocardiography can noninvasively define the anatomy of the heart and great vessels by delineating the cardiac structures' configuration, positioning, and spatial interrelations. The information obtained can be used to accurately diagnose and determine prognosis in complex congenital heart disease. With advances in pulsed and color Doppler echocardiography and improvements in the size and capabilities of transducers and other imaging equipment, pediatric echocardiography has gained rapid acceptance. In many pediatric cardiac tertiary care centers, echocardiography is the only diagnostic test performed before neonatal congenital heart surgery. The technology allows real-time three-dimensional (3D) imaging, assessment of myocardial function, and precise definition of cardiac anatomy from the fetal stage through adulthood. For these reasons, echocardiography has become the standard noninvasive diagnostic imaging modality for pediatric cardiology.

Transthoracic multiplane imaging by two-dimensional (2D) echocardiography defines the anatomy of the heart and great vessels. Analysis of each cardiac segment allows complete definition of the configuration, position, and spatial interrelations of cardiac structures. Because tortuous vessels may be difficult to define by a "slice" technology such as echocardiography or MRI, color flow Doppler echocardiography is customarily used to provide a map of blood velocity and direction that complements the 2D image. Small septal defects and fistulous connections may be recognized only by perturbations in blood flow when the anomaly is too small to be visualized clearly. Pulsed and continuous-wave Doppler echocardiography provide excellent time resolution that allows precise quantification of blood velocity. Positional and velocity information can be combined to assess the presence and severity of a valvular obstruction or insufficiency, the position and size of jets associated with septal defects, and abnormal flow in larger vessels in congenital lesions such as anomalous systemic and pulmonary venous return, coarctation of the aorta, and patent ductus arteriosus.

Transesophageal echocardiography (TEE) allows imaging planes different from those obtained in a standard transthoracic study as well as improved visualization of cardiac structures that are difficult to image by transthoracic echocardiography (TTE). Miniaturization of transducer components now allows TEE to be performed in infants as small as 2.5 kg. Posteriorly located cardiac structures are often not well visualized by TTE but are almost always well visualized by TEE. In the older child or a child in whom there are poor transthoracic windows, TEE can also be useful in evaluating congenital heart disease. During cardiac surgery, it may be important to address specific issues by TEE such as anomalous pulmonary venous return, pulmonary vein stenosis, or atrial baffle flows. In addition, an immediate intraoperative or postoperative assessment of the adequacy of surgical repair is possible. While these targeted perioperative examinations do not substitute for a complete preoperative transthoracic evaluation, the availability of TEE has been of great importance in the surgical correction of complex congenital heart disease.

Fetal echocardiography is the newest frontier in pediatric echocardiographic imaging. With the use of transvaginal transducers, detailed fetal cardiac anatomy can be seen as early as 12 weeks of gestation. Transabdominal imaging can be performed by 16 weeks' gestation, although the optimal time for fetal echocardiography is 18 to 24 weeks. Abnormalities detected then may be important in decisions for further imaging, chromosomal testing, or even pregnancy termination. As with TTE of infants, fetal echocardiography can identify intracardiac anatomy, blood flow across all heart valves, size and orientation of the great vessels, cardiac function, and cardiac rhythm. The order and the windows used in a fetal echocardiogram depend on the fetus' position, size, and motion, and the amount of fluid in the uterus.

TRANSTHORACIC IMAGING IN PEDIATRICS

Each pediatric echocardiography laboratory has specific protocols for acquiring a complete study of cardiac anatomy in children. Because patient cooperation is needed, all images may not be obtained using standardized imaging planes in young children and infants. Some centers use conscious sedation for patients under a certain age to ensure uniformity of studies. Another option is "video sedation": child-friendly videos played to distract the patient and allow time to obtain diagnostic images. As long as clear pictures are obtainable, scanning can be performed with the patient sitting in a parent's lap, feeding, or even in a stroller. This approach substantially decreases the number of patients who must be sedated.

The protocol for a complete study includes views from the four major echocardiographic windows: parasternal, apical, subxiphoid, and suprasternal. Each window provides the image of the heart from a different angle, allowing multiple, corroborating views of the same structures. The image from each window begins from a standard reference view; then a sweep of the heart is made, first with 2D scanning and then with color Doppler. The color Doppler mapping defines the location for pulsed Doppler scanning in each plane. Once pertinent information is obtained, the transducer is rotated 90 degrees to perform an orthogonal sweep. The sonographer and the interpreting physician can reconstruct multiple 2D images into a 3D representation of cardiac anatomy.

Cardiac function and blood flow are calculated from Doppler mapping and from the 2D images. For example, pulmonary and aortic flow are calculated from the mean velocity and diameter of the vessel at the area of interest as follows:

$$\text{Blood flow} = (\text{mean flow velocity}) \times (\text{time}) \times (\text{cross-sectional area of vessel})$$

Peak instantaneous gradients are calculated from a simplified Bernoulli equation, using peak flow velocity within the stenotic jet in the following formula, where V is the peak flow velocity measured by spectral Doppler scanning:

$$\text{Peak pressure gradient} = 4V^2$$

This gradient is used to estimate pressures in the different cardiac chambers. Several different methods can be used to quantify left ventricular (LV) function. LV fractional shortening (FS) is a measurement of the percentage of change in LV diameter:

$$\text{FS} = (\text{LV end-diastolic dimension} - \text{LV end-systolic dimension})/(\text{LV end-diastolic dimension})$$

Ejection fraction is similarly calculated, using measured LV volumes.

Echocardiographic examinations are described below for some common congenital heart lesions, with emphasis on information needed to plan surgical intervention and the best techniques to obtain this information.

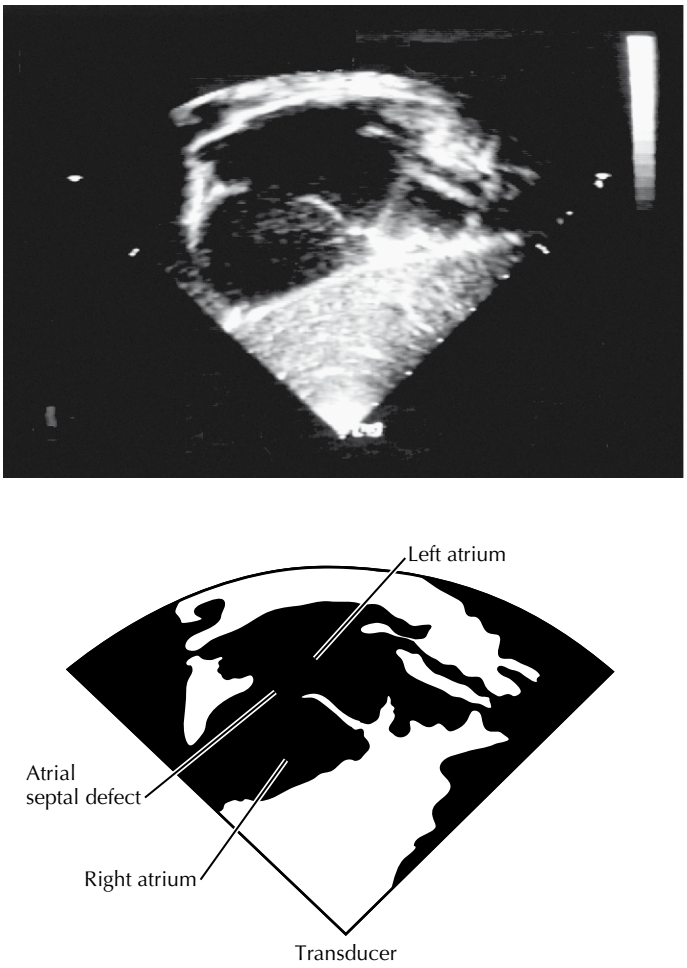


Figure 51-1 *Atrial septal defect.*

ATRIAL SEPTAL DEFECT

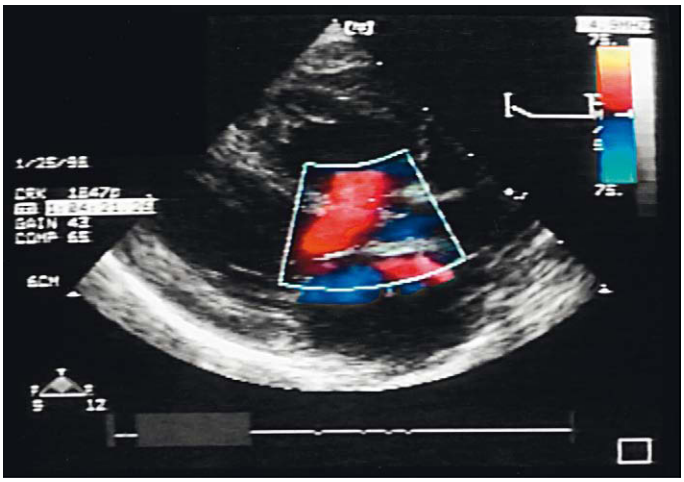
TTE is often sufficient to define the size and location of an atrial septal defect (Fig. 51-1). Pulsed and color Doppler echocardiography identify the direction and amount of shunting at the atrial level. Other findings can confirm the presence of a hemodynamically significant shunt. For instance, right ventricular (RV) volume overload can produce diastolic bowing of the ventricular septum to the left during diastole, with the left ventricle assuming an elliptical shape. Partial anomalous pulmonary veins can be identified by 2D echocardiography and color Doppler, and can be corrected at the time of surgery. Echocardiography is usually sufficient to define the anatomy of the atrial septum and pulmonary veins in infants and small children. For older children and adults, TTE may be needed for full anatomic definition. Cardiac catheterization is not usually needed to evaluate atrial septal defects.

VENTRICULAR SEPTAL DEFECT

Multiple views are needed to visualize the entire interventricular septum. TTE with 2D imaging usually demonstrates the size and location of the interventricular communications. Color Doppler can be used to determine the direction of shunting across the ventricular septal defect (VSD) (Fig. 51-2). By measuring the direction and velocity of flow across the defect with pulsed and continuous-wave Doppler, the pressure gradient across the defect can be determined. Cardiac catheterization is not required before surgery unless the physical and noninvasive findings are atypical or contradictory.

ATRIOVENTRICULAR SEPTAL DEFECT

Echocardiography is also an important tool for the preoperative assessment of atrioventricular septal defects (AVSDs) (Fig. 51-3). 2D imaging defines atrioventricular (AV) valve morphology. If the superior bridging leaflet is divided and has attachments to the crest of the ventricular septum, it is considered a type A valve. Straddling of central superior bridging leaflet attachments to a papillary muscle in the right ventricle defines a type B valve. If the superior bridging leaflet has no attachments to the crest of the interventricular septum and the valve leaflet is free-floating, it is considered a type C valve. Superior bridging leaflet septal attachments can obstruct the ventricular portion of the defect restricting shunting across the LV outflow tract—either of which can obstruct aortic blood flow. Anterolateral papillary muscle insertions tend to be rotated counterclockwise in AVSDs and sit much closer to the posteromedial papillary muscle, which may create a "parachute"-like deformity of the AV valve's left portion. This can be easily defined by echocardiography. Any significant length of suturing of the superior and



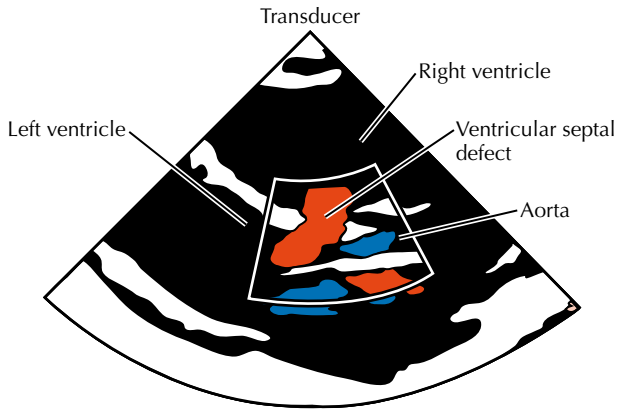


Figure 51-2 *Ventricular septal defect.*

inferior leaflets during surgical repair risks creating LV inflow obstruction. In the intermediate form of AVSD, it is not uncommon to find shortened and immobile leaflets with thick, chordal attachments that limit the ability to surgically fashion a functioning AV valve. Echocardiographic findings can sometimes anticipate this insufficiency of valvular tissue.

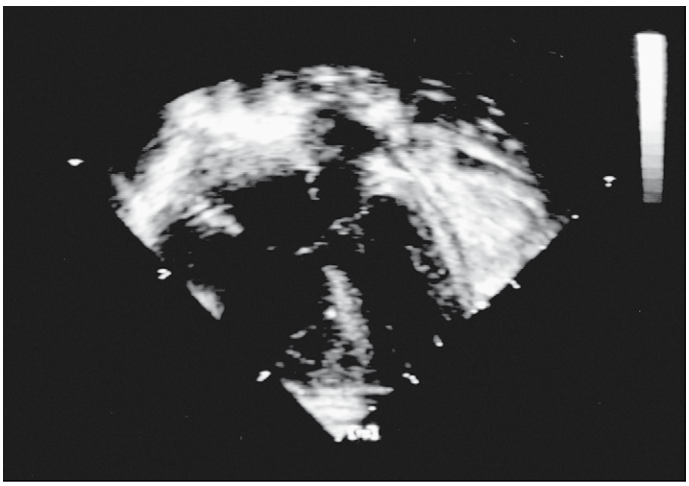
Color, continuous-wave, and pulsed Doppler echocardiography assess potential gradients across the outflow tracts and show the direction of shunting across the septal defect. Color Doppler interrogation of the AV valve usually reveals some degree of insufficiency. A double-orifice mitral valve, present in about 5% of AVSDs, can be identified by echocardiography. The usual ostium primum atrial septal defect is also well visualized with 2D echocardiography. The VSD component of AVSDs is usually single and in the inlet position; however, multiple defects can be ruled out with close color Doppler interrogation of the septum.

COARCTATION OF THE AORTA

Echocardiography can be valuable in diagnosing coarctation of the aorta (Fig. 51-4). The characteristic aortic narrowing with a "posterior ledge" can be identified with 2D imaging but may be difficult to appreciate if patent ductus arteriosus is present. Spectral Doppler scanning may reveal a high-velocity jet at the coarctation site. At the distal transverse arch, antegrade diastolic flow can be seen. Damped pulsatile flow is seen in the thoracic aorta. Often some hypoplasia of the distal transverse aortic arch exists. 2D echocardiography can usually distinguish coarctation of the aorta from interrupted aortic arch, but angiography may be necessary if the findings are ambiguous. It is also important to evaluate the patient for other anomalies that commonly present with coarctation of the aorta including VSDs, bicuspid aortic valve, mitral valve abnormalities, and subaortic obstruction.

TRANSPOSITION OF THE GREAT ARTERIES

Echocardiography can provide a definitive diagnosis of transposition of the great arteries by demonstrating the origin of the aorta from the right ventricle and the pulmonary artery from the left ventricle. Cross-sectional imaging can determine the presence and size of any atrial or ventricular communications. Echocardiography can often define the origins of the coronary arteries, but considerable experience is needed to confidently



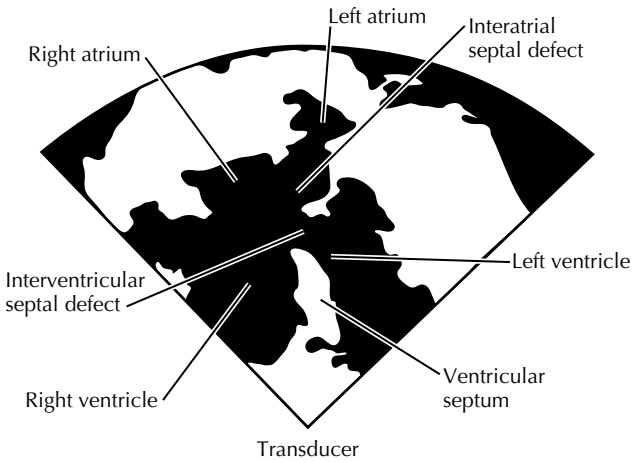
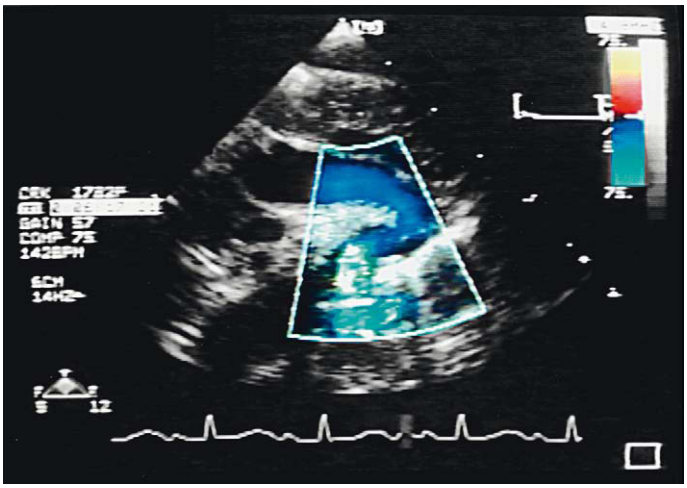


Figure 51-3 *Atrioventricular septal defect.*



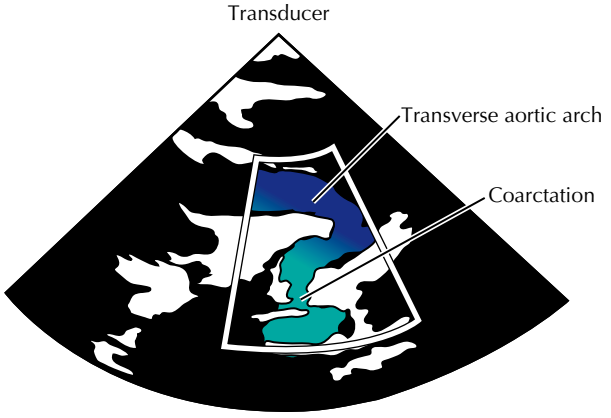


Figure 51-4 *Coarctation of the aorta.*

assess more distal branching patterns. Pulsed and color flow Doppler will identify a patent ductus arteriosus and delineate the magnitude of shunting at the atrial and ventricular levels. Ventricular mass and volumes can be quantified with both 2D and M-mode echocardiography. The shape of the interventricular septum in systole indicates the differential pressures between the right and left ventricles, because the septum bows toward the chamber with the least wall stress. In addition, the LV outflow tract can be interrogated with pulsed and color flow Doppler for signs of obstruction.

TETRALOGY OF FALLOT

Diagnosis of tetralogy of Fallot requires delineation of the structures listed in Box 51-1. Because most of these structures are well visualized with echocardiography, many infants do not need catheterization before repair of tetralogy of Fallot with a patent main pulmonary artery and continuity between the branches (Fig. 51-5). The RV outflow tract is usually well visualized in a combination of different echocardiographic planes. The diameters of the pulmonary valve annulus and proximal pulmonary arteries are measured from parasternal, subxiphoid, and suprasternal views. Careful interrogation of the ventricular septum using both color flow and pulsed Doppler techniques can reveal any additional septal defects, which are seen most often in patients younger than 1 year of age. Both the origins and proximal branches of the right and left coronary arteries must be visualized, because the origin of the left anterior descending coronary from the right coronary artery and the presence of a prominent conal branch are infrequent associations that may significantly influence the surgical management of RV outflow tract in patients who require a transannular patch. Patients with tetralogy of Fallot have an increased incidence of a right aortic arch that can be clearly demonstrated by a combination of plain chest radiography and TTE. Knowledge of this anomaly is critical before a staged shunt operation is considered.

PULMONARY ATRESIA

When an initial echocardiographic examination determines that pulmonary atresia with an intact ventricular septum is present (Fig. 51-6), it is essential to define the level of RV outflow tract obstruction and RV morphology, including the inlet, outlet, and trabecular components. The nature of the interatrial communication must be known to rule out existing or potential restriction to essential right-to-left shunting. Subxiphoid views of the interatrial septum demonstrate the size and position of the foramen ovale or septal defect. The flow dynamics across the atrial septum can be further defined by color flow and pulsed-wave Doppler. Nonpulsatile flow with a velocity in the range of 2 m/sec is strongly suggestive of obstructive atrial communication, especially if the patient has hepatomegaly and evidence of a low-output state.

TOTAL ANOMALOUS PULMONARY VENOUS RETURN

2D echocardiography will accurately delineate pulmonary venous anatomy in circumstances in which total or partial anomalous pulmonary venous return is present. Color and pulsed Doppler examinations are necessary to confirm any venous obstruction. Turbulent, nonpulsatile venous flow with a velocity of at least 2 m/sec signifies hemodynamically significant obstruction. The intracardiac anatomy should also be assessed by echocardiography, because other significant congenital lesions occur in approximately 30% of patients with total anomalous pulmonary venous return, including patent ductus arteriosus, atrial isomerism, VSD, single ventricle, transposition of the great arteries, and systemic venous anomalies. Total anomalous pulmonary venous return is strongly associated with complex congenital heart disease and heterotaxy syndrome.

Box 51-1 Diagnosis of Tetralogy of Fallot

- Levels and severity of RV outflow tract obstruction
- Pulmonary valve annulus size
- Main and branch pulmonary artery size
- VSD (single vs. multiple)
- Origin of the left anterior descending coronary artery
- Aortopulmonary collaterals
- Aortic arch anatomy

RV, right ventricular; VSD, ventricular septal defect.

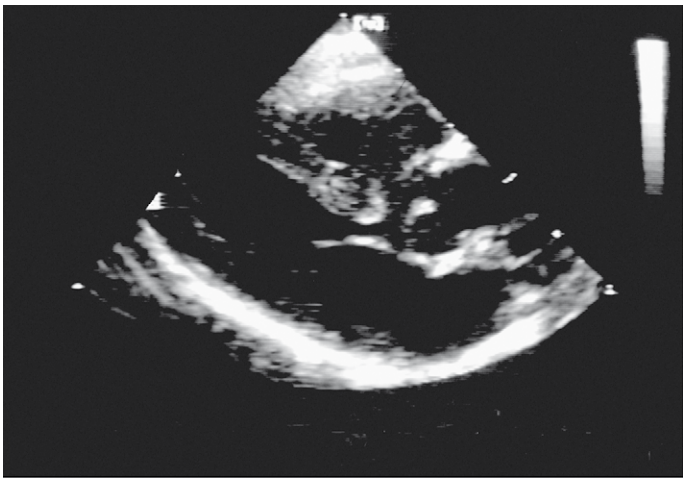


Figure 51-5 *Tetralogy of Fallot.*

SINGLE VENTRICLE

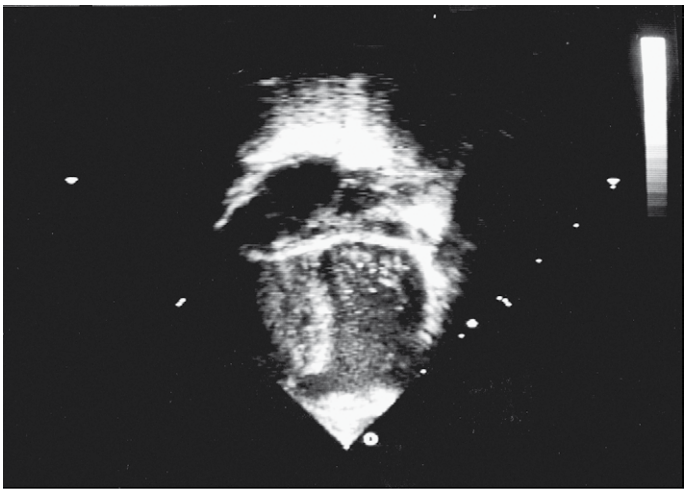
Echocardiography is a powerful tool in defining anatomy of the univentricular heart (Fig. 51-7). Both interatrial and interventricular communications are measured and obstructions noted with color-directed pulsed Doppler. If an outflow chamber (hypoplastic ventricle) is found to communicate with a dominant ventricle via a bulboventricular foramen (VSD), the dimensions of interventricular communication must be obtained with two orthogonal views. With these dimensions, a prediction can be made about whether the connection may become obstructive. Doppler examination of the subarterial outflow can detect even mild obstruction by increased blood flow velocity. When the aorta arises from the hypoplastic chamber, detection of even mild obstruction is particularly important because of the danger that subaortic obstruction will develop. Hence, serial studies are necessary, particularly following interventions that reduce ventricular preload or afterload (including medication use or surgical procedures).

AV valve anatomy is most clearly defined by echocardiographic imaging, and any stenosis or regurgitation should be quantified via color and pulsed Doppler flow imaging. In patients with a pulmonary artery band, echocardiography can evaluate the band position, morphology of the proximal pulmonary artery branches, and gradients at either level.

Ventricular function can be estimated using echocardiography, but the accuracy of echocardiography in this circumstance may be limited by nonuniform ventricular geometry, particularly in patients with a single morphologic right ventricle. Because of large differences in preload and afterload in patients with a single ventricle, measures of contractility that are less load-independent, such as the velocity of circumferential fiber shortening, are of greater value than a simple ejection fraction. However, even these indices are not reliable with subaortic obstruction or when the ventricular geometry does not conform to a prolate ellipsoid, and alternate means for assessing ventricular function (MRI or radionuclide ventriculography) are sometimes needed. A reliable means for assessing ventricular function serially is needed to optimally time the stages of surgical correction and/or palliation.

FUTURE DIRECTIONS

Refinements in pediatric echocardiographic techniques produce a highly accurate picture of the anatomy and evolving physiology of congenital cardiac lesions. For many straightforward lesions, invasive studies may be eliminated entirely. Even for complex lesions requiring cardiac catheterization, advances in



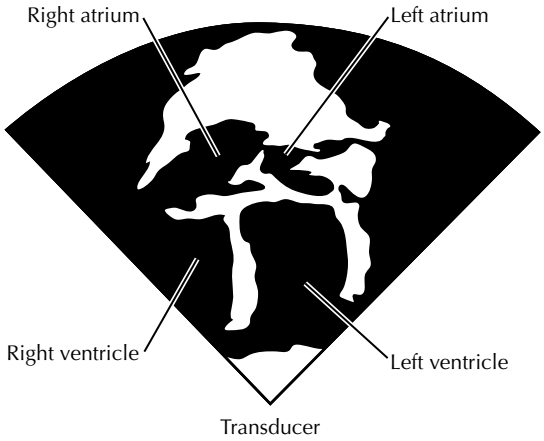


Figure 51-6 *Pulmonary atresia.*

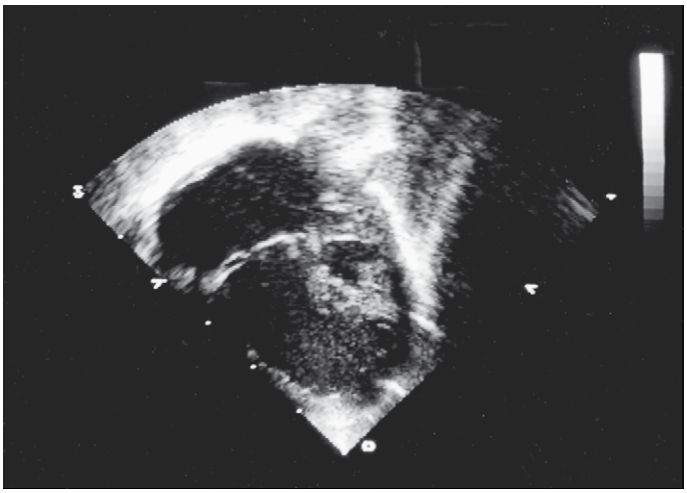


Figure 51-7 *Hypoplastic left heart.*

echocardiography have reduced the number of cardiac catheterizations needed in a patient's lifetime. As technology has evolved, the future direction of pediatric echocardiography has shifted toward 3D imaging and evaluation of myocardial performance. Real-time 3D imaging allows visualization of complex cardiac anatomy, removing the limitations of standard imageing planes. It is becoming an important tool in quantitative assessment of ventricular function. Other new techniques including Doppler tissue imaging, integrated backscatter analysis, and myocardial speckle tracking are being developed as monitoring tools for serial assessment of myocardial function. These advances are expanding the uses of pediatric echocardiography and are closely interrelated with the evolution of cardiac surgery toward the repair of increasingly complex lesions at increasingly younger ages.

ADDITIONAL RESOURCES

American College of Cardiology [home page on the Internet]. Available at: <http://www.acc.org>; Accessed 16.02.10.

An organization dedicated to quality cardiovascular care. Includes patient education, research promotion, and development and application of standards and guidelines for adult and pediatric cardiac care.

American Society of Echocardiography [home page on the Internet]. Available at: <http://www.asecho.org>; Accessed 16.02.10.

An organization committed to excellence in cardiovascular ultrasound and its application to patient care. Multiple guidelines for utilization of echocardiography are included.

Lai W, Geva T, Shirali GS, et al. Guidelines and Standards for Performance of a Pediatric Echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2006;19:1413–1430.

Describes indications for pediatric TTE; defines optimal instrumentation and laboratory setup for pediatric echocardiographic examinations; establishes an examination protocol that defines necessary echocardiographic windows and views and a baseline list of recommended measurements to be performed in a complete pediatric echocardiogram; and discusses reporting requirements and formatting of pediatric reports.

EVIDENCE

George B, Disessa TG, Williams RG, et al. Coarctation repair without catheterization in infants. *Am Heart J.* 1987;114:1421–1425.

Showed that coarctation of the aorta and associated lesions can be diagnosed accurately by 2D echocardiography, permitting proper patient management without the risk of cardiac catheterization.

Leung MP, Mok CK, Hui PW. Echocardiographic assessment of neonates with pulmonary atresia and intact ventricular septum. *J Am Coll Cardiol.* 1988;12:719–725.

In this prospective study, neonates with pulmonary atresia and intact ventricular septum underwent detailed 2D echocardiographic examination before cardiac catheterization. The results suggest that in neonates with pulmonary atresia and intact ventricular septum, preoperative evaluation by echocardiography is usually sufficient for management, and cardiac catheterization should be reserved for selected cases.

Pasquini L, Sanders SP, Parness IA, Colan SD. Diagnosis of coronary artery anatomy by two-dimensional echocardiography in patients with transposition of the great arteries. *Circulation.* 1987;75:557–564.

Showed that echocardiography seemed highly reliable for determining proximal coronary artery anatomy in patients with transposition of the great arteries before cardiac surgery.

Santoro G, Marino B, Di Carlo D, et al. Echocardiographically guided repair of tetralogy of Fallot. *Am J Cardiol.* 1994;73:808–811.

Compared patient outcomes after repair of tetralogy of Fallot with echocardiography alone versus those who underwent cardiac catheterization. Concluded echocardiography evaluation alone was adequate for patients with uncomplicated forms of tetralogy of Fallot for primary repair.

Tworetzky W, McElhinney DB, Brook MM, et al. Echocardiographic diagnosis alone for the complete repair of major congenital heart defects. *J Am Coll Cardiol.* 1999;33:228–233.

Showed that echocardiography alone is an accurate tool for preoperative diagnosis of most major congenital heart defects in children undergoing primary complete repair and may obviate the need for routine catheterization.

Zellers TM, Zehr R, Weinstein E, et al. Two-dimensional and Doppler echocardiography alone can adequately define preoperative anatomy and hemodynamic status before repair of complete atrioventricular septal defect in infants <1 year old. *J Am Coll Cardiol.* 1994;24:1565–1570.

Assessed the ability of echocardiography, without cardiac catheterization, to evaluate infants younger than 1 year of age for complete open-heart repair of complete balanced atrioventricular septal defect. Concluded that these patients can safely undergo surgical correction of this defect on the basis of echocardiographic-Doppler data alone.

Catheter-based Treatment of Congenital Heart Disease

52

Elman G. Frantz

The goals and techniques of cardiac catheterization for patients with congenital heart disease have evolved rapidly. Catheter-based interventional procedures have become increasingly routine, and as noninvasive imaging techniques have improved, these procedures are now performed more frequently than invasive, catheter-based diagnostic procedures. Sometimes interventional procedures are complementary to surgery, eliminating the need for early operation in a growing child or the need for reoperation after primary surgical correction. Increasingly, however, these catheter-based treatments are replacing open-chest surgical procedures, reducing length of hospitalization, cost, and patient discomfort.

BALLOON ATRIAL SEPTOSTOMY

The procedure described by Rashkind remains the basis of balloon atrial septostomy as it is performed today, albeit with advances in imaging and catheter design. A large balloon is passed transvenously across the foramen ovale and pulled forcefully across the atrial septum, tearing the thin tissue in the floor of the oval fossa and thereby creating a larger atrial septal defect (ASD) and improving intracardiac mixing and systemic oxygen delivery (Fig. 52-1). Although prostaglandin and early surgery have reduced the need for balloon atrial septostomy in many infants, it remains a lifesaving palliative procedure for some. Indeed, today balloon atrial septostomy is routinely safely and effectively performed at the bedside under echocardiographic guidance.

BALLOON VALVULOPLASTY

Pulmonary Stenosis

Balloon pulmonary valvuloplasty has become the standard of care for pulmonary stenosis. This procedure is indicated for symptomatic infants and for older children with systolic pressure gradients exceeding 30 mm Hg. After hemodynamics and angiography, an end-hole catheter and wire are placed transvenously across the stenotic valve. A balloon catheter with a diameter 20% to 40% greater than the diameter of the valve annulus is inflated until a "waist" is seen to disappear (Fig. 52-2). Balloon pulmonary valvuloplasty provides similar relief of right ventricular outflow tract obstruction, produces less pulmonary valve insufficiency, has a lower rate of complications when compared to surgery, and is a more comfortable and better tolerated outpatient procedure for the patient. In the neonate with critical pulmonary stenosis, balloon valvuloplasty is more technically challenging and the complication rate is slightly higher, but definitive results are achieved in most patients. The long-term outcome is excellent except occasionally in patients with dysplastic pulmonary valves or in neonates with a hypoplastic valve annulus. The procedure can also be applied in patients with pulmonary atresia with an intact ventricular septum after initial perforation of the atretic valve.

Aortic Stenosis

Balloon aortic valvuloplasty is considered the initial treatment of choice for congenital aortic stenosis, albeit a palliative procedure that most commonly will have to be followed by a subsequent intervention at an older age. Symptomatic infants with critical aortic stenosis and older children with congenital aortic stenosis and peak systolic pressure gradients exceeding 60 mm Hg are candidates for intervention. The valve is usually crossed retrograde, and an exchange wire is looped in the left ventricular apex. A balloon catheter with a diameter 90% to 100% of the diameter of the valve annulus is inflated several times to abolish the waist formed by the valve on the balloon (Fig. 52-3). Reductions of 50% to 70% of the initial pressure gradient are typical. Many patients require repeat intervention within 5 to 10 years of undergoing the procedure. Fewer than half will require surgical aortic valve replacement after 10 years of follow-up. Catheter and surgical intervention are equally effective in relieving the obstruction with a similar incidence of important aortic insufficiency, repeat intervention, valve replacement, and mortality.

BALLOON ANGIOPLASTY AND STENT PLACEMENT

Pulmonary Artery Stenosis

Peripheral pulmonary artery stenosis is a common residuum of surgical reconstruction and is difficult to treat surgically. Despite suboptimal results, angioplasty (rather than stent therapy) is the initial procedure of choice, particularly in smaller growing patients. A balloon catheter with a diameter up to four times the diameter of the stenosis and up to 50% larger than the nearby "normal" vessel is used. Often the waist on the balloon will disappear, but the stenosis will be incompletely relieved. Replacing low-pressure balloons with high-pressure balloons has improved outcomes, but restenosis remains a limitation. Cutting balloons have produced encouraging early results in smaller vessels.

Balloon-expandable stents represent a major advance over angioplasty in the treatment of pulmonary artery stenosis. The use of stents has improved the acute success rate and results in a greater increase in arterial diameter than does angioplasty alone. The stent is mounted and hand-crimped onto a high-pressure balloon dilation catheter. The stent-balloon complex is then advanced over a wire through a long large-caliber sheath positioned across the stenosis. After positioning of the stent and

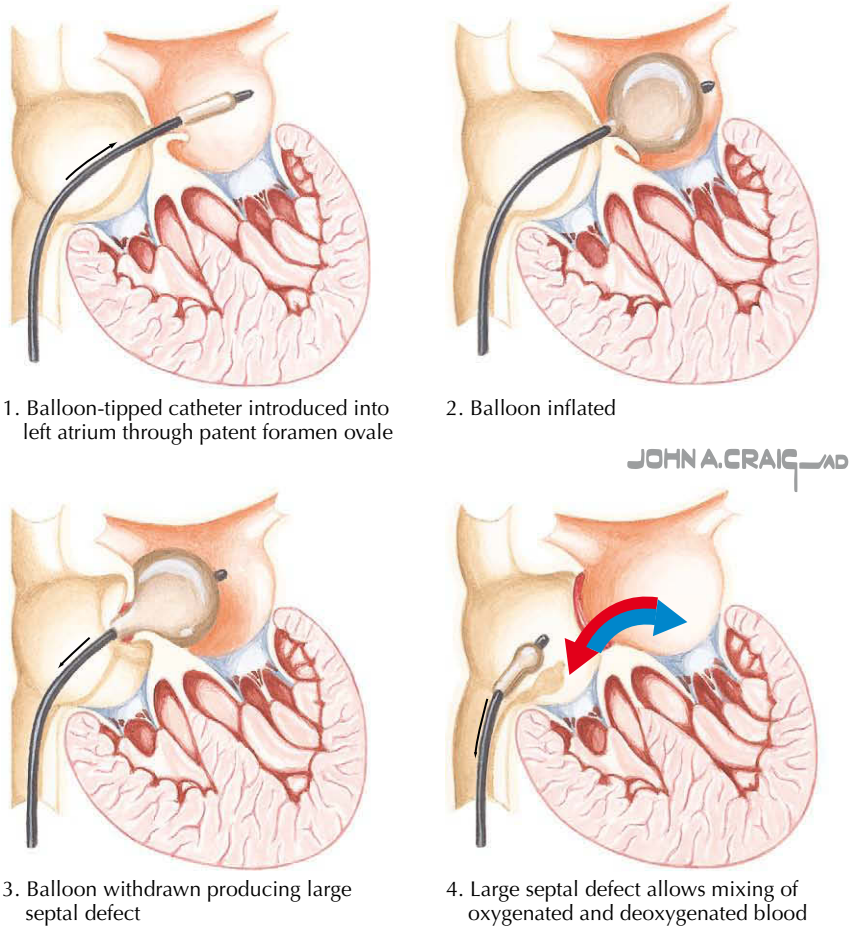
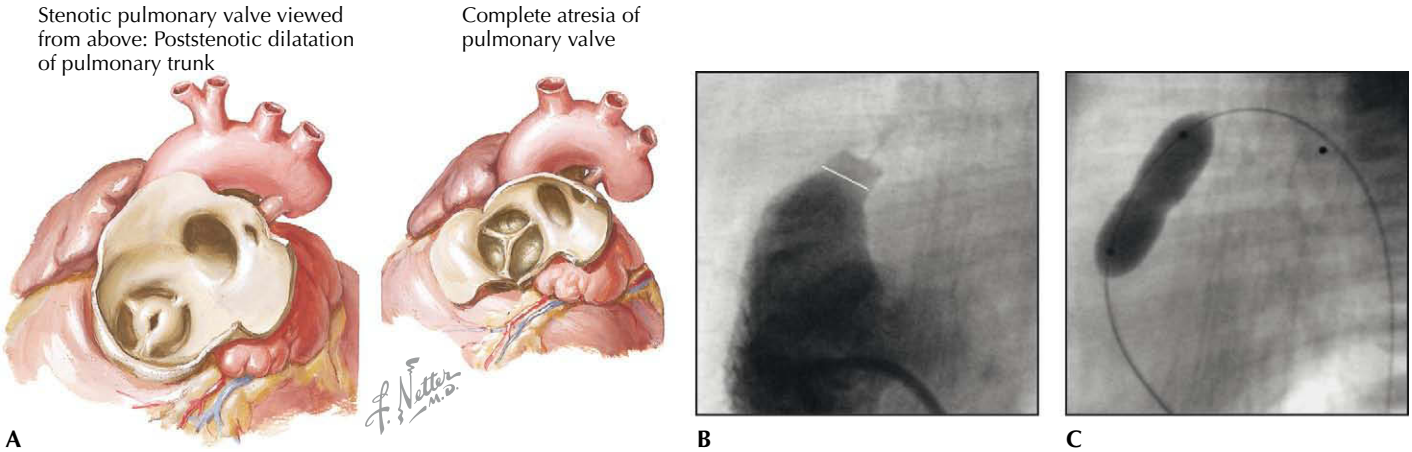
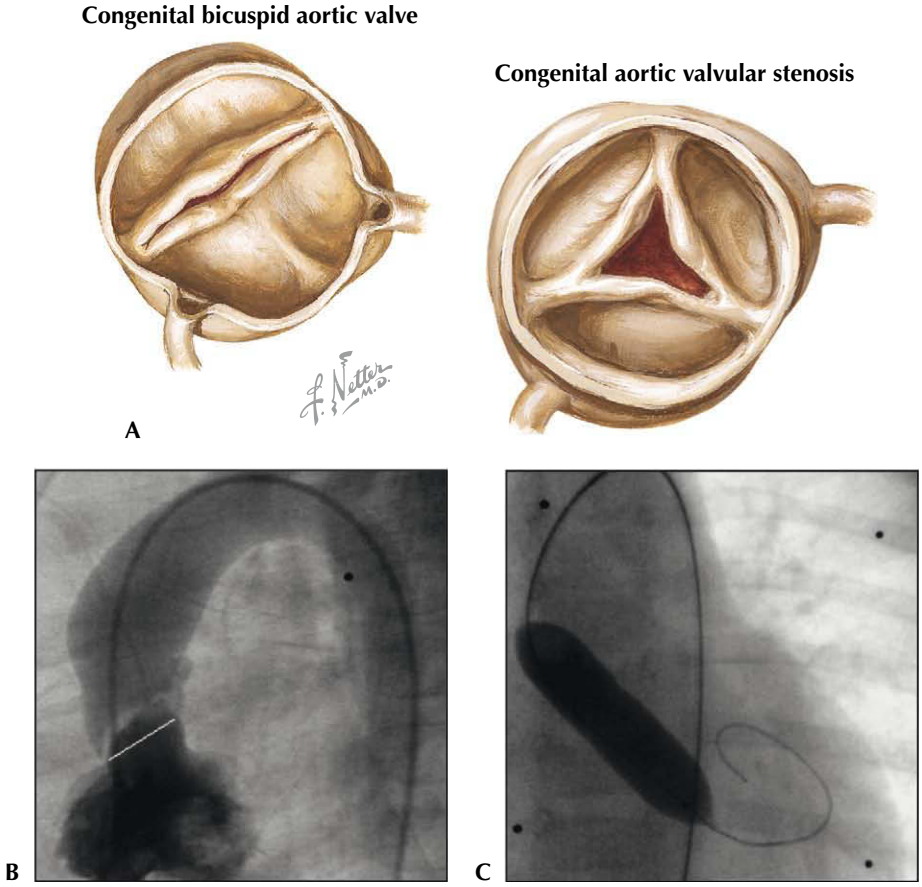


Figure 52-1 *Balloon atrial septostomy for transposition of the great arteries.*



(A) The anatomic features of congenital pulmonary stenosis and atresia are illustrated. **(B)** A lateral-view right ventricular angiogram in a neonate with critical pulmonary valve stenosis shows the doming valve with an annulus diameter of 5.9 mm and a tiny poststenotic jet. **(C)** A lateral view of an 8-mm-diameter balloon dilation catheter fully inflated across the annulus. The balloon has been passed over a guide wire that had been placed across the ductus to the descending aorta.

Figure 52-2 *Pulmonary valvular stenosis and atresia.*



(A) The anatomic features of congenital bicuspid aortic valve stenosis and congenital aortic valvular stenosis are illustrated. **(B)** A lateral-view left ventricular angiogram shows the doming aortic valve with a valve annulus diameter of 9.6 mm and poststenotic dilation of the ascending aorta. **(C)** Anteroposterior view of a 9-mm-diameter balloon dilation catheter fully inflated across the annulus. The balloon has been passed over a guide wire that had been placed retrograde across the valve and looped in the left ventricular apex.

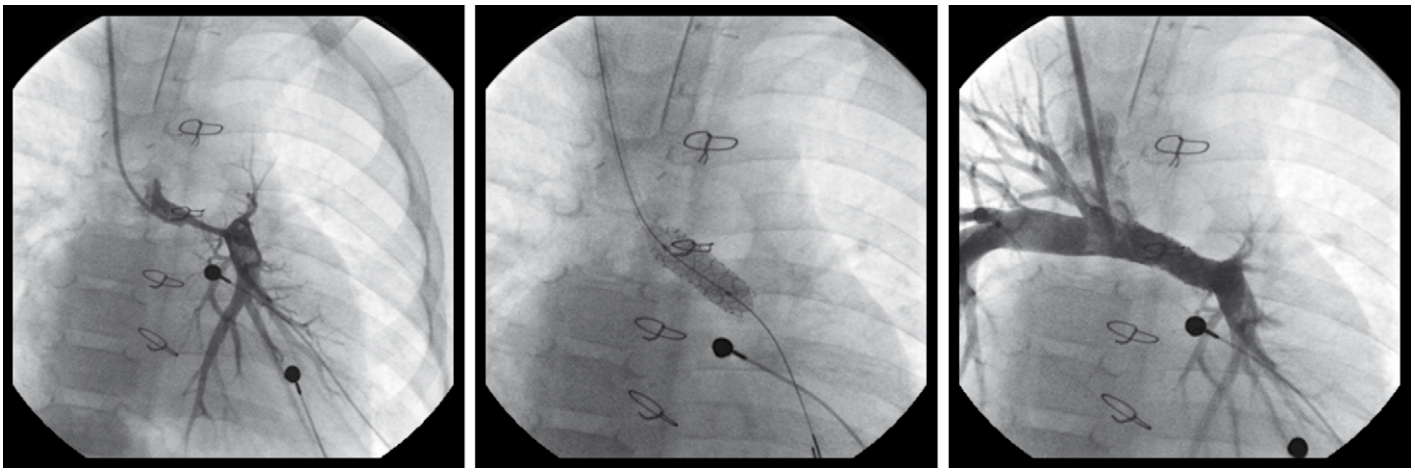
Figure 52-3 *Congenital aortic stenosis.*

test angiograms, the stent is expanded by inflating the balloon (Fig. 52-4). The main limitation to the use of stents is patient size. Although modest further expansion of stents is possible later, placing a stent in a small child is technically challenging and often commits that child to surgery in the future. Improvements in stent design have facilitated the delivery of stents to remote sites, but stents less than 6 to 8 mm in final diameter frequently develop stenosis or local thrombosis.

Coarctation of the Aorta

Native coarctation of the aorta is a congenital discrete stenosis of the juxtaductal aorta. In the critical neonatal form, it is often associated with proximal aortic hypoplasia (Fig. 52-5). Recurrent aortic coarctation may develop after surgery, particularly after neonatal repair. Balloon coarctation angioplasty is well accepted for children with recurrent coarctation, because repeat surgery is associated with significant morbidity. However, angioplasty for native coarctation is less widely accepted because of concerns about restenosis and aneurysm development.

A high-pressure balloon dilation catheter with a diameter two to four times the coarctation diameter but not more than 2 mm greater than the diameter of the proximal aorta is passed over the wire and inflated several times until the waist is abolished. Follow-up pressures and angiography are performed to ensure adequate relief of obstruction and no dissection or aneurysm development (see Fig. 52-5). Balloon angioplasty for recurrent coarctation achieves a residual coarctation gradient of less than 20 mm Hg in 80% to 90% of cases and carries a low risk of complications. The success of balloon angioplasty for native coarctation is generally good except in small infants. Predictors of restenosis are young age, a hypoplastic arch, a coarctation diameter less than 3.5 mm, and a postdilation gradient greater than 20 mm Hg. In contrast to early reports, recent experience suggests a low incidence of aneurysm development, similar to the rate observed after surgical repair. Increasingly, balloon angioplasty for native coarctation is offered as an

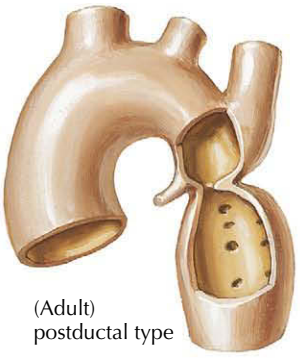


A. An anteroposterior pulmonary arteriogram in a patient with long-segment left pulmonary artery stenosis after a Glenn procedure for hypoplastic left heart syndrome.

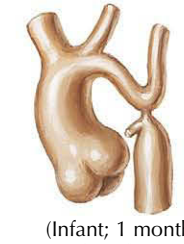
B. A stent is mounted on a balloon filled with dilute contrast and expanded.

C. An anteroposterior arteriogram after stent placement showing excellent relief of the long-segment stenosis.

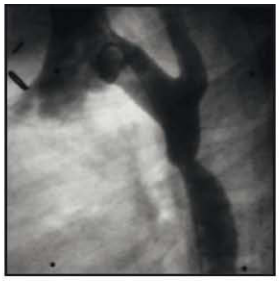
Figure 52-4 *Pulmonary artery stenosis.*



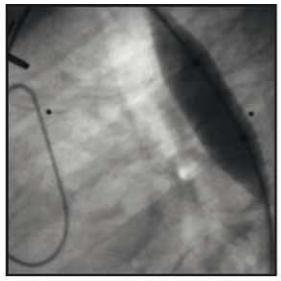
(Adult)
postductal type



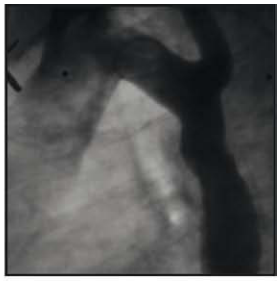
(Infant; 1 month)
preductal type



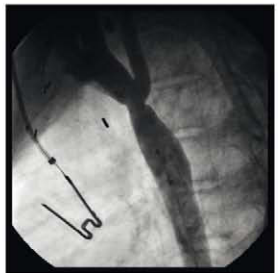
A. A lateral-view aortogram showing a recurrent aortic coarctation distal to the left subclavian artery.



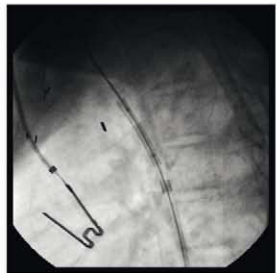
B. A balloon dilation catheter fully inflated in the site of narrowing, guided by a wire looped in the ascending aorta.



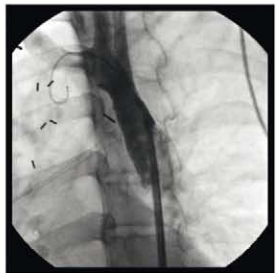
C. Follow-up aortogram showing marked improvement in the caliber of the aorta in the site of coarctation, without aneurysm formation or residual stenosis.



D. An aortogram showing a nondiscrete native coarctation.

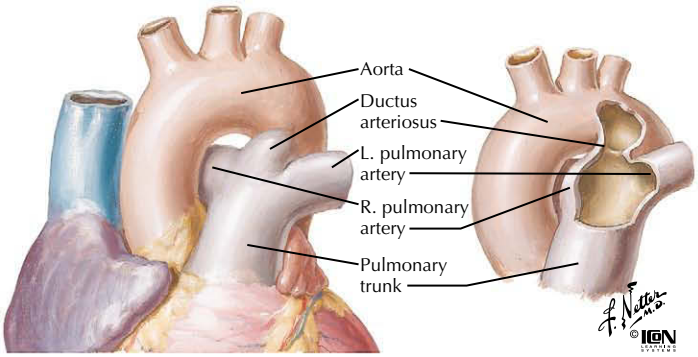


E. A stent is mounted on a balloon and positioned in the area of the coarctation.

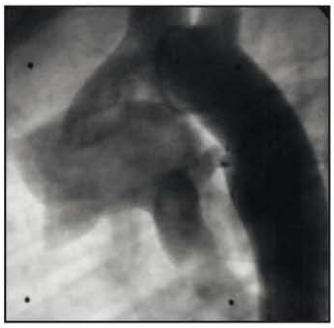


F. An aortogram after stent placement showing relief of the coarctation and "flaring" of the distal stent to oppose the aortic wall.

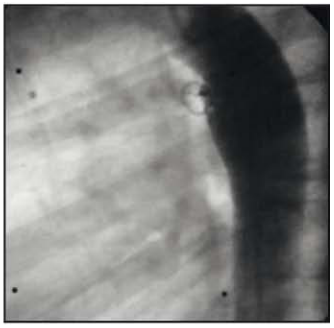
Figure 52-5 *Coarctation of the aorta.*



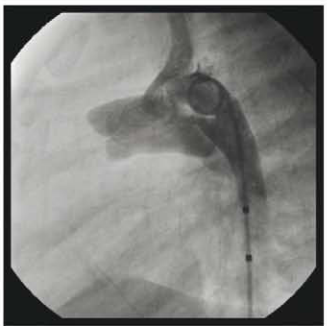
The internal anatomy of a typical "type A" ductus arteriosus, demonstrating the conical aortic ampulla and narrowing near the pulmonary end, making coil placement feasible



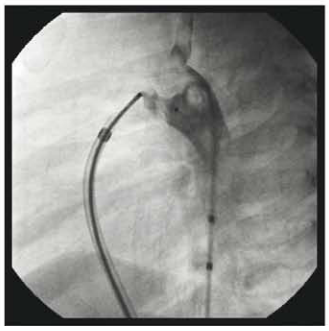
A. A lateral-view aortogram showing residual leakage through a patent ductus arteriosus that had been partially closed with a Rashkind umbrella occluder years previously. Three platinum markers can be seen on the aortic umbrella of the Rashkind device.



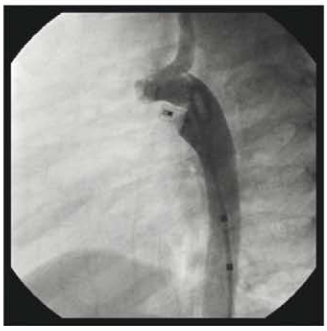
B. Follow-up lateral-view aortogram after snare-assisted coil delivery showing complete closure.



C. Lateral aortogram showing a typical conical ductus opacifying the pulmonary artery.



D. An Amplatzer Duct Occluder has been delivered through a long transvenous sheath and a test angiogram confirms proper position.



E. A final aortogram after release of the occluder shows complete closure.

Figure 52-6 *Patent ductus arteriosus.*

alternative to surgery in patients older than 6 months of age or weighing more than 8 kg.

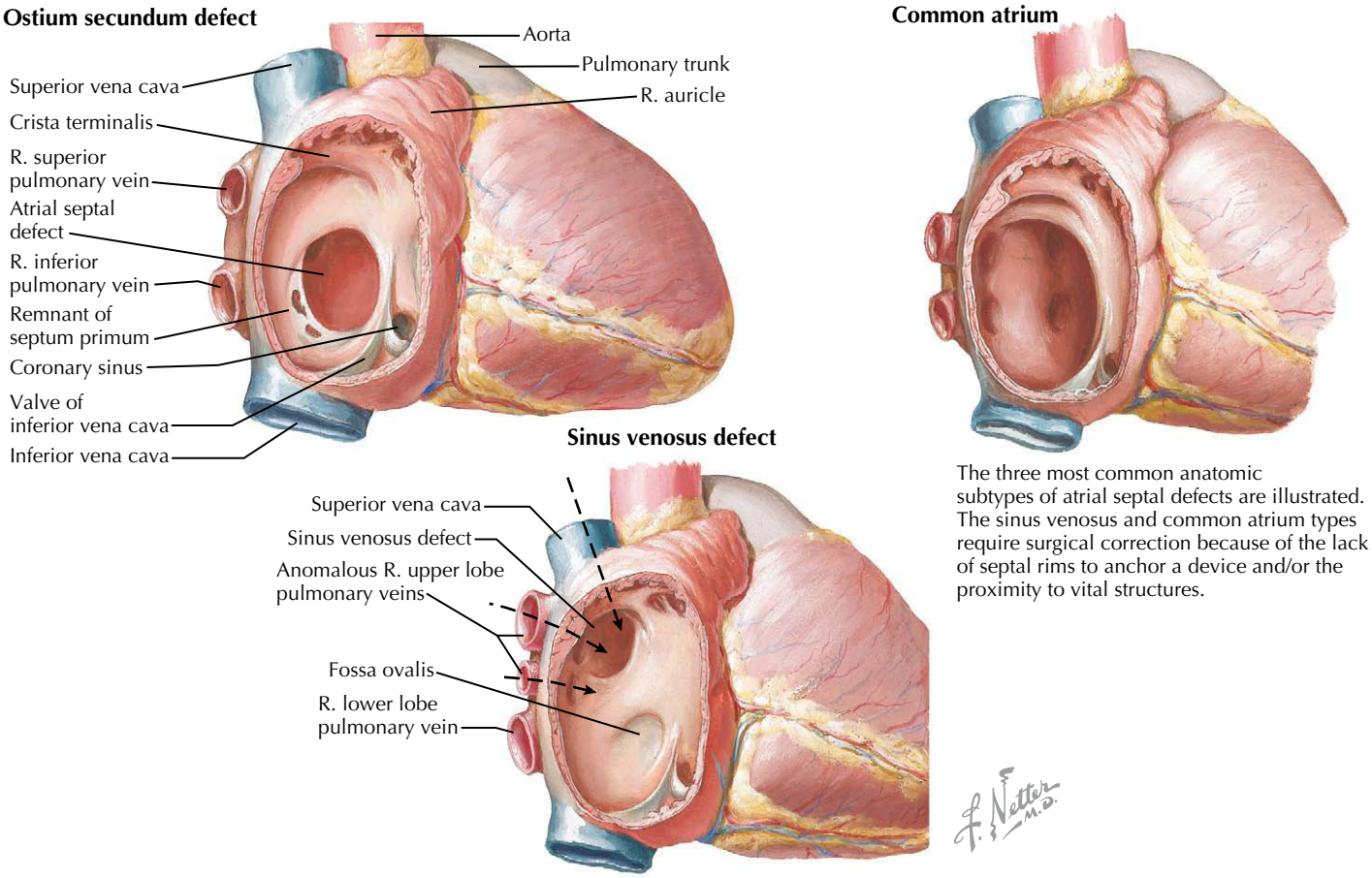
Improvements in intravascular stent design and delivery have led to the increased use of stents in the treatment of recurrent and native coarctation in older patients, particularly those with long-segment coarctation (see Fig. 52-5). Stenting allows a more controlled expansion of the aortic wall and often has a more predictable outcome than angioplasty. As is the case for other lesions, in the growing child, stent placement incurs a significant risk of subsequent stent stenosis. In addition, the required large-caliber sheath may injure the femoral artery. For this reason, stents have been used primarily in nearly full-grown patients, many of whom have undergone multiple surgical procedures. In this setting, excellent results have been achieved.

TRANSCATHETER CLOSURE OF CONGENITAL SHUNTS

Persistent Ductus Arteriosus

Although the ductus arteriosus is a necessary vascular channel in fetal life, the postnatally persistent arterial duct can cause congestive heart failure, pulmonary hypertension, or endarteritis. When the clinically significant ductus persists beyond infancy, it should be closed to prevent such morbidity. Surgical thoracotomy with ligation and division of the ductus is extremely safe and effective but involves hospitalization, pain, and a scar and occasionally leads to scoliosis. In recent years, percutaneous endovascular closure using Gianturco spring coils has become routine (Fig. 52-6). These preformed, stainless-steel coils of varying caliber, diameter, and length have attached strands of Dacron to increase their thrombogenicity. The usual conical or tubular ductal morphology allows placement of a Gianturco coil with a loop diameter at least twice the smallest diameter of the ductus, leaving most of the loops and coil mass within the aortic ampulla. Modifications of the technique allow delivery of coils antegrade, retrograde, "freehand," or assisted by a snare or a bioptome through 4 French delivery catheters. This coil closure method typically achieves complete closure of smaller ducts with minimal complications as an outpatient procedure without general anesthesia.

Another occlusion device, the Amplatzer Duct Occluder (AGA Medical Corp., Plymouth, MN), is superior to coils for transcatheter closure of the larger ductus (see Fig. 52-6). The Amplatzer Duct Occluder is a mushroom-shaped plug of nitinol wire mesh with polyester fabric patches sewn into the framework. The device attached to its delivery cable is delivered through 5 to 7 French sheaths in a controlled fashion. When



The three most common anatomic subtypes of atrial septal defects are illustrated. The sinus venosus and common atrium types require surgical correction because of the lack of septal rims to anchor a device and/or the proximity to vital structures.

Figure 52-7 *Atrial septal defects.*

the device is deployed, the outer walls of the expanded plug "stent" the lumen of the vessel, securing the device in position and achieving complete closure.

Atrial Septal Defect

Deficiencies of the interatrial septum involve all regions of the septum. All but the most common secundum defects require surgical correction (Fig. 52-7). Unrepaired ASDs can lead to pulmonary hypertension, atrial arrhythmias, or right heart failure. Defects large enough to produce right heart enlargement should be closed early in life to preempt these morbidities. Transcatheter closure of ASDs has become one of the most recognized and effective catheter-based procedures because of its widespread application and replacement of the need for exposure to cardiopulmonary bypass.

The Amplatzer Septal Occluder (AGA Medical Corp.) is the first implantable cardiac device approved specifically for use in children, and it has been widely used for a decade. It is a self-expanding, double-disk nitinol frame with a central waist sized to "stent" the atrial septal rims and polyester patches sewn into the frame to aid endothelialization and closure (Fig. 52-8). With transesophageal or intracardiac echocardiographic monitoring, a balloon-sizing catheter is used to obtain the "stop-flow" diameter of the defect. A device with a central waist equal to the stop-flow diameter is selected, attached to the delivery cable, and loaded. The device is then delivered through a 7 to 12 French femoral venous delivery sheath with its tip in the left atrium. After deployment, the device position is evaluated echocardiographically. At that point, if the results are not ideal, the device can be recaptured, repositioned, or completely removed. After proper positioning is confirmed, the device is released by unscrewing the delivery cable. In properly selected patients, the Amplatzer Septal Occluder achieves complete closure with a very low rate of complications. The rare serious complication of late erosion of the atrial free wall or aortic root occurs in less than 0.1% of cases when proper sizing technique is used.

More recently, the Helex Septal Occluder (W.L. Gore and Associates, Inc., Flagstaff, AZ) has been developed and approved for transcatheter closure of ASDs. This occluder is a preassembled, circular, single-wire nitinol frame upon which a thin polytetrafluoroethylene patch is suspended (Fig. 52-9).

The device is delivered by sequentially "unfurling the sail" of the patch, forming one disk on each side of the septum. This occluder has the theoretical advantages of being softer and more compliant, with a lower profile, but it is only applicable to defects smaller than 18 mm in diameter, is not self-centering, and has a higher incidence of early residual shunts.

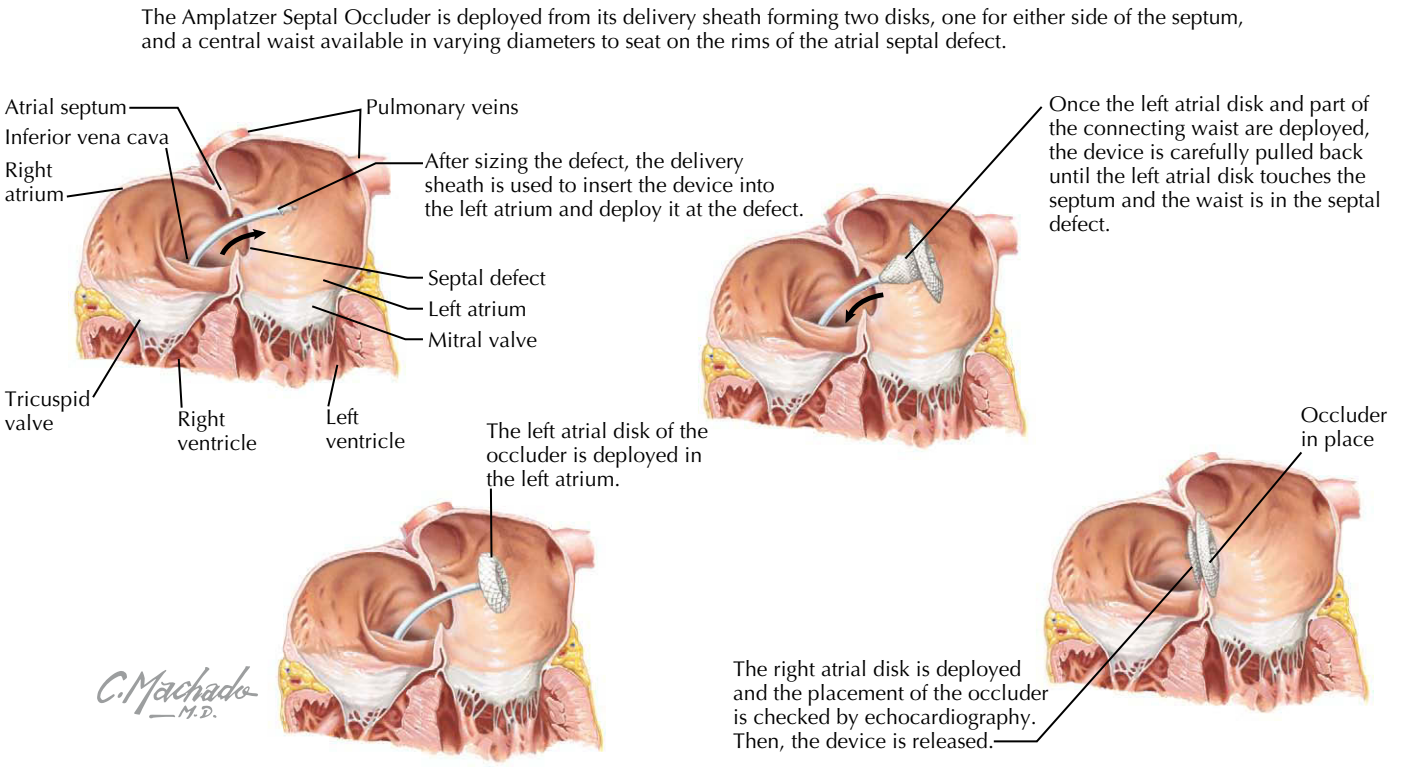


Figure 52-8 *Amplatzer Septal Occluder.*

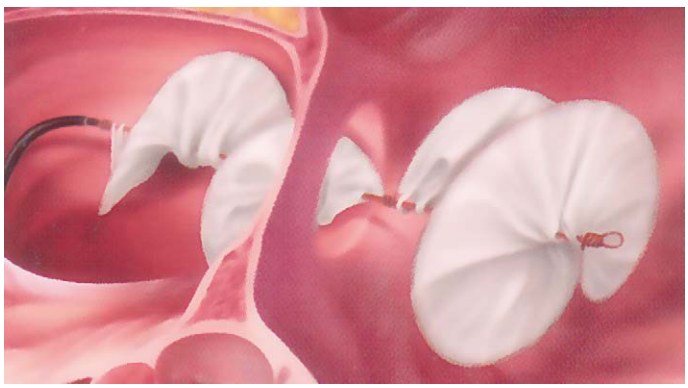


Figure 52-9 *Depiction of a Helex Septal Occluder for catheter-based closure of atrial septal defects.* (Courtesy of Gore Medical Products.)

Although surgical results are excellent, these transcatheter techniques avoid cardiopulmonary bypass, longer hospitalization and recovery time, cosmetic concerns, and patient discomfort.

Ventricular Septal Defect

The precise anatomy of a ventricular septal defect (VSD) determines whether transcatheter closure is feasible. The proximity of perimembranous defects to the aortic valve and atrioventricular node makes device closure challenging (Fig. 52-10). When the defect is a residual of incomplete "aneurysmal" closure, it is more remote from these vital structures and may allow placement of an occluder in selected patients. Muscular VSDs are often difficult to treat surgically because of their remote location, and in this circumstance, the transcatheter method is often preferred. The CardioSeal Double-Umbrella Occluder (NMT Medical, Inc., Boston, MA) is approved for closure of these defects, but delivery is challenging. Recently, the Amplatzer Muscular VSD Occluder, with a design very similar to the ASD occluder, has been approved, and it can be delivered by percutaneous or "hybrid" perventricular approaches.

FUTURE DIRECTIONS

Because of the "orphan" status of many congenital heart diseases, the obstacles to innovation and regulatory approval by industry are considerable. However, continued refinements and advances in catheter-based therapy for congenital heart disease are certain. Promising preliminary outcomes are currently being achieved with stent-mounted pulmonary valve implants and with polytetrafluoroethylene-covered stents for aortic coarctations and aneurysms. So-called hybrid approaches combine surgical and catheter-based techniques for hypoplastic left heart syndrome and complex VSDs. Fetal interventions for critical right- and left-sided obstructive disease are being developed. Miniaturization and improvements in device design will expand the indications to smaller patients. Despite advances in catheter-based therapy, surgical intervention will remain the primary treatment method for many of the more complex forms of congenital heart disease.

ADDITIONAL RESOURCES

Cheatham JP. Stenting of coarctation of the aorta. *Catheter Cardiovasc Interv.* 2001;54:112–125.

This article describes the use of two different stent designs for treating coarctation of the aorta and illustrates the process of innovation in making design improvements in medical devices.

Pediatric and Adult Interventional Cardiac Symposium [home page on the Internet]; Available at: <http://www.picsymposium.com/videos.html>; Accessed 11.03.10.

Provides links and video tutorials for many of the catheter-based procedures discussed in this chapter.

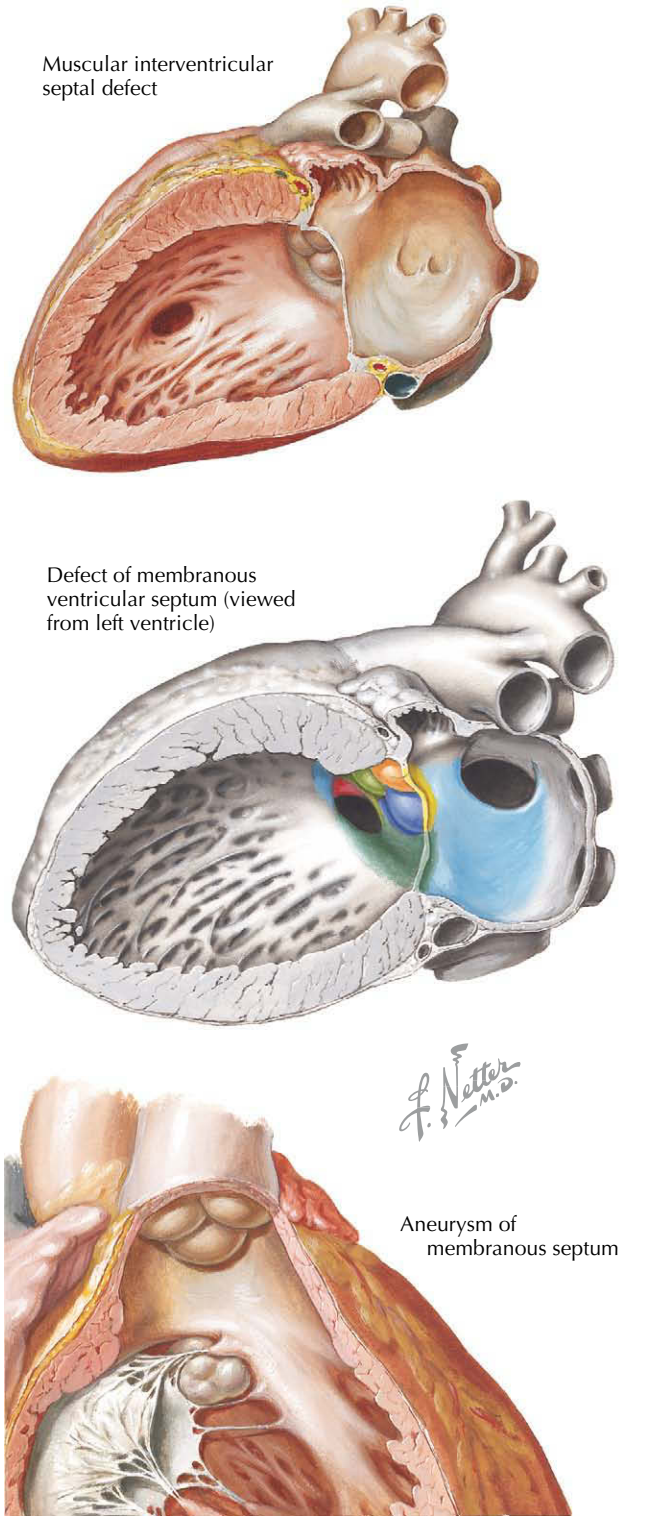


Figure 52-10 *Anatomic features of perimembranous and muscular ventricular septal defects.*

EVIDENCE

Du ZD, Hijazi ZM, Kleinman CS, et al. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol.* 2002;39:1836–1844.

The pivotal multicenter trial showing favorable outcomes for catheter-based closure of atrial septal defects used to win U.S. Food and Drug Administration approval.

Forbes TJ, Garekar S, Amin Z, et al. Procedural results and acute complications in stenting native and recurrent coarctation of the aorta in patients over 4 years of age: a multi-institutional study. *Catheter Cardiovasc Interv.* 2007;70:276–285.

The largest collective experience reporting outcomes of stent therapy for native and recurrent aortic coarctation.

Pass RH, Hijazi Z, Hsu DT, et al. Multicenter USA Amplatzer patent ductus arteriosus occlusion device trial: initial and one-year results. *J Am Coll Cardiol.* 2004;44:513–519.

The pivotal multicenter trial showing excellent results for catheter-based closure of patent ductus arteriosus used to win U.S. Food and Drug Administration approval.

Rashkind WJ, Miller WW. Transposition of the great arteries. Results of palliation by balloon atrioseptostomy in thirty-one infants. *Circulation.* 1968;38:453–462.

The landmark first evidence-based report describing catheter-based treatment of the formerly lethal transposition of the great arteries.

Surgical Interventions for Congenital Heart Disease

53

Robert D. Stewart, G. William Henry, and Michael R. Mill

Our understanding of the complexities of congenital heart disease, a deviation from normal cardiac anatomic development that affects 8 in 1000 births, has progressed immensely since the establishment of the Board of Pediatric Cardiology in 1961. Improvements in diagnostic imaging (including echocardiography, cardiac angiography, and magnetic resonance imaging) and innovations in surgical repair techniques have resulted in greatly improved outcomes for children with congenital heart disease. This chapter provides a broad overview of the most common congenital heart lesions and the role of surgical interventions.

Embryologic development of the heart begins with the fusion of angiogenic cell clusters within the splanchnic mesoderm layer of the primitive embryo to form the heart tube at 18 to 21 days of gestation. The heart begins to rhythmically contract as early as day 17, once functional units of the myocytes begin to form. Myocardial growth proceeds with segmentation and looping of the heart tube and cellular differentiation and migration along the embryologic axes, with the establishment of laterality, and with the organization of the primitive cells into a sophisticated organ. Deviations from this complex process of cardiac development lead to congenital cardiac anomalies, with clinical presentations that in some cases occur in the immediate postnatal period and in other cases, young adulthood.

Therapy for congenital heart disease has evolved with surgical and nonsurgical innovations. The development of pediatric cardiac surgery has led to the survival of many children with complex congenital heart disease. These successes have depended on improved diagnoses, advances in surgical technique, and the development of a means for extracorporeal circulation–cardiopulmonary bypass (CPB). Complex repairs for previously fatal lesions such as transposition of the great arteries (TGA) and hypoplastic left-sided heart syndrome (HLHS) have become routine, with declining mortality rates and improved long-term outcomes. The development of transcatheter procedures has made therapeutic cardiac catheterization a viable alternative to surgery for specific congenital cardiac lesions (see Chapter 52).

SURGICAL TREATMENT

Many congenital heart lesions can be surgically repaired, meaning that approximately normal anatomy and physiology are established. The closure of atrial septal defects (ASDs) and ventricular septal defects (VSDs) can, when successfully accomplished in a young patient, eliminate the long-term consequences of the defect. Other lesions, most notably the single-ventricle defects, cannot be repaired but can be successfully palliated with operative modifications that provide a viable alternative cardiopulmonary physiology. These palliative operations can also be useful as a bridge to complete repair after a period of growth and development.

Palliative Surgical Procedures

The Blalock-Taussig shunt was first performed in 1944 at the Johns Hopkins Hospital to supply blood to the branch pulmonary arteries of a severely cyanotic patient with tetralogy of Fallot. The shunt was created by dividing the right subclavian artery and directly anastomosing it to the right pulmonary artery. Since that time, the creation of a systemic-to-pulmonary artery shunt (a "BT shunt") has been used for a variety of congenital heart defects with severe pulmonary artery stenosis or atresia as a bridge to more definitive surgical correction. The technique of creating a BT shunt has been modified significantly by the use of an interposition graft, most commonly made of expanded polytetrafluoroethylene (ePTFE; Gore-Tex), between the systemic and pulmonary vessels. The "modified BT shunt" operation can be performed through a lateral thoracotomy or a median sternotomy and can be performed on either the right or left. A significant development in congenital heart surgery has been the increasing trend toward definitive repair at an earlier age, including the neonatal period. For this reason, the use of BT shunts is decreasing, but they still remain an important tool for the palliation of cyanotic heart lesions.

The pulmonary artery (PA) band is an important palliative procedure for congenital heart lesions in which there is excessive pulmonary blood flow. The PA band is simply a Teflon tape looped around the main pulmonary trunk and tightened to restrict pulmonary blood flow. The PA band was originally developed to treat large VSDs by decreasing the left-to-right shunt. Currently, the PA band is used most commonly for single-ventricle lesions with nonrestrictive pulmonary blood flow. The band is used to balance the systemic and pulmonary circulations and to protect the pulmonary vasculature from prolonged exposure to high pressure, which could lead to a fixed increase in pulmonary vascular resistance and irreversible pulmonary hypertension. The PA band in these patients with single ventricles is a bridge to eventual "Fontan physiology," or total cavopulmonary blood flow. There are still some instances where a PA band is useful for the treatment of a VSD, most commonly in patients with multiple VSDs, also known as a "Swiss cheese septum."

The superior bidirectional cavopulmonary anastomosis, often referred to as the Glenn shunt, is the second stage in the palliation of all or most defects of the single-ventricle type. This shunt involves the disconnection of the superior vena cava (SVC) from the right atrium and a direct anastomosis of the SVC to the right pulmonary artery (Fig. 53-1). This allows all of the systemic venous return from the upper body to flow directly to the lungs. The Glenn shunt is typically performed between 4 and 9 months of age, allowing for enough lung maturity to permit this passive blood flow. Patients will not be fully saturated following the Glenn shunt, since the venous return

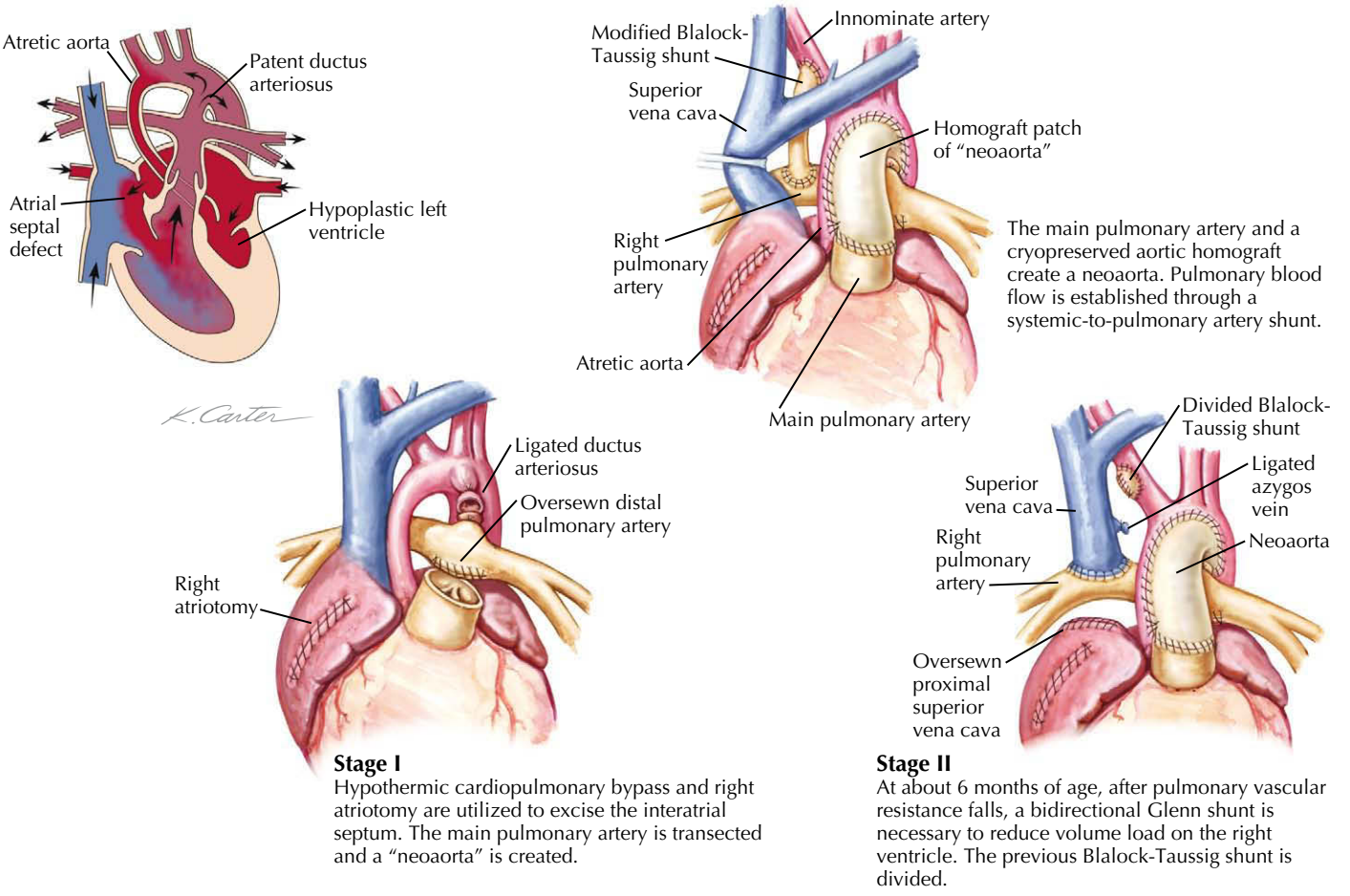


Figure 53-1 *Norwood correction of hypoplastic left-sided heart syndrome.*

from the lower body still returns to the heart to mix with the fully oxygenated pulmonary venous blood. Depending on the particular cardiac defect, the procedure may be combined with the removal of a BT shunt or removal of a PA band with division of the main pulmonary trunk from the heart. In either instance, the attendant decrease in the volume load on the heart is beneficial to the function of the single ventricle and its long-term durability.

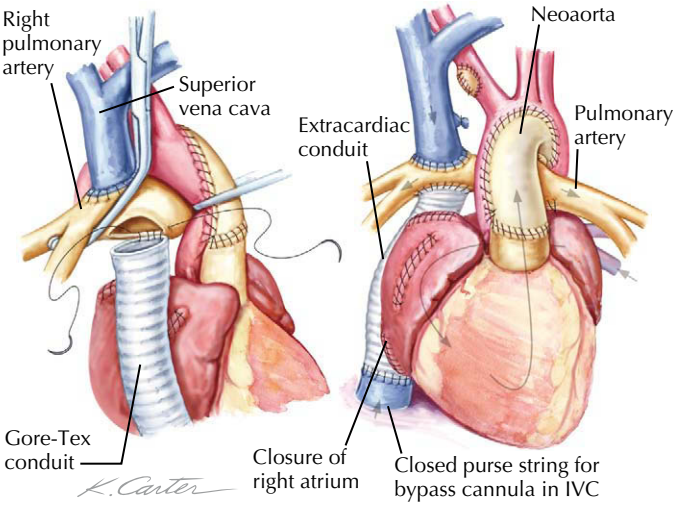
The ability of the pulmonary circulation to accept the entire cardiac output passively is limited and thus the rationale for creating total cavopulmonary circulation in two stages. The Glenn is performed in the first year of life, and the completion of the Fontan is done in the second or third year of life. There are two distinct techniques for completing the Fontan, the lateral tunnel and the extracardiac conduit. The lateral tunnel involves creating a tunnel inside of the right atrium that extends from the opening of the inferior vena cava (IVC) to the opening of the SVC, which is in turn connected to the right pulmonary artery, thus baffling all of the systemic venous return to the lungs. The extracardiac Fontan is created by disconnecting the IVC from the right atrium and sewing a graft of ePTFE from the open end of the IVC to the pulmonary arteries (Fig. 53-2). Using either strategy, a direct connection of the IVC flow to the lungs establishes total cavopulmonary circulation, with the result being that after repair, the patient should have nearly normal oxygen saturation.

Special Considerations for Specific Single-Ventricle Lesions

Tricuspid atresia is a congenital lesion with an absent right-sided arteriovenous connection. Left ventricular preload is dependent on interatrial blood flow via an ASD. This lesion is commonly associated with transposed great vessels, and the pulmonary artery can range anywhere from atretic to enlarged. The physiology of the lesion varies by the amount of pulmonary blood flow. The original surgical repair, the classic Fontan procedure, involved constructing a direct connection between the right atrium and the main pulmonary artery. Present-day conversion to the Fontan circulation usually requires a two-stage surgical approach after early palliation. The initial palliation may involve a BT shunt for lesions that include pulmonary stenosis or a PA band for those with a normal pulmonary artery and excessive blood flow. A Glenn shunt is then created between 4 and 9 months of life, followed by the Fontan procedure, which is performed between 12 months and 3 years of age.

HLHS is a congenital lesion with univentricular physiology. HLHS generally involves a diminutive nonfunctional left

Stage III
A modified Fontan procedure is completed 6–12 months after stage II utilizing an extracardiac Gore-Tex conduit to connect inferior vena cava blood flow to the pulmonary artery.



Systemic venous blood bypasses the right heart directly to the pulmonary arteries and lungs. Oxygenated blood is pumped from the left to right atrium through a septotomy. The "neoaorta" directs oxygenated systemic blood flow from the right ventricle.

Figure 53-2 *Norwood correction of hypoplastic left-sided heart syndrome: Fontan circulation.* IVC, inferior vena cava.

ventricle that results from stenosis or atresia in both the mitral and aortic valves as well as hypoplasia of the ascending aorta. Systemic blood flow is ductal dependent, and the appearance of symptoms in the neonatal period usually correlates with spontaneous closure of the ductus arteriosus. Early management with prostaglandin E_1 to maintain ductal patency is life sustaining. The appropriate balance between pulmonary and systemic blood flow (Qp/Qs) is critical. The most common neonatal palliative approach is the Norwood procedure, in which a "neoaorta" is created by performing an aortopulmonary connection, then augmenting the hypoplastic ascending aorta with a homograft patch. A systemic-to-pulmonary shunt is required for pulmonary blood flow, and an atrial septectomy is always performed to permit unobstructed flow of left atrial blood through the tricuspid valve to the right ventricle (see Figs. 53-1 and 53-2). The surgery is usually performed during the neonatal period and carries a 20% to 30% risk of mortality. The Norwood procedure is followed by a bidirectional Glenn shunt at 4 to 6 months of age and a Fontan procedure at 2 to 3 years of age.

SURGICALLY CORRECTABLE LESIONS

Patent Ductus Arteriosus

Patent ductus arteriosus describes postnatal persistence of a normal fetal vascular connection between the main pulmonary trunk or proximal left pulmonary artery and the descending thoracic aorta. This anomaly accounts for 10% of congenital heart lesions. In full-term infants, the ductus arteriosus is usually functionally closed by 10 to 15 hours after birth. Persistent blood flow through the ductus arteriosus is often associated with other congenital anomalies, and depending on the vascular connections, pulmonary blood flow may be dependent on patency of the ductus, as in lesions with right ventricular (RV) outflow tract obstruction. In this case, the vessel may be kept open with prostaglandin E_1 therapy until a BT shunt is surgically created. When no other associated anomalies exist and ductus closure has not occurred after medical therapy with indomethacin for 48 to 72 hours, direct surgical ligation or division via a left posterolateral thoracotomy or, alternatively, catheter-based device closure is indicated. Surgical closure before 10 days of age reduces the duration of ventilatory support, the length of hospital stay, and overall morbidity.

Ventricular Septal Defects

VSD is the most common congenital cardiac anomaly, occurring in 20% of patients with congenital heart disease. An interventricular communication occurs with the failure of the tissue ridges to fuse during formation of the septum. VSDs are traditionally classified as perimembranous, muscular, and doubly committed subarterial. Perimembranous and muscular VSDs are further classified on the basis of anatomic location as inlet, outlet, or trabecular. Of surgically repaired defects, 80% are perimembranous. The degree of shunting is quantified by the ratio of flow through the pulmonary circulation relative to the systemic circulation, the Qp/Qs. When this ratio is greater than 1.5 : 1, surgical closure is indicated. The primary indications for closure, however, are symptoms of congestive heart failure and failure to thrive. Other indications for closure include development of aortic valve insufficiency or endocarditis, both of which can be caused by the abnormal flow through the VSD. Untreated, a VSD can cause persistent elevation of pulmonary vascular resistance and irreversible changes to the pulmonary vasculature (see Chapter 50). Ultimately, patients can develop Eisenmenger's complex, where the shunt through the VSD is reversed, with the subsequent right-to-left flow resulting in profound cyanosis. Surgical repair is performed by means of a median sternotomy and hypothermic CPB. The majority of defects are exposed through a right atrial incision and retraction of the tricuspid valve leaflets (Fig. 53-3). Subarterial VSDs are approached through the pulmonary trunk, and muscular VSDs located near the apex of the heart are exposed through a ventricular incision. With a few exceptions, the defect is closed with a patch using either running sutures or, as depicted in Figure 53-3, interrupted pledgeted sutures.

Atrial Septal Defects

An interatrial communication accounts for 10% to 15% of congenital cardiac anomalies. The term *atrial septal defect* refers to a spectrum of anomalies that are broadly classified into three categories: oval fossa or secundum defects, defects of the ostium primum also known as *partial atrioventricular septal defects* (partial AVSDs), and sinus venosus defects. Each type of ASD is unique.

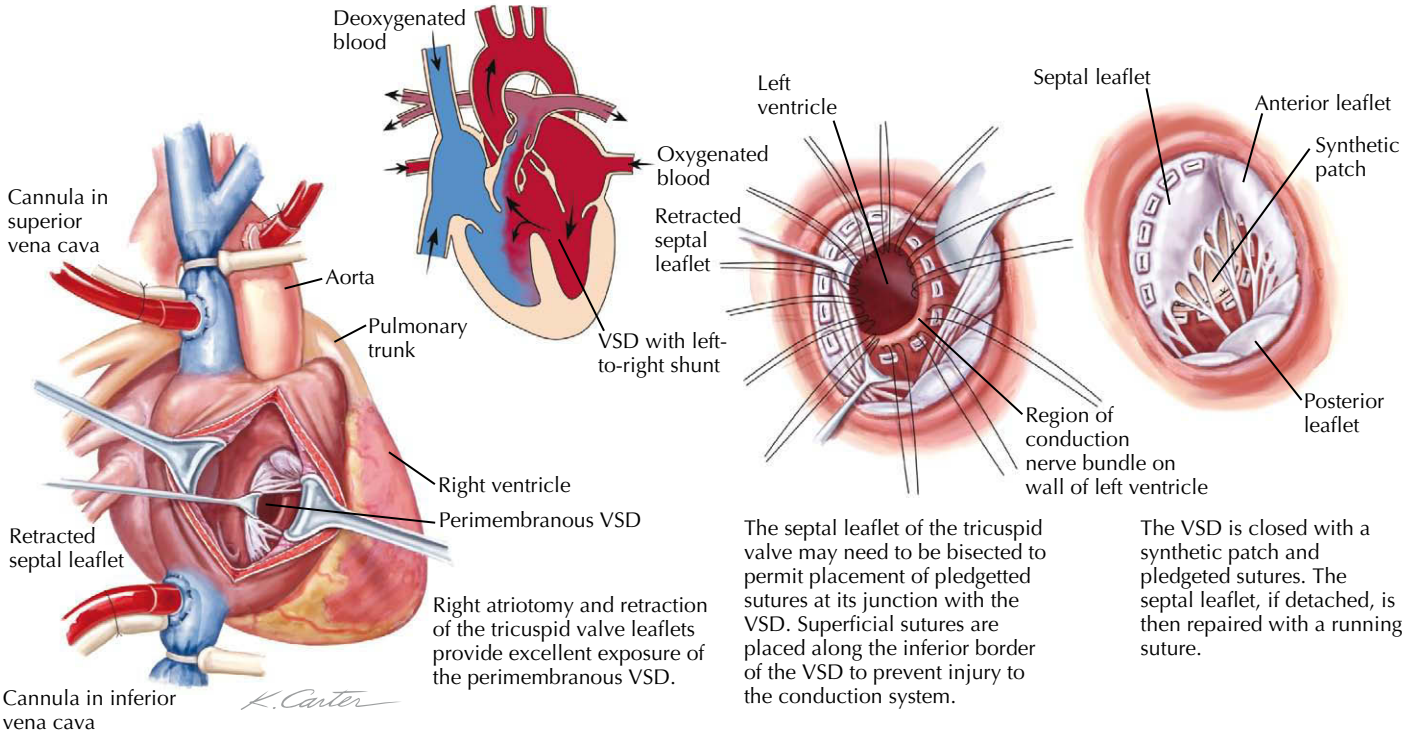


Figure 53-3 *Transatrial repair of ventricular septal defect (VSD).*

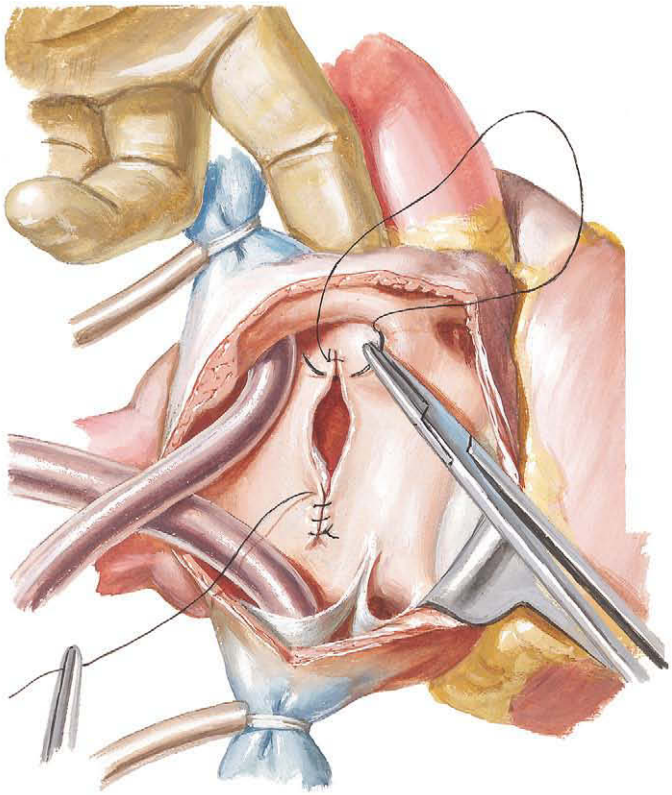
The oval fossa defect is by far the most common (80% to 85%), and the indication for closure is excessive left-to-right shunting with a Qp/Qs greater than 1.5:1 or significant enlargement of the right heart. The majority of oval fossa defects can be closed using a transcatheter device (see Chapter 52). If the defect cannot be closed with a device, it can be closed surgically either with a patch or by direct suture (Fig. 53-4, upper panel). Sinus venosus ASDs result from an overriding SVC that causes an atrial communication superior to the true atrial septum. The vast majority of sinus venosus ASDs are associated with anomalous pulmonary venous drainage (95%) and so cannot be closed by a device. A transatrial repair must include baffling the anomalous pulmonary venous drainage into the left atrium (Fig. 53-4, lower panel). The partial AVSD must also be closed surgically, since the inferior edge of these defects is the atrioventricular valve, and currently available devices would cause valvular dysfunction. Additionally, nearly all partial AVSDs involve a cleft in the anterior leaflet of the mitral valve, which requires simultaneous repair (Fig. 53-5).

Atrioventricular Septal Defects

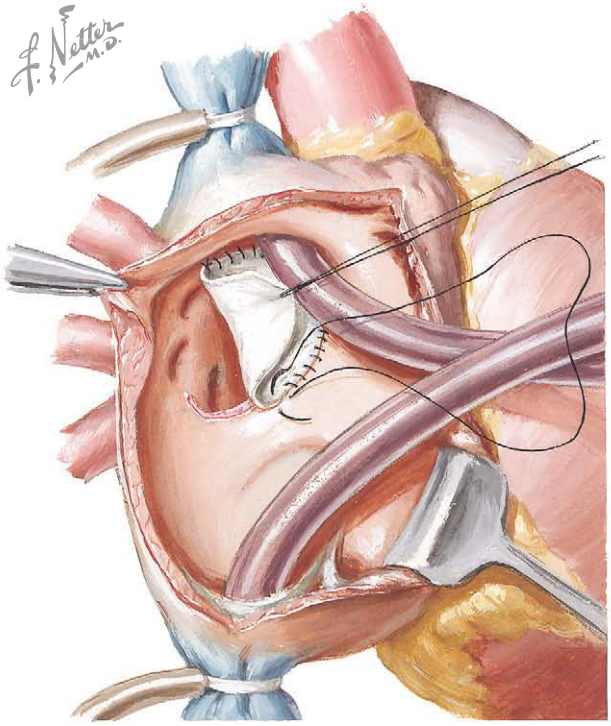
AVSDs are defects involving deficiencies in the AV septum and abnormalities of the AV valves (mitral and tricuspid), sometimes referred to as "endocardial cushion defects." AVSDs account for 4% to 5% of cases of congenital heart disease. There is a wide spectrum of lesions, with a partial AVSD being limited to a deficiency in the atrial portion of the AV septum and a common AV valve (ostium primum ASD), and a complete AVSD referring to a deficiency of the entire AV septum and a common AV valve. Down's syndrome is present in approximately 80% of patients with complete AVSDs. Complete AVSD is also seen in conjunction with tetralogy of Fallot (TOF). The mortality rate for unrepaired complete AVSDs at 2 years of age is as high as 80% because of progressive congestive heart failure and pulmonary vascular disease. Because of the high risk of developing pulmonary vascular disease, surgical repair is performed at 4 to 6 months of age. Repair is performed via a median sternotomy with CPB with exposure through a right atriotomy. The complete AVSD is repaired by either closing both the ventricular and atrial components of the septal defect with a single patch or closing each component with separate patches. The common AV valve is divided into left and right components by the septal closure. The "cleft" in the left AV valve is then closed in a manner similar to that used in the repair of the partial AVSD (see Fig. 53-5). Late insufficiency of the left AV valve following complete AVSD repair requires reoperation in 15% to 25% of patients.

Tetralogy of Fallot

Classically, TOF refers to four major congenital defects: VSD, infundibular pulmonary stenosis, dextroposition of the aorta, and RV hypertrophy (Fig. 53-6). The common anatomic abnormality responsible for all features is anterior malalignment of the outlet septum. TOF can present with a range of clinical findings: from cyanosis at birth to mild oxygen desaturation without cyanosis ("pink tetralogy"). The degree of compromise is determined by the severity of the RV outflow obstruction and the size and location of the VSD. The reported mortality rate



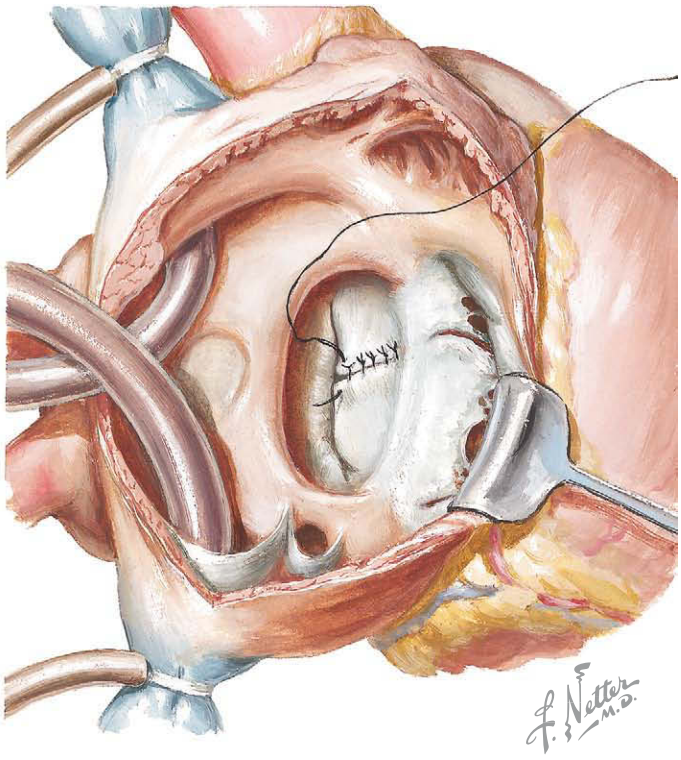
Direct suture of ostium secundum defect



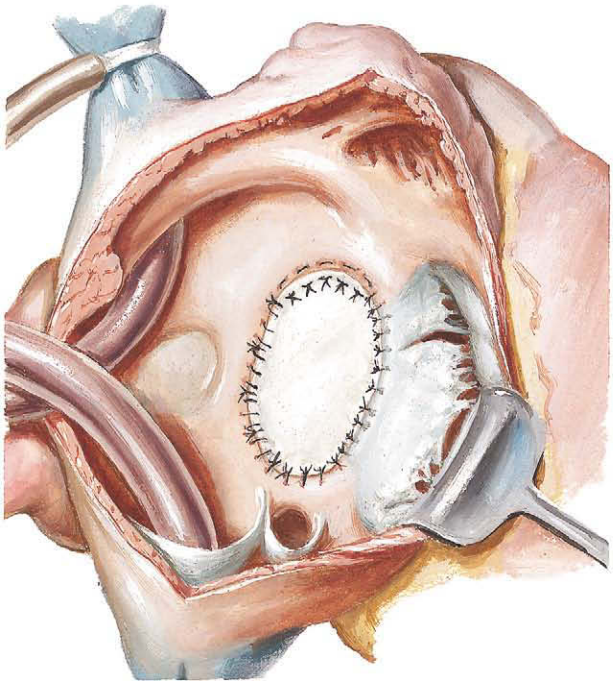
Application of patch for closure of sinus venous defect

Figure 53-4 *Defects of the atrial septum.*

Suture of cleft in mitral valve



Partial atrioventricular septal defect



Patch applied to ostium primum defect

Figure 53-5 *Endocardial cushion defects.*

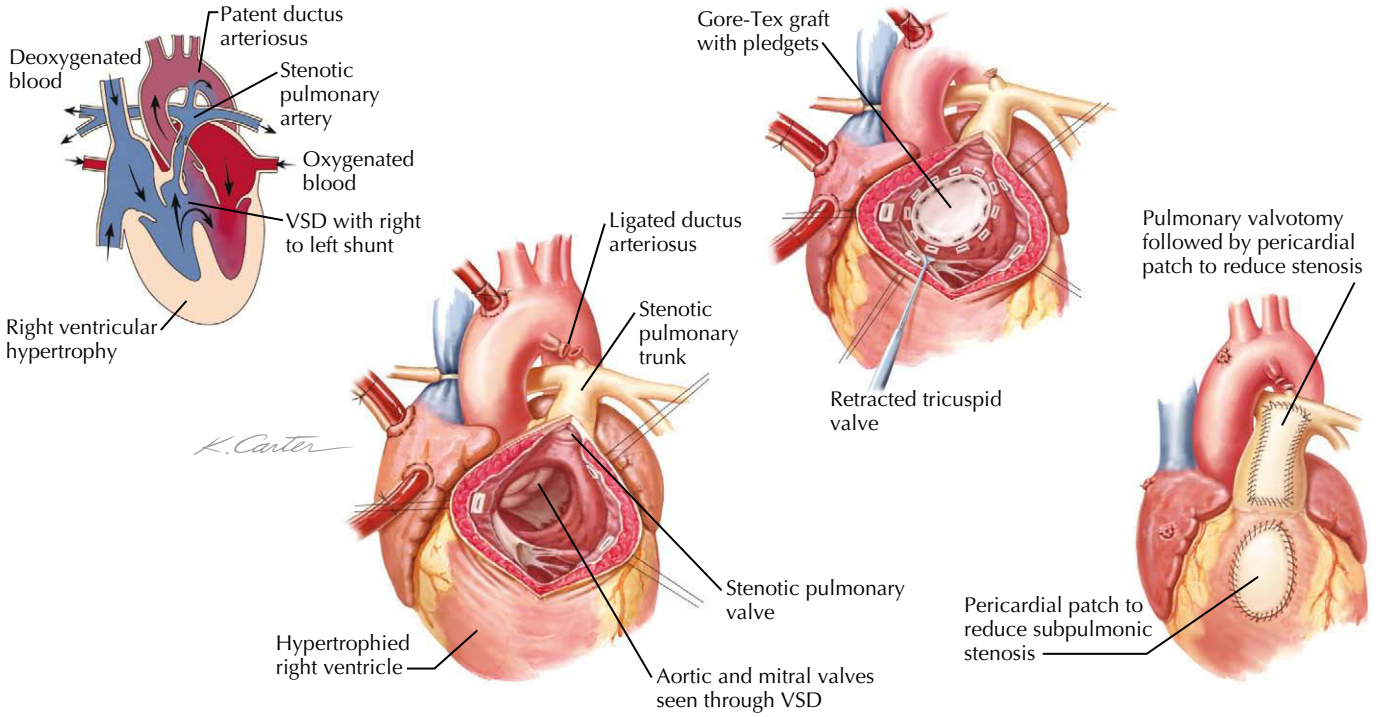


Figure 53-6 *Tetralogy of Fallot.* VSD, ventricular septal defect.

for unrepaired TOF is 30% by 6 months of age, 50% by 2 years, and up to 84% by 5 years. Infants with severe forms of TOF are often maintained on prostaglandin E_1 to support pulmonary blood flow until repair. Total correction is accomplished by closure of the VSD and relief of subvalvular, valvular, and supravalvular pulmonary stenosis. The operation can often be performed through the right atrium and pulmonary trunk, but in cases of severe outflow tract stenosis, an RV incision is required. Frequently, a diminutive pulmonary valve that cannot be repaired is present and is instead removed. The outflow tract obstruction is relieved by means of a transannular patch. The pulmonary regurgitation that results is generally well tolerated for many years, but late follow-up indicates that frequently these individuals will require late pulmonary valve insertion to avoid the development of arrhythmias and RV dysfunction.

Total Anomalous Pulmonary Venous Return

There are three types of total anomalous pulmonary venous return: supracardiac (most common, 50%), with pulmonary venous drainage into the innominate vein through a vertical vein; intracardiac, with drainage into the coronary sinus or the right atrium (least common); and infracardiac, with drainage through a descending vertical vein into the IVC. Total anomalous pulmonary venous return may present with pulmonary venous obstruction and pulmonary edema. This is one of the few true congenital heart surgical emergencies. Without surgery, the mortality rate is 100%. Surgical repair with direct anastomosis of the common pulmonary venous confluence to the left atrium can be accomplished emergently under circulatory arrest or low-flow continuous CPB.

Transposition of the Great Arteries

The neonate with discordant ventriculoarterial connections is dependent on intracardiac mixing for survival and typically presents with cyanosis at birth. The initial management of TGA with prostaglandin E_1 and balloon atrial septostomy (see Chapter 52) to increase atrial mixing is life sustaining, but the mortality rate without surgical repair is very high. Historically, the surgical correction involved an intra-atrial baffle to create AV discordance, which was then "corrected" by the ventriculoarterial discordance. Late right (systemic) ventricular failure and ventricular arrhythmias have led to widespread acceptance of the arterial switch as the optimal repair (Fig. 53-7). For this procedure, the great vessels are first transected at the sinotubular junction, and the coronary arteries are mobilized and then transferred. The ascending aorta is then anastomosed to the original pulmonary valve, which becomes the neoaorta. The pulmonary artery is then connected to the original aorta, thus correcting the discordance. Of patients with TGA, approximately 50% have a VSD that must be addressed at the initial operation.

Truncus Arteriosus

Truncus arteriosus, a relatively uncommon defect, consists of a single semilunar valve (the truncal valve) that regulates outflow from the single arterial trunk to the aorta, pulmonary arteries, and coronary circulation. The single arterial trunk overrides the interventricular septum. Patients are occasionally cyanotic at birth but most often develop symptoms of congestive heart failure within the first weeks of life. The mortality rate for untreated truncus arteriosus is as high as 65% at 6 months.

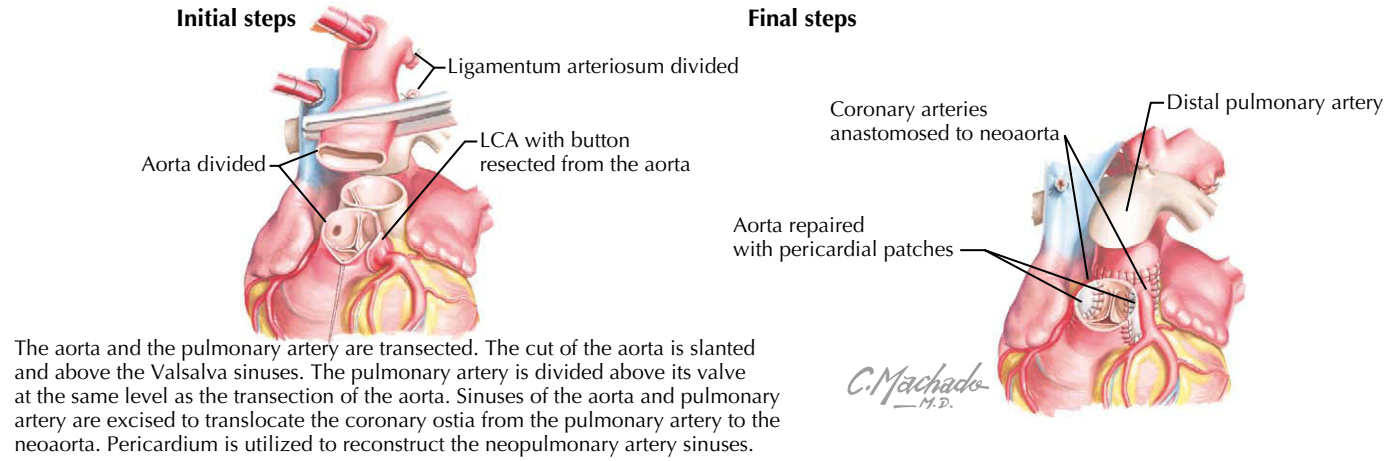


Figure 53-7 *Arterial repair of transposition of the great arteries.* LCA, left coronary artery.

Surgical repair can be accomplished safely in the neonatal period by detachment of the pulmonary arteries from the truncus, patch closure of the VSD committed to the left ventricle, and placement of a conduit from the RV to the pulmonary artery (Fig. 53-8).

AVOIDING TREATMENT ERRORS

Surgical treatment errors can result from incorrect diagnosis, inappropriate timing of treatment, and poor surgical technique. The use of a multidisciplinary team that includes pediatric cardiologists, congenital heart surgeons, pediatric intensive care

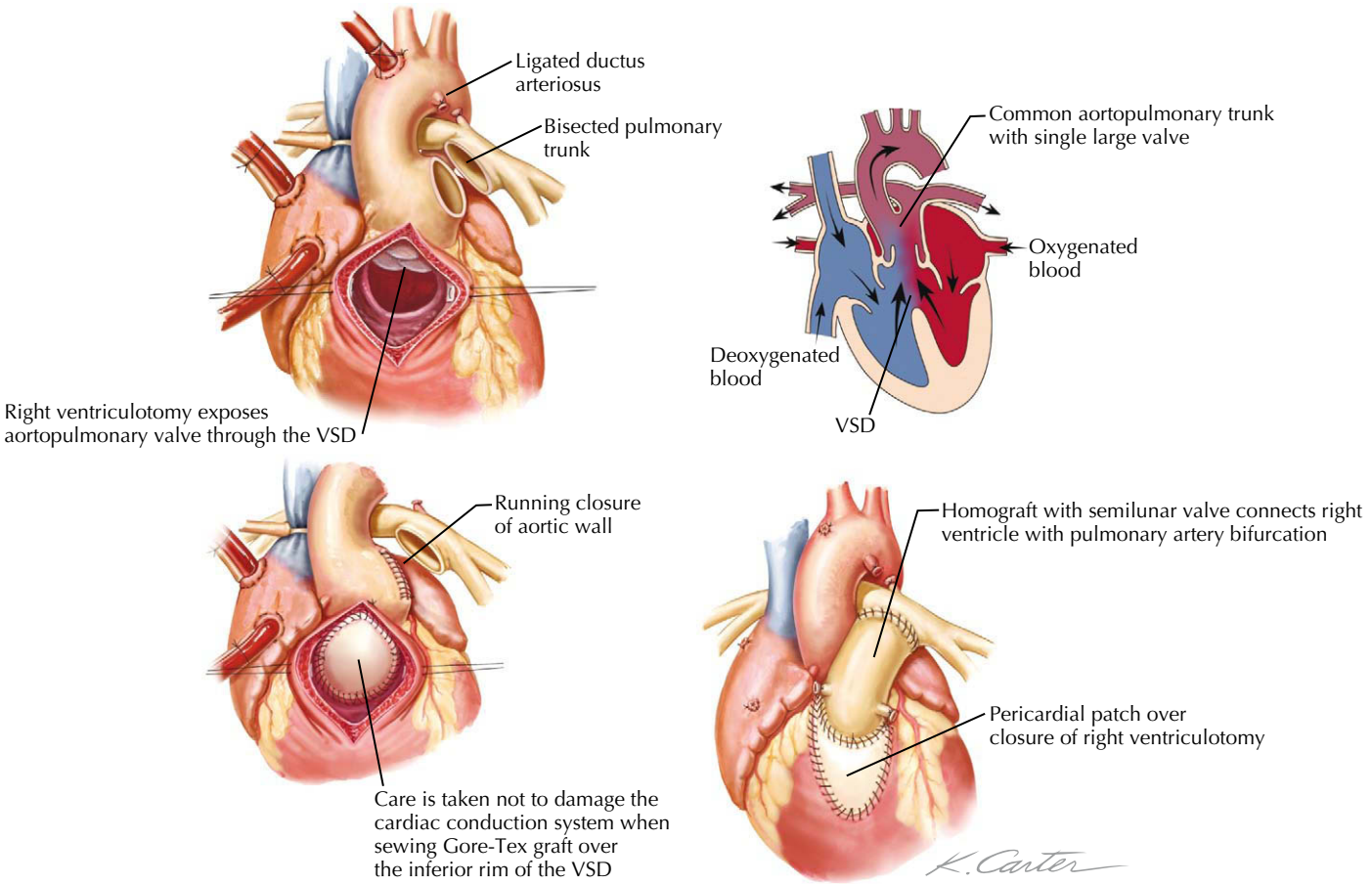


Figure 53-8 *Truncus arteriosus.* VSD, ventricular septal defect.

specialists, and pediatric cardiac anesthesiologists has become the standard of care for patients undergoing surgery for congenital heart defects. Review of preoperative studies and a comprehensive management strategy must be created for each child, with attention to the particular lesion as well as any comorbidities present. This dedicated team approach minimizes the potential complications related to anesthesia, surgery, and postoperative care.

FUTURE DIRECTIONS

The technical excellence in transcatheter techniques achieved by interventional cardiologists in parallel with ongoing efforts by surgeons to find less-invasive means to correct congenital heart defects has led to an emerging field that combines the tools of both disciplines, referred to as *hybrid surgery*. Important examples of hybrid surgery include intraoperative angioplasty and stenting of distal vascular stenoses as part of an open operative repair, perventricular echo-guided device closure of muscular VSDs through a median sternotomy, and bilateral branch pulmonary banding in conjunction with stent placement in the ductus arteriosus as an alternative to the Norwood procedure for stage 1 palliation of HLHS. The primary theoretical benefits of these combined efforts include less-invasive or -extensive operations and the avoidance or reduction in the need for CPB. While some early reports are encouraging, mid- and long-term results are still pending.

ADDITIONAL RESOURCES

Jonas RA, DiNardo J, Laussen PC, Howe R. *Comprehensive Surgical Management of Congenital Heart Disease*. London: Hodder Arnold Publication; 2004.

An outstanding textbook of congenital heart surgery from primarily the scope of a single author, Richard Jonas.

Mavroudis C, Backer CL. *Pediatric Cardiac Surgery*. 3rd ed. Philadelphia: Mosby; 2003.

The collective work of numerous outstanding surgeons, which is beautifully illustrated.

Nichols DG, Ungerleider RM, Spevak PJ, et al. *Critical Heart Disease in Infants and Children*. 2nd ed. St. Louis: Mosby; 2006.

This textbook has a greater scope than congenital heart surgery alone, with significantly more background in the medical aspects of congenital heart lesions.

Wilcox BR, Anderson RH, Cook AC. *Surgical Anatomy of the Heart*. 3rd ed. Cambridge, UK: Cambridge University Press; 2006.

Contains perhaps the most beautiful operative and anatomic photographs of congenital heart lesions ever published.

EVIDENCE

Bacha EA, Cao QL, Galantowicz ME, et al. Multicenter experience with perventricular device closure of muscular ventricular septal defects. *Pediatr Cardiol*. 2005;26:169–175.

Describes the state-of-the-art of hybrid VSD closure, including the lessons learned in developing this technique. The authors are the leading experts in the United States on hybrid congenital heart surgery.

Hjortdal VE, Redington AN, de Leval MR, Tsang VT. Hybrid approaches to complex congenital cardiac surgery. *Eur J Cardiothorac Surg*. 2002;22:885–890.

This article from Great Ormond Street describes the scope of procedures that have been modified with hybrid techniques for the treatment of congenital heart defects.

Arrhythmias in Congenital Heart Disease

54

Scott H. Buck

Advances in medical and surgical care of children with congenital heart disease have dramatically reduced mortality and, consequently, increased the population of children, adolescents, and adults with congenital heart disease. Arrhythmias are an important source of morbidity and mortality among these patients. Arrhythmias can result from congenital anomalies of the conducting system; from effects of chronic cyanosis, chamber distension, hypertrophy, and fibrosis; and from surgical intervention. Although the overall incidence of sudden death related to arrhythmias in congenital heart disease is low, subsets of patients are at considerable risk. Risk stratification continues to evolve, as do strategies for pharmacologic and nonpharmacologic arrhythmia management (Fig. 54-1).

CYANOTIC CONGENITAL HEART DISEASE

Tetralogy of Fallot

Electrocardiographic features of tetralogy typically are right ventricular (RV) hypertrophy and right-axis deviation. Among patients who have not undergone surgical repair, supraventricular and ventricular arrhythmias are rare in childhood but can increase by adolescence (Fig. 54-2). After repair, right bundle branch block is present in most patients and left-axis deviation and PR interval prolongation are also occasionally seen. Although the long-term survival rate is excellent (nearly 90% at 30 years of age), ventricular arrhythmias are common. Significant ventricular arrhythmias are present in 5% to 10% of patients' electrocardiograms (ECGs), in 20% to 40% of treadmill exercise recordings, and in 40% to 60% of ambulatory recordings (Fig. 54-3). The severity of ventricular arrhythmias increases with age at repair, RV pressure, and duration of follow-up. Electrophysiologic testing usually demonstrates a monomorphic macroreentry circuit involving the scarred RV outflow tract or the conal septum. The incidence of sudden cardiac death among long-term tetralogy survivors is 1.5% to 5%; however, the ability to identify those patients at highest risk is limited. Although some studies suggest that ambulatory recordings and/or invasive electrophysiology testing is useful, other reports are less compelling. One finding that is almost always useful is marked QRS prolongation. QRS duration of greater than 180 milliseconds indicates a risk of sustained ventricular arrhythmias and sudden cardiac death. In addition to ventricular arrhythmias, supraventricular arrhythmias are common in long-term follow-up, with atrial flutter or fibrillation present in up to 25% of patients.

D-Transposition of the Great Arteries

Electrocardiographic findings of unoperated D-transposition of the great arteries (D-TGA) primarily reflect the ventriculoarterial discordance of D-TGA (i.e., the right ventricle serving as the systemic ventricle), resulting in RV hypertrophy. Children with D-TGA require surgical repair. Atrial baffle (Mustard and Senning) procedures to direct pulmonary venous blood to the systemic (morphologic right) ventricle and systemic venous blood to the pulmonary (morphologic left) ventricle were for several decades the "repair of choice" for D-TGA (Fig. 54-4). Atrial baffle repair of D-TGA frequently produces direct trauma to the sinus node or its blood supply and creates conduction barriers by suture lines and scars—essentially substrates for atrial reentry rhythms. There is progressive loss of sinus rhythm: 5 to 10 years after atrial baffle surgery, only 20% to 40% of patients remain in sinus rhythm, 7% to 35% are in junctional rhythm, up to 40% are in slow ectopic atrial rhythm, and 10% have intra-atrial reentry. At longer follow-up, nearly half of these patients have supraventricular tachycardia, predominantly intra-atrial reentry. Loss of sinus rhythm and development of junctional rhythm are associated with an increased risk of development of symptomatic bradycardia. Ten years after atrial baffle surgery, approximately 8% of patients need cardiac pacing, which increases to approximately 20% of patients at 20 years' follow-up. Sudden cardiac death occurs in 3% to 15% of patients after atrial baffle repair, with the risk seeming to be greater among patients with decreased right (systemic) ventricular function and among patients with uncontrolled intra-atrial reentry. Since the 1980s, most infants born with D-TGA have undergone the arterial switch procedure, resulting in a significant reduction of complex atrial arrhythmias. However, simple atrial ectopy is frequently seen, speculated to be related to balloon atrial septostomy, venous cannulation, or atrial defect repair.

Tricuspid Atresia

Electrocardiographic findings of tricuspid atresia include right atrial (RA) enlargement, left-axis deviation, and increased left ventricular (LV) forces. A short PR interval is seen occasionally and is usually attributed to enhanced atrioventricular (AV) node conduction rather than to an accessory connection. Initially applied to tricuspid atresia and now increasingly to diverse single-ventricle variants, including hypoplastic left-sided heart syndrome, Fontan palliation (nearly always preceded by anastomosis of the superior vena cava to the pulmonary artery or hemi-Fontan staging) directs systemic venous blood to the pulmonary arteries (Fig. 54-5). In classic Fontan atriopulmonary connections, the sinus node or its blood supply is often interrupted and the atria are subjected to increased pressure, resulting in atrial distension, hypertrophy, and fibrosis. Surgical scars and patches produce conduction barriers that support intra-atrial reentry circuits, frequently involving the lateral atrial wall, the perimeter of the atrial septal defect (ASD) patch, and the inferomedial

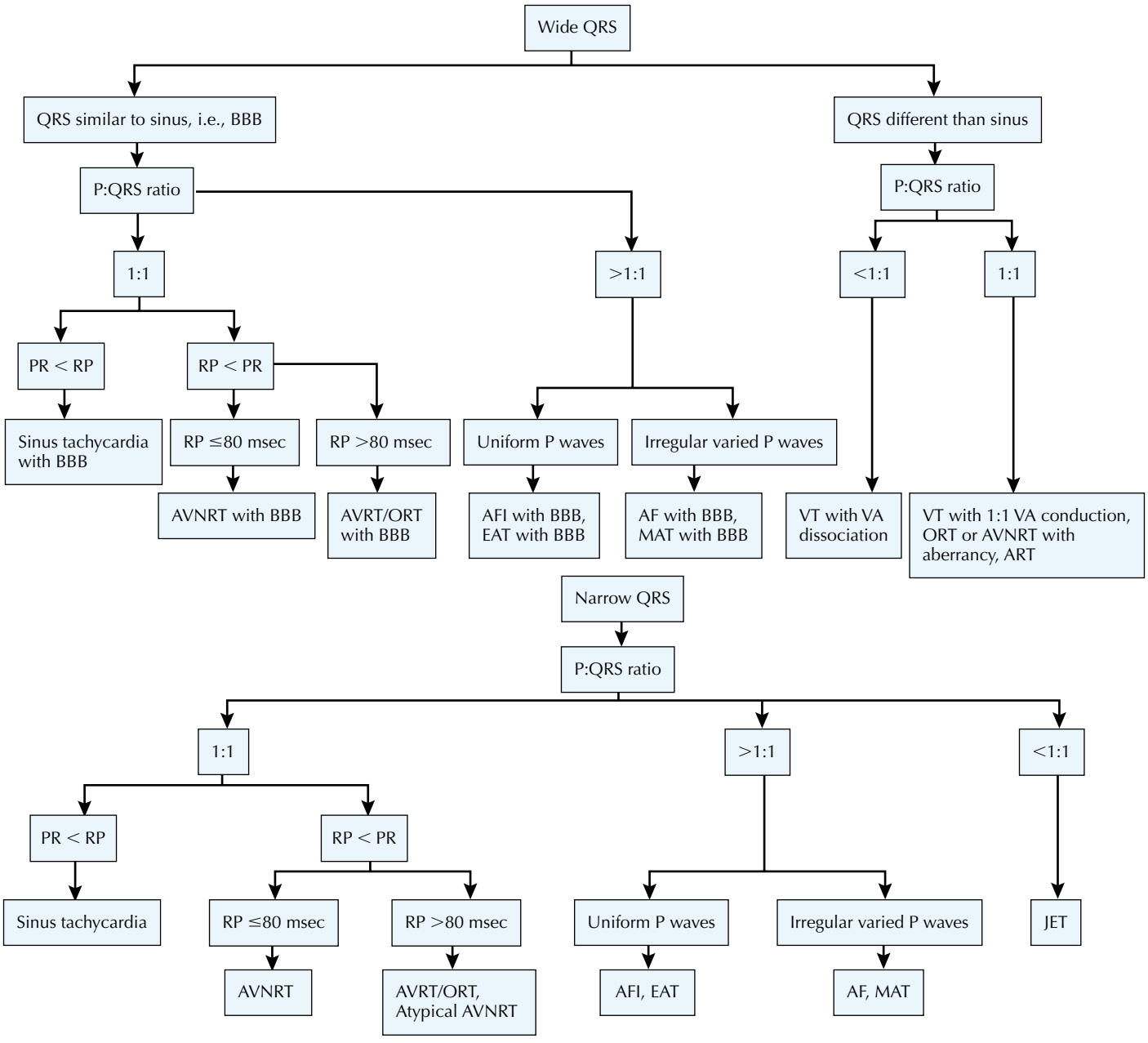


Figure 54-1 *Systematic approach to tachyarrhythmia diagnosis in congenital heart disease.* AF, atrial fibrillation; AFI, atrial flutter; ART, antidromic reciprocating tachycardia; AVNRT, atrioventricular node reciprocating tachycardia; AVRT, atrioventricular reciprocating tachycardia; BBB, bundle branch block; EAT, ectopic atrial tachycardia; JET, junctional ectopic tachycardia; MAT, multifocal atrial tachycardia; ORT, orthodromic reciprocating tachycardia; VA, ventriculoatrial; VT, ventricular tachycardia.

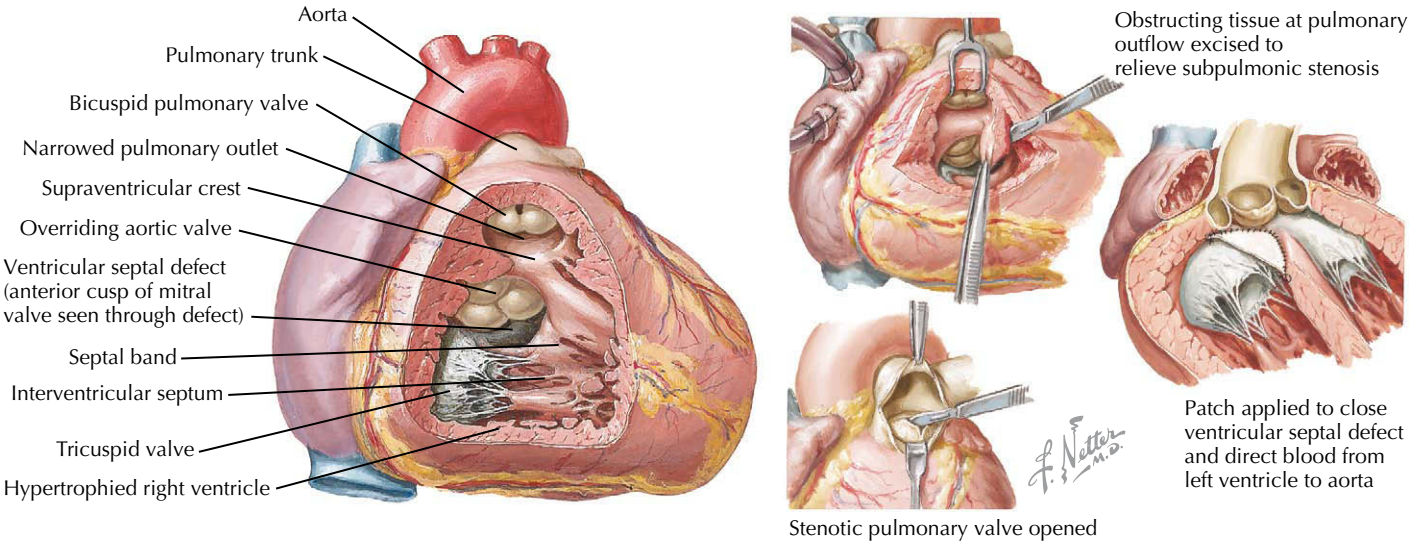


Figure 54-2 *Corrective operation for tetralogy of Fallot.*

RA isthmus, the latter also being a component of typical atrial flutter in structurally normal hearts. The incidence of late atrial tachycardia after Fontan palliation is 30% to 50% at 5 years, and 5% to 15% of these patients require permanent pacemaker implantation. Advanced patient age at follow-up, increased RA size, and increased pulmonary artery pressure are risk factors for atrial arrhythmia development (Fig. 54-6). Late sudden cardiac death occurs in 2% to 3% of patients. Modification of surgical techniques to reduce atrial distension and atrial suture lines (e.g., lateral tunnel and extracardiac conduit modifications) has apparently reduced the incidence of atrial arrhythmias, although long-term follow-up is limited.

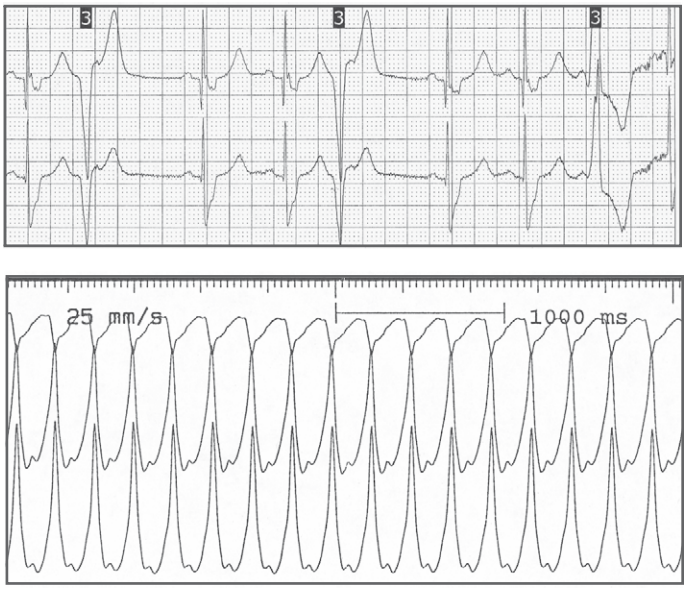


Figure 54-3 *Tetralogy of Fallot.* Sample ambulatory recording of adolescent patient after repair of tetralogy of Fallot in childhood demonstrating frequent multifocal premature ventricular beats **(upper)** and leads I, II, and III recordings from another patient after tetralogy repair with inducible ventricular tachycardia at electrophysiologic study **(lower)**.

Ebstein's Malformation

Electrocardiographic findings of Ebstein's malformation typically include RA enlargement and RV conduction delay. Accessory connection–mediated supraventricular tachycardia is reported in 23% of patients. Most commonly supraventricular tachycardias in patients with Ebstein's malformations are due to Wolff-Parkinson-White–type accessory pathways (Fig. 54-7). Concealed accessory connection–mediated tachycardia and AV node reentry tachycardia are less common. Catheter ablation techniques can be very useful in patients with Ebstein's anomaly and Wolff-Parkinson-White syndrome. However, multiple accessory connections can occur, and the altered tricuspid valve architecture results in higher procedural failure and recurrence rates compared with catheter ablation of accessory connections in structurally normal hearts. Surgical advances for improving tricuspid valve and right-sided heart function have dramatically reduced the development of late atrial reentrant tachycardia (Fig. 54-8).

ACYANOTIC CONGENITAL HEART DISEASE

Ventricular Septal Defect

ECG findings of ventricular septal defect (VSD) generally reflect the hemodynamic impact of the left-to-right shunt, with the smallest defects causing no electrocardiographic changes. Moderate defects are associated with left atrial enlargement and LV hypertrophy, and larger defects are associated with biventricular hypertrophy. Compared with the general population, adult patients who have not undergone surgery for their VSD

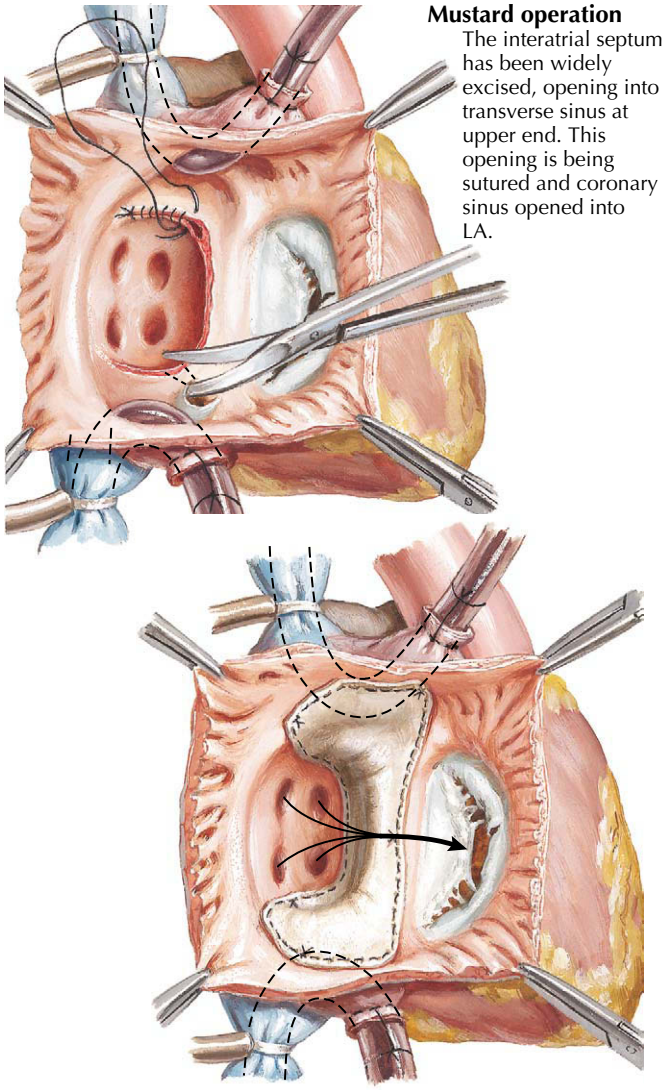


Figure 54-4 *Transposition of the great vessels.* LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

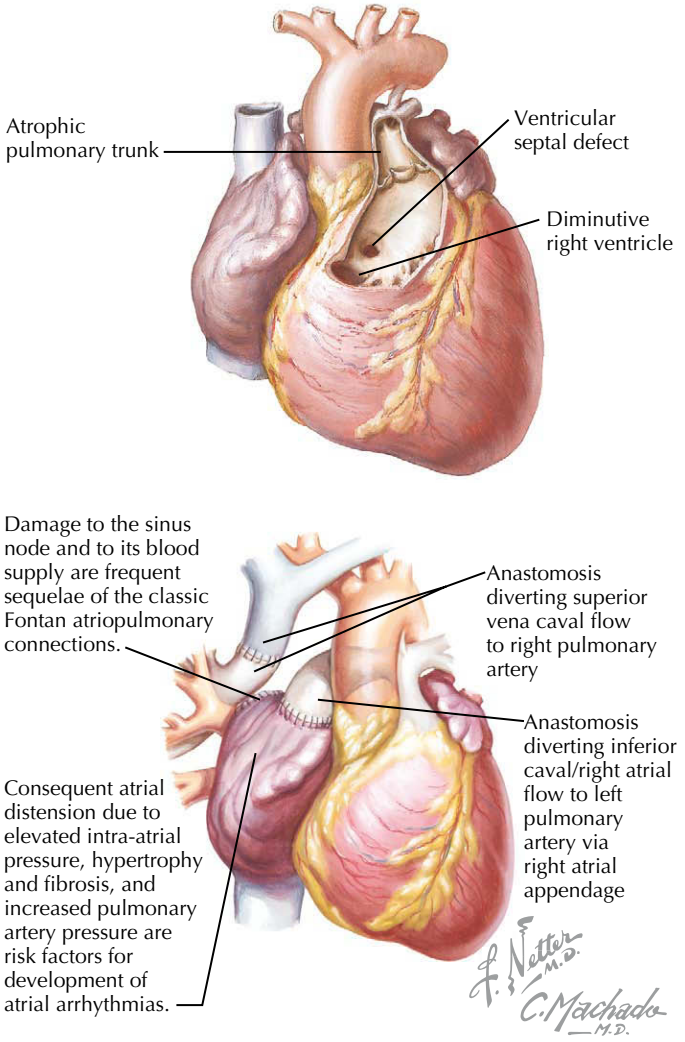


Figure 54-5 *Features of tricuspid atresia* **(upper)** *and final anatomic aspect of the classic two-stage procedure created by Francis Fontan for bypassing the right ventricle* **(lower)**. AV, atrioventricular.

have more frequent premature supraventricular beats, premature ventricular beats, ventricular couplets, and multiform premature ventricular beats by ambulatory monitoring. The incidence of arrhythmias is related to age and pulmonary artery pressure. In long-term postsurgical follow-up, the prevalence of serious arrhythmias (ventricular couplets, ventricular tachycardia, and multiform premature ventricular contractions) in adults correlates with cardiac functional status. The risk of arrhythmia is eightfold greater among patients with congestive heart failure (New York Heart Association classes II–IV) and nearly threefold greater in patients with cardiomegaly compared with patients with normal heart size. Current surgical practices, including earlier age at surgery and minimizing ventriculotomy, are anticipated to reduce the incidence of arrhythmia.

Atrial Septal Defect

ECG findings of secundum ASD typically include a normal P wave, a rightward QRS axis, and a mildly prolonged QRS

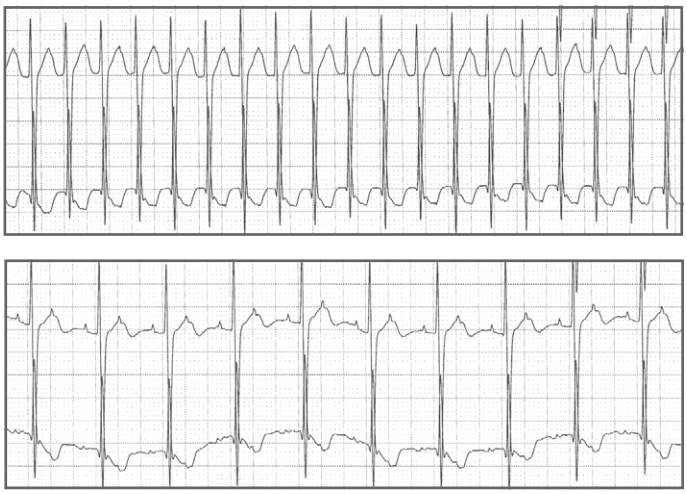


Figure 54-6 *Tricuspid atresia.* Leads V_1 and II recordings of adolescent patient after Fontan repair of tricuspid atresia demonstrating intra-atrial reentry tachycardia with 1:1 atrioventricular conduction **(upper)** and 2:1 atrioventricular conduction **(lower)**.

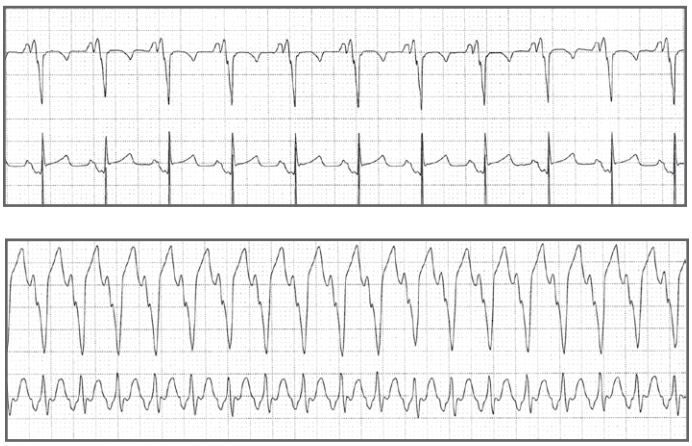


Figure 54-7 *Ebstein's malformation.* Leads V_1 and II recordings of infant with Ebstein's malformation demonstrating sinus rhythm with Wolff-Parkinson-White pattern **(upper)** and supraventricular tachycardia **(lower)**.

complex with an rSr′ or an rsR′ pattern, the latter being attributed to disproportional thickening of the RV outflow tract. Dilation of the right atrium due to left-to-right shunting is thought to be responsible for mild intra-atrial conduction delay, manifested as PR prolongation. Sinus node dysfunction based on electrophysiologic testing is an age-related finding in many children with ASD. However, symptomatic sinus node dysfunction requiring therapy is rare. Among adults who have not undergone surgery for their ASD, the incidence of atrial flutter or fibrillation increases with advancing age, and the risk increases with the magnitude of left-to-right shunting, pulmonary artery pressure, and pulmonary resistance. Sinus node dysfunction complicating ASD repair can result from cannulation for cardiopulmonary bypass but is more likely the result of direct trauma to the sinoatrial node or its blood supply and is more common among patients with sinus venosus than secundum ASD. Long-term follow-up of patients undergoing ASD repair reveals development of atrial flutter and fibrillation proportional to the patient's age at repair: from less than 5% of patients undergoing repair at 11 years or younger to 60% of patients at 40 years or older.

Patent Ductus Arteriosus

ECG findings of patent ductus arteriosus are typically normal with small left-to-right shunts; with larger shunts, LV hypertrophy and left atrial enlargement can be present. Arrhythmias are exceedingly rare in young patients with patent ductus arteriosus. However, atrial fibrillation is common among patients of advanced age who have not had repair and have long-standing volume loading and congestive heart failure.

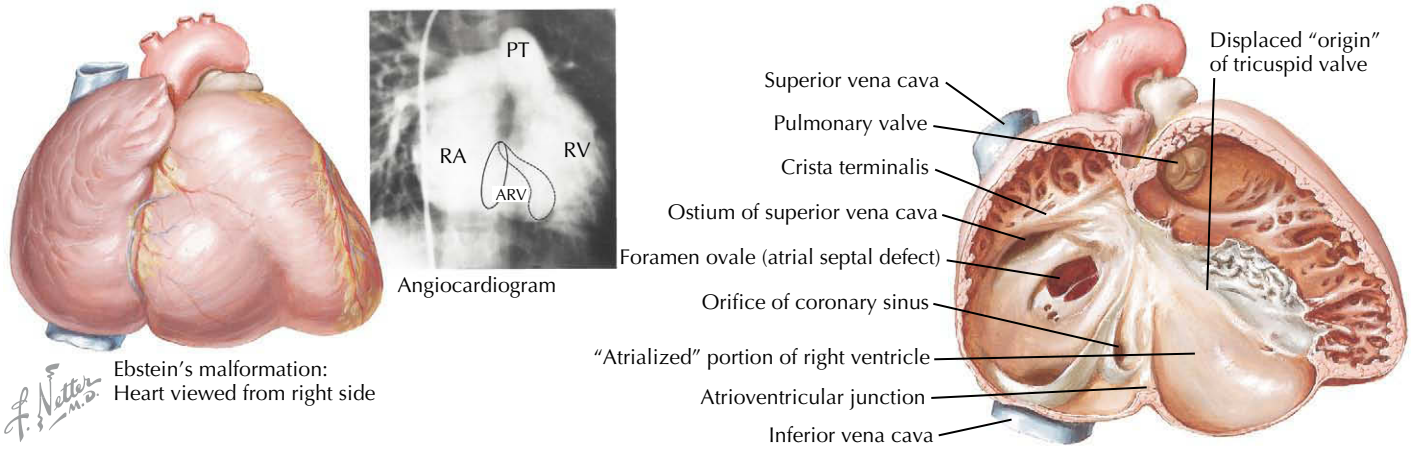


Figure 54-8 *Ebstein's malformation.* ARV, "atrialized" right ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle.

Atrioventricular Septal Defect

ECG findings of atrioventricular septal defect (AVSD) include left-axis deviation and a counterclockwise depolarization pattern. In the presence of a primum ASD or AVSD with a small ventricular component, RA and RV enlargement from left-to-right atrial shunt are present. Among patients with large atrial and ventricular components, biventricular hypertrophy and biatrial enlargement are common, especially with significant AV valve insufficiency. Arrhythmias are rare among children with AVSD who have not had surgical repair; however, a mild intra-atrial conduction delay (PR prolongation) is often seen, attributable to atrial dilatation. After repair of AVSD, atrial arrhythmias are reported in 10% of patients, and ventricular premature beats are observed in 33% by ambulatory monitoring. Arrhythmia incidence is associated with larger patient size, greater RV end-diastolic dimension, larger VSD, and the presence of postoperative right bundle branch block.

Pulmonary Stenosis

ECG features of pulmonary stenosis, right-axis deviation, and RV hypertrophy correlate well with obstruction severity. As observed by ambulatory monitoring, the incidences of premature supraventricular beats, premature ventricular beats, ventricular couplets, and multiform premature ventricular beats are more frequent among adult pulmonary stenosis patients without surgical repair compared with the general population. In long-term follow-up of adults after pulmonary valvotomy, the incidence of serious arrhythmias is approximately 25%.

Despite the relative frequency of arrhythmias and whether or not patients have undergone surgical repair, sudden death is exceedingly rare, approximately one tenth the rate among patients with aortic stenosis.

Aortic Stenosis

ECG findings do not correlate well with the severity of aortic stenosis obstruction, particularly in patients older than 10 years. The most reliable findings of severe obstruction are ST depression and T-wave inversion in lateral precordial leads. In childhood, aortic stenosis is rarely associated with arrhythmias except in individuals with critical aortic stenosis. However, as observed by ambulatory monitoring, premature supraventricular beats, premature ventricular beats, ventricular couplets, and multiform premature ventricular beats are more frequent among adult aortic stenosis patients without surgical repair compared with the general population. The incidence of serious arrhythmias (ventricular couplets, ventricular tachycardia, and multiform premature ventricular contractions) approaches 25% of patients with aortic stenosis. In long-term follow-up of adults after aortic stenosis repair, the incidence of serious arrhythmias exceeds 40% of valvotomy patients and 60% of patients after aortic valve replacement. Serious arrhythmia risk doubles for every increase of 5 mm Hg in LV end-diastolic pressure and increases more than 10-fold in the presence of moderate or severe aortic insufficiency. Sudden death is a well-recognized complication of aortic stenosis, with incidence as high as 20% at 30 years. Current surgical practices are anticipated to reduce the incidence of arrhythmia and the risk of sudden cardiac death.

L-Transposition of the Great Arteries

Electrocardiographic findings of L-transposition of the great arteries (L-TGA) typically include a normal P wave followed by QRS with reversal of the Q-wave pattern in the precordial leads (i.e., presence of the Q wave in the right precordial leads and absence in the left). Among patients with L-TGA, 4% have congenital complete AV block. Acquired AV block occurs in approximately 2% of these patients per year; eventually up to 75% of patients with L-TGA have complete heart block. Associated with Ebstein-like malformation of the tricuspid valve are accessory connection–mediated AV reciprocating tachycardias, seen in 2% to 5% of patients. Additionally, primary atrial arrhythmias increase with increasing patient age, particularly with atrial distension attributed to tricuspid valve regurgitation.

POSTOPERATIVE COMPLETE HEART BLOCK

The most common cause of acquired complete heart block in children is damage of the conduction system during cardiac surgery. It is the most common indication for pacemaker implantation in children. Complete heart block occurs in approximately 3% of operations involving cardiopulmonary bypass, most frequently among patients undergoing surgery for LV outflow tract obstruction, L-TGA, VSD, and tetralogy of Fallot. Recovery of AV conduction is reported in more than half of children, and nearly all who regain AV conduction do so within 10 days. If intact AV conduction is not present within 10 days after surgery, permanent pacemaker implantation is indicated because of the risk of sudden death among patients with junctional rhythm and AV dissociation after congenital heart surgery (Fig. 54-9).

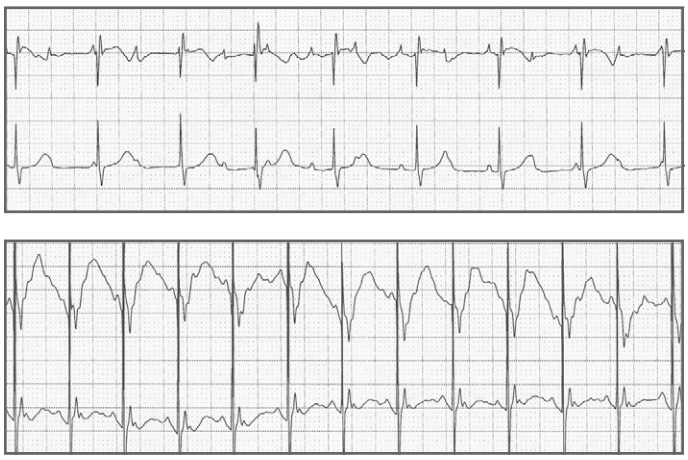


Figure 54-9 *Postoperative complete heart block.* Leads V_1 and II recordings of infant demonstrating postoperative complete heart block **(upper)** and ventricular pacing tracking atrial rhythm **(lower)**.

Table 54-1 Congenital Heart Disease and Associated Arrhythmias

Condition	Arrhythmia Risk	Comment
Atrial septal defect	Atrial flutter, atrial fibrillation, sinus node dysfunction	Arrhythmias are rare in children. Arrhythmias increase with age at repair and with age among unoperated patients.
Ventricular septal defect	Ventricular premature beats, ventricular couplets, ventricular tachycardia, premature supraventricular beats	Arrhythmias are rare among unoperated patients. Arrhythmias are more common among postoperative patients with higher NYHA functional class and with cardiomegaly.
Patent ductus arteriosus	Atrial fibrillation	Arrhythmias are very rare in children. Arrhythmias may be seen among unoperated adult patients of advanced age.
Atrioventricular septal defect	Postoperative premature supraventricular beats, ventricular premature beats	Arrhythmias increase with age at repair and with greater VSD, RV size.
Aortic stenosis	Ventricular couplets, ventricular tachycardia, multiform premature ventricular contractions	Arrhythmias increase with elevated LVEDP and with moderate or severe aortic insufficiency. Sudden death incidence is as high as 20% at 30-year follow-up.
Pulmonary stenosis	Ventricular couplets, ventricular tachycardia, multiform premature ventricular contractions	Sudden death is exceedingly rare.
D-Transposition of the great arteries	Atrial baffle repair: atrial fibrillation/flutter, sinus node dysfunction, AV block, ventricular tachycardia, pacemaker. Arterial switch repair: premature supraventricular beats	Sudden death incidence is 3% to 15% after atrial repair, and increased among patients with depressed RV function and uncontrolled intra-atrial reentry. Atrial arrhythmias are significantly reduced with arterial switch.
L-Transposition of the great arteries	Acquired AV block in ~2% per year. Atrioventricular reciprocating tachycardia in 2% to 5% due to AP.	AV block eventually in up to 75%. AP-mediated tachycardia is associated with Ebstein-like tricuspid valve.
Tricuspid atresia	Atrial fibrillation/flutter, sinus node dysfunction, AV block, pacemaker are common among atriopulmonary Fontan single-ventricle repair patients.	Arrhythmias increase with follow-up duration, RA size, PA pressure. 30% to 50% atrial arrhythmias at 5 years. Pacemaker is required in 5% to 15%. Late sudden death occurs in 2% to 3%.
Ebstein's malformation	AV reciprocating tachycardia due to AP	AP-mediated tachycardia occurs in 23%.
Tetralogy of Fallot	Ventricular premature beats, ventricular couplets, ventricular tachycardia, atrial tachycardia, atrial flutter	There is 90% long-term survival. Severe ventricular arrhythmia and sudden death risk increase with QRS duration >180 ms.
Postoperative complete heart block	Occurs in ~3% of congenital heart repairs involving cardiopulmonary bypass.	Permanent pacemaker is indicated when AV conduction is absent 10 days following surgery.

AP, accessory pathway; AV, atrioventricular; LVEDP, left ventricular end-diastolic pressure; NYHA, New York Heart Association; PA, pulmonary artery; RA, right atrial; RV, right ventricular; VSD, ventricular septal defect.

FUTURE DIRECTIONS

Although most children with congenital heart disease survive into adulthood, the prevalence of arrhythmias poses significant challenges (Table 54-1). It is likely that continuing surgical advances will further decrease the development of arrhythmias. Earlier definitive surgical intervention is being performed to minimize the deleterious effects of chronic hypertrophy, volume loading, fibrosis, and cyanosis in the development of a substrate for arrhythmia. Surgical techniques to minimize ventriculotomy and extensive atrial incisions that result in damage to specialized conduction tissues and to formation of conduction barriers, favoring development of reentrant rhythms, will probably decrease the development of arrhythmias. Despite these advances, arrhythmias will certainly continue to be an important source of risk of morbidity and mortality, necessitating pharmacologic and nonpharmacologic therapies.

The goal of drug therapy is to reduce the occurrence of significant atrial and ventricular arrhythmia while minimizing the risks of drug-induced proarrhythmia and other adverse drug effects. Drug treatment is further complicated by negative inotropy and chronotropy of the majority of available antiarrhythmic agents and could be improved by new antiarrhythmic agents. Invasive electrophysiologic studies and radiofrequency ablation or cryoablation are increasingly important in managing congenital heart disease and arrhythmia.

Although the locations of the specialized conducting tissues and the anatomic cardiac connections are complex, short-term procedural success and freedom from arrhythmia after ablation procedures are favorable. New intracardiac contact and noncontact mapping techniques are particularly useful in characterizing arrhythmia circuits in patients with congenital heart disease. Refinements of ablation energy-delivery systems are improving

long-term results, including specialized catheters capable of greater ablation lesion depth.

Indications for device therapy in the management of arrhythmias in congenital heart disease continue to expand. Antibradycardia pacing in patients with sinus node dysfunction and intra-atrial reentry tachycardia can reduce tachycardia episode frequency and can provide chronotropic competence. General recommendations for implantable cardioverter-defibrillator (ICD) placement in children and adolescents are similar to those for adult patients; however, specific indications in pediatric series are different from adult series because of the heterogeneity of disease processes in pediatric patients compared with the predominance of ischemic or postinfarction disease in adults. In the largest pediatric ICD series thus far, the overall frequency of appropriate shocks was 26%; however, nearly as many patients received inappropriate device discharges. Among adult patients with tetralogy of Fallot and ICD, the reported annual rate of appropriate ICD shocks for primary and secondary prevention was 7.7% and 9.8%, respectively; 5.8% annually received inappropriate discharges, and nearly 30% experienced other complications during the study.

Finally, surgical therapy, such as modifications of the maze procedure for recurrent atrial reentrant rhythms, will continue to be an important component of arrhythmia management. These therapeutic advances, along with contemporary primary surgical management, will continue to improve the long-term outcome of patients with congenital heart disease.

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Cardiopulmonary Exercise Testing in Children with Congenital Heart Disease

55

James P. Loehr

Exercise is a common physiologic stress that places demands on multiple organ systems, including skeletal muscle, cardiac muscle, and the pulmonary and systemic circulations. The physiologic response of the heart (to increase cardiac output by increasing heart rate and stroke volume) and lungs (to increase ventilation capacity) to this stress are tightly coupled with the metabolic demands of exercising muscle.

Increased skeletal muscle contraction that occurs with exercise increases the demand for oxygen delivery and for the clearance of important by-products of metabolic work, including CO_2, lactate, and heat (Fig. 55-1). Several processes, including increased oxygen extraction from blood perfusing the active muscles, vasodilation of selected peripheral vascular beds, increased cardiac output, and increased pulmonary blood flow and ventilation, mediate this increased demand. The body's capacity to deliver and utilize oxygen is determined empirically as maximum oxygen consumption (Vo_{2max}). As defined by the Fick principle, the relationship between oxygen consumption (Vo_2), cardiac output (CO), and the arteriovenous oxygen difference (AVo_2 difference) is

$$Vo_2 = CO \times (AVo_2 \text{ difference}).$$

By further describing CO as the product of stroke volume (SV) and heart rate (HR), the relationship becomes

$$Vo_2 = HR \times SV \times (AVo_2 \text{ difference}).$$

Early in exercise, cardiac output is augmented by increases in stroke volume (contractility) and heart rate. Increased venous return and ventricular filling pressure may in part cause increased stroke volume as predicted by the Frank-Starling relationship. Later in exercise, increases in cardiac output are more closely related to increases in heart rate. The heart rate response to exercise is mediated by increased sympathetic tone and decreased parasympathetic (vagal) influence on the heart. Increased heart rate generally parallels increased oxygen uptake and workload and occurs primarily at the expense of diastolic time, which, in some disease states, can result in inadequate ventricular filling time at elevated heart rates. The AVo_2 difference, which normally results in about 23% extraction of oxygen at rest, may increase more than threefold at Vo_{2max}. Arterial oxygen levels remain essentially normal throughout exercise in individuals with normal cardiopulmonary function.

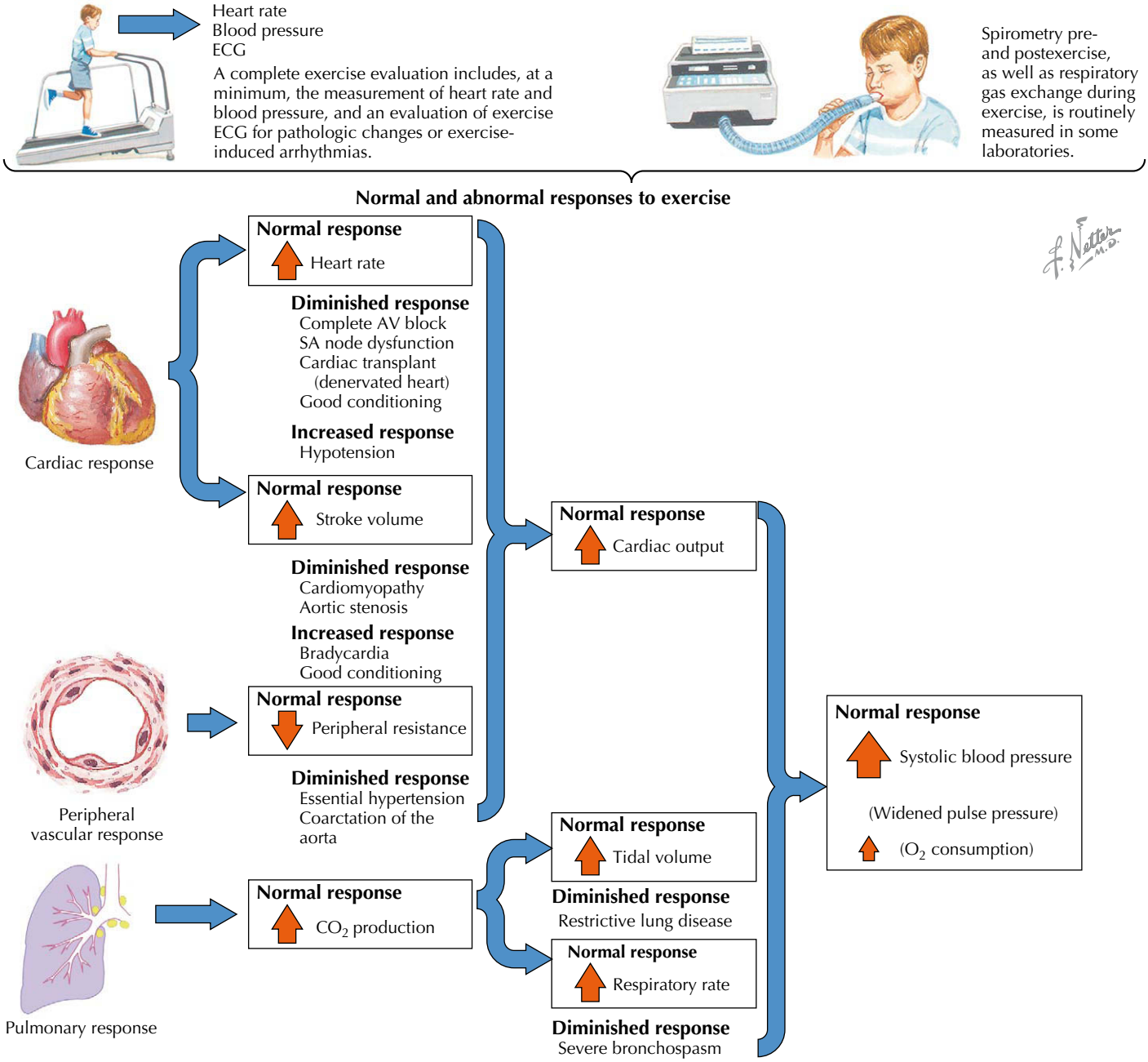
Mean arterial blood pressure is essentially the product of cardiac output and peripheral vascular resistance. The increased cardiac output that occurs with exercise is associated with a marked decrease in peripheral vascular resistance, resulting in a progressive increase in systolic blood pressure and unchanged or mildly decreased diastolic blood pressure. The expected increase in systolic pressure is positively related to body size and age. Attenuated systolic blood pressure responses to exercise may reflect a limitation of cardiac output or an alteration of vascular resistance control.

The ventilatory response to exercise is tightly coupled with production of CO_2. Both tidal volume and respiratory rate increase during progressive exercise to keep pH and Pco_2 (partial pressure of CO_2) constant over a wide range of metabolic work rates. Acidosis occurs only during heavy exercise because of increased blood lactate concentrations. Dyspnea occurring during moderate exercise is due to the increased need for CO_2 release and the tight coupling of minute ventilation to CO_2 production. Further increases in CO_2 production with intense exercise result in a decline in serum sodium bicarbonate, a disproportionate increase in hydrogen ion levels, and consequent acidosis, resulting in a hyperventilatory response.

NORMAL RESPONSES OF CHILDREN TO EXERCISE

A complete exercise evaluation includes, at a minimum, the measurement of heart rate and blood pressure and evaluation of the exercising ECG for pathologic changes and for the presence or absence of exercise-induced arrhythmias. In children, the normal response to exercise is for the heart rate to increase due to sinus tachycardia to a maximum of 190 to 200 bpm, with no evidence of atrioventricular block during exercise. The presence of atrial and/or ventricular ectopy, either of which can be stimulated by exercise, is considered an abnormal response. ECG intervals follow characteristic changes; the PR interval generally shortens with exercise and the resultant tachycardia. The QRS duration remains unchanged or shortens slightly. The normal response of the QT interval is to be unchanged or to shorten, but this shortening is often difficult to document because of the merging of the end of the T wave with the following P wave. The interpretation of the ST segment is sometimes difficult because of physiologic J-point depression, but the normal slope of the ST segment at peak exercise is upward instead of flat or downward.

The normal blood pressure response is dictated by the complex interaction of increased cardiac output, caused by increased heart rate and stroke volume, and vasodilation in the peripheral vascular bed. In normal exercise, systolic blood pressure increases progressively, to levels as high as 230 mm Hg in adolescents and adults, whereas diastolic pressure changes less dramatically. The anticipated increase in blood pressure is related to body size and age of the individual. Pathologically



The physiologic response to the increased metabolic demands of exercise is multifactorial. The ability of the cardiovascular system to respond to such demands may be diminished by congenital structural or electrical abnormalities, which diminish or restrict the response to exercise.

Figure 55-1 *Physiologic effects of exercise.* AV, atrioventricular; ECG, electrocardiogram; SA, sinoatrial.

high blood pressure responses can occur in individuals with resting hypertension and in individuals with either occult or poorly repaired aortic arch obstruction such as coarctation of the aorta. A diminished blood pressure response is generally attributed to an inadequate exercising cardiac output response, which may be secondary to a variety of factors, including an inadequate heart rate response or a limitation of stroke volume caused by obstructive lesions (such as valvular aortic stenosis) or by diminished contractility (in cardiomyopathic states). Individuals with decreased peripheral vascular resistance may also have a diminished blood pressure response to exercise despite adequate cardiac output.

Some pediatric exercise laboratories routinely measure respiratory gas exchange during exercise. The most useful measurement is that of Vo_{2max}, which is influenced by cardiac output, ventilatory capacity, and the degree of extraction of oxygen by exercising tissue. During incremental exercise, oxygen consumption and CO_2 production increase in parallel to workload; at higher rates of oxygen consumption, there is a disproportionate increase in CO_2 production, resulting in further stress on

the respiratory system to compensate for this increase in CO_2. The point at which this phenomenon (disproportionately increased CO_2 production) occurs is called the *ventilatory anaerobic threshold*. In children in whom the ventilatory anaerobic threshold is reached earlier than anticipated, one should consider both congenital (or acquired) cardiac and pulmonary anomalies, as well as deconditioning. Individuals who are especially fit (well conditioned) typically reach their ventilatory threshold later than would be anticipated.

An estimate of stroke volume may be derived by dividing oxygen consumption by the heart rate, referred to as the *oxygen pulse* (oxygen pulse = Vo_2/HR). The oxygen pulse measurement is probably proportional to changes in stroke volume at low levels of exercise, but this measurement loses that proportionality at more rapid heart rates because of the contribution of increased oxygen extraction from the tissues to oxygen consumption. Nevertheless, lesions associated with poor ventricular function are associated with low maximum oxygen pulse.

Finally, the measurement of ventilation is useful. Although the rate of change in ventilation is proportional to the change in CO_2 production, the slope of that increase is higher in patients with congestive heart failure. Spirometry performed before and after exercise can demonstrate exercise-induced bronchospasm, which can be relieved by use of an inhaled bronchodilator.

CHARACTERISTIC PATHOLOGIC EXERCISE RESPONSES IN PATIENTS WITH CONGENITAL STRUCTURAL HEART DISEASE

Coarctation of the Aorta

Characteristically, children with poorly repaired coarctation of the aorta who are asymptomatic have normal exercise capacity, but their systolic blood pressure increases excessively with exercise. This increase in blood pressure tends to occur at both submaximum and maximum effort. Even after successful repair, exertional hypertension may occur, particularly in those who underwent surgery later in life. The potential etiologies of late hypertension include increased aortic stiffness, pressure gradients within the aorta due to differential growth of segments of the aortic arch before repair of the coarctation, and, possibly, increased flow acceleration across the aortic valve from increased left ventricular mass.

Left Ventricular Outflow Tract Obstruction

In contrast to coarctation of the aorta, severe obstruction of left ventricular outflow (from either valvular or subvalvular aortic stenosis) is associated with an attenuated increase, or even a decrease, in blood pressure during exercise. Presyncope or syncope can occur when exertional cardiac output is unable to compensate for the normal peripheral vasodilatory response to activity. Pathologic ST-segment depression can occur during exertion from subendocardial ischemia related to the presence of ventricular hypertrophy, high diastolic ventricular pressures, and low cardiac output. Interestingly, in contrast to adults, ST-segment depression in children is frequently not associated with chest discomfort.

Pulmonary Stenosis

Pulmonary stenosis with an intact ventricular septum is a common anomaly that results in fixed right ventricular outflow tract obstruction, which may limit cardiac output. Exercise tolerance is usually normal in individuals with mild pulmonary stenosis but may be impaired in those with more severe disease. The impairment resolves with relief of the obstruction in childhood.

Atrial Septal Defect

Individuals with an atrial septal defect who have undergone repair in childhood have normal or near-normal exercise tolerance. A decreased maximum heart rate has been reported, however. Exercise intolerance may be related to poor diastolic compliance of either ventricle. If there is both an unrepaired atrial defect and a significant degree of right ventricular dysfunction, oxygen saturation will occasionally fall during exercise.

Tetralogy of Fallot

The principal concern in the adolescent or the adult who has survived tetralogy of Fallot repair is the association of sudden cardiac death with a poor hemodynamic result and the presence of ventricular arrhythmias. Patients with surgically repaired tetralogy of Fallot routinely undergo exercise testing primarily to examine their cardiac rhythm during maximum activity. The finding of exertional ventricular arrhythmias frequently leads to further evaluation and surgical or medical intervention.

Individuals with tetralogy of Fallot who have only undergone palliation with a systemic-to-pulmonary artery shunt have markedly reduced Vo_{2max} and an increased ventilatory response to exercise. If complete surgical repair is performed in childhood, however, and the patient has regular physical activity, the resulting exercise capacity is frequently in the normal range. The mean heart rate and oxygen consumption in this group of patients, however, is mildly decreased compared with normal controls.

Transposition of the Great Arteries

In individuals who have undergone the atrial repair of transposition of the great arteries (the Mustard or Senning procedure), the right ventricle functions as the systemic ventricular chamber. These individuals are subject to frequent atrial arrhythmias and sinus node dysfunction. Although most report that they are asymptomatic early in life, decreased work performance and Vo_{2max} are found on formal testing. This finding is generally associated with a decreased maximum heart rate but may also be partially due to poor right ventricular stroke volume augmentation with activity. Exercise capacity after performance of the arterial switch procedure for transposition of the great arteries is a subject of ongoing investigation.

Physiology of Single-Ventricle Malformation

The heterogeneous group of individuals with single-ventricle malformations usually undergoes the Fontan procedure as

palliation. Before the Fontan procedure is performed in this group of patients, exercise capacity is markedly reduced, associated with an increased ventilatory response to exercise and decreased systemic oxygen levels that are probably the result of decreased pulmonary blood flow and increased intracardiac right-to-left shunting. Performance of the Fontan procedure results in improvement in these parameters, but the patient's exercise capacity after the Fontan procedure remains decreased. Formal measurements of cardiac output support the inference that the decreased capacity results from a diminished heart rate response and a decreased stroke volume response to exercise. A frequent finding is an increase in the ratio of ventilation to CO_2 production (VE/Vco_2) slope, suggesting inefficient gas exchange even after Fontan completion.

Cardiac Rhythm Disturbances

Premature ventricular contractions are a frequent finding in healthy children. The normal response is for exercise to suppress this arrhythmia, although it may only be suppressed at very elevated heart rates. Conversely, the induction of couplets or ventricular tachycardia with exercise is abnormal and warrants further investigation. Premature atrial contractions are common and usually benign in childhood. Unlike ventricular ectopy, the persistence of premature atrial beats with exercise is not considered to be ominous. Patients with congenital complete atrioventricular block have diminished resting and exertional heart rates and may demonstrate ventricular arrhythmias with exercise.

Patients with Wolff-Parkinson-White syndrome may demonstrate supraventricular tachycardia with exercise. Disappearance of the delta wave may result from exertional sinus tachycardia, suggesting a long refractory period for the accessory connection. Disappearance of the delta wave with exertion may be a helpful finding, but it cannot be used as the sole criterion for determining management.

FUTURE DIRECTIONS

Exercise testing provides a unique estimate of the heart's functional capacity and the response of the heart to an important physiologic stress. Although the most common use of exercise testing in adults is in the evaluation of patients for possible coronary artery disease, exercise testing is being used increasingly in the assessment of overall cardiopulmonary function in a variety of disease states. Increasingly, patients facing heart or lung transplantation, patients facing partial lung resection, and patients with a limitation of maximum cardiac output from congenital heart disease are being subjected to exercise testing as part of their overall evaluation. Future investigations of the exercise responses of individuals with inborn errors of metabolism will probably add further insight into the physiology of human exercise.

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Kawasaki's Disease

Blair Robinson

56

Kawasaki's disease is a multisystem vasculitis, first recognized in 1961 and subsequently described in 1967 by Dr. Tomisaku Kawasaki. Kawasaki's disease was initially thought to be a benign, self-limited febrile illness. The association of the disease with the development of coronary aneurysms and subsequent mortality did not become evident until the 1970s. Since then, Kawasaki's disease has been recognized in all populations and is now reported to be the most common acquired heart disease in U.S. children, replacing rheumatic heart disease.

The incidence of Kawasaki's disease varies among ethnic groups. It is highest in children of Asian ancestry (90 per 100,000 in Japan) and lowest in certain Europeans (3 per 100,000 in Britain). The U.S. incidence is 17 per 100,000 in African-Americans, 11 per 100,000 in Hispanics, and 9 per 100,000 in Caucasians. Kawasaki's disease usually occurs in children 1 to 2 years of age, with 80% of cases diagnosed in children younger than 4 years of age. However, the diagnosis has been made in children of all ages. Males are more commonly affected than females (a ratio of 1.5 : 1).

ETIOLOGY AND PATHOGENESIS

The etiology of Kawasaki's disease is unknown. A genetic predisposition to the disease is suggested by the higher incidence in children of Asian ancestry and in siblings. The occurrence of the disease in siblings also suggests exposure to a common causative agent. Various bacteria, viruses, heavy metals, and detergents have come under suspicion as etiologic agents. A superantigen (toxin)-mediated hypothesis has been proposed, but large multicenter studies have failed to conclusively identify any single etiologic agent or group.

Kawasaki's disease is a nonspecific vasculitis that affects small- and medium-sized arteries throughout the body. Its most serious consequences evolve in phases within the coronary arteries (Fig. 56-1).

The acute febrile phase of Kawasaki's disease may last less than a day or up to 10 days. Inflammation in the coronary artery walls consisting mostly of polymorphonuclear cells may occur. An increased ratio of T4 (helper) to T8 (suppressor) cells has been found in vessel walls during the acute phase. Pancarditis may also develop during the acute phase. However, the mortality rate during this phase is low, and death is thought to occur only in severely affected individuals as a result of myocardial dysfunction or arrhythmias.

The subacute phase lasts 10 to 40 days. An accumulation of cytokines, B cells, and T cells in the vessel walls may cause fragmentation of the internal elastic lamina of the coronary arteries and, subsequently, formation of an aneurysm. Thrombocytosis occurs simultaneously and predisposes patients to acute coronary thrombosis, the leading cause of mortality during this phase of the illness.

The convalescent phase (beyond 40 days) consists of healing and fibrosis of the coronary aneurysms formed during the subacute phase. A stenosis may occur at such sites, with resulting ischemia, infarction, and death. Of all deaths, 70% occur in infants younger than 1 year of age, and almost all deaths occur during the convalescent phase.

The risk factors for the development of coronary artery disease include fever lasting more than 14 days, recurrence of fever or rash, treatment with intravenous immunoglobulin (IVIG) more than 10 days into the acute illness, male sex, and age younger than 1 year.

CLINICAL PRESENTATION

Fever is the cardinal presenting sign of Kawasaki's disease and persists for more than 7 days in more than 95% of patients. It responds only temporarily to antipyretic therapy and may last up to 2 weeks in patients who are not treated with IVIG. Within 5 days of the onset of fever, 90% of patients develop a polymorphous rash predominantly over the trunk (Fig. 56-2). This may be a diffuse maculopapular rash, or it may be a more urticarial rash. Rarely, perineal desquamation is seen in the subacute phase. Mucosal changes, erythema, and fissuring of the lips occur in 90% of patients. Pharyngitis and prominent papillae ("strawberry tongue") are also typical signs. Within the first week of the illness, bilateral conjunctivitis, consisting of a discrete vascular injection with absence of corneal clouding or purulent exudates, develops in 90% of patients. The bilateral conjunctivitis persists for 1 to 2 weeks. Anterior uveitis is a common finding on slit-lamp examination. Indurative edema and erythema of the hands and feet occur in 75% to 90% of patients. Desquamation of the fingertips and/or the palms and the soles may occur 2 to 3 weeks after the acute illness. Cervical lymphadenopathy, the least consistent finding, occurs in approximately 50% of patients. It is usually unilateral, and the diameter of the nodes may exceed 15 mm.

Although the diagnosis of Kawasaki's disease generally requires fever plus four of the multiple findings described under Differential Diagnosis, some patients with Kawasaki's disease may have an atypical presentation that does not fulfill the diagnostic criteria. These patients are usually younger than 1 year or older than 8 years, and their condition is commonly misdiagnosed.

Additional clinical findings include gastrointestinal signs, such as emesis, diarrhea, and jaundice (40%); arthralgias (30%); aseptic meningitis (25%); and pancarditis with myocardial dysfunction, pericardial effusion, and valvar insufficiency (50%). Common laboratory findings include leukocytosis, thrombocytosis (platelet count >450,000 in 50% of patients), elevated acute-phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein, immunoglobulin E, α_2-globulin), elevated transaminases, sterile pyuria, and proteinuria.

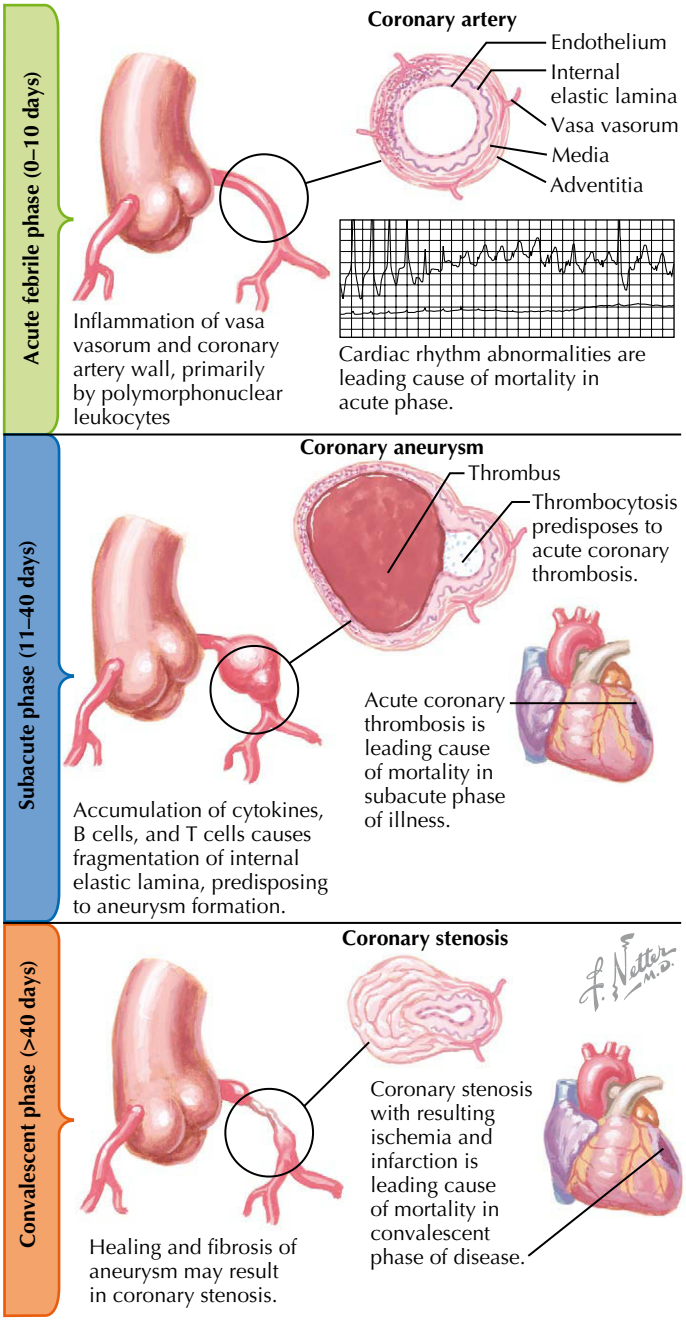


Figure 56-1 *Pathogenesis and clinical course of Kawasaki's disease.*

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC APPROACH

Because the etiology of the disease is unknown, "Kawasaki's disease" remains a clinical diagnosis. Classically, the diagnosis of Kawasaki's disease requires 5 days of fever and four of the following: rash, oral mucosal changes, conjunctivitis, extremity changes, and cervical lymphadenopathy (Box 56-1). Laboratory findings such as elevated white blood cell counts, ESR, and platelet counts are supportive of the diagnosis but are not pathognomonic. The characteristic pathologic findings in the coronary arteries are not visible during the acute febrile illness and therefore are not useful in differentiating Kawasaki's disease from other illnesses with similar clinical presentations.

Because ongoing inflammation is an important risk factor for the development of coronary artery aneurysms, early diagnosis and treatment are imperative. However, as noted, differentiating Kawasaki's disease from other illnesses with similar clinical features can be difficult, thus complicating the decision to treat aggressively.

The differential diagnosis includes measles, scarlet fever, toxic shock syndrome, staphylococcal scalded-skin syndrome, drug hypersensitivity reactions, Rocky Mountain spotted fever, and juvenile rheumatoid arthritis. Distinguishing measles from Kawasaki's disease may be difficult, but important differences are typically found. Both illnesses may present with a polymorphous rash and swelling of the hands and feet. However, in measles, conjunctivitis is exudative and oral lesions (Koplik's

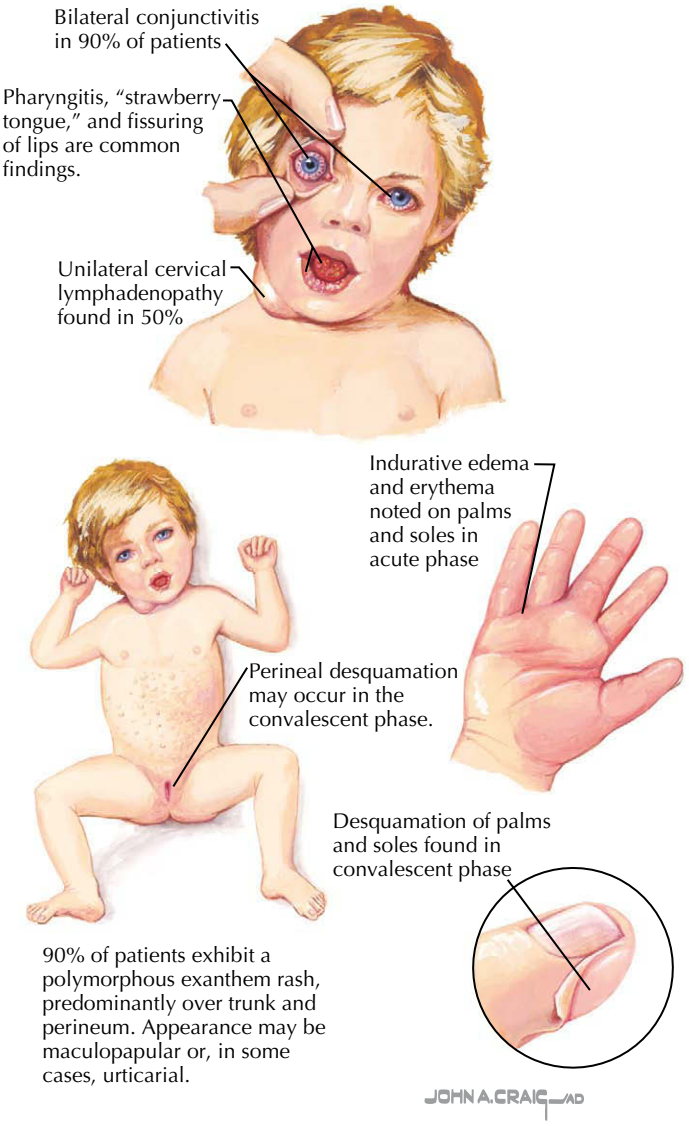


Figure 56-2 *Clinical features of Kawasaki's disease.*

Box 56-1 Diagnostic Findings of Kawasaki's Disease

Fever persisting for more than 5 days plus four of the following:
- Bilateral, nonexudative conjunctivitis
- Polymorphous exanthem
- Peripheral extremity changes: indurative edema, erythema of palms and soles
- Oropharyngeal changes: erythema or fissuring of lips, strawberry tongue
- Nonpurulent cervical lymphadenopathy

spots) are diagnostic. In Kawasaki's disease, the conjunctivitis is nonexudative and there are no discrete oral lesions. The exanthem of measles typically begins on the face, whereas the rash of Kawasaki's disease is found predominantly on the trunk and the extremities. Unlike in Kawasaki's disease, the ESR and the white blood cell count are typically low in measles. Furthermore, the immunoglobulin M antimeasles titer can be used to differentiate these clinically similar entities.

Because of the presentation of fever, strawberry tongue, cervical lymphadenopathy, and rash, Kawasaki's disease has commonly been misdiagnosed as scarlet fever. However, in scarlet fever, conjunctivitis is absent, desquamation is not limited to the extremities, and these findings all typically resolve with antibiotic therapy. Patients with scarlet fever are typically older than 3 years of age at presentation.

Young patients (<1 year of age) with Kawasaki's disease may have an atypical presentation that does not fulfill the diagnostic criteria, and therefore the diagnosis of Kawasaki's disease may not be considered. Fever may be the only initial presenting sign, and other clinical signs may be delayed or may not appear at all. After initial treatment with antibiotics, the rash and conjunctivitis may appear, leading to the incorrect conclusion of a drug hypersensitivity reaction. In the patient with fever of unknown origin who develops desquamation of the fingers and toes 2 to 3 weeks into the illness, it is important to consider the possibility of Kawasaki's disease and to evaluate the coronary arteries accordingly.

MANAGEMENT AND THERAPY

Before the use of IVIG, there was a 25% incidence of coronary aneurysm development in patients with Kawasaki's disease. Early diagnosis and treatment with IVIG have reduced the incidence of aneurysm formation to less than 2% in those treated.

Optimum Treatment

When the patient initially presents with symptoms, echocardiography is performed to evaluate myocardial function and provide a baseline study of the coronary arteries. ECG is performed in the acute phase to detect conduction abnormalities (Fig. 56-3). Patients are treated with anti-inflammatory doses of aspirin (80–100 mg/kg/day in four divided doses, not to exceed 4 g/day) and given a single dose of IVIG (2 g/kg). If a patient is afebrile 48 to 72 hours after IVIG treatment, the aspirin dose is decreased to antithrombotic levels of 3 to 5 mg/kg/day, and this dose is continued throughout the convalescent phase or until the platelet count returns to normal. A recent multicenter study to assess the addition of corticosteroids to IVIG and aspirin therapy showed no significant improvement in outcomes compared to conventional IVIG and aspirin therapy alone. After the single dose of IVIG, approximately 10% of patients remain febrile beyond 48 hours, and repeat dosing of IVIG may be necessary. The use of corticosteroids in "IVIG-resistant" patients reduces fever, but the effects on coronary aneurysm development remain uncertain.

Echocardiography is usually performed again 2 weeks and 6 to 8 weeks after the initial presentation. There is increasing evidence that if coronary aneurysms have not developed within the first 8 weeks of the illness, subsequent aneurysm formation is unlikely. However, these patients may have endothelial dysfunction and may be at risk as adults for early coronary artery disease. Therefore, the current American Heart Association guidelines recommend that patients without aneurysms undergo assessment and counseling every 5 years.

The development of coronary aneurysms requires close follow-up and long-term anticoagulation therapy. Risk stratification may be based on the size of the aneurysms. Small solitary aneurysms resolve without intervention in more than 50% of patients, and aspirin therapy is generally all that is warranted. However, giant aneurysms (>8 mm in diameter) are associated with a much greater risk of thrombosis. Japanese data show that approximately 50% of deaths occur in patients with giant coronary aneurysms. Therefore, these patients are usually maintained on aspirin and warfarin (Coumadin).

Echocardiography is an excellent screening tool for detecting proximal aneurysms, but distal aneurysms are more difficult to visualize. Coronary angiography (see Fig. 56-3) helps delineate more distal aneurysms and the presence of coronary stenoses, and should be performed in patients with evidence of ischemia or extensive coronary involvement on echocardiography. Patients developing a coronary stenosis and ischemia may require surgical revascularization or, rarely, heart transplantation. Exercise restrictions are placed on individuals with significant coronary disease.

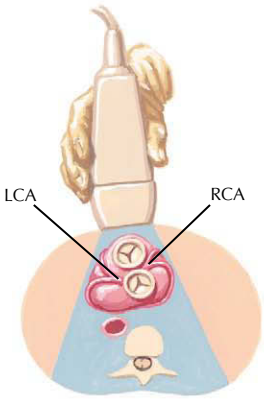
Avoiding Treatment Errors

The most common treatment error is the misdiagnosis or delayed diagnosis of patients with Kawasaki's disease. Delayed treatment results in ongoing inflammation. Treatment delayed beyond 10 days from the onset of fever is an important risk factor for subsequent aneurysm formation.

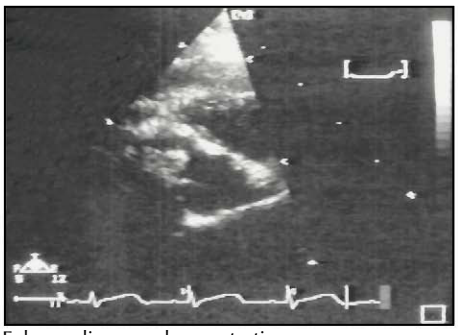
High-dose aspirin therapy can lead to salicylate toxicity, so it is important to reduce the aspirin dose after the acute febrile phase. The risk of Reye's syndrome must also be considered in patients on long-term aspirin therapy.

FUTURE DIRECTIONS

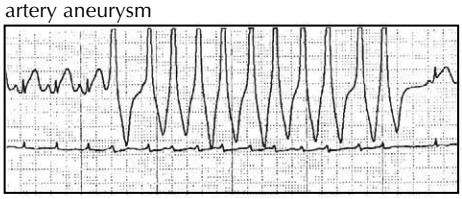
The incidence of Kawasaki's disease appears to be increasing; however, the etiology of the disease remains unknown. Despite the unclear mechanism of action of IVIG, the introduction of IVIG therapy has dramatically altered the natural history of the disease. Kawasaki's disease is self-limited in most cases, and



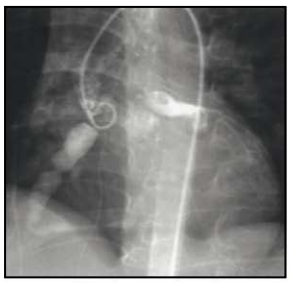
Echocardiography is performed at initial presentation to evaluate myocardial function and to provide baseline study of coronary arteries. Repeat studies performed at 2 weeks, 6–8 weeks, and 6–12 months after initial presentation.



Echocardiogram demonstrating coronary artery aneurysm



Electrocardiogram performed in acute phase to detect cardiac rhythm disturbances



Coronary angiogram demonstrating distal aneurysm of coronary artery

Coronary angiography is useful in detecting distal aneurysms of coronary arteries not easily detected by echocardiography.

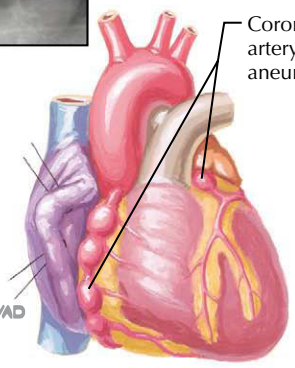


Figure 56-3 *Cardiac evaluation in Kawasaki's disease.* LCA, left coronary artery; RCA, right coronary artery.

many coronary aneurysms resolve without intervention. However, there may be significant endothelial dysfunction in vessels with previous aneurysms, which raises the question whether the children who have had aneurysms may be at increased risk for coronary disease as adults. Future research will be directed at determining etiology, the mechanism of the therapeutic effect of IVIG, other therapies, and long-term patient outcomes.

ADDITIONAL RESOURCES

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Describes outcomes in a large cohort of patient with Kawasaki's disease followed for up to 2 decades.

Leung D, Meissner C, Shulman S, et al. Prevalence of superantigen-secreting bacteria in patients with Kawasaki disease. *J Pediatr.* 2002;140:742–746.

Describes the superantigen hypothesis as the etiology of Kawasaki's disease.

Newburger J, Sleeper L, McCrindle B, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med.* 2007;356:663–675.

Compares outcomes in patients receiving traditional therapy and the addition of steroids.

EVIDENCE

Kawasaki T, Kosaki F, Okawa S, et al. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics.* 1974;54:271–276.

Dr. Kawasaki's original report; outlines the diagnostic criteria for Kawasaki's disease.

Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gammaglobulin. *N Engl J Med.* 1986;315:341–347.

Describes the initial treatment and outcomes using IVIG.

Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation.* 2004;110:2747–2771.

Outlines current diagnosis and treatment guidelines as defined by an expert committee assembled by the American Heart Association.

Congenital Coronary Anomalies

57

Sharon Ben-Or, Michael E. Bowdish, Brett C. Sheridan, and Michael R. Mill

Approximately 5% of patients undergoing cardiac catheterization and 1% to 2% of the general population have a congenital coronary artery anomaly. Congenital coronary anomalies can have a significant impact on myocardial perfusion, causing ischemia, inducing left ventricular (LV) dysfunction, and in some cases causing sudden cardiac death. Patients with congenital coronary anomalies generally do not present until adolescence or adulthood, if symptoms ever arise.

Unfortunately for patients with congenital coronary anomalies, a common presentation is with cardiac arrest or sudden cardiac death. This clinical relevance underpins the necessity of understanding the anatomy and presentation of congenital coronary anomalies and their treatment options. The two primary congenital coronary anomalies, anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) and anomalous aortic origin of coronaries (AAOC), as well as two entities associated with coronary artery anomalies—coronary artery fistulas and anomalous coronary circulation—are the focus of this chapter (Fig. 57-1).

Normally, the two main coronary arteries arise from separate ostia within the sinuses of Valsalva. The left coronary artery (LCA) then divides into the left anterior descending artery, which traverses the anterior interventricular groove, and the left circumflex coronary artery, which courses in the left atrioventricular groove. Normally, the right coronary artery (RCA) originates anteriorly from the right aortic sinus and courses along the right atrioventricular groove, commonly giving rise to the posterior descending artery.

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY

ALCAPA is a rare congenital anomaly, usually an isolated lesion, occurring in 1 in 300,000 live births (Fig. 57-2). The clinical spectrum of ALCAPA is also known as *Bland-White-Garland syndrome*. Infants with myocardial ischemia typically present with failure to thrive, profuse sweating, dyspnea, pallor, and atypical chest pain upon eating or crying. Malignant arrhythmias leading to sudden cardiac death are the most extreme presentation of myocardial ischemia in ALCAPA. During the neonatal period, high pulmonary vascular resistance ensures antegrade flow from the pulmonary artery through the LCA. However, as this resistance diminishes, there is an eventual reversal of flow, with left-to-right shunting through the pulmonary artery. The result is the phenomenon of "coronary steal," with LV perfusion becoming dependent on collateral circulation from the RCA.

Because infantile circulation has little or no coronary collateral development, ALCAPA leads to severe myocardial ischemia, with resultant LV dysfunction and dilation. Dilation of the left ventricle is due not only to the effects of ongoing myocardial ischemia but also to mitral valve regurgitation, because papillary muscle ischemia is common in ALCAPA. Without surgical intervention and correction of the anomaly, patients die within weeks to months after birth. Patients who survive to adulthood, secondary to the presence and formation of collateral circulation, may remain asymptomatic despite subclinical ongoing ischemia. Arrhythmic sudden death purportedly occurs in 80% to 90% of patients by 35 years of age.

Although ALCAPA is rare, a high index of suspicion should be present for infants presenting with signs of myocardial ischemia or dysfunction. The most frequent confounding diagnosis is dilated cardiomyopathy. Both conditions may present with cardiomegaly, a murmur of mitral insufficiency, and ECG evidence of myocardial ischemia. Two-dimensional echocardiography and coronary angiography typically clarify the diagnosis. Echocardiographic examination alone may be sufficient to achieve diagnosis. If echocardiography reveals an enlarged RCA with global hypokinesis and left ventricle dilation, ALCAPA must be considered in the differential diagnosis. Pulsed and color-flow Doppler examination may delineate a left-to-right shunt. In many but not all cases, two-dimensional echocardiographic evaluation will permit visualization of the anatomic origin of the ALCAPA and assessment of the degree of mitral insufficiency. Though not essential, coronary angiography or ventriculography may be performed if ALCAPA is suspected but not visualized on echocardiography. Coronary angiography also assists in excluding other anatomic etiologies for ischemia and ventricular dysfunction.

Surgical correction remains the gold standard of therapy, but important changes in technique have resulted in improved outcomes. Surgical repair involves direct reimplantation of the anomalous LCA into the aorta by transferring it with a button of pulmonary artery (Fig. 57-3). There are several options to customize the surgical approach so as to overcome anatomic challenges of the length and course of the LCA for reimplantation. In adults, in whom reimplantation is more technically challenging, bypass grafting with the left internal thoracic artery is an equally effective approach.

After reestablishment of a two-coronary system, the previously dilated RCA will generally return to normal size, and the intercoronary collateral network that developed before surgery will regress. Operative mortality for all surgical techniques has markedly decreased. The mortality rate today (5% to 25%), though still high, represents a vast improvement compared with the mortality rates reported in the early 1980s (75% to 80%). No differences in LV function or the late mortality rate have been shown comparing the various reimplantation or revascularization techniques used today. A previous approach, direct ligation of the anomalous coronary, was abandoned because of poor outcomes.

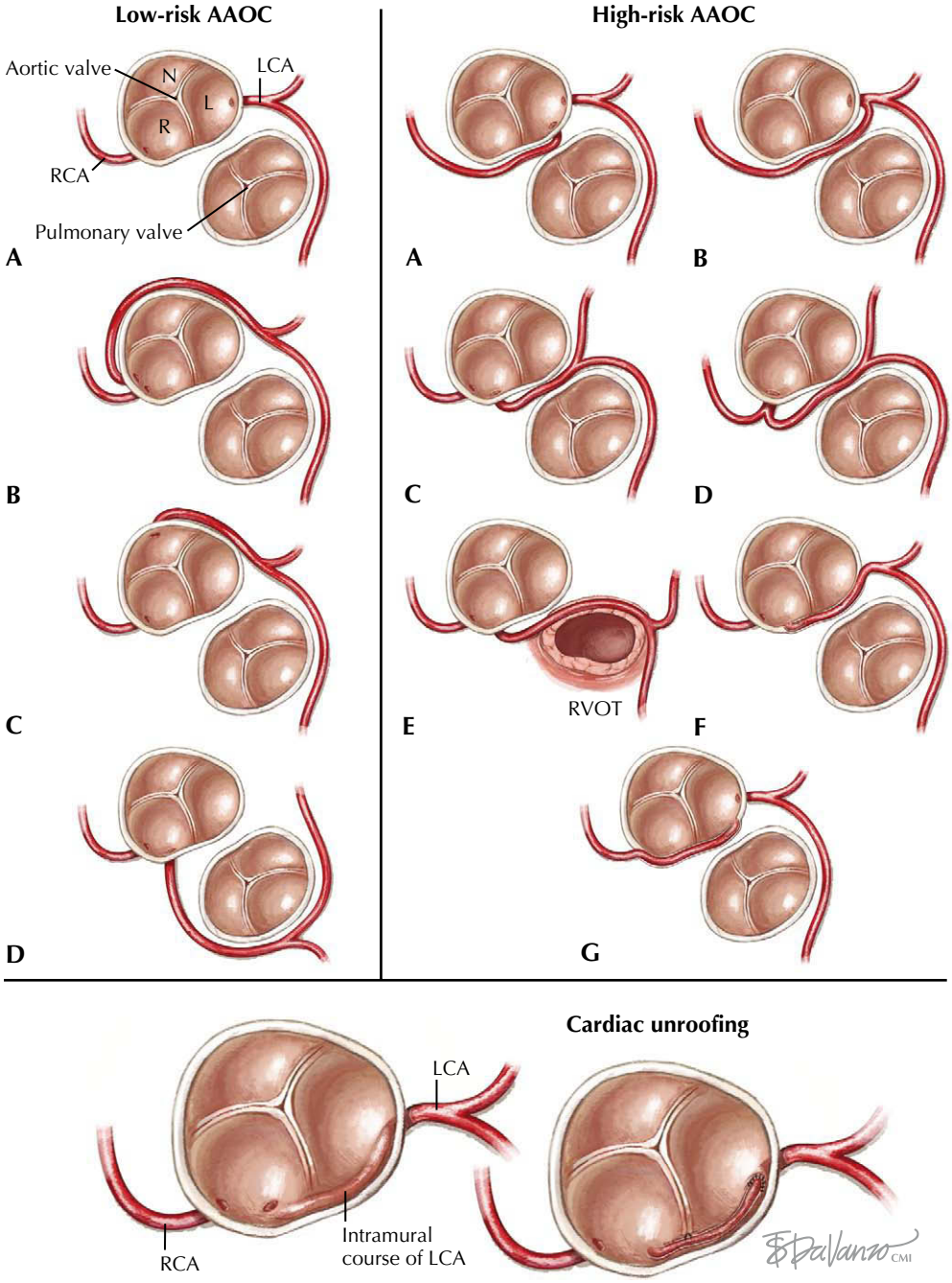


Figure 57-1 *Anomalous aortic origin of coronaries (AAOC): Anatomic variations.* The positions of the anatomic right (R), left (L), and non (N) coronary cusps are shown. LCA, left coronary artery; RCA, right coronary artery; RVOT, right ventricular outflow tract.

ANOMALOUS AORTIC ORIGIN OF CORONARIES

Anomalous aortic origin of coronaries presents much more variably than ALCAPA. Some individuals have myocardial ischemia and can present with sudden death, but in others this can be an entirely asymptomatic incidental finding at the time of cardiac catheterization or coronary artery imaging. The reasons for this variable presentation involve subtle differences in the anatomy and course of the anomalous coronary artery (see Fig. 57-2). The coronary artery's proximal portion may exit the aorta at an acute angle leading to a functional stenosis of the ostium. It may course between the aorta and the pulmonary artery, or it may have an intramural course within the aorta. Surgical correction is indicated in individuals who present with significant symptoms. In asymptomatic individuals, if the LCA arises from the right coronary sinus and courses between the aorta and the pulmonary artery, surgical intervention is indicated because the risk of sudden cardiac death is high in this group. However, if the RCA arises from the left aortic sinus and is nondominant,

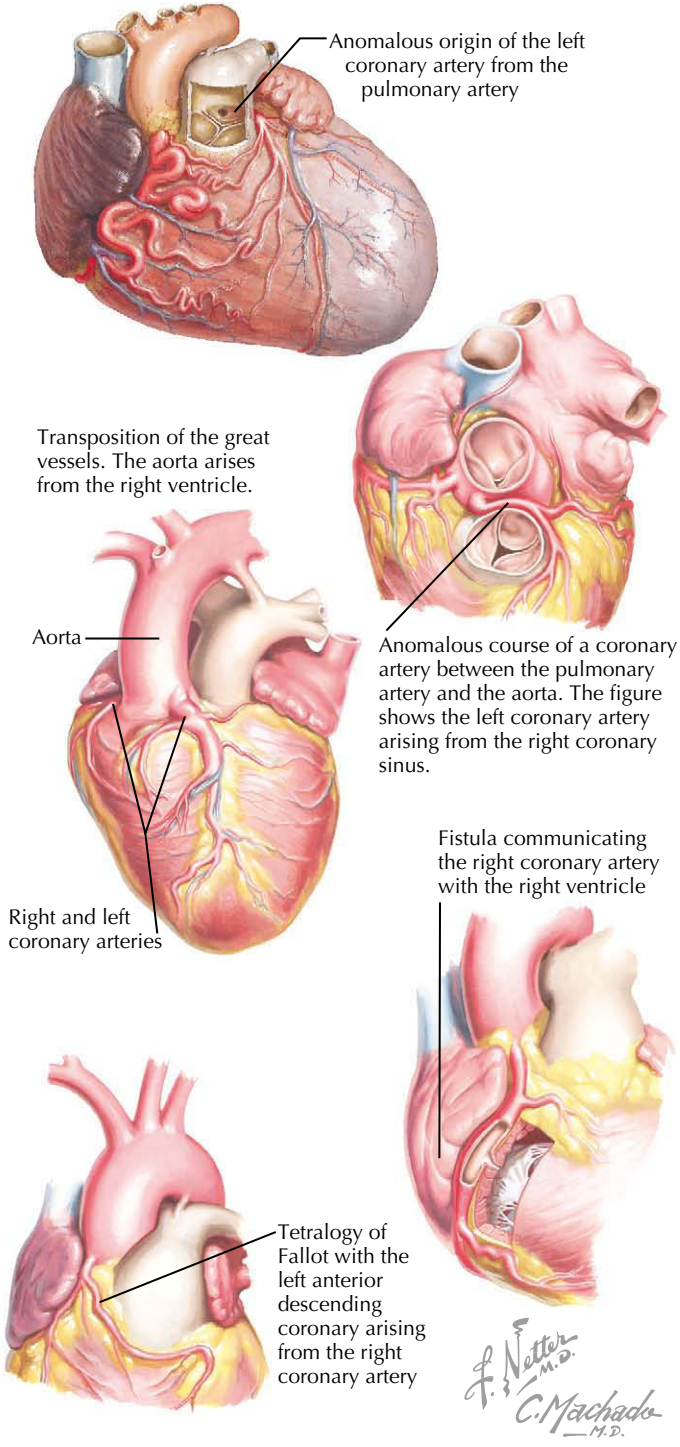


Figure 57-2 *Congenital coronary artery anomalies.*

such an entity may be benign. Surgical intervention is undertaken in patients with this form of the anomaly only if they have demonstrable ischemia.

The incidence and natural history of anomalous course of a coronary artery between the pulmonary artery and aorta (ACCBPAA) are unknown. One review of 126,595 cardiac catheterizations revealed an incidence of 1.15%, constituting 87% of all coronary artery anomalies within this series. The most important review of this abnormality described sudden death in 59% of the 242 patients. There are no pathognomonic clinical features consistent with ACCBPAA. The diagnosis should be considered in patients with exercise-induced myocardial ischemia or sudden death. Although echocardiographic evaluation may provide valuable information, coronary angiography is essential to accurately delineate the anatomy and exclude other associated coronary disease. Noninvasive imaging with CT and MRI has advanced considerably in recent years and may become a standard approach for defining the anatomy of these lesions.

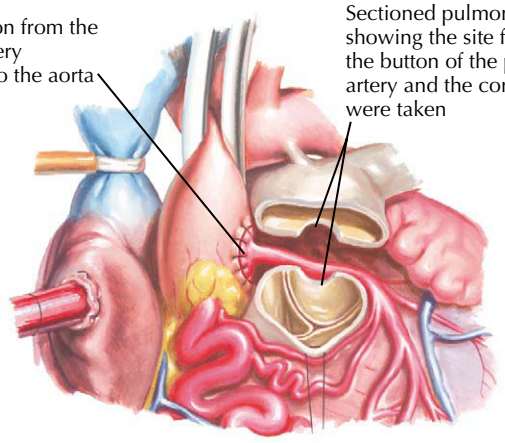
Surgical options to manage this anatomic abnormality include revascularization with an internal mammary artery or a saphenous vein bypass graft, or reimplantation alone. An important issue to consider, however, is that revascularization may lead to competitive flow between the bypass graft and the native circulation, thus increasing the likelihood of bypass graft failure. The advantage of reimplantation is that competitive flow is not an issue, since there is a single conduit vessel providing flow to the myocardium in that distribution. Reimplantation may be more technically difficult; for instance, a transverse aortotomy may become essential to assess the coronary ostia. Also, when the anomalous coronary artery arises from the opposite sinus, it is necessary to detach the aortic valve commissure. The slitlike ostium, characteristic of AAOC and partially responsible for ischemic symptoms, is opened along its longitudinal axis, and a portion of the common wall between the aorta and the coronary artery is excised, with reapproximation of the intimal surfaces. The valve commissure is subsequently resuspended with a pledgeted suture. This unroofing procedure creates a neo-ostium and obliterates the intramural course of the coronary artery.

CORONARY ARTERY FISTULAS

Coronary artery fistulas are defined as communications with right-sided (arteriovenous fistula) or left-sided (arterio-arterial fistula) cardiac structures. The most common fistula is the RCA communicating with the right ventricle. However, fistulas may involve the LCA, and the aberrant connection may be with either heart chamber, the pulmonary artery or vein, the coronary sinus, or a central vein. Patients rarely present with symptoms during infancy and are frequently diagnosed in early adulthood. Often asymptomatic, fistulas are most commonly discovered during evaluation for a murmur. It is not uncommon, though, for patients with a fistula to present with left- or right-sided congestive heart failure or myocardial ischemia due to coronary steal. Echocardiography may reveal evidence of a dilated or enlarged coronary artery, with color-flow Doppler demonstrating the fistula. Preoperative coronary angiography is necessary to ensure accurate anatomic definition and allow for surgical planning.

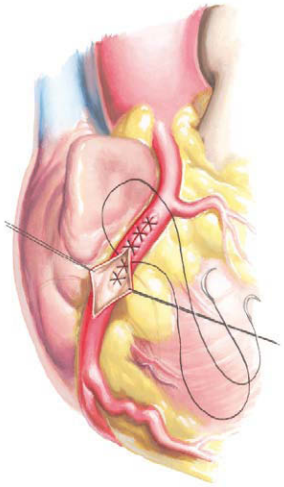
Intervention prevents ventricular volume overload and resulting congestive heart failure. Although observation and transcatheter coil embolization have been described, these management options are limited to highly selected patients, because surgical treatment of coronary artery fistulas is efficacious, reliable, and durable. If the fistula arises from the distal end of the coronary artery, ligation may be performed without cardiopulmonary bypass. Before permanent ligation, a trial occlusion of the affected coronary artery at the distal site should

Surgical correction of ALCAPA



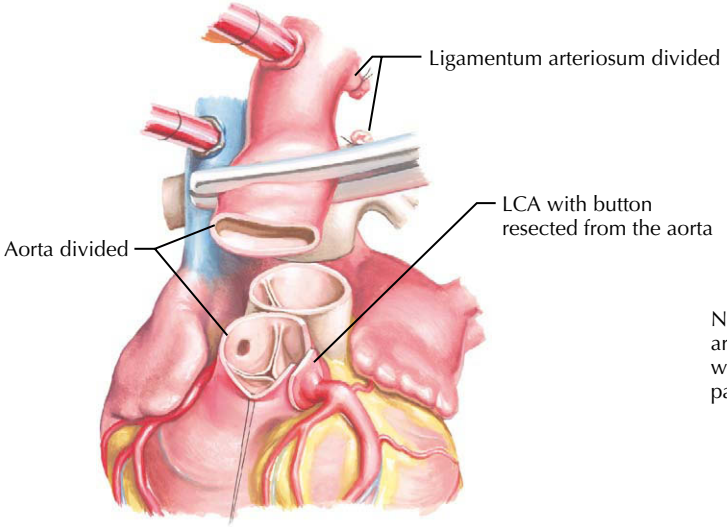
The technique involves direct reimplantation of the anomalous LCA into the aorta by transferring it with a button of pulmonary artery. Seen here: Variation with transection of the pulmonary artery

Technique to close fistula from RCA to RV and plication of coronary aneurysm



The aneurysmal coronary artery is opened and the fistula is sutured. The coronary artery is closed and the aneurysm is repaired by plication.

Arterial repair of transposition of the great arteries—First steps



The aorta and the pulmonary artery are transected. The cut of the aorta is slanted and above the sinuses of the Valsalva. The pulmonary artery is divided above its valve at the same level of the transection of the aorta. Sinuses of the aorta and pulmonary artery are excised to translocate the coronary ostia from the pulmonary artery to the neoaorta. Pericardium is utilized to reconstruct the neopulmonary artery sinuses.

Arterial repair of transposition of the great arteries—Last steps

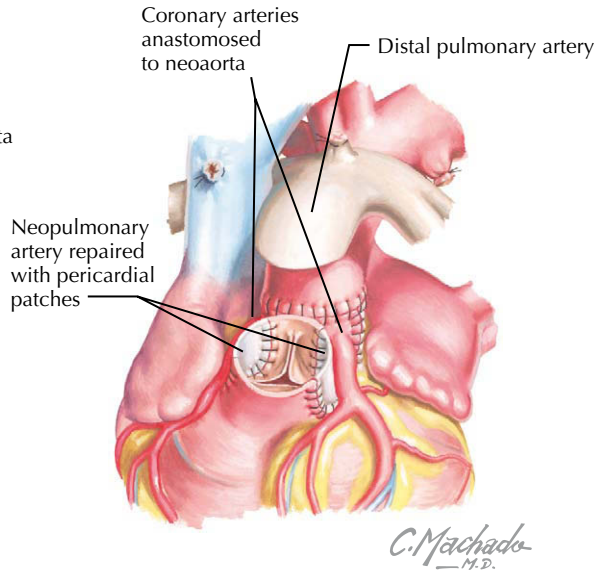


Figure 57-3 *Surgical procedures for correction of congenital coronary artery anomalies.* ALCAPA, anomalous origin of the left coronary artery from the pulmonary artery; LCA, left coronary artery; RCA, right coronary artery; RV, right ventricle.

be performed to observe for signs of ischemia. If signs of myocardial ischemia are absent, ligation may then be performed. If the fistula arises from the midportion of a coronary artery, cardiopulmonary bypass with cardioplegic arrest allows the surgeon to open the abnormal coronary artery and to oversew the fistula at that point. If coronary artery luminal compromise occurs, bypass grafting may be warranted. In other instances, the fistulous tract may be closed internally via access through the involved cardiac chamber (see Fig. 57-3).

CORONARY ARTERY ANOMALIES ASSOCIATED WITH CONGENITAL HEART DISEASE

Several important forms of congenital heart disease are associated with coronary artery anomalies, and this can have major implications for surgical repair. Coronary artery anomalies are particularly important in patients with tetralogy of Fallot, transposition of the great arteries (TGA), and pulmonary atresia with an intact ventricular septum (see Fig. 57-2).

Coronary artery anomalies are reported in 18% to 31% of patients with tetralogy of Fallot. Most commonly, this involves a large coronary artery crossing the right ventricular (RV) outflow tract just below the pulmonary valve. These anomalies include origin of the left anterior descending artery from the RCA, a large conus branch across the RV outflow tract, a paired anterior descending coronary artery off the RCA, and an origin of both coronary arteries from a single left ostium. In each situation, the potential exists for damage to or severing of the coronary artery during a right ventriculotomy to correct RV outflow tract obstruction.

In pulmonary artery atresia with an intact ventricular septum, embryonic sinusoids within the right ventricle may persist and communicate with the epicardial coronary arteries in any of several ways. Usually this occurs in patients with diminutive RV chambers and severe RV hypertrophy. The communications may feed one or both coronary arteries and may be associated with proximal or distal coronary stenosis, or both, at the insertion site of the fistulous communications. In some patients with coronary stenosis, the coronary fistulous connections are sufficiently developed to produce an RV-dependent coronary circulation. Angiography of the RV cavity is required to demonstrate retrograde filling of one or more coronary arteries via the fistulous connection. Coronary angiography can determine whether the LV myocardium is normally perfused or whether substantial segments are perfused from the right ventricle through myocardial sinusoids. In this circumstance, perfusion of parts of the left ventricle from the right ventricle must be identified before surgical repair. Importantly, correction of the RV outflow tract obstruction that is present in tetralogy of Fallot results in a reduced pressure within the right ventricle, which can mean decreased perfusion pressure for the sinusoid-LCA branches, decreased perfusion of the left ventricle, and ultimately myocardial ischemia and/or infarction during surgery.

Patients who have pulmonary artery atresia with an intact ventricular septum usually require an early systemic-to-pulmonary shunt and, if the tricuspid valve and RV chamber have growth potential, surgical relief of the pulmonary atresia. If the right ventricle is miniscule, a Fontan procedure is the definitive treatment. However, if the myocardium is perfused via the right ventricle through sinusoids because of stenotic coronary arteries, then a systemic right ventricle must be preserved as part of the Fontan operation. Cardiac transplantation may be the only option for patients with pulmonary artery atresia with an intact ventricular septum.

The treatment for patients with a simple dextraposed-transposition (D-transposition) of the great arteries (D-TGA) or D-TGA with a ventricular septal defect is an arterial switch operation during the neonatal period (see Fig. 57-3). In D-TGA, both in its simple form and with a ventricular septal defect, the aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle. Until the 1970s, the preferred surgical management was an atrial switch. Subsequently, the preferred procedure has been the arterial switch. During the arterial switch procedure, the coronary arteries are transferred from the anterior semilunar valve to the posterior valve along with reversing the location of the great vessels to the appropriate ventricles. The success of the operation depends on the transfer of the coronary arteries without compromising the blood supply of the coronary circulation. Seven different coronary artery patterns are recognized in patients with a D-TGA, but normal anatomy is present in 60% to 70% of patients. Although certain unusual coronary artery patterns were formerly associated with an increased mortality rate, the specific coronary artery anatomy has become less important as surgical experience with this operation has improved technical approaches and overall outcomes. The presence of an intramural coronary artery, a segment of coronary artery that courses within the wall of the aorta without a separate layer of adventitial tissue between the coronary artery and the aorta, remains a difficult challenge. Although follow-up angiography after the arterial switch operation shows varying coronary artery abnormalities in approximately 10% of patients, most patients are asymptomatic.

FUTURE DIRECTIONS

Several issues of anomalous coronary arteries remain to be explored, including but not limited to choosing the best noninvasive diagnostic imaging technique, further pathophysiologic characterization of myocardial perfusion in patients with anomalous coronary arteries, and defining indications for percutaneous intervention in adults who have symptomatic coronary disease in anomalous coronary vessels.

The tools for noninvasive imaging of anomalous coronary arteries include 16-slice multidetector spiral CT and free-breathing, three-dimensional coronary magnetic resonance angiography (MRA). Spiral CT, a noninvasive imaging modality, has comparable resolution to MRA and is faster and less costly. Free-breathing, three-dimensional coronary MRA is limited by availability, time, cost, and patient comfort. MRA studies are challenging to perform because of the enclosed space in which patients must be placed and the length of time to complete an evaluation. Intravascular ultrasound has been used in some institutions allowing for cross-sectional imaging of the coronary lumen as well as determination of wall thickness, but this invasive procedure is operator-dependent and can be used only in adults. Ultimately, the best method for defining anomalous coronary vessels will depend on the degree of resolution of the technique and other considerations including cost and availability. As imaging techniques improve, noninvasive imaging for anomalous coronary arteries will probably become the standard of care. Advances already made in imaging technologies promise to further improve imaging of anomalous coronary circulation in the future.

Further investigation is warranted into regional myocardial flow reserve in survivors of ALCAPA related to its underlying pathology (i.e., endocardial and subendocardial fibrosis, damage to the papillary muscles, patchy myocardial necrosis, dilation of the ventricle, mitral incompetence, LCA hypoplasia of the media, distal stenosis and hypoplasia of the RCA). Physiologic issues will also require further definition with regard to myocardial perfusion after treatment in long-term survivors of this often lethal condition.

As stated, the use of the arterial switch operation for TGA has resulted in significantly improved outcomes. However, complications in patients who were treated with the atrial switch are now being seen, predominantly related to dysfunction of the right ventricle, tricuspid valve, and the baffle itself. Surgical

management is challenging with these patients, who eventually require a heart transplant.

Anomalous coronary arteries have a reported frequency of approximately 1.33% in nonselected patients undergoing coronary angiography; it can therefore be predicted that adults who have anomalous coronary arteries will present with symptomatic coronary artery disease in these vessels later in life. Because this anatomy may offer unique challenges for interventional cardiologists, specific indications for percutaneous intervention remain to be defined in this area of improving interventional technology.

ADDITIONAL RESOURCE

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Cardiovascular Disease in Pregnancy

58

Patricia P. Chang and Eileen A. Kelly

As more women delay childbearing into their thirties and forties, the interaction between coronary disease, its risk factors, and pregnancy becomes increasingly important in prenatal care. In addition to traditional cardiovascular risk, more women with congenital heart disease are reaching childbearing age. Pregnancy presents unique challenges for the management of cardiovascular diseases, necessitating a multidisciplinary approach to achieve optimal maternal and fetal outcomes. Understanding normal physiologic adaptations to pregnancy and their potential effect on cardiovascular hemodynamics is central to the management of pregnant women with coronary artery, valvular, congenital, or myocardial abnormalities.

PHYSIOLOGIC ADAPTATIONS TO PREGNANCY

Changes during Pregnancy

Important hemodynamic changes occur during pregnancy as a result of increases in red blood cell mass and plasma volume. Red blood cell mass typically increases by 20% to 30%, while plasma blood volume can increase even more—generally by about 50%. The etiology of the increase in blood volume is multifactorial and due mainly to activation of the renin-angiotensin-aldosterone system by estrogen. In addition, other pathways responsible for water retention are stimulated by other pregnancy-related hormones (Fig. 58-1). This relative increase in total blood volume results in a relative anemia, referred to as the physiologic anemia of pregnancy.

Cardiac output increases by approximately 45% during a normal pregnancy, starting as early as 5 weeks after the last menstrual period, predominantly from an increase in stroke volume (during the first and second trimesters) and an increase in heart rate (10–20 bpm during the third trimester). Most of the increase in cardiac output occurs by gestational week 16. This increase is followed by a further, slower increase in cardiac output that peaks at week 24 until week 32. Systemic vascular resistance (SVR) decreases 34% by 20 weeks as a result of decreased aortic compliance and arteriovenous shunting in the uterus. Subsequently, in the final weeks of pregnancy there is a slight decrease in cardiac output that reflects the decrease in stroke volume due to increased SVR (see Fig. 58-1, middle).

Related to these hemodynamic changes are structural changes of the heart. The left ventricular (LV) mass increases because of increased LV end-diastolic volume, decreased LV end-systolic volume, and increased wall thickness. The valvular cross-sectional area also increases, resulting in more physiologic regurgitation, affecting the tricuspid and pulmonary valves more commonly than the mitral valve. Although flow murmurs (due to increased flow across the aortic valve) are common in pregnancy, it is rare that there is sufficient tricuspid or pulmonic regurgitation to result in a murmur or significant hemodynamic effects.

Positional changes also have hemodynamically significant effects on the pregnant woman. Of particular importance is the supine hypotension syndrome characterized by symptoms of near-syncope/syncope caused by compression or occlusion of the inferior vena cava by the gravid uterus when the pregnant woman lies supine. Symptoms can be relieved by assuming another position, particularly the left lateral decubitus position (see Fig. 58-1, lower). The supine hypotension syndrome is one of the primary reasons to advise pregnant women against exercising in the supine position after the first trimester. This positional effect must also be recognized in the event that a pregnant woman (particularly in the second or third trimester) requires cardiopulmonary resuscitation. If this unfortunate situation arises, the woman should be placed in the left lateral decubitus position.

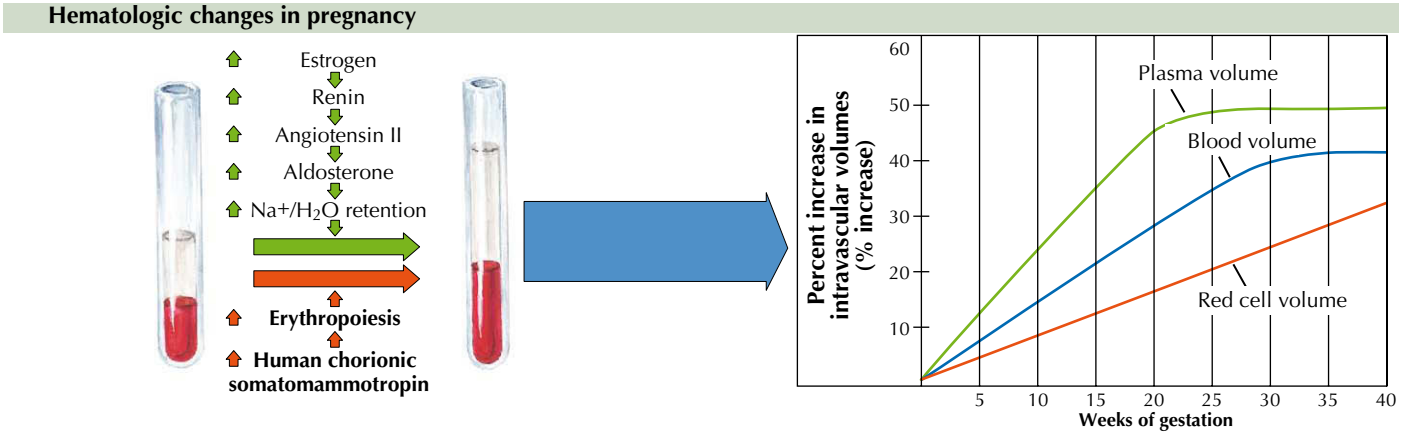
Changes during Labor and Delivery

Marked increases in stroke volume, heart rate, and, subsequently, cardiac output occur during labor and delivery. Blood pressure (both systolic and diastolic) and oxygen consumption also increase significantly. The degree of pain and anxiety during labor has a dramatic effect on these parameters, and modulation via analgesia, sedation, or both can limit the hemodynamic changes and can be very important for women with hemodynamically significant cardiovascular disease.

Hemodynamic changes occur with both vaginal delivery and cesarean section (C-section). The decision to pursue cesarean delivery should be individualized and based on the status of the fetus and the hemodynamic state of the mother. Although counterintuitive, vaginal delivery has been demonstrated to cause fewer hemodynamic alterations than C-section and is generally better tolerated even in women with heart disease. Therefore, vaginal delivery is the recommended mode of delivery unless there is an obstetric indication for C-section. Exceptions in pregnant women with heart disease include individuals with a markedly dilated aortic root (>5.5 cm) as seen in Marfan's syndrome (in whom a hypertensive episode might cause aortic dissection), women with severe aortic coarctation with poorly controlled hypertension, and in the setting of acute severe cardiovascular decompensation.

Changes in the Postpartum Period

After delivery, cardiac output again increases because of increased venous return from relief of vena caval compression, autotransfusion of uterine blood, and fluid mobilization. Most reports show cardiac output returning to prelabor values within 1 hour of delivery and continuing to return toward baseline values within 2 to 6 weeks after vaginal delivery. Fluid shifts are greatest in the first 48 to 72 hours postpartum. Caution should be exercised in volume administration in postpartum patients with heart failure.



Multifactorial stimulation of fluid retention and erythropoiesis in pregnancy results in a 50% increase in plasma volume and a 30% increase in red cell mass, creating a relative "physiologic" anemia and an increased blood volume.

Cardiac output increases 50% in normal pregnancy, predominantly from increased stroke volume in first and second trimesters and increased pulse rate in third trimester.

Positional changes have hemodynamically significant effects on pregnant women. Compression of the inferior vena cava by the gravid uterus in the supine position may cause hypotension and syncope. Condition is relieved by altering position from supine to lateral decubitus to relieve compression and restore venous return and cardiac output.

Figure 58-1 *Cardiovascular adaptations to pregnancy.* Na^+, sodium.

CLINICAL PRESENTATION

Cardiac Examination during Normal Pregnancy

The symptoms of normal pregnancy—including fatigue, dyspnea, palpitations, and even near-syncope—in association with the normal signs of pregnancy (including augmentation of the jugular venous pulsations, normal heart sounds or murmurs, and a modest amount of lower extremity edema) may be misinterpreted as those of cardiac disease. Conversely, pathologic signs and symptoms at times may be attributed to normal pregnancy. Thus, knowledge of the normal cardiac examination during pregnancy is crucial (Table 58-1).

Although the presence of an S_3 sound is generally considered a normal finding in pregnancy and in young adults, it is still relatively rare in the healthy pregnant state. An S_4 is unusual and generally indicates underlying cardiovascular pathology. Because of increased plasma volume and cardiac output, as noted previously, new or more prominent systolic flow murmurs are often present during pregnancy. Although diastolic murmurs

Table 58-1 Normal Physical Findings for the Cardiac Examination during Pregnancy

Examination	Findings
Precordial palpation	Laterally displaced LV impulse Palpable RV impulse
Heart sounds	Increased intensity of S_1 and S_2 Splitting of S_1 Increased physiologic splitting of S_2
Heart murmurs	Midsystolic murmurs (common; usually grades I–II/VI), heard best at left lower sternal border Diastolic murmurs (rare; soft, medium- to high-pitched), heard best over the pulmonic area and over the left sternal border Continuous murmurs: *Cervical venous hum*—heard best over the right supraclavicular fossa *Mammary souffle* (may also be heard as only a systolic murmur)—heard best in the left second to fourth intercostal spaces; decreased by pressing stethoscope firmly against the chest wall in the upright position

LV, left ventricular; RV, right ventricular.

have been reported in normal pregnancy, if a diastolic murmur is identified, further workup is indicated. Transthoracic echocardiography should be performed to evaluate for valvular pathology. With more plasma volume the pregnant woman may show mild jugular venous distention and peripheral edema. The pulse pressure will typically increase with more decrease in the diastolic blood pressure than in the systolic component.

DIFFERENTIAL DIAGNOSIS

Distinguishing between normal and pathologic symptoms during pregnancy is often difficult even with a good understanding of a normal cardiac examination of the pregnant woman. Common cardiac symptoms that may or may not be cardiac in origin include chest pains, palpitations, exertional dyspnea or fatigue, and peripheral edema. Chest pains during pregnancy are rarely cardiac in etiology but should warrant an ECG and, as indicated, further evaluation if symptoms are worrisome for angina. Palpitations are frequently premature atrial or ventricular beats, but a Holter monitor is indicated if any other symptoms accompany palpitations or if their frequency increases significantly during pregnancy. Differentiating normal pregnancy symptoms from heart failure symptoms may be difficult. Evidence of either pulmonary congestion (rales on examination) or ventricular enlargement (a displaced point of maximal cardiac impulse or a right ventricular heave) should always be considered pathologic.

DIAGNOSTIC APPROACH

Taking a comprehensive history of the pregnant patient is important to determine if she has a preexisting cardiac condition that may warrant her obstetric care be managed in a high-risk clinic by a maternal-fetal medicine subspecialist in conjunction with frequent visits to her cardiologist. Peripartum cardiac complications are rare (<1%) and mostly related to hypertension and preexisting chronic cardiovascular disease (congenital heart disease, pulmonary hypertension, aortic pathology, rheumatic heart disease, valvular disease, cardiomyopathies, coronary artery disease). The most severe cardiac complications of peripartum onset are peripartum cardiomyopathy and acute myocardial infarction. When women with no risk factors for coronary atherosclerosis present with symptoms and/or findings suggestive of an acute coronary syndrome, coronary artery dissection (see discussion below) should also be considered. The remainder of this chapter describes the evaluation and management of common cardiovascular conditions in the pregnant woman.

PREEXISTING DISEASE STATES AND PREGNANCY

Maternal and fetal risks of cardiac disease generally depend on the underlying cardiovascular lesion and the functional class of the mother. Overall, women with functional New York Heart Association (NYHA) class I and II have a low mortality rate (<1% during pregnancy), whereas those with NYHA class III and IV have a much higher associated mortality rate (>7%). An updated risk index has been proposed to better risk-stratify pregnant women with heart disease. This index includes four predictors of primary events: prior cardiac events or arrhythmia; baseline NYHA class greater than II or cyanosis; significant left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, or a peak LV outflow tract gradient >30 mm Hg by echocardiography); and reduced systemic ventricular systolic function (ejection fraction <40%).

Ideally, prepregnancy counseling provides the patient with information about case-specific maternal and fetal risks to prepare for the safest pregnancy possible. This also allows the physician and the patient to discuss risk factor modification and potential prenatal surgical correction of the underlying defect if pregnancy is desired.

Congenital Heart Disease

Congenital heart disease is thought to be multifactorial in origin, arising from a genetic predisposition combined with environmental factors. In general, the risk to offspring is modest (~3% to 5%) but much greater than in the general population. It should be noted, however, that reported rates vary between 1% and 18%, depending on the specific type of maternal lesion and the number of affected siblings. Maternal congenital heart disease confers different risks to both the mother and fetus, depending on the type of lesion (Table 58-2).

Uncomplicated acyanotic lesions, including atrial and ventricular septal defects, patent ductus arteriosus (with left to right shunting), and aortic coarctation, are usually well tolerated during pregnancy. Patients with coarctation who develop severe hypertension are at risk for heart failure, cerebral aneurysm rupture, and aortic dissection. Therefore, modest, but not aggressive, blood pressure control is warranted for this population.

Table 58-2 Congenital Heart Disease and Maternal and/or Fetal Risk during Pregnancy (Excluding Valvular Disease)

High Risk	Moderate Risk	Low Risk
• Any disease with NYHA class III or IV symptoms • Severe pulmonary hypertension with septal defects (e.g., Eisenmenger's syndrome) or without septal defects • Severe LV outflow tract obstruction • Cyanotic heart disease with pulmonary hypertension • Marfan's syndrome	• Systemic right ventricle (TGA after atrial switch procedure, congenitally corrected TGA) • Cyanotic lesions without pulmonary hypertension • Fontan-type circulation	• Ventricular septal defects • Atrial septal defects (unoperated) • Patent ductus arteriosus • Coarctation of the aorta (repaired) • Tetralogy of Fallot

LV, left ventricular; NYHA, New York Heart Association; TGA, transposition of the great arteries.

The maternal and fetal outcomes of pregnancy in acyanotic and cyanotic women with congenital heart disease are favorable provided that their NYHA functional class is I or II and the ejection fraction measured at the beginning of pregnancy is normal. However, the outcome of pregnant women with cyanotic or complex lesions depends significantly on the type of lesion, the state of surgical repair (if any), the degree of pulmonary hypertension, the magnitude of hypoxemia, and the functional status of the mother. Hence, it is important to address each case individually.

Pulmonary Vascular Disease and Eisenmenger's Syndrome

The spectrum of pulmonary vascular disease includes primary pulmonary hypertension, secondary vascular pulmonary hypertension, and Eisenmenger's syndrome. Although the morbidity and mortality of these disease states are high in the general population, the coexistence with pregnancy poses an exceptionally high risk of poor maternal and fetal outcomes. Maternal mortality rates in pregnant women with pulmonary hypertension are high—in the range of 30% to 50%. There is considerable variability, based on literature reports, depending on the etiology of pulmonary vascular disease: 36% for Eisenmenger's syndrome, 30% for primary pulmonary hypertension, and 56% for secondary vascular pulmonary hypertension in the most complete series reported. Typically, women with pulmonary vascular disease and Eisenmenger's syndrome are at highest risk shortly after delivery from sudden or progressive heart failure, arrhythmia, or thromboembolic events. It also appears that late hospitalization, operative delivery, pulmonary vasculitis of a systemic disease, and illicit drug use are risk factors associated with maternal death in the secondary vascular but not primary pulmonary hypertension group.

Because of these very high mortality rates, women with pulmonary vascular disease and Eisenmenger's syndrome should be advised against becoming pregnant. If these states are diagnosed in gestation, early termination of the pregnancy is recommended. If the patient refuses termination or if pulmonary vascular disease is diagnosed late in pregnancy, physical activity should be limited, bed rest should be advised for the third trimester, and the patient must be closely monitored. Early hospitalization has decreased mortality in pregnant women with secondary vascular pulmonary hypertension and Eisenmenger's syndrome.

Standard drug therapies include calcium channel blockers, inhaled nitric oxide, and inhaled or intravenous prostaglandins. Anticoagulation therapy is controversial but usually recommended during the third trimester, to be continued for 4 to 6 weeks postpartum. Spontaneous vaginal delivery is preferred, with attempts to shorten the second stage of labor using forceps or vacuum extraction. The use of pulmonary artery catheters for hemodynamic management during labor, though advocated by some, remains controversial.

Marfan's Syndrome

Marfan's syndrome is a connective tissue disorder with an autosomal-dominant pattern of inheritance. It can have significant cardiovascular involvement, most commonly involving mitral valve prolapse and dilation of the aortic root at the level of the sinuses of Valsalva. Mitral regurgitation, aortic regurgitation, and aortic dissection can develop before or during pregnancy in women with Marfan's syndrome. Otherwise healthy pregnant women are at increased risk for aortic dissection, and pregnant women with Marfan's syndrome potentially possess an even greater risk for this devastating event. Pregnant women with Marfan's syndrome and only minor cardiovascular involvement and an aortic root diameter less than 40 mm usually tolerate pregnancy without difficulty and have little change in aortic root diameter. However, pregnant women with Marfan's syndrome and an aortic root measuring greater than 40 mm, aortic regurgitation, or a history of aortic dissection are at higher risk.

Because of these risks, women with Marfan's syndrome are often advised against becoming pregnant. When pregnant, women with Marfan's syndrome should be advised to avoid vigorous activity. Because β-blockers decrease the rate of aortic root dilation and aortic complications in the general population with Marfan's syndrome, they are routinely administered to all pregnant women with Marfan's syndrome. Serial echocardiograms are usually performed to monitor for aortic root dilatation.

Valvular Heart Disease

Rheumatic heart disease (most commonly mitral stenosis) is the most common cause of valvular disease in developing countries and in the United States with increasing immigration. It is not uncommon for mitral stenosis to be diagnosed first during

Table 58-3 Valvular Heart Lesions Associated with High versus Low Maternal and/or Fetal Risk during Pregnancy

Condition	High Risk	Low Risk
Aortic stenosis	1. Severe with or without symptoms 2. With severe pulmonary hypertension (pulmonary pressure >75% of systemic pressures) 3. With severe LV systolic dysfunction (EF <40%)	Asymptomatic with low mean gradient (<25 mm Hg and aortic valve area >1.5 cm^2) and normal LV systolic function (EF >50%)
Aortic regurgitation	1. NYHA class III–IV symptoms 2. With severe pulmonary hypertension (pulmonary pressure >75% of systemic pressures) 3. With severe LV systolic dysfunction (EF <40%)	NYHA class I or II with normal LV systolic function
Mitral stenosis	1. NYHA class II–IV symptoms 2. With severe pulmonary hypertension (pulmonary pressure >75% of systemic pressures) 3. With severe LV systolic dysfunction (EF <40%)	Mild severity (mitral valve area >1.5 cm^2, gradient <5 mm Hg) without severe pulmonary hypertension
Mitral regurgitation	1. NYHA class III–IV symptoms 2. With severe pulmonary hypertension (pulmonary pressure >75% of systemic pressures) 3. With severe LV systolic dysfunction (EF <40%)	NYHA class I or II with normal LV systolic function
Other conditions	1. Mechanical prosthetic valve requiring anticoagulation 2. Marfan's syndrome with or without AR	1. MVP with no MR or with mild to moderate MR with normal LV systolic function 2. Mild to moderate pulmonary valve stenosis

AR, aortic regurgitation; EF, ejection fraction; LV, left ventricular; MR, mitral regurgitation; MVP, mitral valve prolapse; NYHA, New York Heart Association.

Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. *2008;52:e1–e142.*

pregnancy (see below). Guidelines for the management of patients with valvular heart disease have been recently updated and now also summarize management based on associated maternal and/or fetal risk (Table 58-3).

Regurgitant valvular lesions, unless severe, are usually well tolerated in pregnancy because of a physiologic afterload reduction (decreased SVR), increased plasma volume, and a hyperdynamic and tachycardiac state. Mitral valve prolapse is the most common valvular disease and the most common cause of mitral regurgitation in young women, but it may resolve during pregnancy as a result of mitral annulus stretching and LV enlargement. Mitral valve prolapse is generally well tolerated with no increased risk of complications unless there is considerable mitral regurgitation. Both mitral and aortic regurgitation can usually be managed medically with diuretics for pulmonary congestion and vasodilator therapy. Vasodilator therapy is indicated for regurgitant lesions only if there is coexisting hypertension. Rarely, valve surgery is required because of severe NYHA class III to IV symptoms.

Mild congenital aortic stenosis, mild mitral stenosis, and mild to moderate pulmonic stenosis are also fairly well tolerated. Nonetheless, pregnant women with stenotic valvular lesions require close monitoring throughout pregnancy, labor, and delivery. On rare occasions prompt intervention may be necessary if stenotic lesions result in hemodynamic compromise. Ideally, women with significant stenotic valvular lesions should either have their valves repaired or replaced before pregnancy, or be counseled against becoming pregnant. Valvuloplasty of severe aortic and pulmonic stenosis has also been successfully performed during pregnancy. Infrequently, aortic and mitral valves have been replaced during pregnancy for refractory symptoms or deterioration of functional class. Because of the considerable risk this confers to the mother and fetus, surgical valve replacement should be considered only a last resort.

Mitral stenosis often becomes symptomatic and first diagnosed during pregnancy. Symptoms usually develop in the later part of pregnancy from the increase in stroke volume and heart rate, leading to an increase in the transvalvular gradient. In addition, higher left atrial pressure can precipitate pulmonary edema, exacerbated by decreased diastolic filling as heart rates increase during pregnancy. In addition, there is a higher risk of atrial arrhythmias, including atrial fibrillation, with a resultant decrease in cardiac output. Therefore, the institution of modest diuretic (to relieve congestion) and β-blocker therapy (to avoid tachycardia) as well as salt, fluid, and activity restriction are effective. Digoxin may also be of benefit if atrial fibrillation develops. If the stenosis is moderate to severe with NYHA class III or IV symptoms and medical therapy is unsuccessful, percutaneous balloon valvuloplasty should be considered before labor and delivery. However, even with severe mitral stenosis (based on hemodynamic measurements), if symptoms are minimal, generally the pregnancy and delivery are well tolerated.

The most common cause of aortic stenosis in the pregnant woman is congenital. In the case of bicuspid aortic valve disease, aortic root dilation or aortopathy may be an associated finding with potential risk of spontaneous aortic dissection in the

third trimester, especially if there is aortic coarctation. Ideally, moderate to severe aortic stenosis should be corrected before conception. In the pregnant patient with severe aortic stenosis who is asymptomatic or has mild symptoms during pregnancy, conservative management is often sufficient with bed rest, oxygen, and β-blockers. However, for the pregnant patient with symptomatic severe aortic stenosis, percutaneous balloon valvuloplasty or surgery should be considered before labor and delivery. If surgery is pursued with future pregnancy anticipated, the Ross procedure is preferred simply to minimize the complexity of anticoagulation during pregnancy and delivery.

Guidelines for antibiotic prophylaxis for valvular disease to prevent bacterial endocarditis have also been updated. Routine antibiotic prophylaxis is not recommended for uncomplicated vaginal delivery or C-section unless infection is suspected. In the most recently published American Heart Association/American College of Cardiology (AHA/ACC) guidelines, antibiotic prophylaxis for high-risk patients (including those with a prosthetic valve, any degree of valvular stenosis, moderate or severe regurgitant valvular disease, previous history of endocarditis, complex congenital heart disease, or surgically constructed systemic-pulmonary conduits) has been categorized as a class IIa indication.

The pregnant patient with a prosthetic valve presents a challenging scenario, because pregnancy is both a hypercoagulable and hyperdynamic state. Thrombogenic mechanical prosthetic valves require chronic anticoagulation with warfarin, which is associated with a 15% to 25% risk of embryopathy in the first trimester, but the alternatives to warfarin (e.g., heparin) are not as effective. Although the less thrombogenic bioprosthetic valves do not require anticoagulation, they are less durable and carry a higher risk of accelerated degeneration during pregnancy. Thus, the recommendations for anticoagulation in the pregnant patient are as follows: heparin (either low-molecular-weight subcutaneous or unfractionated intravenous) for gestational weeks 6 through 12; if desired, change to warfarin until week 36, then change back to heparin after week 36; and finally, resume warfarin postpartum as soon as the obstetrician approves.

Heart Failure

Managing pregnant women with some form of preexisting cardiomyopathy (dilated, hypertrophic, or restrictive cardiomyopathy) is becoming more common. Prepregnancy counseling is of paramount importance and should be individualized based on a risk-benefit analysis. While medical management should be optimized for women with preexisting cardiomyopathy of any type (see Chapter 23), it is critical that treating physicians avoid medications that are potentially teratogenic. The most common nonteratogenic alternative therapeutic change involves using hydralazine rather than an angiotensin-converting enzyme (ACE) inhibitor for afterload reduction. In addition, close monitoring of systolic function with echocardiography is warranted for those with or at risk of decreased contractility, particularly during the third trimester when hemodynamic changes are greatest. Invasive hemodynamic monitoring may be helpful during labor and delivery and early postpartum management, but this remains controversial.

CARDIOVASCULAR DISEASE UNIQUE TO PREGNANCY

Hypertension in Pregnancy

In 2000, the National Heart, Lung and Blood Institute issued an update to its Working Group Report on High Blood Pressure in Pregnancy. This NHLBI working group classified high blood pressure during pregnancy into five categories based on the Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure guidelines: chronic hypertension, gestational hypertension, transient hypertension, preeclampsia superimposed on chronic hypertension, and preeclampsia-eclampsia. These categories can help predict the course of hypertension and the necessity for treatment. If pharmacologic treatment is required in addition to lifestyle modifications during pregnancy, methyldopa is the preferred first-line therapy, since it has no teratogenic effects (class B). If methyldopa is not tolerated, labetalol is the next choice, although there are no large-scale studies in pregnant women. Other alternatives may be used on the basis of risk-benefit data (e.g., other β-blockers, calcium channel blockers, hydralazine). ACE inhibitors and angiotensin receptor blockers are contraindicated in pregnancy.

Chronic hypertension is defined as hypertension (blood pressure >140/90 mm Hg) diagnosed before pregnancy, before week 20 of gestation, or during pregnancy that does not resolve postpartum. This is more common in African Americans, diabetics, patients with chronic renal disease, and obese patients. Most of the increased risk in this population occurs with superimposed preeclampsia.

Gestational hypertension is high blood pressure diagnosed for the first time after midpregnancy (after week 20) with no accompanying proteinuria. If preeclampsia does not develop and blood pressure returns to normal by 6 to 12 weeks postpartum, the final diagnosis is transient hypertension. However, if postpartum blood pressure remains high, the final diagnosis is chronic hypertension.

Preeclampsia superimposed on chronic hypertension is diagnosed when a patient with hypertension, but without proteinuria before week 20 of gestation, develops proteinuria. This diagnosis is also made when a patient with hypertension and proteinuria before week 20 has a sudden increase in proteinuria, a sudden increase in blood pressure, a platelet count drop to less than 100,000, or an acute elevation in serum transaminases: aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Risk factors for developing preeclampsia are listed in Table 58-4.

The classification of preeclampsia-eclampsia applies to women who develop increased blood pressure associated with proteinuria after week 20 of gestation (Fig. 58-2). Particularly worrisome signs that signal the likelihood of preeclampsia-eclampsia include systolic blood pressure of 160 mm Hg or higher and/or diastolic blood pressure of 110 mm Hg or higher, proteinuria greater than 2.0 g per 24 hours, increased serum creatinine concentration, platelet count below 100,000 with or without evidence of microangiopathic hemolytic anemia, and elevated AST or ALT concentrations. Additional symptoms that should raise concern include persistent epigastric

Table 58-4 Risk Factors for Preeclampsia, Peripartum Cardiomyopathy, and Peripartum Acute Myocardial Infarction

Condition	Risk Factors
Preeclampsia	Hypertension Collagen vascular disease Obesity Black race Insulin resistance Diabetes Increased circulating testosterone Thrombophilias
Peripartum cardiomyopathy	Advanced maternal age (>30 years) Multiparity Multiple gestation Black race Preeclampsia or sustained hypertension Long-term tocolysis
Acute myocardial infarction	Advanced maternal age (≥30 years) Hypertension Thrombophilia Smoking Transfusion Diabetes mellitus Postpartum infection

discomfort, persistent headaches, visual disturbances, and other central nervous system complaints.

The etiology of preeclampsia-eclampsia is unknown. It is a systemic disease that is associated with significant increased morbidity and mortality for the mother and fetus. The severity of preeclampsia varies from mild to severe, and it may progress rapidly and unpredictably. In general, patients with mild preeclampsia may be closely supervised. Those with severe preeclampsia should be admitted to a tertiary care center and monitored closely for signs of maternal and/or fetal distress. Preeclampsia can progress to eclampsia, a convulsive phase that may be fatal. Cerebral infarction and hemorrhage account for most deaths in preeclampsia-eclampsia. Intravenous hydralazine, labetalol, and nitroglycerin are commonly used to treat the hypertension. Magnesium sulfate is recommended to prevent seizures in severe preeclampsia and also to treat and prevent recurrent seizures in eclampsia. Delivery timing should be based on maternal and fetal conditions, including gestational age. Ultimately, delivery is the cure for preeclampsia. Signs and symptoms usually regress within 24 to 48 hours postpartum but can last longer. Therefore, it is important to monitor postpartum women with preeclampsia-eclampsia until the blood pressure and other abnormal parameters have normalized.

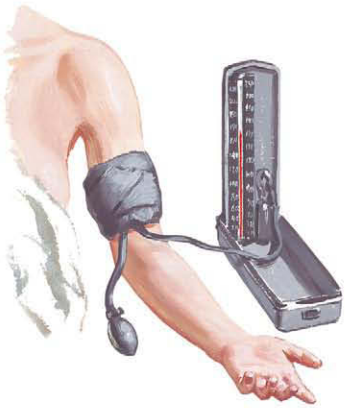
Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare form of heart failure affecting otherwise healthy young women. It is defined as the onset of cardiac failure without identifiable cause within the last month of pregnancy or within 5 months after delivery in the absence of preexisting heart disease. Its case definition was standardized at a National Institutes of Health consensus workshop in 2000 to include strict echocardiographic criteria for LV dysfunction (LV ejection fraction <45% or M-mode fractional shortening <30%, or both, and end-diastolic dimension >2.7 cm/m^2). Its prevalence is estimated at 1 in 3000 to 4000 live births in the United States, but rates have been higher in Africa (1/1000) and highest in Haiti (1/300). The etiology of this disorder remains unknown but is thought to be multifactorial, potentially related to infection, nutrition, hormones, an autoimmune process, and genetic predisposition. An association with tocolytic therapy has also been reported. Risk factors for developing PPCM are shown in Table 58-4. Women with pregnancy-associated cardiomyopathy diagnosed earlier than the last gestational month have similar characteristics.

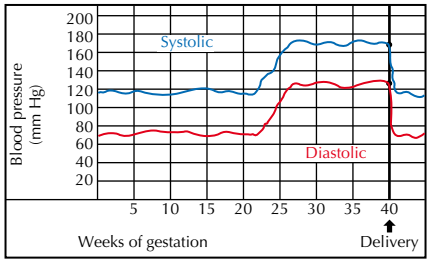
The outcome of patients with PPCM is highly variable and dependent on whether the LV size and function normalize. That said, mortality is high, ranging from 25% to 50%. The majority of deaths occur in the first 3 months after diagnosis. In approximately 50% of patients with PPCM, systolic function returns to normal or near normal within 6 months postpartum. The remaining patients demonstrate persistent cardiac dysfunction or deteriorating function, and experience symptoms and complications associated with chronic heart failure. PPCM accounts for approximately 5% of reported pregnancy-related deaths in the United States with a substantial racial disparity (higher mortality ratio for African American women).

Management of PPCM is supportive and includes standard treatment for heart failure, including an intra-aortic balloon pump or LV assist device or cardiac transplantation when necessary (see Chapters 23 and 24). The risks and benefits of medications should be reviewed before administration, especially if the patient is still pregnant. If the cardiomyopathy is diagnosed before delivery, hydralazine is the afterload-reducing agent of choice (because ACE inhibitors are teratogenic). ACE inhibitors are favored postpartum and are safe for breastfeeding patients. In addition, because of the increased risk of thromboembolic events in patients with severe LV dysfunction combined with the hypercoagulability of the pregnant state, anticoagulation is often recommended.

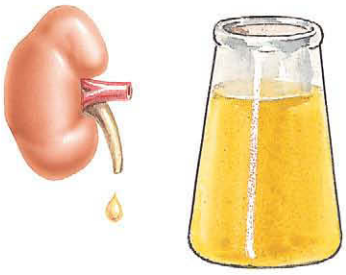
Advisability of future pregnancies is controversial, because recurrence with subsequent pregnancies is common. Patients with persistent LV dysfunction should avoid future pregnancies. For patients whose systolic function returned to normal after the initial incident, there is a variation of opinion. Relapse of LV dysfunction does occur in this group, albeit less frequently and perhaps less severely than in those with persistent systolic dysfunction. Still, the risk of severe LV dysfunction and/or long-term mild to moderate LV dysfunction is much higher in this group than in the general population. A large number of women with prior PPCM in whom LV function normalized experience a considerable decrease in LV function and clinical deterioration. Mechanistically, impaired contractile reserve, which can be demonstrated by dobutamine stress echocardiography, may be contributory. Based on these observations, even for women with prior PPCM in whom systolic function returned to normal, subsequent pregnancy should be considered with



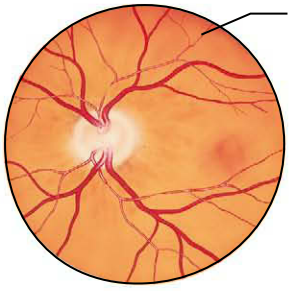
Elevated blood pressure



Preeclampsia-eclampsia is characterized by increase in blood pressure above 160 mm Hg systolic and/or 110 mm Hg diastolic after 20th week of gestation, accompanied by proteinuria, elevation of serum transaminases, and additional clinical findings, which usually resolve within 24–48 hours postpartum.

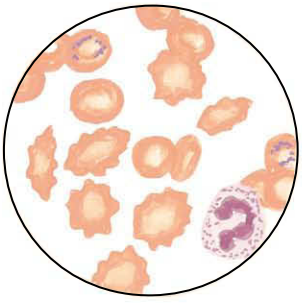


Proteinuria seen in preeclampsia and eclampsia

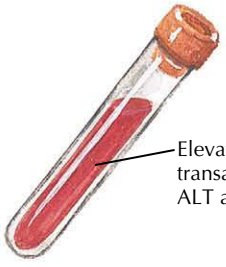


Narrowed retinal arterioles

Visual changes and persistent headaches are common complaints.

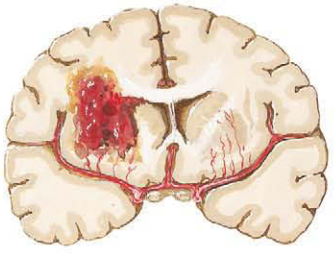


Microangiopathic hemolytic anemia and thrombocytopenia often noted



Elevated serum transaminases, ALT and AST

Elevated serum transaminases common in preeclampsia-eclampsia



Cerebral infarction or hemorrhage most common cause of death

Convulsion in true eclampsia

F. Netter M.D.
JOHN A. CRAIG—AD
C. Machado M.D.

Figure 58-2 *Preeclampsia-eclampsia.* ALT, alanine aminotransferase; AST, aspartate aminotransferase.

caution and realization that there is a strong possibility that PPCM will recur.

Pulmonary Edema Induced by Tocolytic Therapy

Tocolytic agents (commonly β_2-receptor agonists, e.g., terbutaline) are sometimes used to prevent preterm labor. Although these agents are often successful at preventing labor, they have important side effects: tachycardia (ventricular tachycardia has been reported), chest pain without ECG changes, electrolyte abnormalities, and noncardiogenic pulmonary edema. The rate of pulmonary edema induced by these agents is low. It is important, however, because patients are often misdiagnosed with decompensated heart failure, and the question of peripartum cardiomyopathy may also arise. The increased incidence of pulmonary edema seen in women treated with tocolytic therapy is most often associated with short-term (<48 hours) intravenous

infusions. There has been at least one report associating long-term (>4 weeks) oral tocolytic therapy with development of peripartum cardiomyopathy.

Acute Myocardial Infarction

As a greater number of older women become pregnant, the prevalence of coronary artery disease and risk of acute myocardial infarction (AMI) during pregnancy increase. In addition to traditional coronary risk factors, pregnancy increases the risk of AMI three- to fourfold based on a nationwide sample in which the rate was 6.2 per 100,000 deliveries and the case fatality rate was 5.1%. Risk factors for AMI are listed in Table 58-4. The most common etiology is atherosclerosis with or without intracoronary thrombus, similar to acute coronary syndrome presentations in the general population. However, 60% of the time there are other causes of AMI in pregnancy, including coronary thrombus without atherosclerotic disease, coronary dissection, and possible coronary vasospasm. Coronary dissection in the peripartum period is uncommon but must be considered in women with chest pain in the third trimester or postpartum. The mechanisms of coronary dissection in this population are unknown. Often these patients can be treated conservatively with medical therapy (including anticoagulation), but there are times when revascularization is necessary. As in any instance of coronary artery dissection, percutaneous coronary intervention (and stenting) is more difficult and risky in peripartum patients with coronary artery dissection.

Regardless of the etiology, peripartum women who develop AMI should be treated with revascularization as appropriate. However, medical management may be difficult because of the risk of hemorrhage and teratogenesis with antiplatelets and anticoagulants. The risk of fetal death is usually associated with maternal death, which emphasizes the importance of optimizing maternal health.

MANAGEMENT AND THERAPY

Optimum Treatment

Because many cardiovascular diseases may affect the pregnant woman, treatment must be individualized yet follow the standard of care. Ideally, multidisciplinary antenatal discussions should be shared among obstetricians, cardiologists, and primary care providers. Outcomes are improved for both mother and child when there is a thoughtful care plan for the delivery of the pregnant woman with cardiovascular disease.

Avoiding Treatment Errors

Because drugs are rarely tested in pregnant women, safety information on the vast majority of pharmaceuticals in this population is lacking. Most cardiovascular drugs cross the placenta and are also secreted in breast milk. Therefore, when possible, it is advisable to avoid the use of prescription and over-the-counter drugs during pregnancy and during the postpartum period if the mother is breastfeeding.

When this is not possible, every effort should be made to use a medication that has been shown to be safe during pregnancy. The U.S. Food and Drug Administration categorizes drugs according to their potential to cause birth defects, based on data from human and animal studies. The categories range from class A drugs (no documented fetal risks) to class X drugs (contraindicated in part or all of pregnancy due to proven teratogenicity). Very few cardiovascular drugs are class B (animal studies suggest risk, but results are unconfirmed in controlled human studies). Examples of class B drugs include methyldopa, lidocaine, and sotalol. The majority of cardiovascular drugs currently in use are actually class C (animal studies have demonstrated adverse fetal effects, but no controlled human studies are available). Examples include most β-blockers (e.g., labetalol, metoprolol, propranolol), hydralazine, and calcium channel blockers. Finally, class D drugs demonstrate some evidence of human fetal risk, but the benefits from use during pregnancy may be acceptable despite the risk (e.g., if the drug is needed because safer drugs cannot be used or are ineffective). In general, if pharmacologic therapy is needed, drugs that have been in use for longer periods prescribed at the lowest possible dosages are recommended.

FUTURE DIRECTIONS

The increased survival rate of women with congenital heart disease combined with the trend toward delaying childbearing will continue to increase the likelihood that the providers of health care to pregnant women will manage complex cardiovascular disease. Ideally, a multidisciplinary approach to these patients at a tertiary care center is recommended to optimize outcomes for mother and child and to provide data for treatment of other like individuals. As pregnant women are frequently excluded from clinical trials, the evidence for the management of cardiovascular disease during pregnancy is modest and mostly based on case series and registries. Since standard therapies are extrapolated from studies in more generalized populations, further investigation is needed in this specialized population.

ADDITIONAL RESOURCES

Elkayam U, Akhter MW, Singh H, et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation.* 2005;111:2050–2055.

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Describes the epidemiology of AMI in pregnancy.

Royal College of Obstetricians and Gynecologists. Heart disease and pregnancy—study group statement. Available at: <http://www.rcog.org.uk/womens-health/clinical-guidance/heart-disease-and-pregnancy-study-group-statement>; Accessed 18.03.10.

Gives the consensus views arising from the 51st Study Group: Heart Disease and Pregnancy (2006).

Uebing A, Steer PJ, Yentis SM, et al. Pregnancy and congenital heart disease. *BMJ.* 2006;332:401–406.

Reviews common congenital heart diseases in relationship to risks during pregnancy.

EVIDENCE

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These guidelines provide current recommendations for treatment of valvular heart disease based on available data and consensus opinion (class I, IIa, IIb, III; Levels A, B, C).

Gifford RW, August PA, Cunningham G, et al. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol.* 2000;183:S1-S22.

Provides current classification of and recommendations for treatment of hypertension during pregnancy based on consensus opinion.

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Provides current recommendations for treatment of heart disease during pregnancy based on consensus opinion.

Aging and the Cardiovascular System

Walter A. Tan

59

Senescence is a fundamental life process that results from a complex combination of age-related physiologic changes including changes in aerobic respiration, increased oxidative metabolism and stress, genetic and cellular damage due to the accumulation of mutations, and lifelong exposure to various environmental stresses. Together these events outpace endogenous surveillance and repair mechanisms and/or provoke compensatory responses that become maladaptive and cause cellular and organ dysfunction. And while disease should not be misconstrued as an inevitable consequence of aging, distinctions are often arbitrarily defined, and the difference between diminished biologic reserve and overt dysfunction can be thought of as quantitative instead of qualitative. Although the role of genetics in aging in the broadest spectrum remains poorly understood, examples of hereditary syndromes of premature aging, such as Hutchinson-Gilford syndrome (progeria) and Werner's syndrome (wherein affected individuals typically die between the second and fourth decades of life), support the notion that aging is at least partly genetically programmed (see Chapter 72).

Although its histologic features vary little across the age spectrum, the presence and severity of atherosclerosis markedly increase with aging. This atherosclerotic burden, along with maladaptive changes associated with aging, accounts for the high mortality and morbidity rates of myocardial infarction (MI) and heart failure in elderly cohorts. Chronic deconditioning, depression, and other confounding comorbidities in elderly persons add yet another layer of complexity in discerning which changes are attributable to age and which to environment (Table 59-1). This chapter focuses on age-related changes in the cardiovascular system and considers strategies that may decrease the risk of death and disability from cardiovascular diseases in elderly individuals.

CARDIOVASCULAR CHANGES WITH AGE

Myocardial Chambers and Valves

The effects of aging on the myocardium and cardiac valves are dramatic. Deposition of lipids and their peroxidation products occurs throughout the myocardium and the vasculature at the cellular level and in subcellular components such as the mitochondria. DNA denaturization and decreased RNA and protein synthesis accompany these age-related changes, resulting in a diminished capacity for regeneration and repair with age.

Cardiac mass increases for several reasons, including the increased size of individual myocytes and an increased abundance of amyloid, collagen, fat, fibrotic foci, and advanced glycation products, even in the absence of myocardial damage from ischemia or infarction. It is thought that myocyte hypertrophy is a compensatory mechanism in response to the myocyte loss (due to apoptosis, necrosis, or both). Myocyte hypertrophy may also be a physiologic response to the increased hemodynamic stress on the myocardium that results from the chronic increase in peripheral vascular resistance that also occurs with aging. The left atrium tends to enlarge with advancing age, increasing the likelihood that atrial fibrillation (AF) will develop. Fibrosis and calcification of the aortic valve and the mitral annulus may lead to valvular dysfunction.

Investigations have demonstrated that intrinsic myocardial contractility is diminished with age, in large part as a result of higher vascular afterload and the compensatory effects to sympathetic overactivity. Although at rest the normal sitting and submaximal end-systolic volume index is similar in adults between the ages of 20 and 85 years, the response to maximal exercise (seated cycle exercise to >100-watt workload) is significantly attenuated in elderly individuals. A young person can increase left ventricular (LV) ejection fraction by almost 50% to accommodate the demands of intense exercise, from a baseline LV ejection fraction of approximately 62% to 87%. In the elderly heart, only one fifth of this contractile reserve is seen (increasing LV ejection fraction from ~63% to only ~70%), despite the Frank-Starling mechanism and increased LV diastolic pressures. In the elderly, the isovolumic relaxation time may also be prolonged (i.e., the interval increases between the closure of the aortic valve and the opening of the mitral valve) because of slowed ventricular contraction. The peak rate of LV diastolic filling is also reduced approximately 50% with aging. Together these changes lead to the increased propensity toward diastolic dysfunction in elderly individuals and the increased dependence on atrial contraction ("kick") for augmentation and completion of diastolic LV filling. This diminished diastolic capacity makes elderly individuals more vulnerable to the hemodynamic and symptomatic consequences of AF. Because overall function in the elderly is no better than in younger individuals, with aging, overall cardiac output is unable to meet demand when it is increased due to exertion or other causes.

Impulse Formation and Conduction

As with cardiac contractility, multiple factors contribute to the progressive dysfunction of the cardiac conduction system in aging. Minor quantities of amyloid deposits exist in nearly half of otherwise healthy individuals over 70 years of age. The sinoatrial node may also separate physically from the atrial tissue as fat accumulates around it. In addition, the absolute number of pacemaker cells in the sinus node declines substantially after 60 years of age. The number of pacemaker cells in a 75-year-old may be only 10% of that number in young adulthood. These changes are major contributors to the increased prevalence of sick sinus syndrome with aging. Other age-related abnormalities in the conduction system include an increase in fibrous tissue in the internodal tracts and a diminished density of left-bundle fascicles and distal conducting fibers. These conduction abnormalities are exacerbated by the increase in polyunsaturated fatty acids in cardiac cellular membranes that occurs with aging,

Table 59-1 Cardiovascular Changes in Elderly Individuals without Overt Disease

Measured Change	Functional Consequence
Myocardium	
Increased interventricular septal thickness; increased cardiac mass per body mass index in women	Increased propensity for diastolic dysfunction
Prolonged action potential, calcium, transient, and contraction velocity (in animal models); desensitization of myocardial β-adrenergic receptors	Decreased intrinsic contractile reserve and function
Reduced early and peak left ventricular filling rate and increased pulmonary capillary wedge pressure	Greater dependence on atrial kick, and physiologic S_4 heart sound
Cardiac Valves	
Fibrosis and calcification of the aortic valve and the mitral annulus	Valvular stiffening
Vasculature	
Thickening of the media and subendothelial layers; increased vessel tortuosity	Decreased vessel compliance; increased hemodynamic shear stress and lipid deposition in the arterial walls
Large elastic arteries (e.g., aorta, carotid artery) become thicker, tortuous, and more dilated.	Increased peripheral vascular resistance and earlier reflected pulse waves, and consequent late augmentation of systolic pressure
Impulse Formation and Propagation	
Substantial decrease in sinoatrial pacemaker cell population, with separation from atrial musculature due to surrounding fatty tissue accumulation	Diminished intrinsic sinus and resting heart rates Slight PR interval prolongation; increased incidence of ventricular ectopy
Increase in collagenous and elastic tissue in all parts of the conduction system	Propensity toward bundle branch blocks and abnormal conduction
Decreased density of bundle fascicles and distal conduction fibers	Lower threshold for atrial and ventricular arrhythmias; increased fibrosis and myocyte death
Reduced threshold for calcium overload and for diastolic after-depolarizations and ventricular fibrillation	
Autonomic System	
Diminished autonomic tone, especially parasympathetic; increased sympathetic nerve activity and circulating catecholamine levels	Decreased spontaneous and respiratory-related heart rate variability

resulting in changes in ion thresholds and exchange, as well as in myocardial changes that are proarrhythmic.

Large studies support this increase in arrhythmias in elderly individuals. In a study comparing adults older than 60 years of age to young adults, the presence of atrial ectopic beats was demonstrated in 6% by resting electrocardiography, in 39% with maximal treadmill exercise, and in 88% of those who underwent 24-hour ambulatory monitoring in the group over 60 years old. Though not known to be associated with any adverse outcome, short runs of paroxysmal supraventricular tachycardia are nearly twice as prevalent in octogenarians as in septuagenarians, and are observed in about half of those 65 years of age or older. The prevalence of ventricular ectopic beats rises from 0.5% in those under 40 years of age to 11.5% in those 80 years of age and older, and increases further in those with associated cardiac disease. One study demonstrated that in individuals older than 85 years of age with normal cardiac function the prevalence of ventricular ectopic beats was 5%, as compared to 13% and 28% in those with coronary artery disease and heart failure, respectively. The prognostic significance of isolated ventricular ectopic beats for elderly individuals specifically has not been studied, whether experienced at rest, during continuous 24-hour monitoring, or after treadmill exercise. However, subjects with ventricular ectopic beats on a 2-minute rhythm strip were found to have a 14-fold increase in relative risk of sudden cardiac death in a recent study. Sinoatrial function slows with age, but healthy octogenarians and nonagenarians with resting heart rates lower than 40 to 45 bpm or sinus pauses longer than 2 seconds should be followed carefully, since several studies have shown this group to be at increased risk of syncope and other heart rate–related problems. The PR interval is slightly prolonged with age, primarily from delayed conduction proximal to the His bundle, and the prevalence of first-degree atrioventricular block is 6% to 8% in octogenarians. There is an increased incidence of progression from first-degree atrioventricular block to second- and third-degree block in the elderly as well.

Vasculature

Vessel wall stiffness increases with age (Fig. 59-1). There is progressive thickening of medial and subendothelial layers and increased calcium deposition, often initially affecting proximal coronary segments. Autopsies on supercentenarians (people 110 years or older) also reveal senile cardiac transthyretin-related amyloidosis and other β-sheet protein accumulations in the arterial tree. Moreover, blood flow becomes less laminar as vessels become more tortuous and endothelial cells show greater

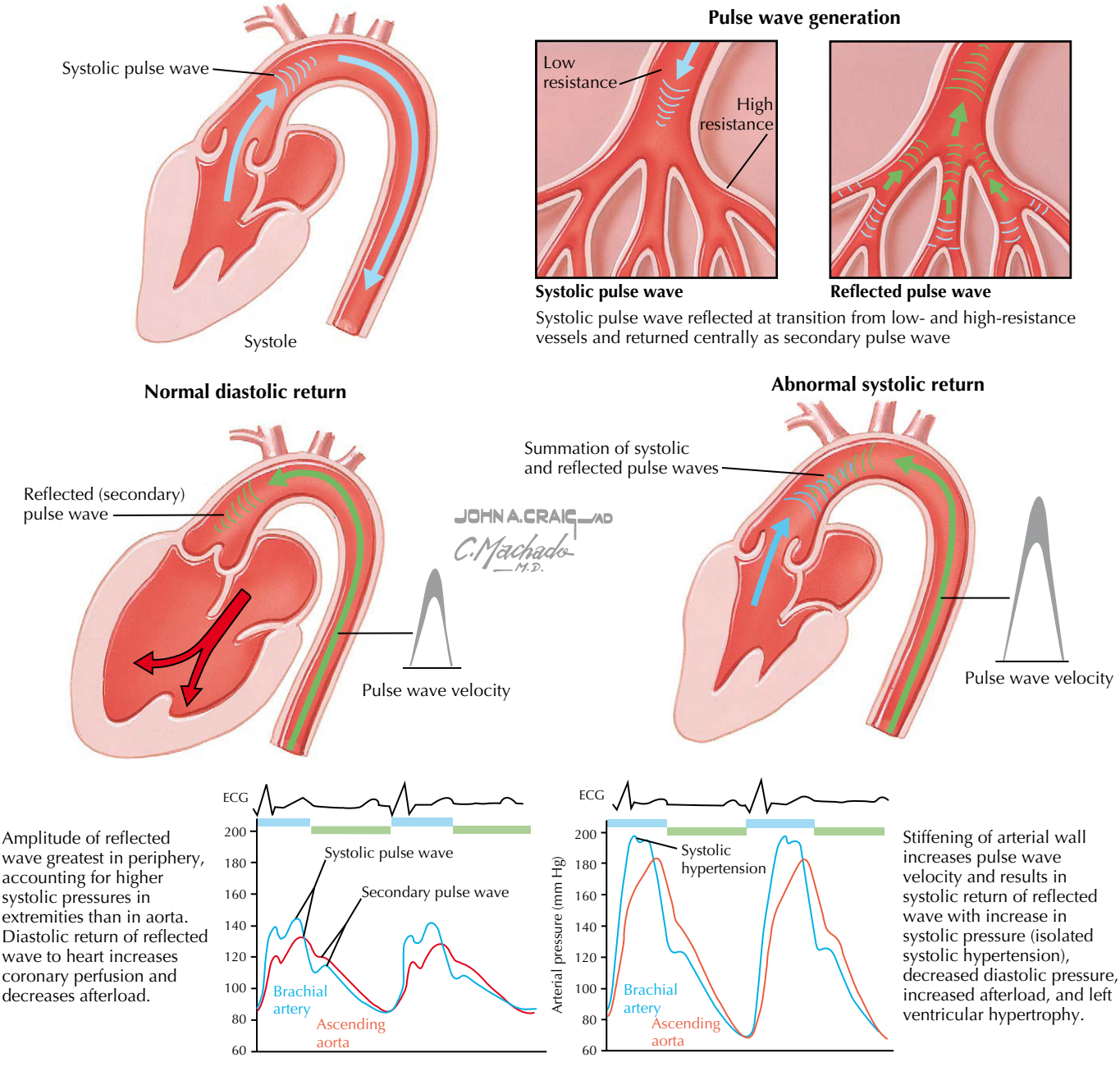


Figure 59-1 *Wave reflection and isolated systolic hypertension.*

heterogeneity in size, shape, and axial orientation. In response to chronic injurious stimuli, vascular smooth muscle cells phenotypically revert to a proliferative, migratory, and secretory mode, and produce more collagen and matrix. Arterial conduit vessels have increased elastase activity and degradation of elastin, with resulting increased stiffness. There may also be diminished reparative capacity, as indicated by in vitro observations of proliferative senescence in endothelial cells and fibroblasts. These factors, plus the increased presence of inflammatory cytokines and metalloproteinases in the vessel wall, predispose one to vascular occlusive and aneurysmal changes.

The peripheral arterial tree also shows morphologic and physiologic decline. The average aortic root size is approximately 14 mm/m^2 for both sexes in the early twenties, increasing to 17 mm/m^2 in healthy octogenarians. With increases in the aortic diameter, individuals have an increased risk of aneurysm formation and aortic dissection. Large-caliber vessels thicken progressively. The intima-medial wall thickness of carotid arteries is 0.03 mm in the young and doubles by age 80. After the fourth decade of life, renal blood flow per gram of kidney weight decreases progressively, probably because of increased renal arterial resistance.

Peak oxygen utilization ($Vo_{2\ max}$), a measure of work capacity and physical conditioning, declines about 50% by 80 years of age compared to the $Vo_{2\ max}$ of a 20-year-old individual (~10% loss per decade of life). Aside from age-associated decline in

cardiac function, up to half of the $Vo_{2\ max}$ impairment is attributable to poor peripheral oxygen extraction and utilization, largely from inefficient redistribution of blood flow to skeletal muscles.

Neurohormones and Growth Factors

Age-related postsynaptic signaling deficits attenuate β-adrenergic modulation of heart rate variability and vascular tone, decreasing heart rates slightly at rest and substantially during exertion. A lower heart rate ceiling with age substantially affects exercise reserve capacity. The maximum heart rate achieved in 20-year-old persons is approximately 180 bpm, but it is only approximately 120 bpm in octogenarians. The maximal cardiac index therefore decreases approximately 30% over 6 decades, 11 and 8 L/min/m^2, respectively, as a result of this phenomenon alone.

Elderly myocytes secrete more stress-related products such as atrial natriuretic factor and opioid peptides. Moreover, ambient plasma catecholamine levels are elevated and the production of nitric oxide is reduced, all contributing to increased afterload and lowered cardiac output.

CARDIOVASCULAR PATHOLOGY AND AGE

Approximately one in four individuals in the United States will be aged 65 years or older by 2025, and it is projected that 80% of all cardiovascular deaths will occur in this cohort. Interestingly, individuals who have survived far into older age are at low risk of a cardiac death. The National Institutes of Health–funded New England Supercentenarian Study notes that people who have survived to at least age 110 years have disproportionately low incidences of vascular or related diseases. This may relate to their overall low-risk profile for cardiovascular diseases: only 3% have diabetes mellitus, 6% have a history of MI, and 22% have hypertension.

Heart Failure

Although congestive heart failure (CHF) is relatively uncommon before 45 years of age, its incidence grows linearly thereafter and geometrically at 85 years of age and older. More than 500,000 hospital admissions per year are for CHF in patients older than 65 years of age. The diagnosis of CHF in elderly individuals can be difficult, the condition sometimes presenting only as altered mental status, anxiety, dyspnea, sleep disturbance, or abdominal discomfort. Even severe LV dysfunction can be occult in sedentary individuals. Conversely, normal or near-normal LV systolic function does not exclude heart failure from diastolic dysfunction, which is the underlying cause in almost half of patients older than 65 years of age with CHF symptoms. Furthermore, many comorbidities mimic heart failure symptoms. Peripheral edema may result from benign causes such as venous stasis, or it may result from liver or renal failure. Given the comorbidities present in the elderly, it is very important not to miss conditions that are contributing to heart failure, such as anemia, aortic stenosis, thyroid dysfunction, bilateral renal artery stenosis, or tachycardia-induced cardiomyopathy.

One additional therapeutic issue of particular importance in elderly individuals is polypharmacy. The clinician must be vigilant against agents considered benign by the patient that may actually exacerbate CHF, such as nonsteroidal anti-inflammatory drugs. The potential for drug interactions (e.g., with warfarin or digitalis) or intolerance from altered renal or hepatic metabolism is magnified, particularly with the standard multidrug therapy for CHF.

Finally, because the prognosis of CHF in the very old is worse than the prognosis of most cancers (<20% 5-year survival rate), it may be appropriate for the primary physician to help patients prepare for "end-of-life" issues for their own and their families' benefit.

Coronary Artery Disease

Recognition of angina or acute coronary syndromes can be difficult in elderly individuals, because up to 90% present with symptoms other than classic chest pain. Between the ages of 65 and 85 years, the prevalence of silent or misclassified ischemia increases by 50% in males and by nearly 300% in females. Underdiagnosis is not trivial in this age group. The 30-day mortality for acute MI in elderly persons can exceed 20%. Even non-Q-wave MI has a significant age gradient of 1-year cardiac mortality rate: 29% in those 70 years of age or older as compared with 14% in younger patients. Corresponding all-cause 1-year mortality rates were recently reported to be 36% and 16%, highlighting the hazard from competing comorbidities in geriatric patients.

The absolute risk reduction in mortality for acute MI patients older than 65 years of age who received thrombolytic therapy was 3.5% as compared with 2.5% for younger patients. However, this came at the cost of nearly 1% excess bleeding complications, including hemorrhagic stroke, and up to 1.5% intracranial hemorrhage rate in those older than 65 years in a Medicare database. For this reason, in many centers emergent percutaneous coronary revascularization is preferred over thrombolytic therapy in elderly patients with ST-elevation MI. One study of elective angioplasty showed similar rates of cardiac death or recurrent angina in patients 75 years of age or older to those in their younger counterparts (mean age 55 years) when complete revascularization was achieved. This is not true for very old (>75 years) individuals who present with cardiogenic shock. Subset analysis from the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) randomized trial showed that most of the benefit from emergency revascularization accrued only to younger patients. Randomized comparisons of elective angioplasty versus coronary artery bypass grafting (CABG) in the elderly showed the following results 3 years after angioplasty and CABG, respectively: 78% versus 100% survival, 15% versus 25% Q-wave MI, 11% versus 0% late CABG, and persistent angina in 29% versus 12%. These data should be interpreted with caution, because there was unequal randomization in this small elderly cohort and because the angioplasty group had a higher prevalence of diabetes and hypertension. Nevertheless, even after successful primary percutaneous coronary intervention, the 1-year survival is markedly worse with age. The risk of death after percutaneous coronary intervention is 2% in the 55- to 65-year group, 7% for those 66 to 75 years old, and 11% for those over 75 years of age.

A final special consideration for elderly patients undergoing invasive procedures or open heart surgery is the risk of stroke or multiorgan atheroemboli commonly attributed to severe atherosclerosis and calcification of the aortic arch and peripheral vessels. Foreknowledge of the concomitant vascular disease distribution and consequent adaptation of surgical technique may minimize these perioperative complications.

Valvular Heart Disease

The most common valvular diseases requiring treatment in elderly individuals are calcific aortic stenosis and mitral regurgitation from myxomatous degeneration or annular dilatation. Aortic stenosis prevalence in adults older than 62 years of age is reported to be approximately 10% mild, 6% moderate, and 2% severe.

Unfortunately, physical examination and screening for significant valvular disease in elderly individuals are less reliable in the elderly than in younger individuals for several reasons (see also Chapter 1). First, many elderly individuals may be asymptomatic, either because they are sedentary by nature or because they have adapted their lifestyles due to severe valvular and myocardial disease. Second, up to half of elderly individuals have systolic murmurs that are of little clinical consequence. Third, many comorbidities in elderly individuals, including kyphosis, chronic obstructive pulmonary disease, and decreased blood flow velocity across the valves (secondary to decreased cardiac output), may obscure the classic signs of aortic stenosis or mitral regurgitation. Fourth, peripheral pulsus parvus et tardus (diminished and slow carotid artery pulses, an excellent indicator of aortic stenosis in young individuals) can be confounded by aortic and carotid arterial stiffening or by heart failure and β-blocker use. Therefore, especially for patients who are in declining health, clinicians should have a lower threshold for suspecting reparable aortic valve disease. Aortic valve replacement has been shown to be safe and effective for otherwise healthy individuals up through the eighth decade of life. The clinician should also actively search for significant mitral regurgitation before the onset of irreversible cardiomyopathy.

The relief of aortic stenosis is associated with substantial improvements in quality of life even in very old individuals, with long-term survival rates similar to age-matched individuals who do not require open heart surgery. Of the septuagenarians and older patients who had operations for aortic stenosis in three studies, more than two thirds were in New York Heart Association functional class III to IV at baseline. The vast majority (80% to 90%) improved to functional class I status and independent living after surgery. Although the risk-to-benefit ratio is acceptable for individuals who are otherwise healthy, the decision to operate is not trivial. The surgical mortality rate doubles with age older than 75 years (12.4% for patients older than 75 years of age, as compared with 6.6% for younger patients). Interestingly, in the studies published thus far, operative risks for aortic stenosis do not continue to increase for those older than 90 years of age, perhaps because of a "survivor effect"; that is, those who survive to old age tend to be healthier. The mortality risk increases substantially when concomitant CABG or other procedures are required. Other predictors of increased risk are impaired LV function, diabetes mellitus, nonsinus rhythm, urgency of surgery, and severe renal or lung disease. Determining what is best for an individual includes considering whether surgery should be done, the feasibility of valve repair, the type of valve to be used for replacement, and the risks associated with anticoagulation. Operative mortality with mitral valve surgery is even higher, mostly because of complex underlying etiologies and the likelihood that LV dysfunction resulting from mitral regurgitation will not improve after surgery.

Percutaneous valvuloplasty is a proven therapeutic method for mitral stenosis but offers only short-term relief for aortic stenosis. The favorable long-term outcomes reported for mitral valvuloplasty are based predominantly on young cohorts who had rheumatic mitral stenosis, and this approach has not been extensively studied in the elderly. The procedural complication-free success rate is lower for older cohorts with degenerative and calcific mitral valve disease.

Arrhythmias

AF is the most important supraventricular arrhythmia in elderly individuals because of its high prevalence and associated morbidity. The prevalence is approximately 3 per 1000 subjects in the general population, but it increases to 3 to 4 per 100 between 60 and 65 years and to 14% in those older than 85 years. Of patients with AF, about 70% are 65 to 85 years of age. Other cardiac comorbidities markedly increase the prevalence of AF. Coronary artery disease doubles the risk of AF for men, whereas heart failure increases the risk by 8-fold in men and by 14-fold in women. Although the incidence of stroke is only approximately 6% to 7% in patients with AF in their sixties, stroke afflicts 26% of nonagenarians with AF, often presenting a therapeutic clinical dilemma because the risk of hemorrhage with anticoagulant therapy also increases with age.

Cerebrovascular Disease

Stroke produces 20% of all cardiovascular deaths in elderly individuals and is the leading cause of neurologic disability resulting in institutionalization. Unlike MIs, for which the initial male predominance in rates (up to 4:1 ratio in those younger than 55 years) narrows with age, there is only a 30% higher incidence of atherothrombotic brain infarction in males compared to females. This mildly increased risk in men is maintained into older age. In brain MRI studies, almost one in three subjects ages 65 to 84 years has evidence of silent strokes.

With the exception of subarachnoid hemorrhage and embolic stroke, the etiology of stroke is similar across age categories. Comparing those aged 65 and older to those aged 35 to 64 years, the proportion of strokes caused by subarachnoid hemorrhage was about half in elderly individuals, but there were more strokes caused by embolic mechanisms. CHF and heart failure gain increasing importance as risk factors for stroke with age. The attributable risk of stroke from AF is 1.5% in the fifth decade of life, rising exponentially to 23.5% by the eighth decade of life. For CHF, the corresponding attributable risks are 2.3% and 6%.

Unfortunately, the consequences of stroke are more severe in very old individuals. For those aged 85 years or older, in-hospital mortality rate is more than 25% compared with 13.5%

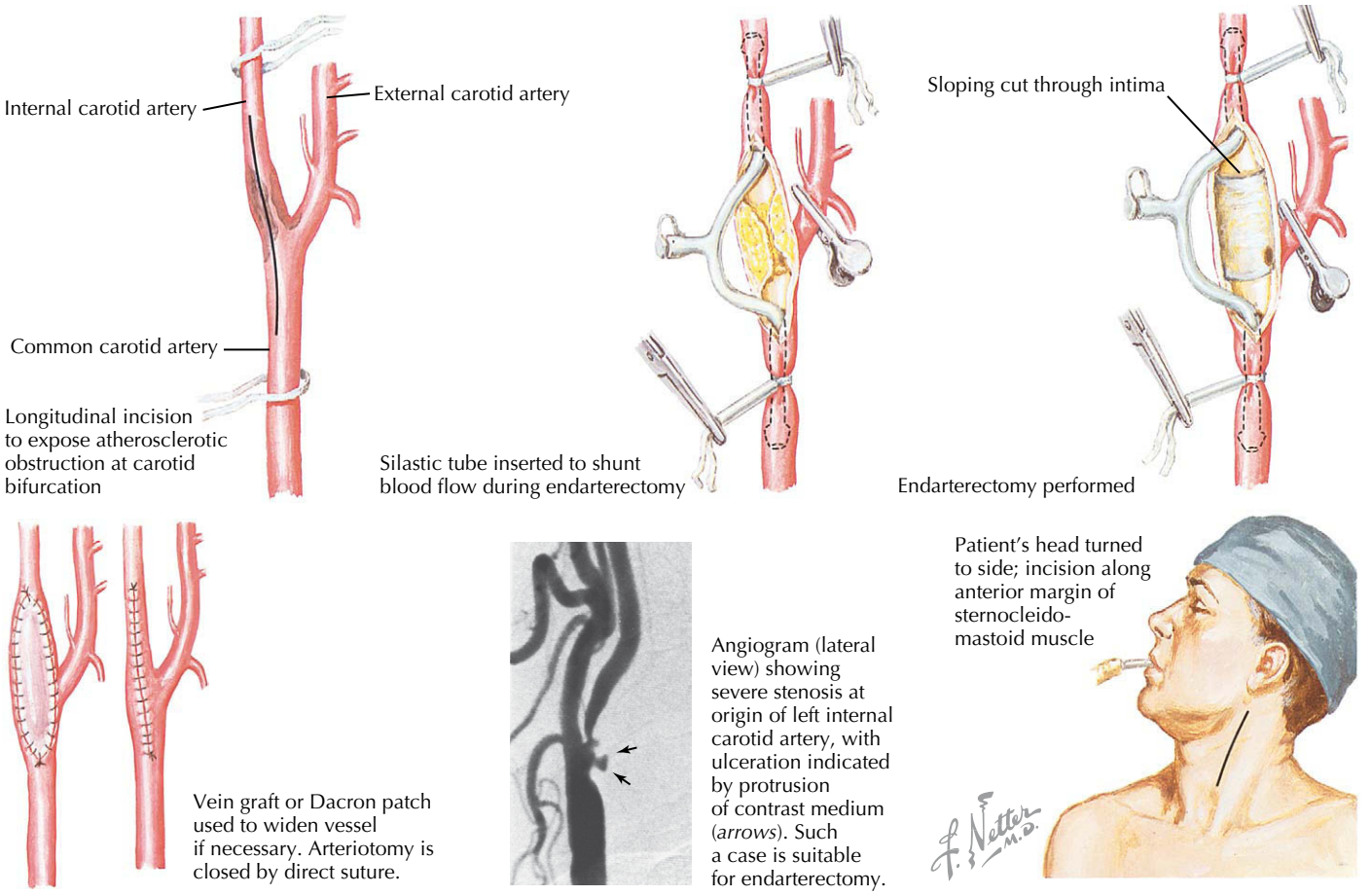


Figure 59-2 *Endarterectomy for atherosclerosis of the extracranial carotid artery.*

for those younger than 85 years of age. Among those who survive to be discharged, only one fifth have minimal or no neurologic deficit compared to one third of a younger cohort. In another study, one third of stroke survivors had dementia (based on a Mini-Mental Status Exam score <24), a threefold higher prevalence than stroke-free subjects. Because dementia with or without stroke is the largest contributor to disability in basic activities of daily living (e.g., dressing, bathing, and transfers), the estimated 18.4% population-attributable risk of dementia from stroke is of great importance.

As with other therapies, the risk of treatment is higher in elderly individuals. Even given the increased risk, therapeutic interventions may reduce risk compared with conservative therapy. For instance, elderly individuals with severe carotid stenosis are at high risk if treated with medications only, but, when patients are carefully selected, carotid endarterectomy reduces the risk of stroke and stroke-related death (Fig. 59-2). Related to stroke risk, isolated systolic hypertension increases with age, most likely because of increased vascular impedance with a recalibration in baroreceptor reflex thresholds (see Fig. 59-1). Fortunately, the absolute and relative risk reductions from antihypertensive therapy increase also, with a 50% relative risk reduction in the 5-year stroke rate in those older than 80 years of age, compared with a 30% relative risk reduction with treatment in sexagenarians.

Peripheral Arterial Occlusive and Aneurysmal Disease

Peripheral vascular wall integrity degenerates with age. For example, the incidence of abdominal aortic aneurysms increases fourfold in subjects older than 65 years of age as compared with those 55 years of age or younger. Peripheral arterial occlusive disease can be considered a late-stage manifestation of atherosclerosis. Although the mean age in clinical trials of European patients requiring coronary interventions is 55 years of age, the average ages for those with extracoronary occlusive disease are 59, 65, 67, and 72 years, respectively, for those with iliac, renal, carotid, and infrainguinal artery stenoses (Fig. 59-3; see also Chapters 47 to 49).

THE THERAPEUTIC WINDOW

Up to 50% of elderly patients do not receive appropriate thrombolytic therapy on the basis of age alone, despite data showing large absolute and relative mortality risk reductions for this

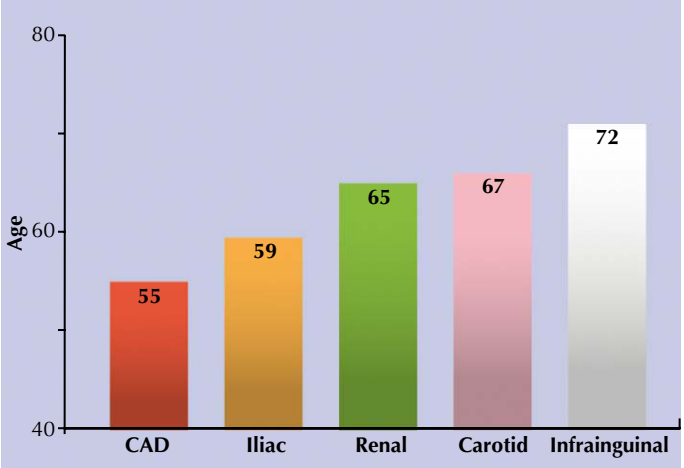


Figure 59-3 *Average age at which different arteries require revascularization.* CAD, coronary artery disease. With permission from Tan WA, Yadav JS, Wholey MH. Endovascular options for peripheral arterial occlusive and aneurysmal disease. In: Topol EJ, ed. *Textbook of Interventional Cardiology.* 4th ed. Philadelphia: WB Saunders; 2002.

group. The increasing use of percutaneous coronary interventions in elderly patients with acute MI is beginning to partially offset concerns about stroke risk with thrombolytic therapy. However, the problem of undertreatment in older individuals extends far beyond the initial therapy. Of Medicare patients with acute MI who had no contraindication to aspirin therapy, only 61% received this proven therapy during hospitalization and less than 50% were instructed to take aspirin at discharge. There has also been debate over lipid-lowering therapy in elderly individuals, even though this population is at highest risk for severe cardiovascular catastrophes. Treatment with simple drugs such as chlorthalidone and atenolol where necessary to control isolated systolic hypertension decreases the relative risk of stroke by 29% in sexagenarians, 30% in septuagenarians, and 49% in octogenarians or nonagenarians. Nonetheless, 55% of eligible octogenarians are not on any antihypertensive medications.

FUTURE DIRECTIONS

The narrower physiologic reserve that accompanies advancing age elevates cardiovascular risk and narrows the therapeutic benefit. However, outcomes have improved markedly with advances in medical and interventional therapies, particularly in more vulnerable populations such as elderly patients. A progressive decrease in 30-day acute MI mortality rate has been documented in octogenarians from 55% in the 1970s to 31% in the 1980s to 22% by 1991. This represents a 72% decrease after statistical adjustment for comorbidities and MI severity. Better and safer monitoring and anesthetic techniques permit necessary surgery even for high-risk patients. Endovascular therapies are less invasive, offering the very old short- and medium-term outcomes that formerly could be obtained only with major surgery (e.g., stent grafting for abdominal aortic aneurysms).

The benefits of prevention and therapy should be extended more aggressively to all age groups, with careful consideration of individual risk profiles and preferences. More important, simply extending life span no longer suffices. The key challenge for health care in the twenty-first century is extension of the "health span" or quality of later life of the older patient.

ADDITIONAL RESOURCE

National Institutes of Health, National Institute on Aging. The Baltimore Longitudinal Study of Aging (BLAS). Available at: <http://www.grc.nia.nih.gov/branches/blsa/blsa.htm>; Accessed 31.03.10.

For more than 5 decades, more than 1400 men and women have been followed in America's longest-running scientific study of human aging, sponsored by the National Institute on Aging.

EVIDENCE

de Boer J, Andressoo JO, de Wit J, et al. Premature aging in mice deficient in DNA repair and transcription. *Science.* 2002;296:1276–1279.

The consequence of XPD mutation in this mouse model was increased vulnerability to oxidative DNA damage. The phenotype for humans with the same mutation, however, is not osteoporosis and early graying as observed in mice, but more typically growth retardation, neurologic abnormalities, and brittle hair and nails, attributed to the depressed RNA synthesis.

Lakatta EG. The cardiovascular system: circulatory function in younger and older humans in health. In: Hazzard WR, ed. *Principles of Gerontology and Geriatric Medicine.* New York: McGraw-Hill; 1999:645–660.

Dr. Lakatta has been one of the principal investigators for the Baltimore Longitudinal Study of Aging and provides an authoritative review on the physiologic and pathologic changes in the aging heart.

Mackey RH, Sutton-Tyrrell K, Vaitkevicius PV, et al. Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. *Am J Hypertens.* 2002;15:16–23.

In these 356 subjects aged 70 to 96 years, baseline insulin resistance, increased common carotid intima-media thickness, elevated heart rate, and decreased physical activity correlated with higher aortic pulse wave velocity years later.

Schoenhofen EA, Wyszynski DF, Andersen S, et al. Characteristics of 32 supercentenarians. *J Am Geriatric Soc.* 2006;54:1237–1240.

Fascinating cohort and well-validated database of people who have lived 110 years and beyond.

Wei JY. Age and the cardiovascular system. *N Engl J Med.* 1992; 327:1735–1739.

Good review of age-related cardiovascular changes in the elderly at the organ system level.

Wenger NK, ed. *Cardiovascular Disease in the Octogenarian and Beyond.* London: Martin Dunitz; 1999:1–439.

A good classic introduction to clinical considerations in the elderly.

Neuromuscular Diseases and the Heart

60

Ajmal Masood Gilani and Nizar Chahin

Diseases affecting skeletal muscle may also involve cardiac muscle, and those involving the peripheral nervous system may affect neurologic control of the heart. Cardiovascular manifestations vary in nature and severity in different patients, even those with the same disease, and in some cases the cardiovascular sequelae result in greater morbidity and mortality than the neuromuscular manifestations attributable to the primary disease. The common neuromuscular disorders likely to have cardiac effects are discussed here.

As a first principle it is important to recognize that distinguishing isolated neuromuscular diseases from those that also involve the heart can be challenging. Although for years measurement of serum creatine kinase (CK) and CK subunits in the bloodstream was used as a screen for myocardial involvement in neuromuscular diseases, it is now recognized that more advanced studies are needed. CK from postnatal skeletal muscle is composed of MM subunits, but CK from fetal and regenerating skeletal muscle is composed of MB subunits. Therefore, in diseases with attempted muscle regeneration, including inflammatory myopathies and some dystrophies, an elevated MB fraction is not specific for myocardial injury and may instead reflect skeletal muscle regeneration. For this reason, clinicians must be vigilant to the possibility that myocardial disease may be present and understand that even with additional cardiac biomarkers (including troponin measurement), the diagnosis may be uncertain and that imaging (and more advanced) studies are most often required to make the appropriate diagnosis.

DISEASES OF MUSCLE

Muscular Dystrophies

Traditionally categorized by mode of inheritance, age of onset, severity, and pattern of clinical presentation, these inherited disorders generally present with progressive muscle weakness. In recent years, advances in molecular biology have identified many dystrophies by specific gene or protein abnormalities.

Dystrophinopathies

Duchenne's and Becker's muscular dystrophies (MDs) are X-linked recessive disorders resulting from abnormalities in dystrophin, an essential component of the cytoskeleton of skeletal and cardiac muscle. Progressive weakness and pseudohypertrophy of muscles, particularly the calves, are characteristic of both.

Clinical manifestations of Duchenne's MD become obvious at 3 to 5 years of age, with contractures and proximal muscle weakness greater than distal weakness. Gower's maneuver is characteristic (Fig. 60-1). Nonprogressive mental retardation occurs in approximately 70% of patients. Severe scoliosis occurs in 90% by early in the second decade of life. There is steady progression to wheelchair use within 10 years, and death usually occurs in the second or early third decade of life from respiratory or cardiac failure. Cardiovascular manifestations include dilated cardiomyopathy, usually of the posterobasal and posterolateral left ventricle; mitral regurgitation; conduction abnormalities, most frequently incomplete right bundle branch block; atrial and ventricular arrhythmias; QT dispersion; and autonomic dysfunction manifested by abnormal heart rate variability.

Becker's MD is less severe, with the age of onset in the second decade of life or later. Progression is slower, with death occurring usually in middle adulthood. Cardiac involvement is independent of the severity of the skeletal muscle disease.

Both conditions result in marked, persistent CK elevation, generally 10 times the upper limit of normal or higher. The diagnosis can be made in more than 90% of patients by confirmation of a deletion or point mutation of the Xp21 gene locus. Analysis of dystrophin content by muscle biopsy is also a reliable diagnostic tool (see Fig. 60-1, lower).

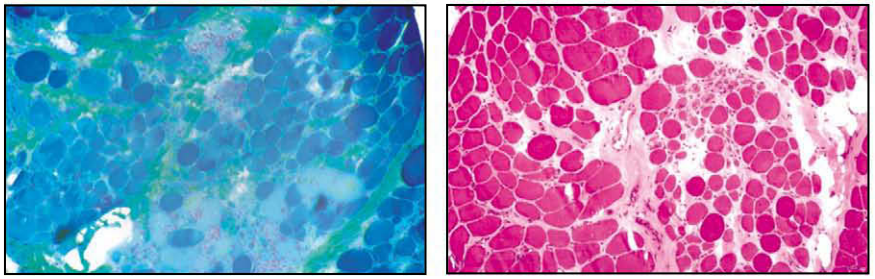
Treatment of the muscle weakness is supportive. Selected patients may benefit from surgery to retard scoliosis, respiratory support, and treatment of cardiac complications. Standard therapies with angiotensin-converting enzyme inhibitors and β-blockers are generally used for cardiac failure and arrhythmias. For drug-refractory ventricular arrhythmias, an implantable cardiac defibrillator may be beneficial. In Becker's MD, some patients with disproportionate cardiac involvement have successfully undergone cardiac transplantation.

EMERY-DREIFUSS MUSCULAR DYSTROPHY

Emery-Dreifuss muscular dystrophy (EDMD) is a rare, genetically heterogeneous disorder characterized by early contractures of the elbows, ankles, and posterior cervical muscles and slowly progressive muscle weakness in a scapulohumeroperoneal distribution. It is caused by mutations in nuclear proteins found in the inner muscle membrane in skeletal and cardiac muscles. Mutations in emerin cause X-linked EDMD (XL-EDMD), and mutations in lamin A/C cause autosomal-dominant EDMD (AD-EDMD). Mutation in the latter also causes limb girdle muscular dystrophy 1B. Cardiac involvement in XL-EDMD is characterized by atrioventricular (AV) conduction defects, heart block, atrial flutter, and complete atrial paralysis. The echocardiogram usually reveals a dilated right atrium; dilated or restrictive cardiomyopathy is rare. In AD-EDMD, cardiac involvement is a common complication; dilated cardiomyopathy is more common than in XL-EDMD. Supraventricular and ventricular arrhythmias, syncopal episodes, and sudden death are common in both disorders.

Clinically, patients usually have an elevated CK, but generally it is less than 10 times the normal level. However, it can be normal in patients with mutations in lamin A/C. Electromyography (EMG) shows a myopathic pattern, and muscle biopsy

Characteristically, the child arises from prone position by pushing himself up with hands successively on floor, knees, and thighs because of weakness in gluteal and spine muscles. He stands in lordic posture.



Muscle biopsy specimens showing necrotic muscle fibers being removed by groups of small, round phagocytic cells (**left**, trichrome stain) and replaced by fibrous and fatty tissue (**right**, H & E stain).

Figure 60-1 *Duchenne's muscular dystrophy.*

reveals a dystrophic picture with prominent fibrosis. Diagnosis is confirmed by genetic testing.

All patients with EDMD should have an annual ECG, echocardiogram, and Holter monitoring. Permanent pacemaker implantation is justified, either in asymptomatic patients or when the ECG becomes abnormal. In AD-EDMD, there is accumulating evidence of sudden death even in patients who have been paced. For this reason, an implantable defibrillator is more appropriate management than a pacemaker in most patients. When atrial fibrillation or atrial standstill is recognized, antithromboembolic prophylaxis with aspirin or warfarin should be considered.

MYOTONIC DYSTROPHY

Myotonic dystrophy, an autosomal-dominant MD, is a multiple-system disease. Two types of myotonic dystrophy have been identified. Type 1, or DM1, is predominantly a distal myopathy caused by an expanding trinucleotide CTG-repeat of a specific protein kinase on chromosome 19. Type 2, or DM2, is a proximal myotonic dystrophy caused by the expansion of a CCTG repeat in the zinc finger protein (ZNF9) on chromosome 3. Disease expression varies within and between affected families. Patients may have facial muscle weakness, especially of the temporalis, levator palpebrae superioris, and masseters, giving typical "cadaveric" facies. Myotonia results in delayed muscle relaxation after contraction or muscle percussion (Fig. 60-2). Systemic features may include frontal balding, cataracts, hypogonadism, insulin resistance, dysphagia, hypersomnia, pickwickian syndrome, and mental retardation. Children of affected mothers with DM1 are more likely to be severely weak and hypotonic and to have mental retardation in infancy. Progression of myotonic dystrophy is variable, with death usually resulting from aspiration pneumonia, respiratory failure, or cardiac involvement.

Cardiac manifestations are similar in both types and include conduction defects, atrial and ventricular tachyarrhythmias (occasionally causing sudden death), mitral valve prolapse, and, rarely, dilated cardiomyopathy. Anesthesia may increase the risk of AV conduction block. A yearly ECG is recommended. In high-risk families or individuals deemed to be at risk, His bundle studies and prophylactic cardiac pacemaker placement are often recommended. β-adrenergic blockers and angiotensin-converting enzyme inhibitors improve cardiomyopathic symptoms. Mexiletine, phenytoin, or other antiepileptic agents can sometimes ameliorate the myotonia. Modafinil or methylphenidate may alleviate hypersomnia.

Genetic testing can confirm the diagnosis of myotonic dystrophy. Serum CK may be elevated or normal. Myotonic discharges have a characteristic "dive bomber" sound on EMG, although this feature is not generally present in infants.

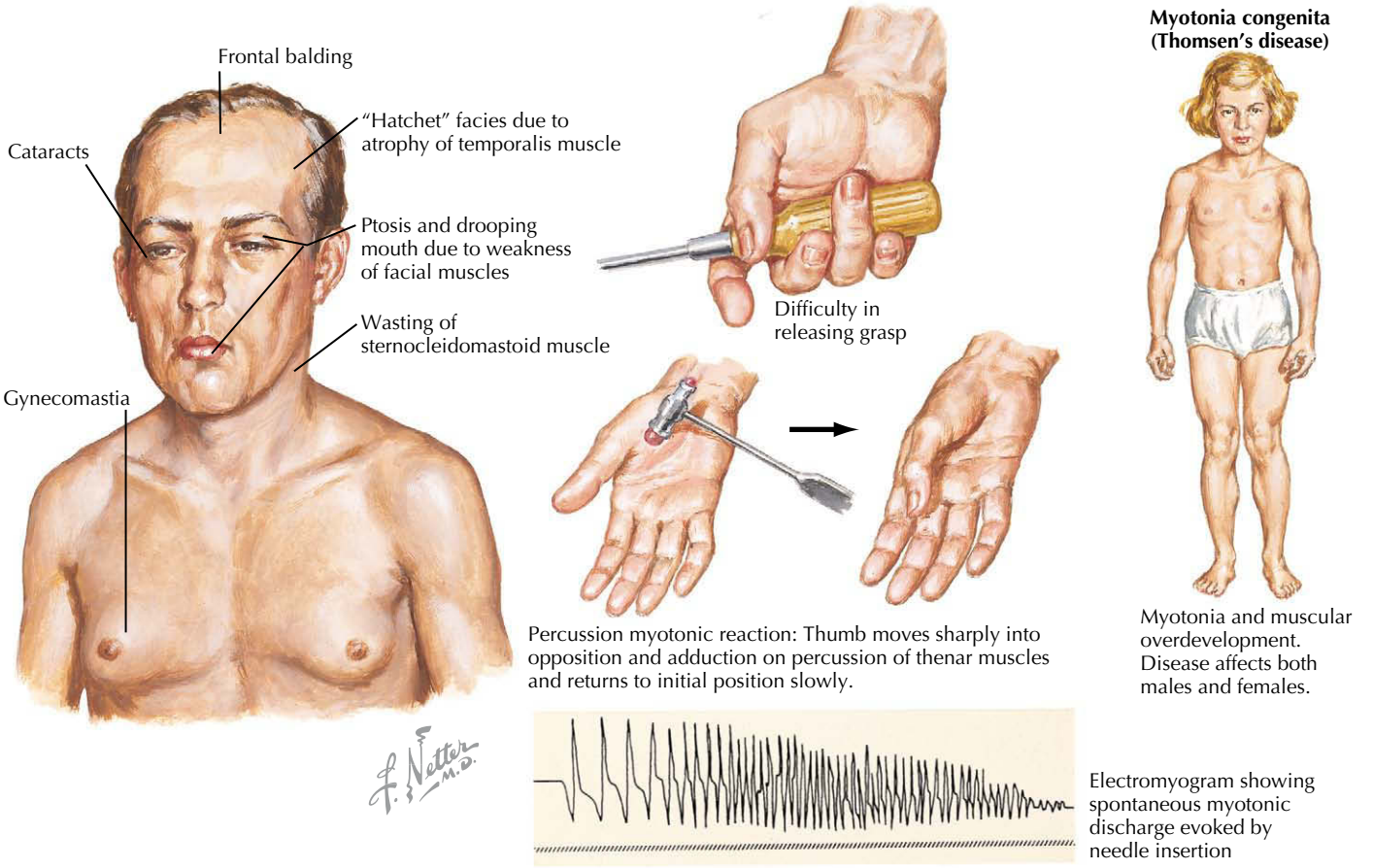


Figure 60-2 *Myotonic dystrophy.*

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Many families affected by this usually autosomal-dominant condition show a deletion at the 4q35 gene locus. The prevalence is 1 to 2 in 100,000, and onset varies from the first through fifth decades. Facial, scapular, and humeral muscles are involved earliest and most prominently, but there is often progression to extraocular, peroneal, pectoral, and respiratory muscles. The involvement of various muscle groups is often asymmetric. Patients commonly have a transverse smile with poor emotional expression; failure of complete eye closure, particularly in sleep; and dysarthria. Other systemic manifestations may include sensorineural deafness, retinal telangiectasia, epilepsy, and mental retardation. Cardiac manifestations are less common and include labile hypertension, conduction block, and arrhythmias. The diagnosis is based mainly on clinical appearance but may be supported by elevated CK (although in a substantial number of patients the CK is normal), EMG, and muscle biopsy. Treatment is primarily supportive. Although life expectancy is near normal in most of these patients, approximately 20% advance to wheelchair use, and some die of respiratory failure.

LIMB GIRDLE MUSCULAR DYSTROPHY

Limb girdle muscular dystrophy (LGMD) is a genetically heterogeneous group of autosomal-dominant or autosomal-recessive myopathies characterized by weakness and wasting of the shoulder and pelvic girdle muscles. It is caused by mutations in proteins of the sarcolemma and extracellular matrix, proteins with enzymatic activity, sarcomeric proteins, and nuclear-associated proteins. Mutations in sarcoglycans α, β, γ, δ, caveolin 3, fukutin, myotilin, laminin α2, and lamin A/C can be associated with cardiac involvement. No significant cardiac involvement has been reported with mutations in dysferlin, calpain, or collagen VI.

Associated cardiac abnormalities include AV conduction block, atrial and ventricular arrhythmias, and dilated cardiomyopathy. In sarcoglycanopathies, the severity of cardiac involvement differs among the subunits. Cardiac involvement is more severe in β/δ LGMD than α/γ. Clinically the cardiac disease follows a similar natural history to the dystrophinopathies with predilection for posterobasal predominant cardiomyopathy that can progress to serious congestive heart failure (CHF). At autopsy, myocardial histology often reveals progressive focal ventricular damage secondary to infarction. The coronary vasculature is histologically abnormal with abnormal vasoconstrictive response. Use of the calcium channel blocker verapamil has been recommended to ameliorate clinical progression of the cardiac manifestations of LGMD.

The diagnosis of LGMD is supported by elevated CK, although it could be normal in myotilin and lamin A/C

mutations. EMG produces a myopathic pattern. Muscle biopsy shows dystrophy, and special immunostaining may reveal the abnormal protein. The diagnosis can be confirmed by genetic testing. No specific treatment is available. Serial ECG and echocardiographic evaluations are recommended.

MYOFIBRILLAR MYOPATHY

Myofibrillar myopathy is a genetically heterogeneous group of disorders that result from mutations of the Z-disk–related proteins, leading to myofibrillar disorganization followed by accumulation of myofibrillar degradation products and ectopic expression of Z-disk–associated proteins. Clinical features resulting from different gene mutations are similar. Some cases are characterized by a triad of myopathy, cardiomyopathy, and peripheral neuropathy. Mutations in desmin, α-B-crystallin, myotilin, Z-band alternatively spliced PDZ-containing protein, and filamin C can all result in similar pathologic alterations in skeletal muscle that are characteristic of myofibrillar myopathy.

The distribution of muscle weakness can be proximal, distal, or both proximal and distal. The CK can be mildly elevated or normal. EMG shows myopathic changes with abnormal electrical irritability, including myotonic discharges. Dilated, hypertrophic, and restrictive cardiomyopathies have been associated with these disorders. Arrhythmias and incomplete right bundle branch block have been reported rarely.

DISTAL MYOPATHIES

This heterogeneous group of MDs starts in the distal limbs and usually has a benign course. They include Miyoshi's myopathy, which starts in the feet and calves, and Welander's myopathy, which starts in the hands. Cardiac conduction abnormalities are common, and periodic ECG is recommended.

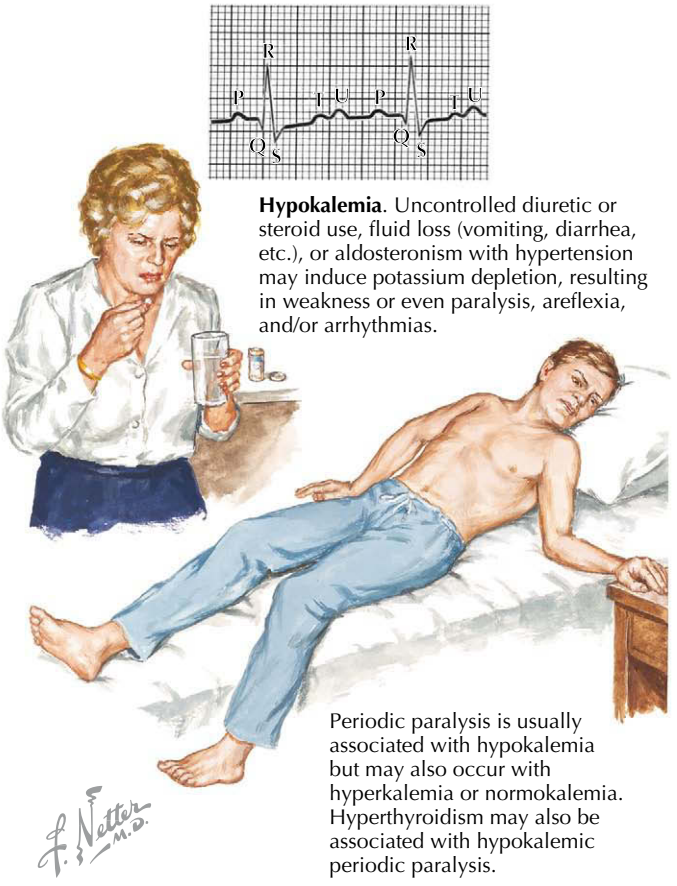
OTHER HEREDITARY CONDITIONS AFFECTING MUSCLE AND THE HEART

These conditions include McLeod's syndrome (myopathy with elevated CK, polyneuropathy, movement disorders, psychiatric syndromes, seizures, and dilated or restrictive cardiomyopathy); X-linked vacuolar cardiomyopathy and myopathy (Danon's disease); Barth's syndrome (X-linked myopathy, cardiomyopathy, cyclic neutropenia, short stature, low cholesterol, and mitochondrial abnormalities), which is due to mutation of the tafazzin gene; scapuloperoneal MD with mental retardation and lethal cardiomyopathy; and neuromuscular junction disorders, including familial limb girdle myasthenia and slow-channel syndrome.

Metabolic Disorders Causing Myopathy and Cardiac Disease

ELECTROLYTE DISORDERS

Hypokalemic periodic paralysis (PP), a calcium channel defect, hyperkalemic PP, a sodium channel defect, and potassium-sensitive PP are autosomal-dominant disorders characterized by attacks of weakness of variable severity and duration, generally lasting for hours to days (Fig. 60-3). Precipitants may include exposure to cold. Symptoms also often come during a period of rest following vigorous activity. Fasting and supplementation of potassium can trigger attacks of hyperkalemic PP and ameliorate hypokalemic PP. Ingestion of carbohydrates can precipitate hypokalemic PP and ameliorate hyperkalemic PP. Cardiovascular manifestations, including ventricular bigeminy, bidirectional tachycardias, and an increased QT interval, are more common in hyperkalemic PP and potassium-sensitive PP. Ventricular arrhythmias rarely result in sudden death in these patients. Nonetheless, therapeutic decisions should be made as would be



Hypokalemia. Uncontrolled diuretic or steroid use, fluid loss (vomiting, diarrhea, etc.), or aldosteronism with hypertension may induce potassium depletion, resulting in weakness or even paralysis, areflexia, and/or arrhythmias.

Periodic paralysis is usually associated with hypokalemia but may also occur with hyperkalemia or normokalemia. Hyperthyroidism may also be associated with hypokalemic periodic paralysis.

Hyperkalemia. Addison's disease (primary adrenocortical insufficiency), characterized by bronzing of skin, weakness, weight loss, and hypotension, is associated with elevated serum potassium. Manifestations may be mild in early stages, with weakness predominating.

Figure 60-3 *Myopathies related to disorders of potassium metabolism.*

the case in those without PP with ventricular arrhythmias (see Chapter 30). The diagnosis is suspected on the basis of familial occurrence of transient attacks of weakness. Abnormalities in potassium and sodium levels during the attacks can often be ascertained and are diagnostic. Genetic testing is available for some of these conditions.

Mexiletine, calcium gluconate, glucose, and insulin are effective in treating hyperkalemic PP. Administration of oral potassium is effective in hypokalemic PP. Acetazolamide and dichlorphenamide may be helpful in both conditions. Management of the electrolyte imbalance usually improves muscle weakness but not cardiac arrhythmias.

GLYCOGEN STORAGE DISEASES

The autosomal-recessive glycogen storage diseases result from deficiency or absence of specific enzymes in the glycogen degradation pathway. At least nine different enzyme abnormalities can result in glycogen-containing vacuoles in muscle. Generally, cardiac involvement is not important, with the exception of acid maltase deficiency, wherein cardiomyopathy can occur in the infantile and childhood form but usually is not seen in the adult form.

The infantile form, or Pompe's disease, is most severe, with liver, spleen, and (often) tongue enlargement from abnormal glycogen storage. The ECG typically shows cardiomegaly with high-amplitude QRS complexes. Measurement of acid maltase concentration in leukocytes, muscle, or cultured fibroblasts confirms the diagnosis. Death is generally a result of cardiac or respiratory failure. Administration of alglucosidase alfa intravenously has been approved by the U.S. Food and Drug Administration as the treatment for Pompe's disease.

CARNITINE DEFICIENCY

The lipid storage myopathies are characterized by abnormal fat accumulation in muscle, resulting from many different metabolic defects. Carnitine deficiency is the only one of these that produces significant cardiac involvement. Most patients who experience this condition have a systemic deficiency associated with enzymatic defects or a secondary deficiency from renal disease or use of drugs such as sodium valproate. Further molecular analysis will be needed to determine whether isolated muscle carnitine deficiency is a discrete entity. Clinical features of carnitine deficiency include recurring acute encephalopathy, developmental delay, myopathy, and recurring hypoketotic hypoglycemia. One form of carnitine deficiency is manifested as a progressive and potentially fatal cardiomyopathy with recurring hypoglycemia, and in this form there is rarely involvement of other organs. The diagnosis of carnitine deficiency is established by measurement of carnitine levels in plasma, urine, and muscle tissue. Treatment consists of dietary carnitine supplementation and glucose infusion during acute episodes.

MITOCHONDRIAL DISORDERS

Mutations in mitochondrial DNA result in defective energy-generating pathways and oxidative phosphorylation with eventual cellular apoptosis. A variety of different syndromes have been recognized, and each may be accompanied by hypertrophic cardiomyopathy. Kearns-Sayre syndrome results in progressive external ophthalmoplegia, cardiac conduction defects, and dilated cardiomyopathy. Leber's hereditary optic neuropathy manifests clinically as progressive blindness and may be associated with a shortened PR interval and supraventricular tachycardias, mitochondrial encephalomyopathy with lactic acidosis and stroke, and myoclonic epilepsy with ragged red fibers. Genetic testing is available for some but not all of these diseases. Skeletal muscle biopsy shows ragged red fibers on Gomori trichrome staining and abnormalities of numbers or structure of mitochondria or both on electron microscopy. Biochemical analysis of mitochondrial activity from muscle tissue is useful.

No accepted treatment regimen exists. Administration of L-carnitine may slow the progession of cardiomyopathy, and prophylactic pacing may improve survival rates in individuals with mitochondrial disorders.

Inflammatory Myopathies

The classification of these immune-mediated acquired muscular disorders is controversial because features of inflammatory myopathy accompany all collagen-vascular diseases, and some experts feel that these are localized manifestations of one or another collagen-vascular disorder. Generally, conditions isolated to the muscle are categorized as polymyositis or dermatomyositis. Although they probably have different immune etiologies, the major clinical difference is the presence of a heliotrope rash in dermatomyositis, most frequently found in the periorbital region and over the knuckles, knees, and elbows. Not uncommonly, the new presentation of polymyositis or dermatomyositis heralds the presence of an occult neoplasm.

These disorders are characterized by progressive symmetric weakness of proximal limb muscles, often with myalgias. Wasting typically occurs only late in the course of the disease, when there may also be distal involvement. Neck flexor weakness is common. Dysphagia may occur secondary to esophageal dysmotility. Respiratory muscle involvement and pulmonary fibrosis may lead to respiratory failure. This is probably more common in patients with a positive anti-Jo antibody. Raynaud's phenomenon and joint involvement are often systemic features found in individuals with inflammatory myopathies. Cardiac manifestations include myocarditis, diffuse hypokinesia, and ventricular enlargement with or without heart block. CK is elevated in the active stage of the disease. With effective treatment, the total CK may return toward normal, but the percentage MB fraction may rise.

The EMG may show nonspecific or characteristic changes. Muscle biopsy is generally definitive, with perivascular and endomysial inflammatory responses. However, the disease is patchy and can be missed on biopsy. In adults, the diagnostic approach should include evaluation for occult malignancy.

The standard therapy for inflammatory myopathies is immunosuppressive therapy, beginning with prednisone. High-dose intravenous immunoglobulin infusion may be effective but necessitates periodic administration for months to years. Antimetabolites, including methotrexate, azathioprine, and cyclosporine, may have a role in steroid-resistant disease.

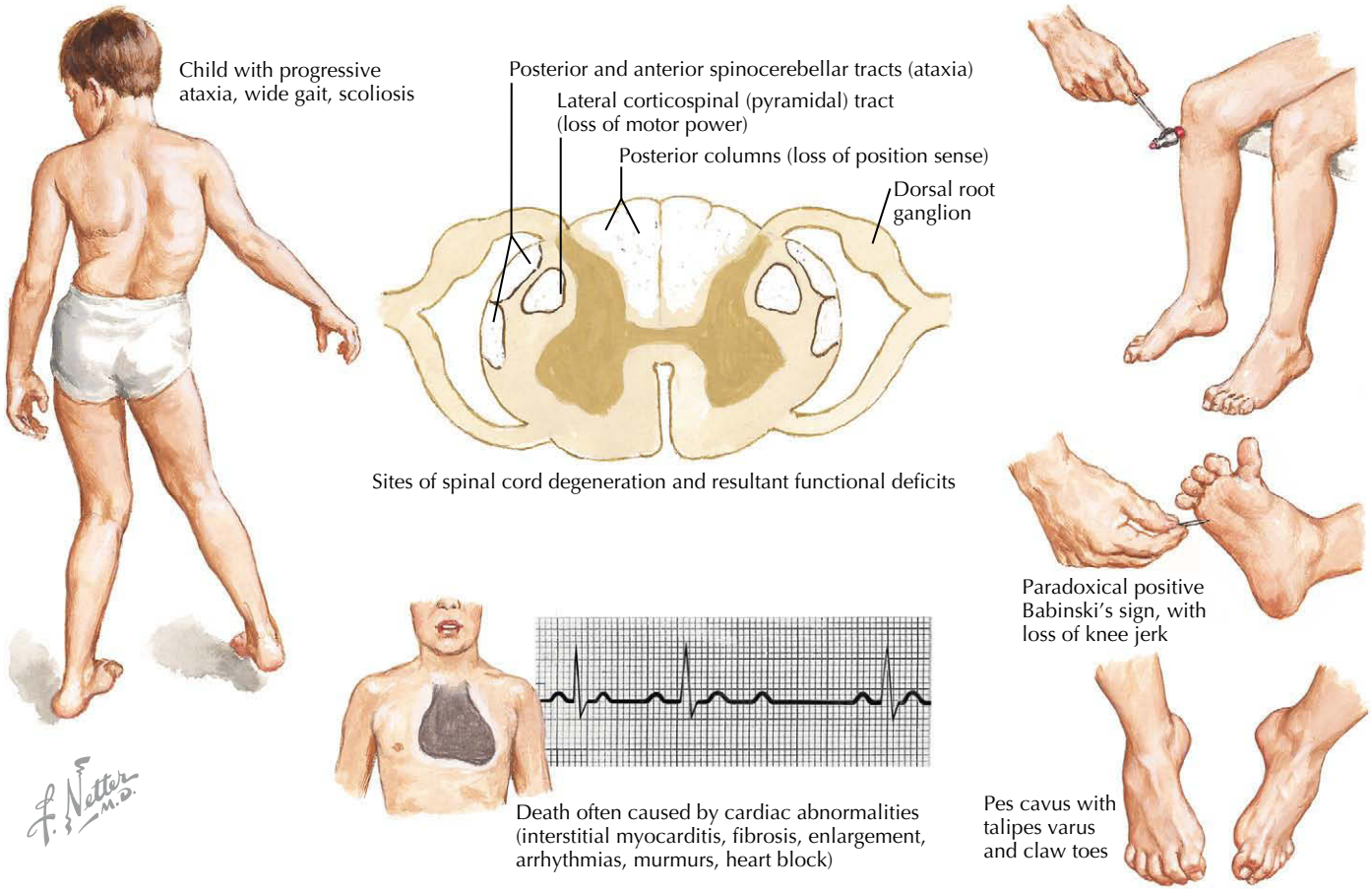


Figure 60-4 *Friedreich's ataxia.*

Cardiac and respiratory involvement often proves resistant to therapy.

Alcoholic Myopathy

Long-term alcohol abuse may be associated with acute necrotizing myopathy, myopathy with hypokalemia, or progressive proximal myopathy. Alcoholic cardiomyopathy, which occurs in some individuals with heavy, long-term alcohol use, may be associated with any of these conditions. Cardiac involvement has been described in three stages: (1) palpitations and vague chest wall pain often accompanied by atrial arrhythmia, (2) left ventricular hypertrophy, and (3) cardiac dilatation and CHF. Advanced alcoholic myopathy has a high mortality rate, even if the patient becomes abstinent.

NERVE DISEASES

Many peripheral neuropathies are associated with cardiac disease, although the degree of cardiac involvement varies among patients with the same disease. Neuropathies with prominent autonomic involvement, such as alcoholic and diabetic neuropathy, are likely to show abnormalities of heart rate variability. They may also have clinically obvious cardiac disease; whether this results from neuropathy, cardiovascular disease, or both is difficult to determine.

Hereditary Diseases

The hereditary motor and sensory neuropathies are the most common inherited neurologic diseases. They rarely involve the heart, but arrhythmias frequently accompany the less common hereditary sensory and autonomic neuropathies.

FRIEDREICH'S ATAXIA

Friedreich's ataxia is a progressive autosomal-recessive degenerative disease. The genetic deficit is a trinucleotide repeat (GAA) linked to chromosome 9, with resulting abnormality of frataxin, a mitochondrial protein important in iron homeostasis and intracellular respiratory function. Neurologic features include cerebellar ataxia, dysarthria, a combination of spasticity and lower limb neuropathy, weakness and sensory deficit (particularly vibration and position), and absence of deep tendon reflexes with extensor plantar responses (Fig. 60-4). Most patients are no longer able to walk 12 to 15 years after the onset of symptoms. Heart disease, scoliosis, and an increased incidence of diabetes are characteristic. Cardiac manifestations

include atrial and ventricular tachyarrhythmias, hypertrophic cardiomyopathy, hypokinetic and dilated left ventricle, and muscular subaortic stenosis.

The molecular diagnosis of Friedreich's ataxia is made based on the presence of an expanded repetition of trinucleotide GAA, which encodes frataxin. There is no specific treatment.

ACUTE INTERMITTENT PORPHYRIA

Generally an autosomal-dominant condition, acute intermittent porphyria manifests as acute abdominal pain and a variety of psychiatric and neurologic symptoms. These include axonal neuropathy with a major autonomic component, including marked changes in blood pressure and tachycardia. Treatment consists of respiratory support, use of β-blocking agents if tachycardia and hypertension are severe, and pyridoxine. Use of intravenous glucose and hematin is recommended as the most direct and effective therapy.

Storage Diseases

AMYLOIDOSIS

Clinical manifestations of hereditary and acquired amyloidosis depend on the organs involved. Neuropathy is the most common presentation of familial disease but also occurs in acquired systemic amyloidosis. Autonomically mediated orthostatic hypotension is common. The heart is generally infiltrated, with resulting cardiomegaly, CHF, arrhythmia, and, at times, pericarditis. Treatment is symptomatic.

ABETALIPOPROTEINEMIA

Symptoms of hereditary storage disease may include acanthocytosis, retinitis pigmentosa, malabsorption, and devastating neurologic features, including mental retardation, spinocerebellar degeneration, and occasionally peripheral neuropathy. Cardiac involvement includes ventricular enlargement, repolarization (T-wave) changes, and arrhythmias. Many of the complications may be prevented by use of D,L-α-tocopherol (vitamin E).

REFSUM'S DISEASE

The result of inadequate oxidation of phytanic acid, Refsum's disease is characterized by the presence of retinitis pigmentosa, cerebellar degeneration, peripheral neuropathy, and sometimes ichthyotic skin changes, skeletal changes, and hearing loss. Cardiomegaly, arrhythmias, and conduction defects may result in sudden death. Phytanic acid levels in serum and α-oxidation capacity in cultured skin fibroblasts confirm the diagnosis of Refsum's disease. Efforts to reduce dietary phytanic acid are effective in arresting disease progression and amelioration of the complications.

Guillain-Barré Syndrome

Guillain-Barré syndrome, an acute inflammatory neuropathy, is characterized by peripheral, autonomic, and cranial nerve dysfunction. Generally, a history of infection, immunization, or surgical procedure precedes clinical onset by days to weeks.

The first symptoms are usually symmetric lower limb sensory changes, followed by ascending distal weakness. Onset may be in the proximal limb or cranial nerve distribution. Weakness progresses rapidly, with loss of tendon reflexes. Facial diplegia and oropharyngeal and respiratory weakness occur in 30% to 40% of patients. Clinical progression may continue for up to 3 weeks, followed by gradual improvement to normal or near normal over weeks or months in more than 70% of patients. Death is generally a result of respiratory or cardiac disease. Autonomic dysfunction produces cardiac involvement, including orthostatic hypotension, hypertension, ST-segment abnormalities, tachyarrhythmias or bradyarrhythmias, and loss of heart rate variability from reduction of sympathetically mediated peripheral vascular tone, vagal dysfunction, or both. As a rule, severe cardiac involvement only occurs with severe motor weakness.

By the second week, the syndrome's laboratory hallmark—elevated protein levels without an increase in cells in the cerebrospinal fluid—is present in more than 80% of patients. EMG and nerve conduction study results may be normal in the first week.

Treatment with plasmapheresis or intravenous immunoglobulin within the first 2 weeks improves outcomes. Careful observation of respiratory function is essential until progression stabilizes; ventilatory support may be necessary. Volume replacement or treatment with pressor agents may be necessary to counter hypotension.

Diphtheric Polyneuropathy

Diphtheria is rare in the United States but does occur in unvaccinated patients. It is estimated that a neuropathy develops in 20% of diphtheria patients. Bulbar paralysis occurs in week 3 or 4. Intact pupillary light response with failure of accommodation is a classic feature of this disease. Generalized peripheral neuropathy may occur from weeks 3 through 15 or later. Cardiac arrhythmias and CHF are the most common causes of death and may occur from the second week to the late convalescent period. In the early period, this may be because of myocardial involvement; later, it may be because of involvement of the vagus nerve. Strict bed rest is recommended in the acute stages, and in later stages if there is cardiac involvement. The diagnosis of diphtheria is most commonly missed in those who are unaware of exposure and whose initial presentation is with a mild throat infection.

Toxin-Induced Neuropathies

Acute muscarinic effects of organophosphate exposure may result in hypotension and bradycardia, and nicotinic effects may result in hypertension and tachycardia. Peripheral neuropathy may occur as a delayed effect. The neuropathy of thallium exposure may be accompanied by subacute hypotension and tachycardia.

FUTURE DIRECTIONS

Linking clinical syndromes with specific genetic and proteomic defects is the subject of intense research activity. The sensitivity

and specificity of diagnosis have been greatly aided by the development of molecular testing in the past decade. It is anticipated that in the coming years, molecular testing will be available for most neuromuscular diseases, and it is hoped that specific genetically oriented treatments will be developed. This would revolutionize the treatment of this group of degenerative diseases.

ADDITIONAL RESOURCES

Muscular Dystrophy Association website. Available at: <http://www.mda.org/>; Accessed 18.03.10.

Provides the latest information about the various neuromuscular disorders and continuing clinical trials.

National Center for Biotechnology Information GeneTests Website. Available at: <http://www.geneclinics.org/>; Accessed 18.03.10.

Current information about various neuromuscular disorders and valuable genetic testing.

EVIDENCE

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Comprehensive review of clinical presentation, pathophysiology, and treatment of peripheral nerve diseases.

Engel AG, Franzini-Armstrong C, eds. *Myology.* 3rd ed. New York: McGraw-Hill; 2004.

Comprehensive review of clinical presentation, pathophysiology, and treatment of muscle diseases.

Goodwin FC, Muntoni F. Cardiac involvement in muscular dystrophies: molecular mechanisms. *Muscle Nerve.* 2005;32:577–588.

Review outlining the pathogenesis of cardiomyopathy associated with different types of MD.

Selcen D. Myofibrillar myopathies. *Curr Opin Neurol.* 2008;21:585–589.

Review describing the different gene mutations of the Z-disk–related proteins that cause myofibrillar myopathy, a disorder that can be associated with cardiomyopathy.

Cardiovascular Manifestations of Endocrine Diseases

61

David R. Clemmons

Endocrine system diseases generally affect multiple organ systems, because hormones secreted into the general circulation act on multiple tissues that are distant from their sources of synthesis and secretion. Nearly all hormones and accompanying hormonal disorders are occasionally associated with a pathophysiologic disarrangement of some component of the cardiovascular system. This chapter focuses on the most common disorders and those with the most important deleterious consequences for cardiovascular function.

PITUITARY GLAND DISORDERS

The seven peptide hormones secreted by the anterior pituitary gland and two secreted by the posterior pituitary gland all affect the cardiovascular system. Most indirectly cause changes in salt or water metabolism or affect vascular tone. The anterior pituitary hormones and their direct and indirect effects on cardiovascular function are listed in Table 61-1. Three disorders can result in major changes in cardiovascular function: hypopituitarism, acromegaly, and disorders of antidiuretic hormone (ADH) secretion.

Hypopituitarism

Hypopituitarism in adults often results from mass lesions arising in the hypothalamus or pituitary fossa. Growth hormone (GH) deficiency and gonadotropin deficiencies are often present. If the lesion causing the deficit is extensive, thyroid-stimulating hormone (TSH) (thyrotropin) and adrenocorticotrophic hormone (ACTH) secretion may also be impaired. GH deficiency per se does not lead to cardiomyopathy or loss of vascular tone; however, patients with GH deficiency most commonly present with a lack of energy and stamina. Therefore, cardiac output (CO) may not be adequate to sustain peak exercise activity and endurance may be moderately impaired. Treatment with GH replacement therapy for periods as long as 3 years improves treadmill performance, suggesting that GH deficiency leads to a decrease in exercise tolerance. However, whether or not this improvement is due solely to GH stimulation of myocardial function is unclear, because GH also increases red cell mass, which could alter exercise tolerance. TSH and ACTH deficiencies lead to changes in cardiovascular function, as discussed here in the sections on hypothyroidism and hypoadrenalism. Loss of gonadotropin secretion, particularly in men, can lead to low testosterone concentrations. This can lead to impaired exercise performance, loss of skeletal muscle mass, and decreased stamina. Replacement with testosterone improves muscle function and exercise performance.

Acromegaly

Sustained hypersecretion of GH by a pituitary tumor can lead to overgrowth of several tissues and to considerable cardiovascular changes (Fig. 61-1). Cardiovascular function is an important determinant of morbidity and mortality in untreated acromegaly. The most common comorbid cardiovascular condition accompanying acromegaly is hypertension, present in 50% of inadequately treated patients. Hypertension in acromegaly is usually mild but can be difficult to manage conventionally. Left ventricular (LV) mass can be significantly increased compared with that of normotensive patients. Curing the acromegalic condition is the most effective way to lower blood pressure (BP). A concentric ventricular hypertrophic cardiomyopathy unassociated with hypertension but associated with long-standing acromegaly develops in some patients and can result in both diastolic and systolic dysfunction. Cardiomegaly can be disproportionate to the changes in size that occur in other organs in severe acromegaly. The severity of cardiomyopathy correlates with the duration of exposure to high levels of GH. Diastolic dysfunction and hypertrophy develop first and are common in untreated patients. These changes are reversible with adequate treatment of GH excess. If left untreated, there is progression to systolic dysfunction, and heart failure and severe ventricular arrhythmias can occur. Histologic evaluation of the myocardium in patients with long-standing acromegaly shows interstitial fibrosis, lymphocytic infiltration, and sometimes necrosis.

Other changes in acromegaly can lead to secondary effects on the cardiovascular system. Some patients have sleep apnea that causes chronic recurrent hypoxemia, approximately 25% of patients have diabetes mellitus, and up to 40% of patients have hypertriglyceridemia. Premature mortality is increased in acromegaly, and cardiovascular diseases are the cause of death in 38% to 62% of patients. Normalizing GH and insulin-like growth factor 1 concentrations with conventional treatment restores normal life expectancy, preventing premature death resulting from cardiovascular disease.

Disorders of ADH Secretion

Unlike diseases of the anterior pituitary gland, the etiology of ADH deficiency is often hypothalamic lesions (in ~60% of patients). Most cases of ADH deficiency are acquired, and many result from attempts to remove the pituitary tumor surgically, damaging the pituitary stalk or the posterior pituitary. Severe ADH deficiency leads to polyuria, polydipsia, and, if untreated, vascular collapse. The most common hypothalamic causes are mass lesions, principally tumors of the hypothalamus, such as craniopharyngioma and dysgerminoma.

ADH is a potent pressor agent and stimulates direct vasoconstriction of blood vessels. This action is conferred at the level

Table 61-1 Pituitary Hormones and Their Actions on the Cardiovascular System

Hormone	Direct	Indirect
ACTH	Stimulates cortisol secretion Stimulates aldosterone	Cortisol increases arteriolar tone. Aldosterone stimulates Na^+ retention and K^+ excretion.
TSH	Stimulates thyroxine and triiodothyronine synthesis	Thyroxine stimulates HR, pulse pressure, and LV contractility.
LH	Stimulates estrogen and testosterone synthesis	Estrogen acts as a vasodilator.
ADH	Stimulates water retention, increases plasma volume; acts through a central mechanism to increase vasoconstriction	
GH	Stimulates vasomotor force and LV function	Through IGF-1, it stimulates HR.

ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; GH, growth hormone; HR, heart rate; IGF-1, insulin-like growth factor I; K^+, potassium; LH, luteinizing hormone; LV, left ventricular; Na^+, sodium; TSH, thyroid-stimulating hormone.

of the regional arterioles, and physiologic concentrations can induce this effect. Loss of ADH leads to a significant increase in serum osmolarity of greater than 295 mOsm/L, with inappropriately dilute urine of less than 300 mOsm/L. The diagnosis is established by detecting abnormally high serum osmolarity with low plasma vasopressin and low urinary osmolarity.

Administering vasopressin quickly reverses the changes in these parameters. Vasopressin acts on the kidney to increase free-water clearance. It also affects the brain to maintain central BP control; these brain actions are probably necessary for the maintenance of normal upright BP. The use of ADH antagonists illustrates the importance of endogenous arginine vasopressin for maintaining normal BP.

SYNDROME OF INAPPROPRIATE ADH SECRETION

Several central nervous system and primary pulmonary diseases, as well as medications, can cause inappropriately high concentrations of ADH, leading to decreases in plasma osmolarity. In these syndromes, high levels of ADH secretion continue, despite the low osmolarity. Arginine vasopressin concentrations can be increased up to 10 to 20 times greater than normal in this disorder. This does not lead to hypertension per se but rather to water intoxication. Serum sodium continues to decrease because free-water clearance is consistently impaired, thus leading to severe hyponatremia, sometimes manifested as seizures. Identification of the source of inappropriate ADH secretion or correction of the underlying lesion is needed for successful treatment. Empiric treatment is undertaken by severely restricting free-water intake. Recently, a new class of ADH receptor antagonists (vaptans) has been shown to improve hyponatremia associated with euvolemic inappropriate secretion of ADH.

THYROID DISORDERS

Hyperthyroidism

Hyperthyroidism causes some of the most impressive and sustained disarrangements of cardiovascular function related to endocrine abnormalities. Graves' disease, the most common cause of hyperthyroidism, is triggered by an autoimmune process whereby thyroid antigens that are recognized as foreign stimulate the production of an autoantibody that stimulates the TSH receptor. The autoantibody directly binds to the TSH receptor on thyroid tissue and stimulates thyroid function. The effect of this stimulating antibody is unremitting and necessitates specific therapy to block thyroid hormone. The second most common cause of hyperthyroidism is a toxic multinodular goiter. This condition can account for 40% of the cases in patients over 60 years of age.

The symptoms of cardiac dysfunction that occur most commonly in thyrotoxicosis include fatigue, palpitations, dyspnea, heat intolerance, increased sweating, and weight loss.

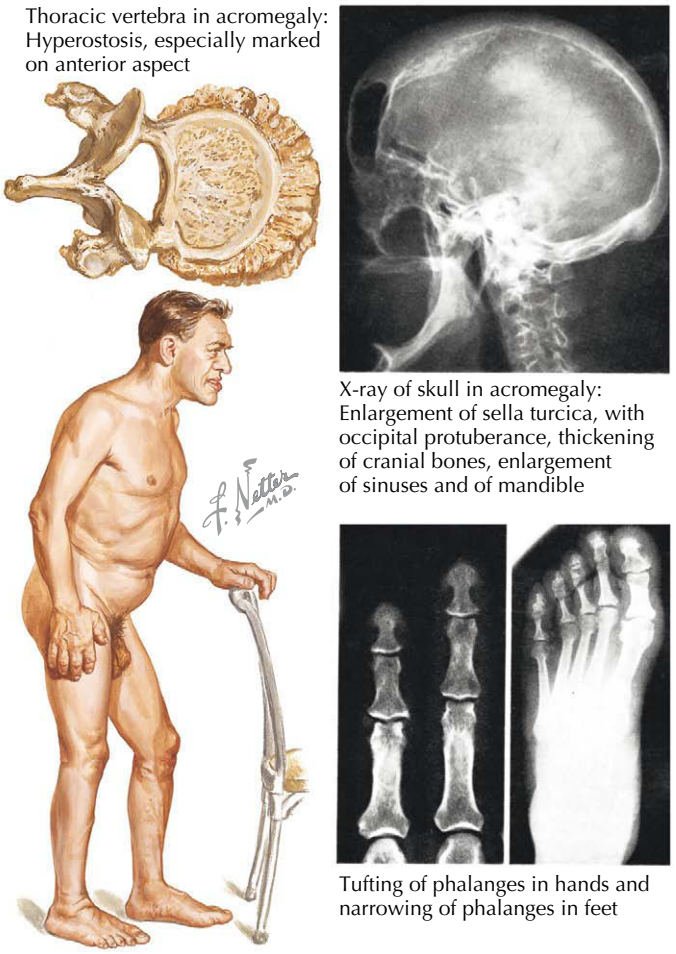

Figure 61-1 *Acromegaly.*

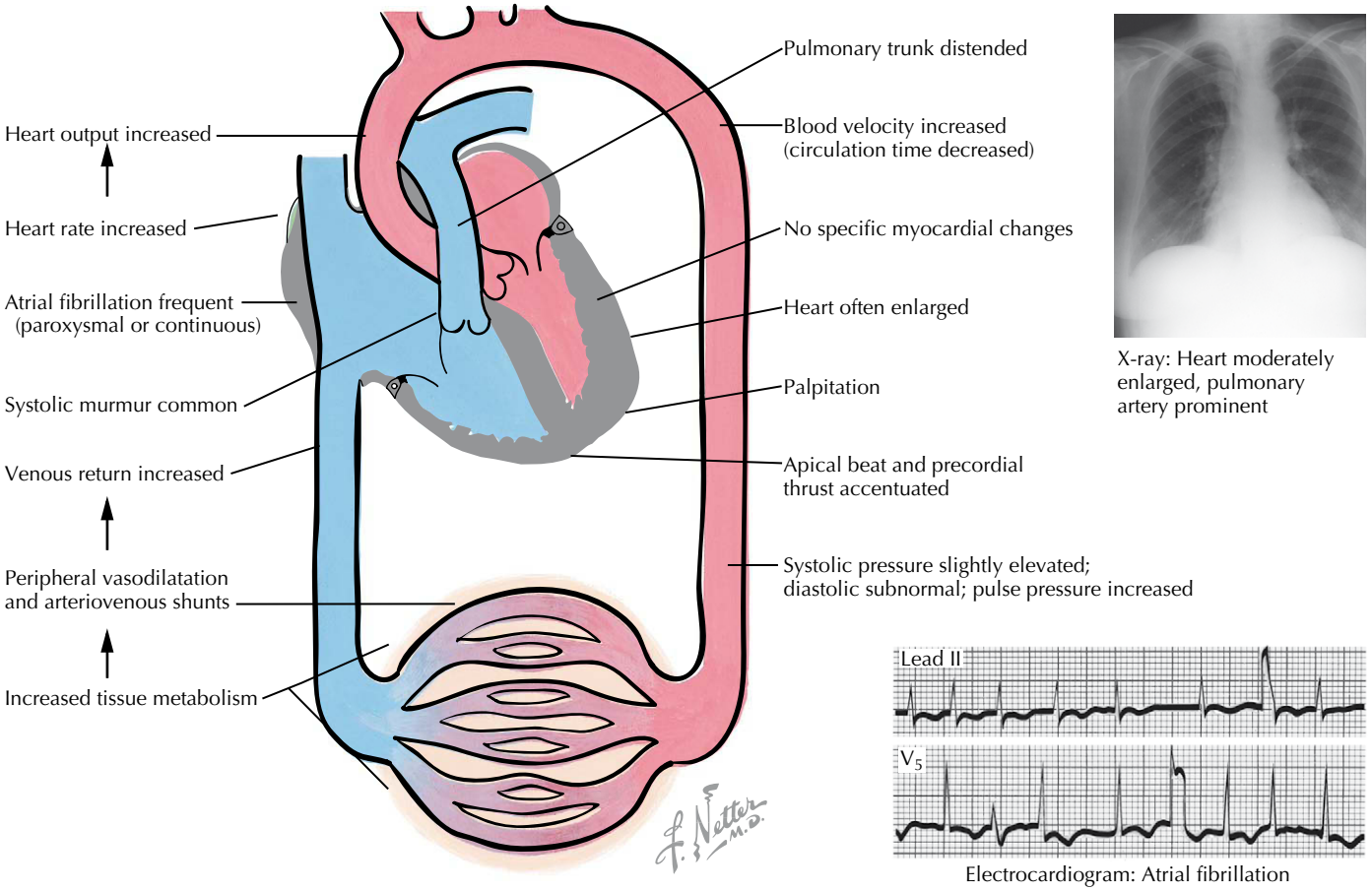

Figure 61-2 *The hyperthyroid heart.*

Tachycardia and palpitations occur in 80% to 90% of untreated patients (Fig. 61-2). Elderly patients in whom Graves' disease develops may also experience heart failure. In this circumstance, the failing heart cannot meet metabolic requirements that are raised by increased thyroid hormone, resulting in overt congestive heart failure (CHF). Similarly, angina pectoris may be an important symptom in elderly patients with hyperthyroidism. Myocardial oxygen consumption can increase by as much as 70% in untreated hyperthyroidism. In the presence of fixed coronary lesions, blood flow may be inadequate to supply the increased metabolic need. In younger patients, thyrotoxicosis is associated with increased inotropic and chronotropic effects on the heart. Palpitations and occasionally atrial arrhythmias are the initial symptoms. Atrial fibrillation occurs in 33% to 47% of patients who are older than 60 years. Vascular resistance is decreased by peripheral vasodilation; the net effect is a marked increase in CO, which results in increased oxygen consumption. Peripheral edema is the most common symptom of overt heart failure in Graves' disease, although dyspnea on exertion can also be prominent.

Physical findings typically include a hyperdynamic precordium, accentuated heart sounds, and a systolic murmur that can be heard over the precordium because of increased flow across the aortic valve. Mitral valve prolapse may also be present. Arrhythmias can range from sporadic premature beats to overt atrial fibrillation. Thyrotoxicosis is present in approximately 11% of patients with atrial fibrillation who are older than 60 years. Indeed, atrial fibrillation due to either hyper- or hypothyroidism is common enough that thyroid disease must be excluded at an early stage in the evaluation of this arrhythmia. ECG findings are nonspecific. Heart failure in younger patients is generally reversible with adequate treatment. Whether a distinct thyrotoxic cardiomyopathy exists is debated; however, extensive cardiac remodeling occurs in some patients. This may also be aggravated by long-standing tachyarrhythmias. In elderly patients in whom underlying cardiac abnormalities exist, heart failure can be severe and may trigger atrial fibrillation. Acceleration of angina pectoris can be dramatic in the elderly, and overt myocardial infarction can occur in these patients if left untreated.

The diagnosis is established by elevated serum thyroxine (T_4) in the presence of a suppressed TSH concentration. Early in the disease, triiodothyronine (T_3) is elevated, which is usually followed by a T_4 elevation.

Initial treatment of Graves' disease with antithyroid drugs blocks thyroid hormone synthesis. Treatment of the thyroid disease does not always restore normal sinus rhythm. If patients fail to undergo remission in a reasonable period on antithyroid drugs, or if they do not tolerate these medications, they are generally treated with radioactive iodine. In elderly patients with multiple cardiac complications, initial therapy

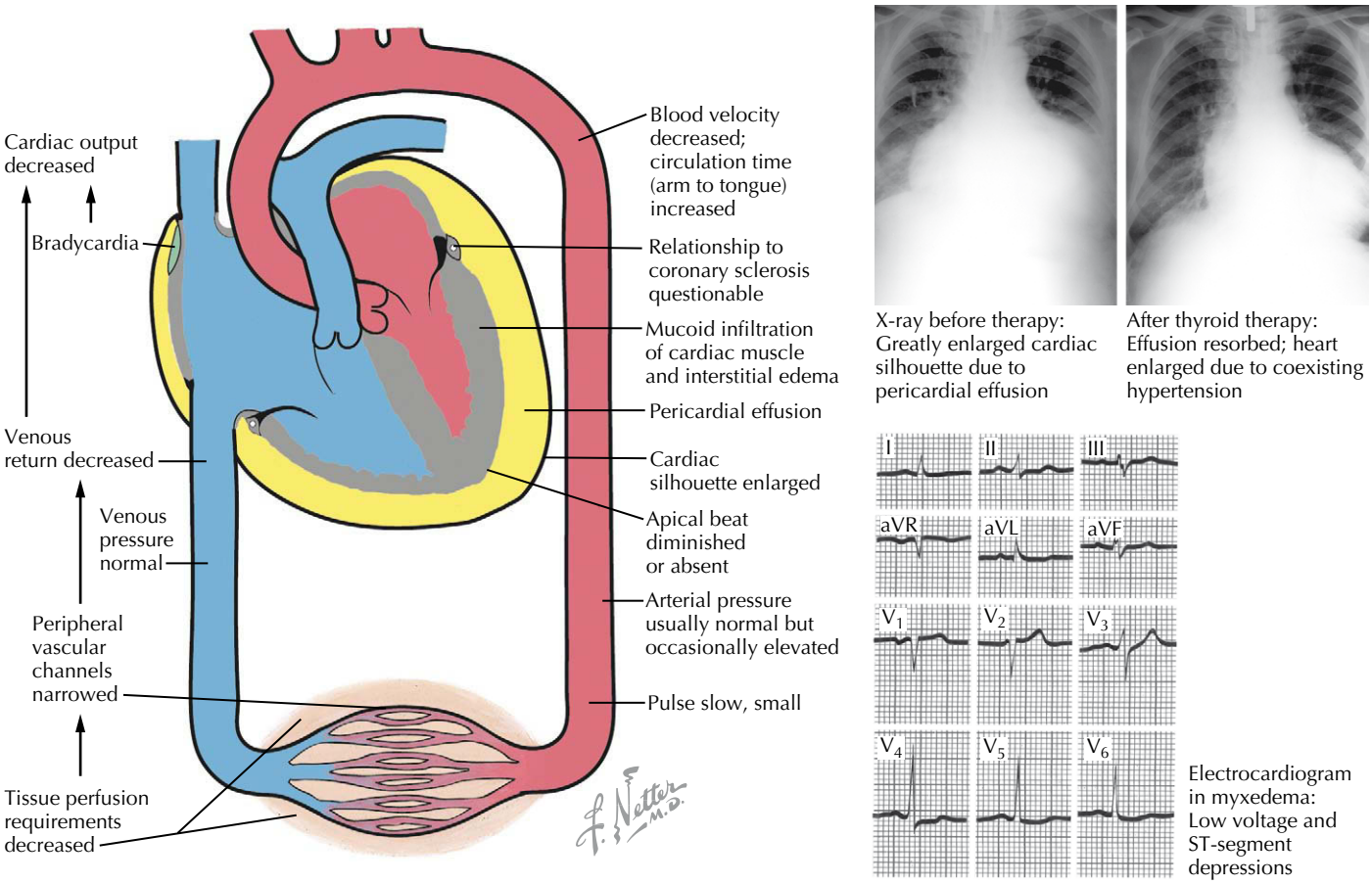

Figure 61-3 *Cardiovascular effects of hypothyroidism/myxedema.*

with radioactive iodine may be indicated. While reversal of the thyrotoxic state generally restores cardiac abnormalities due to thyrotoxicosis to normal in younger patients, this is not always the case in elderly patients. Both sets of patients may benefit initially from therapy with β-blockers, which limits most effects of catecholamines on the cardiovascular system—effects that are accentuated in Graves' disease. If a toxic multinodular goiter is present, the usual treatment is radioactive iodine.

An increasingly recognized, important cause of hyperthyroidism in cardiac patients is amiodarone-induced thyrotoxicosis (AIT). This usually occurs in patients during the first year of therapy. There are two different pathophysiologic mechanisms that induce hyperthyroidism. In the first (AIT type I), the iodine in aminodarone induces hyperthyroidism. These patients have a low radioactive iodine uptake, and color flow Doppler shows increased vascularity. They respond to potassium perchlorate and antithyroid drugs. Type II AIT patients have a distinctive thyroiditis induced by an amiodarone metabolite. These patients have a very low radioactive iodine uptake and absent vascularity. They respond to high-dose corticosteroid therapy.

Hypothyroidism

Like hyperthyroidism, hypothyroidism is almost always caused by autoimmune thyroid disease. The most common cause of thyroid failure is Hashimoto's thyroiditis, which occurs in 80% of women with hypothyroidism. In this disease, an autoantibody to the thyroid gland is produced that blocks thyroid function and thyroid hormone action. Eventually, this may result in destruction of the thyroid gland as a result of lymphocytic infiltration. However, it occurs over a period of several years, so the onset and progression are usually insidious and unrecognized by the patient. Hypothyroidism also develops in almost all patients who receive radioactive iodine treatment for hyperthyroidism. Hypothyroidism can result from a pituitary tumor or other causes of anterior pituitary gland destruction, but these are rare compared with Hashimoto's thyroiditis.

Changes in the cardiovascular system are also common in patients with severe long-standing hypothyroidism (Fig. 61-3). These patients have an increased peripheral vascular resistance, decreased stroke volume, and, as a result, decreased CO. Although systolic pressure may be decreased and diastolic pressure increased in these individuals, mean arterial pressure is often normal. The mechanism of increased vascular resistance is related to reduced compliance and impaired nitric oxide availability. The pre-ejection and isovolumetric contraction times are prolonged, and the ventricular relaxation rate during diastole is slower. The mechanism of reduced cardiac contractility is multifactorial. T_3 stimulates the synthesis of calcium regulatory proteins that have been implicated in the cardiac

manifestations of hypothyroidism. Blood volume is decreased, and pericardial as well as pleural effusions are common. Echocardiographic evidence of pericardial effusion is present in approximately 40% of patients.

Physical examination reveals a slow pulse, diastolic hypertension, and soft first and second heart sounds. Cardiac enlargement, when present, is generally caused by a pericardial effusion. Peripheral edema may be present, but it is generally nonpitting and not caused by heart failure. The ECG may show bradycardia and low voltage with nonspecific ST-segment or T-wave changes and a prolonged QT interval. First-degree heart block is also common. There is decreased myocardial contractility and slowing of the isovolumic relaxation phase of diastolic function. In hypothyroid patients with known coronary artery disease (CAD), silent myocardial ischemia may occur. Although symptomatic angina is not common, it can occur during thyroid hormone replacement therapy, particularly in patients with severe long-standing hypothyroidism. This problem is accentuated by the anemia that is often present in hypothyroidism. Hypothyroidism secondarily results in severe lipoprotein abnormalities, including hypercholesterolemia and low concentrations of high-density lipoprotein cholesterol (HDL-C). Increased homocysteine levels may also occur in hypothyroidism.

The treatment of hypothyroidism is thyroid hormone replacement therapy. Young patients can tolerate full replacement doses; however, elderly patients with angina need extremely low-dose therapy with gradual incremental increases as tolerated.

PARATHYROID DISORDERS

Hyperparathyroidism is an unusual cause of vascular pathogenesis. In one study, 69% of patients with primary hyperparathyroidism were found to have systolic and diastolic hypertension. Generally, the degree of BP elevation is minimal. The cause of hyperparathyroidism in 85% of patients is a parathyroid hormone–producing tumor, which leads to hypercalcemia, the most common presenting sign. The hypercalcemic state can also cause LV hypertrophy, increased heart muscle contractility, and arrhythmias. Calcium deposition in the myocardium, the heart valves, or the coronary arteries occurs in up to 69% of patients with hyperparathyroidism as compared to 17% of age-matched controls. Usually, these changes occur with severe long-standing hyperparathyroidism. In recent years, however, the presentation and treatment of hyperparathyroidism have changed markedly, and probably a much lower percentage of patients have these abnormalities at the time of diagnosis because they are diagnosed and treated much earlier in the course of their illness. Secondary hyperparathyroidism (not due to a parathyroid gland tumor) is common in patients with chronic renal failure. These patients have elevated serum phosphorus that leads to a secondary increase in parathyroid hormone. Vascular calcification and reduced arterial compliance are common. Although patients with primary hyperparathyroidism are usually treated by surgical removal of the tumor, until recently there was no effective treatment for secondary hyperparathyroidism. The development of a calcium-sensing receptor antagonist (cinacalcet) has provided an effective means for treating secondary hyperparathyroidism. Whether this will result in long-term improvement in cardiovascular function is under investigation.

ADRENAL DISORDERS

Both glucocorticoid and mineralocorticoid excesses can lead to marked cardiovascular abnormalities.

Cushing's Disease and Syndrome

The most common cause of glucocorticoid excess is from pituitary tumors that overproduce ACTH, termed "pituitary Cushing's disease." Less common but equally deleterious to cardiovascular function are primary adrenal adenomas that overproduce glucocorticoids or ectopic tumors (tumors outside the pituitary) that overproduce ACTH.

Cushing's syndrome, or excess glucocorticoid production, often leads to severe skeletal muscle myopathy, because glucocorticoids inhibit protein synthesis in muscle (Fig. 61-4). Because of its rapid onset, dramatic presentation, and severe deleterious effects, Cushing's syndrome is generally treated before a severe atrophic cardiomyopathy develops. Therefore, it is rare for patients to present with cardiomyopathic symptoms. Hypertension is common in Cushing's syndrome because of mineralocorticoid overproduction that leads to increased plasma volume and sodium retention. Severe hypokalemia can cause characteristic ECG changes. Whether atherosclerosis occurs independently of the changes in lipoprotein metabolism that result from excess glucocorticoid is not clear. However, marked increases in atherosclerosis in patients who receive long-term glucocorticoid therapy in pharmacologic doses have been reported.

Treatment involves removing the cause of the excess cortisol or ACTH. Generally, the cardiovascular abnormalities are easily ameliorated. Patients who receive pharmacologic doses of glucocorticoids for prolonged periods for underlying inflammatory disorders are just as susceptible to cardiovascular complications. Cushing's syndrome may precipitate CHF in susceptible patients, because the resulting increase in mineralocorticoids causes salt retention.

Addison's Disease

Hypoadrenalism is most often caused by a primary autoimmune disorder, Addison's disease, in which the adrenal glands are progressively destroyed, leading to marked sodium loss with increased serum potassium. Orthostatic hypotension and decreased plasma volume are generally present. Decreased plasma volume can manifest as a reduction in the size of the cardiac silhouette on chest radiographs.

Occasionally, in patients with undiagnosed chronic adrenal insufficiency, acute adrenal insufficiency develops, usually in the setting of underlying physical stress, such as a car accident or bacterial infection. During stress, healthy individuals secrete up to 10 times more cortisol than under normal conditions. Because this requirement cannot be met in patients with adrenal failure, symptoms of acute adrenal insufficiency develop: nausea and vomiting, hypotension, dizziness, and eventually vascular

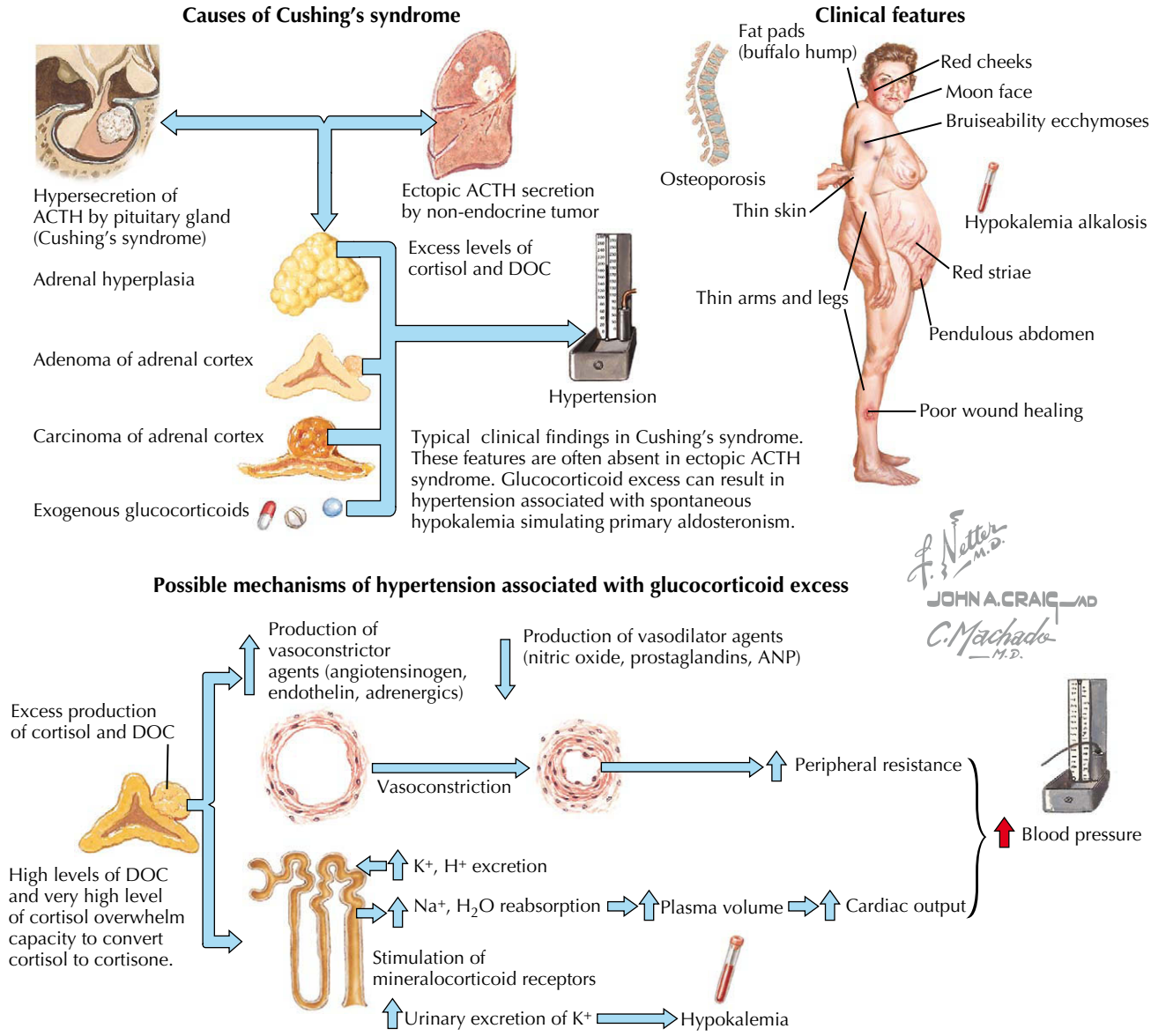

Figure 61-4 *Cushing's syndrome–mineralocorticoid hypertension.* ACTH, adrenocorticotrophic hormone; ANP, atrial natriuretic peptide; DOC, deoxycorticosterone; H^+, hydrogen; K^+, potassium; N^+, sodium.

collapse and shock. The diagnosis should be suspected in patients with these findings and a low serum sodium concentration, a high potassium concentration, and evidence of low plasma volume. It is confirmed by administering 1 µg of cosyntropin (synthetic ACTH) intravenously and measuring the plasma cortisol level after 30 or 60 minutes. A normal response to the ACTH challenge is a plasma cortisol level of 18 to 20 µg/dL. Treatment consists of fluid replacement and administration of hydrocortisone.

Several other hormones also have profound effects on salt and water balance and therefore on cardiovascular function. The most important of these are atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and endothelin. ANP is a 28–amino acid peptide produced by the left atrium. A circulating precursor form, 1-126, is believed to be biologically inactive. Normally, ANP-28 is made solely in the left atrium; however, in pathologic states such as LV hypertrophy or failure, ANP-28 can also be released from the left ventricle. Atrial wall tension is the primary factor that controls synthesis and secretion of ANP-28. Therefore, ANP-28 is increased in acute and chronic volume expansion, CHF, and other conditions associated with elevated intra-atrial pressure. It functions to stimulate vasodilation in both small and large arteries. Negative feedback regulation of ANP-28 occurs, and volume contraction decreases its synthesis and secretion. ANP-28 binds to specific receptors in the kidney, where it increases capillary permeability, glomerular filtration rate (GFR), renal filtration fraction, urinary filtration, and excretion of sodium. This in turn lowers plasma volume and decreases BP. ANP is active in patients with acute renal failure, and its administration improves glomerular function.

A related peptide, BNP, is released by neural tissue. BNP is also stored in nerve endings in the atrium. This site of synthesis and release can be stimulated by many of the same stimuli that cause ANP-28 release. In general, BNP is released in response to more chronic changes in plasma volume. BNP acts on the same renal receptors that are activated by ANP and has similar effects on kidney function. Both peptides have direct effects on arterial smooth muscle cells and bring about vasodilatation. Administration of ANP or BNP to patients with heart failure results in beneficial effects on plasma volume and CO. Recent reports suggest that plasma BNP levels provide useful information in the longitudinal treatment of patients with CHF (see Chapter 23).

Endothelin is a small peptide that is released by vascular endothelium and whose three isoforms are closely related. Endothelin receptors are present on vascular smooth muscle cells, cardiac myocytes, and renal glomerular endothelium. Endothelin is a potent vasoconstrictor, an action that can be opposed by the release of nitric oxide, and a potent vascular mitogen. In addition to its effects on blood vessels and kidney function, endothelin also has direct inotropic and chronotropic effects on the heart; however, endothelin also decreases coronary blood flow because of its vasoconstrictive effects. Endothelin may also act secondarily to decrease plasma volume by increasing ANP and BNP release.

Mineralocorticoid Disorders

In addition to glucocorticoids, the adrenal gland synthesizes a group of steroids with sodium-retaining activity. Aldosterone is the principal steroid among this group. Unlike cortisol, which is regulated primarily by ACTH secretion, the primary stimulus for aldosterone synthesis is the renin-angiotensin system. In hypovolemic states, the afferent arterioles of the kidney contain specialized juxtaglomerular cells that sense low-flow or low-pressure states in these vessels. This triggers the kidney's release of the enzyme renin directly into the blood. Renin acts on angiotensinogen, a peptide precursor that is synthesized in the liver, enzymatically converting angiotensinogen into angiotensin I. Angiotensin I passes through the pulmonary circulation and is cleaved by a second enzyme, termed angiotensin-converting enzyme (ACE), to angiotensin II. Angiotensin II is the most biologically active component of the renin-angiotensin system. This peptide, though labile, has direct vasoconstrictive effects on blood vessels and serves as a stimulus to maintain arteriolar tone. This stimulus is particularly important in maintaining normal BP when a person is assuming an upright posture. In addition to its acute effects on arteriolar tone, angiotensin II stimulates the adrenal gland to synthesize aldosterone. This is the principal mechanism for regulating aldosterone production.

Aldosterone acts on the distal convoluted tubule and collecting duct to increase sodium absorption (Fig. 61-5). This effect occurs via a sodium-potassium transporter. For each molecule of sodium that is reabsorbed, the tubular cells secrete a molecule of potassium. Under normal circumstances, this maintains a normal sodium-potassium balance and a normal plasma volume. Expansion of the plasma volume results in increased flow through the renal afferent arterioles, and this signals the system to decrease renin, thus maintaining equilibrium.

Another important stimulus that controls the release of angiotensin II is potassium, which directly stimulates angiotensin II and aldosterone production. ACTH can also stimulate aldosterone secretion and is needed to maintain normal rates of aldosterone synthesis.

Primary disorders of this system are uncommon causes of hypertension and plasma volume expansion.

Primary tumors in which aldosterone is the principal secretory product are the most common disorder. Of patients with hyperaldosteronism, approximately 60% have an aldosterone-producing adenoma. Another 34% have idiopathic bilateral enlargement of the zona glomerulosa in both adrenal glands and overproduce aldosterone, leading to increased sodium retention and potassium excretion. These patients usually present with mild hypertension, evidence of volume overload, and hypokalemia. Other than direct effects on the vasculature, hyperaldosteronism also leads to increased salt retention, which can precipitate CHF in elderly patients.

The diagnosis is usually established by obtaining the ratio of plasma aldosterone to renin. Because renin is suppressed by the increased plasma volume, this ratio is usually greater than 20:1, necessitating further investigation. Adrenal MRI often confirms the diagnosis of an aldosterone-producing tumor.

Treatment for an adrenal adenoma consists of surgical removal, which cures hypertension in approximately 60% of patients. Patients with bilateral hyperplasia and no tumor respond well to diuretics that directly antagonize the effects of aldosterone, such as spironolactone. Eplerenone is a more selective aldosterone antagonist. It has little affinity for other steroid receptors, thus reducing the incidence of bothersome adverse effects such as gynecomastia and menstrual irregularities experienced with spironolactone. These drugs are effective in inhibiting the sodium-retaining and vasoconstrictive properties of aldosterone. They can induce hyperkalemia, and their usefulness is therefore limited to patients with a GFR greater than 30 mL/min. ACE inhibitors are effective for the treatment of CHF in which secondary hyperaldosteronism is present.

Adrenal Medullary Tumors

Pheochromocytoma, while rare, is an important cause of acute changes in BP and cardiovascular function. These tumors are generally unilateral, but they can occur bilaterally and outside the adrenal medulla, for example, anywhere in the sympathetic ganglia chain (Fig. 61-6). The rapid release of norepinephrine or epinephrine from the tumor results in dramatic cardiovascular signs and symptoms.

Because catecholamines work directly on arterioles to cause severe vasoconstriction, the principal signs are rapid elevation of BP, palpitations, sweating, tremulousness, anxiety, and nervousness. Other symptoms can include headache, chest pain, extreme weakness, and fatigue. Acute symptoms occur in approximately 50% of patients and include severe headache, dyspnea, palpitations, sweating, and tremor. Signs that are notable on physical examination are hypertension, postural hypotension, tachycardia, weight loss, increased respiratory rate, and tremor. Postural hypotension occurs in approximately 90% of patients as a result of contraction of intravascular volume. Patients with underlying angina pectoris or heart failure

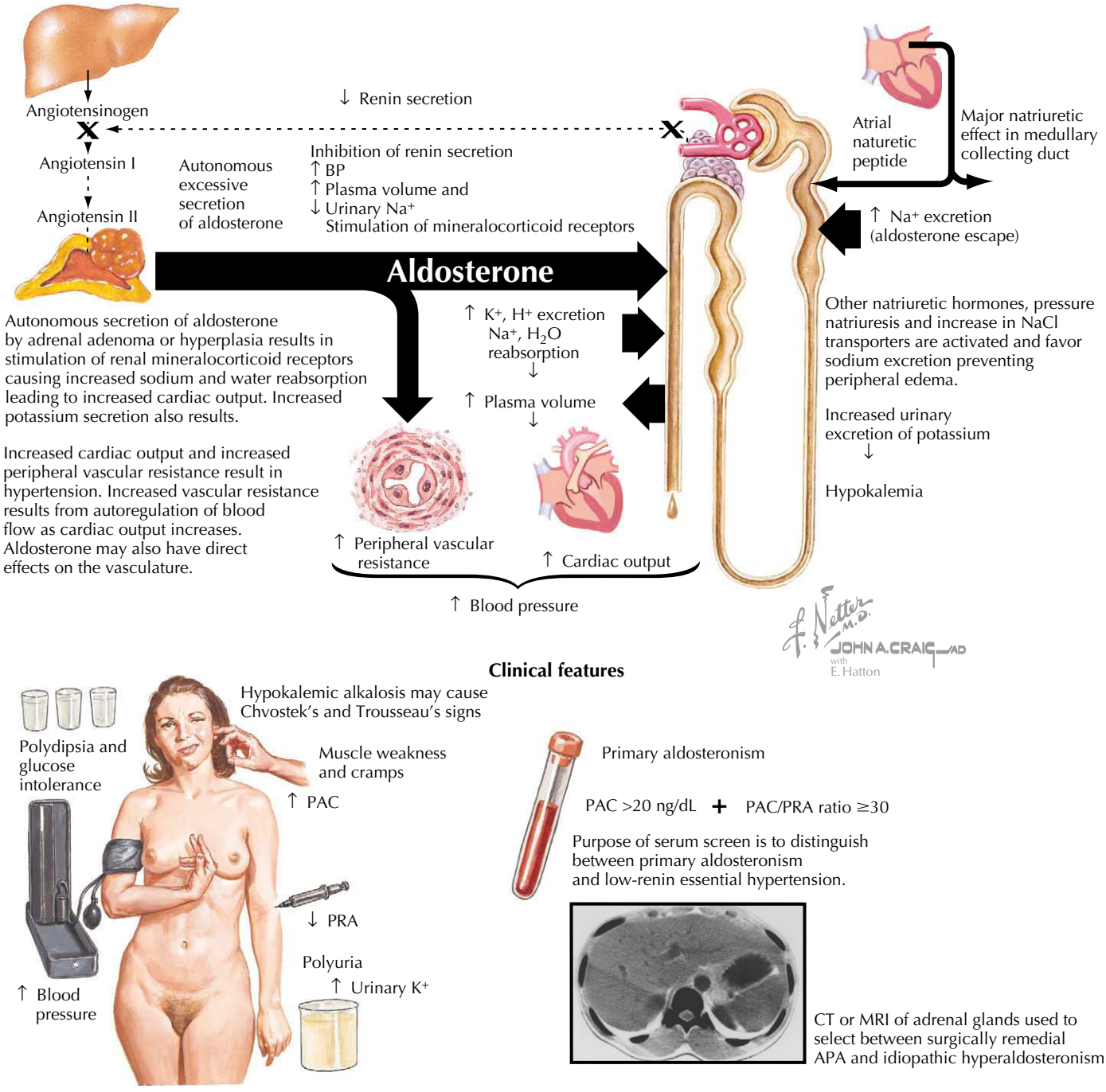

Figure 61-5 *Primary hyperaldosteronism–mineralocorticoid hypertension.* APA, aldosterone-producing adenoma; BP, blood pressure; CT, computed tomography; H+, hydrogen; K^+, potassium; MRI, magnetic resonance imaging; Na^+, sodium; NaCl, sodium chloride; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

may severely decompensate in the presence of an untreated pheochromocytoma. The diagnosis is established by measuring plasma catecholamines directly, urinary catecholamines, and the principal metabolites of epinephrine and norepinephrine, which include metanephrine.

Administration of β-adrenergic blocking agents can precipitate a hypertensive crisis by leaving α-adrenergic activity unopposed. Other medications that can precipitate a crisis include monoamine oxidase inhibitors, tricyclic antidepressants, and catecholamine reuptake inhibitors. The hypertension responds well to α-adrenergic blocking agents, including phenoxybenzamine (Dibenzyline). Management is usually surgical unless the tumor is malignant, in which case long-term therapy with α-blockers is necessitated.

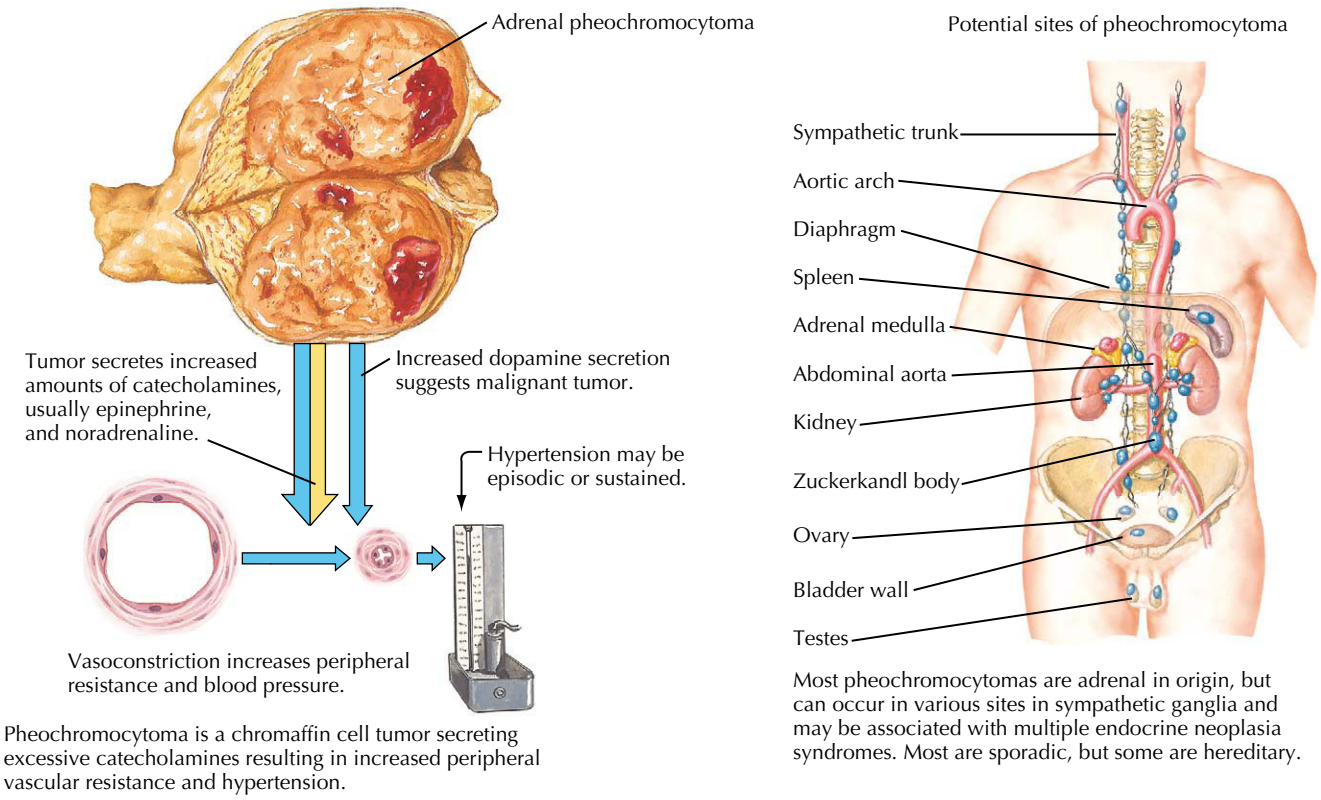

Figure 61-6 *Pheochromocytoma.* CT, computed tomography; MRI, magnetic resonance imaging.

DIABETES

Both types of diabetes (type 1 from severe insulin deficiency and type 2 primarily from insulin resistance combined with insulin deficiency in the later stages) increase the incidence of atherosclerosis. Hypertension is also common in patients with long-standing diabetes, contributing to the high incidence of vascular disease in these patients. Patients in whom even moderate degrees of azotemia develop often become seriously hypertensive as a result of diabetic nephropathy.

In the majority of patients who have long-standing diabetes, significant lipoprotein abnormalities also develop. Therefore, multiple risk factors all contribute to extensive vascular disease, which occurs in 80% of patients with long-standing diabetes. As a factor that increases the relative risk for CAD, diabetes ranks second, only behind smoking.

It is difficult to separate the degree of risk conferred by diabetes from that conferred by hyperlipidemia. However, both are independent risk factors. It should be noted that the

dyslipidemic syndrome that occurs in diabetes involves a profile that confers high risk for CAD. The lipoprotein phenotype common to patients with diabetes is overproduction of triglycerides and apolipoprotein B. Low-density lipoprotein cholesterol (LDL-C) levels are normal in approximately 65% of patients, but the small dense LDL-C fraction is often elevated, particularly in patients with extreme hypertriglyceridemia and low HDL-C levels. This is due in part to the activity of hepatic lipase, increased in type 2 diabetes, which results in processing of LDL-C to the small dense particles. Likewise, overproduction of triglycerides can lead to suppression of HDL-C, particularly the most important subfraction, HDL_2. This combination of abnormalities constitutes the dyslipidemic syndrome common in patients with type 2 diabetes. The presence of nephropathy further aggravates the dyslipidemic syndrome in diabetes. Hypertriglyceridemia and a low HDL-C level are often accentuated, and dialysis can further worsen the profile.

A low HDL-C level is a strong predictor of CHD in patients with diabetes. Total triglycerides seem to have some predictive value, although the predictive value of total cholesterol in diabetic individuals is debated. The non-HDL-C fraction of cholesterol, which includes LDL-C plus very low-density lipoprotein cholesterol, is an excellent predictor of risk. Intimal medial thickness is increased in patients with diabetes, suggesting the presence of a diffuse atherosclerotic process, even in those who have not had a myocardial infarction. Case fatality rates after an ischemic event are substantially higher among patients with diabetes.

The low HDL-C levels in persons with diabetes are associated with poor glycemic control. Improving glycemic control often lowers triglycerides and raises HDL-C. Treatment with oral hypoglycemic agents or insulin improves both triglyceride and HDL-C levels. Weight loss also improves both of these parameters.

Not surprisingly, peripheral vascular disease is also widespread in patients with diabetes. Many patients with coronary disease also have disease in the large peripheral arteries. Leg and foot amputations are far more frequent among patients with diabetes. Bilateral occlusive disease in medium-sized arteries below the knee is common in patients with long-standing disease. Medical treatment of peripheral vascular disease generally has limited success. Vascular surgery is the only option for many patients. Indications for Doppler ultrasonography followed by arteriography are pain at rest, ulcerations that fail to heal, and gangrene.

Cardiomyopathy

The possibility of a distinct diabetic cardiomyopathy has been debated. Postmortem examinations reveal cardiomegaly and myocardial fibrosis. Unexplained CHF occurs in a substantial number of patients with diabetes. Echocardiography of patients with extensive microvascular disease shows compromised cardiac function. Impaired diastolic filling has been demonstrated in a substantial number of patients with type 1 diabetes with long-standing disease. A delayed increase in the ventricular ejection fraction during dynamic exercise is present in 29% of patients. The pathogenesis seems to be varied and multifactorial.

FUTURE DIRECTIONS

Several recently developed drugs are being analyzed for their ability to improve cardiovascular manifestations of endocrine disorders. Studies of a GH receptor antagonist show that it significantly improves cardiomyopathy in acromegaly. Administration of this drug (pegvisomant) to patients with severe cardiomyopathy results in marked improvement in LV function. Pegvisomant lowers insulin-like growth factor I into the normal range and therefore brings about ventricular remodeling. The aldosterone receptor antagonists are being studied in patients with heart failure to determine if they provide patients who have an adequate GFR with another treatment option. Eplerenone is also being analyzed for its efficacy in hypertension that accompanies renal failure in patients on dialysis, because these patients have a high rate of vascular disease progression. Both this drug and ACE inhibitors show promise improving rates of vascular events in this patient population.

Several drugs are in development for the treatment of hyperlipidemias. New medications that work to lower LDL-C levels by mechanisms other than the LDL-C receptor are in phase III development; it is presumed that their administration with a statin will further improve LDL-C levels in patients whose LDL-C level cannot be normalized on statin therapy. No primary drug therapy for low HDL-C levels has been approved, but there are drugs in development for patients who have only a low HDL-C level as a manifestation of their lipid disorder (e.g., most patients with diabetes). Such a drug would allow treatment of many patients who have no means other than exercise and alcohol ingestion to raise their HDL levels. Ongoing clinical studies will define the safety and efficacy of this approach and whether this approach will reduce mortality and morbidity rates in patients at risk.

Studies to determine long-term cardiovascular outcome in patients with secondary hyperparathyroidism who are receiving calcium-sensing receptor mimics are continuing. This is a population at high risk for vascular diseases; therefore, the results will be of great interest. The role of estrogen replacement therapy in postmenopausal women for decreasing cardiovascular risk is under intense investigation. While the combination of estrogen plus progesterone was found to increase cardiovascular risk, no increased risk was noted with estrogen alone. However, whether estrogen therapy alone confers a benefit both in terms of reducing high BP and in terms of atherosclerosis remains unproven. Epidemiologic studies indicate that women treated with estrogen alone in early menopause, ages 50 to 60, show marked cardiovascular benefit. However, the potential to increase the risk for ovarian and breast cancer has not been definitively determined.

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Connective Tissue Diseases and the Heart

62

Kinga Vereczkey-Porter and Mary Anne Dooley

Connective tissue disorders commonly affect the cardiovascular system. The endocardium, myocardium, and pericardium all can be injured through different mechanisms by any rheumatologic disease. Similarly, the conducting system is affected by different mechanisms in connective tissue disorders. Each disorder has a particular pattern of involvement. Aortic root disease is more common in ankylosing spondylitis. Pericarditis is prevalent in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Direct inflammatory infiltration or fibrosis frequently causes conduction system damage and may result in bundle branch blocks, atrioventricular (AV) blocks, and various electrophysiologic abnormalities; these can be associated with myocarditis, especially in polymyositis and scleroderma. In utero conduction damage may be associated with anti-Ro/SSA and anti-La/SSB antibodies passively transferred from the mother's circulation through placental blood flow. Valvular disease, coronary lesions, and pulmonary hypertension associated with various connective tissue diseases can also lead to secondary bundle branch blocks, atrial fibrillation, and other arrhythmias. Autonomous nervous system abnormalities in RA, SLE, and ankylosing spondylitis decrease parasympathetic activity and variability. Rheumatic disease severity and activity often correlate with cardiac manifestations. However, heart disease can be the first sign of a rheumatic disease.

For all these reasons, it is important to screen for cardiovascular diseases in rheumatic disease patients. Even in the absence of traditional risk factors, cardiovascular diseases are common and are major causes of mortality and morbidity in this patient population.

ETIOLOGIES

With rare exception, the etiology of connective tissue diseases remains unclear but is probably multifactorial. It is thought that connective tissue diseases occur when individuals with a susceptible genetic background encounter an inciting factor such as infection, drugs, or environmental agents. Varying patterns of complement activation, T- and B-cell interactions, or tissue macrophage infiltration produce inflammation and damage in rheumatic disorders but are also vital to normal blood vessel homeostasis. The specific factors promoting pathogenic instead of homeostatic effects are unknown and probably involve vascular, fibrotic, and immunologic features. Clinically significant heart disease may be caused by direct immunologic injury to the myocardium, endocardium, or pericardium or to the blood vessels supplying these tissues.

Certain antibodies are associated with cardiac involvement in rheumatologic diseases. Antibodies to endothelial cells found in SLE, antiphospholipid syndrome (APS), scleroderma, and different forms of vasculitis correlate with disease activity and severity of involvement. Antibodies to myocardium are found in lupus and other connective tissue diseases. Anti-Ro/SSA and anti-La/SSB antibodies are associated with cardiac involvement and are known to cause neonatal lupus with congenital heart block. Certain major histocompatibility complex haplotypes are associated with increased risk of particular rheumatologic diseases. Classic examples include the link between human leukocyte antigen (HLA) B27 and spondyloarthropathy, as well as HLA DR4 and RA. The interaction between inflammatory cells, endothelial injury response, and repair processes may influence clinical expression of vasculitides.

SYNDROMES

Rheumatoid Arthritis

RA, characterized by a symmetric, additive, destructive synovitis, occurs in 1% of most populations. The most frequent cardiac manifestations in patients with RA are pericarditis and valvular heart disease (Fig. 62-1). These features are more common in patients with nodular seropositive RA than in RA patients without extra-articular pathology. With routine screening echocardiograms, pericardial thickening with or without a pericardial effusion may be seen in up to 60% of patients, though clinically evident in less than 5% (Tables 62-1 and 62-2). Pericardial fluid due to RA involvement is exudative, serosanguineous, or hemorrhagic with high acidity. Adhesions and loculations are common, often making pericardiocentesis ineffective. A significant proportion of patients with clinical pericarditis have constriction or tamponade with a grave prognosis. These patients, under some circumstances, may benefit from surgical pericardiectomy.

Despite frequent occurrence (up to 70%), valvular lesions are rarely symptomatic in RA. Pathologically, endocardial lesions can be caused by fibrosis, nonspecific inflammation, or rarely, rheumatoid granulomas. Aortic or mitral insufficiency and aortic root dilation are the most common manifestations. When due to inflammation these lesions may progress rapidly and require surgical intervention. Myocarditis is rarely clinically evident but can be associated with arrhythmias. Vasculitis of coronary vessels has been described, although the clinical significance is unknown. Recently, serum levels of antibodies directed against cyclic citrullinated peptide (anti-CCP) have been detected in the sera of RA patients earlier than rheumatoid factor (RF). It has been suggested that anti-CCP may define a subset of individuals at increased risk for destructive arthritis. Strong gene-environment interactions also exist between cigarette smoking and homozygosity for HLA DRB1 shared-epitope (SE) alleles DRB1*04 or DRB1*01. Heterozygous individuals who carry at least one copy of the SE and are exposed to cigarette smoking also have a markedly increased risk of anti-CCP-positive RA. Increased cardiovascular risk occurs in RA independent of traditional risk factors and has been attributed

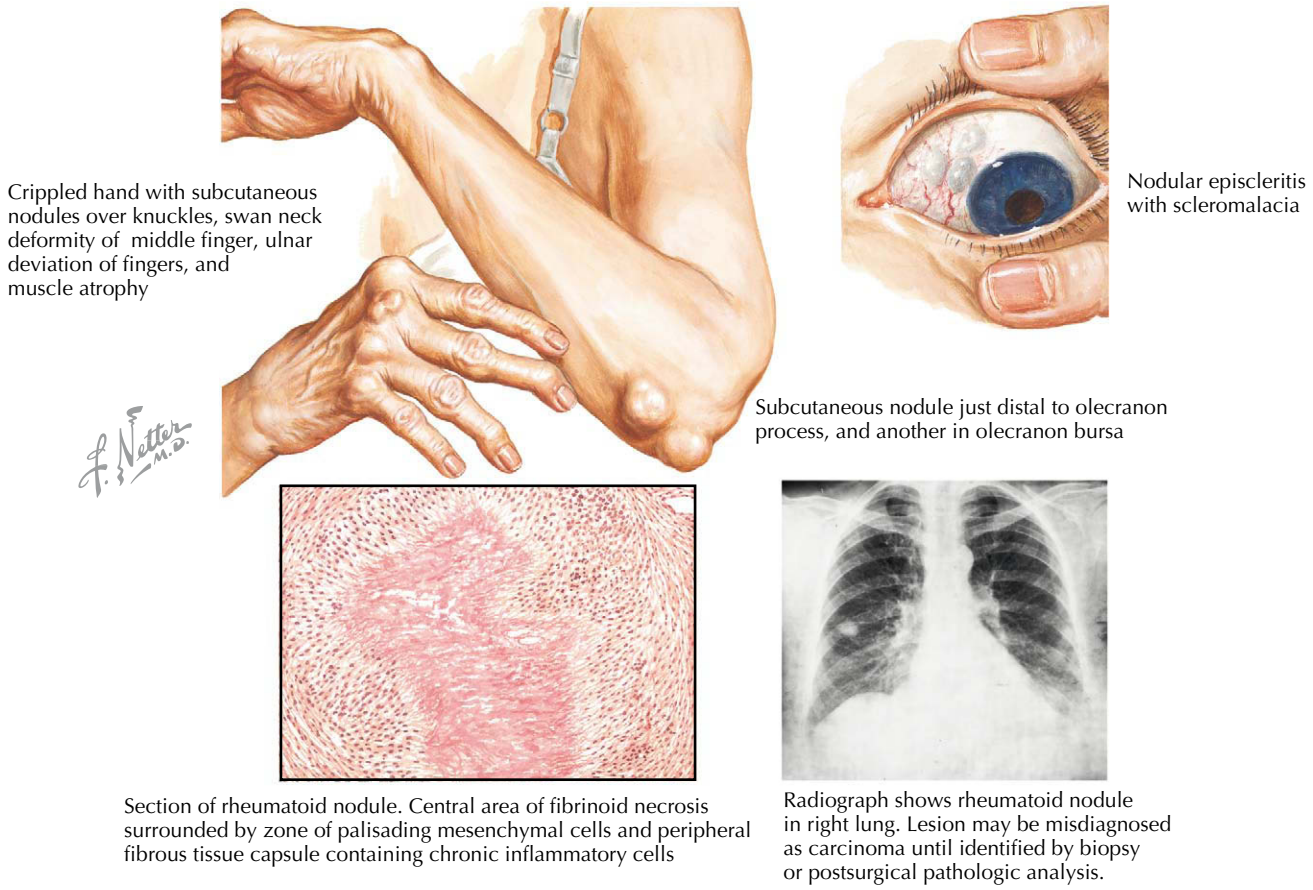

Figure 62-1 *Extra-articular manifestations in rheumatoid arthritis.*

to ongoing inflammation. More aggressive management of inflammation in RA as well as traditional risk factors may lead to marked improvements in outcomes for patients with RA.

Systemic Lupus Erythematosus

SLE (also called *lupus*) is a multisystem autoimmune disorder characterized by the production of autoantibodies and a striking female predominance in the reproductive years (10:1 female-to-male). Autoantibodies and immunocomplexes with complement activation are thought to be the major factors in cardiovascular injury. In SLE, as in RA, the pericardium and endocardium are most commonly involved. Serositis in SLE is often associated with disease flares. Pericarditis is clinically evident in up to 20% of patients, with a prevalence by echocardiography and in autopsy series as high as 60% in individuals

Table 62-1 Clinical Cardiac Manifestations in Rheumatologic Disorders

Disorder	Common	Less Common/Rare
Rheumatoid arthritis	Pericarditis Valvular lesions/endocardial involvement	Myocarditis Arrhythmia
Systemic lupus erythematosus	Valvular lesions/endocardial involvement Pericarditis	Myocarditis Arrhythmia
Ankylosing spondylitis	Valvular lesions/endocardial involvement Aortitis Arrhythmia	Pericarditis Myocarditis (very uncommon)
Inflammatory myopathy	Myocarditis Arrhythmia	Valvular lesions Pericarditis
Scleroderma	Cardiomyopathy with microvascular dysfunction Arrhythmia	Pericarditis Valvular disease
Antiphospholipid syndrome	Valvular lesions/endocardial involvement Coronary artery disease	

Table 62-2 Prevalence of Cardiac Involvement in Rheumatologic Disorders

Disorder	Noninvasive Tests	Autopsies
Rheumatoid arthritis	Pericarditis 20% to 60% (echo) Valvular lesions/endocardial involvement 30% to 40% (echo)	Pericarditis 20% to 60% Valvular lesions/endocardial involvement 30% to 50%
Systemic lupus erythematosus	Pericarditis 20% to 60% (echo) Valvular lesions/endocardial involvement 30% to 40% (TTE), 53% to 73% (TEE)	Pericarditis 40% to 70% Valvular lesions/endocardial involvement 10% to 70% Myocarditis 8% to 81%
Ankylosing spondylitis	Aortic regurgitation 3% to 10% (echo) Conduction abnormalities 22% to 50% (ECG/Holter)	Aortic root thickening and dilation 20% to 60%
Inflammatory myopathy	Arrhythmias 30% to 50% (ECG/Holter) Pericarditis 10% to 25% (echo) Valvular lesions/endocardial involvement 8% to 20% (echo)	Myocarditis 30%
Scleroderma	Arrhythmias 50% (ECG) Pericarditis 30% to 50% (echo)	Cardiomyopathy 12% to 89% Pericarditis 30% to 70% (echo)

ECG, electrocardiogram; Echo, echocardiogram; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

with SLE. Tamponade occurs in 1% to 2% of patients; constriction is even less common. Analysis of pericardial fluid is similar to that of RA, with high acidity and increased polymorphonuclear cells.

Asymptomatic valvular involvement, usually mitral and aortic, is found in up to 70% of patients by transesophageal echocardiography. Libman and Sacks first described noninfectious endocarditis-like lesions in SLE. These consist of thrombotic-fibrinous clusters with proliferating endothelial cells, edema, and areas of necrosis. Immunoglobulins and complement deposits are often detected. The etiology of the lesions commonly found on the posterior mitral leaflet, advancing to the papillary muscles and chordae tendinae, is controversial. APS may influence valvular pathology of patients with SLE. Acute valvular insufficiency can lead to hemodynamic instability and require surgical correction. Libman-Sacks endocarditis may predispose patients to infectious endocarditis. Lupus endocarditis also can cause various thromboembolic phenomena requiring anticoagulation, especially when associated with APS.

Conduction abnormalities, including AV block, bundle branch block, and dysautonomia, are found in up to 10% of patients with SLE. However, most of these are not clinically significant. In pregnant patients with SLE, screening for anti-Ro/SSA and anti-La/SSB antibodies is important to identify those at risk for neonatal lupus with congenital heart block. Most infants with congenital heart block, however, are born to mothers without SLE, who were not known to be seropositive for SSA or SSB before delivery. In pregnant women with SLE, only 1% to 3% of their infants are clinically affected by the antibodies. Nonetheless, for women with positive antibodies, weekly fetal echocardiography between 17 and 24 weeks of gestation is recommended. In women with a prior history of an infant with neonatal lupus (rash or heart block), the risk for affected future offspring rises to 20%.

Another important manifestation of SLE, myocarditis, is clinically evident in less than 10% of patients but can cause severe systolic dysfunction. Myocarditis often develops with other organ involvement and may occur early in the course of SLE. Treatment with steroids or cytotoxic agents can be lifesaving.

New data suggest that homocysteine has an important role in the pathogenesis of coronary artery disease (CAD) in lupus. Among its many beneficial effects, hydroxychloroquine use lowers homocysteine levels. Vitamin B_{12} and folic acid supplementation should also be considered in SLE patients with hyperhomocysteinemia.

Seronegative Spondyloarthropathies

Seronegative spondyloarthropathies (Spas) include ankylosing spondylitis, psoriatic arthritis, postinfectious arthritis, and Behçet's syndrome and arthritis associated with inflammatory bowel disease. All of these conditions are associated with HLA B27, although the association is strongest in ankylosing spondylitis, which is considered the prototype Spa. The pathophysiology of cardiac lesions in Spa is characterized by mononuclear cellular inflammation with progressive fibrosis. Ankylosing spondylitis most commonly affects valvular structures and the aortic root and may present with aortic insufficiency (Fig. 62-2). Aortic thickening, dilation with some degree of aortic regurgitation, or both are found in 82% of patients with ankylosing spondylitis by means of transesophageal echocardiography. Aortic insufficiency is often associated with long-standing disease and older age. Aortic dissection may also occur. Progressive aortic dilation in ankylosing spondylitis may respond to corticosteroid and cytotoxic therapy. Mitral valve pathology is less common than aortic and is characterized by leaflet fibrosis or regurgitation. Diastolic dysfunction and left ventricular hypertrophy in ankylosing spondylitis are often consequences of valvular lesions. Conduction disturbances are usually caused by myocardial fibrosis. Bradyarrhythmias are associated with HLA B27 spondyloarthropathies.

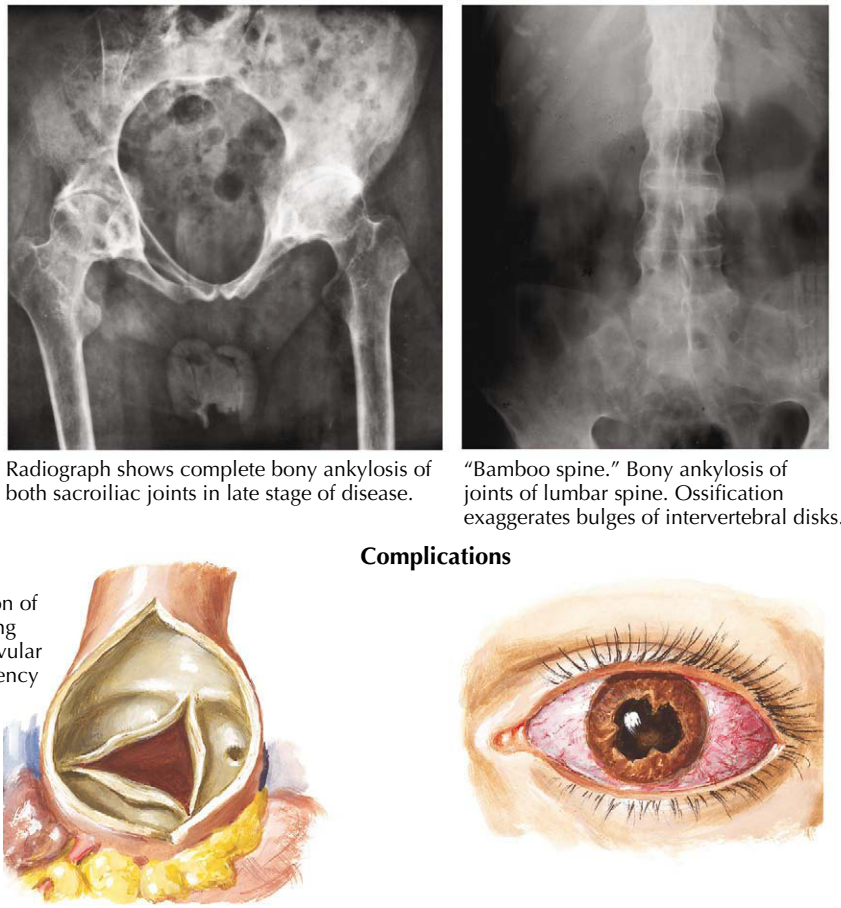

Figure 62-2 *Ankylosing spondylitis.*

Dermatomyositis and Polymyositis

Noninvasive tests identify cardiac lesions in more than 70% of patients with dermatomyositis or polymyositis, but only 10% are symptomatic (Fig. 62-3). Dermatomyositis typically presents with vascular damage and microvasculopathy, whereas polymyositis shows marked T-cell muscle infiltration. The pathology observed ranges from active inflammation to fibrosis and small-vessel disease. Myocardial involvement can cause conduction abnormalities and life-threatening ventricular arrhythmias. Myocarditis often correlates with skeletal muscle disease. Pericarditis is usually asymptomatic but is detected by echocardiography in up to 25% of patients; valvular lesions are rare.

Scleroderma

Systemic sclerosis (SS), or scleroderma, is a chronic connective tissue disorder characterized by inflammation, fibrosis, and degenerative changes in the skin, blood vessels, joints, skeletal muscle, and internal organs, such as the gastrointestinal tract, kidney, and lungs. SS is classified into diffuse scleroderma and limited scleroderma with skin changes prominently in the distal extremities (Fig. 62-4). Scleroderma leads to immune-mediated endothelial injury with extensive fibrosis, producing a bland, intimal hyperplasia associated with tissue ischemia. It commonly involves the cardiovascular system. Mortality as a result of cardiopulmonary causes is more common than that from renal disease. The proposed mechanism for the myocardial injury in scleroderma is a myocardial Raynaud's phenomenon with microvascular dysfunction. Endomyocardial biopsy shows myocardial fibrosis, contraction band necrosis, and myocytolysis in up to 80% of patients. Pericardial pathology is detected clinically in approximately 10% of patients, often being detected during life by echocardiography, or after death at autopsy. A high frequency of arrhythmias and electrophysiologic abnormalities is characteristic of scleroderma; sudden cardiac death is also increased in patients with SS. Diastolic dysfunction often begins early in the disease and frequently precedes other cardiac abnormalities. Limited scleroderma less commonly affects the heart. Noninvasive methods in asymptomatic patients with limited SS detect approximately 10% each of arrhythmia, pericarditis, and cardiomyopathy. Pulmonary disease, particularly pulmonary hypertension, contributes significantly to cardiac abnormalities in limited and diffuse SS.

Vasculitis

The vasculitides are a heterogenous group of disorders characterized by destruction of blood vessels by several methods: direct

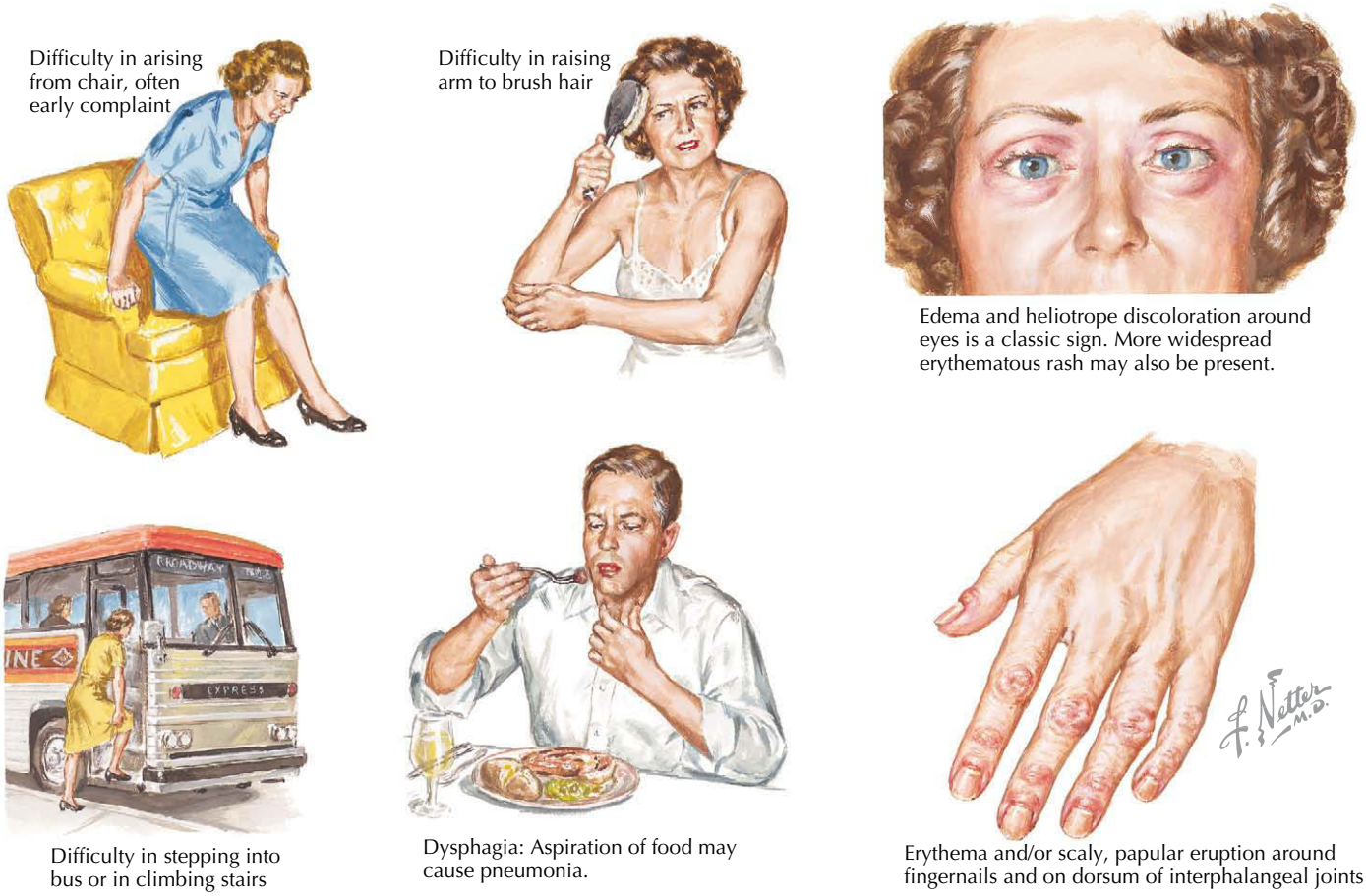

Figure 62-3 *Polymyositis/dermatomyositis.*

antibody attack, immune complex formation, and cell-mediated. Systemic vasculitis embraces a range of relatively rare disorders, with an estimated incidence of 19.8 per million cases. When the inflammatory process compromises critical organ function, patients can experience severe symptoms or death. The prognosis for these disorders has improved; in most patients the disorders have become chronic diseases, with longer patient survival and greater likelihood of remission. Treatment with corticosteroids and immunosuppressive drugs is beneficial both at presentation and for flares.

Classification of these disorders is based on several features: the size of the blood vessels involved, knowledge of disease pathophysiology, and the patterns of organ involvement. Large-vessel arteritis includes giant cell arteritis (GCA) and Takayasu's vasculitis. They primarily affect the aorta and main branches but may also involve medium-sized arteries including the coronary arteries. Medium-vessel vasculitis includes polyarteritis nodosa and the childhood vasculitis Kawasaki's disease. Although polyarteritis nodosa typically spares the heart, Kawasaki's disease causes coronary artery aneurysms in up to 25% of untreated children and pericardial effusions in 30%, along with myocarditis and valvular regurgitation. These patients are also noted to have increased cardiovascular mortality. Small-vessel vasculitis adversely affects a variety of tissues and organs, including the skin, lungs, and kidneys. These diseases can be among the most devastating of rheumatic diseases. Cardiovascular diseases are also a major cause of mortality.

SECONDARY CAUSES OF CARDIOVASCULAR DISEASE

Cardiac pathology in connective tissue disorders is increased through adverse cardiac effects of the medications used to treat the rheumatic disorders and comorbidities associated with the frequent use of corticosteroids. Methotrexate elevates homocysteine levels, an established risk factor for CAD. The anti-tumor necrosis factor-α (TNFα) inhibitors are associated with worsening cardiac function, exacerbating congestive heart failure. Long-term steroid use increases the risk of hypertension, diabetes, and advanced atherosclerosis, which are all associated with cardiovascular disease (see Chapter 61).

Chronic inflammation with long-standing autoimmune disorders such as RA can lead to amyloidosis that may cause restrictive cardiomyopathy and conduction abnormalities. Felty's syndrome (splenomegaly with cytopenia in patients with RA) can cause severe immunodeficiency and theoretically can affect the pathogenesis of endocarditis on already damaged valves. Renal involvement in SLE is often associated with

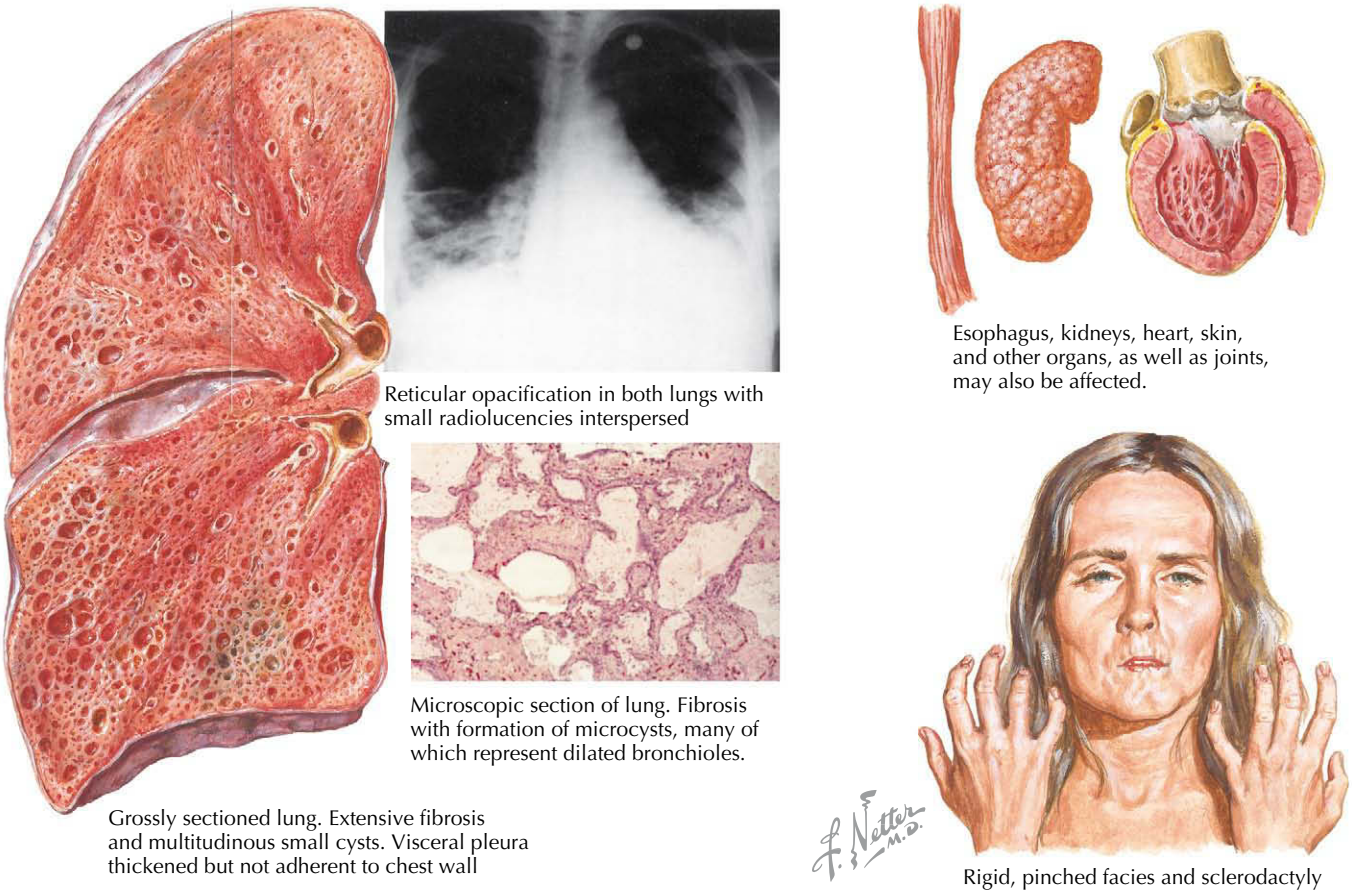

Figure 62-4 *Progressive systemic sclerosis with lung involvement.*

hypertension, contributing to cardiomyopathy. Many patients with rheumatic disease have limited physical activity; their sedentary lifestyle may contribute to CAD and increase the risk of thromboembolic complications. Chronic inflammation, one of the key features of rheumatologic diseases, can directly lead to accelerated atherosclerosis and CAD. Pulmonary fibrosis, common with dermatomyositis or scleroderma, may be complicated by pulmonary hypertension leading to right-sided heart failure. APS and pulmonary hypertension, commonly associated with many rheumatologic conditions, warrant additional discussion.

With or without coexistent rheumatic disease, APS is associated with recurrent arterial and venous thrombosis and fetal loss, and may lead to considerable morbidity and mortality. The two most common cardiac manifestations of APS are valvular lesions and coronary disease, including myocardial infarction in 4% of patients. APS causes endothelial cell activation and atherosclerosis. It may have an important role in the pathogenesis of CAD in patients without classic cardiac risk factors. Endocardial damage usually occurs in the mitral valve. Moderately or strongly positive titers of antibodies to cardiolipin often correlate with the frequency and degree of valvular involvement.

Pulmonary hypertension is an important cause of morbidity and mortality in connective tissue disorders, especially in scleroderma and dermatomyositis as a result of arterial and myocardial effects of the disease process. Pulmonary hypertension can also occur as a result of pulmonary embolism secondary to a hypercoagulable state, most commonly in association with APS. Pulmonary hypertension decreases cardiac tolerance, with a significant increase in right ventricular pressures. This is probably why, in scleroderma, electrophysiologic abnormalities and arrhythmias originate mainly from the right side of the heart, in contrast to patients with CAD who do not have rheumatic disease, in whom left-sided arrhythmias predominate. Normalization of pulmonary pressure frequently improves cardiac function, especially if done early in the course of disease.

CAD in connective tissue disorders causes significant cardiac mortality and morbidity in RA, SLE, and ankylosing spondylitis. The risk of premature CAD in SLE is markedly increased. Rates of myocardial infarction and death secondary to coronary disease in premenopausal women with lupus are 50 times higher than in controls. CAD is often silent, or if it causes pain, patients may ignore it, overwhelmed with multiple musculoskeletal symptoms. For these reasons, patients with SLE, RA, and other rheumatologic disorders warrant aggressive diagnosis and treatment of CAD, despite younger age at onset, female predominance, or the absence of classic risk factors.

DIFFERENTIAL DIAGNOSIS

Because rheumatic diseases often present with constitutional symptoms, possible underlying infection or malignancy should be excluded given the overlap in symptomatology. Hepatitis B and C, possibly associated with cryoglobulinemia, can lead to medium- or small-vessel vasculitis. Subacute bacterial endocarditis, Lyme disease, and other chronic infections, such as tuberculosis and brucellosis, may complicate the diagnosis.

Rheumatic disease without identifying autoantibodies may be especially difficult to diagnose. Diagnosis of polymyalgia rheumatica may prove most challenging. Polymyositis predominantly produces muscle weakness instead of pain. Elevated creatine kinase (CK), electromyography, and muscle biopsy findings confirm the diagnosis. Multiple myeloma may present similarly; however, the presence of paraproteins on serum and urine electrophoresis in multiple myeloma can distinguish the two. Other disorders, including cholesterol emboli, may mimic rheumatic disease. Hypothyroidism, spondyloarthropathy, polymyositis, and, rarely, amyotrophic lateral sclerosis can present similarly to polymyalgia rheumatica. Amyloidosis can mimic GCA, including jaw or arm claudication, and should be excluded.

Temporal artery biopsy results are abnormal in up to 80% to 90% of GCA cases. Since the lesions of GCA are patchy, this biopsy specimen should be 3 to 5 cm optimally, and, if results are negative, a contralateral biopsy should be considered to yield accurate results. The temporal artery biopsy shows fragmentation of the elastica lamina, luminal narrowing, intimal edema, granulomas with multinucleated giant cells, and monocellular infiltrate. Magnetic resonance angiography and angiography can assess vessel involvement, particularly large-vessel involvement in GCA. Noninvasive vascular studies identify only patients with pronounced luminal narrowing. More recently, positron emission tomography scanning has emerged as a useful tool to assess the extent of blood vessel inflammation and avoid repetitive arterial instrumentation and contrast exposures.

Drug-induced connective tissue disorders include vasculitis and lupus. Drug-induced lupus may be associated with several medications, most frequently procainamide and hydralazine. More recently, minocycline, α interferon, and TNFα-blockers have been associated with antinuclear antibody (ANA) and formation of antibodies to double-stranded DNA. Other agents such as propylthiouracil may induce lupus-like disorders or vasculitis. Environmental factors may also induce autoimmune disorders. In RA, cigarette smoking is associated with anti-CCP-positive disease. Patients who test positive for anti-CCP are more likely to have severe erosive disease.

Laboratory Abnormalities

There is no single diagnostic test for connective tissue diseases. The diagnosis relies on the history in combination with appropriate physical findings, and laboratory and pathologic results. The American College of Rheumatology and other expert groups have established criteria that are useful clinically. ANA testing is a sensitive screening test, since more than 95% of patients with lupus have positive test results when the test is performed using a substrate containing human nuclei such as HEP-2 cells. However, a positive test result for ANA is not specific for SLE. Positive ANA test results may occur in healthy individuals, especially in older adults; 15% of patients aged older than 65 years have ANAs, usually at a low titer. It is important to exclude other autoimmune diseases, particularly those associated with a positive ANA result, such as RA, Sjögren's syndrome, scleroderma, isolated Raynaud's syndrome, or organ-specific autoimmune diseases, including idiopathic thrombocytopenic purpura, autoimmune thyroid disease, and hemolytic anemia. Family members of patients with SLE often manifest an ANA without development of clinical SLE features. Many autoimmune diseases have overlapping features, making strict classification difficult. The presence of antibodies to the Smith antigen, though found in only 15% to 30% of patients, is pathognomonic for SLE. RF is elevated in 80% of patients with RA, although it can be positive in various infectious, autoimmune, and oncologic disorders. Anti-CCP is a newly recognized autoantibody in a subset of patients with RA and is associated with more severe erosive arthritis. It may be positive earlier in the course of arthritis than RF and demonstrates a significant gene-environment interaction. Individuals homozygous for the high-risk SE who are cigarette smokers are at a selective and substantial risk of developing CCP-positive RA, although their risk of RA without anti-CCP is not changed.

Acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein are often elevated in rheumatologic conditions and may correspond with flare of disease. An exception is the Spas, in which these test results may remain normal despite active disease.

DIAGNOSTIC APPROACH

The diagnosis of rheumatologic diseases relies on the history and physical examination. Antibody tests and acute-phase reactants should be considered in the context of clinical presentation, and diagnosis cannot rely on serologic tests alone. When evaluating cardiac involvement by rheumatologic condition, specific cardiac enzymes are used with some limitations; the MB fraction of CK can often be elevated from muscle injury and repair in myositis, and may be less specific in these settings. CK and troponin levels are frequently normal in lupus cardiomyopathy, necessitating further investigation. Myocardial biopsy can help differentiate the pathologic process, particularly to distinguish active inflammation from fibrosis before instituting cytotoxic therapy with potentially serious side effects.

MANAGEMENT AND THERAPY

Optimum Treatment

The choice of immunosuppressive medications to treat underlying rheumatologic disorders is often based on clinical experience, with few large randomized trials available. These medications include methotrexate, azathioprine, hydroxychloroquine, leflunomide, cyclophosphamide, and mycophenolate mofetil, among others. Large-scale clinical trials have been recently published in the area of biologic therapies including anti-TNF therapy, costimulatory blockers such as CTLA4-Ig, and anti-interleukin-6 (anti-IL-6). While these therapies may also reduce the cardiovascular complications that occur in rheumatologic diseases, this

has yet to be conclusively established. The therapy of cardiac diseases in these individuals should also include conservative or surgical management of heart failure, ischemia, arrhythmia, and valvular disease, as discussed in other chapters.

Symptomatic pericarditis is best managed with nonsteroidal anti-inflammatory drugs and steroids. If hemodynamic compromise is present, close monitoring is warranted. Pericardial tamponade occurs more commonly in rheumatic diseases than formerly recognized. Pericardiocentesis can be lifesaving but is effective for only a short time, and, although initial relief may result, pericardiocentesis rarely "cures" pericardial tamponade associated with collagen vascular diseases. Cardiothoracic surgery may be necessary to create a pericardial window for continued drainage. However, as noted earlier, resistant pericardial effusions or constrictive pericarditis may necessitate pericardiectomy.

High-dose steroids and cytotoxic therapy are effective in SLE with inflammatory myocarditis. Myocardial biopsy often confirms inflammation and excludes other cardiomyopathy causes. Management of valvular lesions secondary to rheumatologic conditions is similar to other valve defects, except that inflammatory valvular lesions tend to progress more rapidly, necessitating close follow-up. Pulmonary hypertension therapy includes administration of calcium channel blockers, prostacyclin analogues, and endothelin antagonists.

Anticoagulation is indicated in most patients with significant pulmonary hypertension regardless of the cause but certainly including patients with primary rheumatologic diagnoses. Symptomatic APS often necessitates lifelong anticoagulation treatment.

Avoiding Treatment Errors

Recognizing that a rheumatic disease may be the cause of the patient's presentation is the first step to avoiding treatment errors. Typically, the patient may relate a scenario of new, seemingly unrelated symptoms that coalesce into a pattern suggesting a specific disorder. In a young woman presenting with a large pericardial effusion, recognizing that her new-onset Raynaud's syndrome, esophageal reflux, newly developing hypertension, and renal insufficiency may reflect onset of scleroderma renal crisis can be lifesaving. It may also prevent the choice to use high-dose steroids that may precipitate renal crisis in scleroderma. Consultation with a rheumatologist and/or other appropriate subspecialists can be very useful for management of patients with such complex presentations. Most important, with the development of newer biologics for the treatment of rheumatic diseases is a clear understanding of the risks, side effects, and the implications of continuing or halting therapy. Currently, these therapies are not indicated specifically for treating or preventing cardiovascular diseases in patients with connective tissue and/or rheumatologic diseases.

FUTURE DIRECTIONS

The main cause of CAD in connective tissue disorders remains atherosclerosis. The role of coronary vasculitis is widely debated, and the precise molecular mechanisms remain to be elucidated. The roles of immune complex deposition, APS, pro-oxidant environment, inflammation, and dyslipidemia are under investigation. Monoclonal antibodies directed against TNF, IL-1 receptor A, CD-20–expressing B cells, and IL-6 are used more often in rheumatologic conditions; case reports showing the efficacy of biologic agents to treat endocarditis and myocarditis associated with connective tissue disorders have been published. Genetic and immunologic studies will continue and offer hope in earlier diagnosis and institution of appropriate therapy for these patients. New biomarkers of disease activity will continue to arise. Understanding complex gene-environment interactions, such as the SE with cigarette smoking in RA associated with anti-CCP, will undoubtedly foster research on new pathways important to the etiology of this rheumatic disease.

ADDITIONAL RESOURCES

The Arthritis Foundation [homepage on the Internet]. Available at: <http://www.arthritis.org>; Accessed 18.03.10.

The Arthritis Foundation site has resources for patients with a variety of rheumatic diseases.

European League against Rheumatism. Available at: <http://www.eular.org/>; Accessed 18.03.10.

Offers a variety of resources including practice guidelines, meetings, and online courses on rheumatic diseases. The general course consists of 42 modules, runs over 2 years, and covers all aspects of rheumatology. Specialized reviews of specific diseases are also offered.

Klippel JH, Stone JH, Crofford LJ, White PH. *Primer on the Rheumatic Diseases.* 13th ed. New York: Springer and the Arthritis Foundation; 2008.

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American College of Rheumatology. Classification criteria for rheumatic diseases. Available at: <http://www.rheumatology.org/practice/classification/index.asp>; Accessed 18.03.10.

The American College of Rheumatology website is continually updated with information for patients and practitioners as well as physicians. It offers many patient resources in Spanish as well as English and is easily searchable.

Firestein GS, Budd RC, Harris ED, et al, eds. *Kelley's Textbook of Rheumatology.* 8th ed. Philadelphia: WB Saunders; 2008.

An excellent text resource that also may be loaded onto the computer as a searchable database.

Koopman WJ, Moreland LW, eds. *Arthritis and Allied Conditions.* 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2004.

This excellent text is also available for computer access and searching. It has a focus on specific clinical dilemmas with expert opinion on management in challenging areas. Very well organized.

National Institute of Arthritis and Musculoskeletal and Skin Diseases. Available at: <http://www.niams.nih.gov/>; Accessed 18.03.10.

This highly accessible resource for information on rheumatic diseases and current therapies has patient material that can be downloaded and is available in English and Spanish. It is easily searchable for information and for current clinical trials and locations.

Cardiac Tumors

Hanna K. Sanoff and Mark A. Socinski

63

Until the second half of the twentieth century, cardiac tumors were diagnosed almost exclusively at autopsy, and no treatment options existed for those rare instances of antemortem discovery. Advances in cardiac imaging—principally echocardiography—and the advent of cardiopulmonary bypass made cardiac tumors treatable. Primary tumors of the heart are rare and typically benign. Because of their critical location, however, they are almost never clinically benign. Secondary tumors are more common, particularly in the setting of metastatic disease.

Data from autopsy series place the incidence of primary heart tumors around 0.02%, of which 75% are benign. Myxomas represent half of all benign primary tumors. Of primary malignant neoplasms, approximately 95% are sarcomas.

Secondary malignant neoplasms have an autopsy incidence of 1% and occur most commonly in the setting of widely disseminated metastatic disease. Of patients who die of metastatic cancer, 20% have some degree of cardiac involvement, frequently asymptomatic. The cancers most likely to involve the heart are lung cancer, breast cancer, lymphoma, and myeloid leukemia. Melanoma has a predilection for the heart; cardiac involvement is present in 50% of patients with advanced disease.

CLINICAL PRESENTATION

The clinical presentation of a cardiac tumor depends on its location. Tumors located on the endocardial surface, such as myxomas, usually present with various embolic phenomena or symptoms of valvular obstruction. Tumors that arise within the myocardium are more likely to produce arrhythmias and disruption of the conduction system. Diffuse myocardial infiltration can result in heart failure from systolic or diastolic dysfunction. Epicardial and pericardial involvement may manifest as pain, effusion, or heart failure in the form of constriction or tamponade. Myxomas also present with systemic illness—principally constitutional symptoms and hematologic abnormalities.

DIFFERENTIAL DIAGNOSIS

Primary tumors of the heart should be considered in the differential diagnosis of embolic phenomena, valvular disease, heart failure, and arrhythmia. Infectious endocarditis may present in a manner virtually indistinguishable from that of a cardiac tumor—particularly myxomas that present with constitutional symptoms—and is a key component of the differential diagnosis. Other diagnostic considerations include atrial or ventricular thrombosis, endocrine derangements (particularly thyroid disease), and rheumatologic diseases such as lupus and systemic vasculitis.

Embolization

Emboli from cardiac tumors result from dislodgement of adherent thrombus or tumor fragments. The clinical picture from embolization of multiple small fragments may resemble small-vessel vasculitis or endocarditis. Larger emboli can cause stroke, infarction of visceral organs, and peripheral ischemia from arterial emboli. Tumor emboli should always be included in the differential diagnosis of embolic phenomena. Hence, a pathologist should review all resected emboli.

Obstruction

Valvular obstruction by a tumor produces symptoms similar to valvular heart disease. Because atrial tumors are more common, obstruction of the atrioventricular valves mimicking mitral and tricuspid stenosis is typical. Classic symptoms caused by tumor obstruction can be distinguished from valvular disease by the paroxysmal and positional nature of obstruction by a mobile tumor.

Arrhythmia

Infiltration of the myocardium and irritation by an endocardial tumor can cause supraventricular and ventricular arrhythmias. Disruption of the conduction system may cause all degrees of atrioventricular nodal block. Sudden cardiac death is a risk; however, this presentation is unusual in patients with cardiac tumors.

DIAGNOSTIC APPROACH

Transthoracic echocardiography is the standard means by which many cardiac tumors are diagnosed. Echocardiography is most sensitive in the diagnosis of endocardial tumors and least well suited for diagnosing tumors originating from the pericardium. Transesophageal echocardiography allows further evaluation of right-sided tumors and better characterization of questionable masses seen on transthoracic cardiac imaging. MRI can further assess pericardial disease and the extent of cardiac involvement of a tumor. Both MRI and CT scans may help further characterize the tumor, allowing for a presumptive diagnosis in the absence of biopsy. Biopsy of cardiac tumors is typically not warranted if operative intervention is planned, since the risk of complication—particularly embolization—often outweighs the need for a preoperative diagnosis.

PRIMARY BENIGN CARDIAC TUMORS

The majority of benign cardiac tumors are myxomas; however, a wide variety of tumors arise within the heart (Table 63-1).

Table 63-1 Histologic Distribution of Primary Benign Cardiac Neoplasms

	Percentage of Tumors	
Benign Tumor	**Adults**	**Children**
Myxoma	45	15
Lipoma	21	0
Papillary fibroelastoma	16	0
Rhabdomyoma	2	45
Fibroma	3	15
Hemangioma	5	5
Teratoma	1	13
Other	6	6

With permission from Allard MF, Taylor GP, Wilson JE, et al. Primary cardiac tumors. In: Goldhaber S, Braunwald E, eds. Atlas of Heart Diseases. *Philadelphia: Current Medicine; 1995:15.1–15.22.*

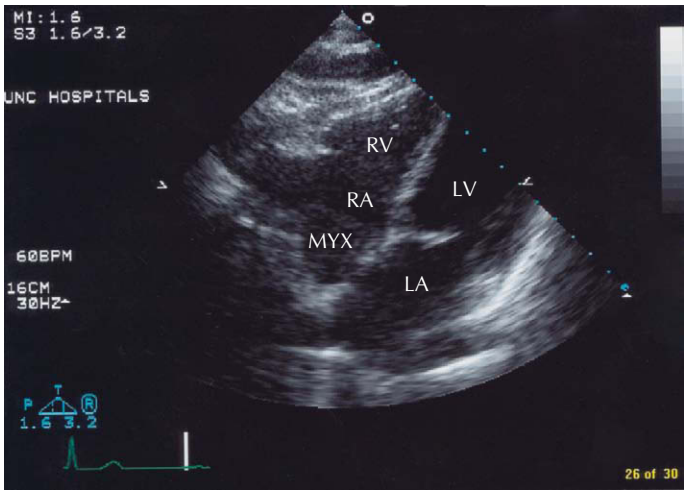

Image courtesy of Dr. Alan Hinderliter.

Figure 63-2 *Echocardiographic image of a right atrial tumor.* At the time of resection, the tumor was found to be a myxoma. LA, left atrium; LV, left ventricle; MYX, myxoma; RA, right atrium; RV, right ventricle.

Myxoma

Myxomas are the most common primary cardiac neoplasm, accounting for 50% of all benign cardiac tumors (Fig. 63-1). There is a female predominance of 2:1 to 3:1, and the median age of presentation is 50 years, although myxomas can occur at any age. Myxomas arise in the left atrium 75% of the time, usually on the interatrial septum near the fossa ovalis. Right atrial myxomas account for 20% of tumors (Fig. 63-2). The balance of myxomas occur in either ventricle and, in rare cases, on the cardiac valves. The majority of myxomas (>90%) are solitary.

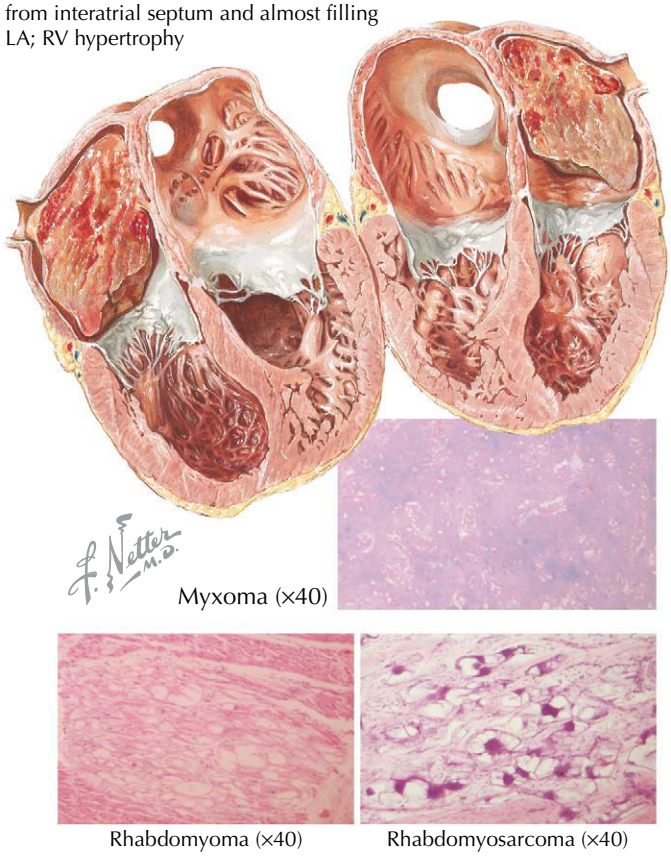

Figure 63-1 *Heart tumors.* LA, left atrium; RV, right ventricular.

An autosomal-dominant, familial myxoma syndrome, the Carney's complex, has been described. Affected individuals demonstrate variable phenotypic expression but have in some form at least two of the main features: heavy facial freckling, endocrine hyperactivity (i.e., Cushing's syndrome), both myxomatous and nonmyxomatous endocrine neoplasia, noncardiac myxomas (typically breast and skin), and cardiac myxomas. Cardiac myxomas associated with the Carney's complex have an equal male-to-female ratio, occur at a younger age (mean age of diagnosis, 25 years), and are more likely to be multiple or ventricular and to recur after resection. Linkage analysis has mapped gene loci to 17q12–q13, 17q22–q24, and 2p16. Mutations in the *PRKAR1A* gene, encoding a protein kinase A regulatory subunit, seem to be responsible for as many as 70% of cases of the Carney's complex.

Myxomas originate from multipotent mesenchymal cells. Grossly, they are gelatinous, pedunculated tumors with an average size of 4 to 8 cm. The tumor surface may be friable or smooth. A smooth surface is associated with systemic signs and symptoms. Friable tumors are more likely to present with embolization.

CLINICAL PRESENTATION

Myxomas typically present with embolization, obstruction, and arrhythmia, but may also cause systemic signs and symptoms similar to those of collagen vascular disease, endocarditis,

vasculitis, and malignant neoplasms. Typical signs and symptoms are fever, anorexia and weight loss, malaise, arthralgia, increased erythrocyte sedimentation rate and C-reactive protein, leukocytosis, thrombocytopenia, hypergammaglobulinemia, and anemia. The mechanism by which myxomas cause systemic manifestations is not fully understood; however, many myxomas produce interleukin-6, which leads to hepatic synthesis of acute-phase reactants and subsequent systemic illness. These constitutional symptoms usually resolve with resection of the tumor. In addition, antineutrophilic and antimyocardial antibodies may be found at presentation and then resolve with removal of the myxoma. It is unclear whether these antibodies play a pathologic role or are an incidental finding. Of these presentations, cardiac symptoms are the most common, followed equally by embolization and constitutional symptoms.

The physical examination may direct the differential diagnosis toward myxoma. In the setting of left atrial tumors, auscultation may reveal a tumor "plop" that occurs in early diastole and is often confused with an S_3 gallop. Mitral diastolic rumbles and mitral systolic murmurs may be present.

MANAGEMENT AND THERAPY

Optimum Treatment

Given the propensity of myxomas to cause serious, life-threatening complications, surgical resection should be performed without delay. With thorough resection of the tumor, including a wide resection of the myocardium at the base of the tumor stalk, recurrence is rare. Patients with sporadic myxomas have a recurrence rate of 1%, whereas patients with familial myxoma syndrome have a 7% to 22% rate of recurrence or second myxoma. Recurrence is usually within the first 4 years after resection. Follow-up echocardiography is recommended for patients with Carney complex but may not be necessary following surgical resection of a sporadic myxoma, given the high cure rate.

Avoiding Treatment Errors

In persons with a short life expectancy and serious comorbid conditions, the morbidity of operative resection may outweigh the benefits. In these instances, it is prudent to initiate lifelong anticoagulation.

Lipoma

Lipomas are the second most common benign primary cardiac tumor. Lipomas can occur at any age and have no predilection to either sex. They are encapsulated tumors usually located in the epicardium or the myocardium, although endocardial tumors do occur. Most are small and asymptomatic, but they occasionally grow to massive proportions. Symptoms, when present, are usually referable to effusion or infiltration of the myocardium, with subsequent arrhythmia or conduction defect. Large, asymptomatic lipomas are sometimes found incidentally on the chest radiograph or during echocardiography. Similar to all cardiac tumors, symptomatic lipomas may necessitate at least partial resection.

Lipomatous hypertrophy warrants consideration, because the treatment is drastically different from that for the presence of a circumscribed lipoma. Lipomatous hypertrophy of the atrial septum is a relatively common non-neoplastic condition characterized by massive fatty infiltration of the interatrial septum. This condition is found in obese persons 50 years or older—typically older than 65 years. Septal thickening may be marked: up to 7 cm. Atrial tachyarrhythmias are common. The only effective therapy for lipomatous hypertrophy is weight loss.

Fibroma

Fibromas are tumors of childhood, occurring in the ventricular myocardium, often located in, or extending to, the intraventricular septum. Symptoms result from involvement of the conduction system, which may lead to sudden death. Because the tumors are located in a crucial part of the myocardium, resection is usually not feasible. Cardiac transplantation may be the only treatment option.

Rhabdomyoma

Rhabdomyoma is the most common benign cardiac tumor type of infancy and childhood. Multiple tumors usually occur and appear within the ventricular myocardium, although some project into the ventricular cavity. One third of rhabdomyomas are associated with tuberous sclerosis. It is not uncommon for tumors to regress spontaneously; as a result, conservative management is generally recommended.

Papillary Fibroelastoma

Papillary fibroelastomas are the most common "tumors" of the cardiac valves. These are not truly neoplasms, but avascular growths resembling a sea anemone because of their frondlike arms around a central base of attachment. The pathogenesis of fibroelastomas is unknown. They may originate from endocardial trauma and organization of thrombus. Formerly diagnosed only at autopsy, they are seen frequently during echocardiography and may be confused with valvular vegetations. Fibroelastomas occur most commonly on the ventricular surface of the aortic valve or on the atrial surface of the mitral valve. They are usually small (measured in millimeters), solitary, and mobile. Fibroelastomas usually do not cause valvular dysfunction but can be a source of embolization to the coronary or cerebral vasculature. Given this, patients should either undergo surgical removal of fibroelastomas or initiate lifelong anticoagulation to lessen the risk of embolic complications.

Pericardial Cysts

Also known as *springwater cysts*, these benign, non-neoplastic, congenital cysts are usually located in the right costophrenic angle outside the pericardial cavity. The diagnosis is usually made by an incidental finding of a mass on chest radiograph or echocardiograph. No intervention is recommended except in the rare case of symptomatic cysts that cause chest pains, dyspnea, cough, or tachycardia.

Table 63-2 Histologic Distribution of Primary Malignant Cardiac Tumors

	Percentage of All Tumors	
Malignant Tumor	**Adults**	**Children**
Angiosarcoma	33	0
Rhabdomyosarcoma	21	33
Mesothelioma	16	0
Fibrosarcoma	11	11
Lymphoma	6	0
Osteosarcoma	4	0
Thymoma	3	0
Neurogenic sarcoma	3	11
Leiomyosarcoma	1	0
Liposarcoma	1	0
Synovial sarcoma	1	0
Malignant teratoma	0	44

With permission from Allard MF, Taylor GP, Wilson JE, et al. Primary cardiac tumors. In: Goldhaber S, Braunwald E, eds. Atlas of Heart Diseases. *Philadelphia: Current Medicine; 1995:15.1–15.22.*

PRIMARY MALIGNANT CARDIAC TUMORS

Approximately 25% of primary cardiac neoplasms are malignant. A majority (95%) are sarcomas (Table 63-2). Lymphomas, though rare, represent most of the remaining primary tumors of the heart. The incidence of primary lymphoma may be increasing given the number of people with impaired cellular immunity from AIDS and organ transplantation.

Sarcoma

Sarcomas are aggressive tumors that present most commonly in the third to fifth decades of life with signs and symptoms of cardiac dysfunction from obstruction or myocardial infiltration. The most common sites of involvement, in descending order, are the right atrium, the left atrium, the right ventricle, the left ventricle, and the interventricular septum. Sarcomas grow quickly, and affected individuals usually have a rapidly downhill course. Death within a few weeks or months is typical; rarely do patients survive for a few years after diagnosis. Death is a result of heart failure from myocardial replacement by tumor, tumor obstruction, or distant metastasis. At the time of death, 75% of individuals have distant metastases; the lungs, thoracic lymph nodes, mediastinal structures, and vertebral column are the sites most commonly affected. Sarcomas derive from mesenchymal cells and therefore may present as subtypes. The two most common sarcomas are angiosarcoma and rhabdomyosarcoma.

Angiosarcoma, including Kaposi's sarcoma, is the more common subtype. There is a 2:1 male predominance. Angiosarcomas typically arise in the right atrium. Malignant cells form vascular channels, and a continuous precordial murmur may be present. Death results from obstruction of the heart's right side, either by tumor or thrombus, or from rupture of the sarcoma with hemopericardium and subsequent hemorrhagic tamponade. Rhabdomyosarcomas have no chamber predilection and often involve multiple sites. Death is a result of obstruction or infiltration of the myocardium.

The prognosis for all morphologic subtypes of cardiac sarcoma is poor. Complete resection is the treatment of choice. The role of postoperative, adjuvant chemotherapy has not been proven. Unfortunately, resection is usually not an option, because the degree of cardiac involvement precludes adequate operative resection. The role of preoperative chemotherapy is not defined.

Lymphoma

Primary cardiac lymphomas are almost exclusively non-Hodgkin's and usually are diffuse B-cell lymphomas. These constitute approximately 1% of all cardiac tumors and 0.5% of extranodal non-Hodgkin's lymphomas. Cardiac lymphomas usually present with effusion, heart failure, or arrhythmia. Because these tumors typically are rapidly progressive, many patients die before initiation of chemotherapy. In recent studies, patients who survived to undergo standard therapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or an equivalent regimen still had a median survival of only 7 months, even though diffuse B-cell lymphomas are generally chemotherapy-sensitive and are likely to respond to treatment, at least initially. However, immediately after initiation of chemotherapy, tumor necrosis may cause death as a result of refractory heart failure and refractory ventricular tachycardia.

Pericardial Mesothelioma

Pericardial mesothelioma is a rare tumor that occurs in young people, presenting as constriction or pericardial effusion with or without tamponade. Primary cardiac mesotheliomas typically involve the parietal and the visceral pericardium, but usually do not invade the myocardium. Suspected links to asbestos exposure are insufficiently substantiated. Chemotherapy and radiation therapy may give temporary improvement in a palliative setting, but the disease is uniformly and rapidly fatal.

SECONDARY MALIGNANT CARDIAC TUMORS

Metastatic disease involving the heart is much more common than primary cardiac neoplasms. At autopsy 1% of unselected persons had secondary tumors of the heart. In comparison with primary cardiac neoplasms, which are rare but never clinically silent, only 10% of secondary tumors are symptomatic. The majority of symptomatic individuals have pericardial metastases. A diagnosis of cardiac metastasis should be considered when patients with known malignant neoplasms have any new onset of cardiac dysfunction (heart failure, arrhythmia, cardiomegaly, among others). Rarely, cardiac involvement, in the form of a large pericardial effusion, is the initial presentation of a malignant process.

Cancers that most commonly metastasize to the heart are lung cancer, breast cancer, lymphoma, and leukemia (Fig. 63-3). Lung and breast cancers involve the heart via local spread and subsequent infiltration of the pericardium, causing effusion and constriction. Lung cancer can invade the left side of the heart

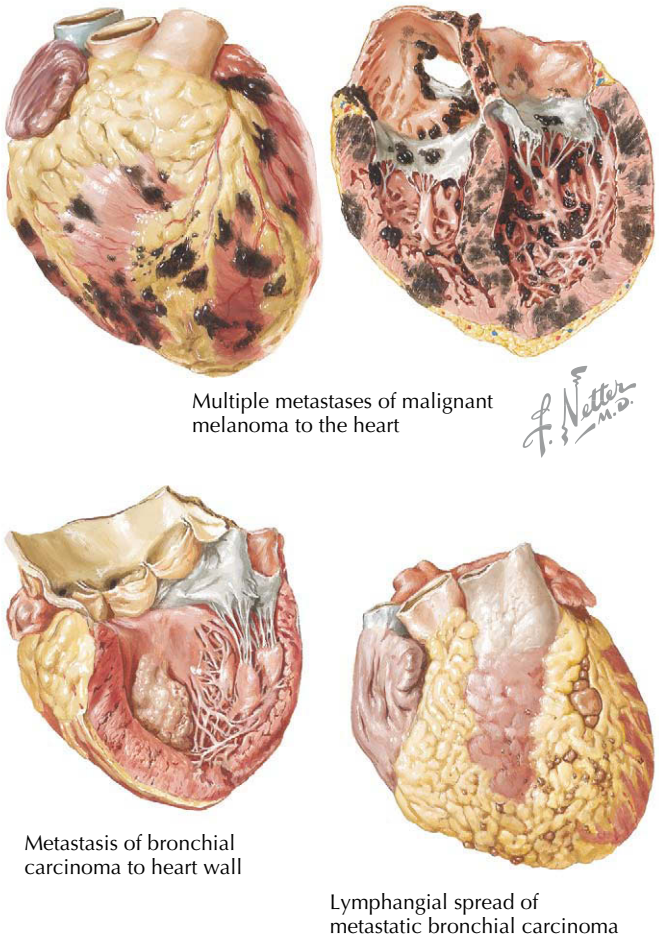

Figure 63-3 *Metastatic tumors of the heart.*

through the pulmonary artery, and its adrenal metastases can invade the right side of the heart via the inferior vena cava. In myeloid leukemias, leukemic cells are seen on light microscopy infiltrating between myocytes. As a result, thrombocytopenic patients may experience fatal hemorrhages into the myocardium or the pericardial space. Non-Hodgkin's lymphomas have a high rate of cardiac involvement—up to 25% of patients may have grossly visible epicardial or myocardial disease—but it is often clinically silent. Melanomas are rare and constitute a small portion of secondary cardiac tumors. However, for unknown reasons, melanoma has the highest rate (~50%) of cardiac metastasis. It may involve any site and is often present in all four chambers of the heart. Most cancers, with the exception of primary central nervous system malignant neoplasms, can metastasize to the heart; therefore, cardiac involvement should be considered if consistent symptoms arise.

MANAGEMENT AND THERAPY

Optimum Therapy

Advances in echocardiography and surgical technique have allowed for prompt diagnosis and safe, curative operative intervention for most benign tumors. Unfortunately, malignant disease of the heart is largely a fatal disease, since resection for cure is typically not feasible. In addition, with the exception of lymphoma, most primary cardiac tumors are not sensitive to chemotherapy or radiation therapy. As such, chemotherapy and radiation largely serve as temporary palliative measures. Cardiac transplantation has been suggested as an alternative curative method for benign tumors in critical locations that preclude resection and for unresectable malignant disease without evidence of metastasis. Micrometastatic disease is a valid concern, however, given the suppression of cell-mediated immunity that must follow cardiac transplantation. In children with inoperable benign tumors, transplantation is probably the only option.

Avoiding Treatment Errors

As with all malignancies, it is critical to obtain a proper diagnosis before initiating treatment, since the chemotherapeutics used differ greatly between sarcomas and lymphomas. Given the complicated management of primary cardiac neoplasms, treatment should be undertaken at a tertiary care center by a multidisciplinary team consisting of a cardiac surgeon, a cardiologist, and a medical oncologist.

FUTURE DIRECTIONS

Successes in the treatment of cardiac tumors have stemmed from advances in modern imaging and surgical techniques. Cardiac transplantation is a compelling treatment method in the young and healthy. Demand already significantly outstrips the supply of organs, however, and transplantation is unlikely to become a prevalent solution. Future progress in the realm of cardiac tumors will probably come from our increasing knowledge about the molecular and genetic pathology of this diverse group of neoplasms. Recent identification of gene loci implicated as causative in the Carney complex may lead to genetic testing. Affected family members could be identified early and receive targeted surveillance and treatment before complications arise. Drugs designed to target specific cell-surface markers and proteins within tumors have had excellent early success in other neoplasms—most notably the tyrosine kinase inhibitor imatinib used to treat chronic myelogenous leukemia. As researchers develop a better understanding of the molecular derangements of these tumors, similar targeted, tumor-specific therapy may become available.

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A large series documenting the most common presenting symptoms of myxoma.

Rolla G, Bertero MT, Pastena G, et al. Primary lymphoma of the heart. A case report and review of the literature. *Leukemia Res.* 2002; 26:117–120.

A review of available literature on the rare disease of cardiac lymphoma.

Pulmonary Hypertension and Thromboembolic Disease

64

Timothy C. Nichols and Thomas R. Griggs

Under normal conditions, the arterial pressure in the pulmonary vasculature is much lower than the systemic arterial blood pressure, even though the volume of blood flow through the pulmonary vasculature equals the volume of blood flow through the peripheral vasculature. This reflects, to a major degree, the large cross-sectional area of the pulmonary capillary bed and the ability of small pulmonary vessels to respond to numerous vasodilatory and vasoconstrictive influences. The pulmonary vascular system has enormous reserve, so major challenges, such as surgical excision of lung tissue or advanced pulmonary disease, are usually tolerated with minimal symptoms. However, when the pulmonary circuit is suddenly occluded, as with a massive pulmonary thromboembolism (PE), or when chronic disease overwhelms the anatomic and physiologic reserve, with resulting pulmonary hypertension, severe disability and/or death can result.

PULMONARY HYPERTENSION

Etiology and Pathogenesis

Pulmonary artery pressure (PAP), the pressure that must be sustained by the right ventricle, is equal to pulmonary flow (PF) times pulmonary vascular resistance (PVR) plus pulmonary venous pressure (PVP) [PAP = (PF × PVR) + PVP]. Normal PAP in systole is 18 to 25 mm Hg, and mean PAP is 12 to 16 mm Hg. The normal PVP is approximately 6 to 10 mm Hg, giving a total pressure gradient that averages approximately 5 mm Hg.

A complicated array of physiologic and pathologic responses to perturbations of any of these variables will cause changes in the others. For this reason, the underlying cause of end-stage pulmonary hypertension in an individual patient may be difficult to determine. For instance, chronically elevated pulmonary flow caused by systemic arterial-venous shunting will lead to increased PVR that requires concomitantly greater increases in PAP for maintenance of blood flow. In another example, chronically elevated left atrial pressures due to mitral stenosis create a requirement for increased PAP. However, over time, PVR increases in patients with mitral stenosis by yet unknown mechanisms and can lead to persistent pulmonary artery hypertension even after the mitral stenosis is relieved.

Pulmonary artery hypertension can therefore be secondary to many diseases. Some of these can be treated with the reversal or slowing of pulmonary artery hypertension progression. Additionally, an important minority of patients has pulmonary artery hypertension as a primary disease with no identifiable cause. Therefore, in approaching the patient presenting with pulmonary artery hypertension, the optimal approach is to characterize pulmonary hemodynamics and use the data obtained to aggressively search for treatable underlying causes and for manageable elements of the pathophysiology. Critical in this responsibility is to recognize and address pulmonary artery hypertension as early as possible.

An expert committee of the World Health Organization has created a comprehensive diagnostic classification of pulmonary hypertension (Box 64-1). Of the many potential causes of pulmonary hypertension, the World Health Organization classification group 1—which includes idiopathic pulmonary artery hypertension (IPAH) and familial pulmonary artery hypertension (FPAH), diseases formerly referred to as "primary pulmonary hypertension"—merits special consideration. These diseases, characterized by proliferative and necrotic obliteration of the pulmonary microvasculature, are clinically indistinguishable except for family history. Both are devastating, despite advances in our understanding of their causes and treatment. Unlike the situation for many other causes of pulmonary hypertension, there are no reversible structural factors that can be addressed for individuals with IPAH and FPAH.

Clinical Presentation

Symptoms of pulmonary hypertension are common to multiple etiologies. Most patients with mild or moderate pulmonary hypertension are asymptomatic. Initial symptoms may be dyspnea with exertion, fatigue, and exertional intolerance. Many patients experience chest pain. Syncope suggests severe pulmonary hypertension with marked limitation of flow reserve. Hemoptysis is not common, but in some patients it is serious and fatal. Clinical presentation depends in part on the chronicity of the process. Adaptive changes in the right ventricle allow patients with chronic pulmonary hypertension to sustain near-systemic levels of pressures with minimal symptomatic effects. However, acute increases in pulmonary pressure, as with massive PE, cause immediate overt distress and, in many cases, collapse and death (Fig. 64-1).

Two keys to the diagnosis of pulmonary hypertension are a high degree of suspicion raised by the clinical history and physical findings that suggest right ventricular (RV) failure and systemic congestion (see also Chapter 1). Increased PAPs are reflected in elevated RV systolic and, later, diastolic pressures. Because of chronically elevated RV systolic and diastolic pressure, the geometry of the right ventricle is altered, usually sufficiently to render the tricuspid valve incompetent. Tricuspid regurgitation creates a prominent *v* wave in the jugular venous pulse. Generally, the jugular venous pressure will be increased substantially in these patients, with filling of the deep neck veins above the clavicle visible with the patient sitting upright. Significant tricuspid regurgitation can also often be appreciated as pulsation of the liver. Less common and subtler physical findings with pulmonary hypertension are an RV precordial

Box 64-1 2003 World Health Organization Classification of Pulmonary Hypertension

Pulmonary Artery Hypertension

Idiopathic pulmonary hypertension
Familial pulmonary hypertension

- Collagen vascular disease
- Congenital systemic-to-pulmonary shunts
- Hepatic portal vein hypertension
- HIV infection
- Drugs and toxins
- Others

Associated with venous or capillary involvement

- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

Pulmonary Venous Hypertension

Left atrial, left ventricular, aortic valve, and mitral valve disease
Cor triatriatum
Left atrial myxoma

Pulmonary Hypertension associated with Hypoxemia

Chronic obstructive lung disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude

Pulmonary Arterial Hypertension due to Chronic Thrombotic or Embolic Disease

Miscellaneous

- Sarcoidosis
- Compression of pulmonary vessels
- Sickle cell disease
- Others

HIV, human immunodeficiency virus.
Adapted from Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based practice guidelines. *Chest*. 2004;126:7S–10S.

heave, an RV third heart sound, and increased intensity of the pulmonic component of the second heart sound.

Differential Diagnosis

Among numerous causes of pulmonary hypertension, the most common are chronic left ventricular dysfunction with or without valve disease and chronic lung diseases (see Box 64-1). These are usually recognized by history, and treatment is focused on the primary disease. All potential causes of secondary pulmonary hypertension should be excluded before a diagnosis of IPAH or FPAH is considered.

Diagnostic Approach

Table 64-1 lists the diagnostic tests and potential findings in the evaluation of patients with suspected pulmonary hypertension. Critical information on the degree and possible cause of pulmonary hypertension can be gained from a transthoracic echocardiogram. PAP can be estimated from the Doppler-derived velocity of tricuspid regurgitation and from the degree of RV dilation and hypertrophy. Echocardiography also provides data on left ventricular function, mitral valve structure and function, and the existence of an intracardiac shunt, all clues to the possibility that the pulmonary hypertension is an effect of cardiac disease.

Information about primary pulmonary disease must also be pursued as a potential cause for pulmonary hypertension. Pulmonary function testing provides information on parenchymal and functional lung diseases. Ventilation/perfusion (V/Q) scans are useful in excluding chronic PE as the underlying etiology for pulmonary hypertension. The need to document thromboembolism is so critical to treatment and survival that pulmonary angiography must be considered for every patient with otherwise undiagnosed pulmonary hypertension. However, particularly in patients with severe pulmonary hypertension, pulmonary angiography presents an increased risk of morbidity and death. For this reason, pulmonary angiography in this setting should be performed in a center and by an operator with experience in dealing with these patients.

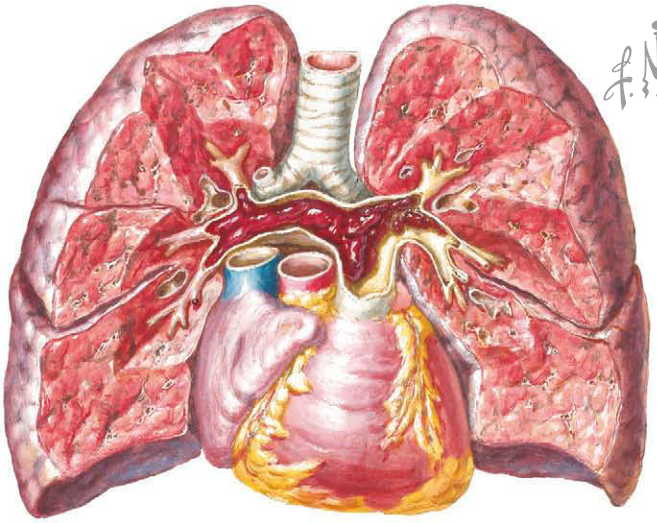
Evaluation by teams experienced with pulmonary hypertension should always be considered for patients who have disease that evades diagnosis by noninvasive means. For most of these patients diagnosed as having IPAH or FPAH, the prognosis is grave and survival depends on sophisticated evaluation and management. Key to this evaluation are the levels of pulmonary hypertension and PVR and documentation of the effects of vasodilators on PVR and PAP. Testing the effect of vasodilators on PVR is accomplished in part by right-sided heart catheterization. Response to acute vasodilators such as nitric oxide, adenosine, and epoprostenol is associated with subsequent response to long-term therapy with various drugs (Table 64-2). The desired response to a vasodilator challenge is reduction of PAP, with associated increases in cardiac output but without systemic hypotension or hypoxemia.

Management and Therapy

The severity of pulmonary hypertension and the patient's degree of functional limitation are accurate predictors of prognosis. Pulmonary hypertension most often is a progressive disease, particularly in individuals with IPAH and FPAH in whom their disease virtually always leads to death.

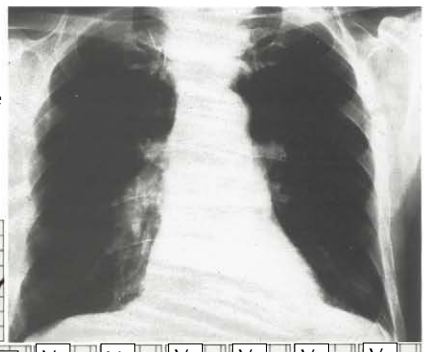
OPTIMUM TREATMENT

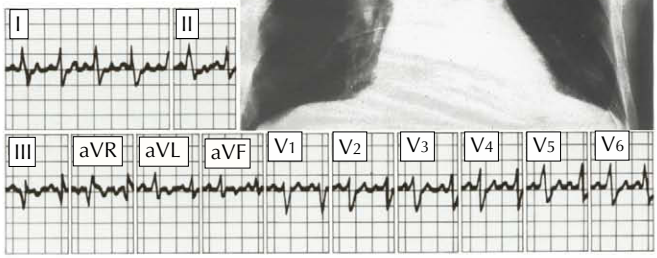
Several important decisions must be made when the diagnosis of either IPAH or FPAH is confirmed. First, warfarin anticoagulation is recommended for all patients without contraindications, because it doubles survival time. A second important consideration is whether genetic testing should be performed on the patient and at-risk relatives. The known mutations associated with familial causes of pulmonary hypertension are transmitted in an autosomal-dominant fashion, meaning that first-degree relatives have a 50% risk of carrying the causative mutation. Penetrance is generally incomplete, and overall a penetrance rate of 20% has been reported. Thus, the chance of



Saddle embolus completely occluding the RPA and partially obstructing main and left arteries

X-ray film showing dense shadow of the RPA with increased luminescence of peripheral lung fields





Characteristic electrocardiographic findings in acute pulmonary embolism. Deep S_1; prominent Q_3 with inversion of T_3; depression of ST segment in lead II (often also in lead I) with staircase ascent of ST_2; T_2 diphasic or inverted; right-axis deviation; tachycardia

Figure 64-1 *Massive pulmonary embolization.* RPA, right pulmonary artery.

Table 64-1 Evaluation of Patients with Suspected Pulmonary Hypertension

Diagnostic Test	Potential Findings
Electrocardiography	P pulmonale (P wave in lead II greater than 3 mV) Right-axis deviation R wave greater than S wave in lead V_1
Chest radiography	Enlarged pulmonary arteries RV enlargement Parenchymal lung disease Skeletal abnormalities
Echocardiography	PAP estimated by TR velocity RV hypertrophy RV enlargement LV function/LA size Valvular disease Imaging to detect ASD or VSD
Pulmonary function testing with ABG	COPD Restrictive lung disease Hypoventilation
Ventilation/perfusion lung scan, CT angiogram (MRI in special cases)	To diagnose or exclude pulmonary embolism
PA angiography	For further evaluation of indeterminate lung scan to exclude thromboembolism
Cardiac catheterization	Pressure determinations at rest and after inhalation of 100% oxygen Pulmonary wedge pressure Response to vasodilators

ABG, arterial blood gas; ASD, atrioventricular septal defect; COPD, chronic obstructive pulmonary disease; CT, computed tomography; PA, pulmonary artery; PAP, pulmonary artery pressure; LA, left atrial; LV, left ventricular; MRI, magnetic resonance imaging; RV, right ventricular; TR, tricuspid regurgitation; VSD, ventricular septal defect.

Table 64-2 Approved Treatments for Pulmonary Artery Hypertension and Their Common Side Effects

Drug and Year Approved	Drug Class	Route of Administration	Doses	Frequency	Common Side Effects	Comments
Epoprostenol (Flolan), 1995	Prostaglandins	IV	Initiate 1–2 ng/kg/min IV and titrate to efficacy and side effects.	Continuous IV	Central venous catheter infection and malfunction; side effects related to prostacyclin*	Therapy complicated, and it is recommended that patients be referred to PAH treating centers for initiation and management; effective in patients with severe PAH and RHF; agent most frequently used as rescue therapy; long-term survival data available
Bosentan (Tracleer), 2001	ERA	PO	62.5 and 125 mg	BID	Decrease in hematocrit and hemoglobin; headache, hepatotoxicity, hypotension, peripheral edema	Need LFTs checked monthly, hematocrit, hemoglobin every 3 months; contraindicated with cyclosporine and glyburide, decreases effectiveness of oral hormonal contraceptives; drug interaction with sildenafil; long-term observational survival data available
Treprostinil (Remodulin SC), 2002	Prostaglandins	SC	Initiate 1.25–2.5 ng/kg/min SC; can reduce to 0.625 ng/kg/min if not tolerated.	Continuous SC	Injection site pain and erythema; side effects related to prostacyclin*	Effective for PAH, but site pain can affect majority of patients; experienced centers have reported successful outcome in managing patients with site pain issues; long-term survival data available
Trepostinil (Remodulin IV), 2004	Prostaglandins	IV	Initiate 1.25–2.5 ng/kg/min IV; can reduce to 0.625 ng/kg/min if not tolerated.	Continuous IV	Central venous catheter infection and malfunction; leg pain; side effects related to prostacyclin*	Therapy less complicated to manage than Flolan; need higher dose than Flolan for transitioning patients to achieve similar efficacy; long-term data not yet available
Iloprost (Ventavis), 2004	Prostaglandins	Inhaled	2.5 and 5 μg	6–9 inhalations per day while awake; not more than q2hr	Cough, flushing, headache, hypotension, nausea, transient jaw pain	Selective delivery of prostacyclin into lungs; compliance can be an issue with need for frequent treatments; good as combination treatment with oral therapies
Sildenafil (Revatio), 2005	PDE-5 Inhibitor	PO	20 mg	TID	Diarrhea, epistaxis, flushing, headache	Contraindicated with nitrates; some patients may require increased dose titration. Doses >20 mg TID are not recommended.
Ambrisentan (Letairis), 2007	ERA	PO	5 and 10 mg	QD	Headache, nasal congestion, peripheral edema, sinusitis	Need LFTs checked monthly but less incidence of LFT abnormality compared with other ERAs; more reported incidence of edema compared with other ERAs; decreases effectiveness of oral hormonal contraceptives; no drug interaction observed in combined treatment with sildenafil

*Side effects related to prostacyclin include chest pain, diarrhea, dizziness, flushing, headache, hypotension, jaw pain, nausea, and tachycardia.
BID, twice a day; ERA, endothelin receptor antagonist; IV, intravenous; LFTs, liver function tests; PAH, pulmonary artery hypertension; PDE-5 inhibitor, phosphodiesterase-5 inhibitor; PO, orally; QD, every day; RHF, right heart failure; SC, subcutaneous; TID, three times a day.
Adapted from Park MH. Advances in diagnosis and treatment in patients with pulmonary arterial hypertension. Catheter Cardiovasc Interv. *2008;71:205–213*, with permission from John Wiley & Sons.

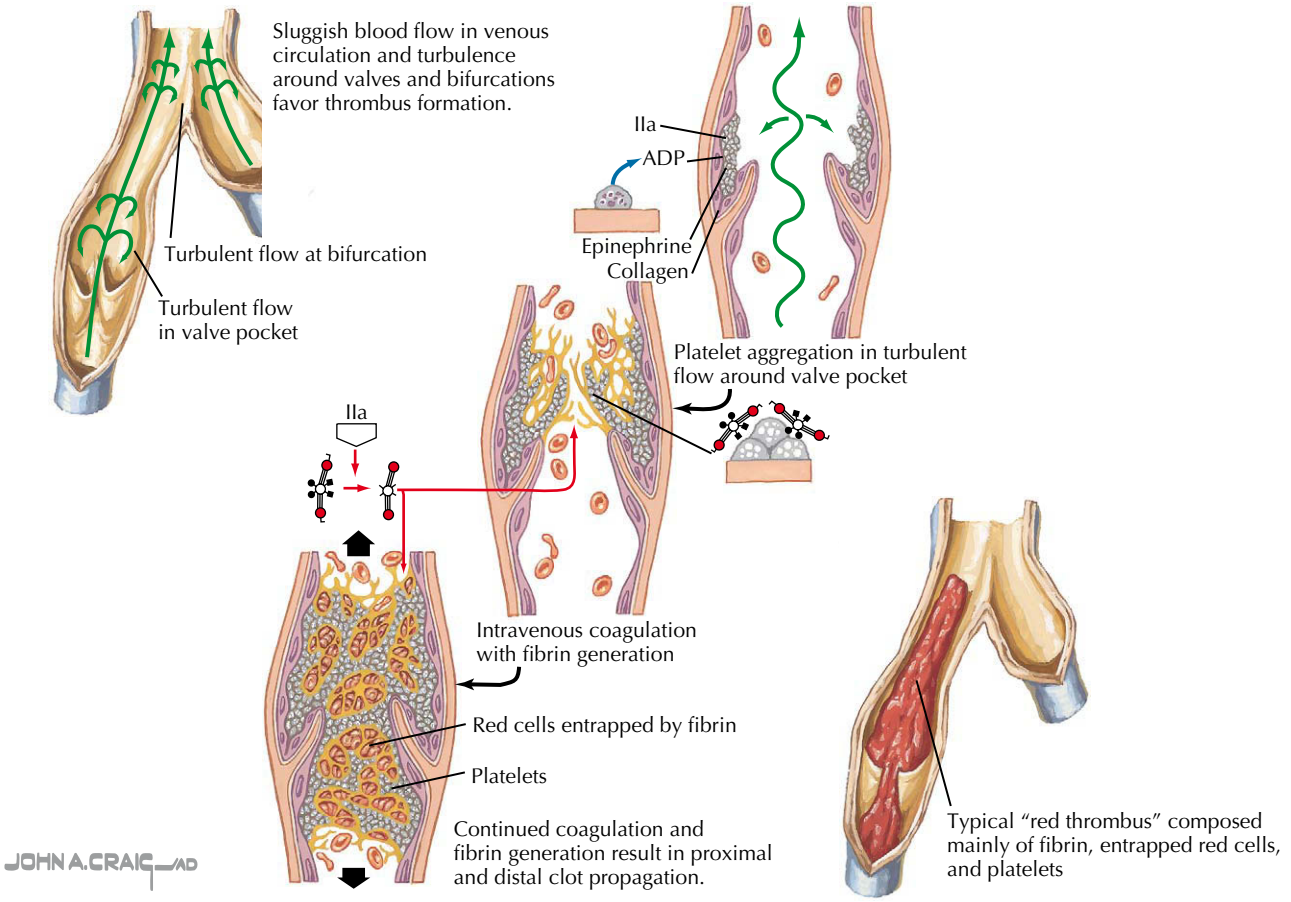


Figure 64-2 *Deep venous thrombosis.* ADP, adenosine diphosphate; IIa, thrombin A (activated coagulation factor II) or prothrombin.

a first-degree relative developing pulmonary hypertension is 10% (50% × 0.20 = 10%). Testing can be helpful if potential family members at risk would benefit from early diagnosis, but appropriate genetic counseling must be available if testing is done. A summary of laboratories performing genetic testing for the currently identified mutations is described in Additional Resources. The third decision is whether to use medications to lower PAP. The currently available drugs, drug profiles, and drugs for which there are data on improvement in survival are listed in Table 64-2. Patients who respond to calcium channel blockers have a 95% survival rate at 5 years. Because treatment is complicated and requires a team approach, it is recommended that these patients be referred to a center with substantial clinical experience treating patients with pulmonary hypertension.

Despite improved survival rates with anticoagulants, vasodilators, and other drug therapies, a large subset of patients has no improvement in hemodynamic parameters or symptoms. These patients are candidates for lung or heart-lung transplantation. The post-transplantation mortality rates for patients with severe pulmonary hypertension are higher than the rates for patients who undergo organ transplantation for other reasons. The 1-year survival rate for those with pulmonary hypertension is approximately 65%.

Individuals with pulmonary hypertension caused by chronic PE constitute an important subset of patients. These patients benefit from pulmonary thromboendarterectomy followed by long-term anticoagulant therapy.

PULMONARY THROMBOEMBOLISM

Etiology and Pathogenesis

PE occurs when thrombi migrate from the deep veins of the legs through the right side of the heart into the pulmonary arteries. The fundamental pathophysiologic mechanisms all favor thrombosis in peripheral veins. These may involve one or a combination of factors, including venous stasis, hypercoagulability, and vessel wall injury. These three factors are termed *Virchow's triad*. Inflammation is now also considered an inherent part of this syndrome. Stasis and turbulence around venous valves promote platelet deposition, platelet aggregation, and formation of a fibrin thrombus. The thrombi formed include entrapped red blood cells, giving the thrombus a deep red color. Pulmonary thrombi, when recovered intact from the lungs at autopsy, most often are a "cast" of the peripheral vein, complete with the impressions formed by the venous valves (Fig. 64-2).

Clinical Presentation

PE should be suspected in patients with acute dyspnea, chest pain, syncope, or hemoptysis. Patients may also present in cardiovascular crisis with hypotension, shock, mental status changes, or cardiac arrest. Death within minutes to hours occurs in approximately 30% of cases. Risk factors that reinforce clinical evidence of PE include advanced age, immobilization, and a history of recent surgery, malignant neoplasms, and prior thromboembolic disease. Recent travel, obesity, pregnancy, and a family history of thrombosis are also clues. In some seriously ill or debilitated patients, the presentation may be subtle, with events such as mental status changes, fever, or otherwise unexplained hypoxemia leading ultimately to the diagnosis.

Differential Diagnosis

Acute and chronic PE can mimic pulmonary artery hypertension; thus, the differential diagnoses for these disorders overlap. Pneumonia, acute heart failure, myocardial infarction, pericarditis, aortic dissection or rupture, esophageal rupture, and pleural disease must be considered.

Diagnostic Approach

Patients who present with a high clinical probability of acute PE and any evidence of hemodynamic compromise, including sinus tachycardia or mild hypoxemia, must be treated immediately with intravenous heparin, unless there is a contraindication. Diagnostic tests can then be done to provide definitive proof of presence or absence of PE or deep vein thrombosis (DVT). Furthermore, patients who present with hemodynamic or pulmonary compromise must be stabilized with oxygen therapy and ventilatory and vasopressor support as needed.

A large number of approaches to diagnosis of PE have developed, including several based upon sophisticated imaging techniques. However, there is as yet no single noninvasive test with perfect sensitivity and specificity for PE in every patient. The gold standard for PE diagnosis is pulmonary arteriography. This invasive procedure involves placement of a catheter into the pulmonary artery and injection of a contrast medium (Fig. 64-3). The technical and logistical challenge and perceived risk of the procedure have prevented its wide application for diagnostic screening.

The current and best approach to diagnosis of PE, therefore, enhances the technical information from tests by first classifying individual patients according to a formal analysis of pre-test probability. An expert panel supported by the American College of Physicians and the American Academy of Family Physicians has outlined this process in guidelines published in 2007.

The initial diagnostic intervention, therefore, is the use of a validated clinical prediction instrument to estimate the patient's pre-test probability of either DVT or PE (Figs. 64-4 and 64-5). The "Wells Prediction Rules" are recommended by the guidelines (Table 64-3). Upon the establishment of estimated pre-test probability, the remainder of the evaluation continues and is based upon appropriate testing.

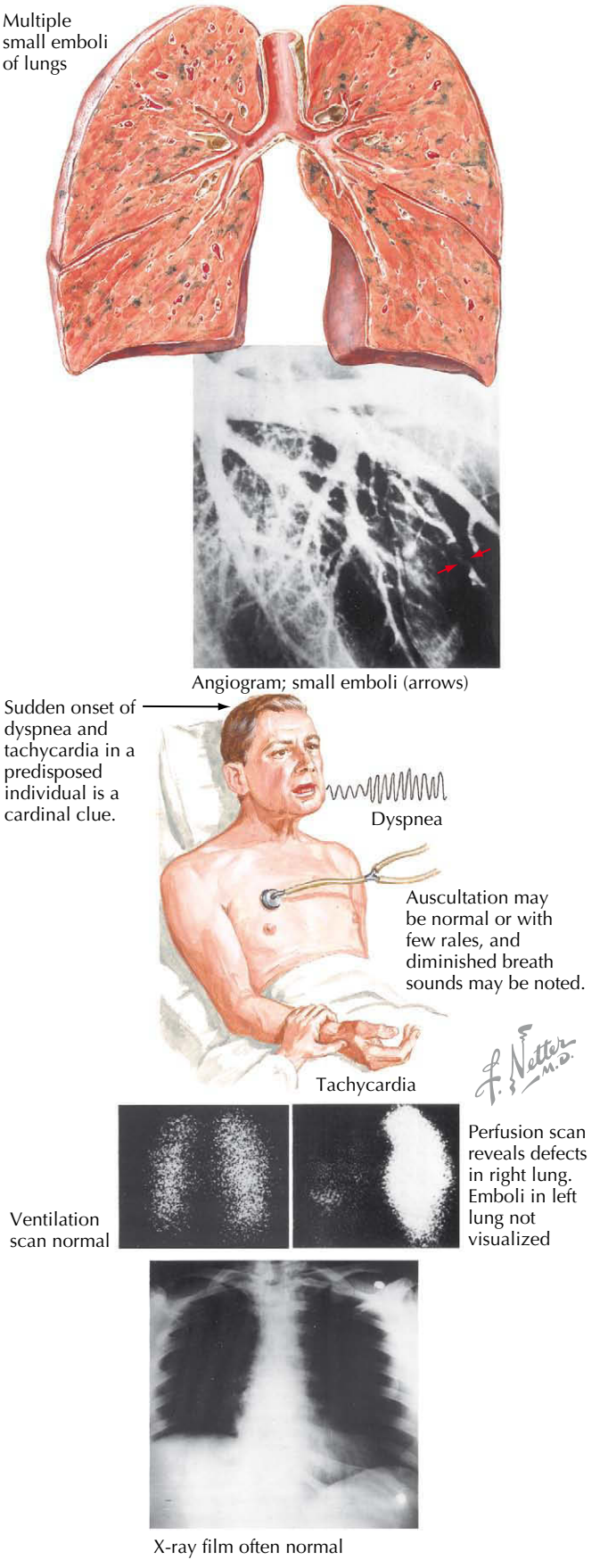


Figure 64-3 *Pulmonary embolism of lesser degree without infarction.*

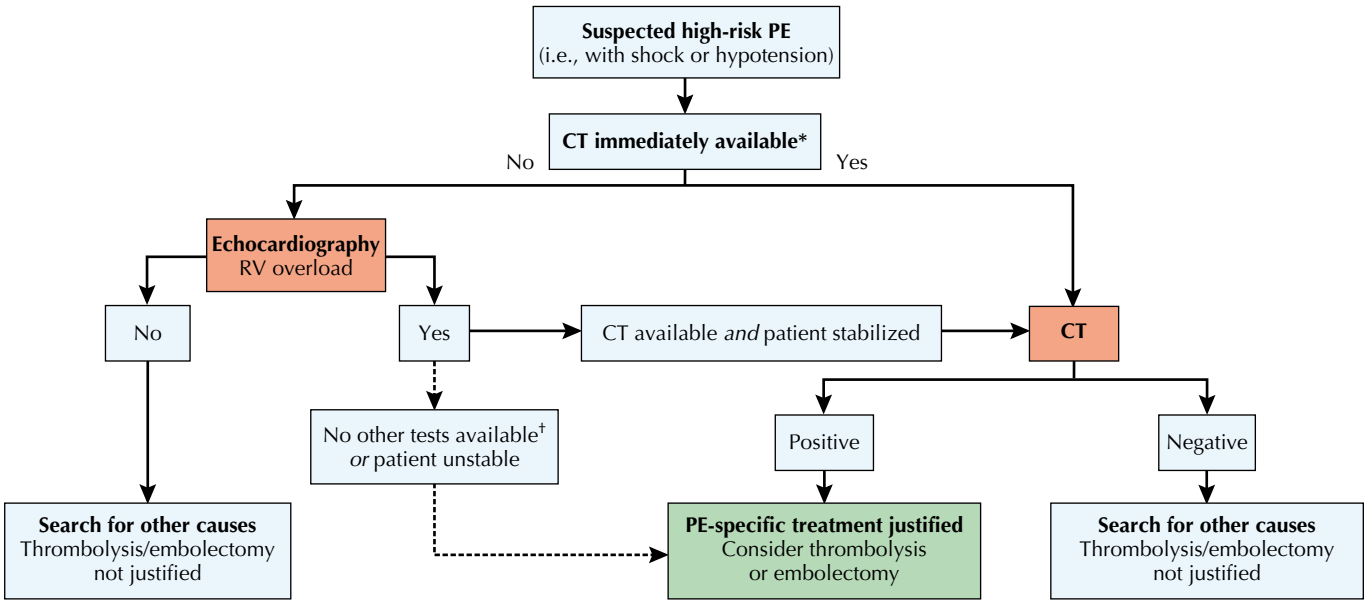


Figure 64-4 *Algorithm for patients with suspected high-risk pulmonary thromboembolism (PE).* CT, computed tomorgraphy; RV, right ventricular. *CT is considered not immediately available if the critical condition of a patient allows only bedside diagnostic tests. †Transoesophageal echocardiography may detect thrombi in the pulmonary arteries in a significant proportion of patients with RV overload and PE that is ultimately confirmed by multidectector CT; confirmation of DVT with bedside Compression Ultrasonography of leg veins might also help in decision-making. Adapted from Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J.* 2008;29:2276–2315.

A reasonable diagnostic algorithm using this approach was validated in the Christopher Study of 3306 patients with suspected PE (Table 64-4). This group used a modification of the Wells Rules whereby they classified patients as "PE unlikely" if the score was 4 or lower and "PE likely" if the score was greater than 4. The algorithm used this modified Wells score, D-dimer testing, and either single-detector row or multidetector row CT to determine the indication for treatment or no treatment for PE. The results showed a low risk of venous thromboembolism in patients not treated based upon the algorithm (1.3% in 3 months). By protocol, patients with a modified Wells score suggesting "PE unlikely" and D-dimer levels less than 500 ng/mL did not undergo CT and were not treated with anticoagulation. In this large group ($N = 1028$), there were five late events, four PEs, and one DVT.

Other diagnostic tests may also be useful in selected circumstances. In the acute setting, the traditional initial diagnostic tests are ECG and chest radiography. Although neither is diagnostic of acute PE, both can yield clues to the astute clinician. Classic changes of acute massive pulmonary embolism on ECG are sinus tachycardia, right-axis deviation, and new incomplete right bundle branch block, producing a pattern sometimes described as "S_1-Q_3-T_3" (see Fig. 64-1, right). Unfortunately, this pattern is noted in a minority of patients with documented PE. More commonly, the ECG shows only nonspecific ST- and T-wave changes or is normal. Chest films in patients with acute PE may be normal or show atelectatic segments and patchy infiltrates. Rarely, pleural-based infiltrates associated with pulmonary infarction are documented.

Transthoracic echocardiography can demonstrate RV hypokinesis and dilation and can be a rapid, noninvasive way to heighten the suspicion of acute PE. Doppler measures of tricuspid regurgitant velocity are reliable estimates of pulmonary systolic pressure (see also Chapter 6). These data help establish the hemodynamic effects of acute PE. Rarely, a thrombus in transit in the right ventricle can be imaged. However, there are many causes of RV dysfunction and tricuspid regurgitation other than PE, and, conversely, echocardiograms may be normal in patients with small emboli.

The most long-standing imaging procedure for suspected PE is V/Q lung scanning, but this technique is most useful in a minority of patients. The consensus in most of the literature is that normal lung scan results essentially exclude the diagnosis of PE. Unfortunately, PE is commonly a complication of other disease processes affecting the lungs, meaning that few ventilation scans are normal in those patients evaluated. Therefore, in only a minority of patients with suspicious clinical presentation but no PE is the V/Q scan normal. Scans that show multiple segmental or lobar defects in flow with normal ventilation, on the other hand, reflect PE in 85% to 90% of cases (with PE documented subsequently by pulmonary angiography). However, scans of many patients with suspected PE are neither normal nor high probability. These intermediate, or indeterminate, probability scans are not diagnostic and must be

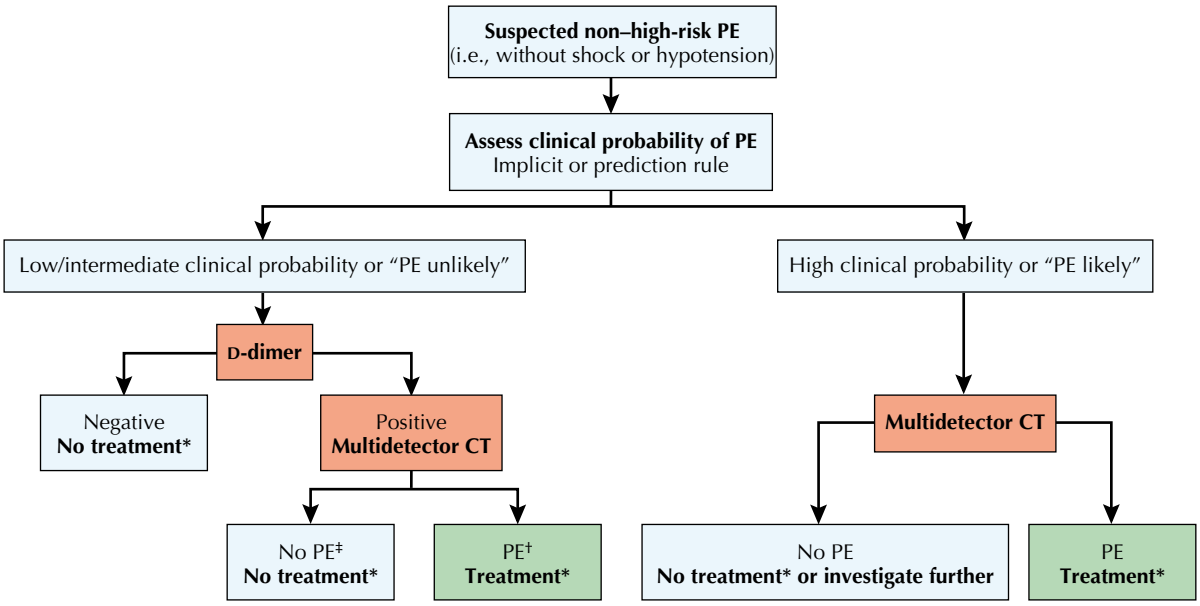


Figure 64-5 *Algorithm for patients with suspected non-high-risk pulmonary embolism.* Two alternative classification schemes may be used to assess clinical probability: a three-level scheme (clinical probability low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with a low clinical probability or a "PE unlikely" classification, while highly sensitive assays may be used in patients with a low or intermediate clinical probability of PE. Plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients. CT, computed tomography; PE, pulmonary thromboembolism. *Anticoagulant treatment for PE. †CT is considered diagnostic of PE if the most proximal thrombus is at least segmental. ‡If single-detector CT is negative, a negative proximal lower limb venous compression ultrasonography is required in order to safely exclude PE; if multidetector CT is negative in patients with high clinical probability, further investigation may be considered before withholding PE-specific treatment. Adapted from Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J.* 2008;29:2276–2315.

Table 64-3 Variables Used to Determine Patient Pre-Test Probability for Pulmonary Embolism*

Variable	Value
Clinical signs and symptoms of DVT	3.0 points
PE more likely than an alternate diagnosis	3.0 points
Heart rate greater than 100 beats/min	1.5 points
Immobilization or history of surgery in the previous 4 weeks	1.5 points
Previous DVT or PE	1.5 points
Hemoptysis	1.0 point
Malignant neoplasm (at treatment, treated in the last 6 months, or palliative)	1.0 point

*Low probability, <2.0 points; moderate probability, 2.0–6.0 points; high probability, >6.0 points.
DVT, deep vein thrombosis; PE, pulmonary embolism.
With permission from Rodger M, Wells PS. Pulmonary embolism. Thromb Res. *2001;103:V225–V238.*

supplemented to confirm or exclude PE. A highly specific diagnosis is necessary, because the only alternative is empiric treatment with full anticoagulation, a treatment that carries the risk of serious complications.

The place for V/Q scanning in evaluation of suspected PE has been challenged by contrast-enhanced spiral CT of the chest. Spiral CT is highly sensitive for emboli in the proximal pulmonary arteries and large branches; however, emboli in small, distal arteries are not reliably detected. Hence, the sensitivity of CT varies. Nonetheless, CT has gained widespread acceptance because it has a much higher degree of specificity than V/Q scanning, reliably demonstrates the large emboli that are probably the most clinically important, and can document an array of alternate diagnostic possibilities. Moreover, CT scans are generally available more quickly and can be more easily interpreted than V/Q scans. MRI scans may be useful in the diagnosis when reducing exposure to radiation is of paramount importance (e.g., pregnancy).

Another alternative is the use of venous ultrasound imaging of the leg. This approach is based on the knowledge that virtually all large PEs originate in the deep veins of the legs. When spiral CT or lung scans suggest low probability of PE and ultrasound studies repeated serially over a 2-week period remain negative, the risk of recurrent PE is so low as to justify withholding anticoagulation. Unfortunately, this approach is inconvenient and costly, and for this reason it is used routinely in only a few centers.

D-dimer, a degradation product of cross-linked fibrin measured in blood, is a sensitive marker for thrombosis. However, the test also represents "acute-phase reactivity," as found in many disease states other than PE. A negative D-dimer assay result is useful in clinically low-risk patients who have a low pre-test probability—reliably predicting the absence of PE. Even in patients with a high pre-test probability, a negative D-dimer test result has only a 64% negative predictive value. Because the sensitivity and specificity of each of these tests are imperfect, the concept of pre-test probability is critical (see also Chapter 1).

Management and Therapy

The goals in treating PE are to stabilize critically affected patients and then prevent recurrence of emboli by treating the underlying venous thrombosis. Patients with hypotension, shock, cardiac arrest, or refractory hypoxemia may require inotropic support and mechanical ventilation. In this subset of unstable patients, thrombolysis may be lifesaving. Although multicenter studies have shown a mortality benefit for thrombolytic therapy in unstable patients, no such benefit is seen (in comparison with conventional therapy using heparin; see later discussion) in stable patients with PE. Patients with refractory shock or hypoxemia who do not respond to thrombolysis, or who have contraindications to thrombolytic therapy but not surgery, are candidates for surgical thrombectomy. Because the mortality rate is high, surgical thrombectomy is a consideration for only the highest-risk patients. Percutaneous catheter suction or dislodgement of massive proximal emboli may be other options, although no randomized studies using these approaches have been conducted.

OPTIMUM TREATMENT

Fortunately, most patients who survive the first few minutes after PE are relatively stable and can be evaluated and managed in a deliberate manner. The accepted treatment initially or after thrombolysis is heparin. Unfractionated heparin or low-molecular-weight heparin should be started when the diagnosis is considered, assuming there are no serious contraindications, such as active bleeding; history of recent surgery, stroke,

Table 64-4 Decision Matrix for Patients with Suspected Pulmonary Embolism

	D-Dimer Negative	D-Dimer Positive	CT Negative	CT Positive
Wells score ≤ 4 "PE unlikely"	No CT No treatment	CT	No treatment	Treatment
Wells score > 4 "PE likely"	CT	CT	No treatment	Treatment

CT, computed tomography; PE, pulmonary embolism.
Approach taken from Writing Group for the Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. *2006;295:172–179.*

intracranial malignancy, or documented heparin-associated thrombocytopenia. Contraindications to thrombolytic therapy for patients with PE are the same as those for acute myocardial infarction (see Chapter 14). The dose of unfractionated heparin should be adjusted for weight with an initial bolus of 80 U/kg followed by an infusion of 18 U/kg/hr by intravenous infusion (dosing may vary between institutions and clinical laboratories). Subsequent adjustments should be made to achieve an activated partial thromboplastin time of 1.5 to 2.5 times control or to a plasma heparin level of 0.3 to 0.7 IU/mL anti-Xa activity. Use of low-molecular-weight heparin is increasingly popular because of its ease of administration, reduced laboratory costs, and reduced propensity to precipitate thrombocytopenia. Regardless of the type of heparin used, the administration should be aggressively managed, because inadequate doses are associated with increased recurrence of PE. Heparin-associated thrombocytopenia is a potentially serious complication of heparin therapy. Platelet counts of all patients on heparin should be monitored frequently (at baseline, within 24 hours of initiation, and then every other day or every third day thereafter, depending on the individual physician practice standards) to surveil for heparin-induced thrombocytopenia with or without thrombosis. If suspected, all sources of heparin should be discontinued and direct inhibitors of thrombin, such as argatroban or lepirudin, can be initiated.

Heparin administration should continue for a minimum of 5 days after the initiation of warfarin therapy. This allows time for adequate reduction of the plasma procoagulant factors II, VII, IX, and X and prevents the state of thrombophilia that occurs early after initiation of warfarin therapy when the anticoagulant factors S and C are reduced more quickly than the procoagulant factors. The intensity of warfarin therapy should be sufficient to prolong the prothrombin time international normalization ratio to 2 to 3. Treatment duration is individualized but should continue for a minimum of 3 months in all patients until possible precipitating issues have resolved.

Placement of an inferior vena cava filter device should be considered in several settings. These devices can be used in patients with absolute contraindications to anticoagulation, either at the time of initial therapy or thereafter. In addition, inferior vena cava filters reduce the likelihood of recurrent PE in patients who are undergoing adequate anticoagulation or who have had multiple PEs over time.

AVOIDING TREATMENT ERRORS

Major pitfalls in management of patients with pulmonary artery hypertension and PE occur with the initial clinical assessment. Both conditions have protean presentations that challenge even the most alert clinician. With pulmonary artery hypertension, minor symptoms at presentation can delay critical early therapy. Treatment of PE requires anticoagulant medications that are difficult to administer. Careful attention is required to guarantee adequate anticoagulation without unnecessary risk of bleeding. Platelet count during heparin therapy must be carefully monitored.

FUTURE DIRECTIONS

The discovery that mutations in the bone morphogenic receptor II gene are associated with FPAH has increased understanding of the disease's familial transmission. This protein probably also has a role in nonfamilial causes of pulmonary artery hypertension. Basic studies of vascular biology will continue to bring new therapies for safer and more convenient treatment of pulmonary hypertension.

For thromboembolism, the challenge is improvement of prevention and detection of DVT in populations at increased risk. Diagnostic testing for PE will improve as experience with high-definition imaging evolves. The new antithrombotic agents being developed are easier to manage than warfarin and have a reduced risk of heparin-associated thrombocytopenia.

ADDITIONAL RESOURCES

Faber JW, Loscalzo J. Mechanisms of disease: pulmonary arterial hypertension. *N Engl J Med.* 2004;351:1655–1665.

A concise review of the multiple pathophysiologic elements involved in development of IPAH and FPAH.

Konstantinides S. Clinical practice. Acute pulmonary embolism. *N Engl J Med.* 2008;359:2804–2813.

Provides a concise review of the current diagnostic and treatment strategies used to document PE and reviews the evidence that supports these strategies.

Lloyd JE, Phillips J. *BMPR2*-related pulmonary arterial hypertension. *GeneReviews*. Available from: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pph> (last revised 7 November 2007). Accessed 25.03.10.

A summary of genetic mutations and testing sites for mutations for pulmonary artery hypertension. Includes a discussion of medical treatment of pulmonary artery hypertension. This is from the Research Registry of PPH Families.

Newman JH, Phillips 3rd JA, Lloyd JE. Narrative review: the enigma of pulmonary arterial hypertension: new insights from genetic studies. *Ann Intern Med.* 2008;148:278–283.

A review of new findings linking a receptor in the transforming growth factor-β superfamily with pulmonary artery hypertension. This article discusses the potential treatment opportunities associated with this discovery.

Pulmonary Hypertension Association. Available from: <http://www.phassociation.org>; 2008; Accessed 25.03.10.

Provides a registry of physicians with special interest in pulmonary artery hypertension that includes their self-provided information on credentials and experience.

EVIDENCE

Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA.* 2006;295:172–179.

Prospective cohort study of consecutive patients with clinically suspected acute PE. A diagnostic management strategy using a clinical decision rule, D-dimer testing, and CT imaging was effective in directing management. Its use was associated with a low risk for subsequently fatal and nonfatal venous thromboembolism.

McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation*. 2006;114:1417–1431.

This "Contemporary Review in Cardiovascular Medicine" includes a helpful algorithm for risk assessment and the appropriate recommended medical treatment of pulmonary artery hypertension.

Qaseem A, Snow V, Barry P, et al. Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med.* 2007;146:454–458.

Snow V, Qaseem A, Barry P, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med.* 2007;146:204–210.

The above two companion articles describe diagnosis and management guidelines for venous thromboembolism. They are relatively concise and include focused information on clinical prediction rules, D-dimer testing, and imaging for both DVT and PE. Specific recommendations for choice of anticoagulant medication and duration of treatment are provided. Both articles are well-referenced.

Substance Abuse and the Heart

David A. Tate

65

Substance abuse has enormous social, economic, and medical consequences. Although abuse of both legal and illegal substances can have adverse effects on the cardiovascular system, as discussed in this chapter, it is important to note that two legal substances—tobacco and alcohol—have the greatest impact on cardiovascular health of citizens of the United States and other industrialized countries (Fig. 65-1, upper and middle).

TOBACCO

From a cardiologic perspective, given the impact of smoking on coronary artery disease, tobacco is by far the most lethal of abused substances. Although the adverse effects of smoking on atherosclerotic disease have been known for years, studies continue to emphasize the striking magnitude of the effect. The incidence of coronary disease in smokers is approximately twice the incidence in nonsmokers. The deleterious effects of smoking were recently demonstrated in the Women's Health Study, which suggested that half of all coronary deaths in women could be attributed to smoking. In primary prevention trials of the use of statins for hypercholesterolemia, coronary event rates were 74% to 86% higher in smokers than in nonsmokers. Following myocardial infarction (MI), recurrent MI is twice as frequent among those who continue to smoke compared with those who quit. It can therefore be argued that smoking cessation is likely to be more effective than statins for primary prevention of cardiovascular disease and more effective than aspirin, β-blockers, or angiotensin-converting enzyme inhibitors for secondary prevention. Despite a decline in smoking in recent decades, approximately 20% of adult Americans remain addicted to tobacco. Moreover, smoking among adolescents, particularly young women, rose for several years and has shown no decline in recent years.

The medical and lay communities share a pessimistic view of smoking cessation that may not be fully justified. Caregivers must recognize that tobacco is a genuinely addictive substance, documented as such by the U.S. Surgeon General's Office. It must also be acknowledged that smokers who want to quit often fail in their attempts to stop smoking. Nevertheless, many smokers do ultimately succeed in quitting, and by facilitating smoking cessation, the health care provider is likely to have a more salutary effect on a patient's health than with almost any other medical intervention. Counseling by physicians makes a difference, and the efficacy of counseling is directly related to the intensity of the counseling program. Efficacy can be greatly increased by the use of questionnaires, written materials, and follow-up. Smoking cessation rates are also substantially increased when a cardiovascular event has heightened patient concern. In a group of smokers with MI, cessation rates of 24.5% with standard advice and 63.2% with intensive advice were achieved.

Several pharmacologic adjunctive agents for smoking cessation are available that increase success rates beyond counseling alone. In a standard outpatient setting, modest but significant success has been achieved with nicotine replacement therapy, with abstinence rates of approximately 20% at 1 year. Considerable success has also been achieved with bupropion, which affects noradrenergic and dopaminergic function in the central nervous system; this has resulted in approximately a twofold increase in successful smoking cessation. Modest additional efficacy has been apparent when nicotine replacement therapy is combined with bupropion. The most recently approved pharmacologic therapy for smoking cessation is varenicline. This partial agonist of nicotinic acetylcholine receptors seems to be somewhat more effective than bupropion, with abstinence rates at 1 year of 23% versus 16% with bupropion in one study. Side effects of nausea or abnormal dreams may limit therapy, however, and there have been reports of suicidal thoughts and erratic behavior in some patients.

Regardless of the method, it is clear that determining a specific "quit day" enhances the chance of success, as opposed to gradual tapering. Thus, physicians should advise their patients on the hazards of smoking and assess their readiness to quit. In those who seem motivated, intensive initial counseling and follow-up supportive care should be provided and adjunctive pharmacologic therapy offered. Given the remarkable reduction in cardiovascular morbidity and mortality that occurs with smoking cessation, aggressive efforts at helping patients to stop smoking are warranted.

ALCOHOL

Alcohol abuse takes an enormous toll, with the strictly medical effects (e.g., liver disease, pancreatitis) compounded by the sociobehavioral health effects (e.g., suicide, homicide, trauma, domestic abuse). The effect of alcohol on the heart, however, is complex, with a mix of adverse and possibly beneficial effects.

The apparent beneficial effect of modest alcohol intake was first noted in France, where a surprisingly low coronary disease mortality rate was observed despite a high intake of dietary fat. This observation came to be called the "French paradox." Since this initial observation, a J-shaped relationship between alcohol intake and total mortality has been defined. The initial descending portion of the curve derives from the reduced cardiovascular mortality associated with modest alcohol intake (one to three drinks per day). Although the effect may be somewhat more apparent with red wine (and related to the potential cardioprotective effects of nonalcohol components of red wine), most evidence suggests that the majority of the beneficial effect is from alcohol per se. The mechanism may relate to a variety of factors, including increased high-density lipoprotein cholesterol, decreased low-density lipoprotein cholesterol, antioxidant effects, decreased platelet aggregation, and enhanced fibrinolysis.

It is important to note that despite this finding, there are no controlled trials that suggest a benefit from advising or instigating modest alcohol intake. The potential beneficial effect must be weighed against the catastrophic effect of immoderate

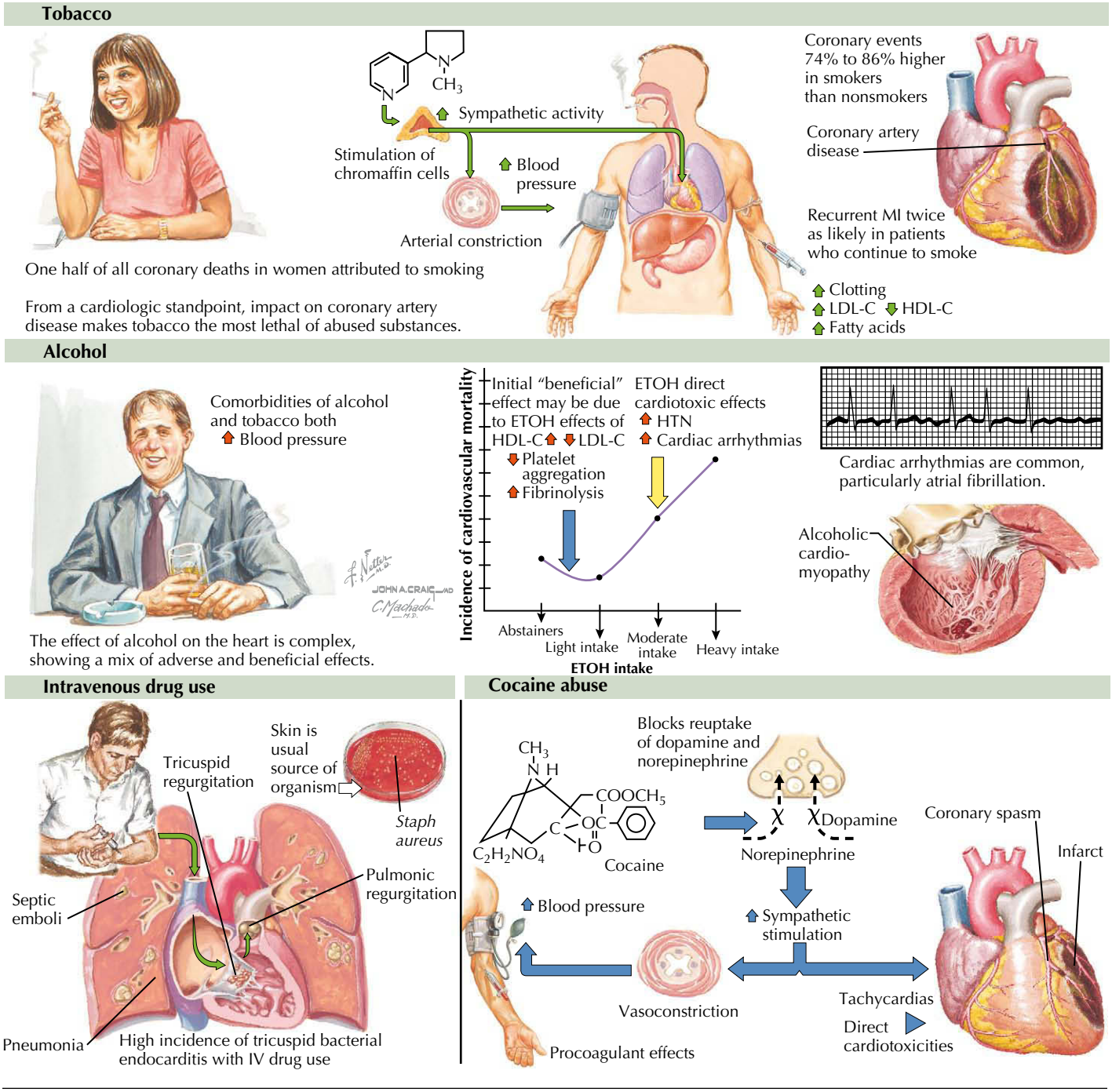


Figure 65-1 *Substance abuse and the heart.* ETOH, ethyl alcohol; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

consumption or even of moderate consumption in at-risk segments of the population (e.g., genetic risk for alcoholism, women of childbearing age, drivers). Thus, it is likely that an intervention trial would demonstrate both positive and negative effects, and for this reason it is unlikely that this question will ever be studied in a prospective, randomized trial.

Importantly, alcohol has numerous deleterious effects on the cardiovascular system, particularly in high doses. The most commonly encountered of these effects are alcoholic cardiomyopathy, alcohol-associated arrhythmias, and aggravation of hypertension. Ethanol and its metabolites have direct cardiotoxic effects on systolic and diastolic function. When severe, these direct cardiotoxic effects produce a clinical syndrome identical to idiopathic dilated cardiomyopathy. In general, therapy for alcoholic cardiomyopathy is similar to that used for other forms of heart failure (see Chapters 18 and 23). The cessation of alcohol intake is of paramount importance. In patients with alcohol-induced cardiomyopathy who abstain

from alcohol consumption, cardiac function stabilizes or improves in more than half. In patients who continue to consume alcohol, the disease is usually persistent and often progressive and fatal.

Alcohol use may trigger a wide range of cardiac arrhythmias, from premature atrial and ventricular contractions to ventricular fibrillation and sudden cardiac death. By far the most common arrhythmia associated with alcohol use, however, is atrial fibrillation. Indeed, this symptom has been noted commonly enough after weekends and holidays to be labeled "holiday heart." The mechanisms may include heterogeneous delayed cardiac conduction, QT prolongation, electrolyte imbalance, and excess catecholamine activity.

The most common deleterious cardiovascular effect of alcohol is its contribution to hypertension. Even low levels of alcohol intake cause a mild increase in systolic blood pressure, and in hypertensive patients the effect may be quite marked. This is of great significance given the high prevalence of both hypertension and moderate alcohol intake. At high doses, alcohol exerts a significant pressor effect and is a leading cause of reversible hypertension.

INTRAVENOUS DRUG USE

Regardless of the substance involved, intravenous (IV) drug use may cause endocarditis. Whereas other patients in whom endocarditis develops generally have a predisposing valvular lesion, the vast majority of IV drug users with endocarditis do not have such a lesion. In addition, there is some evidence from echocardiographic studies that chronic IV drug use may cause a mild degree of tricuspid and pulmonic regurgitation, even in the absence of endocarditis.

Endocarditis associated with IV drug use is usually right sided, involving the tricuspid valve. Not surprisingly, therefore, IV drug-related endocarditis is often associated with pneumonia or septic pulmonary emboli. The infectious agent that causes the endocarditis is most commonly a skin organism, rather than a contaminated agent itself. *Staphylococcus aureus* is the most common organism causing endocarditis in IV drug users, comprising approximately 60% of cases (see Fig. 65-1, lower). Interestingly, cocaine use is also a predisposing factor for development of left-sided endocarditis, perhaps a result of valvular trauma from cocaine-induced extreme hemodynamic stress (as discussed in the next section), creating a nidus for bacterial infection.

COCAINE

Cocaine inhibits the reuptake of norepinephrine and dopamine at sympathetic nerve terminals. It thereby produces intense activation of the sympathetic nervous system, leading to severe hypertension and tachycardia. Cocaine also has complex interactions with cellular ion transport (sodium, potassium, and calcium), and these interactions probably contribute to the vasospastic and arrhythmogenic effects of cocaine. Finally, cocaine has procoagulant, atherosclerotic, and direct myocardial toxic effects. Therefore, although MI and ischemia are the most common complications of cocaine abuse, myocarditis, cardiomyopathy, coronary artery aneurysm, arrhythmia, aortic dissection, and stroke may also occur (see Fig. 65-1, lower).

Cocaine-induced MI or ischemia can occur via several mechanisms. In individuals with preexisting coronary disease, the severe tachycardia and hypertension associated with cocaine use may lead to a supply-demand imbalance. Even in the absence of underlying coronary disease, however, focal or diffuse coronary vasospasm may occur, mediated predominantly by stimulation of α-adrenergic receptors. Thrombosis may develop in some subjects because of endothelial disruption caused by the mechanisms just mentioned or because of direct procoagulant effects.

Cocaine-induced MI typically occurs within 3 hours of use but may occur up to 15 hours after, and acute MI up to 4 days after cocaine use has been reported. It is important to note that individuals who use cocaine over prolonged periods of time are often found to have advanced coronary atherosclerosis, out of proportion to their underlying risk factor profile. Thus, in a young individual with chest pain and a history of cocaine abuse, coronary atherosclerosis must always be considered.

Appropriate therapy for cocaine-associated cardiac toxicity must take into account the many complex pharmacologic actions of cocaine. An understandable but potentially catastrophic mistake with these patients, whose sympathetic nervous systems are stimulated by the cocaine, is the use of β-blockers. β-blockade produces unopposed α-receptor stimulation, which may lead to severe hypertension and coronary vasoconstriction. Benzodiazepines in substantial doses, along with nitroglycerin and aspirin, are the preferred therapeutic agents, followed, if necessary, by calcium channel blockers. Agents with combined α- and β-blocking effects, such as labetalol and carvedilol, remain somewhat controversial but are generally best avoided as well. As with any acute coronary syndrome, refractory patients are best treated by proceeding to coronary angiography. This is particularly preferred in patients with ST elevation not responding to nitroglycerin, because fibrinolysis may be associated with higher rates of intracranial hemorrhage in cocaine users. Refractory severe hypertension may be treated with the α-blocker phentolamine.

Antiarrhythmic drugs should be avoided if possible in patients with cocaine intoxication, because drug interactions involving electrolyte transport may lead to proarrhythmic effects or hemodynamic instability. Given the relatively short half-life of cocaine (30–60 minutes), it is generally best to simply monitor the patient until the cocaine-induced arrhythmias subside. Electrical cardioversion may be necessary for treatment of hemodynamically unstable rhythms, and adenosine is probably safe for termination of sustained supraventricular arrhythmias.

Amphetamine, LSD, and psilocybin intoxication are often associated with marked tachycardia, hypertension, and arrhythmia and are managed in much the same way as cocaine intoxication.

NARCOTICS

Depressant effects on the respiratory and central nervous systems dominate the clinical picture of narcotic intoxication. However, narcotic agents such as heroin and morphine also have potentially life-threatening cardiovascular effects. These agents act directly on the vasomotor center to reduce sympathetic activity and enhance parasympathetic activity. These agents also stimulate histamine release from mast cells and

increase electrophysiologic automaticity. Narcotic intoxication may therefore be associated with profound bradycardia and hypotension, as well as with supraventricular and ventricular arrhythmias. In addition, narcotic use may precipitate noncardiogenic pulmonary edema, which can mimic and complicate true cardiovascular effects.

Therapy for narcotic overdose is predominantly supportive. Severe hemodynamic instability is treated with naloxone, a narcotic-receptor antagonist. Experience with antiarrhythmic drugs is limited in the setting of narcotic overdose, and as with cocaine, it is best to avoid pharmacologic agents if possible and allow the narcotic to be metabolized. Electrical cardioversion is appropriate for hemodynamically unstable rhythms. If necessary, supraventricular arrhythmias may be treated with adenosine, β-blockers, or calcium antagonists.

SUBSTANCE ABUSE AMONG ATHLETES

Competitive athletes and bodybuilders often abuse substances with a goal of enhancing performance or building muscle mass. The primary ingredients of most cardiac stimulant products used by this population are ephedrine, often called by its Chinese name, *ma huang*, and caffeine. Ephedrine and caffeine may cause or exacerbate hypertension and, rarely, can be associated with a catecholamine cardiomyopathy. In addition, the effects of ephedrine and caffeine on myocardial contractility, myocardial irritability, and coronary vasoconstriction may sometimes be hazardous, particularly in the occasional subject with hypertrophic cardiomyopathy or a preexcitation syndrome.

Anabolic steroids are widely used in this population and have multiple adverse effects on the cardiovascular system. Anabolic steroids promote atherogenesis by markedly increasing low-density lipoprotein cholesterol and decreasing high-density lipoprotein cholesterol. Anabolic steroids seem to promote left ventricular hypertrophy secondarily by causing hypertension but possibly also by a direct anabolic effect on the myocardium. Finally, anabolic steroids may have effects on platelet aggregation and cardiac conduction. Sporadic cases of MI and sudden cardiac death have been reported among anabolic steroid users.

FUTURE DIRECTIONS

Substance abuse is epidemic in Western societies and is likely to remain so. Primary prevention in this area relies on public education. The legal substances tobacco and alcohol exacerbate two of the major killers in cardiovascular medicine, coronary artery disease and hypertension. Public policy aimed at discouraging these behaviors, particularly tobacco use, has had a significant effect, both through discouraging individual use and by limiting secondhand exposure, but all practitioners must continue to emphasize the significance of alcohol and tobacco as contributors to cardiovascular mortality and morbidity. Novel therapies for smoking cessation are under investigation, including not only nicotine antagonists but also cannabinoid-receptor antagonists, dopaminergic agonists, monoamine oxidase B inhibitors, and even vaccines to promote antibodies to nicotine. The use of illegal substances takes a disproportionate toll on youth, who otherwise would be expected to be free of cardiovascular disease. Physician awareness of and attention to these issues can highlight their importance for the general public.

ADDITIONAL RESOURCES

American Cancer Society Website. Guide to quitting smoking. Available at: <http://www.cancer.org/docroot/PED/content/PED_10_13X_Guide_for_Quitting_Smoking.asp> (last revised 23.11.09); Accessed 31.03.10.

A concise but thorough patient-oriented guide to why and how to quit smoking.

Substance Abuse and Mental Health Services Administration facility locator. Available at: <http://findtreatment.samhsa.gov/>; Accessed 31.03.10.

A regularly updated searchable directory of drug and alcohol treatment programs useful for both patients and practitioners.

U.S. Surgeon General Website. Treating tobacco use and dependence: 2008 update. Available at: <http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf> (May 2008); Accessed 31.03.10.

A comprehensive, government-sponsored guide to smoking cessation.

EVIDENCE

Burt A, lllingworth D, Shaw PR, et al. Stopping smoking after myocardial infarction. *Lancet.* 1974;1:304–306.

One of several studies suggesting that intensive counseling is particularly useful in patients who have experienced a cardiac event.

Hurt RD, Sachs DL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med.* 1997;337:1195.

Documents the efficacy of bupropion for smoking cessation.

Jorenby DE, Hayes JT, Rigotti NA, et al. Efficacy of varenicline, an $\alpha_4\beta_2$-nicotinic acetylcholine receptor partial agonist vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296:47–55.

Documents the modestly increased efficacy of varenicline versus bupropion.

Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med.* 2001;345:351–358.

Thorough review providing both practical recommendations and an authoritative review of the pharmacology and pathophysiology of cocaine toxicity.

McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation.* 2008;117:1897–1907.

This thoroughly referenced article provides consensus guidelines for management of cocaine-related chest pain syndromes from a panel of experts assembled by the American Heart Association.

HIV and the Heart

Kristine B. Patterson and Joseph J. Eron

66

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) affect more than 45 million people worldwide. AIDS—defined immunologically as a CD4 T-cell count of 200 cells/mm^3 or less, or by the occurrence of an opportunistic illness—is the most advanced manifestation of HIV infection. The spectrum of disease is diverse, and the period between HIV acquisition and the development of AIDS can be many years. The prognosis for HIV-infected individuals who have access to antiretroviral therapy (ART) has greatly improved. The long-term management has therefore evolved to focus on traditional age-related illnesses, especially cardiovascular disease (CVD). Formerly common cardiac manifestations of HIV, including dilated cardiomyopathy, myocarditis, pericardial disease, and pulmonary hypertension, are now relatively rare in individuals receiving ART. Complications from ART such as dyslipidemia are now common. As a result of ART and increased longevity, HIV-infected individuals are at risk for CVD. HIV infection itself may increase the risk for CVD, and this risk may increase with decreasing levels of immune function. This chapter explores the most common cardiac diseases in HIV-infected individuals and the ways in which the etiologies of these diseases differ compared with the general population (Fig. 66-1). Whichever cardiac disease is being addressed, care should be integrated among the cardiologist, the HIV care provider, and the primary care provider. Special considerations in evaluating CVD risk and treating lipid abnormalities are also discussed.

ETIOLOGY AND PATHOGENESIS

The underlying etiology of cardiac diseases in HIV patients can be divided into three categories that may overlap: (1) HIV itself and infections and opportunistic diseases associated with HIV; (2) therapies used in HIV treatment, including certain nucleoside analogues that have been associated with cardiomyopathy and protease inhibitors (PIs) that have been associated with myocardial infarction (MI) (probably predominantly due to their effect on lipids); and (3) factors common to the general population such as hyperlipidemia, smoking, hypertension, and so forth. In particular, atherosclerosis may be related to the ART used, the virus itself, or immune dysregulation. In all cases, treatment is directed toward the underlying etiology and any modifiable risk factors.

CLINICAL PRESENTATION

Dilated Cardiomyopathy

In the pre-ART era, dilated cardiomyopathy (DCM) was found in 20% to 40% of patients with long-standing HIV infection, even in the absence of an AIDS-defining diagnosis or a CD4 cell count of 200 cells/mm^3 or less. Currently, HIV-associated DCM is rare and is thought to be related to impaired immune function, direct cardiotoxic effect of HIV infection or HIV proteins, and/or nutritional deficiencies; DCM may also be drug-induced. Specific opportunistic infections that have been implicated include viral (cytomegalovirus, herpes simplex), protozoal (*Toxoplasma gondii*), bacterial (*Mycobacterium tuberculosis*, *Mycobacterium avium-intracellulare*), and fungal (*Cryptococcus neoformans*, *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Candida* spp.).

Pulmonary Hypertension

The prevalence of pulmonary hypertension is estimated to be 1 in 200 in HIV-infected individuals compared with 1 in 200,000 in the general population. However, most of these estimates were made in the pre-ART era. Recent studies suggest that asymptomatic pulmonary hypertension may be as high as 5.5% in well-controlled HIV-infected patients receiving ART. The etiology of pulmonary hypertension in HIV-infected individuals is obscure but may be related to sequelae of opportunistic pulmonary infections or effects of HIV on pulmonary endothelial function. Conflicting data exist with respect to whether ART contributes to the pathogenesis of pulmonary hypertension or is beneficial for treatment.

Cardiac Neoplasm

Both Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL), the two most common malignancies associated with HIV/AIDS, may involve the heart. Cardiac KS is always associated with disseminated KS. Cardiac findings are usually subclinical; however, fatal cardiac tamponade and pericardial constriction may occur. Pericardiocentesis is considered a high-risk procedure because of the vascular nature of KS lesions. In such suspected cases, a pericardial window is the procedure of choice for providing decompression in addition to establishing the diagnosis.

NHL is usually high grade, is of B-cell origin, and disseminates early. Cardiac involvement of NHL may present with intractable heart failure, pericardial effusion, cardiac tamponade, or arrhythmias. Patients with mechanical obstruction may benefit from surgical resection.

Cardiotoxicity from chemotherapy for either malignancy is also possible depending on the agents used.

Pericardial Effusions and Pericarditis

Pericardial effusions are commonly seen in HIV-infected individuals. Clinical manifestations include asymptomatic effusions detected on echocardiography, pericarditis with or without constriction, and tamponade. The clinical presentation of pericarditis alone is not different in HIV-infected and uninfected individuals. The etiology of pericarditis in HIV infection is most often not determined. Specific considerations in this population

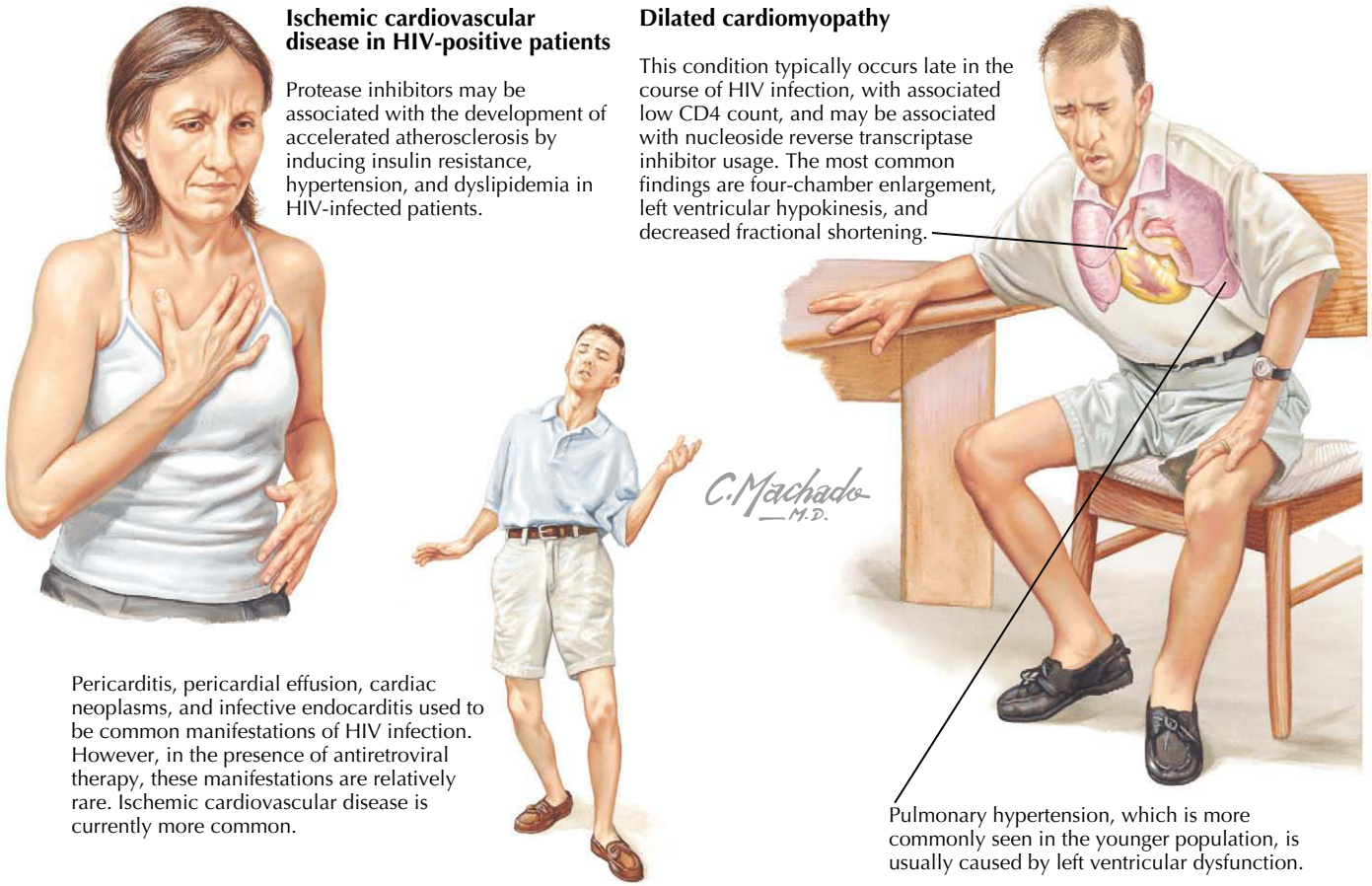


Figure 66-1 *Cardiac manifestations of acquired immunodeficiency syndrome.* HIV, human immunodeficiency virus.

include infections (viral, fungal, and mycobacterial, with tuberculosis as a particular concern in patients at high risk for this co-infection), malignancies (KS and NHL), and other diseases (e.g., HIV-associated nephropathy).

Nonbacterial Thrombotic Endocarditis

Nonbacterial thrombotic endocarditis has an estimated prevalence of 3% to 5%, most commonly in those older than 50 years and in patients with HIV wasting syndrome. These estimates are predominantly from the era before effective ART. The friable sterile vegetations that form on the cardiac valves are associated with disseminated intravascular coagulation and systemic embolization.

Infective Endocarditis

Infective endocarditis in HIV-infected individuals has similar prevalence to that in individuals with the same risk behaviors, and, in general, the clinical presentation is also similar in HIV-infected and noninfected individuals. *Staphylococcus aureus* and *Streptococcus viridans* are the major responsible organisms. However, a limited number of pathogens cause endocarditis more frequently in HIV-infected individuals. Notably, HIV-infected patients are at higher risk of developing *Salmonella* bacteremia resulting in endocarditis than are immunocompetent patients. Other than *Candida* species, fungal endocarditis (*Aspergillus fumigatus*, *Histoplasma capsulatum*, and *Cryptococcus neoformans*) is also more common in HIV-infected individuals; however, these remain relatively rare. Individuals with late-stage HIV infection have higher mortality than those who are earlier in the disease course.

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

The widespread use of ART has markedly decreased mortality for HIV-infected individuals. Greater survival means HIV-infected persons are aging and subsequently facing the same comorbidities as the general population, especially atherosclerotic CVD. In general, HIV-infected individuals seem to be at greater risk for CVD than HIV-uninfected persons. This may be due partly to the higher prevalence of traditional risk factors, especially smoking. CVD tends to occur at a younger age in HIV-infected individuals, and there is a higher rate of hospitalizations for CVD and acute MIs in this population. The interface between the increased risk of CVD, HIV, and ART can occur in three ways: (1) HIV may serve as a marker to identify higher-risk individuals (e.g., increased rate of smoking in HIV-infected persons); (2) HIV or ART may alter traditional

risk factors (e.g., dyslipidemia); or (3) HIV or ART may affect the underlying pathogenesis associated with CVD (e.g., proinflammatory process and endothelial dysfunction). Thus far, there is no clear evidence that any one of these factors supersedes the others.

Risk Factors

TRADITIONAL MODIFIABLE RISK FACTORS

Cigarette smoking, hypertension, diabetes, and obesity are all strong predictors of CVD in HIV-infected persons. As in the general population, these factors remain the most powerful predictors of CVD risk. Rates of smoking are consistently higher in HIV-infected persons than age-matched controls. The ratios of total cholesterol to high-density lipoprotein cholesterol (HDL-C) and of low-density lipoprotein cholesterol (LDL-C) to HDL-C, as well as triglyceride (TG) levels, are also higher. With the use of ART, a paradoxical worsening of CVD risk occurs in some HIV-infected individuals who become obese as they experience a "return to health" phenomenon and adopt a sedentary lifestyle. As with other populations, the Framingham risk equation can be used. However, this equation may underestimate the true risk due to as yet undefined intrinsic factors associated with HIV, such as diminished arterial elasticity, especially in untreated individuals.

ANTIRETROVIRAL THERAPIES

Observational studies have shown that both the presence and the absence of ART may contribute to CVD risk. While ART is associated with dyslipidemias, uncontrolled HIV replication is associated with endothelial dysfunction. One observational study, the Data Collection on Adverse Events of Anti-HIV Drugs" (D:A:D Study), detected a relative risk of 16% for MI associated with PI (but not nonnucleoside reverse transcriptase inhibitor [NNRTI]) use for every year of ART exposure. However, PI-associated risk was lower than the annual risk associated with age, male sex, or tobacco usage. A second large observational study, Strategies for Management of Anti-retroviral Therapy (SMART), demonstrated an increased risk of CVD among patients who episodically discontinued ART on the basis of CD4 count—presumably due to the proinflammatory state that ensues with lower CD4 cell counts. The risk decreased on reinstitution of ART but not back to baseline. Additional evidence supports the concept that endothelial dysfunction rapidly improves and is maintained following the initiation of ART in ART-naive individuals.

Specific ARTs may be more likely to increase CVD risk. The D:A:D Study (with 30,000 patient years' follow-up) found current or recent use of the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) abacavir and didanosine was associated with a doubled risk of cardiovascular event. The SMART study supported the association of abacavir with increased CVD risk. However, the increased risk was not seen in a longitudinal observational study for individuals who have been in treatment trials (AIDS Clinical Trials Group ALLRT) and randomized to receive or not receive abacavir. These studies and others have evaluated changes in inflammatory markers associated with abacavir use. Overall, increases in highly sensitive C-reactive protein, interleukin-6, soluble vascular cell adhesion molecule, and other inflammatory markers were not enhanced, whereas platelet hyperreactivity and worsening endothelial function were seen in individuals receiving abacavir. Whether abacavir actually contributes to CVD risk has yet to be definitely determined. But given this uncertainty, abacavir should be avoided in individuals with known CVD, if possible.

DYSLIPIDEMIA

Dyslipidemia has become an important focus of HIV care. Even before ART, HIV-infected patients had perturbations in lipid metabolism. Increased serum TG levels, lower levels of HDL-C and LDL-C, and lower levels of total cholesterol are more commonly seen in individuals with AIDS. Initiation of ART frequently reverses these effects.

ART agents are now thought to contribute significantly to lipid perturbations, but the pathogenesis of this effect is not well understood. Differences exist between and within ART class; therefore, the effects of specific classes on lipids cannot be generalized. Additionally, certain regimens may be favorable for one lipid parameter and detrimental for another.

PROTEASE INHIBITORS

The most common way to administer PIs is in combination with ritonavir (RTV), which is now used exclusively at low dose to boost the levels of other PIs. When PIs are administered with low-dose RTV, all lipid values increase to some degree. Increased TG levels are more variable depending on the PI, with TG levels (and total cholesterol levels) increasing to a greater degree with lopinavir-RTV than with other commonly used boosted PIs. Ratios of total cholesterol to HDL-C may or may not increase, since HDL-C increases may be substantial. Elevations in TGs may be extreme—to more than 750 mg/dL—particularly with lopinavir-RTV or tipranavir-RTV (a less commonly used PI combination). Atazanavir when administered without RTV has less effect on total cholesterol and TGs. Effects of PIs on lipids vary substantially from individual to individual.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The NNRTIs nevirapine and efavirenz increase HDL-C and are associated with modest adverse effect on lipids. Nevirapine has less of an effect on LDL-C, while efavirenz increases total cholesterol, TGs, and LDL-C. Efavirenz, when used in combination with lopinavir-ritonavir, markedly increases TG levels. Lipid effect of the newest NNRTI, etravirine, has only been assessed in highly treatment-experienced individuals and was associated with increases in total cholesterol.

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

The association between NRTIs and lipids is less clear. The thymidine analogue zidovudine is associated with hypercholesterolemia and increases in LDL-C, although not associated with an increased risk of MI. Stavudine is associated with

hypertriglyceridemia, hypercholesterolemia, and increases in insulin resistance (IR). Lamivudine, emtricitabine, and tenofovir are all considered to be lipid-neutral. Abacavir, as discussed, may be associated with an increased risk of MI but is relatively lipid-neutral.

CCR5 ANTAGONISTS AND INTEGRASE INHIBITORS

Most of the experience with these two new classes of ART is in treatment-experienced patients. The available data suggest they are lipid-neutral.

INSULIN RESISTANCE

IR reflects a state wherein increased amounts of insulin are required to exert its normal physiologic functions. The high prevalence of IR in HIV-positive individuals, between 35% and 50%, is multifactorial. Important contributors include traditional risk factors (genetics, physical inactivity, and obesity) and HIV-specific factors (proinflammatory effects of HIV, direct effects of antiretrovirals (especially PIs), and consequences of the lipodystrophy syndrome. Although the gold standard for measuring IR is the euglycemic insulin clamp coupled with an intravenous glucose tolerance test, various measurements (fasting insulin level, homeostasis model assessment, quantitative insulin sensitivity check index, and insulin-to-glucose ratio) are more practical and available for everyday clinical use. There is marked variation between the different PIs, with atazanavir having the least effect on IR. Treatment of IR should include exercise and consideration of a more metabolically friendly ART regimen. There may be some benefit from the addition of metformin.

MANAGEMENT AND THERAPY OF LIPID ABNORMALITIES

Optimum Treatment

A fasting lipid profile should be obtained before initiation of ART and 3 to 6 months later. As with the general population, lifestyle modifications (diet and exercise) should be attempted first. If treatment goals are not reached by 4 to 8 weeks, pharmacologic therapy should then be initiated. In individuals with established CVD, medical intervention should be initiated concurrently. The treatment of dyslipidemia in HIV-infected individuals should be in conjunction with the primary care provider and the HIV specialist who is managing the ART. In some instances, ART may be altered to assist in the management of dyslipidemia.

Therapy should follow the National Cholesterol Education Program Treatment Guidelines. For patients with significant isolated hypertriglyceridemia (defined as >500 mg/dL), therapy should begin with a fibrate. For patients with elevated LDL-C or non-HDL-C and TG levels less than 500 mg/dL, therapy should begin with a statin. The statins most frequently used in HIV-infected patients on ART include pravastatin, atorvastatin, and rosuvastatin. Starting doses should be relatively low and gradually increased to reach treatment goals. Monitoring for muscle toxicity, increased creatine kinase, hepatotoxicity, and increasing HIV RNA should be performed on a regular basis. With refractory hypertriglyceridemia and hypercholesterolemia, both a fibrate and a statin may be necessary, although the risk of toxicity may be compounded. Niacin lowers LDL-C but potentially worsens IR and should be avoided in patients taking PIs.

Avoiding Treatment Errors

Treatment for dyslipidemia in HIV-infected patients can be challenging. Many statins are metabolized by cytochrome P450 3A4 (CYP3A4), which also metabolizes many of the HIV therapeutics. Therefore, interactions between these dually essential classes of drugs are likely. There is an increased propensity toward skeletal muscle toxicity (myalgias) or liver toxicity from increased levels of statins when coadministered with PIs. Lovastatin and simvastatin are extensively metabolized by CYP3A4; therefore, their use should be avoided in HIV-infected patients receiving PIs because of an increased risk of toxicity. Pravastatin may be less effective when administered with ritonavir, nevirapine, or efavirenz. The NNRTIs nevirapine and efavirenz, which induce CYP3A4, lower serum concentrations of the statins. As with all cardiac diseases, treatment should be integrated between the cardiologist, the HIV care provider, and the primary care provider.

FUTURE DIRECTIONS

Since the introduction of ART, the overall incidence of nonatherosclerotic cardiac disease in HIV-infected individuals has significantly decreased, especially the incidence of pericarditis and DCM. This reduction most likely reflects a decrease in opportunistic infections, increased control of HIV replication, and improved immune function. Unfortunately, dyslipidemia and atherosclerosis will increase as more people receive ART and age. In addition to lipid management, special focus should also be placed on smoking cessation. Aggressive treatment of CVD and the associated risk factors should be implemented into the standard treatment of HIV-infected individuals.

ADDITIONAL RESOURCES

Currier JS, Lundgren JD, Carr A, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation.* 2008;118:e29–e35.

Outlines the present state of evidence supporting the epidemiologic evidence linking CVD and HIV and the specific risk factors for CVD in the HIV population. Specific gaps in knowledge are also highlighted.

Dube MP, Lipshultz SE, Fichtenbaum CJ, et al. Effects of HIV infection and antiretroviral therapy on the heart and vasculature. *Circulation.* 2008;118:e36–e40.

Discusses the supporting evidence by which protease inhibitors are involved in endothelial dysfunction, insulin resistance, and accelerated atherosclerosis.

Grinspoon SK, Grunfeld C, Kotler DP, et al. State of the science conference: initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary. *Circulation.* 2008; 118:198–210.

A multidisciplinary conference was convened in 2007 to discuss the state of the science as related to CVD disease and HIV infection. This executive summary outlines the conclusions and specific topics of this conference.

EVIDENCE

El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. *N Engl J Med.* 2006;355:2283–2296.

This pivotal longitudinal trial randomly assigned participants to continue or interrupt ART based on CD4 cell counts. The SMART Trial demonstrated that interruption of therapy is associated with greater mortality and increased CVD events.

Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med.* 2007;356:1723–1735.

Supports the previous work that suggested increased risk of CVD in HIV-infected individuals is partly related to the antiretroviral-associated dyslipidemia. There was not an association with NNRTIs; however, the amount of person-years of follow-up was smaller.

Kaplan RC, Kingsley LA, Gange SJ, et al. Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men. *AIDS.* 2008;22:1615–1624.

This cross-sectional study is nested within the two largest North American HIV-related observational cohorts. Even after controlling for viral load and ART, CD4 count <200 remained the single most important factor associated with increased carotid intimal thickness. This supports other work that HIV in itself may be atherogenic.

Lewis W. Cardiomyopathy in AIDS: a pathophysiological perspective. *Prog Cardiovasc Dis.* 2000;43:151–170.

Summarizes the multiple factors that contribute to cardiomyopathy in HIV-infected individuals. The complex relationship between cellular and viral factors is specifically outlined.

Kuller LH, Tracy R, Belloso W, et al, and the INSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med.* 2008;5:e203.

In a nest case control study, the INSIGHT SMART Study Group assessed study biomarker associations with mortality. Discontinuation of ART was associated with greater mortality, possibly due to greater inflammatory responses.

Phillips AN, Carr A, Neuhaus J, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antivir Ther.* 2008;13:177–187.

The initial SMART Trial demonstrated an increased risk of CVD in individuals who have CD4-guided antiretroviral treatment interruption. This exploratory analysis could not identify a specific cause as to the increased CVD events other than more pronounced lipid perturbations.

The SMART/INSIGHT and the D:A:D Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS.* 2008;22:F17–F24.

The SMART and D:A:D Study Groups identified an increased risk of CVD in some populations. This analysis identified that the current use of abacavir was associated with greater risk of CVD events that were not related to lipid effects. Instead, vascular inflammation may be the underlying factor driving this risk.

Sleep Disorders and the Cardiovascular System

67

Elizabeth Boger Foreman and Bradley V. Vaughn

Sleep is a reversible physiologic state that is essential for and a benchmark of good health. Even though we do not understand the underlying purpose, sleep stabilizes regulation of the autonomic and endocrine systems, enhances attention and concentration, and promotes a sense of well-being. Disruption of sleep may lead to an array of central nervous system and systemic consequences. Approximately one in three individuals will present with a sleep-related complaint to their physician. Over 90 distinct sleep disorders have been identified. These disorders result in complaints of excessive daytime sleepiness and/or difficulty initiating or maintaining sleep or events associated with sleep. The impact of sleep disruption on cardiovascular functioning is complex and widespread. Some disorders such as sleep apnea are a risk factor for cardiovascular disease, whereas other disorders such as heart failure influence sleep maintenance. There is a bidirectional influence and a dynamic relationship between sleep and the cardiovascular system.

NORMAL SLEEP PHYSIOLOGY

The state of sleep is determined by an array of coordinated neuronal processes. Sleep is typically divided into stages based on electroencephalogram (EEG) features, eye movements (electro-oculography), and muscle tone (electromyogram). Stages N1 through N3 are called collectively non-rapid eye movement (NREM) sleep. Stage N1 sleep is frequently associated with the perception of drowsiness and is characterized by EEG features of mild slowing and vertex sharp waves. Stage N2 (light sleep) is characterized by the presence of K complexes or sleep spindles. In stage N3 (deep sleep), high-amplitude slow waves predominate in EEG activity. Rapid eye movement (REM) sleep (or stage R) is characterized by a low-amplitude mixed-frequency pattern on EEG, absence of muscle tone in voluntary muscles, and intermittent REMs. Dreams can occur in all stages of sleep but are more vividly recalled from REM sleep. Healthy adults display a reproducible pattern of sleep organization. They enter sleep through stage N1, progress to stage N2, and after 15 to 25 minutes progress to stage N3, followed by reemergence of stage N2 sleep. The first REM sleep period occurs after approximately 90 minutes. This pattern repeats approximately every 90 minutes throughout the sleep period with progressively less slow-wave sleep and longer periods of REM sleep in each cycle.

All of these stages have other physiologic correlates. As we progress normally through the stages of sleep there are variations in heart rate, blood pressure, peripheral vascular tone, oxygen delivery, coronary blood flow, and respiration. In a healthy individual, transitional periods between quiet wakefulness and light sleep are characterized by mild instability in breathing, making these periods particularly subject to the occurrence of central apnea events and periodic breathing. As the individual becomes drowsy, the heart rate may decrease with a subtle drop in blood pressure. In sustained NREM sleep, parasympathetic regulation of cardiovascular activity predominates, characterized by decreased blood pressure, greater high-frequency heart rate variability, and more regular breathing as compared with quiet wakefulness. In REM sleep, muscle atonia results in a decrease in peripheral vascular tone, and surges in sympathetic output cause increased variability of heart rate, blood pressure, and respiratory rate. Respiratory response to hypercapnia and hypoxia is also reduced. This fluctuation in sympathetic output leads to accelerations and pauses of heart rate and breathing and increased afterload. Thus, in individuals with underlying cardiac disease (e.g., heart failure, conduction disturbances, coronary artery disease) or pulmonary disease, this physiologic vulnerability during REM sleep may increase the risk of arrhythmias, reduced coronary blood flow, hypoxia, and/or obstructive apneas.

SLEEP LENGTH AND HEALTH

Our society has progressively shortened the amount of time dedicated to sleep. At the beginning of the twentieth century, it is estimated that individuals spent approximately 9 to 10 hours per night in bed. As of 2008, the average working American is sleeping less than 7 hours per night. Sleep deprivation in the short term is associated with greater sympathetic nerve activation, higher blood pressure, increased appetite, lower leptin levels, higher cortisol levels, and increased inflammatory markers. Epidemiologic studies suggest that chronic sleep deprivation is associated with weight gain and obesity. Additionally, individuals who sleep fewer than 5 hours per night are at greater risk for coronary artery disease and development of diabetes, and have a higher mortality risk at 10 years, even after adjustment for other risk factors. Similarly, individuals who sleep longer than 9 hours are also at greater risk for diabetes and cardiovascular events. The underlying mechanism for the link of sleep deprivation and disease is unclear. Yet some believe that dysregulation of the endocrine and autonomic nervous systems and increases in inflammation contribute to the development of hypertension, vascular disease, and weight gain. Regardless of the mechanism, sleep duration may impact cardiovascular health.

SLEEP-RELATED BREATHING DISORDERS

Sleep can be disrupted by several disorders (Box 67-1), many of which have not been extensively studied for their relationships to cardiovascular health. Patients presenting to a sleep disorders center are typically those with sleep-related breathing disorders. Common sleep problems including obstructive sleep apnea (OSA), central sleep apnea (CSA), and obesity hypoventilation

Box 67-1 Categories of Sleep Disorders

Circadian rhythm disorders
Sleep-related breathing disorders
Insomnias
Hypersomnias
Parasomnias
Sleep-related movement disorders
Other disorders

can adversely impact cardiovascular health. Sleep-related breathing patterns, such as Cheyne-Stokes respiration (CSR), may reflect underlying cardiovascular issues. These disorders offer an opportunity to identify predisposing and exacerbating factors of cardiovascular disease and improve long-term risks.

Obstructive Sleep Apnea

OSA is defined by repetitive collapse of upper airway structures for 10 seconds or longer, causing cessation of airflow in the setting of continued respiratory effort (Fig. 67-1). These events are commonly accompanied by a decrease in the blood oxygen saturation and a constellation of clinical symptoms (Box 67-2). Significant pathophysiology is also seen with hypopnea events, defined as airflow diminished by more than 30% and oxygen desaturation of at least 4%. The number of apnea and hypopnea events per hour, termed apnea-hypopnea index (AHI), is used to determine disease severity (Table 67-1). Population studies estimate that 1 in 5 individuals has at least mild disease, being more prevalent in males. The mechanisms for both obstructive apnea and hypopnea are linked to airway compromise at one of three levels: the nose, the retroglossal and retropalatal regions, and the pharynx (Box 67-3; Fig. 67-2). Common factors associated with increased risk of OSA include male sex, older age, obesity, anatomically small airway, and others (Box 67-4).

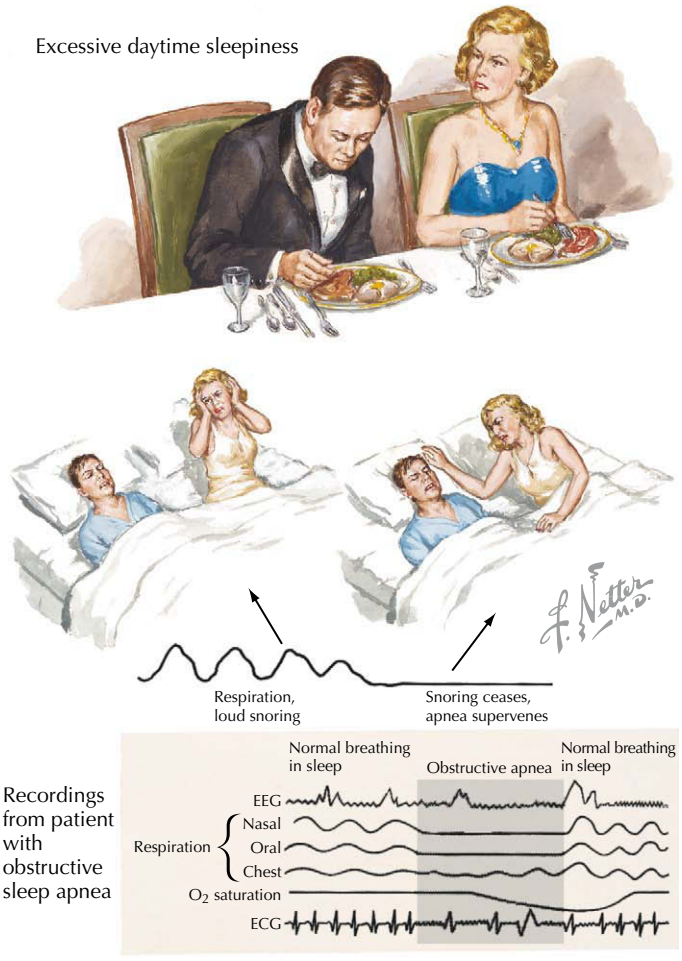


Figure 67-1 *Obstructive sleep apnea.* ECG, electrocardiogram; EEG, electroencephalogram.

Box 67-2 Symptoms of Obstructive Sleep Apnea

Snoring
Daytime sleepiness
Witnessed apneas or gasping events during sleep
Insomnia
Hypertension
Decreased cognition
Morning headaches
Sexual dysfunction

OBSTRUCTIVE SLEEP APNEA LINK TO HYPERTENSION

OSA is associated with a gradual increase in peripheral vascular tone and decrease in cardiac output. This is followed by a sudden opening of the airway, and the cardiac output increases against high peripheral vasoconstriction and results in a dramatic increase in blood pressure. Beyond repetitive apnea events, other influences may increase systemic blood pressure. Possible mechanisms of causation include intermittent, repeated hypoxia episodes causing chemoreceptor stimulation, increased sympathetic activation, decreased baroreceptor responsiveness, cardiovascular remodeling, and activation of the renin-angiotensin system. Epidemiologic studies suggest a moderate link between OSA and hypertension. Analysis of data from the Wisconsin Sleep Cohort shows a linear relationship between severity of the AHI and elevations in 24-hour blood pressure monitoring. OSA can also precede the appearance of hypertension, as evident in the prospective analysis of this group. Clinicians should suspect OSA in patients who have failed to respond to three or more antihypertensive medications and in those lacking a physiologic nocturnal dip in blood pressure.

This relationship of sleep apnea to hypertension provides therapeutic opportunities. In short-term studies, treatment with continuous positive airway pressure (CPAP) decreased

Table 67-1 Apnea Severity

AHI	Apnea Severity
0–5	Normal
5–15	Mild
15–29	Moderate
≥30	Severe

AHI, apnea-hypopnea index.

Box 67-3 Mechanisms of Obstructive Sleep Apnea

Pharyngeal muscular relaxation
Infiltration of pharyngeal tissues (adiposity, tumor, mucopolysaccharidoses)
Tonsillar hypertrophy
Retrognathia or micrognathia
Macroglossia
Nasal obstruction
Chronic mucosal edema (allergies, sinusitis, gastroesophageal reflux)
Medication effect—muscular relaxation
Diminished response to upper airway load

Box 67-4 Risk Factors Associated with Increased Risk of Obstructive Sleep Apnea

Male
Age older than 65 years
Obesity (body mass index of 30 or higher)
Micrognathia or retrognathia
High arched palate
Large adenoids and/or tonsils
Snoring
Neck size greater than 16.5 inches

sympathetic activity during sleep and modestly improved both nocturnal and daytime blood pressure. Those with more severe OSA and hypertension had greater reductions in blood pressure after treatment of OSA, although more studies are needed to determine longer-term outcomes. Treatment of hypertension is not known to significantly decrease severity of sleep apnea or disturb normal sleep architecture.

OBSTRUCTIVE SLEEP APNEA AND CARDIAC DISEASE

Evidence from the Sleep Heart Health Study, a cross-sectional study of more than 6000 adults, indicates that blood oxygen desaturations of at least 4% correlate with a higher prevalence of cardiovascular disease independent of other risk factors. Untreated OSA is associated with an increased incidence of hypertension, myocardial ischemia, infarction, early cardiac death, heart failure, pulmonary hypertension, and arrhythmias (particularly atrial fibrillation). OSA is frequently found in patients with congestive heart failure (~11% to 50% have OSA) and is more common in men of any age and women older than 60 years. OSA can lead to and exacerbate heart failure by repeated oxygen desaturations, increased sympathetic activation, and increased afterload. Additionally, increased swings in intrathoracic pressure caused by untreated OSA also lead to increased myocardial oxygen demand. The greater negative intrathoracic pressure also results in atrial stretch causing the release of atrial natriuretic peptide, which can result in nocturia. Compounding the effect is an inflammatory cascade characterized by the release of interleukins, cytokines, and tumor necrosis factor-α. This increase in inflammation plays a role in advancing coronary artery disease and elevating C-reactive protein levels. Additionally, release of vasoactive substances such as endothelin and nitric oxide synthetase lead to endothelial dysfunction and increase platelet activation and aggregation. However, a link to a true hypercoagulable state has not been clearly established.

Cardiovascular diseases can also have a significant impact on sleep. Heart failure can disrupt normal sleep architecture, selectively decreasing REM sleep and leading to REM sleep deprivation. Untreated OSA results in more fragmented, less restorative sleep, due to frequent arousals.

TREATMENT OF HEART FAILURE AND OBSTRUCTIVE SLEEP APNEA

Optimal management of fluid status in heart failure can improve the AHI due to decreased airway edema, according to studies in otherwise healthy volunteers. The effect of the treatment of OSA on heart failure is better established. Usage of CPAP improves left ventricular ejection fraction, subjective dyspnea, and daytime sleepiness. Data have yet to be collected on end points such as hospitalization rates and mortality, but a recent observational trial demonstrated a trend toward decreased mortality in patients on CPAP with heart failure.

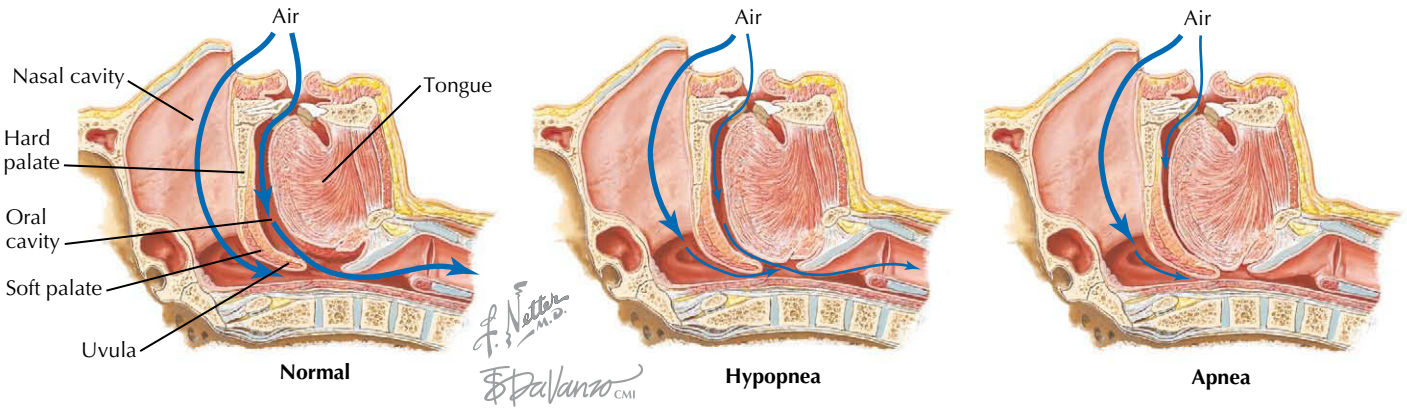


Figure 67-2 *Anatomic representation of obstructive sleep apnea.*

OBSTRUCTIVE SLEEP APNEA AND STROKE

Given the above associations, OSA has been implicated as a risk factor for stroke. Current evidence does not allow clear establishment of OSA as an independent risk factor for stroke, but OSA severity does correlate with the risk of stroke or death. Individuals who suffered stroke and have OSA have a higher mortality than those without OSA. Similar to cardiac disease, possible mechanisms for the association of OSA with stroke include hypertension, reduction in cerebral blood flow, release of vasoactive substances leading to endothelial damage, and inflammatory and prothrombotic states. Additionally, snoring may cause chronic vibration of carotid arteries and is associated with intimal thickening. Observational studies show individuals who are compliant with therapy for OSA have better motivation and cognitive capacity as well as lower risk of recurrent events.

CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH

Common symptoms of OSA include snoring and daytime sleepiness, but nearly half of individuals with OSA do not express somnolence. The Epworth Sleepiness Scale is a validated measure of sleepiness, and other tools such as the Berlin Sleep Apnea Questionnaire and the Sleep Apnea portion of the Sleep Disorders Questionnaire identify patients with potential OSA (Box 67-5). Although obesity is a risk factor, patients with OSA do not have to be obese or have narrow upper airways. Overnight pulse oximetry has limited utility in OSA screening due to lack of sensitivity. Many individuals with normal lung function will not exhibit repetitive oxygen desaturations on overnight pulse oximetry and yet still have mild to moderate disease. The gold standard for diagnosis of OSA is attended polysomnography in which EEG, electro-oculography, electromyography, ECG, two parameters of respiratory flow (nasal temperature and nasal pressure), and chest and abdominal movements are monitored continuously. Unattended respiratory monitoring has recently been approved by the Center for Medicare Service for use in patients without cardiovascular or respiratory comorbidities, under the supervision of an experienced sleep specialist.

Box 67-5 Individuals Who Need Further Evaluation for Obstructive Sleep Apnea

Snoring with:
- Excessive daytime sleepiness
- Insomnia

Excessive daytime sleepiness, insomnia, or snoring in:
- Coronary artery disease
- Heart failure
- Hypertension
- Stroke
- Malignant arrhythmias
- Recurrent atrial fibrillation
- Chronic obstructive pulmonary disease
- Asthma
- Neuromuscular disease
- Metabolic syndrome
- Diabetes type 2

Figure 67-3 *Continuous positive airway pressure therapy for obstructive sleep apnea.*

DIFFERENTIAL DIAGNOSIS

The constellation of snoring, excessive sleepiness, and witnessed apnea is highly associated with OSA. Other disorders that may present with similar features include primary snoring, CSR with obstructive features, and obesity hypoventilation. Adding to the dilemma is that individuals may vary from night to night in the degree of upper airway obstruction. Although most patients do not jump from normal to severe categories, factors influencing upper airway patency such as alcohol, nasal congestion, and position may contribute significantly to severity.

MANAGEMENT AND THERAPY

Optimum Treatment

In addition to maximizing treatment of comorbid conditions, treatment options for OSA include CPAP therapy, surgery, custom-fit oral appliances, weight loss, and, in specific cases, positional therapy (Fig. 67-3). CPAP is the first-line therapy indicated for all patients with an AHI over 10 and those with an AHI between 5 and 10 with symptoms. Key points to successful compliance relate to education of the patient, comfortable mask or interface, quick response to therapeutic hurdles, and frequent patient follow-up. Oral appliances advancing the mandible are best targeted for patients with mild to moderate sleep apnea with appropriate dentition.

If a surgical approach is chosen, all three areas of concern in OSA (nose, retroglossal and retropalatal regions, and posterior oropharynx) should be evaluated and treated to achieve best success. This may require several surgeries, possibly including septoplasty, radiofrequency ablation of turbinates, genioglossus advancement, tongue reduction, bimaxillary advancement, uvulopalatopharyngoplasty, tonsillectomy, and adenoidectomy.

Although not commonly performed since the introduction of CPAP, tracheostomy is curative, ensures compliance, and may be the best choice in morbidly obese patients. Often a combination of treatment approaches is used in severe cases. All patients with sleep-disordered breathing should avoid excessive alcohol intake and medications that suppress respiratory drive.

Avoiding Treatment Errors

Treatment errors typically occur in three realms: CPAP titration, device setup, and patient usage. CPAP titrations, to meet the gold standard of optimum therapy, must be performed in an accredited sleep center and result in complete resolution of breathing disturbance in the supine position in REM sleep. Treatment errors can arise if the titration does not demonstrate resolution of events in all sleep states or positions. Another pitfall may occur if the titration is not performed with the same physiologic challenges the patient incurs at home (e.g., allergies, alcohol, medication effect). Setup errors may occur from the assumption that the ordered therapy is the one delivered, or that the patient is using the device correctly. This can be avoided by physicians requiring patients to bring the device to the clinic and demonstrate its usage. Physicians can quickly determine patients' proficiency with the equipment by watching patients don the mask and headgear and turn on the machine. Patients who have difficulty putting on the mask or are unaware of the power button are unlikely to be using the device. Compliance and pressure settings may be verified by examining the machine's pressure setting, blower, and therapeutic hours (standard on all newer machines).

Central Sleep Apnea

CSA results from a loss of ventilatory drive and airflow for 10 seconds or more. Brief respiratory pauses are commonly seen even in healthy individuals during transitions from wakefulness to light sleep. However, when these events become lengthy, frequent (more than five per hour), persist into deeper stages of sleep, and/or are accompanied by oxygen desaturations or arousals, daytime consequences may ensue. Central apneas typically indicate a dysfunction of the regulatory process controlling breathing. CSR, one common form of central apnea, is described in the next section.

CSA, excluding CSR, may occur from endogenous brain dysfunction inducing a high CO_2 apnea threshold, increased CO_2 sensitivity, or abnormal primary respiratory cycling. Central apneas also occur with narcotic use, excessive alcohol, increasing age (over 65), and acute brain injury or stroke. Individuals with CSA may complain of insomnia or disrupted sleep, or have bed partners noting apneas. Clinicians should evaluate for underlying heart failure, alveolar hypoventilation, thyroid or neurologic disease, or drug use that suppresses respiratory drive. Maximal medical therapy for the underlying condition and removal of respiratory depressants are the primary treatments. Other treatment options include respiratory stimulants, supplemental oxygen, and bilevel positive airway pressure with a backup respiratory rate. The role of CPAP in these individuals is unclear at present but may be helpful.

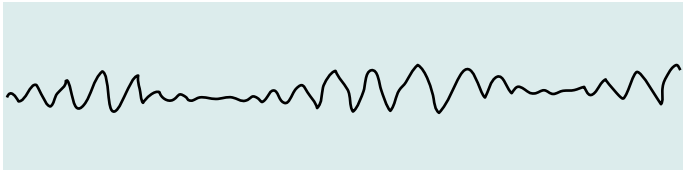


Figure 67-4 *Cheyne-Stokes respiration.*

Due to the complexity of etiology in central apneas, treatment errors may arise by not recognizing the underlying drivers of the respiratory disturbance. Patients who use narcotics or respiratory suppressants should have medication minimized. Heart failure patients should have cardiac output maximized, and individuals who are CO_2 or oxygen responsive should have therapies directed toward these drivers. Additionally, some individuals will need further pulmonary or neurologic evaluation to assess primary organ issues.

Cheyne-Stokes Respiration

CSR, a form of central apnea, is characterized by a repetitive crescendo-decrescendo pattern (Fig. 67-4). This breathing pattern is typically related to heart failure or central nervous system deficits. CSR is an example of an underdampened oscillator, swinging from hyperventilation to hypoventilation. Classic CSR becomes more apparent during light sleep and improves in REM sleep and slow-wave sleep due to the diminished response to CO_2. Underlying mechanisms of CSR include a high-sensitivity response to CO_2 and hypoxemia, a high apnea CO_2 threshold, and prolonged cardiac cycle time. In heart failure patients with CSR, sympathetic nervous system activity is higher during day and night as compared with healthy patients, and the presence of daytime CSR indicates a poorer prognosis.

Patients may present with symptoms of snoring at night, witnessed apneas, paroxysmal nocturnal dyspnea, frequent awakenings, and unrefreshing sleep. Clinicians should have a high index of suspicion. All patients with heart failure should be queried regarding the presence of symptoms of sleep-disordered breathing. Diagnostic polysomnography is the best study to detect this breathing disorder. Therapy for patients with CSR focuses on two key elements: maximization of cardiac output and improving ventilation. In some patients, supplemental oxygen and increasing end-tidal CO_2 improve the ventilatory pattern, whereas other patients may need noninvasive ventilator support.

CSR is very sensitive to positive airway pressure and changes in overall health. Patients with heart failure should have the positive airway pressure titration performed once cardiac output is maximized. Patients with strokes should be re-titrated after brain function has stabilized, typically after 3 months. In both cases, a common error occurs by increasing the positive airway pressure settings, which often increases the central apnea component.

Obesity Hypoventilation

The true pickwickian syndrome describes an obese individual who is excessively sleepy and probably suffering from obesity

hypoventilation syndrome. This disorder is defined as a body mass index greater than 30 kg/m^2 and a resting arterial pCO_2 greater than 45 mm Hg. These individuals may present with daytime sleepiness, fatigue, unrefreshing sleep, insomnia, or morning headache, but may lack a history of snoring. Because of their large thoracic and abdominal girth, these patients have lower pulmonary functional reserve capacity and breathe at lower overall lung volumes in wakefulness. During sleep, the loss of muscle tone translates into further reduction of lung volume, resulting in events of prolonged oxygen desaturation. These events are more pronounced during REM sleep because of the associated atonia. Thus, the diaphragm must push unaided against a large abdomen. The diagnosis of sleep-related hypoventilation is attained on overnight polysomnography with calibrated continuous end-tidal CO_2 measurements and correlated with morning arterial blood gas sampling. A surrogate measure predicting obesity hypoventilation is venous bicarbonate levels greater than 27 mmol/L.

Untreated obesity hypoventilation is associated with higher posthospitalization mortality rates. Observational studies suggest individuals with obesity hypoventilation experience higher rates of other vascular events, even when controlled for obesity. This syndrome can be readily treated with positive airway pressure, but patients may require ventilation beyond pressure support.

OTHER SLEEP DISORDERS

Restless Legs Syndrome

Restless legs syndrome (RLS) is defined by four criteria: an uncomfortable urge to move, the symptoms are improved by movement, the symptoms are made worse by rest, and there is a circadian pattern of increased symptoms in the evening (Box 67-6). This disorder is associated with periodic limb movements in sleep, but these are not necessary for the diagnosis. In observational studies, individuals with RLS have higher risks of hypertension and potentially cardiovascular events. The mechanistic link is unclear, and studies have yet to be performed showing the effect of treatment on vascular consequences. No studies have as yet been performed to show treatment reduces these associations. RLS is a complex disorder that requires investigation into potential etiologies such as renal failure, spinal cord disease, inherited neuropathy, anemia, and medications. Treatment focuses on improving underlying identifiable causes and symptom management, but currently it does not alter the disorder's progression.

Cardiovascular Medications and Sleep

The commonly used cardiovascular medications have not been well studied in sleep, although some effects are known. Angiotensin-converting enzyme inhibitors commonly cause cough and low-grade nasal and pharyngeal edema, which may worsen OSA. In patients with OSA, angiotensin-converting enzyme inhibitors, when not producing airway edema, are more effective in lowering nocturnal blood pressures than are other choices. α_2-adrenergic agonists such as clonidine cause a decrease in REM sleep and consequently the opportunity for REM-related apnea events; however, these agents may exacerbate daytime somnolence. β-adrenergic antagonists (β-blockers) seem to have varying effects on lowering nocturnal versus daytime blood pressures but as a class do not provide significant reduction of nocturnal blood pressures related to sleep apnea. β-blockers are associated with fatigue, nightmares, insomnia, depression, and mental cloudiness. Diuretics dosed in the evening can result in significant nocturia and disruption of sleep. Conversely, some patients with hypersomnia are treated with stimulant medications that may increase daytime blood pressure and increase risk of cardiovascular events.

Box 67-6 Criteria for Restless Legs Syndrome

Discomfort or urge to move
Worse with rest
Better with movement
More prominent in the evening

FUTURE DIRECTIONS

The complex interaction of sleep and cardiovascular diseases challenges astute clinicians to be aware of the diagnostic and therapeutic opportunities in sleep and heart health. Treatment of sleep-related breathing disorders offers great hope in providing reduction of risk of further events and mortality. CSR in sleep may serve as a marker of cardiac function. Current knowledge highlights the importance of diagnosing and adequately treating sleep-disordered breathing to improve overall health and maximize function. However, research is needed to clarify these interactions and the impact of treatment of both cardiovascular disease and sleep.

Our understanding of the mechanisms involved in the effects sleep disorders have on the cardiovascular system is rapidly expanding. Further work is needed in understanding mechanisms by which sleep balances the immune, autonomic, and endocrine systems, and how these pathways may be beneficial to the heart. Through these opportunities we can offer novel therapies that incorporate the circadian and neural systems in improving function and quality of life.

ADDITIONAL RESOURCES

American Academy of Sleep Medicine. *The international classification of sleep disorders.* 2nd ed. Westchester, Ill.: American Academy of Sleep Medicine; 2005.

Reviews the characteristic features, requirement for diagnosis, and associated findings for all recognized sleep disorders.

Kryger M, Roth T, Dement W. *Principles and practice of sleep medicine.* 4th ed. Philadelphia: Elsevier Saunders; 2005.

Comprehensive review of all sleep physiology, sleep disorder pathophysiology, and treatment including technical features of sleep studies. An excellent reference with insightful chapters and sections highlighting current knowledge in sleep medicine.

Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *Circulation.* 2008;118:1080–1111.

AHA/ACC scientific statement for association of OSA and cardiovascular disease; an excellent review of current evidence.

EVIDENCE

Kaneko Y, Floras JS, Ussi K, et al. Cardiovascular effects of continuous positive airway pressure in obstructive sleep apnea and heart failure. *N Engl J Med.* 2003;348:1233–1241.

This small but significant study showed that treatment of OSA with CPAP can improve ejection fraction and lower daytime heart rate.

Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapuetic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized parallel trial. *Lancet.* 2002;359:204–210.

This randomized control trial shows a reduction in blood pressure with the treatment of OSA, demonstrating the preventive value of effective therapy.

Punjabi NM, Newman A, Young T, et al. Sleep disordered breathing and cardiovascular disease: an outcome based definition of hypopneas. *Am J Respir Crit Care Med.* 2008;177:1150–1155.

Examines data from the Sleep Heart Health Study to demonstrate what features of hypopnea are associated with cardiovascular events, particularly showing that desaturation plays an important role.

Cardiovascular Toxicity of Noncardiac Medications

68

Eric H. Yang

Several noncardiac medications have deleterious effects on the cardiovascular system. These effects can be classified as transient or permanent and can result in functional and/or structural abnormalities in the heart and vasculature. Cardiotoxic drugs with permanent structural effects are the most harmful and are the focus of this chapter. Shown in Box 68-1, these drugs can be classified based on the location of their cardiotoxic effects: myocardium, valves, or coronary arteries.

MYOCARDIAL TOXICITY

Anthracyclines

Doxorubicin, daunorubicin, and idarubicin are anthracycline chemotherapeutic agents commonly used in the treatment of a large number of malignancies. Since the first use in the 1960s, several reports have linked high doses of doxorubicin to cardiomyopathy. The cardiotoxic effects are almost certainly dose-related. Cardiomyopathy occurs in approximately 4% of patients who receive a maximum lifetime dose of 550 mg/m^2 of doxorubicin or 450 mg/m^2 of daunorubicin or idarubicin and in up to 18% of those treated with higher doses of the drugs. The risk of doxorubicin-induced (or daunorubicin- or idarubicin-induced) cardiomyopathy is increased in patients who are older than 70 years of age, receive radiation therapy to the chest, and/or have baseline structural heart disease. The exact mechanism of cardiotoxicity is unknown. Current thinking is that oxidative stress is increased in individuals treated with these drugs. Given its high metabolic demand, the heart is sensitive to changes in oxidative stress, and increases can result in cardiomyocyte apoptosis. The effects seem to be permanent but may be avoided with limited exposure and by pretreatment with β-blockers and angiotensin-converting enzyme inhibitors.

Trastuzumab

Approximately 25% of breast cancers overexpress the HER2 (human epidermal growth factor receptor) protein or are associated with amplification of the *HER2* gene. Trastuzumab (Herceptin; Genentech, South San Francisco, CA) is a monoclonal antibody specific to the extracellular domain of the HER2 protein. When used in conjunction with conventional chemotherapy, trastuzumab improves survival in patients with breast cancer who are HER2-positive. Combined data from the initial clinical trials show that the occurrence of overt clinical heart failure is rare, but up to 14% of patients have an asymptomatic decline in their ejection fraction during therapy. The exact mechanism is unclear but appears not to involve free radical generation or oxidative stress. It has been proposed that trastuzumab may interfere with cell signaling within myocytes and inhibit the natural response to cardiac stress, which then results in an increased risk of irreversible loss of function when the myocytes are further stressed. Thus, unlike doxorubicin toxicity, trastuzumab toxicity may be reversible if the drug is discontinued early. Left ventricular function in patients receiving trastuzumab therapy should be monitored closely, and any reduction in left ventricular function should prompt consideration of whether therapy can be discontinued or delayed.

Ethanol

Ethanol abuse has been demonstrated to result in dilated cardiomyopathy. Of patients with a history of excessive alcohol use longer than 10 years (>125 mL/day), approximately 20% develop cardiotoxicity. It was once thought that the pathophysiology is related to nutritional deficiencies, but the mechanism may be more complex and probably involves ethanol itself as well as its metabolites. Ethanol is oxidized by alcohol dehydrogenase to form acetaldehyde, which is believed to have direct cardiotoxic effects. In addition, ethanol can react with nonesterified fatty acids to form fatty acid ethyl esters that interfere with mitochondrial function. During the early stages of ethanol-induced cardiomyopathy, the effects are reversible with cessation of alcohol intake. The cardiotoxic effects, however, become permanent in the latter stages and cannot be reversed with cessation of alcohol use.

Hydroxychloroquine

The antimalarial drug chloroquine and its oxidized metabolite hydroxychloroquine have been used extensively in the treatment of systemic lupus and rheumatoid arthritis. Excessive use results in retinopathy, neuropathy, as well as myopathy. Several case series and reports have also shown that long-term use at high doses can result in cardiotoxic effects, including conduction disorders, as well as a hypertrophic cardiomyopathy. On light microscopy, chloroquine cardiomyopathy seems to be similar to Fabry's disease; however, the two can be distinguished with the use of electron microscopy. Curvilinear bodies can be seen in the myocardium of patients with chloroquine-induced cardiomyopathy but are absent in Fabry's disease. The exact mechanism and prognosis of the disease are unknown.

VALVULAR TOXICITY

Phentermine and Fenfluramine

Phentermine and fenfluramine were initially approved by the U.S. Food and Drug Administration (FDA) as individual appetite suppressant agents in 1959 and 1973, respectively. Both agents are synthetic analogues of amphetamine. Fenfluramine

Box 68-1 Classification of Cardiotoxic Medications

Myocardial Toxicity
Anthracycline derivatives
Trastuzumab
Ethanol
Chloroquine, hydroxychloroquine

Valvular Toxicity
Phentermine and fenfluramine
Ergot alkaloids
  Ergotamine
  Methysergide
  Pergolide

Coronary Artery Toxicity
Protease inhibitors

also inhibits presynaptic reuptake of serotonin (Fig. 68-1). Combination use of the two drugs became prevalent in the 1980s, and by the late 1990s, case reports on an unusual valvular disease in patients taking combination therapy were published. The mitral, aortic, and tricuspid valves were reported to be most affected. Acquired abnormalities of the mitral valve included thickening of the anterior leaflet and immobilization of the posterior leaflet, resulting in mitral regurgitation. Aortic valve involvement included valve thickening along with retraction of the leaflets resulting in aortic valve insufficiency. The anterior leaflet of the tricuspid also becomes thickened and immobile with subsequent tricuspid regurgitation. These observations resulted in an FDA investigation that revealed significant valvular abnormalities in approximately 25% of patients receiving combination phentermine and fenfluramine therapy. Both drugs were then withdrawn from the market. The exact pathophysiology is still not completely understood. Notably, however, the valvular abnormalities resemble those seen in individuals with serotonin-producing tumors—suggesting that serotonin itself may be important in the valvular abnormalities that were reported.

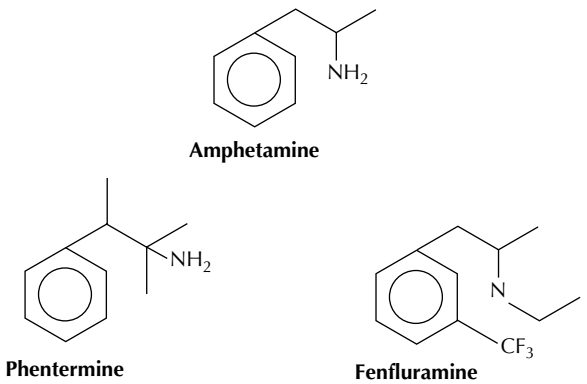


Figure 68-1 *Chemical structures of amphetamine, phentermine, and fenfluramine.*

Ergot Alkaloids

Ergotamine and methysergide are serotonin analogues that have been used for the treatment of migraine headaches (Fig. 68-2). Long-term use of these agents has been associated with mitral and aortic valvular disease. Both compounds can cause a carcinoid-like fibrotic reaction on the endomyocardial surface of the aortic and mitral valves. The subvalvular structures can also be affected. The exact mechanism is not known but, as with phentermine and fenfluramine, may involve the drugs' serotonin-like effects.

Pergolide is an ergot-derived dopamine receptor agonist that has been used in the treatment of patients with Parkinson's disease. Long-term use has been associated with pericardial fibrosis. In some patients, restrictive mitral valve disease has also occurred. As with the other ergot derivatives, the mechanism is believed to involve its serotonin-like effects. As a result of these safety concerns, pergolide was voluntarily withdrawn from the U.S. market in March 2007.

CORONARY ARTERY TOXICITY

Protease Inhibitors

Highly active antiretroviral therapy (HAART) has become the cornerstone of treatment for HIV/AIDS. Several classes of drugs are commonly used, including protease inhibitors. Since their approval in 1995, there has been concern that there may be an increased risk of myocardial infarction (MI) in individuals who receive long-term HAART. Evaluation of data from a prospective observational study of 23,437 patients revealed that use of protease inhibitors for longer than 6 years resulted in a fourfold increase in the incidence of MI. The mechanism for increased cardiac events probably involves the dyslipidemia caused by protease inhibitors along with the traditional cardiac risk factors present in patients using these medications. Other mechanisms may also contribute, since the odds ratio for MI was 1.10 after adjustment for lipid levels as well as other traditional risk factors. For most individuals receiving HAART, the benefit from suppression of HIV outweighs the risk of MI. However, given the increased risk associated with dyslipidemia, most centers recommend concurrent administration of a statin to individuals receiving HAART.

CONCLUSION

In summary, long-term use of several different classes of clinically useful drugs has been shown to result in cardiotoxicity. For some medications the effects are reversible if detected during the early phases of therapy. Appropriate cardiac monitoring and cardioprotective strategies should be implemented in all patients using these medications.

FUTURE DIRECTIONS

Cardiotoxicity is an uncommon but serious adverse effect of pharmacologic agents used to treat both cardiac and noncardiac disease in humans. Cardiotoxicity, however, was formerly not an end point in many Phase II and III trials. The growing

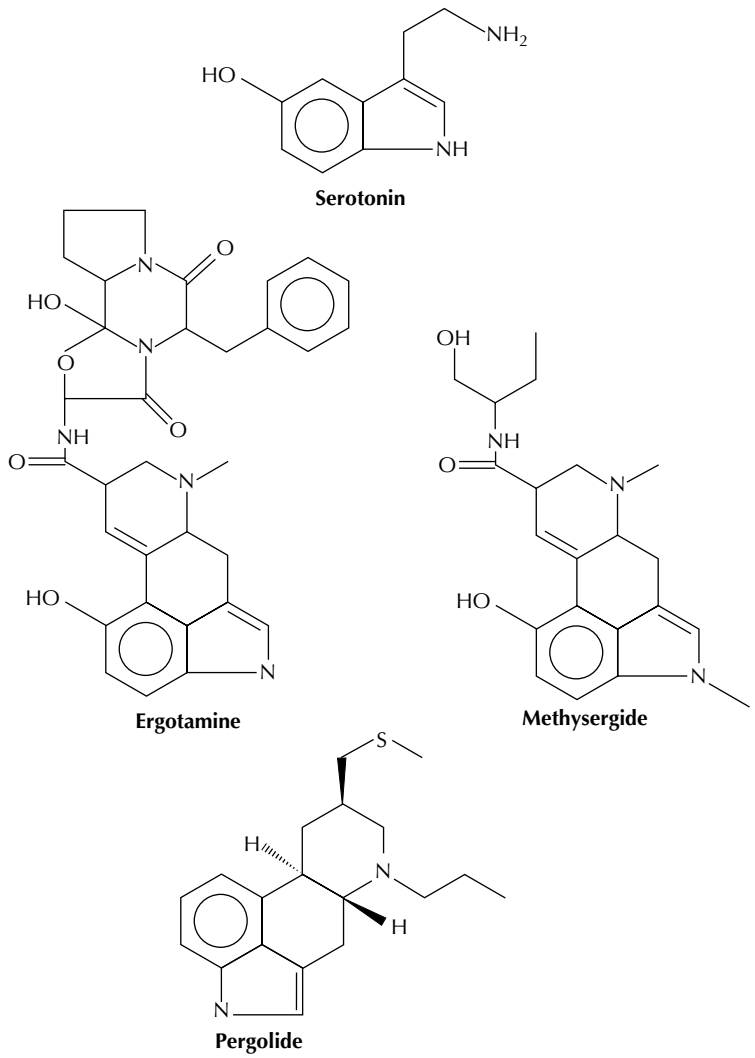


Figure 68-2 *Chemical structures of serotonin, ergotamine, methysergide, and pergolide.*

concern over long-term cardiac effects will hopefully lead to a greater portion of safety studies that look at potential harmful cardiac effects of new medications.

EVIDENCE

Connolly HM, McGoon MD. Obesity drugs and the heart. *Curr Probl Cardiol.* 1999;24:745–792.

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The DADSG. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med.* 2007;356:1723–1735.

Analysis of a database from a large prospective observational study of over 23,000 patients treated with protease inhibitors.

Piano MR. Alcoholic cardiomyopathy: incidence, clinical characteristics, and pathophysiology. *Chest.* 2002;121:1638–1650.

Comprehensive discussion of the epidemiology, mechanism, and pathophysiology of ethanol cardiotoxicity.

Roos JM, Aubry MC, Edwards WD. Chloroquine cardiotoxicity: clinicopathologic features in three patients and comparison with three patients with Fabry disease. *Cardiovasc Pathol.* 2002;11:277–283.

Case discussion of patients with chloroquine cardiotoxicity.

Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med.* 1998;339:900–905.

Excellent review article discussing all aspects of doxorubicin-induced cardiomyopathy.

Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet.* 2004;363:1179–1183.

Prospective study of 78 patients treated with pergolide followed by serial echocardiographic evaluations.

Sudden Cardiac Death in Athletes

69

Willis Wu and Marschall S. Runge

More Americans than ever engage in athletics—from occasional exercisers to highly competitive, high-profile amateur and professional athletes. Sudden death in athletes, especially from cardiovascular causes, is an uncommon occurrence, with an estimated prevalence of 1 in 200,000 athletes per year. Despite this low prevalence, sudden death in athletes is a noteworthy event for the media and the community for many reasons: athletes often enjoy celebrity status in American culture, athletes are typically young, and their deaths are deemed to be tragically premature. Moreover, their deaths contradict popular perception that young athletes personify health and vitality. As the number of highly trained athletes increases, more attention has been placed on the cardiovascular assessment of athletes as well as physicians' abilities both to diagnose potentially lethal diseases and to prevent early death.

CAUSES OF SUDDEN CARDIAC DEATH IN ATHLETES

Epidemiologic evidence suggests that sudden death in young athletes, ages 12 to 40 years, occurs more often in males than females, and that participation in basketball and football is implicated in greater than two thirds of cases. Of deaths not related to trauma or accidents, 90% occur during or immediately following a training workout or an athletic event. While the most common cause of death in athletes at least 35 years of age is coronary atherosclerotic disease, the two most common causes of cardiovascular death in younger athletes are hypertrophic cardiomyopathy (HCM; 36%) and anomalous origin of coronary arteries (17%). Among other cardiovascular causes of death, rupture of an aortic aneurysm associated with Marfan's syndrome, mitral valve disease, dilated cardiomyopathy, aortic stenosis, and arrhythmogenic right ventricular cardiomyopathy account for 2% to 6% of cases, while drug abuse, long QT syndrome, cardiac sarcoidosis, and other cardiovascular causes account for 0.5% to 1% of cases. Commotio cordis represents the most frequent cause of traumatic death in athletes and is the etiology of death in approximately 20% of cases. Other causes of traumatic death include head and spine injuries from bodily contact, and even vascular injury to coronary, vertebral, and internal carotid arteries from incoming projectile objects such as balls and hockey pucks. The challenge for physicians evaluating athletes for cardiac risk is to rule out potentially lethal pathology that could lead to sudden cardiac death. This chapter focuses on four of the common causes of sudden cardiac death that must be considered in evaluation of athletes.

Hypertrophic Cardiomyopathy

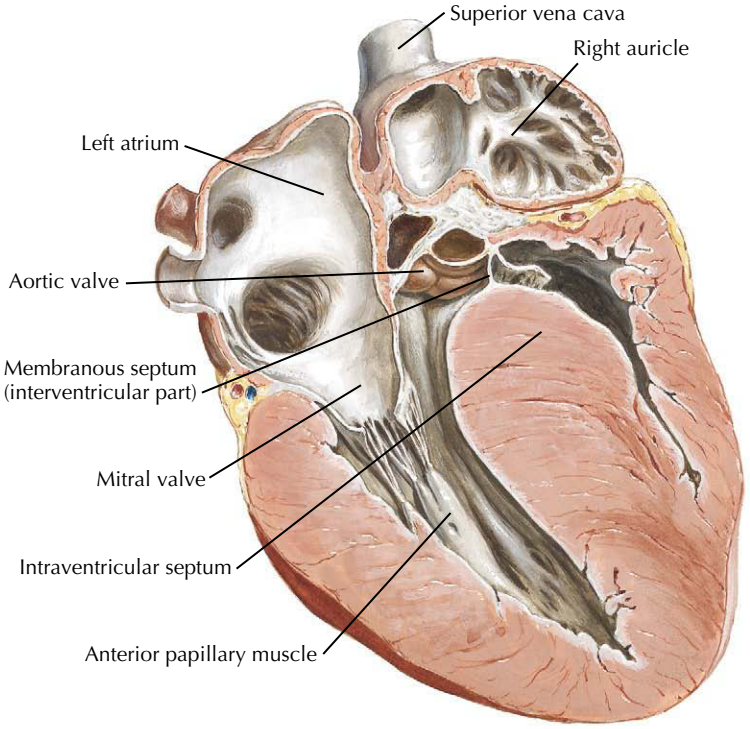
HCM, transmitted in an autosomal-dominant fashion, results from mutations in any of 10 genes that encode specific constituents of the cardiac sarcomere. Over 200 mutations have now been identified. The most common mutations involve the β-myosin heavy chain and myosin-binding protein C. The estimated prevalence of HCM in the healthy, young, general population has been estimated at 0.17% in the United States. Worldwide, the prevalence of HCM in athletes is probably lower, estimated at approximately 0.07%. Although the prevalence is low, early diagnosis of HCM is crucial for those engaged in competitive sports because of the risk of sudden cardiac death. The risk of sudden cardiac death in individuals with HCM varies considerably, depending on the causative mutation and other genetic and environmental factors that are not fully understood. Because it is not possible at present to define HCM individuals who have minimal risk, and because competitive and even strenuous exercise are associated with sudden cardiac death across the spectrum of HCM, most experts recommend against competitive athletics in individuals with HCM. Furthermore, individuals with HCM identified through this kind of screening should also be considered for potentially lifesaving therapy, including cardioverter-defibrillator implantation, depending on numerous factors.

Ventricular tachycardia and ventricular fibrillation are the most frequent etiologies of sudden cardiac death in patients with HCM. The six features associated with greatest risk for sudden cardiac death are prior cardiac arrest or sustained ventricular tachycardia, family history of one or more premature HCM-related deaths, syncope, hypotensive blood pressure response to exercise, multiple or prolonged episodes of nonsustained ventricular tachycardia on ambulatory monitoring, and left ventricular (LV) wall thickening greater than 30 mm (Fig. 69-1).

Because the hearts of highly conditioned athletes are often enlarged and proportionally hypertrophied, it is equally important not to label individuals with an "athlete's heart" as having HCM. Cardiac enlargement and hypertrophy in athletes may simply represent a physiologic response to increased myocardial demand in training, and after cessation of vigorous training these changes can resolve over time. Doppler echocardiography can help distinguish normal athletes' hearts from HCM. Normal diastolic filling patterns are generally present in enlarged and hypertrophied athletes' hearts, whereas the hearts of patients with HCM show abnormal diastolic function including decreased early peak flow velocity, slowed deceleration of early diastolic flow velocity, and increased late peak flow velocity associated with atrial systole. Besides echocardiography, metabolic exercise stress testing can distinguish HCM from athlete's heart; specifically, athletes with LV hypertrophy without HCM can achieve a peak maximum oxygen consumption of 50 mL/kg/min, but athletes with true HCM generally cannot. Cardiac MRI has also emerged as a useful tool in HCM diagnosis and may be even more sensitive than echocardiography in identifying areas of hypertrophy, especially in the anterolateral wall.

Traditionally, screening tools for HCM include a history and physical examination along with ECG and echocardiogram. Screening for HCM typically begins at age 12, unless there are

Although not always the case, massive hypertrophy of the intraventricular septum is common in hypertrophic cardiomyopathy.



Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young athletes. Although athletes may have prodromal symptoms of presyncope, an initial presentation of sudden loss of consciousness is common in these individuals.

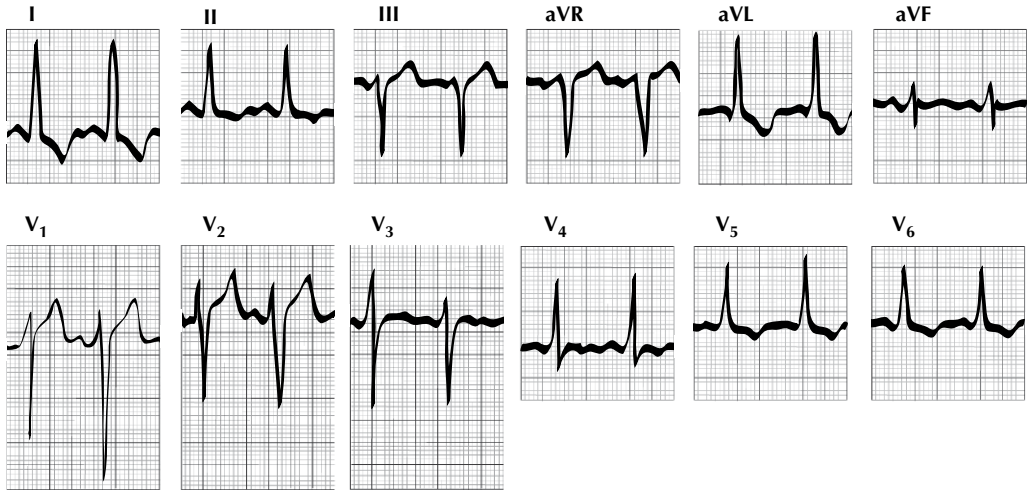


Figure 69-1 *Sudden cardiac death in hypertrophic cardiomyopathy.*

factors that would provoke an earlier or a more in-depth evaluation, including a family history of premature death related to HCM, onset of symptoms, other evidence of early LV hypertrophy, or participation in competitive athletics requiring intense physical training. Generally, screening with traditional methods has been recommended every 12 to 18 months between ages 12 and 21, when adult physical maturity is achieved. Evidence indicates that phenotypic appearance of HCM can occur well into adulthood and, in some mutations, as late as in the fifth or sixth decade of life. Thus, the absence of morphologic characteristics of HCM at early adulthood should not be viewed as conclusively ruling out HCM for either patients or practitioners. Recent recommendations have suggested continuing screening with serial ECGs and echocardiograms at 5-year intervals into midlife and perhaps beyond.

Because patients with HCM may not manifest symptoms or signs of hypertrophy until later in life and because phenotypic expression is so variable even among family members, athletes with a positive family history for HCM should be considered for further testing, to include echocardiography and MRI. Genetic analysis of families with certain HCM mutations has demonstrated that not all individuals who carry the mutation

show phenotypic or imaging evidence of HCM. Thus, many experts now also recommend genetic testing for individuals with a family history of HCM. Although some genotype-phenotype correlation studies suggest that mutations in some genes are "malignant" (associated with a high incidence of sudden cardiac death) while other mutations are "benign" (associated with a normal life expectancy), other studies have illustrated that patients with either the malignant or benign genotype can have a variable clinical course. Because of this variability, athletes identified as having any mutation associated with HCM should be considered high risk for sudden death.

Coronary Artery Anomalies

Congenital coronary artery anomalies account for a significant proportion of sudden death in athletes in the United States, especially in athletes age 35 or younger. Screening for these abnormalities is difficult, because initial clinical suspicion is lacking and routine testing is unable to identify this particular abnormality. Individuals with anomalous coronary arteries often have repetitive episodes of myocardial ischemia and/or microinfarcts that can result in an increased risk for ventricular arrhythmias. Ventricular tachycardia and ventricular fibrillation are the most common causes of sudden cardiac death in individuals with congenital coronary anomalies. Other potential causes of death include obstruction or closure of a slitlike ostium, spasm of the anomalous coronary artery, compression of the anomalous artery (due to vigorous myocardial contraction), and endothelial injury. Early identification of coronary abnormalities is particularly important, because intense physical activity should be avoided before surgical correction. At this time, coronary artery bypass grafting remains the therapy of choice, but other investigations are exploring the efficacy of reimplanting the anomalous vessels into the proper coronary sinus.

A review of two large U.S. and Italian registries demonstrated that the most common coronary artery anomalies included abnormal origin of the left main coronary artery from the right aortic sinus and origin of the right coronary artery from the left sinus.

On pathologic examination, hearts with this anomaly demonstrate a sharp takeoff of the artery at the ostium of the improper aortic sinus as well as an anatomic course passing between the aorta and the pulmonary trunk. In some specimens, the proximal portion of the anomalous artery was intramural and contained within the aortic wall. Many specimens had evidence of acute ischemia, including contraction band necrosis, wavy fibers, and early neutrophilic infiltrate in the myocardial territory supplied by the anomalous artery. There was also evidence of chronic ischemic injury and patchy replacement-type fibrosis. These pathologic specimens support the hypothesis that both acute and chronic ischemic injuries predispose athletes with anomalous coronary arteries to fatal ventricular arrhythmias. The majority of patients who died as a result of having anomalous coronary arteries were male and 60% were Caucasian, with the others being African American or Asian. Deaths have occurred at all levels of competitive athletics, from teenagers in amateur recreational sports to collegiate and professional athletes.

Although their diagnosis remained undetected, more often than not the athletes admitted to prior signs and symptoms of cardiovascular disease, including syncope, chest pain, dizziness, and palpitations. Of the 27 athletes identified in one review as having died from an anomalous origin of a coronary artery, 4 had reported at least one prior episode of syncope, and in 2 athletes, the syncopal episode occurred within 11 to 24 months of death. Recurrent syncope had occurred in 2 individuals who later died. Five athletes experienced chest pain, usually during physical exertion. In some cases, the chest pain occurred within a few days of death, while in others it occurred within 24 months of death. The presence of symptoms should alert the clinician to perform further evaluation. Importantly, routine noninvasive examinations may be misleading; 9 patients had ECGs performed before death, all of which were within normal limits. Six of the athletes underwent exercise stress testing, all the results of which were within normal limits. Two athletes had two-dimensional echocardiograms performed that were both normal. CT angiography is now capable of defining anomalous coronary arteries and should be considered in individuals with worrisome symptoms but normal examinations, ECGs, echocardiograms, and stress tests.

Commotio Cordis

Commotio cordis refers to a blunt, nonpenetrating blow to the chest wall that results in sudden cardiac death. Based on experimental data, it is thought that commotio cordis primarily occurs only when chest trauma occurs just before the peak of the T wave during repolarization. In a swine model of commotio cordis, it was demonstrated that the vulnerable point in the cardiac cycle was between 15 and 30 ms before the peak of the T wave. In this model, 90% of the chest blows (either with a ball or a wooden bat) during this portion of the cardiac cycle induced ventricular fibrillation. Blows to the chest outside of this time period did not induce ventricular fibrillation but did produce brief episodes of polymorphic ventricular tachycardia. In settings of electrolyte abnormalities or underlying cardiac disease, the induction of polymorphic ventricular tachycardia may also result in ventricular fibrillation and sudden cardiac death. Complete heart block, ST-segment elevation, and left bundle branch block were observed when impacts to the chest occurred during the QRS complex and not during the vulnerable phase. Complete heart block was only observed with chest blows during the QRS complex and not with impacts at other times during the cardiac cycle. Coronary angiography performed after blunt injury did not reveal significant coronary artery abnormalities, such as spasm, dissection, or stenosis, consistent with the idea that the cause of sudden cardiac death was arrhythmic (Fig. 69-2).

Commotio cordis has been reported in athletes engaged in sports involving a projectile ball, including baseball, softball, cricket, basketball, soccer, and lacrosse, as well as other sports such as hockey and martial arts. In a large series of 128 documented cases of commotio cordis, 58% of events occurred during baseball or softball games whereas 16% of events occurred during hockey games. Most cases of commotio cordis during athletic events involved a projectile causing blunt force to the chest wall. Most of these projectiles were

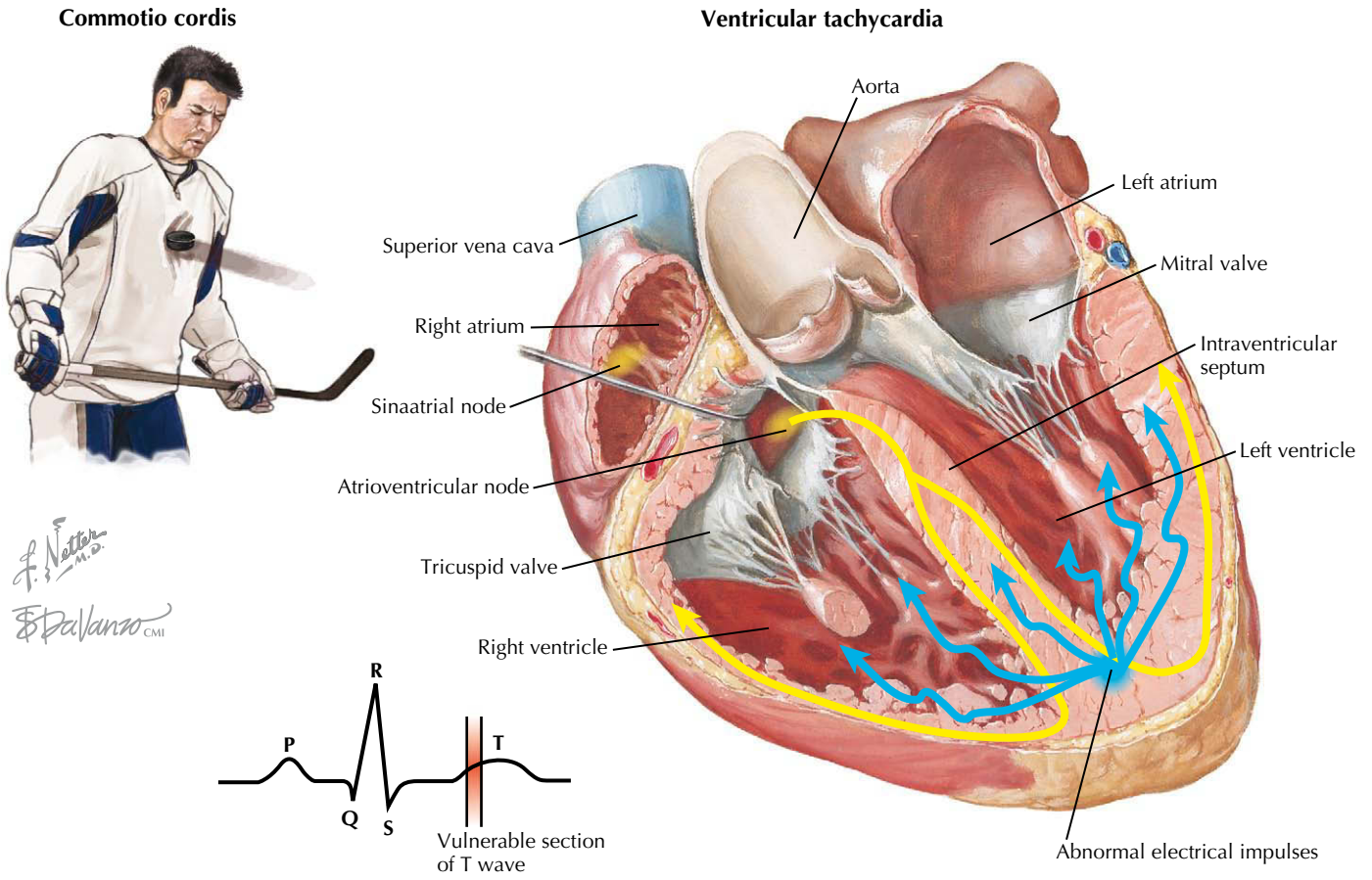


Figure 69-2 *Mechanism of sudden cardiac death in commotio cordis.*

balls composed of a solid core rather than an air-filled ball (i.e., soccer or basketball). Nonprojectile causes of commotio cordis included bodily contact between players with a shoulder, elbow, knee, or foot. Of particular importance is that a large percentage of commotio cordis events occurred during recreational activities outside of organized sports, including those residential backyards and homes. One such episode included a 5-year-old child who died after being struck in the chest by a plastic sledding saucer; another involved a man who died after his friend struck him on the chest to help alleviate his hiccups.

Survival of commotio cordis is probably related to timing of resuscitative efforts. Of the 128 cases documented in this series, 106 had cardiopulmonary resuscitation performed, mostly by trained professionals, including physicians, nurses, firefighters, and emergency medical services technicians. Of the 68 cases in which cardiopulmonary resuscitation was initiated within approximately 3 minutes or less, 17 patients survived. When cardiopulmonary resuscitation was initiated after 3 minutes, only 1 person out of 38 survived.

Although commotio cordis can occur with both hard and soft objects, there does seem to be a correlation between the object's hardness and the induction of ventricular fibrillation. In the swine model discussed previously, a wooden object simulating a bat and four types of baseballs with varying degrees of hardness were used to strike the chest wall: very soft (designed for 5- to 7-year-olds), medium-soft (designed for 8- to 10-year-olds), least soft (designed for children 11 years and older), and regulation Little League. There was a significant difference between the very soft baseball and the regulation Little League baseball, with the very soft baseball inducing ventricular fibrillation in 2 of 26 blows to the chest and the regulation baseball inducing ventricular fibrillation in 8 of 23 impacts. There was also a significant difference in induction of ventricular fibrillation between the wooden object and all baseballs. Blows to the chest with the wooden object resulted in ventricular fibrillation 90% of the time, whereas ventricular fibrillation occurred after impact with baseballs at a maximum frequency of 35% with the regulation baseballs. Unfortunately, commercially available protective equipment does not provide a total safeguard against death. The impact from a baseball traveling at 40 miles per hour can induce ventricular fibrillation up to 49% of the time despite the use of commercially available protective chest gear. Similarly, lacrosse chest protectors allowed ventricular fibrillation to occur up to 50% of the time when impact was delivered with a lacrosse ball traveling at 40 miles per hour.

Marfan's Syndrome

Marfan's syndrome is a connective tissue disorder inherited in an autosomal-dominant pattern that can present with any of several manifestations including involvement of the cardiovascular, musculoskeletal, dermatologic, neurologic, ophthalmologic, and gastrointestinal systems. It is most commonly the result of mutations of the fibrillin 1 gene (also called *FBN1*), which is located on chromosome 15. FBN1 is a glycoprotein that composes the predominant structural foundation of the extracellular matrix in elastic and nonelastic tissue. In the medial layer of the arterial wall, defective fibrillin glycoproteins elongate, causing arterial dilatation and formation of arterial aneurysms.

The prevalence of Marfan's syndrome is estimated to be 1 in 5000, although the percentage of highly trained athletes with it is not accurately known. Diagnosis is based on the Ghent nosology; patients without a family history of Marfan's need to fulfill major criteria in two different organ systems and have a third organ involved, whereas those with a confirmed mutation in *FBN1* or a positive family history of Marfan's only require one major criterion and involvement in one other organ system.

The most serious cardiovascular complication of Marfan's syndrome is aneurysm development, most commonly in the ascending aorta. Both the increased wall stress that occurs with aneurysmal dilatation and defects in the medial layer of the aorta predispose Marfan's patients to the risk of sudden death resulting from aortic dissection and/or rupture. Because the aortic root and proximal aorta are the most commonly involved segments, careful evaluation of Marfan's patients for aortic insufficiency from aortic root dilatation should be performed on a regular basis. Individuals with Marfan's also commonly present with mitral valve prolapse, with or without significant valvular regurgitation. Rupture of chordae tendineae may be present as well. Careful chest auscultation for these specific murmurs during preparticipation screening of athletes can be helpful in identifying otherwise undiagnosed Marfan's syndrome.

Extracardiac manifestations of Marfan's vary. Typical features, alone or in combination with other classic characteristics, should raise the possibility of the diagnosis. The general appearance includes a tall and thin body habitus, with long arms and an arm span that often exceeds the patient's vertical height. Ligamentous and tendon laxity with hyperextensibility of joints are typical features. Other musculoskeletal complications can include a pectus carinatum or excavatum. Spinal curvature has been described as well, with kyphosis being more common than scoliosis or lordosis. Striae atrophicae can be present in areas prone to stress through stretching of the skin. Myopia is a common ophthalmologic complication, and lens dislocation is present in up to three quarters of affected individuals. Slit-lamp examinations should be performed to evaluate for this potentially serious complication. Pulmonary features include an increased risk of emphysema and spontaneous pneumothorax. Early development of abdominal hernias may be one of the gastrointestinal warning signs of Marfan's. Neurologic sequelae are seen with dural ectasias.

Evaluation of Marfan's syndrome patients with transthoracic echocardiography or other methods should be performed regularly (many authors recommend yearly and more frequently if any interval changes are present) to monitor for aortic dilatation. Individuals with Marfan's syndrome should be restricted to low-impact exercising such as walking, biking, and swimming, with the goal of working at half of maximum capacity and maintaining a pulse rate less than 100 to 110 bpm to decrease shear forces on the aorta. Contact sports or other activities involving rapid acceleration and deceleration should be avoided.

The mainstay of therapy to slow or halt progression of aortic dilation and to improve survival has been the use of β-blocking drugs. However, studies have suggested that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, through inhibition of transforming growth factor-β, may also be efficacious in slowing aortic root enlargement. Prophylactic surgical correction of aortic root aneurysms is recommended when the diameter reaches 50 to 55 mm. Earlier intervention may be warranted if other high-risk features are present, including family history of aortic dissection, rapid expansion of aneurysm, or significant aortic regurgitation, or before major noncardiovascular surgery.

STRUCTURAL CHANGES OF THE HEART AS A RESULT OF INTENSE TRAINING

Distinguishing hearts that have become enlarged with training from those due to HCM or other cardiovascular syndromes is both challenging and important. As noted, physiologic adaptations of the heart to intense exercise include ventricular dilatation and hypertrophy. These findings were first described over a century ago in cross-country skiers and were deemed at that time to be benign and even advantageous structural changes that could produce enhanced cardiac output. Cardiac adaptations to aerobic exercise, such as long-distance running and swimming, differ from those that occur in response to anaerobic exercise, for instance weight-lifting. Physiologic changes attributed to aerobic exercise include increases in maximum oxygen consumption, stroke volume, and cardiac output, and decreased peripheral vascular resistance. In contrast, predominantly anaerobic "resistance" exercise produces mild increases in maximum oxygen consumption and cardiac output, but much larger increases in blood pressure, peripheral vascular resistance, and heart rate. As a result, the impact of aerobic and anaerobic exercise on the structural morphology of the heart varies. Aerobic/endurance-type sports such as endurance cycling and swimming increase LV end-diastolic dimensions and increase LV wall thickness of similar magnitude such that the heart is enlarged but in appropriate proportions. In elite aerobic athletes with cardiac enlargement, deconditioning for 5 years causes regression of LV chamber enlargement, LV hypertrophy, and increased LV mass. Aerobic/power sports such as weightlifting and wrestling have much more of an effect on wall thickness than internal dimension, and regression to normal is often only partial (Fig. 69-3).

As noted earlier, the term "athlete's heart" refers to the heart of a highly trained athlete that has undergone physiologic changes secondary to the intense physical training. It is often difficult to distinguish athlete's heart from pathologic conditions. Between one third and half of athletes have an LV

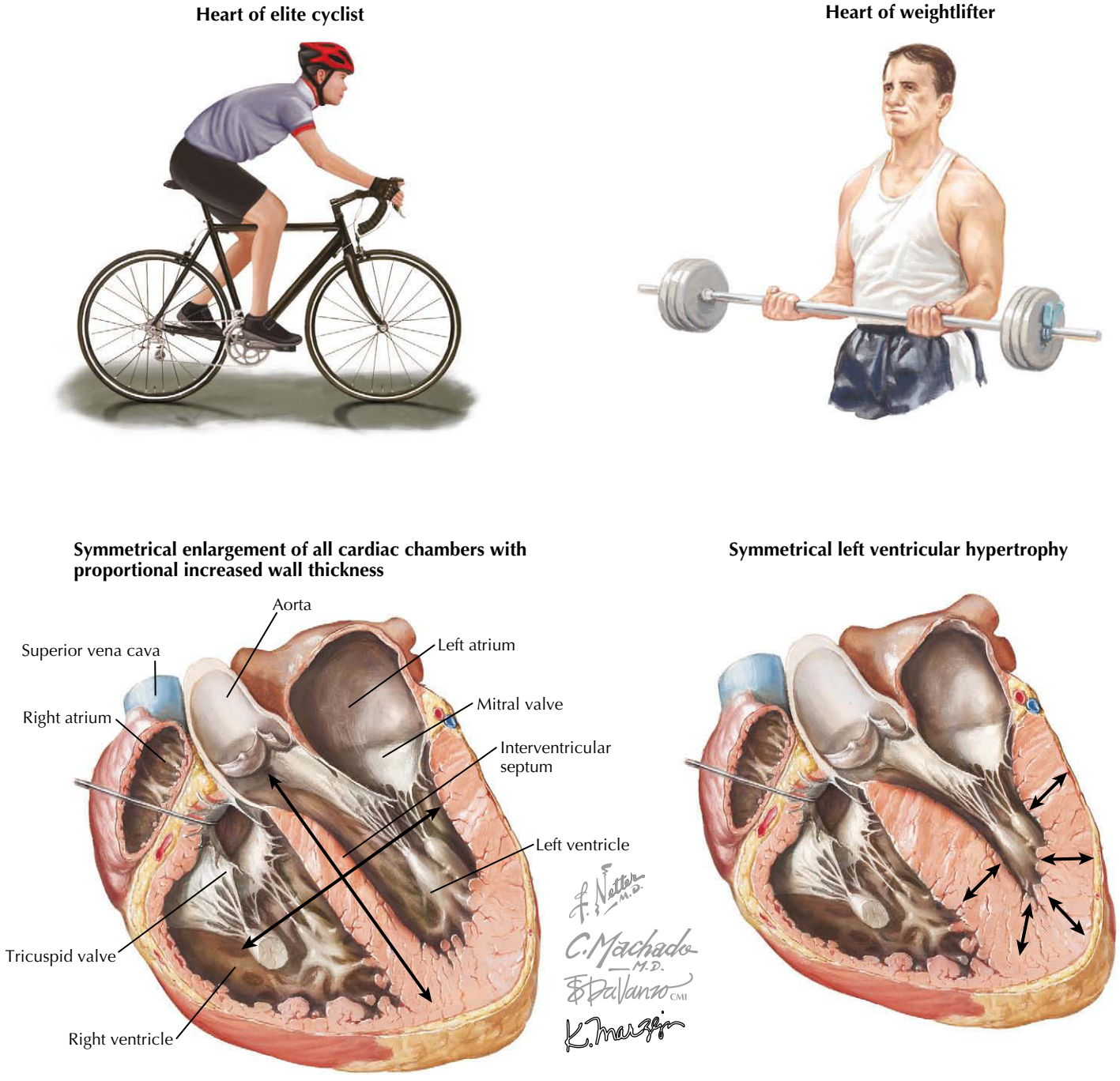


Figure 69-3 *Left ventricular hypertrophy resulting from aerobic training.*

dimension larger than 55 mm, and 14% have an LV dimension larger than 60 mm. Intraventricular septal hypertrophy, a hallmark of HCM, is not as prevalent in athlete's hearts. Only 1.1% to 1.7% of elite athletes have a wall thickness of at least 12 mm. When an athlete's LV thickness falls on the boundary between physiologic adaptation to training and true pathology (i.e., 13–15 mm), other factors may have to be considered to make an accurate distinction. For example, an LV cavity dimension greater than 55 mm, evidence of regression of LV thickness with deconditioning, and a normal Doppler diastolic filling pattern all suggest a diagnosis of athlete's heart and not HCM.

DIAGNOSTIC APPROACHES

Electrocardiographic Findings in Elite Athletes

Although the ECGs in highly trained athletes may be normal up to 60% of the time, often distinct abnormalities are present. These include repolarization abnormalities, increased voltages

suggestive of LV hypertrophy, atrial chamber dilatation, Q waves, and T-wave abnormalities. It can be difficult to discern whether these abnormalities are simply physiologic changes from intense training or if they represent true pathology. Conventional wisdom has been that repolarization abnormalities on ECG do not necessarily imply significant clinical implications in athletes. While this may be true in general, long-term marked repolarization abnormalities are associated with a somewhat increased long-term risk of cardiac abnormalities. One study compared the long-term outcomes of athletes with normal ECGs and no evidence of structural heart disease to those with markedly abnormal repolarization abnormalities on resting ECG (defined as inverted T waves >2 mm in depth in at least three leads, but exclusive of lead III, and predominantly in the precordial leads V_2 through V_6) but without evidence of structural heart disease. Significant repolarization abnormalities were found in 1% of the total population of athletes. Of athletes with repolarization abnormalities, 6% developed later manifestations of cardiomyopathy, including HCM and dilated cardiomyopathy. Seven percent of athletes later demonstrated evidence of cardiovascular disease, including systemic hypertension, coronary atherosclerosis requiring bypass grafting, myocarditis, and supraventricular tachycardia requiring ablation. Importantly, however, none of the athletes in the control group (normal ECGs) developed a cardiomyopathy, and only 2% developed cardiovascular disease, including myocarditis, pericarditis, and supraventricular tachycardia. The overall incidence of cardiovascular disease was 14% in those with repolarization abnormalities, compared with 2% in the control group.

Premature ventricular contractions frequently can be seen on ECGs of highly trained athletes as well, but whether these changes represent true pathology is unclear. One study found that 7% of athletes who complained of palpitations or who had three or more premature ventricular contractions on their ECG had concomitant cardiac abnormalities, including mitral valve prolapse, valvular regurgitation, arrhythmogenic right ventricular cardiomyopathy, myocarditis, and dilated cardiomyopathy. Many of these patients also had nonsustained ventricular tachycardia. Despite these abnormalities, the frequency of death in this population was quite low. For those athletes who do show premature ventricular beats or ventricular tachycardia on ECG or Holter monitor, withdrawal from training can significantly decrease the amount of ventricular ectopy.

Screening

There is a precedent for nationwide screening of athletes. The Italian government has implemented legislation intended to screen sports participants for potentially life-threatening diseases. In 1963, a program targeting elite athletes, those participating at a national or international level, was implemented and run by the Institute of Sports Science. Medical care for these elite athletes includes screening for cardiac disease, including routine use of 12-lead ECG, exercise stress test, and echocardiography. In addition, athletes were subject to general and orthopedic physical examinations, routine blood tests, evaluation of nutritional habits, chest x-ray, and physiologic evaluation. In 1971, the Italian government broadened its screening program and enacted the "Medical Protection of Athletic Activities," a formalized screening program for citizens of all ages participating in organized athletics at any level. Revised in 1982, this legislation mandated that citizens participating in official competitive sports activities pass periodic examinations intended to screen for potentially life-threatening conditions. This law affects approximately 6 million citizens, representing 10% of the entire population. Yearly physical examinations, 12-lead ECG, and submaximal exercise tests are required for this population with further testing required if clinically indicated. Of approximately 22,000 elite athletes screened by the Institute of Sport Science from 1963 through 1995, 2.2% were withheld from competition because of cardiovascular abnormalities. Of these disqualified participants, 0.6% died after ignoring medical advice to stop competing.

Interestingly, in the general athletic population in Italy the most common cause for sudden death in athletes was determined to be right ventricular cardiomyopathy, unlike in North America, where HCM is the predominant cause of sudden death (Fig. 69-4). One possible explanation for this difference is that the national screening program in Italy is designed to identify and subsequently disqualify those with HCM before they can participate in athletics.

Unlike the European Society of Cardiology recommendations, the American Heart Association (AHA) does not advocate routine use of noninvasive testing such as ECG as part of preparticipation screening. The rationale for this stance is primarily logistical. The vast number of athletes to be screened (over 10 million), the low prevalence of significant cardiovascular disease causing sudden death in this population, the economic burden (estimated at approximately 2 billion dollars per year), and the lack of physician and health care provider resources to execute such a plan are significant impediments to being able to successfully screen athletes in the United States. In addition, given the prevalence of ECG abnormalities in athletes (both physiologic and pathologic), the high rate of false-positive results could lead to further testing (thus increasing economic costs) and could also have psychological consequences on the athlete. The AHA does recommend follow-up screening 2 years after the initial evaluation for a small subset of high-school athletes, and each subsequent year for the same subset of college students.

Death in U.S. student athletes, although rare—occurring in 1 in 200,000 students per academic year—is a devastating occurrence. As a result, efforts have been implemented to screen for cardiovascular disease in this population. The updated 2007 AHA recommendations for preparticipation screening in competitive athletes include five components of personal history (exertional chest pain/discomfort, unexplained syncope/near-syncope, excessive exertional and unexplained dyspnea/fatigue associated with exercise, elevated systemic blood pressure, and prior recognition of a heart murmur); three components of family history (premature death before age 50 years due to heart disease in one or more relatives, disability from heart disease in a close relative younger than 50 years of age, or specific knowledge of certain cardiac conditions in family members including hypertrophic or dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan's syndrome, or clinically important arrhythmias); and four components of the physical examination (heart murmur, femoral pulses to exclude

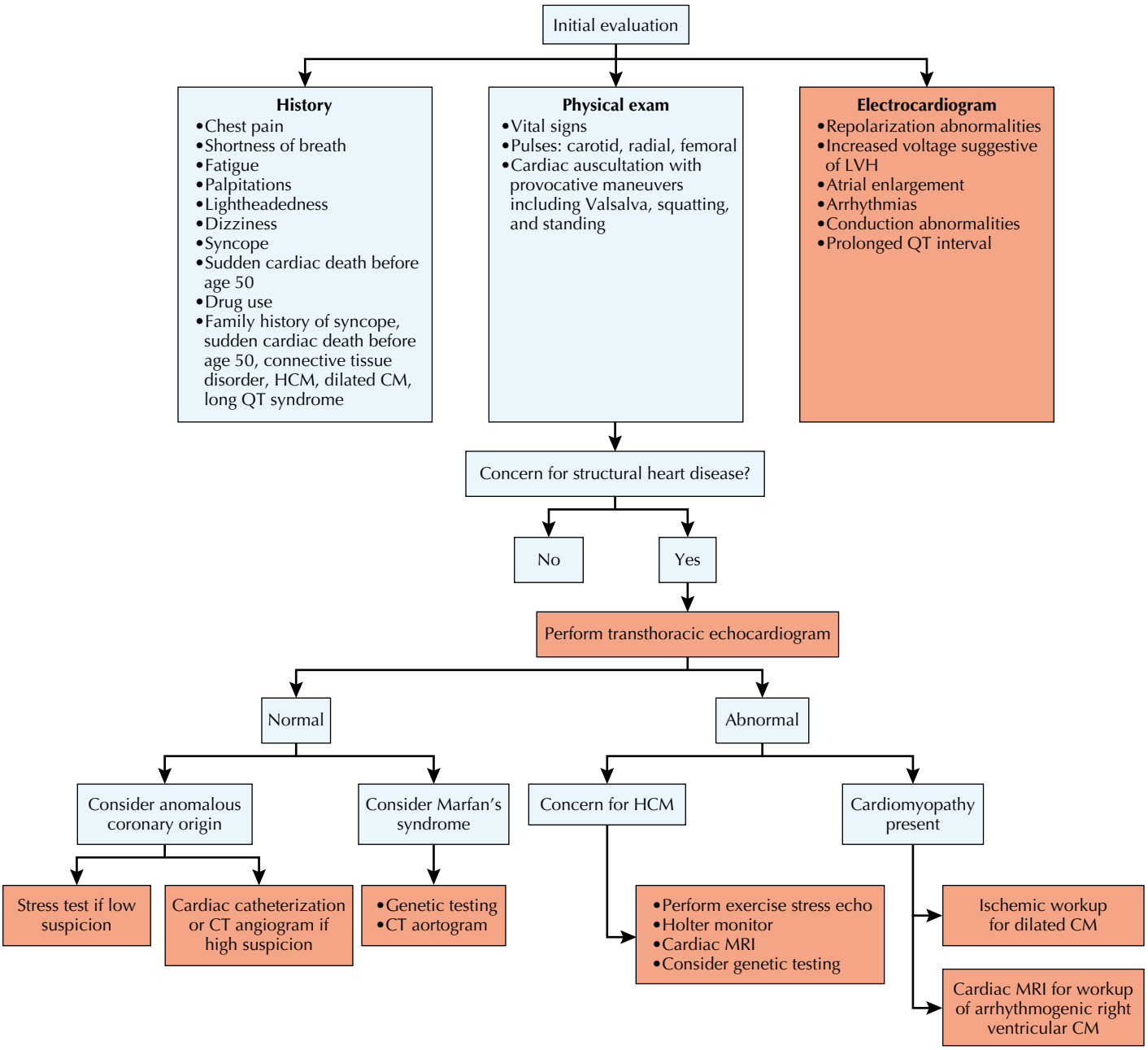


Figure 69-4 *Algorithm for the diagnosis of hypertrophic cardiomyopathy (HCM).* CM, cardiomyopathy; CT, computed tomography; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging.

aortic coarctation, physical stigmata of Marfan's syndrome, and brachial artery blood pressure) that should be evaluated before participation in competitive athletics.

Although similar recommendations have been published since 1996, they have not been adhered to adequately. A recent study evaluated the preparticipation screening process for 625 colleges and universities; only 26% of schools utilized at least 9 of the 12 recommendations outlined by the AHA panel, and 24% of the schools utilized 4 or fewer of the recommendations. The recommended items in the personal and family history were included in 9% to 75% of the school's preparticipation forms. Recommended physical examination items including assessment of blood pressure and heart murmurs were included on approximately 99% of the forms, but screening for Marfan's syndrome and evaluation of femoral pulses were only included on 2% of the forms. Most screening was performed by orthopedic surgeons, family practitioners, internal medicine physicians, and pediatricians, in descending order of frequency. Only 5% of the physicians performing the screening had formal cardiovascular training. Only 7% of the schools performed noninvasive testing with ECG, exercise stress testing, echocardiography, or chest x-ray on a routine basis.

Screening practices for American professional athletic teams are more uniformly applied, probably because of the

smaller sample size and greater financial resources. A recent survey of 122 professional teams, representing the four major professional leagues (National Hockey League, Major League Baseball, National Football League, and the National Basketball Association), demonstrated that personal and family history taking, in addition to physical examination, were required by 94% of these teams. Similarly, 97% of these teams also required annual cardiovascular screening. Cardiovascular specialists were involved in the screening process for 30% of the teams, which is substantially higher than that for collegiate athletes. Frequent parameters assessed included blood pressure, lipid panel, blood glucose levels, and assessment for prior tobacco use. Routine ECG was performed by almost all teams (92%), but routine echocardiography, exercise stress testing, and stress echocardiography were routinely ordered by less than 15% of the teams.

The four major professional leagues differ in screening approaches. Major League Baseball has implemented screening guidelines that include 10 of the 12 AHA screening recommendations, in addition to ECG, lipid assessment, and glucose monitoring. National Hockey League screening practices include eight AHA screening recommendations. National Football League screening practices includes only three AHA screening recommendations in addition to limited history and physical examination, ECG, chest radiography, lipid profile, and glucose monitoring. The National Basketball Association does not have standardized recommendations for screening.

AVOIDING TREATMENT ERRORS

Prevention of sudden cardiac death in athletes is less an issue of treatment than of early diagnosis. Despite the challenges inherent in adequately screening large populations with subtle abnormalities, the objective finding that screening efforts are often less than recommended indicates that more comprehensive screening could reduce the incidence of sudden cardiac death.

FUTURE DIRECTIONS

The potential for more accurate and efficient screening is high. Genetic analysis is just beginning and without doubt will become increasingly valuable in screening athletes. There is, as well, the potential for definitive therapy for the heritable cardiac abnormalities discussed. Though not on the immediate horizon, it is likely that investigation into both of these areas will result in fewer instances of sudden cardiac death in young athletes.

ADDITIONAL RESOURCES

COMMOTIO CORDIS

Maron BJ, Gohman TE, Kyle SB, et al. Clinical profile and spectrum of commotio cordis. *JAMA.* 2002;287:1142–1146.

An analysis of 128 confirmed cases of commotio cordis entered into the U.S. Commotio Cordis Registry as of 1 September 2001. It describes the demographics of the patients, event setting, resuscitation success rates, and effectiveness of chest wall protection.

Weinstock J, Maron BJ, Song C, et al. Failure of commercially available chest wall protectors to prevent sudden cardiac death induced by chest wall blows in an experimental model of commotio cordis. *Pediatrics.* 2006;117:e656–e662.

This study used a swine model of commotio cordis investigating the effectiveness of commercially available chest protectors in preventing ventricular fibrillation. Neither baseball nor lacrosse chest protectors significantly reduced the incidence of ventricular fibrillation compared with no chest protector.

ELECTROCARDIOGRAPHIC ABNORMALITIES

Pelliccia A, Di Paolo F, Quattrini F, et al. Outcomes in athletes with marked ECG repolarization abnormalities. *N Engl J Med.* 2008;358:152–161.

A case-control study composed of 81 trained athletes with deeply inverted T waves who were followed for a mean of 9 years. Of these athletes, 6% had cardiomyopathies compared with none of the 229 matched controls.

Sharma S, Whyte G, Elliott P, et al. Electrocardiographic changes in 1000 highly trained junior elite athletes. *Br J Sports Med.* 1999;33:319–324.

This study characterizes the spectrum of ECG findings in 1000 elite junior athletes ages 14 to 18 years of age. ECG abnormalities are similar to those found in more senior athletes, including signs of LV hypertrophy and T-wave inversions.

CORONARY ARTERY ANOMALIES

Basso C, Maron BJ, Corrado D, et al. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. *J Am Coll Cardiol.* 2000;35:1493–1501.

A retrospective analysis of 27 cases of athletes who died suddenly who were found to have congenital coronary anomalies at autopsy. Cardiac symptoms, including chest pain and syncope, had preceded death in many of these patients.

SCREENING

Corrado D, Pelliccia A, Halvor Bjornstad H, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J.* 2005;26:516–524.

A consensus statement made by cardiovascular specialists and other expert physicians that urges the importance of preparticipation screening of young athletes and stresses the utility of the 12-lead ECG in screening for serious cardiovascular diseases.

Harris KM, Sponsel A, Hutter AM, et al. Cardiovascular screening practices of major North American professional sports teams [brief communication]. *Ann Intern Med.* 2006;145:507–511.

Examines the preparticipation screening practices for 122 professional sports teams in North America using information derived from questionnaires and compares them with recommendations made by the AHA.

Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update. A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* 2007;115:1643–1655.

Statement addressing the advantages, limitations, and feasibility of screening for serious cardiovascular diseases in competitive athletes in the United States. It is an update of the 1996 AHA preparticipation screening scientific statement.

Pelliccia A, Di Paolo FM, Corrado D, et al. Evidence for efficacy of the Italian national pre-participation screening programme for identification of hypertrophic cardiomyopathy in competitive athletes. *Eur Heart J.* 2006;27:2196–2200.

A cohort study composed of 4500 young athletes demonstrated the success of the preparticipation screening program in Italy in identifying patients with HCM using 12-lead ECG, history, and physical examination.

Pfister GC, Puffer JC, Maron BJ. Preparticipation cardiovascular screening for US collegiate student-athletes. *JAMA.* 2000;283:1597–1599.

This study utilized information gathered via questionnaires from 1110 National Collegiate Athletic Association institutions, which demonstrated the variability in the preparticipation screening process implemented by American collegiate teams.

HYPERTROPHIC CARDIOMYOPATHY

Basavarajaiaj S, Wilson M, Whyte G, et al. Prevalence of hypertrophic cardiomyopathy in highly trained athletes. *J Am Coll Cardiol.* 2008; 51:1033–1039.

Examines ECG and echocardiographic findings of 3500 elite British athletes and demonstrates that the prevalence of HCM is rare and screening with echocardiography is not cost-effective.

Maron BJ, Seidman JG, Seidman CE. Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2004;44:2125–2132.

Describes the genotypic and phenotypic characteristics of HCM and proposes a more intensive screening practice for patients with a positive family history of the disease.

ATHLETE'S HEART AND SUDDEN DEATH

Maron BJ. Sudden death in young athletes. *N Engl J Med.* 2003;349: 1064–1075.

Review article covering many topics including the causes of sudden cardiac death in athletes, structural changes in the heart of athletes, and preparticipation screening practices.

Maron BJ, Pelliccia A. The heart of trained athletes. *Circulation.* 2006; 114:1633–1644.

Review article that focuses on the structural changes that occur in the hearts of highly trained athletes and addresses the causes of sudden death.

EVIDENCE

COMMOTIO CORDIS

Link MS, Wang, PJ, Pandian NG, et al. An experimental model of sudden death due to low-energy chest-wall impact (commotio cordis). *N Engl J Med.* 1998;338:1805–1811.

This study uses a swine model to demonstrate that ventricular fibrillation follows impacts to the chest wall occurring 30 to 15 ms before the peak of the T wave on ECG. Ventricular fibrillation did not occur following chest blows at any other time in the cardiac cycle. Reported that the likelihood of inducing ventricular fibrillation is related to the ball's hardness.

Maron BJ, Link MS, Wang PJ, et al. Clinical profile of commotio cordis: an under appreciated cause of sudden death in the young during sports and other activities. *J Cardiovasc Electrophysiol.* 1999;10: 114–120.

Describes certain characteristics of 70 patients from the United States Commotio Cordis Registry as of 1 July 1998. Relevant issues include mechanism of events, survival characteristics, principles of protection, and prevalence of commotio cordis.

Maron BJ, Poliac LC, Kaplan JA, et al. Blunt impact to the chest leading to sudden death from cardiac arrest during sports activities. *N Engl J Med.* 1995;333:337–342.

The authors describe the demographic characteristics, type of impact to the chest, circumstances of collapse, resuscitative efforts, protective padding, and autopsy findings of 25 victims of commotio cordis. Cases were selected from registries and news media reports.

ELECTROCARDIOGRAPHIC ABNORMALITIES

Biffi A, Maron BJ, Verdile L, et al. Impact of physical deconditioning on ventricular tachyarrhythmias in trained athletes. *J Am Coll Cardiol.* 2004;44:1053–1058.

Examines the effect that withdrawal from intense physical training has on the frequency of premature ventricular contractions and ventricular tachycardia in 355 athletes. Withdrawal from sports for even 3 months resulted in significantly less ventricular arrhythmias.

Biffi A, Pelliccia A, Verdile L, et al. Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. *J Am Coll Cardiol.* 2002;40:446–452.

The authors evaluate the frequency of cardiac abnormalities in 355 athletes who have frequent premature ventricular beats and other ventricular tachyarrhythmias. Cardiac abnormalities were detected in 7% of patients, but the incidence of death was low.

Pelliccia A, Culasso F, DiPaolo FM, et al. Prevalence of abnormal electrocardiograms in a large, unselected population undergoing pre-participation cardiovascular screening. *Eur Heart J.* 2007;28: 2006–2010.

The authors prospectively evaluated 32,652 patients to assess the prevalence of ECG abnormalities in a large, unselected population of athletes and found that almost 12% of subjects have abnormal ECGs.

Pelliccia A, Maron BJ, Culasso F, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation.* 2000;102: 278–284.

Authors correlate ECG patterns (labeled as normal, mildly abnormal, and distinctly abnormal) with echocardiographic findings in 1005 highly trained athletes in Italy.

Serra-Grima R, Estorch M, Carrio I, et al. Marked ventricular repolarization abnormalities in highly trained athletes' electrocardiograms: clinical and prognostic implications. *J Am Coll Cardiol.* 2000;36: 1310–1316.

Examines repolarization abnormalities in 26 athletes and offers a viewpoint that such abnormalities are probably benign and should not preclude participation in sports.

CORONARY ARTERY ANOMALIES

Zeppilli P, dello Russo A, Santini C, et al. In vivo detection of coronary artery anomalies in asymptomatic athletes by echocardiographic screening. *Chest.* 1998;114:89–93.

This prospective study of 3650 athletes evaluated the utility of transthoracic echocardiography in the detection of anomalous coronary arteries. The prevalence of anomalous coronary arteries was low at 0.09% and could be detected by surface echocardiography.

SCREENING

Maron BJ. How should we screen competitive athletes for cardiovascular disease? *Eur Heart J.* 2005;26:428–430.

This editorial addresses the feasibility and limitations of implementing a nationwide screening practice for athletics in the United States similar to the European model.

Maron BJ, Douglas PS, Graham TP, et al. Task force 1: preparticipation screening and diagnosis of cardiovascular disease in athletes. *J Am Coll Cardiol.* 2005;45:1322–1326.

Offers strategies for preparticipation screening and diagnostic testing for athletes developed by the 36th Bethesda Conference.

Pelliccia A, Maron BJ. Preparticipation cardiovascular evaluation of the competitive athlete: perspectives from the 30-year Italian experience. *Am J Cardiol.* 1995;75:827–829.

Provides historical perspective and results from the national preparticipation screening program of athletes in Italy.

HYPERTROPHIC CARDIOMYOPATHY

Corrado D, Basso C, Schiavon M, et al. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med.* 1998;339:364–369.

Prospective study of sudden death in athletes from Italy from 1979 to 1996. The main cause of death was arrhythmogenic right ventricular cardiomyopathy, and HCM was significantly less common.

Lewis JF, Spirito P, Pelliccia A, et al. Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing "athlete's heart" from hypertrophic cardiomyopathy. *Br Heart J.* 1992;68:296–300.

Compares echocardiographic findings of 16 trained athletes, 12 patients with HCM, and 35 normal subjects, and demonstrates differences in diastolic indices between patients with HCM and controls.

Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. *Circulation.* 1995;92:785–789.

This article uses data from 4111 patients participating in the Coronary Artery Risk Development in (Young) Adults Study (CARDIA) and reports a prevalence of 0.17% for HCM based on echocardiographic criteria.

Rickers C, Wilke NM, Jerosch-Herold M, et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. *Circulation.* 2005;112:855–861.

Authors evaluate the thickness of LV segments via echocardiography and cardiac MRI. MRI provides an accurate means of measuring LV wall thickness and may be even more sensitive in identifying abnormal thickness of the anterolateral wall.

Sharma S, Elliott PM, Whyte G, et al. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol.* 2000;36:864–870.

Evaluates metabolic exercise testing in eight athletes with HCM. Athletes with LV hypertrophy without HCM could achieve a peak oxygen consumption of 50 mL/kg/min, whereas athletes with HCM could not.

ATHLETE'S HEART AND SUDDEN DEATH

Maron BJ, Gohman TE, Aeppli D. Prevalence of sudden cardiac death during competitive sports activities in Minnesota high school athletes. *J Am Coll Cardiol.* 1998;32:1881–1884.

Review of Minnesota State High School League records from 1985 to 1997 showed the risk for sudden cardiac death in high school athletes to be close to 1 in 200,000.

Pelliccia A, Culasso F, Di Paolo FM, et al. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med.* 1999;130:23–31.

Assessment of 1309 healthy athletes with Doppler echocardiography to evaluate the range of LV dilatation seen in this population.

Pelliccia A, Maron BJ, De Luca R, et al. Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. *Circulation.* 2002;105:944–949.

This prospective study followed 40 athletes with LV dimension greater than 60 mm, wall thickness of 13 mm, or both. The authors concluded that deconditioning results in decrease in LV size and LV wall thickness.

Pluim BM, Zwinderman AH, van der Laarse A, et al. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation.* 1999;100:336–344.

A meta-analysis of available echocardiographic studies in the medical literature from 1975 to 1998 demonstrated differential structural changes in the heart based on type of exercise.

Cardiovascular Epidemiology

Georgeta Vaidean

70

Cardiovascular epidemiology originated from the necessity to quantify the likelihood of developing a coronary event; it emerged as a bridge between basic sciences, population, and clinical research, and triggered interdisciplinary research in pharmacogenetics, proteomics, biomarkers, bioinformatics, and functional imaging. This explosive growth of information is illustrated by MEDLINE searches for "cardiovascular risk factors": one restricted to the years 1960 through 1990 retrieves 845 articles, whereas similar searches for the years 1991 through 1999 and 2000 through 2008 retrieve 2569 and 7840 articles, respectively. A better understanding of the pathogenesis, etiology, natural history, underlying mechanisms, and molecular basis of cardiovascular disease (CVD) and a better approach to design and interpretation of interventional studies have revealed multiple applications for cardiovascular epidemiology research.

CARDIOVASCULAR RISK FACTORS

Cardiovascular epidemiology and evidence-based preventive cardiology evolved around the concept of cardiovascular risk factors, which became an integral part of clinical assessment and decision making. A cardiovascular risk factor is a personal or environmental (natural or social) characteristic associated with an increased likelihood that a particular cardiovascular outcome will develop at a later time in the short or long term. Characteristics of these factors include the following: their distribution and influence are different in different populations; they are not always necessary and/or sufficient for development of clinically apparent coronary heart disease (CHD); they have a probabilistic character, because their importance resides in their statistical associations in populations; and they are not necessarily elastic. The magnitude of risk reduction achieved by therapy may not be equivalent to the increment in risk.

Categories of Risk Factors

CHD is a multifactorial disease with multilayered and overlapping "causes" (Box 70-1). More than 300 factors are described as "associated" with CHD. A National Heart, Lung and Blood Institute workshop on cardiovascular risk assessment classified factors implicated in the pathogenesis of a major coronary event into several levels: major atherogenic, plaque burden, conditional, underlying, susceptibility, undetermined, and protective. The multilayered, overlapping paradigm has a variety of mechanisms of action and interactions between levels.

CARDIOVASCULAR RISK PREDICTION: APPROACHES TO GLOBAL RISK ASSESSMENT

Clinical Importance of Global Estimates for CHD Risk

Assessment of global cardiovascular risk based on major cardiovascular risk factors has three purposes of clinical interest: identification of high-risk patients who should have immediate attention and undergo immediate intervention, motivation of patients to adhere to risk-reduction therapies, and modification of the intensity of risk-reduction efforts on the basis of the total risk estimate (Fig. 70-1). Therapeutic decisions based on quantifiable measurements improve clinical decision making, increase motivation and compliance of patients, and can be evaluated for economic planning. Guidelines for management of individual risk factors recommend matching the intensity of preventive therapy to the absolute global cardiovascular risk. Cardiovascular epidemiologic research strives to quantify this global risk via predictive models.

The most common predicted event is the incidence of CHD, which can be defined as including angina pectoris, unstable angina, unrecognized myocardial infarction (MI), recognized MI, and CHD death. When risk cut points are defined to select patients for specific therapies, definitions of coronary end points have critical importance. However, of increased interest are symptomatic heart failure, hospital admission for unstable angina, need for revascularization procedures, and changes in functional capacity and quality of life.

Relative versus Absolute Risk

Absolute global risk is defined as the likelihood that CHD will develop in a person over a specified period, given the presence of cardiovascular risk factors. Absolute risk is considered the crucial determinant of whether and when to initiate pharmacologic therapy. Absolute risk can be calculated as short-term (usually 10 years) and long-term, or lifetime risk. Relative risk is the ratio of the likelihood of CHD developing in persons with and without given risk factors or at a given intensity of a risk factor. The difference between relative and absolute risk can be explained with an example of serum cholesterol concentration.

A young adult with a very high serum cholesterol concentration is at a low absolute risk for CHD but a high relative risk compared with a young adult with a low serum cholesterol concentration. CHD is unlikely to develop in the hypercholesterolemic young adult in the next 10 years, but the individual's chances of experiencing premature CHD in the long term (e.g., before age 65) are high.

The goal for reducing elevated serum cholesterol concentration in young adults, therefore, is to retard atherogenesis throughout life, not only to prevent MI in the next decade.

Methods of Risk Assessment

Cardiovascular risk assessment uses two major approaches: simple counting and mathematical models.

COUNTING

Simple counting of the major cardiovascular risk factors can grossly rank asymptomatic subjects by the likelihood of a

Box 70-1 Categories of Risk Factors for CHD

Plaque Burden as Risk Factor
- Age (relating to the length of time an individual is exposed to risk factors)

Major Risk Factors
- Smoking
- Increased blood pressure
- Increased serum TC and LDL-C concentration
- Low serum concentrations of HDL-C
- History of diabetes mellitus

Conditional Risk Factors
- Increased serum triglyceride concentration
- Small LDL-C particles
- Increased serum lipoprotein (a) concentration
- Increased serum homocysteine concentration
- Prothrombotic factors: PAI-1, fibrinogen
- Inflammatory markers (e.g., CRP)

Underlying Risk Factors
- Overweight, obesity (especially abdominal obesity)
- Lack of physical activity
- Male sex
- Family history of premature CHD death
- Insulin resistance
- Socioeconomic factors
- Psychological and behavioral factors related to inadequate reaction to stress

Other Risk Factors with Value to Be Established
- Uric acid
- Hematocrit
- Heart rate at rest
- Infectious agents
- Environmental factors: air pollution

CHD, coronary heart disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAI-1, plasminogen activator receptor-1; TC, total cholesterol.
With permission from Smith Jr SC, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. American Heart Association. Circulation. *2000;101:111–116.*

coronary event developing. It is a rapid approach of limited complexity for daily practice and easy to implement. However, it does not apply the intensity of risk factors nor their synergistic impact on global cardiovascular risk. Hence, simple counting has a reduced predictive ability.

RISK SCORES BASED ON MATHEMATICAL MODELS

A more refined approach is the use of predictive equations, which offer quantification of the absolute risk. Predictive equations have been generated by several cohort studies, the most well known being the Framingham risk equations.

Estimating Risk Using the Framingham Risk Scores

The Framingham Heart Study has generated prediction equations based on multivariate regression models to estimate CHD risk. The outcomes predicted are total CHD and "hard CHD." In the Framingham Study, approaches based on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), whether as continuous or categorical variables, are similar in their ability to predict initial CHD events. However, extensive clinical data and clinical trial results suggest that LDL-C is the major atherogenic lipoprotein. Therefore, the use of LDL-C concentrations in the clinical setting is important whenever fasting samples are available. Despite studies advocating the use of the ratio of TC to high-density lipoprotein cholesterol (HDL-C), it was not used in Framingham predictions for two reasons. At the extremes of the TC or LDL-C distribution, equal ratios may not signify the same CHD risk, and, equally important, the use of a ratio may make it more difficult for physicians to focus on the separate values.

The blood pressure (BP) value used in the Framingham Risk Score is obtained at the time of assessment, whether the patient is taking antihypertensive drugs or not. The average of several BP measurements is needed for an accurate determination of the baseline concentration. Diabetes is defined as a fasting plasma glucose concentration greater than 126 mg/dL. The designation of "smoker" indicates any use of cigarettes within the past month.

Framingham Risk Scores provide two ways to estimate cardiovascular risk.

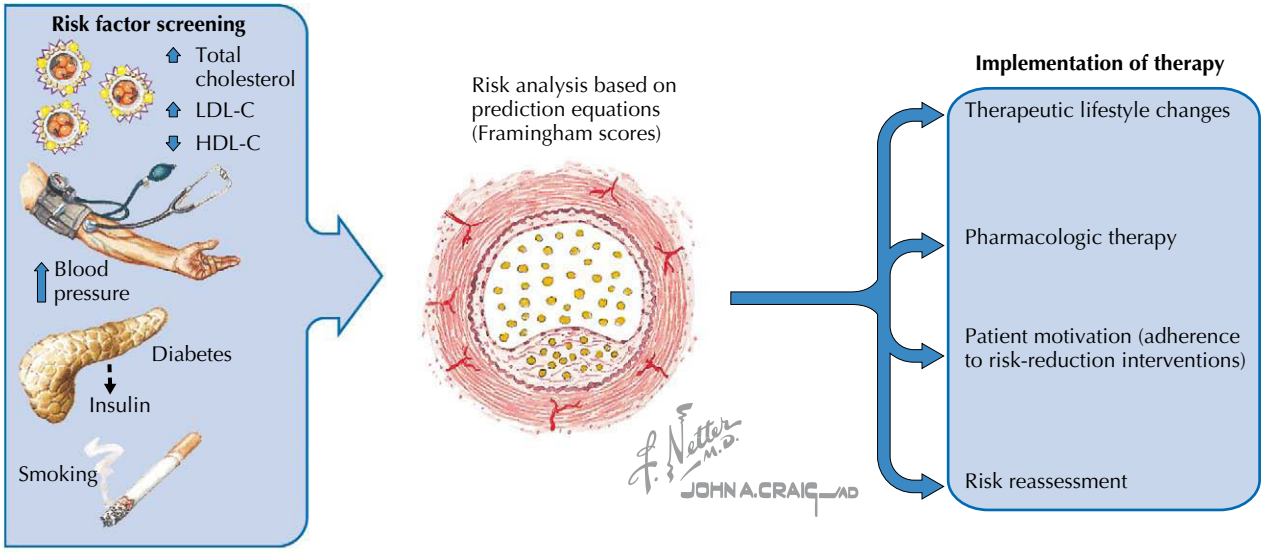
1. Comparison of an individual's estimated risk with the absolute risk of an individual at low risk, that is, a person who is largely without risk factors. This is the best way to assess the full potential for risk reduction, when introduced relatively early in life (Box 70-2). Total excess risk for an individual patient can be estimated by subtracting the absolute risk of a person of the same age and sex who is at low risk from that of the individual in question.
2. Comparison of an individual's estimated risk with the risk of an average person of the same age and sex. This approach is commonly used, although it tends to underestimate the preventable component of coronary risk because of the high prevalence of coronary atherosclerosis in the United States and most developed countries. To facilitate the use of risk prediction in clinical practice, based on these equations, simple risk score sheets are widely distributed and available for public use (see Additional Resources at the end of this chapter).

These risk prediction equations can be confidently extrapolated to other settings. Comparisons show that within sampling fluctuations, the Framingham equations discriminate reasonably well between subjects in whom clinical CHD developed and those in whom it did not. They also apply reasonably well to other (non-Framingham) populations. However, when applied to Japanese American, Hispanic, and Native American men and women, some recalibration is needed by using data on prevalence and CHD event rates specific to the population of interest.

IMPLEMENTATION: THE FINAL FRONTIER OF PREVENTIVE CARDIOLOGY

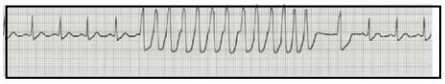
A large body of evidence supports the efficacy of risk factor modification in subjects with atherosclerosis. Cardiovascular

Coronary heart disease risk assessment

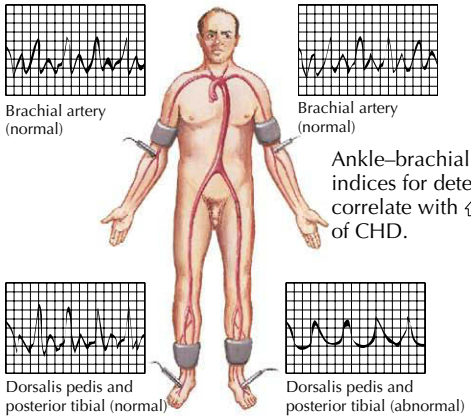


In the clinical setting, CHD risk analysis is important in identification of high-risk patients who should have immediate intervention, motivation of patients to adhere to risk-reduction therapy (including exercise and maintenance of appropriate BMI), and modification of risk-reduction efforts based on total risk estimate.

Screening to detect subclinical atherosclerosis



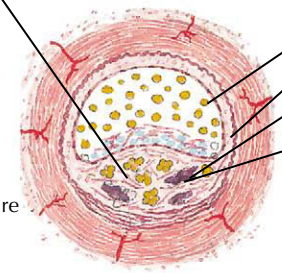
Risk of CHD death increases threefold in men with ECG abnormality. ECG indices such as heart rate variability, spatial aspects of repolarization or heart rate recovery post-exercise may have utility.



Ankle–brachial blood pressure indices for detection of PAD correlate with ⇧prevalence of CHD.

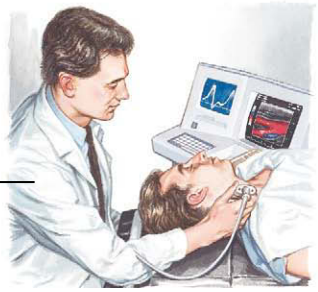
Magnetic resonance coronary angiography images plaque composition and size and detects areas prone to rupture.

C-reactive protein is an established marker of low-grade inflammation.



PET scans may be useful in detection of early endothelial dysfunction and in noninvasive monitoring of aggressive risk factor modification.

Coronary artery calcium detected by EBCT is a potentially valuable index to assess coronary artery plaque burden.



Carotid intima-media thickness is good indicator of presence and extent of coronary atherosclerosis.

A major objective of preventive cardiology is to measure and monitor atherosclerosis in asymptomatic individuals and identify appropriate candidates for aggressive primary prevention.

Figure 70-1 *Cardiovascular risk prediction.* BMI, body mass index; CHD, coronary heart disease; EBCT, electron beam CT; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; PET, positron emission tomography.

Box 70-2 Low Risk

Definition

The Framingham Heart Study defines low risk as the risk for CHD at an age that is conferred by a combination of all of the parameters listed below.

Parameters

- Serum total cholesterol 160–199 mg/dL or LDL-C 100–129 mg/dL
- HDL-C ≥45 mg/dL in men and ≥55 mg/dL in women
- SBP <120 mm Hg and DBP <80 mm Hg
- Nonsmoker
- No history of diabetes mellitus

CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
With permission from Grundy SM, Pasternak R, Greenland P, et al. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation. *1999;100:1481–1492. Available at: http://circ.ahajournals.org/cgi/reprint/100/13/1481.pdf.*

risk factors are seen interventionally through their amenability to be changed, from proven effective interventions to those that are unlikely to be effective (Box 70-3).

Guidelines for risk factor management have been developed based on convincing results of pathophysiology, molecular biology, epidemiologic studies, and randomized clinical trials, in primary and secondary prevention. However, guidelines often fall short of implementation and often fail to influence clinical practice, despite the wide dissemination of algorithms for the screening for cardiovascular risk factors and management of hypertension and lipid disorders.

Screening and Management of Cardiovascular Risk Factors in Medical Practice

It is often claimed that approximately 50% of MIs occur in patients without prior manifestations of risk factors. Recently, some investigators have argued that this number is less than 50%; it nonetheless remains significant and has stimulated efforts in the research community to search for new risk factors that could aid early identification and treatment, and could prevent future events. Of equal importance, however, is the question of whether adequate preventive strategies were used for the other 50%, in whom traditional cardiovascular risk factors were present at the time of symptoms. In a random sample of retrospective chart reviews of patients admitted to coronary care units, rates of physician screening for CHD risk factors; rates of counseling for cigarette cessation, diet, and exercise; and extent of use of National Cholesterol Education Program (NCEP) algorithms were disappointing. Approximately 50% of smokers report that their physician has never advised them to quit. Even in secondary prevention, the management of risk factors is less than satisfactory.

BP control rates are poor. Data from the National Health and Nutrition Examination Survey—the barometer of hypertension awareness, treatment, and control—show that the initial improvements since the publication of the recommendations of the Fifth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in 1993 have begun to deteriorate.

Aggressive lipid-lowering therapy prevents recurrent cardiac events and lowers total mortality rate in patients with known CHD, as well as in asymptomatic individuals. Despite strong evidence of benefits, patients continue to be underscreened and undertreated for hyperlipidemia. For instance, in numerous studies performed in varying clinical settings (such as coronary care units, Veterans' Administration hospitals, or medical practices), 33% of patients with CVD were not screened using lipid panels, only approximately 35% of those in whom medical therapy was indicated—according to NCEP guidelines—actually received lipid-lowering medications in primary prevention, and only approximately 67% received medications in secondary prevention. Furthermore, among patients taking prescribed lipid-lowering medications, only a fraction achieved acceptable LDL-C reduction. In the Lipid Treatment Assessment Project, overall, target LDL-C concentrations or values lower than the goal were attained in only 38% of the patients.

Box 70-3 Classification of Cardiovascular Risk Factors from the Intervention Point of View

Factors for Which Interventions Have Been Proven to Lower CAD Risk

- Diet
- TC and LDL-C
- Antithrombotic therapy
- Smoking
- Hypertension
- Multifactorial risk modification

Factors for Which Interventions Are Likely to Lower CAD Risk

- History of diabetes
- Physical inactivity/exercise
- Obesity
- HDL-C
- TG and small, dense LDL-C

Factors That If Modified Might Lower CAD Risk

- Psychosocial factors
- Oxidative stress
- Lipoprotein (a)
- Hyperhomocysteinemia

Factors That Cannot Be Modified or for Which Modification Would Be Unlikely to Lower CAD Risk

- Family history and genetics
- Age

CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
Data from Forrester JS, Merz CN, Bush TL, et al. 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 4. Efficacy of risk factor management. J Am Coll Cardiol. *1996;27:991–1006.*

Moreover, the greater the number of risk factors, the lower the proportion of target concentrations achieved in patients.

Barriers to Implementation of Preventive Services and Strategies to Improve Guideline Adherence

It is inevitable that there are delays before research results are accepted by the medical community and adopted into routine clinical practice. However, it is important that validated guidelines and new findings be adopted as widely and quickly as possible. Potential barriers to the adoption of new approaches comprise three areas: those relating to the patient, those relating to the health-care system and society as a whole, and those affecting physician behavior (Box 70-4).

FUTURE DIRECTIONS

Major objectives of preventive cardiology are to measure and monitor atherosclerosis in asymptomatic individuals and to identify appropriate candidates for aggressive primary prevention. Although noninvasive imaging of atherosclerosis and identification of serum markers hold great promise to quantify atherosclerotic burden and predict coronary events, they are not substitutes for traditional risk factor screening, but instead have a complementary role. In evaluating their potential as screening and predictive tools, these novel tests should answer whether screening with a new tool has incremental value in assessing cardiovascular risk and whether such a screening test would further improve outcomes over currently advocated guidelines for risk reduction. Tests with promise include recently appreciated ECG findings, electron beam CT, coronary magnetic resonance angiography (MRA), positron emission tomography (PET), ankle-brachial BP index (ABI), carotid intima-media thickness on ultrasound, C-reactive protein (CRP), and possibly evidence of exposure to certain infectious agents.

Box 70-4 Barriers to Implementation of Preventive Services

Patient
- Lack of knowledge and motivation
- Lack of access to care
- Cultural and social factors

Physician
- Problem-based focus
- Feedback on prevention negative or neutral
- Time constraints
- Lack of incentives
- Lack of training
- Lack of specialist-generalist communication
- Lack of perceived legitimacy

Health Care Settings
- Acute care priority
- Lack of resources and facilities
- Lack of systems for preventive services
- Time and economic constraints
- Poor communication specialists and primary care providers
- Lack of policies and standards

Community/Society
- Lack of policies and standards
- Lack of reimbursement

Reprinted from Pearson TA, McBride PE, Miller NH, et al. 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 8. Organization of preventive cardiology service. J Am Coll Cardiol. *1996; 27:1039–1047, with permission from the American College of Cardiology Foundation.*

In the Multiple Risk Factors Intervention Trial Study, the risk of CHD death for men with any ECG abnormality was three times that of men without abnormalities. Novel ECG indexes, such as heart rate variability, spatial aspects of repolarization, and heart rate recovery after the exercise test, may add clinical and epidemiologic utility.

Because coronary calcification increases with age, the highly sensitive electron beam CT score might be able to replace age as a surrogate for coronary plaque burden. However, because it lacks the ability to detect noncalcified atheroma, electron beam CT may offer an improvement over conventional risk factors in predicting the angiographic burden of atherosclerosis, but not in predicting coronary events. Multidetector CT, while promising, is yet to be refined in terms of reproducibility and risks; trials assessing the impact of this technology on improved clinical outcomes are continuing. Whether the use of these technologies can change patients' behavior remains an open question. Additionally, these novel tests may have utility in refinement of risk assessment and treatment options for individuals with an intermediate Framingham Risk Score; yet, such levels of risk represent low absolute risks, and thus the cost-effectiveness of these tools in primary prevention remains a difficult issue to overcome.

Coronary MRA is a research tool intended to image plaque composition and size and detect areas vulnerable to rupture. Although it cannot accurately detect small stenoses, it is a potential source of information on anatomic and functional significance of atherosclerotic plaques, by allowing three-dimensional visualization of coronary arteries and evaluation of perfusion, coronary flow and flow reserve, contractility, stress-induced wall-motion abnormalities, and cardiac metabolism. PET, as used today, has limited screening-test applicability; it is unable to detect coronary stenoses less than 50%. However, PET may have a future role in detection of early endothelial dysfunction and in noninvasive monitoring of aggressive risk factor modification in asymptomatic individuals.

ABI detection of peripheral artery disease, a simple and inexpensive test, correlates with a higher prevalence of CHD and demonstrates the atherosclerotic involvement of multiple vascular beds. An ABI less than 0.90 in either leg indicates peripheral artery disease; the lower the index value, the more severe the obstruction. An abnormal ABI elevates asymptomatic individuals to a higher risk category.

Correlation between carotid intima-media thickness and cardiac risk has been demonstrated within populations, but this less clearly predicts CHD risk in individuals. Carotid intima-media thickness is a good indicator of the presence and extent of coronary atherosclerosis; a direct relation

exists between intima-media thickening and the likelihood of coexistent significant CHD.

CRP, especially measured by highly sensitive assays, is an established marker of low-grade systemic inflammation, and its association with CVD is well-documented. CRP advantages include sensitivity, safety, convenience, and cost-effectiveness; standardized assays provide good validity and repeatability. Despite these advantages and its biologic plausibility, CRP did not prove to add significantly to risk prediction scores in several large-cohort studies: Atherosclerosis Risk in Communities, Women's Health, Framingham Offspring, Framingham Heart, and Cardiovascular Health Studies. In the JUPITER Study, which enrolled apparently healthy men and women with elevated CRP levels but no hyperlipidemia, rosuvastatin significantly reduced the incidence of major cardiovascular events; however, this study cannot answer whether the observed effects were due to cholesterol-lowering or CRP-lowering effect. The debate on the utility of CRP testing in guiding patients' risk stratification and therapy remains open.

Several large-scale clinical trials are studying infectious agents (*Helicobacter pylori*, *Cytomegalovirus*, *Chlamydia pneumoniae*) and their role in atherogenesis and CHD end points, but it is not yet clear whether evidence of these infectious agents represents causation or whether these are, in effect, "innocent bystanders."

Research in cardiovascular epidemiology has contributed to understanding the atherosclerosis process and shaped development of intervention tools in individuals and communities. Answers obtained have prompted new questions and generated new hypotheses. Future avenues for research will probably seek better understanding of how the identified cardiovascular risk factors modify genetic predispositions and of the interplay between behavioral and environmental factors, and the development of more accurate risk prediction tools and more targeted prevention strategies.

ADDITIONAL RESOURCES

Framingham Heart Study. Risk score profiles. Available at: <http://www.framinghamheartstudy.org/risk/index.html>; Accessed 09.02.10.

CHD risk score sheets as well as score sheets for stroke, intermittent claudication, and recurring CHD.

National Institutes of Health; National Heart, Lung and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>; Accessed 24.03.10.

Provides updated clinical guidelines for cholesterol testing and treatment. These evidence-based guidelines address multiple risk factors assessment, lipid and lipoprotein classification, recommendation for screening/detection, and strategies for promoting adherence. Current updates and PowerPoint slides are available.

Online assessment is available at: <http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof>. Download on Palm OS available at: <http://hin.nhlbi.nih.gov/atpiii/atp3palm.htm>; Accessed 24.03.10.

A risk assessment tool for estimating 10-year risk of developing hard CHD (MI and coronary death); uses information from the Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years. Useful for patient education.

National Institutes of Health; National Heart, Lung and Blood Institute; National Cholesterol Education Program (NCEP). Available at: <http://www.nhlbi.nih.gov/about/ncep/>; Accessed 24.03.10.

Through educational efforts directed at health professionals and the public, the NCEP aims to raise awareness and understanding about high blood cholesterol as a risk factor for CHD and the benefits of lowering cholesterol levels as a means of preventing CHD.

EVIDENCE

D'Agostino RB, Grundy S, Sullivan LM, Wilson P, for the CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores results of a multiple ethnic groups investigation. *JAMA.* 2001;286:180–187.

Reports on the validity and transportability of the Framingham CHD prediction functions to other populations. The sex-specific Framingham CHD prediction functions perform well among whites and blacks in different settings and can be applied to other ethnic groups after recalibration for differing prevalences of risk factors and underlying rates of CHD events.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486–2497.

Guidelines and recommendations focusing on dyslipidemia but also considering metabolic syndrome and other risk factors in gauging the intensity of therapy to the degree of coronary heart disease risk. The risk assessment is difficult, however, and sometimes inconsistent by utilizing both counting of categorical CHD risk factors and calculation of CHD using the Framingham model. Updates are available as well as interactive tools.

Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med.* 2006;166:1368–1373.

Evaluates whether various novel risk factors can enhance existing CHD prediction models, beyond traditional risk factors. With data from 15,792 adults in the Atherosclerosis Risk in Communities (ARIC) population, this study shows that the CRP level did not add significantly to CHD prediction accuracy, as estimated by the area under the curve.

Forrester JS, Merz CN, Bush TL, et al. 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 4. Efficacy of risk factor management. *J Am Coll Cardiol.* 1996;27:991–1006.

Discusses the evidence available for risk factor modifications by various lifestyle and drug interventions.

Gottlieb I, Lima JA. Screening high-risk patients with computed tomography angiography. *Circulation.* 2008;117:1318–1332.

Argues the need to screen high-risk asymptomatic individuals, discusses CT measures of coronary calcification, and focuses on the use of coronary multidetector CT angiography as a potential addition to the use of Framingham Study–derived algorithms.

Greenland P, Abrams J, Aurigemma GP, et al. Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden. Writing Group III. *Circulation.* 2000;101:E16–E22.

Considers the status of several measures of subclinical disease in CHD risk assessment: ankle-brachial blood pressure index, intima-media thickness as measured by ultrasound, coronary calcium scores, MRI, endothelial function studies, and CRP. Literature supporting the use of such tests is cited; however, no attempt is made to suggest ways these tests can be unified with traditional risk scores in clinical practice.

Grundy SM, D'Agostino Sr RB, Mosca L, et al. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood Institute workshop. *Circulation.* 2001;104:491–496.

A workshop on cardiovascular risk assessment, sponsored by the National Heart, Lung and Blood Institute, addressed whether risk equations developed in the Framingham Heart Study for predicting new-onset CHD apply to diverse population groups.

Kramer CM. All high-risk patients should not be screened with computed tomographic angiography. *Circulation.* 2008;117:1333–1339.

Argues against the mass screening of asymptomatic individuals with multidetector CT invoking the low absolute risk for CHD, the risks of radiation exposure, the unfavorable cost-benefit ratio, and the lack of current evidence supporting a positive behavior change consecutive to such a test.

Pearson TA. New tools for coronary risk assessment. What are their advantages and limitations? *Circulation.* 2002;105:886–892.

Addresses global risk assessment and highlights the evidence supporting the role of various tests: exercise ECG, electron beam CT, coronary MRA, PET, the ankle-brachial blood pressure index, intima-media thickness as assessed by ultrasound, as well as CRP and homocysteine.

Pearson TA, McBride PE, Miller NH, et al. 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 8. Organization of preventive cardiology service. *J Am Coll Cardiol.* 1996;27:1039–1047.

Addresses the "treatment gap" and disparity between endorsed guidelines and current practice, and objectively describes barriers to the implementation of preventive services.

Ridker PM, Danielson E, Fonseca FA. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195–2207.

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity CRP levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Smith Jr SC, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. American Heart Association. *Circulation.* 2000;101:111–116.

A central theme for this conference was the emphasis on establishing a prognosis for high-risk patients without clinical evidence of CHD. Three writing groups were established to report on the following areas: (1) medical office assessment, (2) tests for silent and inducible ischemia, and (3) noninvasive tests of atherosclerotic burden. Each working group reviewed research on existing risk assessment strategies relevant to the prediction of risk in patients without clinical evidence of CHD.

Cardiovascular Disease in Women and Special Populations

71

Paula F. Miller and Sidney C. Smith, Jr.

There has been a marked increase in the diversity of the U.S. population, and with it, an increase and shift in risk factor prevalence. These changes necessitate a broader understanding of cardiovascular disease (CVD) in special and underserved populations, which include women, patients with diabetes, the elderly, various ethnic groups, and an emerging population—the intellectually disabled. Although age-adjusted events from CVD in the general population are decreasing, among patients in these special groups there is no decrease, and in some cases CVD is increasing. Disappointingly, women in general, including women in ethnic and special subgroups, have seen no significant change in CVD morbidity and mortality in recent years. Interestingly, individuals with intellectual disabilities have increasing incidence of CVD when compared to the general population. This group has been moved from institutions to group homes, personal homes, or family homes in an attempt to enhance their lifestyle. However, this has changed their risk factors, since they have lost some control over their diet and their environment, thereby increasing risk factors (obesity in particular). This chapter reviews some of these special populations and makes suggestions on identifying, managing, and modifying risk factors with the goal of decreasing CVD.

DIABETES

In the United States, approximately 15 million adults have clinically diagnosed diabetes mellitus, with 1.5 million new cases each year. Almost 35 million Americans and 35% of elderly Americans have some degree of glucose intolerance. As many as 5.7 million people may have unrecognized diabetes. At least 65% of people with diabetes mellitus die of some form of heart disease or stroke. After adjusting for population, age, and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than expenditures among those without diabetes. The direct costs related to treatment of these patients were U.S. $116 billion with an additional indirect cost of U.S. $58 billion (disability, work loss, and premature mortality).

The rates of morbidity and mortality from CVD and from atherosclerotic disease involving the cerebral and peripheral vessels are two to eight times higher among individuals with diabetes (Fig. 71-1). Diabetes was the seventh leading cause of death on U.S. death certificates in 2006. Among ethnic minorities older than 18 years of age, diabetes is present in 13.6% of Native Americans, 6.5% of Asians, and 9.8% of Hispanics. The increase in type 2 diabetes among children and adolescents is likely to result in further increases in the incidence of premature coronary heart disease (CHD). The National Cholesterol Education Program Adult Treatment Panel (ATP) III identifies diabetes as a CHD equivalent and recommends the same intensive risk factor modification and preventive therapy for patients with diabetes as for patients with known CHD.

Evaluation of the patient with diabetes begins with a careful medical history (see also Chapter 1). Symptoms of atherosclerotic vascular disease, such as claudication and angina, deserve special attention, although diabetic individuals often have atypical symptoms or no symptoms at all in the presence of significant CHD. Patients with diabetes should also be evaluated for signs and symptoms of congestive heart failure. The resting ECG should be evaluated for evidence of left ventricular hypertrophy as well as new left bundle branch block, both being markers for increased cardiovascular risk. The use of medical therapies such as lipid-lowering treatment should be based on the presence of diabetes, a CHD equivalent, rather than on symptoms or the identification of an abnormality on noninvasive testing. The updated ATP III recommends a target low-density lipoprotein cholesterol (LDL-C) below 100 mg/dL, with an optional goal of less than 70 mg/dL for patients with diabetes. The American Heart Association (AHA)/American College of Cardiology (ACC) secondary prevention statement recommends that blood pressure be kept below 130/80 mm Hg and hemoglobin A_{1c} below 7.0 as treatment goals for patients with diabetes. For patients who have triglyceride levels above 200 mg/dL despite appropriate diet and exercise and who have received statin therapy, treatment with a fibrate is recommended. Because a prothrombotic state accompanies diabetes, patients with diabetes should be considered high risk, and treatment with daily aspirin even in the absence of clinical CHD may be considered. Physical activity and maintenance of body mass index below 25 improve control of diabetes and reduce the risk of CHD-related events.

The hospitalization and long-term mortality rates following acute myocardial infarction (MI) are two to four times as high in individuals with diabetes. Diabetes is a major risk factor for adverse outcomes in patients with unstable angina. Often acute MI is the first symptom of CVD in a patient with diabetes. Because symptoms may be atypical, late recognition by the patient may delay implementation of reperfusion therapies, thus leading to a poorer prognosis. The ventricle in patients with diabetes has a higher likelihood of undergoing maladaptive remodeling, which may contribute to heart failure and cardiogenic shock. Among diabetic individuals presenting with acute MI who are undergoing primary coronary intervention, the use of a glycoprotein (GP) IIb/IIIa receptor antagonist results in better outcomes. Similar benefits have been observed with GP IIb/IIIa receptor antagonists in patients with diabetes who have unstable angina or non–ST-segment elevation MI. For patients with diabetes, the use of β-blockers results in early and late survival benefits. The admission glucose level is an independent predictor of early and late mortality in diabetic patients admitted with MI. In several studies among patients hospitalized with

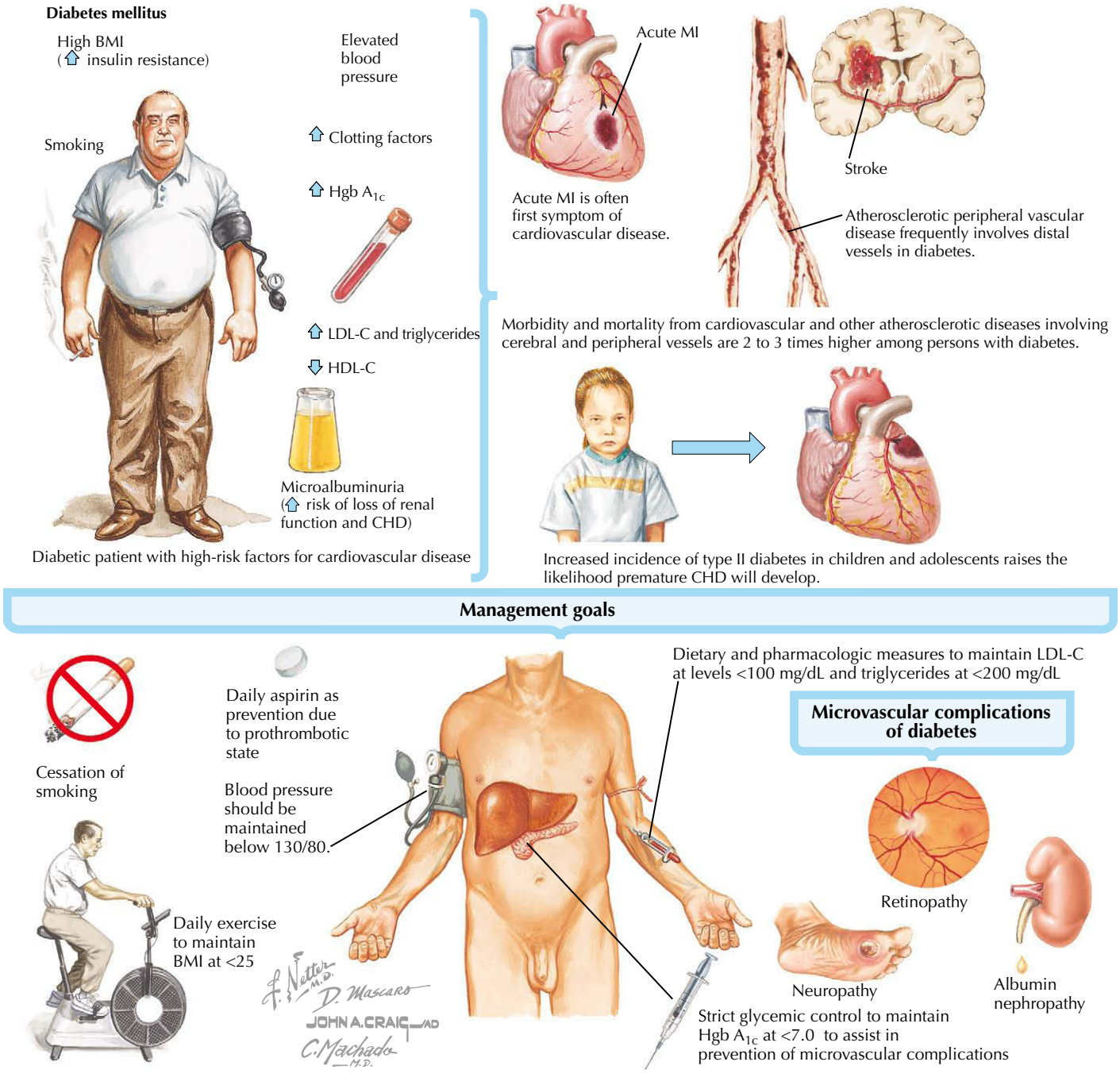


Figure 71-1 *Cardiovascular disease in diabetes.* BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; Hgb A_{1c}, hemoglobin A_{1c}; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

MI, strict glycemic control improved cardiovascular outcomes. Studies of MI survivors with diabetes show a significant survival benefit among those with optimal glycemic control for up to 3 years following their MI.

The control of cardiovascular risk factors in patients with diabetes must be a high priority. In patients with diabetes who smoke cigarettes, cardiovascular risk is doubled. The benefit of glycemic control coupled with treatment of high blood pressure and lipid abnormalities significantly reduces microvascular complications of diabetes (nephropathy, neuropathy, and retinopathy). Diabetes is the leading cause of end-stage renal disease in the United States (accounting for 44% of the new cases of renal failure in 2005), with a 5-year survival of only 20%. Microalbuminuria is a major predictor of impaired renal function as well as for the development of CHD. The early use of angiotensin-converting enzyme inhibitors among patients with diabetes,

even in the absence of hypertension, reduces the rates of cardiovascular morbidity and mortality.

Of the nearly 1.5 million percutaneous and surgical revascularization procedures carried out annually in the United States, roughly 25% are performed on patients with diabetes. In this group, comorbidities such as hypertension, dyslipidemia, systolic and diastolic heart failure, nephropathy, and peripheral vascular, cerebrovascular, and microvascular diseases contribute to poorer outcomes as compared with patients without diabetes. In addition to the extent of coronary artery disease (CAD), the presence of diabetes alone may govern the revascularization approach chosen. For instance, significant differences in survival, favoring surgical revascularization, exist for patients with diabetes and two- or three-vessel CAD who are randomized to coronary artery bypass graft surgery compared with percutaneous coronary intervention. The benefits of coronary artery bypass graft surgery are seen only when at least one arterial conduit is used. The increased use of stents and GP IIb/IIIa receptor antagonists in percutaneous revascularization procedures has improved outcomes from percutaneous revascularization. Further studies that will help define the relative benefits of coronary artery stenting using drug-eluting stents versus surgical revascularization among patients with diabetes are continuing.

THE ELDERLY

Although cardiovascular events can occur at any age, the absolute risk increases incrementally as the population ages and is greatest in the elderly population (65 years and older); approximately two thirds of cardiovascular deaths occur after age 65. In the United States alone, more than 25 million people are 65 years or older. In 2000, elderly individuals represented 12.7% of the population. By 2020, the elderly population will increase to 16.5%. The 31% increase in this group of individuals with a high prevalence of CVD will further increase the demands on the health care system, underscoring the importance of treatment strategies for elderly individuals (Fig. 71-2, upper).

Clinically, CHD in elderly individuals often presents in an atypical manner, with dyspnea, decreased exercise tolerance, fatigue, or heart failure as the initial symptom. Though not always the case, CHD in elderly individuals is frequently asymptomatic. When symptoms are present, their atypical nature often delays diagnosis and treatment. This delay combined with an increase in comorbidities and the underuse of proven beneficial therapies (pharmacologic and interventional) contributes to increased rates of morbidity and mortality among post-MI elderly patients. The increased incidence of comorbid conditions contributes to polypharmacy in elderly patients—with the attendant risk of adverse effects—and prevents the addition of medications that would probably lower cardiac risk. Despite the need for multiple medical therapies, risk factor modification in elderly patients translates into decreased cardiovascular events.

Elevated LDL-C has an important role in the pathogenesis and lifelong risk of CHD, and reduction of LDL-C levels decreases risk of cardiovascular events. Despite widespread information indicating a therapeutic benefit, underdiagnosis and undertreatment of dyslipidemia continue among elderly individuals. In fact, preventive therapies (pharmacologic and nonpharmacologic) in elderly individuals may decrease cardiovascular events even more dramatically than in younger cohorts, probably because of the increased risk and incidence of CHD in elderly individuals. Age should not exclude patients from treatment for LDL-C lowering, especially as a therapeutic strategy for secondary prevention. In primary prevention, treatment of elevated LDL-C has been more controversial. However, benefits of preventive treatment in this population are substantiated by several smaller trials and by the Heart Protection Study, which included patients up to the age of 80. The ATP III recommends therapeutic lifestyle changes as an important component of therapy to reduce LDL-C.

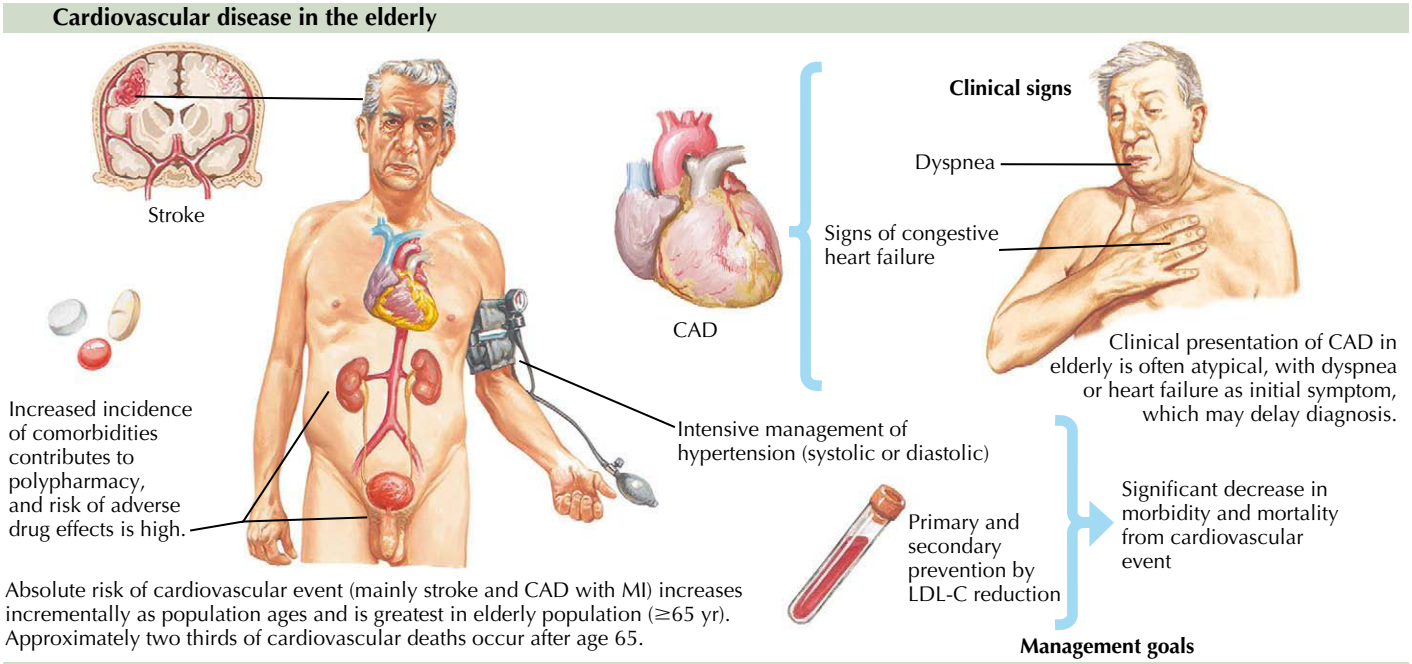
Hypertension (blood pressure of 140/90 or higher) occurs in more than 50% of the population aged 65 years and older. In 2004, 63.6% of men and 73.9% of women ages 65 years or older had high blood pressure. Hypertension is a major risk factor for stroke, heart failure, and CHD. Although hypertension was once considered part of "normal aging," the benefit of treating elderly patients with elevated systolic and/or diastolic blood pressure is clear. Intensive treatment of isolated systolic hypertension can provide a 30% reduction in the combined fatal and nonfatal stroke rate, a 26% reduction in the rates of fatal and nonfatal cardiovascular events, and a 13% reduction in the total mortality rate.

WOMEN

CVD is the leading cause of death in men and women. In the United States in 2004, CVD claimed the lives of 459,056 women (~100,000 more than men). Since 1984, the number of deaths for females has exceeded that for males. Unfortunately, although the cardiovascular mortality rate has declined steadily for men, it has remained virtually unchanged or increased for women. It is uncertain whether this difference reflects a gap in awareness and education, undertreatment of women, or an increase in the prevalence of CHD in women. Interestingly among respondents to an AHA survey, most women believed that cancer was their biggest health threat. However, in 2004, the morbidity in women from CVD was 459,096 as compared with 40,954 for breast cancer.

In addition to receiving information on disease prevalence, women must be educated that their CHD symptoms can differ from symptoms that men commonly report. Women often have dyspnea on exertion, "heartburn," fatigue, decreased exercise tolerance, or back pain as their "anginal equivalent." When questioning women further, there may also be some "typical" symptoms in the majority of women. However, the presence of somewhat vague or confusing symptoms often contributes to delayed or missed diagnoses of CHD (see Fig. 71-2, lower).

Most CHD risk factors and strategies for preventing disease applicable to men also apply to women. Risk factors beyond the typical risk factors frequently occur in women, including isolation, depression, and lower socioeconomic status. The magnitude of the effects of these risk factors and prevention strategies may be different. For example, diabetes is an even more powerful risk factor for CHD in women. It is associated with a three- to sevenfold increase in the frequency of CHD development. A woman with diabetes is twice as likely to have a recurrent MI



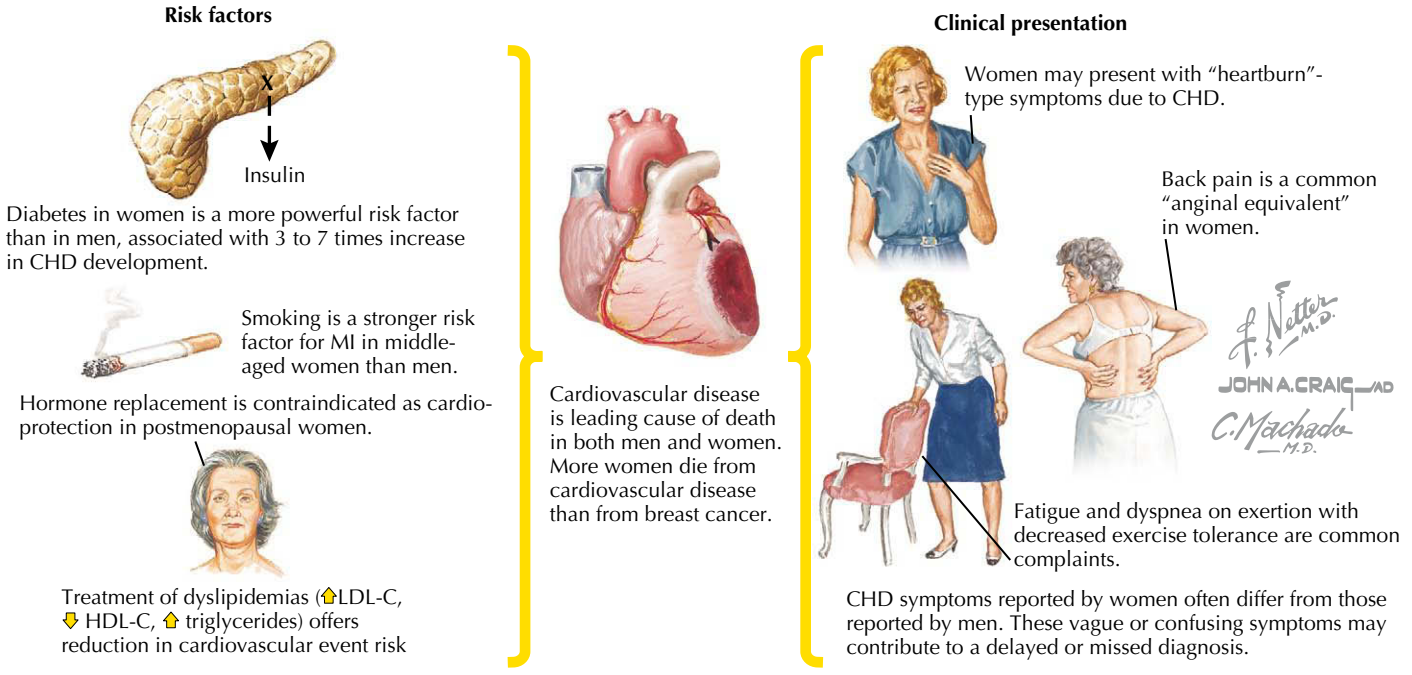


Figure 71-2 *Cardiovascular disease in women and the elderly.* CAD, coronary artery disease; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

compared with a man with equal risk factors. Smoking is also a stronger risk factor for MI in women than in men (a woman who smokes has her first heart attack an average of 19 years earlier than a woman who does not smoke). This is a concern, because smoking rates are declining at a slower rate among women than among men. Hypertension is more prevalent in men up until the age of 45. From ages 45 through 54, the incidence of hypertension for men and women is similar. After age 54, a significantly higher percentage of women have high blood pressure. Since this is a modifiable risk factor, education of women about the dangers of hypertension as well as intensive screening becomes important. Dyslipidemias, especially elevated triglycerides and low high-density lipoprotein cholesterol (HDL-C), are more commonly seen with CHD in women and are most commonly seen in postmenopausal women. Low HDL-C in women is a potent risk factor. Strategies to reduce LDL-C with statins provide at least an equivalent reduction in risk in women compared with men. In fact, in some studies, the

risk of primary or secondary cardiovascular events was more favorably influenced by statin therapy in women than in men. Risk factors unique to women include menopause, with its associated estrogen loss and effect on the lipid profile, and hormone replacement therapy (HRT). Historically a cardioprotective effect of HRT in women was inferred, based largely on observational data, regardless of the woman's CVD status. However, no benefit in the rates of nonfatal MI or death from CHD in women with known heart disease receiving combined HRT was found in the largest randomized clinical trial conducted thus far. Indeed, an increase in CHD events was observed during the first year of HRT use in that trial. Consequently, the AHA has released a statement for health care professionals recommending that HRT *not* be initiated for prevention of heart attack or stroke in women with CVD. Furthermore, a large-scale trial investigating the primary-prevention benefits of combined HRT was stopped early, principally because of the risk of associated invasive breast cancer. However, a significant increase in cardiovascular events was also observed. Taken together, clinical trials do not support the use of combined HRT in primary or secondary prevention of cardiovascular events.

Prediction of 10-year mortality by the ATP III guidelines has been advanced by the Reynolds Risk Score. This model includes as variables diabetes mellitus, family history, and high-sensitivity C-reactive protein, an inflammatory marker. The Reynolds risk predictor can be adjusted for age with predictions for CVD at current age as well as 10, 20, or 30 years into the future, providing a projection of how treatment of certain risk factors might improve risk.

The updated 2007 AHA/ACC guidelines for prevention of CVD in women have several new recommendations, including dietary (increased fresh fruits and vegetables), increased activity (30 minutes a day to maintain weight and 60–90 minutes to lose weight), including oily fish in the diet at least twice a week or using fish oil supplements, and the use of aspirin routinely in women over the age of 65 and earlier in those at high risk.

RACIAL AND ETHNIC CONSIDERATIONS

The U.S. population has become increasingly diverse, with an increase in Hispanics, African Americans, Native Americans, and Asian/Pacific Islanders. The prevalence and incidence of CVD varies among these ethnic and racial groups in the United States. These variations are important in developing strategies for prevention and treatment as these minority populations increase in number. CVD mortality rate varies significantly by U.S. region, with a greater than twofold difference between states with the lowest and the highest rates. Factors influencing these differences are complex. As an example, in the southern United States, more than 25% of individuals are obese. This in turn puts the population at a higher risk for diabetes mellitus and CVD. The key to reducing CVD in these populations lies in education and intervention. Many, however, do not have health insurance and do not see a doctor regularly. Improved access to health care coupled with education and modification of risk factors can reduce cardiovascular events. The highest mortality rates from CVD are seen in the Mississippi Delta, Appalachia, and the Ohio River Valley, where the numbers of people in the lower socioeconomic category are highest.

African Americans have the highest mortality rates in the United States for CHD and stroke. In 2004, the overall death rate from CHD in the United States was 288/100,000, while the death rate for African Americans was 454/100,000 for men and 333.6/100,000 for women. The mortality rate from CHD is lower among the Hispanic, Asian, and Native American populations. Among Asians, probably because of the high prevalence of hypertension, the mortality rate from stroke is higher. A high mortality rate from stroke continues to exist in the southeastern United States, especially among the African American population, but stroke rates have increased in the northwestern United States, possibly because of an increase in the Asian population of those states. The areas with the highest CVD mortality in the United States are frequently poor and rural.

Racial differences in health care outcomes are well documented in the United States. Members of minority populations, especially African American individuals, are less likely to receive invasive cardiovascular procedures shown to improve outcomes, are less likely to see doctors and other health care providers, and tend to smoke more than nonminority members. As the ethnic populations increase, more attention must be directed toward identifying those at risk and intervening with recommended therapies.

LOWER SOCIOECONOMIC GROUPS

Socioeconomic differences in CVD mortality rates are reported for many countries, including the United States. In most reports, a clear gradient in mortality rates exists; the CVD mortality rate is higher in individuals with lower education levels and in those in lower occupational classes. Socioeconomic status is a more potent risk factor in women. In western Europe, a north-south gradient exists for CHD, with a higher mortality rate in the north. These differences may reflect differences in risk factors, such as diet, cigarette smoking, and obesity. Unfortunately, reports suggest that the gap in the CVD mortality rates between the poor and undereducated and the wealthy and well educated has not narrowed and may even be widening.

FUTURE DIRECTIONS

Future directions for prevention of CHD in special populations must target the special needs of each population. Clinical trials testing new strategies must establish appropriate guidelines for revascularization strategies in patients with diabetes. The Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial, which is comparing good diabetic control with and without various revascularization procedures, should contribute significantly to the understanding of appropriate strategies for managing patients with diabetes.

CVD in elderly individuals, the most rapidly expanding U.S. subgroup, is an important public health issue. Prevention efforts should be initiated in this group. Elderly individuals must be included in clinical trials and comprehensive risk factor identification and modification pursued. Because of the potentially debilitating nature of cardiovascular events, primary and secondary prevention therapies in elderly individuals are especially beneficial.

CHD is largely preventable in women through diet and lifestyle modification, as well as detection and treatment of risk factors. Education, lifestyle changes, and prevention efforts will make a difference in this patient population.

Major federal initiatives have been launched to eliminate the racial and ethnic differences in cardiovascular outcomes. The challenges of changing behavior and CVD risk are magnified among those of lesser educational background and lower economic income, where resources may be lacking to understand and afford necessary measures. Developing effective interventions for risk factor reduction among lower socioeconomic groups must be a priority.

ADDITIONAL RESOURCE

Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women. The Reynolds Risk Score. *JAMA.* 2007;297:611–619.

The Reynolds Risk Score provides a way to further risk-stratify women using the traditional ATP III risk factors while incorporating family history and high-sensitivity CRP. The tool can be accessed on the Internet at: <http://www.reynoldsriskscore.org/>; Accessed 22.03.10.

EVIDENCE

American Heart Association. Heart disease and stroke statistics—2008. Update. Dallas: American Heart Association. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3000090>; Accessed 09.02.10.

Offers information for medical professionals as well as the lay public to educate and provide guidelines for risk factor modification. Information includes diet, exercise, and specific disease states (hypertension, CAD, and so forth) in women and special populations.

Benjamin EJ, Smith SC, Cooper RS, et al. Magnitude of the prevention problem: opportunities and challenges. 33rd Bethesda Conference. *J Am Coll Cardiol.* 2002;40:588–603.

The 33rd Bethesda Conference provides a comprehensive review of problems associated with the prevention of CVD and outlines strategies for implementation.

Cooper R, Cutler J, Desvigne-Nickens P, et al. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States. *Circulation.* 2000;102:3137–3147.

Significant disparities exist for the use of medical and interventional therapies among patients with CHD in the United States. These disparities relate to difference in treatment related to gender, race/ethnicity, and socioeconomic groups.

Executive Summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486–2497. (Update; *Circulation.* 2004; 110:227–239.)

Recommendations and concepts for treatment of dyslipidemia are outlined with background information in this publication. Further updates to the target goals noted in this article are found in the 2006 AHA/ACC Secondary Prevention Update.

Grundy SM, Howard B, Smith Jr S, et al. Prevention Conference VI: Diabetes and Cardiovascular Disease: Executive Summary: Conference proceeding for healthcare professionals from a special writing group of the American Heart Association. *Circulation.* 2002;105:2231–2239.

The magnitude of and need for therapies related to the increasing prevalence of obesity and diabetes are reviewed in this important conference summary.

Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation.* 2007;115;1481–1501.

Provides the latest data and references regarding the efficacy of cardiovascular preventive strategies and therapies for women.

Mosca L, Mochari H, Christian A, et al. National Study of Women's Awareness, Preventive Action, and Barriers to Cardiovascular Health. *Circulation.* 2006;113:525–534.

Provides important evidence indicating low awareness among women that cardiovascular disease is the leading cause of death for women.

Smith SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *Circulation.* 2006;113;2363–2372.

The AHA/ACC guidelines for secondary prevention were updated in 2006 to reflect the results of the latest randomized clinical trials. Important changes include the addition of recommendations for flu vaccine, new optional targets for LDL-C, and recommendations regarding angiotensin-converting enzyme inhibitor use among patients with normal left ventricular function.

Genetics in Cardiovascular Disease

72

Marschall S. Runge and Cam Patterson

It has been nearly 60 years since Watson and Crick published their landmark manuscript on the molecular structure of nucleic acids. Since that time, genetics has changed profoundly. The human genome (and the genomes of many other species) has been sequenced, and the search to identify and characterize the estimated 30,000 genes in the human genome continues. Genetic testing for both common and unusual diseases is becoming increasingly available, even if the clinical utility of these tests is not always clear.

A major challenge for physicians and health care providers will be fluency in the language of genetics as decisions on who should be screened for genetic causes of disease, how to best approach families with heritable diseases, and, ultimately, selection of patients for genetic-based therapies become more common. This information will be particularly important for caregivers of patients with cardiovascular diseases, a field dominated by common diseases with complicated genetics.

This chapter on genetics is not comprehensive. Many excellent texts describe all aspects of genetics, from the genetic basis of disease to gene therapy. Instead, the goal of this chapter is to introduce the clinically important principles of genetics and the application of these principles to clinical medicine, with particular emphasis on the genetics of cardiovascular diseases (Fig. 72-1). A brief glossary of the clinically important terms in this chapter is shown in Box 72-1.

MODERN HUMAN GENETICS IN THE ETIOLOGY OF DISEASE

Before Mendel described the principles of genetics on the basis of his plant studies, it was recognized that a wide variety of diseases were familial. Although not the first, Sir William Osler is the most recognized modern physician to propose that familial clusterings of diseases were linked to specific gene abnormalities. Medical genetics became a specialty with the recognition that a detailed pedigree made it possible to understand the genetic basis of a given familial disease. However, in the mid-twentieth century, genetic screening was only a concept, and no quantitative tools existed for it. Biochemical screening tests, reflecting the downstream effects of a genetic abnormality, were the first "genetic tests" developed. Population-wide screening for Tay-Sachs disease, a disease with autosomal-recessive inheritance found predominantly in Ashkenazi Jews, was one of the first successful applications of such a test. A combination of biochemical screening and genetic counseling has resulted in a greater than 90% decrease in the occurrence of the disease over the past 2 decades, underlining the importance of this type of screening.

In the late twentieth century, with the advent of reliable DNA sequencing, it became possible to demonstrate that diseases could be assigned to a single-nucleotide change in a specific, important gene. This development led to the idea that single mutations "caused" disease, extending the principles of Osler: one abnormality, one disease.

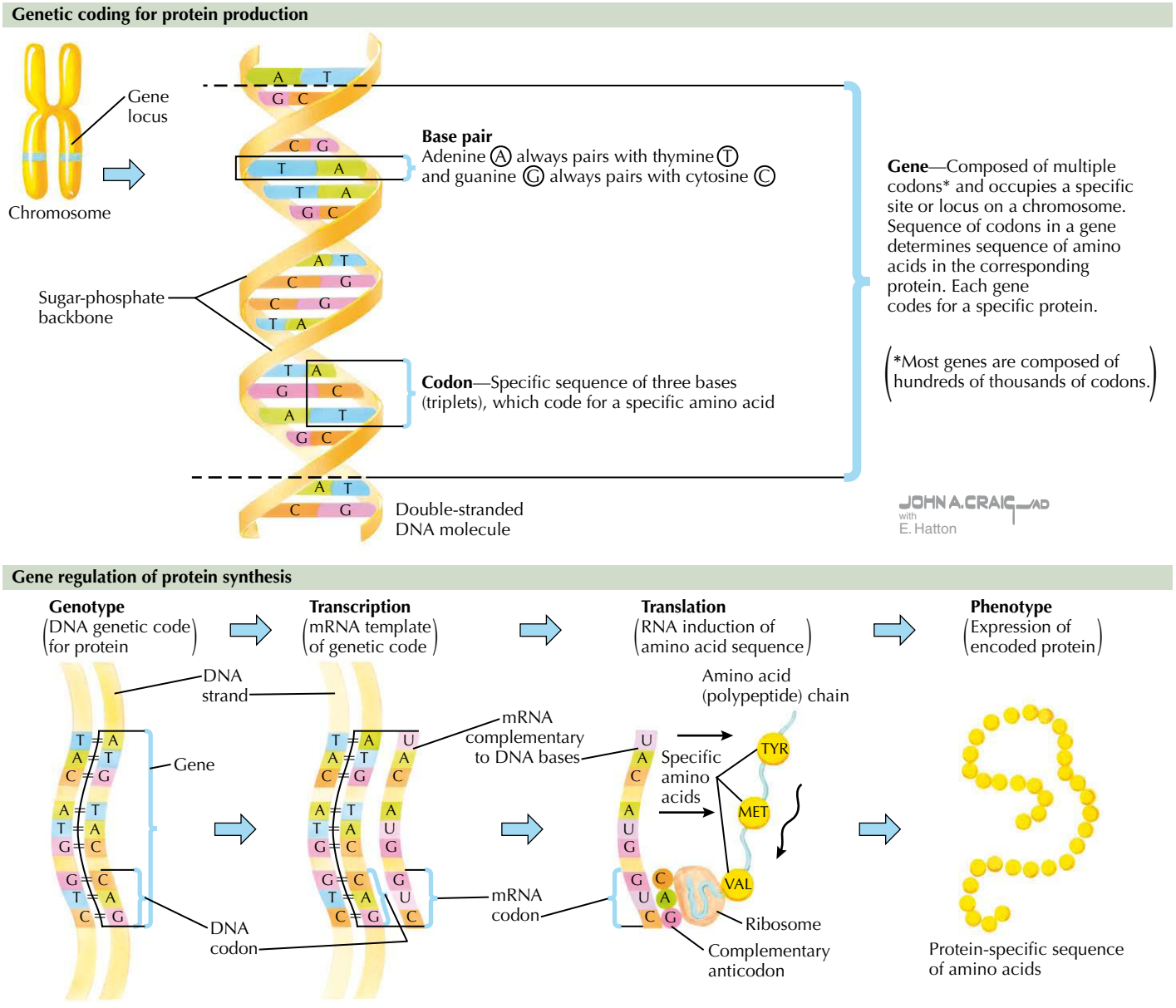
With the advent of high-speed DNA sequencing, it has become clear that the genetic basis of human disease is much more complex than was formerly recognized. There are several reasons for this greater complexity. First, mutations in specific genes are rarely unique; the same phenotype can result from any of a number of mutations in the same gene. Second, nearly identical phenotypes can result from a mutation in more than one gene. Third, just as genes do not act in isolation, mutations often do not have a strict cause-and-effect relationship with disease (Fig. 72-2). Often an interaction of a mutation with a broad array of environmental factors leads to a given phenotype. Finally, humans are not a product of changes in single genes in isolation but of many, perhaps hundreds, of polymorphisms (Fig. 72-3, upper). Commonly, susceptibility to environmental effects depends not on a single gene but on the interactions of many genes—often genes for nuclear factors that regulate the expression of entire classes of genes. Practical examples are discussed in the following section.

GENETIC EVALUATION: SELECTED EXAMPLES

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM), a common disorder (occurring in 1 in 500 individuals), was first described as a myocardial abnormality that clinically mimicked aortic stenosis, often resulted in sudden cardiac death, and pathologically was characterized by asymmetric septal hypertrophy and myocardial fiber disarray (see Chapter 19). The genetic characterization of HCM was first reported in the late 1980s in a study that implicated an abnormality on chromosome 14. Subsequently, it was found, on the basis of studies of a large family, that a single mutation in the β-myosin heavy chain was responsible for HCM. However, in less than a decade, more than 300 mutations in at least 13 genes (ranging from myosins to troponins and including other proteins of the contractile apparatus) have been reported to produce the phenotype of HCM (see Fig. 72-3, middle). Specific mutations in certain genes are associated with more or less severe phenotypes and outcomes. Further complicating the genetic analysis of HCM is the status of HCM as an autosomal-dominant disorder characterized by incomplete penetrance. Thus, even though siblings may all carry a mutation, the phenotype's severity varies on the basis of factors yet to be elucidated.

For these reasons, HCM is an excellent example of the types of genetic diseases that cardiovascular specialists see. A single mutation may be necessary, but not sufficient, to cause HCM, and the precise mutation does not entirely predict the disease outcome. The genetics for other cardiovascular diseases are likely to be even more complicated. Given the sensitivity of



A gene is a segment of DNA that directs the synthesis of one (sometimes more than one) specific polypeptide or protein. Synthesis of a polypeptide occurs in a stepwise sequence in which the DNA base triplets (codons) are translated into a complementary set of mRNA codons, which then induce formation of anticodons, identical in sequence to the DNA codons (except "U" (uracil) replaces "T" in mRNA sequences). The three-base genetic code then directs the sequential synthesis of amino acids into a polypeptide chain. Of note, on any particular segment of a chromosome, DNA sequences are considered to fall into two general categories: (1) **exons**, which are nucleotide sequences that code information for protein synthesis that is copied and spliced together with other sequences to form mRNA, and (2) **introns**, which are nucleotide sequences that do not code information for protein synthesis and are removed before translation of mRNA. For simplicity, a single exon is shown in the diagram.

Figure 72-1 *Genetics in cardiovascular medicine.* mRNA, messenger ribonucleic acid.

present genetic assays to identify disease-causing mutations (now greater than 70%), the debate regarding the usefulness of genetic testing for HCM is diminishing. Genetic testing may be useful for diagnosis in situations where diagnosis by other methods is uncertain (for example, in highly conditioned athletes who may have physiologic hypertrophy of the heart), for risk stratification (certain mutations are associated with a higher incidence of sudden cardiac death), and to identify mutations that may be present in first-degree relatives of the patient. Genetic counseling services should be available for all patients undergoing testing. For these reasons genetic testing should generally be ordered and interpreted in a specialized setting.

Long QT Syndrome

Long QT syndrome (LQTS) describes a group of diseases whose common phenotypic feature is an abnormal QT interval on the ECG, usually patients with a corrected QT interval greater than 440 ms. QT prolongation is associated with sudden

Box 72-1 Terminology

Alleles—*Copies of a specific gene.* Humans have two alleles for each gene (one each from the biologic father and mother). Alleles may have functional differences in their DNA sequence. A person with two identical copies of an allele is termed homozygous; a person with two different copies of an allele is called heterozygous.

Dominant mutation—*A mutation in one allele of a gene that is sufficient to cause disease.* More severe disease or lethality may result from a dominant mutation in both alleles of a gene.

Environmental effects—*For this chapter, any potentially controllable influence on an individual.* Examples are diet, exercise, air quality, a response to a prescribed or an over-the-counter medication, cigarette smoking, and alcohol use.

Genotype—*The genetic makeup of an individual.* Genotype can refer to specific genes or to the overall genetic profile.

Mutation—*Changes in the DNA sequence of a gene that result in a gene product (protein) that has an altered sequence.* For this chapter, mutations are considered to be changes in the DNA sequence of a gene that result in either loss of function or severely altered function.

Phenotype—*The functional effects of genetic changes together with environmental influences.* For instance, a person's appearance (body build, muscularity, hair color), the presence of measurable abnormalities that may reflect underlying disease processes, or other physical features demonstrate phenotypes. The list of measurable abnormalities is almost infinite, from blood pressure abnormalities to abnormal biochemical measurements (e.g., serum glucose levels) to ECG abnormalities reflecting ion channel abnormalities (as occur in LQTS) to coronary heart disease measured by angiography or endothelial dysfunction measured by forearm blood flow variability.

Polymorphism—*An inherited variation in the DNA sequence of a gene that occurs at a greater frequency than would be expected of a mutation.* Humans have thousands of polymorphisms, none of which are thought to be solely responsible for disease. Technically no different from mutations (a change in DNA sequence from "normal"), polymorphisms typically alter the gene product more subtly than mutations. It is thought that many human phenotypes result from the interplay between an individual's mix of polymorphisms and the environment.

Recessive mutation—*A mutation that requires alterations in both alleles of a gene to cause disease (except in the case of mutations in the X and Y chromosomes).*

LQTS, long QT syndrome.

cardiac death, presumably because of the propensity for polymorphic ventricular tachycardia when a premature ventricular contraction occurs in the refractory period (prolonged in these cases; see Chapter 29). More than 200 mutations in five different genes (all coding for sodium or potassium channel proteins) have been reported to cause LQTS (see Fig. 72-3, lower). Unlike in families with HCM, both autosomal-dominant and autosomal-recessive inheritance are described for LQTS, the inheritance depending on the gene involved. Some forms of LQTS manifest only when a secondary cause of QT prolongation is present, such as electrolyte abnormalities, medications, or myocardial ischemia. As with HCM, the diagnosis of LQTS can be made by noninvasive (ECG) testing in most cases (except in the case of LQTS provoked by a secondary cause). For individuals from families with a history of sudden cardiac death, careful analysis of the ECG is necessary, and provocative testing may be indicated in some circumstances. Nevertheless, the genetic basis for LQTS may be highly informative in terms of prognosis and as a guide to clinical therapy, as well as for identifying family members at risk for sudden death. LQTS is an excellent example of a spectrum of diseases, once clustered together as a single entity, that benefit from principles of pharmacogenomics, the use of specific medications based on genotype.

Atherosclerosis

Atherosclerosis is the most common polygenic disorder seen by cardiovascular specialists. The genetics of atherosclerosis ranges from individuals with defects in the low-density lipoprotein receptor (familial hypercholesterolemia) or in lamin A/C (progeria), who almost all die prematurely of heart attack or stroke regardless of therapy, to the much larger group whose disease progression is highly dependent on environmental factors, such as diet, exercise, and cigarette smoking. The genetics of this latter group, even with what we have learned thus far, remains challenging to understand.

Recent studies of the genetics of atherosclerosis have made important advances in the identification of risk alleles for atherosclerosis, yet have also raised important questions about the utility of applying information about the presence of these risk alleles to clinical decision making. Using genome-wide studies of genetic variants, several groups simultaneously identified polymorphisms on chromosome 9 that identified individuals at increased risk for developing coronary atherosclerosis. The immediate cross-validation of this risk locus provided a high degree of certainty that it does indeed incur increased risk of cardiovascular disease. Less certain are the merits of screening individuals for these risk alleles. For individuals who are known to have clinically significant atherosclerosis, knowledge of risk allele status is of no value, at least until or if specific therapies are developed for patients bearing these polymorphisms. For individuals concerned about their future risk of cardiovascular disease, it is unclear whether knowledge about risk allele status confers additional information beyond known clinical risk factors. Time and additional research will clarify these issues, but at present the clinical value of genetic testing for these risk alleles is not established, even if the tests are now easily available.

Metabolic Factors and Cardiovascular Diseases

With regard to the large group of individuals at risk for heart attack, some advances have been made in understanding the interplay of obesity, diabetes, and atherosclerosis. Although much progress has been made in reducing the prevalence of most cardiac risk factors (including hypertension,

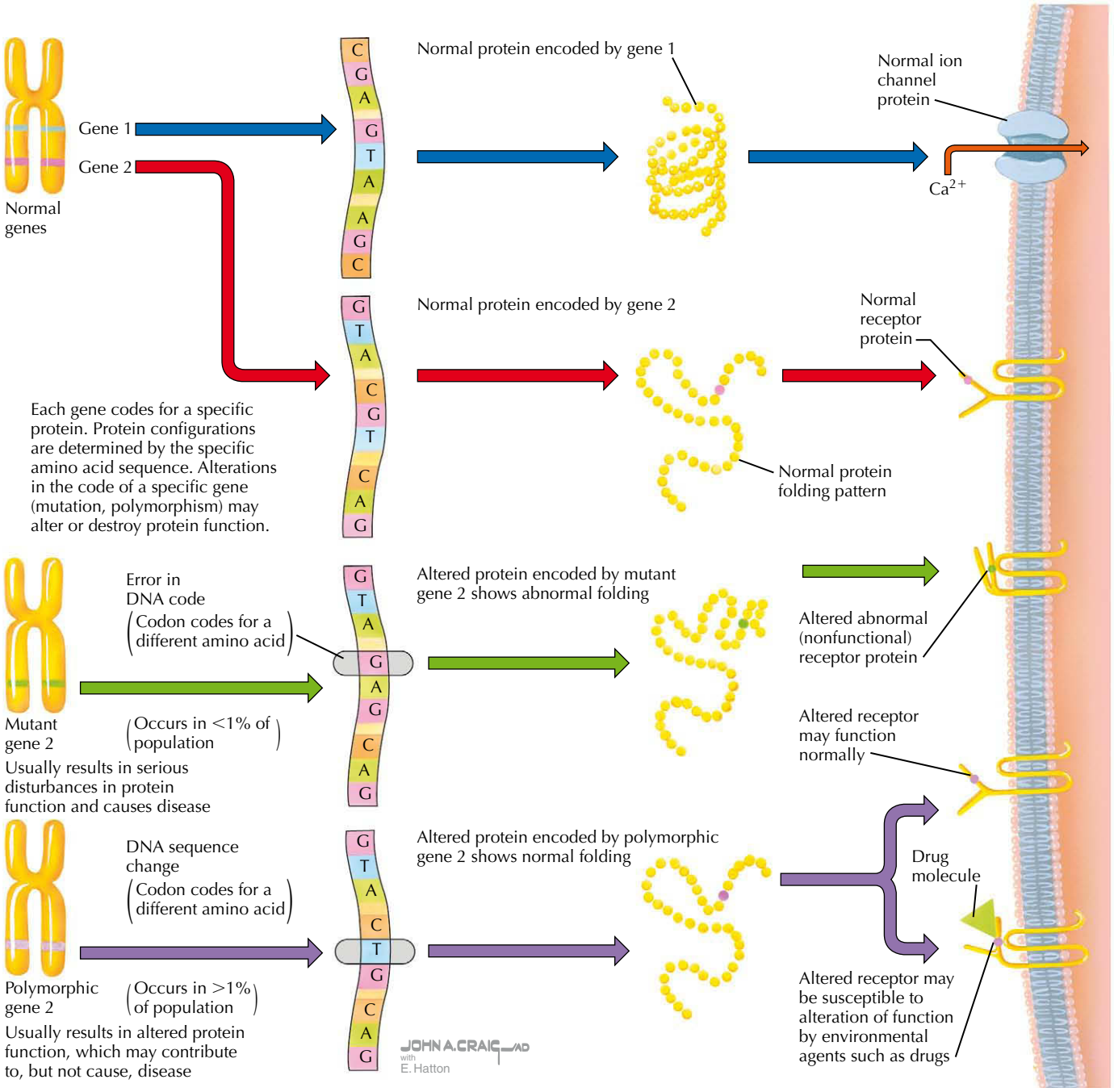
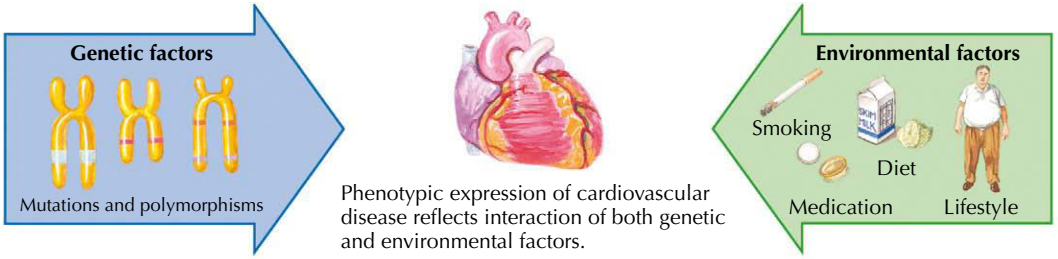


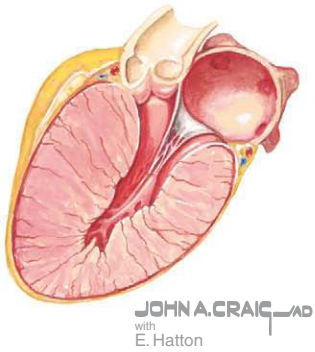
Figure 72-2 *Normal, mutant, and polymorphic gene expression.* A, adenine; C, cytosine; G, guanine; T, thymine.

hypercholesterolemia, and cigarette smoking), this favorable trend has been counterbalanced by increases in obesity and diabetes. As discussed in Chapters 2, 11, and 70, there is a powerful relationship between diabetes mellitus and atherosclerosis. According to the Framingham risk calculator, the presence of diabetes is equivalent to the presence of some degree of coronary heart disease.

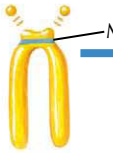
Analogous to the genetics of familial hypercholesterolemia, some individuals with diabetes mellitus have well-described mutations, whereas the vast majority of individuals with diabetes mellitus probably have a spectrum of polymorphisms that makes them particularly susceptible to environmental influences. This susceptibility can often be most easily detected in genetically homogeneous populations. One of the best characterized groups with a genetic susceptibility to diabetes is the Pima Indians. In a manner analogous to how studies of Amish family pedigrees have identified autosomal-recessive genes important for diseases ranging from dwarfism to metabolic syndromes to developmental disorders—or more recently as genes important for colon cancer were elucidated based on studies in



Hypertrophic cardiomyopathy

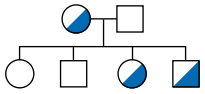


Myocardial abnormality marked by asymmetric septal hypertrophy and myocardial fiber disarray. Clinically, it mimics aortic stenosis and often results in sudden cardiac death, particularly in young athletes. Causes are multifactorial, but genetic predisposition is a strong factor.

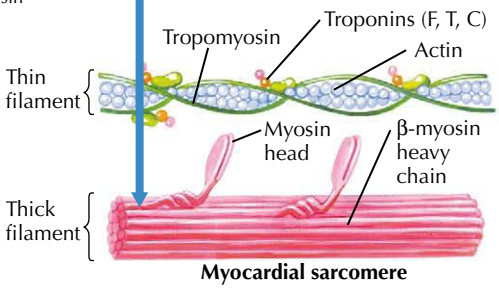


Chromosome 14

Original genetic studies revealed mutation in gene encoding β-myosin heavy chain. Subsequently, 200 mutations in 10 genes coding for contractile proteins have been identified.

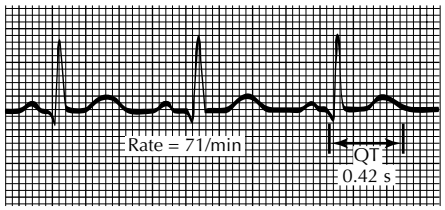


Inheritance pattern of familial-type hypertrophic cardiomyopathy is autosomal dominant with incomplete penetrance.

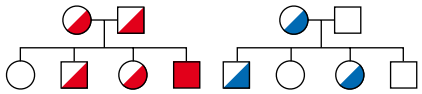


Myocardial sarcomere

LQTS

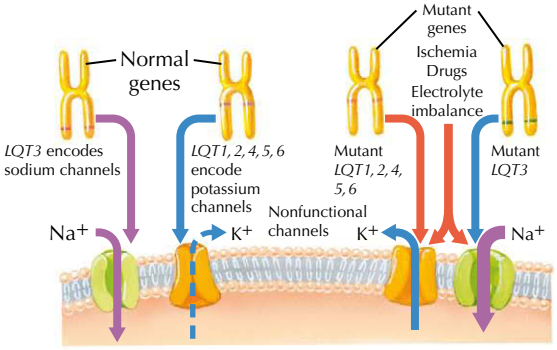


Abnormal prolongation of QT interval on ECG is phenotypic expression of all causes of LQTS. QT prolongation is associated with sudden cardiac death.



Autosomal recessive **Autosomal dominant**

LQTS exhibits either an autosomal dominant or a recessive inheritance pattern, depending on specific gene involved.



The genetic factors that underlie the LQTS involve the genes that encode for sodium and potassium ion channel proteins. To date, six genes (*LQT1–LQT6*) on five chromosomes have been identified. Mutations in these genes alter ion channel function and repolarization. Some forms of LQTS become manifest only when a secondary cause of QT prolongation (electrolyte disturbance, drugs, myocardial ischemia) is present.

Figure 72-3 *Genetic and environmental factors in cardiovascular disease.* ECG, electrocardiogram; LQTS, long QT syndrome.

Mormon families—Pima families from the Gila River Indian Community in Arizona are being intensively studied in the search for genes and polymorphisms important in obesity, diabetes, and even the propensity for the metabolic syndrome. Interestingly, in the early 1900s, these individuals were lean and the incidence of diabetes was low. By the year 2000, nearly all of these individuals were morbidly obese and had diabetes. During the intervening 100 years there was little genetic change, but major environmental changes occurred, as the members of these families became more sedentary and their diets became richer in animal fats. Insulin resistance (uniformly present in patients with the metabolic syndrome) seems to underlie the propensity for diabetes in these individuals. At least two different groups of genes (those encoding fatty acid–binding proteins, such as FABP2, and protein phosphatases, such as protein phosphatase 1) are being studied. It is likely that polymorphisms are present in this population (either in the target genes being studied or in nuclear factors that regulate the expression of those

genes) that were benign under the environmental conditions of the nineteenth century but that cause significant morbidity today. Studies such as these will lead to a better understanding of atherosclerosis risk mechanisms and diagnostic and therapeutic approaches for intervention.

Molecular Signatures of Gene Expression

The previous discussion focused on the identification of alterations at the DNA level that predict cardiovascular disease. It is also possible to assess gene regulation at the messenger RNA (mRNA) level simultaneously for hundreds to thousands of genes using technology commonly referred to as "microarray" analysis. A microarray consists of probes for expressed mRNA species genes robotically placed on a microscope slide. A single slide may hold tens of thousands of specific probes, approaching coverage of the entire human genome. Blood or tissue samples are then processed, and the mRNA samples or proteins are hybridized to the microarrays. The relative signal for a specific gene or protein from the patient can be quantified, comparing expression in "normal" and "abnormal" tissue or blood samples. The goal is to use the assessment of these complex, multivariate patterns of gene expression to predict the likelihood of disease, disease progression, and response to therapy.

Results obtained from microarray analysis suggest that by analyzing the response of large classes of genes, it will be possible to account for the intrinsic variation resulting from the interplay of polymorphisms with the environment. Much of what is known is based on analysis of gene expression at the mRNA level. It is likely that analysis of gene expression at the protein level will provide even more meaningful data, but this technology lags behind that of mRNA analysis at present.

Molecular signatures are still under investigation for patients with cardiovascular disease, but molecular signatures have been used in patients with cancer. One of the best examples is in women with breast cancer. Gene expression patterns in breast cancer tumor biopsy samples have been examined with regard to disease progression and the efficacy of chemotherapy. Several studies have shown that gene expression patterns can accurately predict high-risk versus low-risk status. Many studies are continuing to determine whether molecular signatures will allow clinicians to predict the presence of disease and the response to therapy for atherosclerosis, hypertension, diabetes, and other cardiovascular diseases.

FUTURE DIRECTIONS

As our knowledge of the genetics of cardiovascular diseases grows, tools for the treatment of cardiovascular diseases will emerge. Many of the approaches described here will become clinically useful in coming years. We must be circumspect in speculating on when use of these technologies will become commonplace; in cardiovascular diseases, optimal clinical outcomes often lag decades behind the development of new technologies. Gene therapy, the replacement of defective genes with normally functioning genes or the use of exogenously administered genes to alter function at the cellular level, has been performed for several single-gene diseases, with variable efficacy. In the field of cardiovascular diseases, several studies have reported the use of angiogenic factors or genes for the treatment of severe angina or severe peripheral vascular disease. The results are minimally positive, sufficient to continue studies but not sufficient to indicate clinical usefulness. A more promising approach than single-gene replacement is the use of stem cells to replace entire classes of genes and even to effect tissue repair. The use of stem cells is an area of active investigation, considered more promising than single-gene therapy by many, which is also being tested in clinical trials. It is hoped that it will become possible to individualize therapeutic choices. It is also hoped that it will even be possible to develop entire new portfolios of pharmacologic approaches that are customized to particular genetic backgrounds.

ADDITIONAL RESOURCES

McKusick VA. *Mendelian Inheritance in Man: A Catalogue of Human Genes and Genetic Disorders.* 12th ed. Baltimore: Johns Hopkins Press; 1998.

Dr. McKusick was the father of human genetics. His compendium on genetic causes of human diseases is a useful reference for anyone involved in the care of patients.

Watson JD, Crick FH. Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature.* 1953;171:737–738.

A classic article describing the structure of DNA. Watson and Crick were awarded the Nobel Prize for this work.

Watson JD. *Molecular Biology of the Gene.* 6th ed. Menlo Park, CA: Benjamin/Cummings; 2007.

An excellent reference for students seeking to better understand biology at the molecular level.

EVIDENCE

Arad M, Seidman JG, Seidman CE. Phenotypic diversity in hypertrophic cardiomyopathy. *Hum Mol Genet.* 2002;11:2499–2506.

Describes the widely variable effects specific mutations have on cardiac development and the phenotype of HCM due to other genetic and environmental influences.

Bogardus C, Tataranni PA. Reduced early insulin secretion in the etiology of type 2 diabetes mellitus in Pima Indians. *Diabetes.* 2002; 51(suppl 1):S262–S264.

One of the early descriptions of the mechanisms responsible for diabetes in the Pima Indian population.

Khoury MJ, McCabe LL, McCabe ER. Population screening in the age of genomic medicine. *N Engl J Med.* 2003;348:50–58.

Addresses issues related to the use of genetic tools in screening populations.

National Center for Biotechnology Information (home page on the Internet). Available at: <http://www.ncbi.nlm.nih.gov>. Accessed 22.03.10.

Provides valuable, constantly updated information on the genetics of human diseases.

Vincent GM. The long-QT syndrome: bedside to bench to bedside. *N Engl J Med.* 2003;348:1837–1838.

A useful review of the genes that have been implicated in LQTS, the mechanisms by which these genes cause QT prolongation, as well as diagnostic and therapeutic approaches to individuals with LQTS.

Effects of Exercise on Cardiovascular Health

73

Gina T. Eubanks, Richard S. Schofield, Eileen M. Handberg, and David S. Sheps

With approximately 1.2 million new cases each year, coronary heart disease (CHD) is the leading cause of mortality and morbidity in the United States. Epidemiologic studies show that low levels of habitual physical activity and physical fitness are associated with markedly increased all-cause mortality rates. Individuals with a sedentary lifestyle have a relative risk of 1.9 for CHD, compared with those with an active occupation and/or lifestyle. As many as 250,000 deaths per year in the United States, approximately 12% of all deaths that occur in the United States annually, are probably attributable to a lack of regular physical activity. It has been estimated that the direct medical costs of physical inactivity in 2000 were U.S. $76.6 billion. The number of Americans with a sedentary lifestyle continues to increase despite its designation as a modifiable risk factor for CHD.

It is never too late to change behavior and achieve health benefits. Even a midlife increase in physical activity is associated with a decreased risk of death and disability. Epidemiologic research has shown that physical activity lowers the risk of CHD, stroke, hypertension, metabolic syndrome, and non–insulin-dependent diabetes mellitus. Physical activity also results in weight loss when combined with diet, improved cardiorespiratory fitness, and prevention of falls. The recently published Physical Activity Guidelines Advisory Committee Report, 2008 provides the most current, comprehensive review of the exercise literature and the evidence of a lifetime benefit from regular exercise. These guidelines recommend that adults (ages 18–64 years) should exercise 2 hours and 30 minutes per week at moderate intensity or 1 hour and 15 minutes a week at vigorous intensity. This exercise should involve aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Activities should be performed in episodes of at least 10 minutes in duration and ideally should be spread across the week. In addition, muscle-strengthening activities that involve all major muscle groups should be performed on 2 or more days a week. The Physical Activity Guidelines Advisory Committee Report also recommended increasing the duration of weekly moderate-intensity physical activity to 5 hours weekly for additional health benefits. Older adults are advised to follow the same guidelines. If adopted by the public at large, these guidelines would result in substantial improvement in physiologic health throughout the population. In addition to physiologic health, exercise improves psychological health. The psychological benefits of exercise include positive changes in mood; relief from tension, depression, and anxiety; increased ability to cope with daily activities; and improved cognitive function. These benefits bring about positive changes in self-perception, well-being, self-confidence, and awareness, and may result in more health-promoting behaviors.

Increasing physical activity is extremely important, but achieving a higher level of fitness is even more important, especially for individuals who are at high risk for CHD or have experienced a cardiac event and require rehabilitation. Participating in a high-level exercise program, whether before or after a cardiac event, results in substantial improvement in cardiovascular (CV) risk factors including resting blood pressure (BP), lipid levels, body composition, and insulin sensitivity. This chapter addresses specific issues related to exercise, primary and secondary prevention, and the rationale for exercise prescription to patients with heart failure (HF).

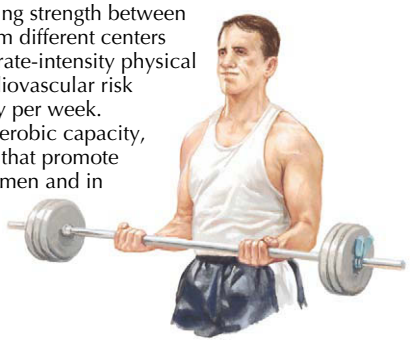
DEFINITIONS

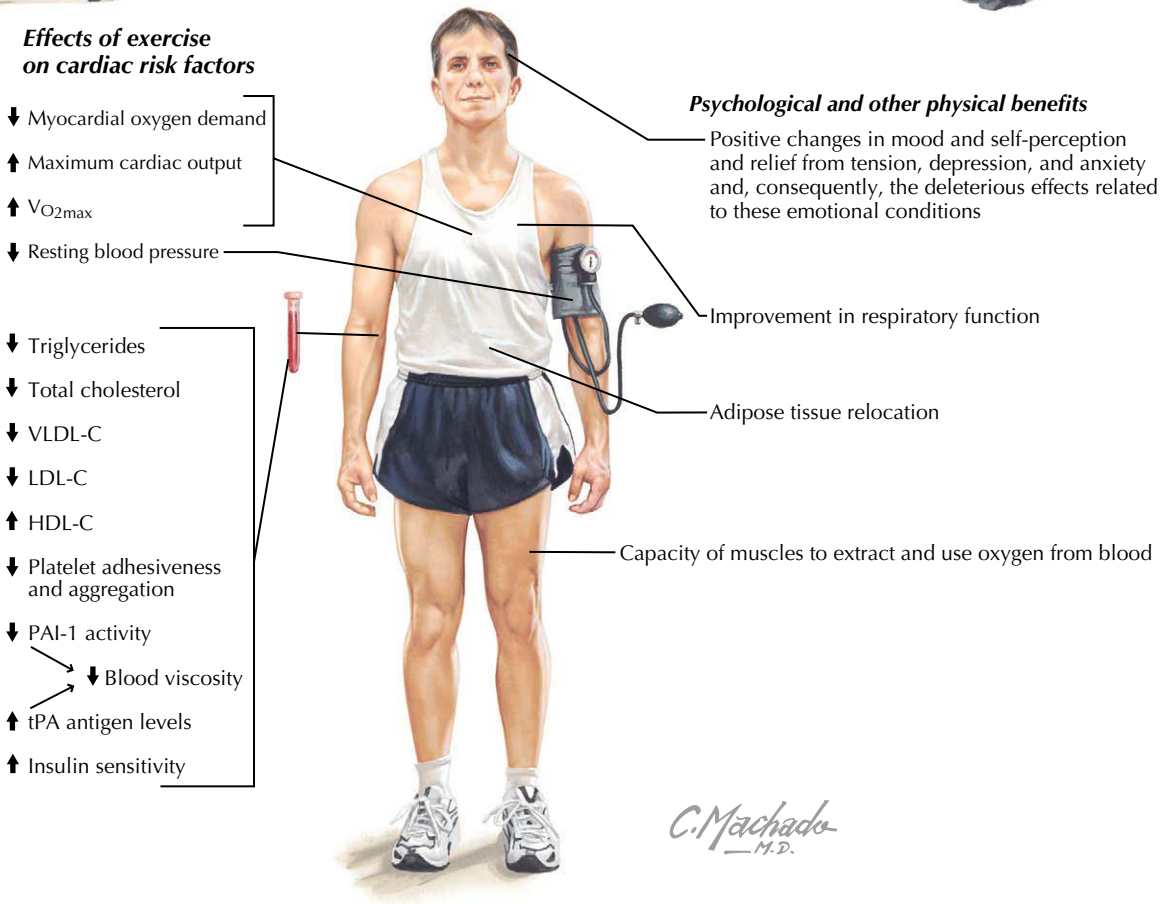
Numerous terms are used in the literature in reference to exercise and physical activity. In this chapter, we have used these terms as they are commonly defined. Physical activity is any bodily movement produced by contraction of skeletal muscle that increases energy expenditure above the basal level. Physical activity is generally categorized by mode, intensity, and purpose. Leisure activities are considered to be physical activities performed by a person that are not required as essential activities of daily living and are performed at the discretion of the person. Leisure activities include sports participation, exercise conditioning or training, and recreational activities such as going for a walk, dancing, and gardening. Exercise is considered a subcategory of physical activity that is "planned, structured, and repetitive" and generally has a purpose to improve or maintain some aspect of physical fitness. Physical fitness has been defined in many ways, but an accepted definition is "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and meet unforeseen emergencies." There are many components to fitness, both performance and health related. Health-related fitness consists of cardiorespiratory fitness, muscle strength and endurance, body composition, flexibility, and balance.

PRIMARY PREVENTION

There is a strong inverse relationship between physical activity and the risk of coronary disease and death. Across studies there is an estimated 30% risk reduction in all-cause mortality, comparing the most physically active subjects with the least active subjects. Similar CV benefit from fitness also exists in both sexes and across different races and ethnic groups (Fig. 73-1). The inverse dose-response relation for total volume of physical activity is curvilinear, meaning that those with the lowest physical activity levels have the largest risk reduction with increased physical activity. Several studies in men support a role for physical activity in reducing the risk of mortality. In nonsmoking,

Epidemiologic research has demonstrated protective effects of varying strength between physical activity and risk for coronary heart disease. Guidelines from different centers of research now strongly recommend at least 150 minutes of moderate-intensity physical activity per week; however, even greater benefits are seen and cardiovascular risk factors are even more reduced with 200 minutes of physical activity per week. In addition to the recommendations to increase activity related to aerobic capacity, the current guidelines strongly encourage participation in activities that promote flexibility and strength. Benefit from fitness has been found both in men and in women and across different races and ethnic groups.





Physical activity guidelines are targeted to increase physical activity to promote health, but they will not necessarily result in physical fitness and should not diminish the importance of achieving physical fitness.

Figure 73-1 *Effects of exercise on cardiovascular health: primary prevention.* HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAI-1; plasminogen activator inhibitor type 1; tPA, tissue plasminogen activator; $V_{O_{2max}}$, oxygen consumption; VLDL-C, very-low-density lipoprotein cholesterol.

retired men aged 61 through 81 years who had other risk factors controlled, the distance walked daily at baseline inversely predicted the risk for all-cause mortality during a 12-year follow-up. Of 10,269 Harvard alumni born between 1893 and 1932, those individuals who began moderately vigorous sports between 1960 and 1977 had a reduced risk of all-cause and CHD-related death over an average of 9 years of observation compared with those who did not increase sports participation. This finding was independent of the effects of lower BP or lifestyle behaviors related to low cardiac risk, such as cessation of smoking and maintenance of lean body mass. Data on the leisure-time physical activity levels of men participating in the Multiple Risk Factor Intervention Trial (MRFIT) support a reduction of risk for all-cause and CHD-related fatalities when leisure time is spent doing moderate or high (as compared with low) levels of physical activity. The effect was retained when confounding

factors, including baseline risk factors and MRFIT intervention group assignments, were controlled. Mortality rates for the high and moderate physical activity groups were similar. The Lipid Research Clinics Mortality Follow-up Study found that men with a lower level of physical fitness, as indicated by heart rate (HR) during phase 2 (submaximal exercise) of the Bruce Treadmill Test, are at significantly higher risk for death due to CV causes within 8.5 years as compared with men who are physically fit.

The same benefits from physical activity accrue for women. In women, higher physical activity level has been related to an improved health outcome in several longitudinal studies. The Iowa Women's Health Study observed 40,417 postmenopausal women for 7 years; moderate and vigorous exercise were associated with a reduced risk of death. This reduction of risk was present for all-cause mortality and specifically for deaths resulting from CV and respiratory causes.

Women who increase their frequency of activity from rarely or never to four or more times per week also have a reduced risk of death. The Women's Health Initiative (73,743 postmenopausal women) and the Nurses' Health Study (72,488 women aged 40–65 years) assigned subjects into quintiles based on energy expenditure. Age-adjusted risk decreased incrementally from the lowest to the highest energy expenditure group, was statistically significant when other CV risk factors were controlled, and was similar in white and black women. In addition, energy expenditure from vigorous exercise or walking and time spent walking were linked to a lowered risk for the development of CHD. This inverse relation between CHD risk and activity level has also been observed in groups of women with other high-risk factors, including smokers and women with high cholesterol levels, though not for hypertensive women. In one study of postmenopausal women, the odds ratios for nonfatal myocardial infarction (MI), adjusted for confounding factors, decreased across the second, third, and fourth highest quartiles of energy expenditure compared with the lowest quartile. Exercise equivalent to 30 to 45 minutes of walking 3 days per week decreased the risk for MI by 50%.

Studies show that in black and white men and women, lack of exercise is associated with a higher risk of 5-year all-cause mortality, independent of age, male sex, low income, BP, or a number of CV measures (left ventricular [LV] ejection fraction, abnormal ECG) or other physiologic measures (e.g., glucose level, creatinine level). A community-based study of elderly adults (aged 65 years or older) with no history of heart disease showed that walking at least 4 hours weekly significantly reduced the risk of hospitalization due to CV disease events during the subsequent 4 to 5 years.

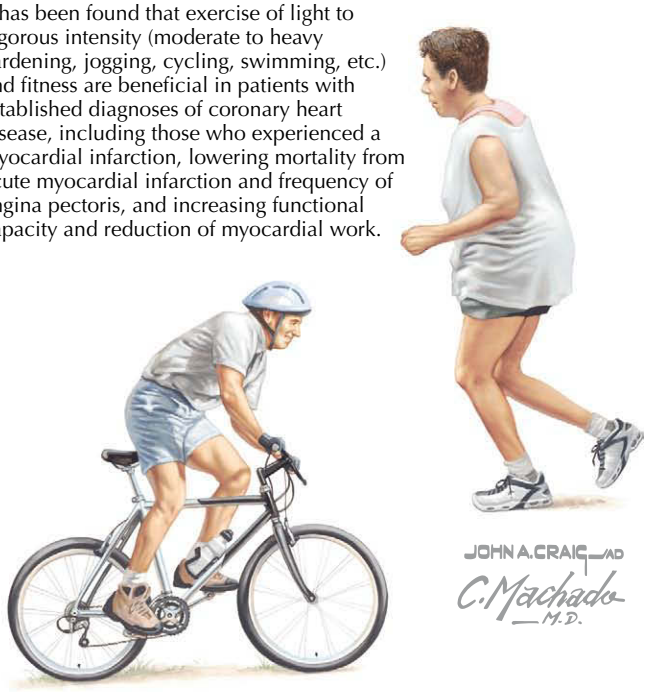
The epidemic of obesity in the United States has significantly impacted the development of CHD, hypertension, diabetes, and other atherosclerosis risk factors. In 2005, it was estimated that approximately 66% of the adult population over the age of 20 was overweight with a body mass index (BMI) of over 25, and 31% were obese (BMI >30). The prevalence of obesity differs across racial/ethnic and socioeconomic groups. Native Americans, African Americans, Hispanics, and Pacific Islanders have significantly higher BMIs when compared with whites and Asian Americans. There is also a significant sex-ethnicity interaction. African American women have a much higher prevalence (54%) compared with Mexican American (42%) and white (30%) women. This holds true for men as well, although the prevalence is lower (34%, 32%, and 31%, respectively). The total estimated costs in 2002 related to obesity were U.S. $132 billion. There is a dose-response relationship between physical activity and weight loss, but in general, successful weight loss and maintenance is a complex issue, which includes caloric restriction in addition to increased physical activity. Several studies have shown that anthropometric measures (BMI, waist circumference, waist-hip ratio) are associated with CHD risk factors and/or adverse events. The increased risk is partially explained by the milieu of insulin resistance, inflammation, and other atherosclerotic risk factors associated with obesity. While weight loss is important and improves CV risk factors, the direct benefit of weight reduction alone on CV risk is not clear. However, physical activity reduces CV risk. A study of women being evaluated for suspected myocardial ischemia found that measures of increased BMI, waist circumference, waist-hip ratio, and waist-height ratio were not independently associated with coronary artery disease (CAD) or adverse CV events. Lower levels of self-reported physical fitness scores were associated with higher prevalence of CHD risk factors and angiographic CAD and higher risk of adverse events during follow-up, independent of other risk factors. This supports the findings that fitness may be more important than overweight or obesity in women and men.

SECONDARY PREVENTION

Recent studies have conclusively demonstrated that exercise and fitness are as beneficial for patients with an established diagnosis of CHD as for those who do not have known CHD (Fig. 73-2). In subjects with higher levels of physical activity, there is a 20% to 35% lower risk for CV disease, CHD, and stroke compared with those with the lowest levels of activity. In a large study of men with established heart disease, regular light to moderate activity (such as 4 hours per week of moderate to heavy gardening or 40 minutes per day of walking) was associated with reduced risk of all-cause and CV mortality compared with a sedentary lifestyle. Another large study assessed men's health status and physical fitness during two medical examinations scheduled approximately 5 years apart. Men who were unfit at both examinations (baseline and 5 years later) had the highest subsequent 5-year death rate (122/10,000 man-years). The death rate was substantially lower in initially unfit men who improved their fitness (68/10,000 man-years) and lowest in the group who maintained their fitness from the first to the second examination (40/10,000 man-years). The mortality risk decreased almost 8% for each minute that the maximal treadmill exercise time at the second examination exceeded the baseline treadmill time. These results were retained when subjects were stratified by health status, demonstrating that unhealthy as well as initially healthy individuals benefited from exercise fitness.

Exercise intervention experiments have documented better health and survival even in patients who have experienced an MI. In one randomized study, patients were enrolled in a rehabilitation program of three 30-minute periods of exercise weekly, while other patients—matched by age, sex, coronary risk factors, site and level of cardiac damage, and acute-phase complications—served as controls. At 9 years after the initial

It has been found that exercise of light to vigorous intensity (moderate to heavy gardening, jogging, cycling, swimming, etc.) and fitness are beneficial in patients with established diagnoses of coronary heart disease, including those who experienced a myocardial infarction, lowering mortality from acute myocardial infarction and frequency of angina pectoris, and increasing functional capacity and reduction of myocardial work.



Studies have also shown that intensive exercise on a regular basis associated with a low-fat, low-cholesterol diet may be associated with regression in atherosclerotic coronary lesions, an increase in myocardial oxygen consumption, and a decrease in stress-induced myocardial ischemia.

Figure 73-2 *Secondary prevention.*

MI, the rate of death caused by acute MI and the frequency of angina pectoris were lower in the treatment group. In the National Exercise and Heart Disease Project, male post-MI patients were randomly assigned to a 3-year program of supervised regular vigorous exercise (jogging, cycling, or swimming) or to regular care not involving an exercise program. Subjects were reevaluated at 3, 5, 10, 15, and 19 years to determine total and CV-related mortality. A moderate advantage of the treatment versus control condition in reducing the risk of all-cause and CV death was seen at the first follow-up time point but diminished and eventually reversed as the time since baseline increased. This may indicate that the benefits of an intensive exercise program are time-limited or may also be related to several other factors (see later discussion). In any case, that each metabolic equivalent unit by which the participant's work capacity increased from the outset to the completion of the 3-year program resulted in an incremental reduction in total and CV-related mortality suggests that increasing exercise fitness did promote survival and that failure to observe a long-term benefit in the treatment group versus the control group may have resulted from crossover between the two groups during the protracted follow-up period, improvements in medical therapy (routine use of statins), and/or revascularization approaches.

A large meta-analysis of 10 randomized clinical trials of post-MI patients showed that cardiac rehabilitation with exercise reduced all-cause mortality by 24% and CV death by 25% versus control subjects. However, the risk of nonfatal recurrent MI did not differ between groups.

Exercise training plays an important role in post-MI rehabilitation. Significant increases in functional capacity (10% to 60%) and reductions of myocardial work at standardized exercise workloads (10% to 25%) have been observed after 12 weeks of post-MI cardiac rehabilitation. The Exercise in Left Ventricular Dysfunction Trial demonstrated that exercise training after an MI may also improve ventricular remodeling and LV function. The American Heart Association (AHA) guidelines on physical activity in secondary prevention after MI, bypass surgery, or clinical ischemia recommend that the maximal benefit occurs when an exercise–cardiac rehabilitation program is initiated at supervised facilities where symptoms, HR, and BP can be monitored. A symptom-limited exercise test is essential for all participants before starting an exercise program.

Limiting Coronary Atherosclerotic Progression

Several randomized intervention studies have evaluated the influence of exercise training on progression of coronary atherosclerosis. In one, patients with a history of stable angina were randomized to receive a behavioral intervention (2 or more hours per week of intensive exercise group training sessions, at least 20 minutes per day of exercise, and a low-fat, low-cholesterol diet) or usual care. After 1 year, 32% of the treatment group versus 9% of the control group had regression in atherosclerotic coronary lesions, and, conversely, 48% of the control group versus 23% of the treatment group had progression of lesions. These differences were statistically significant. Other changes in the treatment group included reductions in weight, total cholesterol, and triglyceride levels, and increases in high-density lipoprotein cholesterol (HDL-C) levels, work capacity, and myocardial oxygen consumption. Stress-induced myocardial ischemia also decreased from the intervention, which was presumably attributable to enhanced myocardial perfusion. At 6 years' follow-up, the progression of CAD was still significantly slowed in the treatment group compared with the controls. Retrospective analysis of exercise intensity and angiographic data revealed that eliciting a regression of coronary stenosis necessitated expenditure of at least 2200 kcal/week (equivalent to 5–6 hours of exercise).

In the Stanford Coronary Risk Intervention Project, patients received a behavioral risk reduction intervention or usual care. Intervention programs were similar to those in the aforementioned studies, but smoking cessation and pharmacologic treatment of lipid profiles (according to established treatment guidelines) were added. Evaluation at 4 years after baseline revealed that the risk reduction intervention significantly improved levels of low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, HDL-C, triglycerides, body weight, exercise capacity, cholesterol, and intake of dietary fat. These positive changes were not seen in the control group. The rate of coronary stenosis progression and the number of hospitalizations were also lower for the intervention group, although each group experienced the same number of deaths.

The Lifestyle Heart Trial used an intervention program to transform lifestyle behaviors, including a low-fat vegetarian diet, aerobic exercise, stress management training, smoking cessation, and group psychosocial support. Follow-up angiograms at 1 and 5 years after baseline showed an average relative decrease in stenosis of 4.5% and 7.9%. Conversely, individuals in the control group showed a 5.4% and 27.8% average relative *worsening* of stenosis. The 5-year risk of adverse cardiac events was also significantly greater in the control group.

Based on these findings, it is apparent that programs introducing intensive measures to alter coronary risk-promoting behaviors, especially via exercise training and cholesterol reduction, can limit or even reverse the progression of coronary stenosis. Although the associated changes in coronary diameter were relatively small and therefore unlikely by themselves to explain the accompanying improvements in myocardial perfusion, improvements in vascular tone and reduction in the risk of plaque rupture (see Chapters 2 and 11) may have contributed to the observed outcomes.

PHYSIOLOGY OF EXERCISE EFFECTS ON CARDIOVASCULAR HEALTH

Oxygen Supply and Demand

Ventilatory oxygen uptake is increased by exercise training via enhanced maximum cardiac output (blood volume ejected by the heart per minute, which determines the amount of blood delivered to exercising muscles) and the muscles' capacity to extract and use oxygen from blood. Increased exercise capacity in turn favorably affects hemodynamic, hormonal, metabolic, neurologic, and respiratory function. Exercise training reduces the myocardial oxygen demand associated with a given level of work, as represented by a decrease in the product of HR times systolic arterial BP, and allows persons with CHD to attain a higher level of physical work before reaching the threshold at which an inadequate oxygen level results in myocardial ischemia (Box 73-1).

Lipids

Exercise training regimens in general all favorably alter lipid and carbohydrate metabolism. The positive effect of a low-saturated-fat, low-cholesterol diet on blood lipoprotein levels is enhanced by a strict regular exercise regimen in overweight adults.

Box 73-1 Benefits of Exercise Training

- Reduces all-cause mortality risk
- Reduces cardiovascular mortality risk
- May limit atherosclerotic progression
- Enhances oxygen uptake
- Reduces myocardial work
- Constructively alters lipid and carbohydrate metabolism
- Influences adipose relocation
- Enhances insulin sensitivity
- Reduces the conversion of HDL-C into LDL-C and VLDL-C
- May suppress platelet adhesiveness and aggregation
- Increases activity of mitochondrial enzymes
- Lowers blood pressure
- Improves functional capacity and peak oxygen consumption in heart failure

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol.

Training also influences adipose tissue relocation, which is thought to be important in lowering CV risk. Intense endurance training also enhances insulin sensitivity and has a highly salutary effect on fibrinogen levels in healthy older men.

The beneficial effects of exercise on lipids are at least part of the benefits that result in primary and secondary prevention of heart disease in the studies reviewed here. Kraus and colleagues examined the effects of graded exercise on serum cholesterol in sedentary and overweight adults with hyperlipidemia who completed a 6-month protocol. Comparing the three treatment exercise programs—high-amount, high-intensity exercise; low-amount, high-intensity exercise; and low-amount, moderate-intensity exercise—with controls, all exercising groups showed improvements in plasma lipoprotein levels, including a decrease in very-low-density lipoprotein cholesterol (VLDL-C) triglycerides and an increase in the size of LDL-C particles. Increased HDL-C levels and particle size occurred only in the high-amount, high-intensity group; the largest improvements in LDL-C measures were also seen only in this group. These effects were independent of weight loss, and higher amounts of exercise were associated with greater benefits in lipoproteins. A recent meta-analysis supports the findings that volume of exercise exposure is the primary determinant of HDL-C change.

Mechanisms that link exercise with an improved lipoprotein profile may include increased lipoprotein lipase activity and reduced hepatic lipase activity, leading to HDL-C increases and decreased conversion of cardioprotective HDL_2 into smaller HDL_3 particles. Exercise reduces the conversion of HDL-C into LDL-C and VLDL-C by decreasing serum concentrations of cholesterol ester transfer protein. It increases the conversion of HDL_3 to HDL_2 by increasing levels of serum lecithin cholesterol acyltransferase. LDL-C does not seem to be as responsive to exercise training as HDL-C and triglycerides.

Triglyceride levels are consistently and robustly affected in direct correlation to the total amount of exercise, similar to those changes seen in HDL-C (10–20 metabolic equivalent tasks—hours per week), although some reports suggest that

women are more resistant to changes in triglycerides with exercise than men.

Metabolic Syndrome and Diabetes

Metabolic syndrome is a cluster of metabolic risk factors that promote development of atherosclerotic CV disease. Risk factors include atherogenic dyslipidemia, hypertension, elevated blood glucose, central adiposity, and proinflammatory and prothrombotic markers. Prospective studies have demonstrated a twofold increase in the relative risk of atherosclerotic events and, for those without diabetes, a fivefold increase in the risk for developing diabetes. The Adult Treatment Panel III criteria for diagnosis of metabolic syndrome is the presence of any three of the following criteria: (1) waist circumference greater than 40 inches in men and greater than 35 inches in women, (2) triglycerides greater than 150 mg/dL or drug treatment, (3) low HDL-C or drug treatment (<40 mg/dL in men; <50 mg/dL in women), (4) elevated BP or drug treatment (>130/85 mm Hg), and (5) fasting glucose greater than 100 mg/dL or drug treatment.

Regular physical activity is associated with a 30% to 40% lower risk for developing metabolic syndrome. There is an inverse dose-response association between level of activity and risk. The minimal amount of activity necessary to prevent metabolic syndrome ranges from 120 to 180 minutes of activity per week. These findings are consistent for both men and women. There have been no prospective trials to examine exercise training as a treatment to reverse metabolic syndrome.

Currently it is estimated that 17.9 million Americans have been diagnosed with diabetes and that another 6 million are undiagnosed. There were 1.6 million new cases of diabetes diagnosed in 2007, and it is estimated that the prevalence will double by 2050. The death rate from diabetes in 2004 was 24.5%, with the majority dying from some form of heart disease. Numerous large-cohort studies have demonstrated the benefit of physical activity in preventing type 2 diabetes. In the Nurses' Health Study, walking and vigorous activity were associated with a decreased risk for diabetes, with greater physical activity providing the most benefit. The estimate across studies is a 30% to 40% lower risk for developing type 2 diabetes for those with moderate levels of activity. The benefits are seen for both men and women, as well as young and old and for different races–ethnic groups. The data indicate that at least 120 to 150 minutes of moderate to vigorous physical activity are needed to significantly lower risk for diabetes.

Type 2 diabetes is associated with reduced exercise capacity, which is associated with cardiac and hemodynamic abnormalities. Exercise increases the activity of mitochondrial enzymes, which improves muscle energetics. Even modest levels of exercise increase insulin sensitivity and reduce visceral adipose tissue and plasma triglycerides. Women with diabetes who exercise moderately or vigorously for at least 4 hours per week have a 40% lower risk of developing coronary disease than those with lower exercise levels. Low physical activity in men with diabetes is an independent predictor for CHD. Several cohort studies have shown that CV fitness and physical activity levels are inversely correlated with mortality and/or CV disease event rates in subjects with type 2 diabetes. In the Nurses' Health Study of 5000 diabetic women followed for 14 years, the relative risk for CV events decreased progressively with increasing weekly volume of moderate to vigorous activity. This relationship remained after adjusting for smoking, BMI, and other CV risk factors.

Blood Pressure

Maintaining a habitual exercise routine can lower BP by as much as 5 to 15 mm Hg in patients with critical hypertension; mean reductions of 4 to 5 mm Hg systolic pressure and 3 to 5 mm Hg diastolic pressure are widely reported. Just as perseverance with an exercise program elicits a hypotensive response, detraining is associated with an increase in BP toward the preexercise level. Reductions in circulating norepinephrine level, plasma volume, and cardiac index parallel the reduction in BP and are probably involved in the antihypertensive consequences of exercise. Reduced systemic vascular resistance resulting from decreased sympathetic activity probably also affects BP.

ROLE OF EXERCISE TRAINING IN HEART FAILURE

Heart failure (HF) is a growing problem in the industrialized world and has reached epidemic proportions in the United States. Although the central effects of HF are pulmonary and peripheral vascular congestion, many patients believe that exercise limitation is the most troubling feature. Traditional therapies, such as angiotensin-converting enzyme inhibitors, β-blockers, and spironolactone show impressive reductions in mortality with somewhat less significant improvement in functional capacity. Hence, there is a need for therapies targeted at improving functional capacity. Exercise training was once prohibited in HF patients out of concern for patient safety. However, it is now recognized as a therapeutic option for improving functional capacity in patients with HF (Fig. 73-3).

In HF, mechanical function and functional capacity do not always have a direct correlation. LV ejection fraction is a poor index of exercise capacity in patients with chronic HF; therefore, other factors must contribute to exercise intolerance in HF. The physiologic mechanisms for exercise intolerance in HF, albeit incompletely understood, help to explain the potential benefits of exercise training.

Among the factors contributing to exercise limitation are impaired LV systolic and diastolic function, baroreflex desensitization, sympathetic nervous system activation, impaired vasodilator capacity, skeletal muscle abnormalities, and abnormalities of pulmonary function. Skeletal muscle abnormalities in patients with HF include atrophy of highly oxidative, fatigue-resistant (type I) muscle fibers; increased glycolytic, less fatigue-resistant (type II) muscle fibers; decreased mitochondrial oxidative enzyme concentration and activity; reduced mitochondrial volume and density; and reduced muscle bulk and strength. As HF progresses, patients become more physically limited because of pulmonary congestion and therefore reduce physical activity, causing a downward spiral in which cardiac limitation aggravates skeletal muscle deconditioning. The increases in circulating cytokines, part of the HF syndrome, further worsen muscle

Once prohibited in heart failure, exercise training has only recently been recognized as a viable therapeutic option for improvement of functional capacity. Most of the abnormalities seen in HF can be improved or even reversed by exercise training.

Some of the abnormalities seen in HF that can be improved or even reversed by exercise training

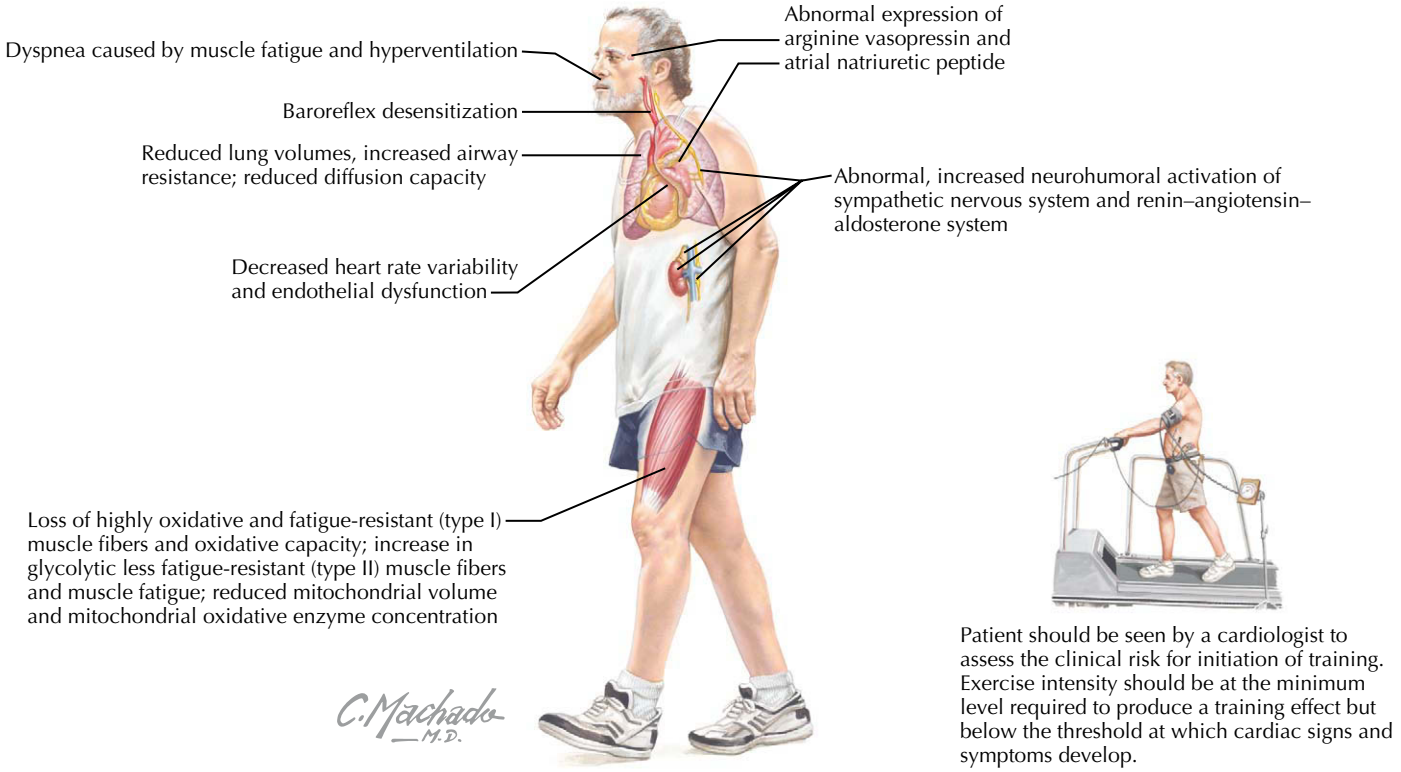


Figure 73-3 *Exercise training in heart failure (HF).*

atrophy. Reduced peak skeletal muscle blood flow with exercise limitation also reduces shear stress and thereby depletes tissue vasodilator reserve.

Pulmonary abnormalities are also common in HF, including reduced lung volumes and respiratory muscle strength and endurance; increased airway resistance with reduced flow rates; reduced diffusion capacity as a result of alveolar edema; and increased ventilatory drive, minute ventilation, respiratory rate, and dead space–to–tidal volume ratio. The effects of training on these ventilatory abnormalities in patients with HF include reduction in minute ventilation, reduced perceived sense of dyspnea, and improved respiratory muscle function.

The well-documented, abnormal activation of neurohormones in chronic HF is associated with a poor prognosis. An exercise training program can correct the increased plasma levels of angiotensin II, aldosterone, arginine vasopressin, and atrial natriuretic peptide in chronic HF to near-control values. Decreased HR variability, which is markedly abnormal in patients with HF, is a further marker of sympathetic activation. A physical conditioning program can improve HR variability and endothelial dysfunction in patients with chronic HF.

Clinical trials of exercise training in HF show improvements in exercise time, functional capacity, and peak oxygen consumption. Exercise training seems to be safe and generally well tolerated in patients with HF. One randomized trial found a reduction in cardiac events, an improvement in Minnesota Living with Heart Failure scores, and, most importantly, an improved survival rate in patients with HF who were randomized to exercise training. The Heart Failure—A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) Trial was sponsored by the National Institutes of Health and designed to test the hypothesis that patients with LV systolic dysfunction and New York Heart Association class II through IV symptoms who are given exercise training in addition to usual care would have a 20% lower rate of death and hospitalization over 2 years as compared with usual care. The initial results reported at the AHA Scientific Sessions in 2008 showed a balanced randomization of 2331 patients to exercise or usual care. Exercise consisted of a 36-week supervised training program followed by a home-based program. The mean follow-up was 2.5 years. The rates of all-cause mortality and all-cause hospitalizations combined were not significantly different between the two groups. Using a prespecified adjustment for prognostic factors, there was a significant reduction in the composite primary outcome by 11% (HR 0.89, confidence interval [CI] 0.81–0.99, $P = 0.03$), and a composite of CV mortality–HF hospitalizations were reduced by 15% (HR 0.85, CI

0.74–0.99, $P = 0.03$). Importantly, there were no differences in adverse events between the two groups, indicating that exercise training in this population is safe. There was also a statistically significant improvement in quality of life in the exercise training group. The findings of HF-ACTION offer good evidence for recommending exercise as a safe but modestly effective treatment for patients with HF.

Exercise training in patients with HF is best initiated within a traditional phase II (outpatient) cardiac rehabilitation program. Patients should be prescreened by a cardiologist to assess the clinical risk for training initiation. Most patients with New York Heart Association class II through IV symptoms can exercise safely; however, patients with unstable symptoms, recent MI, unstable angina, severe aortic stenosis, uncontrolled arrhythmias, significant hypotension (systolic BP <85 mm Hg), or acute myocarditis should be excluded. Chronotropic response may be blunted in patients with HF, so the level of perceived exertion and dyspnea should be used as a termination point and should be no higher than 11 to 14 on the Borg scale (light to somewhat difficult exertion). Patients with HF require prolonged warm-up and cool-down periods compared with healthy individuals and should avoid resistance training initially. Patients also should be counseled to avoid exercise after meals. The usual recommended activities, walking and cycling, arm ergometry (e.g., using arm motion, instead of leg motion, to peddle an upright stationary bicycle), and rowing, are well suited for individuals whose walking or cycling is limited by arthritis or conditions other than CV fatigue.

Exercise intensity should be at the minimum level needed to produce a training effect but below the threshold at which cardiac signs and symptoms develop. A baseline maximal oxygen consumption (MVo_2) study can be helpful in designing the exercise prescription but is not mandatory. Target intensity should begin at 40% of the MVo_2 and progress to 75% of the MVo_2 (roughly 70% to 85% of peak HR) over 4 to 6 weeks. Initially, the frequency of exercise generally should be three times per week. MVo_2 plateaus when the frequency of exercise exceeds three to five sessions per week, and the injury rate increases exponentially. In frail or high-risk individuals, two sessions per week may also be effective for initial conditioning. The frequency of exercise should eventually increase to five sessions per week.

Exercise sessions should begin with a 10- to 15-minute warm-up and end with a 10- to 15-minute cool-down. The initial duration of exercise should be 10 to 20 minutes. Interval training may be required in markedly deconditioned patients, with 2 to 6 minutes of exercise alternating with 1 to 2 minutes of rest. Duration should increase gradually to 20 to 40 minutes per session. After 12 weeks, patients can proceed to unsupervised exercise and can consider light to moderate resistance training.

FUTURE DIRECTIONS

Increasing physical activity and exercise in patients at risk for and with CHD should be a primary intervention in all patients. The documented benefits for CV risk reduction, as well as reduction in the progression of (and in some cases normalization of) metabolic syndrome and type 2 diabetes, make this one of the most effective therapies in a practitioner's arsenal. It must be noted that the obstacles to convincing a patient to engage in regular exercise are significant and begin with patient motivation. Further research is needed to learn more about dosing of exercise and physical activity, as well as better methods to improve subject compliance and adherence with prescribed exercise. In addition, public policy changes are necessary to alter aspects of our society that promote sedentary habits in children and adults, which contribute to obesity, diabetes, and CHD progression.

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Treatment of Lipid Abnormalities

Ross J. Simpson, Jr., and Sidney C. Smith, Jr.

74

For most individuals at risk of coronary heart disease (CHD), elevated serum lipid levels are a dominant modifiable risk factor. Lipid levels can be modified by several types of interventions—appropriate dietary, exercise, and drug programs to lower key components of serum lipid levels—which together represent the most important strategies for reducing an individual's risk for CHD. This chapter reviews mechanisms by which key blood lipid components can be altered favorably.

Low-density lipoprotein cholesterol (LDL-C) levels are strongly associated with atherosclerosis and CHD events. The lowering of LDL-C levels with drug and diet therapies is consistently related to a reduction in CHD events. The Heart Protection Study demonstrated that, among patients with known cardiovascular disease, regardless of the initial cholesterol value, the lowering of LDL-C with simvastatin, an inhibitor of the enzyme HMG-CoA reductase (which, as part of the mevalonate pathway, controls the rate of cholesterol synthesis), substantially lowers the risk for subsequent CHD events. The Heart Protection Study reaffirmed the primary importance of reducing LDL-C levels in individuals at high risk for CHD events and provided strong evidence that LDL-C reduction should remain the focus of preventive efforts.

High-density lipoprotein cholesterol (HDL-C) levels are influenced by diet, exercise, alcohol, exogenous estrogens, obesity, smoking, diabetes, and certain drugs (e.g., diuretics and anabolic steroids). Of these factors, exercise, estrogens, and alcohol are known to increase HDL-C. However, it should be emphasized that for both estrogens and alcohol, the primary evidence suggesting a benefit in reducing cardiac risk is epidemiologic, and neither is recommended for prevention. Estrogen administration in postmenopausal women has been studied extensively, and currently estrogen is not recommended as a primary or secondary prevention measure for atherosclerotic cardiovascular disease. The cardiovascular benefits of alcohol have been demonstrated in surveys of individuals only among those whose alcohol consumption is in the range of 1 to 3 ounces per day. Initiation of alcohol consumption to reduce cardiovascular risk is not recommended because of the potential for alcohol abuse.

Although a strong inverse relationship exists between HDL-C levels and CHD risk, clinical evidence is not adequate to support the primary use of therapies to increase HDL-C to reduce CHD events independent of lowering LDL-C or triglyceride levels. Moreover, the results of therapy with drugs that raise HDL-C levels often are not as consistent as are the results of drug therapies used to lower LDL-C levels. In the absence of compelling data from large populations of both sexes, the National Cholesterol Education Program (NCEP) recommends that treatment of HDL-C not be the primary therapeutic strategy, but instead that the initial focus be on reducing LDL-C. Increased HDL-C remains a secondary goal. Although recent studies were done on small numbers of individuals using various strategies to increase HDL-C, large randomized clinical trials are needed to ascertain whether therapies that raise HDL-C levels are useful as a primary strategy for CHD prevention.

Triglycerides are important plasma lipids found in varying concentrations in all plasma lipoproteins. The relationship between plasma triglycerides and CHD is debated. Moderately elevated triglycerides are often found in nephrotic syndrome, metabolic syndrome, diabetes, and hypothyroidism. Although triglyceride levels seem to be associated with CHD, there is only limited evidence that lowering triglyceride levels has a protective effect in terms of CHD events. Therapies to lower triglyceride levels are well established and include treatment of the underlying diseases, such as diabetes, reduction of the dietary intake of simple carbohydrates, weight loss, alcohol avoidance, and increased exercise. In patients with diabetes, control of diabetes with a hemoglobin A_{1C} goal of less than 7% should be the first therapeutic strategy. Very high levels of triglycerides (>500 mg/dL) are associated with the development of pancreatitis and eruptive xanthomas and should be treated intensively with therapy targeted to lower triglycerides for these indications.

DIAGNOSTIC APPROACH

Lipids are commonly measured by β quantification: total cholesterol, triglycerides, and HDL-C levels are measured directly; LDL-C levels are estimated by the Friedewald equation (LDL-C = total cholesterol − HDL-C − [triglycerides/5]). The LDL-C measurement is useful for monitoring lipid therapy and for assessing a patient's risk for a CHD event. In general, as with the other lipid profile components, measurement of LDL-C on a single occasion is not a basis for therapeutic intervention. For patients for whom long-term therapy is indicated, two fasting measurements of the lipoprotein profile, taken at least 1 week apart, should be obtained.

Direct measurement of LDL-C levels, particle size, and particle density can be accomplished by ultracentrifugation, gradient gel electrophoresis, and MRI methods. While measurement of lipoprotein (a) and other lipid fractions may provide additional information on the lipid lipoprotein characteristics, detailed clinical studies that indicate the usefulness of drugs that target these individual lipid components have yet to be reported. In many patients, it is useful to measure these components to further assess risk and occasionally to guide therapy. However, the primary focus is still on lowering LDL-C through drug therapy, diet, and exercise.

Lipid management requires the assessment of the patient's short-term (10-year) risk for CHD events. The therapy and specific goals are then based on the patient's absolute risk for a CHD event. The NCEP Adult Treatment Panel III recommends that patients with established coronary disease, diabetes, carotid artery disease, or lower extremity arterial disease be considered to be in the highest risk group (10-year risk >20%). Increasingly, metabolic syndrome and diabetes are

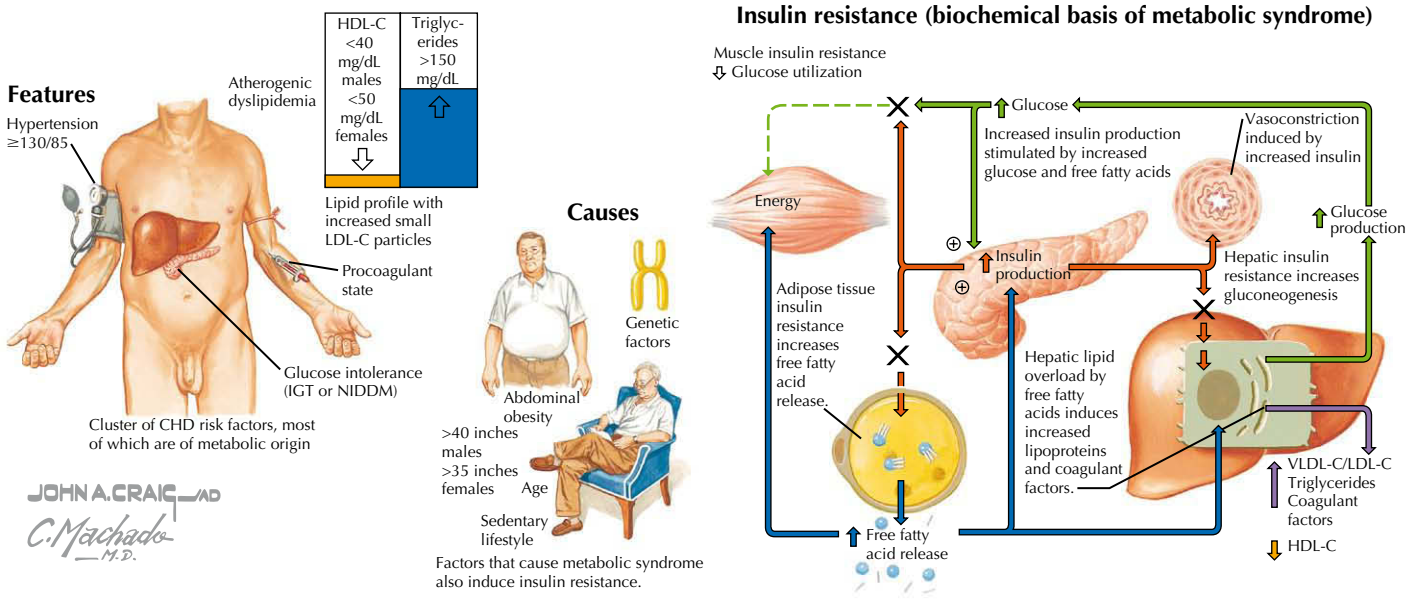


Figure 74-1 *Metabolic syndrome.* CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; NIDDM, non–insulin-dependent diabetes mellitus; VLDL-C, very-low-density lipoprotein cholesterol.

becoming dominant cardiovascular risk factors, as the incidence of obesity in the United States and industrialized countries continues to increase (Fig. 74-1; see also Chapter 61). In the absence of such disease, patients' global risk should be determined by the Framingham risk equation. Global risk is considered high if the 10-year risk is greater than 20%. The global risk of patients in the intermediate-risk (10-year risk of 10%–20%) and low-risk (10-year risk <10%) groups should be considered in light of the presence or absence of major CHD risk factors. The most important CHD risk factors are age (≥45 years for men, ≥55 years for women), a history of premature CHD in a first-degree relative, current cigarette smoking, the presence of hypertension, and HDL-C below 40 mg/dL. Patients with two or more major risk factors in addition to high LDL-C are considered to be at intermediate risk. Patients with one major risk factor in addition to high LDL-C are considered to be at low risk. Using the Framingham risk equation, the 20-year probability of the development of a CHD event can be estimated for patients with two or more risk factors. When the number of risk factors is 0 to 1, the Framingham scoring is not needed (see Chapter 11).

MANAGEMENT AND THERAPY

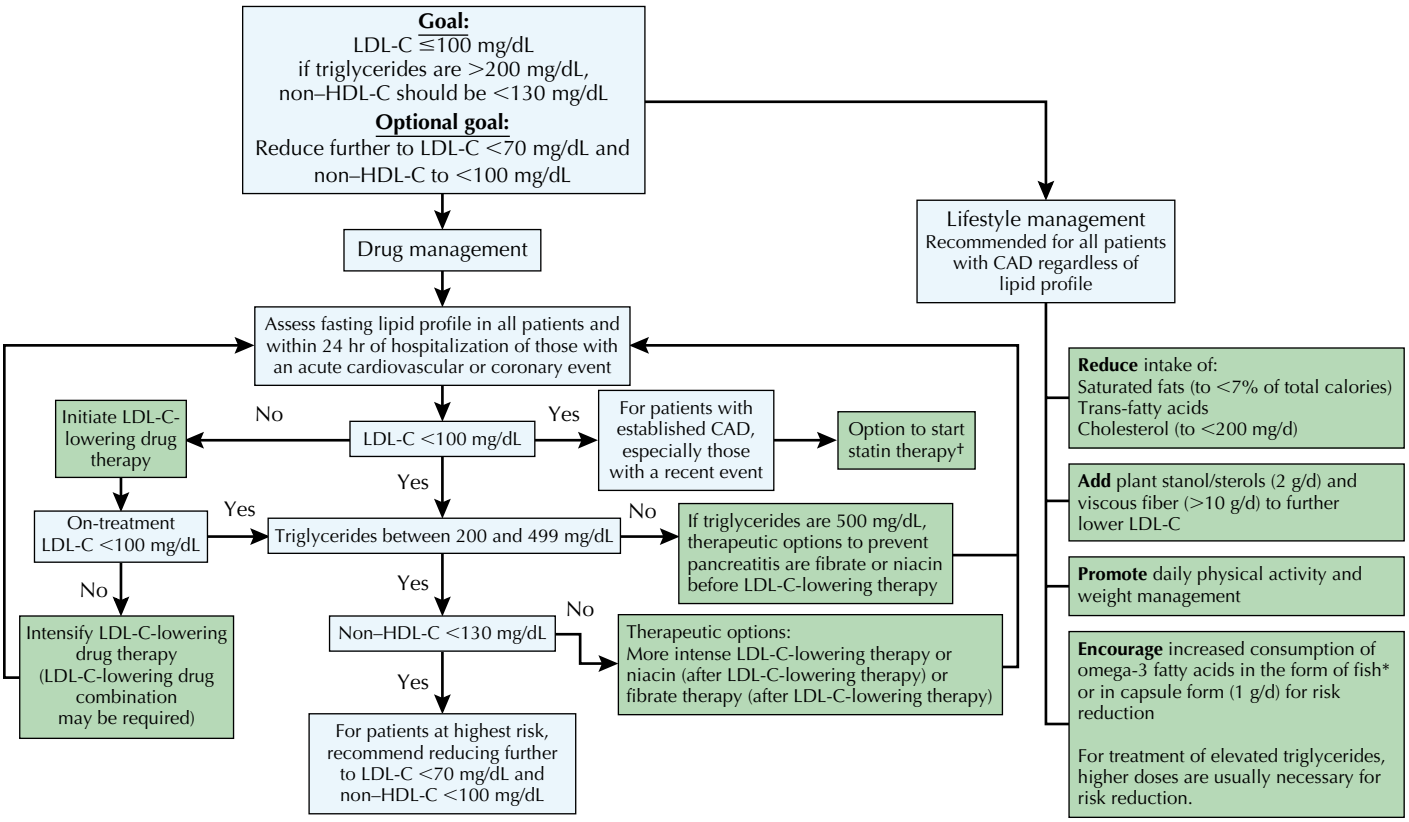
Optimum Treatment

Therapy is based on the probability of a CHD event and the estimated risk. In patients with CHD or a CHD risk equivalent (e.g., cerebrovascular disease, lower extremity arterial disease, or diabetes), therapy to lower LDL-C levels should be intensive. These patients require drug therapy to achieve the recommended LDL-C goals of less than 100 mg/dL. The Heart Protection Study strongly suggested that in high-risk patients, even if their LDL-C level is below 100 mg/dL, there is benefit from further lowering LDL-C by the addition of statin therapy to their regimen (Fig. 74-2).

The goal for patients in the intermediate-risk group (a 10-year 10%–20% risk of a CHD event) is an LDL-C level below 130 mg/dL. For patients in the low-risk group (10-year risk <10%), the goal is an LDL-C level below 160 mg/dL. The majority of patients in this lower risk group will not require drugs to achieve their LDL-C goal. Lower LDL-C goals may be appropriate for patients with familial hyperlipidemia or for patients with a strong positive family history of CHD.

The NCEP Adult Treatment Panel III recommends that the primary therapeutic target be LDL-C and not HDL-C, triglycerides, or other lipid fractions. This recommendation is based on clinical trial results and epidemiologic evidence showing that lowering LDL-C levels substantially reduces the risk of future CHD events. Other lipid fractions, particularly HDL-C and triglyceride levels, should be secondary therapeutic targets until the LDL-C level is within the goal range.

A low HDL-C level is a strong predictor of future CHD events. However, because of the lack of large randomized trials showing that raising HDL-C levels with drugs is effective and safe in reducing CHD events, therapy should be aimed at lowering LDL-C levels. Similarly, elevated triglyceride levels may pose an additive risk for patients with high LDL-C levels, multiple risk factors, diabetes, or established CHD. Reduced triglyceride levels should be a secondary goal, provided these levels are below 500 mg/dL. When triglycerides are elevated but below this value, hypothyroidism, nephrotic syndrome, metabolic syndrome, and obesity should be considered as probable causes of the elevation. If one of these is present, therapy should focus on that condition, and lipid-lowering treatment should be directed at the LDL-C level. When triglyceride levels exceed 500 mg/dL, primary therapy should be directed at



*Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.
†The safety of statins has not been assessed in pregnant women.

Figure 74-2 *Algorithm for management of lipid goals.* CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Modified from Smith SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *Circulation.* 2006;113:2363–2372.

lowering triglycerides, through the use of a fibrate or nicotinic acid, with an important goal being the prevention of pancreatitis.

SPECIFIC MANAGEMENT

Appropriate diet therapy and exercise are highly effective in helping patients manage their cholesterol levels and CHD risk (Fig. 74-3). Clinical trials showing the efficacy of statin drugs and other drug therapies are built on effective diet counseling and therapy. Patients should receive dietary counseling by a trained physician, nurse, or nutritionist. The NCEP Adult Treatment Panel III recommends that daily saturated-fat intake be limited to less than 7% of calories and daily cholesterol intake be limited to less than 200 mg. Plant stanols and sterols are recommended in quantities up to 2 g/day. Trans-fatty acids and hydrogenated fats should be avoided. Monosaturated fatty acids and fish oils are also encouraged through increased intake of fish and other foods found in the traditional Mediterranean diet. Calorie restriction is recommended for patients who are overweight. In addition, a fish oil mixture containing 2 to 5 g of alpha omega-3 fatty acids is a promising dietary supplement to reduce triglycerides.

Exercise is another important component of the management of dyslipidemia (see also Chapter 73). Exercise counseling make take the form of a referral to a formal rehabilitation or wellness program, a formal physical fitness assessment, an exercise prescription, or an increase in the patient's daily living activities. One helpful home measurement device is a "step counter." A step counter records the number of steps a patient takes in a normal day. The patient is then able to increase the step counts toward a specific count goal depending on the patient's baseline activity level. Another strategy is to ask what type of physical activities the patient enjoys and negotiate with the patient to achieve a higher level and a greater frequency of these or similar activities. All patients undergoing cholesterol treatment with drugs should receive periodic diet, exercise, and reinforcement counseling sessions from their primary care physician or other specialist.

DRUG THERAPY

Drug therapy (Fig. 74-4) is now predominantly based on the use of HMG-CoA reductase inhibitors (statins). Statins are effective at lowering LDL-C and have an excellent safety profile. They inhibit cholesterol synthesis, thereby increasing LDL-C

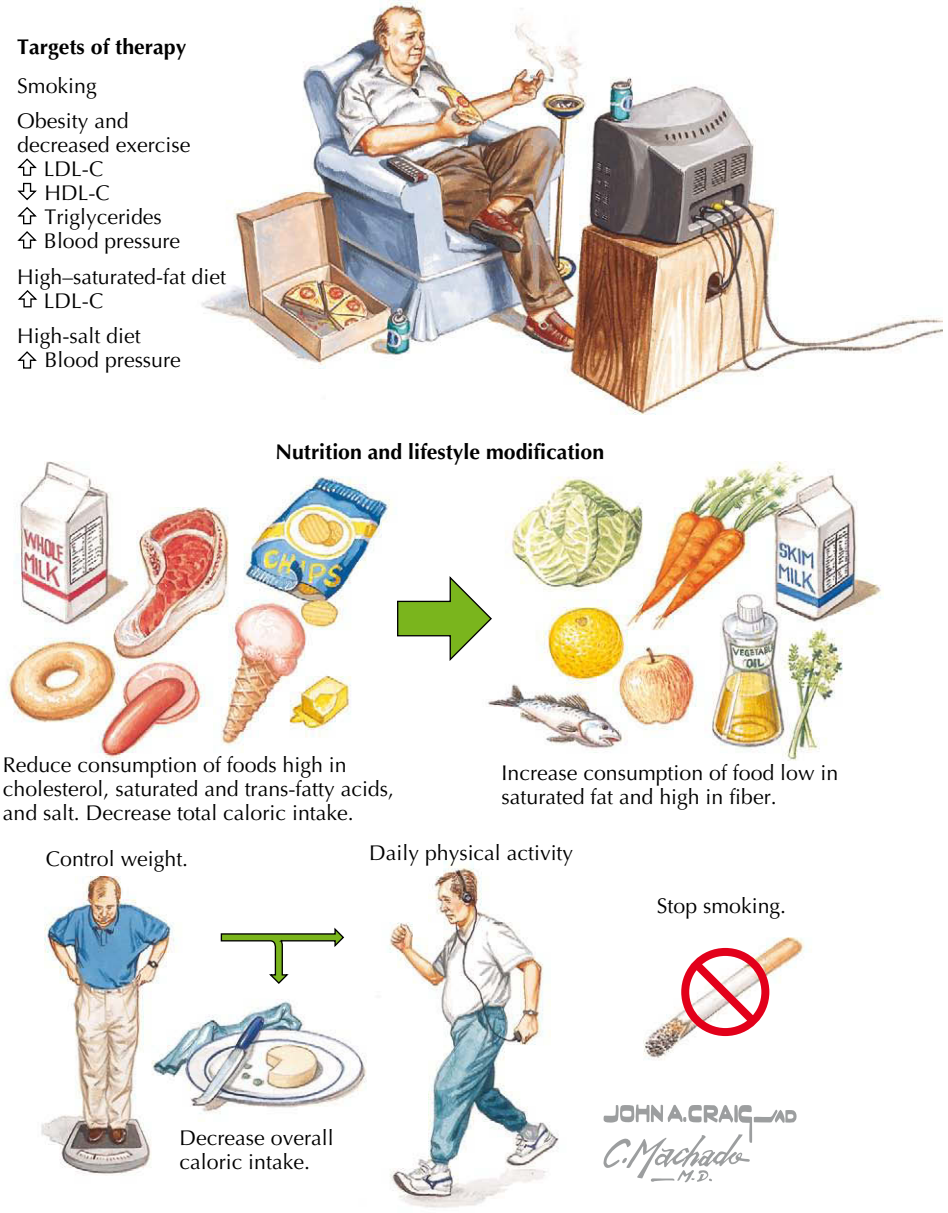


Figure 74-3 *Nonpharmacologic therapy for management of lipid goals.* HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

receptors on the liver cell membrane and potentiating LDL-C clearance from the blood. On average, statin therapy can reduce LDL-C levels by up to 50% in a dose-dependent manner and may lower triglycerides by 30% while simultaneously raising HDL-C by up to 15%.

The recommended starting dose of each statin varies, based on the drug's ability to lower LDL-C. Statins generally have a predictable dose-response relationship with regard to LDL-C. For each doubling of the statin dose, there is an approximately 6% further lowering of the LDL-C level. Statin drugs may be combined with cholesterol-binding resins to provide an additive effect on the lowering of LDL-C.

Although these drugs are well tolerated, there is a small risk of myopathy, particularly at higher doses or when the statins are combined with fibrates or niacin. Interactions with antibiotics and drugs used to treat HIV or to prevent organ rejection may also lead to rhabdomyolysis. Patients who develop muscle aches or pains should consult their physician about discontinuing their statin drug and should have their serum creatine kinase level measured.

Liver toxicity can also occur with statins and is manifested as increased liver enzymes to more than three times the upper limit of normal. This may occur at higher doses and can be avoided by monitoring the transaminase enzymes and, if necessary,

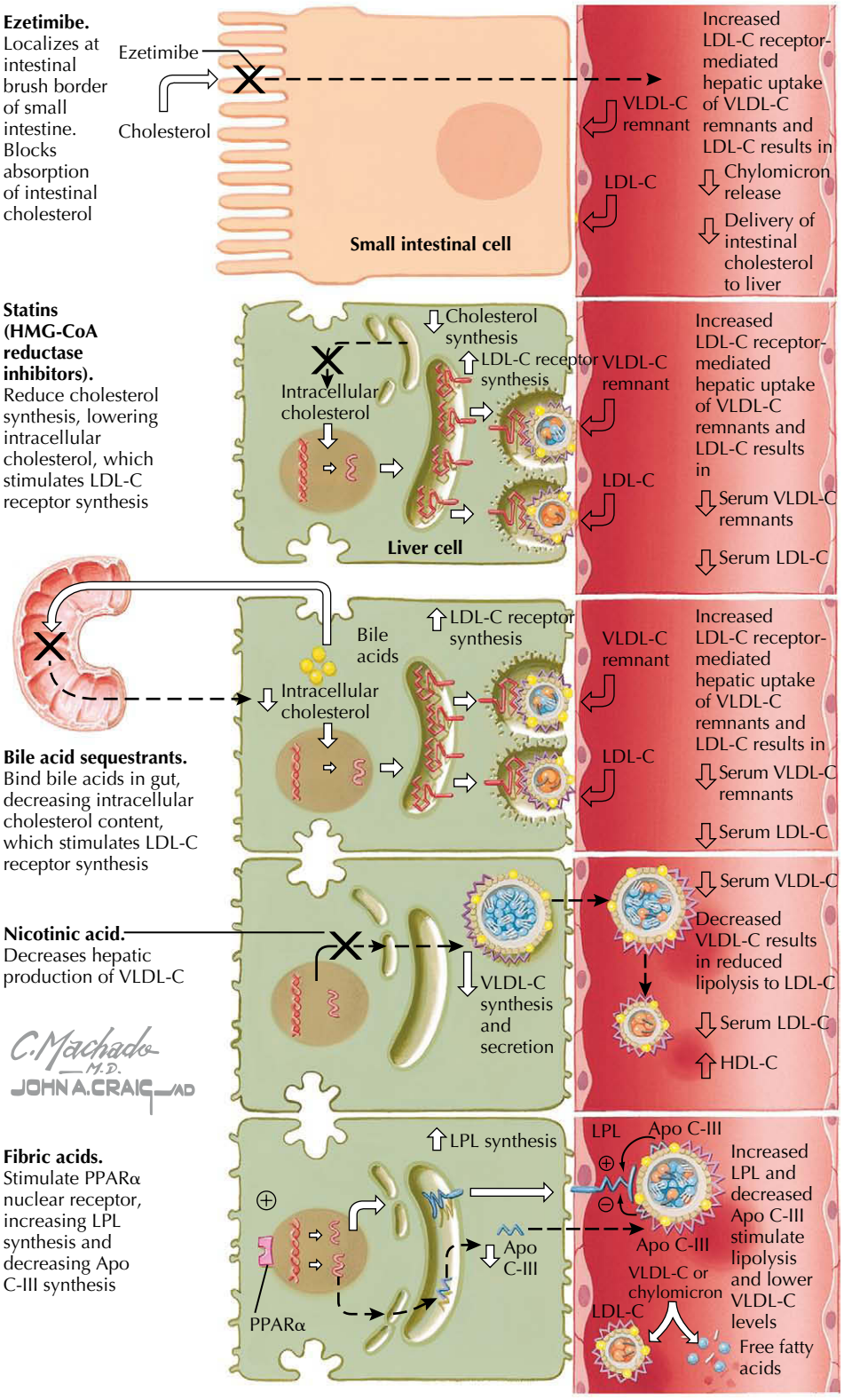


Figure 74-4 *Mechanism of action of lipid-lowering drugs.* Apo C-III, apolipoprotein C-III; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; PPARα, peroxisome proliferator activator receptor α; VLDL-C, very-low-density lipoprotein cholesterol.

decreasing the dose of (if elevation of liver enzymes is present but less than three times the upper limit of normal) or discontinuing the medication.

Second-line medications include bile acid sequestrants such as cholestyramine (4–24 g/day), colestipol (5–20 g/day), and colesevelam (1875–3750 mg/day). These drugs prevent bile acid reabsorption and potentiate LDL-C uptake by liver LDL-C receptors. At maximum doses, they can reduce LDL-C by up to 30% in a dose-dependent manner. However, bile acid sequestrants should be avoided in patients with elevated triglyceride levels, because they may further increase triglyceride values. These drugs are not systemically absorbed, and their side effects are generally limited to their potential to interfere with the absorption of vitamins and other drugs and to complaints of constipation and bloating. These drugs are usually taken in combination with a statin.

Ezetimibe lowers LDL-C by approximately 17%, has an additive effect on LDL-C lowering when combined with a statin, and is recommended as a second-line medication when patients cannot achieve their guideline-recommended LDL-C goal with statins alone or due to statin intolerance. The dosage is 10 mg/day. Another second-line medication is niacin, which acts to reduce tissue lipase activity and very-low-density lipoprotein cholesterol synthesis. Moderate to high doses (1500–2500 mg/day) of niacin may lower LDL-C levels by as much as 25%, decrease triglyceride levels by as much as 50%, and raise HDL-C levels by as much as 35%. The side effects of the drug include flushing, elevated blood sugar, hyperuricemia, abdominal pain, and, in rare cases, hepatotoxicity. Niacin is available in intermediate-release (1–6 g/day), extended-release (1–2 g/day), and long-acting (1–2 g/day) forms. It is highly effective and has a demonstrated safety record. Compliance is dependent on the form of medication used and the availability of experienced counseling. Compliance can be improved through the use of the extended-release form, starting the patient at 500 mg/day to be taken in the late evening with a snack, an aspirin 30 minutes before taking the niacin, and gradually increasing the dose.

Niacin can be also combined with a statin drug to treat patients with extremely high levels of cholesterol. This must be done with care, and, as with the statins, it is important to monitor liver enzymes and watch for symptoms of muscle pains. When niacin is combined with a statin, lower doses of the statin, as recommended in the package insert, should be used.

Fibrates (gemfibrozil 600 mg twice a day; fenofibrate 48–145 mg once a day) are particularly effective at lowering triglycerides and, to a lesser extent, LDL-C. Fibrates have an effect on lipoprotein lipase activity and can be expected to lower LDL-C by as much as 20% (particularly fenofibrate), to raise HDL-C by up to 20%, and to lower triglycerides by up to 50%. The side effects of fibrates are dyspepsia, the possible development of gallstones, and myopathy, particularly when combined with statins. Fibrates are contraindicated in patients with renal or hepatic diseases.

PLASMAPHERESIS

Patients with familial hypercholesterolemia (in which LDL-C values exceed 300 mg/dL) are at high risk for CHD. These patients usually cannot reach their target LDL-C levels and may require plasmapheresis. Plasmapheresis seems to be effective and safe at lowering LDL-C. Regional centers throughout the United States offer plasmapheresis on a biweekly basis. Because of its expense and required technical expertise, plasmapheresis for LDL-C lowering is not routinely available.

Avoiding Treatment Errors

Despite the extensive data supporting the safety and efficacy of statins to lower LDL-C, many patients are not at their guideline-recommended LDL-C goals. The reasons for patients' failure to achieve these goals are complex but include poor patient compliance with medication regimens and physician beliefs about the importance of lipid management in preventing heart attacks and strokes. Office-based programs that support diet and exercise counseling and medication adherence are often necessary to help patients achieve their LDL-C goals.

FUTURE DIRECTIONS

Additional diagnostic tests to more precisely define patients' risk of developing CHD events and to better characterize their lipid profile are being developed. These include blood tests to assess new risk factors and quantitative measurements to assess early atherosclerotic disease. Diagnostic tests include the high-sensitivity C-reactive protein assay to measure chronic inflammation; assessment of lipid particle size and density; electron beam tomography to assess calcium scores in the coronary arteries; carotid Doppler ultrasound to test intima-media thickness ratios; and the ankle-brachial index for peripheral vascular disease. The combination of new diagnostic tests to better identify individuals at risk for CHD events and expanded therapies to treat dyslipidemia should result in major advances in the prevention of the epidemic of CHD.

ADDITIONAL RESOURCE

Knoops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA.* 2004;292:1433–1439.

Excellent review and description of the Mediterranean diet and outcomes.

EVIDENCE

Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk. *Diabetes Care.* 2008;31:811–822.

Practical review of lipid management in patients with metabolic syndrome and diabetes.

Gotto Jr AM. *Contemporary Diagnosis and Management of Lipid Disorder*. 2nd ed. Newtown, PA: Handbooks in Health Care; 2001.

Easy-to-read summary of lipid metabolism and the relationship of lipid fractions to atherosclerosis.

Greenland P, Smith Jr SC, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation.* 2001; 104:1863–1867.

Good overview of risk predictors and tests to assess asymptomatic atherosclerotic disease.

Grundy SM, Cleeman JI, Merz CN, et al. National Heart, Lung and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239. Erratum in: *Circulation* 2004;110:763.

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LaRosa JC, Grundy SM, Waters DD, et al, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425–1435.

Example of a recent trial to assess safety and efficacy of a statin to lower LDL-C and improve outcomes in patients with CHD.

MRC/BHF Heart Protection Study collaborative group. MRC/BHF Heart Protection Study of cholesterol lowering therapy with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002;360:7–22.

Much-quoted study of the lowering of LDL-C in patients with a broad range of baseline LDL-C levels.

Pearson TA, Mensah GA, Alexander RW, et al. AHA/CDC Scientific Statement: Markers of Inflammation and Cardiovascular Disease, Application to Clinical and Public Health Forum. A statement for health-care professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003;107:499–511.

Excellent summary of the role of inflammation in atherosclerosis.

Ridker PM, Danielson E, Fonseca F, et al, for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195–2207.

Efficacy and safety of lowering LDL-C with a statin in patients with average LDL-C and elevated C-reactive protein levels.

Smith Jr SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *J Am Coll Cardiol.* 2006;47:2130–2139.

The most recent AHA/ACC statement on secondary prevention provides the evidence base for current recommendations regarding treatment of lipid abnormalities with medication and diet.

Third Report of the National Cholesterol Education Program Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Panel III). Grundy S, Chair. Bethesda, MD: National Heart, Lung and Blood Institute; 2001. See also *JAMA* 2001;285:2486–2497.

The gold standard for recommendations for the treatment of cholesterol for adults.

Cardiovascular Effects of Air Pollutants

Wayne E. Cascio, Milan J. Hazucha, Susan Lyon Stone, and Robert B. Devlin

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Risk factors for atherosclerotic coronary artery disease—including hypertension, lipid abnormalities, diabetes mellitus, obesity, physical inactivity, and tobacco use—provide targets for the prevention or progression of heart disease (see Chapters 46, 61, 65, 70, 73, and 74). Yet these risk factors account for only approximately 50% to 75% of cases of ischemic heart disease and cardiac events. For this reason it is logical to assume that other factors contribute independently or modify the known risk factors to produce vascular disease and trigger cardiac events. Air pollution is the best-studied environmental factor known to impact hospitalizations and deaths from heart disease. Of the various air pollutants, the evidence for a causative role in cardiovascular diseases is strongest for particles derived from combustion. Indeed, the World Health Organization estimates that more than 2 million premature deaths each year are attributed to urban outdoor air pollution and indoor air pollution from the burning of solid fuels. However, the effects of air pollutants on the cardiovascular system are generally not appreciated by patients or their health care providers. The major air pollutants include particulate matter (PM), ozone (O_3), nitrogen oxides, carbon monoxide (CO), and sulfur dioxide (SO_2). This chapter reviews the links between air pollution and cardiovascular disease, describes plausible physiologic mechanisms accounting for these effects, and provides an educational resource for physicians and patients to decrease exposure and risk.

HISTORY

During the twentieth century, three notable extreme air pollution episodes focused the attention of the public and governments on air pollution's adverse public health impact. These events occurred in the Meuse Valley, Belgium; Donora, Pennsylvania; and London, England, as a consequence of weather conditions that trapped combustion products and other pollutants from coal fires, vehicles, power plants, and industrial emissions. The best known of these events was the Great London smog. In London, between 5 December and 9 December 1952, a cold air inversion trapped combustion products of the entire city of 8.3 million persons and its industry, resulting in an extreme air pollution episode claiming more than 10,000 lives. During this event, daily mortality increased nearly fourfold, and the mortality rate remained significantly higher than usual for several weeks after the air pollution event had resolved. Surprisingly, these additional deaths that continued to mount were not explained solely by pulmonary disease. Instead a majority of deaths were attributed to cardiovascular etiologies. These important historical events had a profound impact on local and governmental responses to air pollution and contributed significantly to the passing of the Clean Air Act in the United States in 1963, which has been updated and modified several times since. Through the Clean Air Act, the U.S. Environmental Protection Agency (EPA) has statutory responsibility to regulate ambient air pollutants, including PM, CO, nitrogen dioxide (NO_2), O_3, SO_2, and lead. The levels of permissible air pollutants are established by the doses at which a measurable health risk is anticipated, allowing for an adequate margin of safety. This risk assessment is based on scientific data updated every 5 years and published as the U.S. National Ambient Air Quality Integrative Science Assessment. While urban air pollution continues to be a significant challenge overall, since the implementation of the Clean Air Act, the quality of the air in the United States has improved continuously. The improvement in air quality has translated into decreased overall mortality and cardiopulmonary mortality associated with exposure to air pollutants. Yet, despite the remarkable progress made in air quality, health risks of air pollution remain because intermittent increases in air pollution persist, the risk extends to relatively low levels encountered by most persons in the United States, and some people are more sensitive and vulnerable to the effects of air pollution, particularly elderly people with cardiovascular disease.

PARTICULATE MATTER

Airborne PM is not a single compound but a mixture of materials having a carbonaceous core and associated constituents such as organic compounds, acids, metals, crustal components, and biologic materials, including pollen, spores, and endotoxins. Combustion processes, such as those in vehicles and power plants, account for most human-generated PM. Importantly, particles generated by mechanical processes, windblown dust, and wildfires also contribute to the mass of PM. Particles are classified as "ultrafine," "fine" or "coarse" based on their size. Ultrafine particles have an equivalent aerodynamic diameter smaller than 0.1 μm (about one one-thousandth the diameter of a human hair). Fine particles ($PM_{2.5}$) have a diameter of 2.5 μm or less. Coarse particles ($PM_{2.5–10}$) have a diameter between 2.5 and 10 μm. Only particles smaller than 10 μm in diameter are respirable (Fig. 75-1, upper). Ultrafine and fine fractions are more likely to be produced by combustion, whereas the coarse fraction is more likely to contain crustal and biologic material. Outdoor PM readily penetrates into homes and buildings depending on building stock and use of air conditioning and heating, and thus increases in outdoor PM can result in increased indoor levels of PM. Cooking, smoking, dusting, and vacuuming also contribute to indoor PM, although not much is known about cardiovascular effects induced by exposure to indoor sources of air pollution in the United States. The national air quality standard for the allowable level of $PM_{2.5}$ averaged over 24 hours is 35 $\mu g/m^3$, and the annual average is 15 $\mu g/m^3$. The standard for PM_{10} averaged over 24 hours is 150 $\mu g/m^3$.

Generally it is agreed that PM exposure, even at low concentrations, influences cardiovascular events and mortality rates, yet some skepticism exists. In part, uncertainty over the cardiovascular effects of some pollutants is due to the reliance on epidemiologic data showing positive but weak associations between

fluctuating levels of air pollution and cardiovascular health, difficulty assessing exposure accurately, and significant confounding from many factors including but not limited to other pollutants, meteorologic factors, and medications. Also, the strong intercorrelation among outdoor air pollutants to increase cardiovascular risk makes it difficult to attribute observed cardiovascular effects to specific air pollution components. Nevertheless, time-series and cross-sectional epidemiologic studies show a positive association between exposure to airborne PM and cardiovascular morbidity and mortality rates. The association seems to be strongest with fine particles and in the eastern United States. Deeper penetration of fine particles into the lung before deposition may contribute to the apparent biologic activity of these particles. These findings implicate the aerodynamic diameter, regional sources, and composition of PM as factors that affect health.

The causal link between inhaled particles depositing on respiratory surfaces and cardiovascular health effects remains poorly understood. PM air pollution is associated with acute coronary syndrome (unstable angina and myocardial infarction), deep venous thrombosis, rhythm disturbances, stroke, and worsening of heart failure. Biochemical and physiologic responses of exposure to ambient air PM include changes in blood proteins, including acute-phase reactants, coagulation proteins, and proinflammatory cytokines; endothelial function; and neural modulation of the heart. Such changes would be expected to increase the risk of cardiovascular events secondary to thrombosis and arrhythmia (Fig. 75-1).

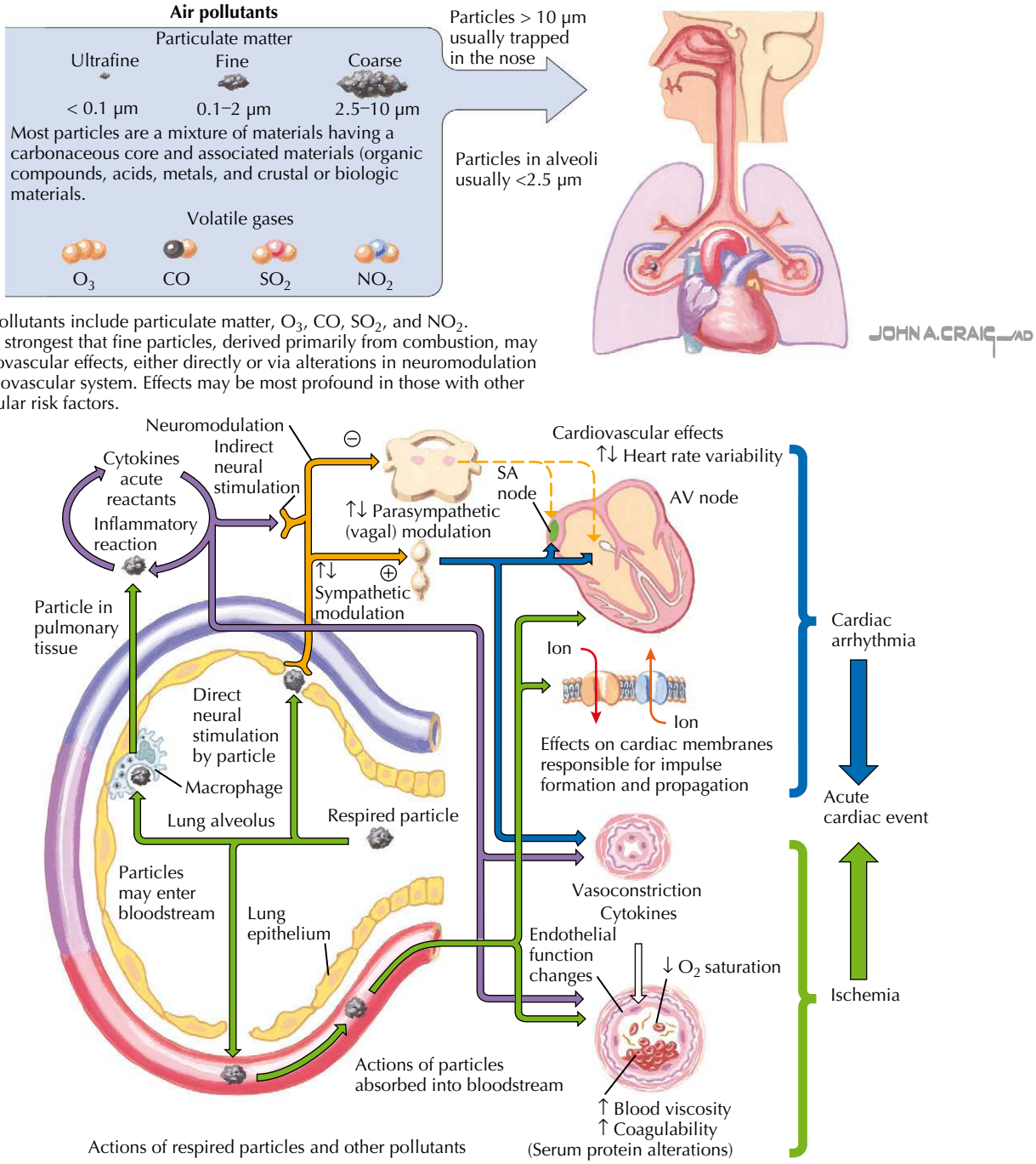
Possible cardiovascular effects associated with PM exposure can be categorized as short-term (hours or days) or long-term (years). Exposure to PM can increase heart rate and blood pressure, and can decrease oxygen saturation within hours. PM also affects pulmonary oxygen transport and neural modulation of the sinus node and the vascular system, although the magnitude of these changes is small. An increase in heart rate might be caused by an increase in sympathetic input to the heart or a decrease in parasympathetic input. Exposure to PM decreases cardiac vagal input, as suggested by a decrease in heart rate variability (HRV). Yet the association between changes in HRV and ambient PM concentrations is inconsistent. Whether the differences relate to the chemical composition of PM, other associated pollutants, age, gender, genetic background, concurrent cardiac disease, medications, or the HRV methodology is not known. Nor is it known whether change in HRV associated with PM exposure represents an independent measure of risk.

Many epidemiologic studies investigating the associations between air particle pollution and cardiovascular mortality and morbidity in single cities and multiple cities throughout the world show concordance that ambient air particle pollution is associated with increased cardiovascular mortality and hospitalizations. Two of the most notable studies are the National Morbidity, Mortality and Air Pollution Study and the Air Pollution and Health: A European Approach Project. These studies addressed the effect of air pollution in many U.S. and European cities, showing that air particle pollution was associated with an increased relative risk of cardiovascular mortality—ranging from 0.4% to 1.5% for each 20 $\mu g/m^3$ increase in PM_{10}. Likewise, other epidemiologic studies have linked exposure to PM, particularly traffic-related particles, to the onset of myocardial infarction or hospitalization for acute coronary syndrome, stroke, rhythm disturbances, and heart failure, associations that are stronger among individuals with prevalent heart disease.

Long-term effects of air pollution were established in three important cohort studies: the Harvard Six-Cities Study, the American Cancer Society Study, and the Women's Health Initiative Observational Study. In contrast to previous studies, these investigated the long-term health effect of fine PM for several years in multiple cities characterized by a large gradient in the concentration and types of air pollution. These studies showed a positive association between $PM_{2.5}$ and sulfate, and cardiopulmonary mortality and cardiovascular events. Subjects residing in the most heavily polluted of the Harvard six cities lived on average 2 years less than those residing in the least polluted city, after potential confounding and effect-modifying factors were taken into consideration.

There are at least three possible mechanisms by which PM induces changes in cardiac physiology: a neural reflex from afferents in the lung that interact with PM directly or indirectly through associated pulmonary inflammation; secondary effects of inflammatory cytokines and acute-phase reactants produced systemically and in the lung; and direct effects of particles or adsorbed soluble constituents of PM on cardiac membrane currents responsible for impulse formation and repolarization. The observations that inhalation of fine-particulate air pollution and O_3 causes arterial vasoconstriction and that sympathetic activation reduces endothelium-dependent flow-mediated vasodilation provide a mechanistic link between the changes in HRV and the changes in vascular reactivity, a known risk for cardiac events. Because sudden shifts in neural input to the heart may be arrhythmogenic, changes in HRV imply changes in neural input to the heart as a mechanism of arrhythmia.

The effects of long-term exposure to fine-particulate air pollution have been inferred from linking of cardiovascular risk factors and estimates of air pollution exposure to the cause of death in epidemiologic studies. These observational studies showed that fine-particulate air pollution increased the rate of mortality from cardiopulmonary causes. The risk of cardiopulmonary mortality was most strongly associated with fine particles when compared with larger particles. Although the mechanisms are unknown, possible explanations of the risk include acceleration of atherosclerosis progression secondary to increased oxidative stress or systemic inflammation, and modulation of factors that enhance coronary plaque instability or electrical instability. Data are emerging showing that PM accelerates atherosclerosis in humans and in animal models of chronic PM exposure, although the effect is probably indirectly mediated through increased inflammation and oxidant stress. For instance, high-sensitivity C-reactive protein (CRP) correlates with cardiac events. The liver produces CRP in response to the cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-α. Measurement of cytokines, and even high-sensitivity CRP, may provide a mechanism to assess cardiovascular risk in response to PM exposure. Because of the complexity of the mechanisms that regulate initiation and progression of atherosclerosis, and the complex constituents of PM, proof of a causal effect of PM on the development of atherosclerosis will be a challenge, but this is the aim of a continuing longitudinal substudy of the Multi-Ethnic Atherosclerosis Study known as the MESA Air Study.



Major air pollutants include particulate matter, O_3, CO, SO_2, and NO_2. Evidence is strongest that fine particles, derived primarily from combustion, may exert cardiovascular effects, either directly or via alterations in neuromodulation of the cardiovascular system. Effects may be most profound in those with other cardiovascular risk factors.

Figure 75-1 *Cardiovascular effects of air pollutants.* AV, atrioventricular; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; SA, sinoatrial; SO_2, sulfur dioxide.

It is possible that PM has a direct effect on cardiac autonomic function, on cardiac repolarization, or on both, and that PM increases the individual's susceptibility to myocardial ischemia and to ventricular fibrillation during regional myocardial ischemia. Chronic exposure to airborne PM might initiate cellular signaling that affects the expression of cellular proteins important to electrical impulse formation and conduction in the heart. Potential protein targets include structural proteins, as well as voltage- and ligand-gated channels and ion exchangers. Thus, cardiac deaths associated with exposure to PM are likely to result from interaction of the direct effects of PM on vascular function, cardiac electrophysiology, autonomic regulation, and/or coronary thrombosis in individuals at high risk for sudden cardiac death.

Exposure to secondhand tobacco smoke is a reasonable model for understanding how exposure to PM mediates changes

in the cardiovascular system and contributes to cardiac events. Acute exposure activates platelets and decreases endothelial function in humans, whereas long-term exposure accelerates the formation of atherosclerosis.

SULFUR DIOXIDE

SO_2 is a gas produced by coal-burning power plants, smelters, refineries, pulp mills, and food-processing plants. Typical ambient air reactions include formation of sulfuric acid (acid rain) and sulfates. A positive correlation exists between SO_2 levels and hospital admissions, the mortality rate in aged adults, and the presence of cardiovascular disease. It is often difficult to separate the contributions of individual components of air pollution and attribute them to health effects. For example, in one study the total mortality rate was estimated to increase by 5% for each 0.038 parts per million (ppm) increase in SO_2; yet the effects were no longer significant when respirable particles were included in the statistical model. Thus, SO_2 is likely to be a surrogate marker of PM because of the common sources of SO_2 and PM. The national air quality standards for SO_2 are 0.14 ppm averaged over 24 hours, and 0.03 ppm averaged over 1 year.

NITROGEN DIOXIDE

NO_2 and nitric oxide (NO) are reactive gases produced by gasoline and diesel fuel combustion, electric power generation, chemical manufacturing, soil emission including fertilizers, and solid waste disposal. NO_2 is also a major indoor air pollutant produced by gas stoves and gas heaters. Both gases are critical components of the photo-oxidation cycle and O_3 formation. NO is also produced endogenously at levels that can exceed 1 ppm. It is a mediator and a strong vaso- and bronchodilator. The ultimate fate of NO_2 and NO in ambient air and biologic fluids is the formation of nitrite and nitrate.

NO_2 is primarily associated with chronic respiratory effects. Children and adults with existing respiratory disease are at increased respiratory risk from NO_2 inhalation. Healthy individuals have shown slightly reduced cardiac output when inhaling NO_2 during exercise. Increased levels of NO_2 and black carbon are positively associated with arrhythmias. A positive significant association also exists between NO_2 and an increased risk of myocardial infarction. Numerous epidemiologic studies have linked elevated levels of NO_2 to coronary heart disease. Prolonged exposure of coronary heart disease patients to NO_2 has been shown to correlate with reduced HRV. Daily exposure to NO_2, particularly of the elderly, was significantly associated with daily emergency department visits for ischemic heart disease. The U.S. national air quality standard for NO_2 is 0.053 ppm (100 $\mu g/m^3$) averaged over 1 year.

CARBON MONOXIDE

CO is produced by combustion. When inhaled, CO binds avidly to hemoglobin, thereby reducing the capacity of blood to deliver oxygen to the tissues. Within tissue, CO may bind to cytochrome P-450, cytochrome oxidase, and myoglobin, affecting intracellular function. Individuals most susceptible to these effects have flow-limiting coronary disease.

A study of the chronic health effects of CO exposure in a comparison of bridge and tunnel workers showed that the relative risk of coronary artery disease was greater in tunnel workers. Prolonged exposure to CO and attendant carboxyhemoglobin (COHb) concentration in excess of 10% increased heart rate, systolic blood pressure, red blood cell mass, and blood volume. CO has been implicated in atherogenesis and in increased risk of myocardial infarction. In general, controlled exposure to CO reduces the time to onset of electrocardiographic evidence of exercise-induced ischemia and angina in individuals with ischemic heart disease and increases the frequency of ventricular arrhythmias during exercise. These effects occur at COHb levels as low as 2.9%. The baseline COHb in healthy nonsmokers is 0.5% to 1.0%. Prolonged exposure to 9 ppm CO would produce a blood COHb level of approximately 2%. Thus, the U.S. national air quality standards for CO (35 ppm averaged over 1 hour, and 9 ppm averaged over 8 hours) should provide protection even for a sensitive population with ischemic heart disease.

OZONE

O_3 is a secondary air pollutant formed in the atmosphere by photochemical reactions involving primary pollutants, volatile organic compounds, and nitrogen oxides. The U.S. national ambient air quality standard for ground-level O_3 is 0.075 ppm averaged over 8 hours and 0.12 ppm averaged over 1 hour. Exposure to O_3 irritates mucous membranes, decreases lung function, increases the reactivity of airways, and causes airway inflammation. Consequently, O_3 exposure can cause symptoms of chest pain and decreased exercise capacity. Initial epidemiology studies showing associations between PM and mortality were not able to reproducibly show similar relationships between O_3 and mortality, primarily because there is a close correlation of these two pollutants in many cities. However, several epidemiology studies have shown associations between exposure to O_3 and increased mortality and morbidity. In one study an increase in O_3 of 21.3 parts per billion increased the cardiovascular disease mortality rate by 2.5% and the respiratory disease mortality rate by 6.6%; the effect of O_3 was independent of that of other pollutants. Whether O_3 and PM affect the cardiovascular system by similar or different mechanisms remains unknown.

WHAT PATIENTS CAN DO TO AVOID RISK

Patients with heart disease should be made aware of the increased risk associated with exposure to air pollution and educated about strategies to decrease exposure. Patients can reduce their exposure and risk by decreasing their time outdoors when air pollutants are present at concentrations believed to impart a health risk and/or decreasing the intensity of outdoor physical activity. For example, if a patient usually jogs, exercising indoors in an air-conditioned environment can be recommended. If an alternative and acceptable indoor location is not available, one should walk instead of jog. Outdoor PM contributes to indoor PM.

When conditions are severe, for example with wood smoke secondary to a wildfire, activities should be restricted indoors as well and consideration given to using high-efficiency particulate air filter air cleaners to reduce indoor PM levels. PM and NO_2 are typically elevated in the morning and afternoon when automotive and truck traffic increases during rush hour commutes. O_3 concentration increases in the heat of the day and therefore is highest in the midday and in the summer months. In general, patients can reduce exposure by the following: limiting exercise outdoors in the afternoons when air pollutant concentrations are high; exercising indoors or away from roadways; closing doors and windows and using air conditioning; seeking air quality reports and forecasts; and utilizing the Air Quality Index (AQI) to guide outdoor activities. The AQI provides a national standard for reporting daily air quality and providing anticipated health effects for the quality reported. The AQI can be reviewed daily in the local media or on the EPA website.

In some areas of the United States, state and local environmental agencies in cooperation with the EPA provide a service, EnviroFlash, that provides air-quality alerts by email. Patients can customize reports so that they are notified of only those conditions that would pose a health risk for their specific clinical condition.

FUTURE DIRECTIONS

More information is needed to establish the cardiovascular health effects of specific pollutants. The dose dependence of these effects is key for determining air quality standards. Environmental concentrations of air pollutants vary widely, as do their sources and toxicities. Source apportionment is important for identifying origins of the various PM constituents so that health effects might be linked to specific PM constituents and sources.

Many questions about the cardiovascular effects of air pollutants remain. Does the interaction of air pollutants lead to additive, synergistic, or decreased health effects? Do the signaling pathways responsible for short- and long-term health effects differ? Why do older individuals and individuals with prevalent cardiovascular and pulmonary disease, diabetes, and hypertension have a greater susceptibility to the effects of air pollution? What is the role of PM-induced systemic inflammation in the development and progression of atherosclerotic vascular disease? To what extent does gene-environment interaction determine the health effects of air pollution exposure? Further investigation is needed to answer these questions.

ADDITIONAL RESOURCES

AIRNow. Available at: <http://www.epa.gov/airnow>; Accessed 01.03.10.

A U.S. EPA-supported website providing a national and local overview of air quality in the United States. Includes the AQI, providing information about the level of anticipated health risk for any reported level of air quality. Several other learning and information resources are available.

Bhatnagar A. Environmental cardiology: studying mechanistic links between pollution and heart disease. *Circ Res.* 2006;99:692–705.

A comprehensive review of environmental cardiology with an overview of clinical health effects associated with air pollution and an in-depth discussion of possible mechanisms. Provides an excellent overview of regional differences in the constituents of air pollution.

Brook RD, Fanklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the expert panel on population and prevention science of the American Heart Association. *Circulation.* 2004;109:2655–2671.

AHA scientific statement compiled by experts in the field providing a comprehensive review of the literature before 2004.

Simkovich BZ, Kleinman MT, Kloner RA. Air pollution and cardiovascular injury: epidemiology, toxicology and mechanisms. *J Am Coll Cardiol.* 2008;52:719–726.

Recent review of the effect of air pollution on cardiovascular injury.

U.S. Environmental Protection Agency (home page on the Internet). Available at: <http://www.epa.gov>; Accessed 01.03.10.

The U.S. EPA home page providing the portal to science and technology, laws and regulations, and health information including continuing medical education programs related to air pollution.

EVIDENCE

Chen Y, Craig L, Krewski D. Air quality risk assessment and management. *J Toxicol Environ Health A.* 2008;71:24–39.

Comprehensive review of air pollution's effects on health with a good discussion of the health effect of gases.

Dockery DW, Pope CA III, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med.* 1993; 329:1753–1759.

Large-cohort study including six U.S. cities characterized by long-term follow-up and gradients in air pollutants that was specifically designed to investigate the association between air pollutants and mortality. This is the first large-cohort study that provided a quantitative assessment of the impact of air pollution on mortality.

Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA.* 2006;295:1127–1134.

Ambitious and comprehensive study of the short-term cardiovascular and respiratory health effects of air pollution across the United States in the Medicare population.

Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med.* 2007;365:447–458.

The Women's Health Initiative cohort was utilized to investigate the effects of air pollution on postmenopausal women. Findings are consistent with those of the Harvard Six-Cities Study and American Cancer Society Study and indicated that increases in $PM_{2.5}$ were associated with an increased risk of cardiovascular death. The study also supported the hypothesis that increases in $PM_{2.5}$ correlate with cardiovascular events.

Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA.* 2002;287:1132–1141.

The large longitudinal American Cancer Society Study was utilized to test the hypothesis that air particle pollution is associated with an increase in cardiopulmonary mortality. Like the Harvard Six-Cities Study, this study showed a positive association between long-term exposure to inhaled PM and an increase in cardiopulmonary mortality and lung cancer.

Pope CA III, Muhlestein JB, May HT, et al. Ischemic heart disease events triggered by short-term exposure to fine particulate air pollution. *Circulation.* 2006;114:2443–2448.

Describes the adverse cardiovascular health impact of short-term exposure to air pollution in the Wasatch Front area of Utah. A case-crossover design was utilized to demonstrate that increased ambient $PM_{2.5}$ was associated with an increase in acute coronary syndrome as defined by unstable angina and myocardial infarction.

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