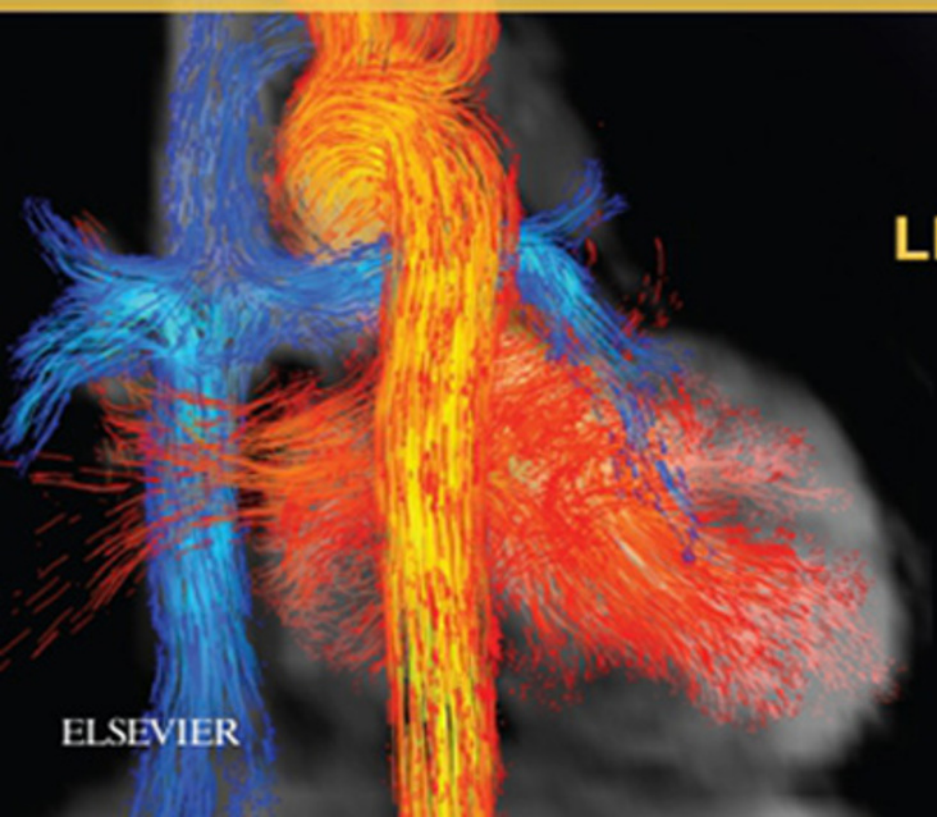
BRAUNWALD'S HEART DISEASE

REVIEW AND ASSESSMENT

ELEVENTH EDITION



LEONARD S. LILLY

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REVIEW AND ASSESSMENT

ELEVENTH EDITION

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Preface

Review and Assessment is a comprehensive study guide designed to accompany the 11th edition of *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, edited by Dr. Douglas Zipes, Dr. Peter Libby, Dr. Robert Bonow, Dr. Douglas Mann, and Dr. Gordon Tomaselli. It consists of 706 questions that cover key topics in the broad field of cardiovascular medicine. A detailed answer is provided for each question, often comprising a "mini-review" of the subject matter. Each answer refers to specific pages, tables, and figures in *Braunwald's Heart Disease* and to additional pertinent citations. Topics of greatest clinical relevance are emphasized, and subjects of particular importance are intentionally reiterated in subsequent questions for reinforcement.

Review and Assessment is intended primarily for cardiology fellows, practicing cardiologists, internists, advanced medical residents, and other professionals wishing to review contemporary cardiovascular medicine in detail. The subject matter is suitable to help prepare for the Subspecialty Examination in Cardiovascular Disease offered by the American Board of Internal Medicine.

All questions and answers in this book were designed specifically for this edition of *Review and Assessment.* I am grateful for the contributions by my colleagues at Brigham and Women's Hospital who expertly authored new questions and updated material carried forward from the previous edition: Dr. David Berg, Dr. Brian Bergmark, Dr. Akshay Desai, Dr. Sanjay Divakaran, Dr. Bradley Maron, Dr. Fidencio Saldaña, and Dr. Garrick Stewart. I also acknowledge with appreciation the following colleagues who provided additional material or support to this edition: Dr. Ron Blankstein, Dr. Sharmila Dorbala, Dr. Raymond Kwong, and the Brigham and Women's Hospital team of cardiac ultrasonographers, led by Jose Rivero, who expertly obtained several of the images that appear in this book.

It has been a pleasure to work with the editorial and production departments of our publisher, Elsevier, Inc. Specifically, I thank Ms. Jennifer Ehlers, Ms. Dolores Meloni, Ms. Beula Christopher, and their associates for their expertise and professionalism in the preparation of this edition of *Review and Assessment*. Finally, I am very thankful to my family for their support and patience during the long hours required to prepare this text.

On behalf of the contributors, I hope that you find this book a helpful guide in your review of cardiovascular medicine.

Leonard S. Lilly, MD
Boston, Massachusetts

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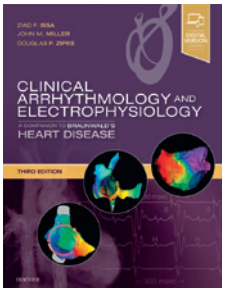

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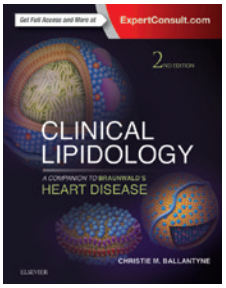

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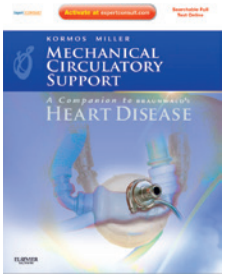

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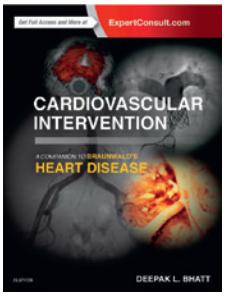

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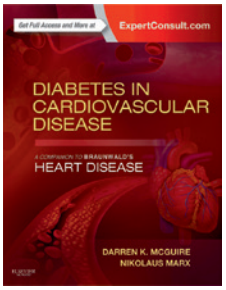

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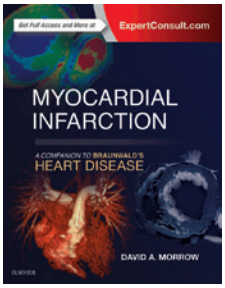

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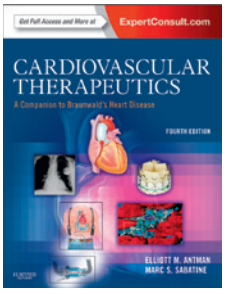

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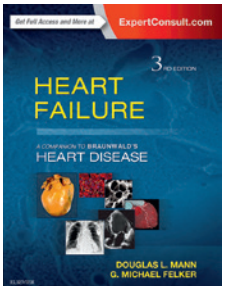

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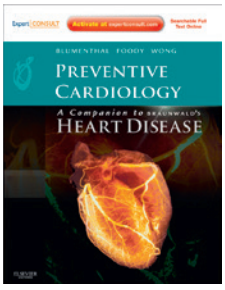

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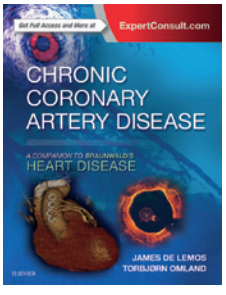

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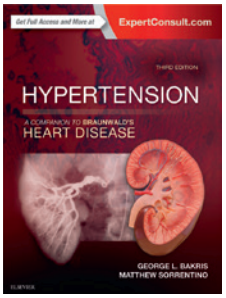

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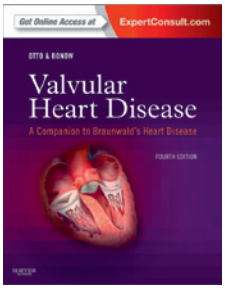

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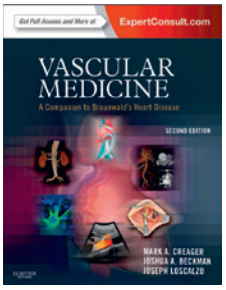

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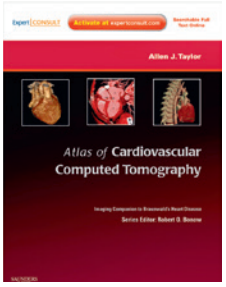

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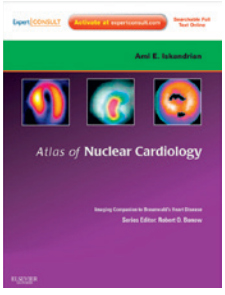

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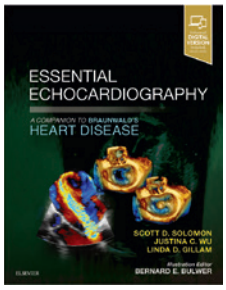

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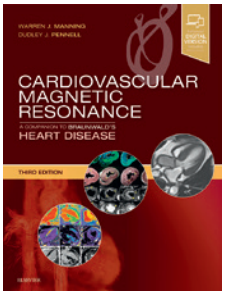

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SECTION I QUESTIONS

(CHAPTERS 1 TO 20)

Fundamentals of Cardiovascular Disease; Genetics and Personalized Medicine; Evaluation of the Patient

Sanjay Divakaran and Leonard S. Lilly

Directions:

For each question below, select the ONE BEST response.

QUESTION 1

A 54-year-old African-American man with a history of hypertension and hypercholesterolemia undergoes a treadmill exercise test using the standard Bruce protocol. He stops at 11 minutes 14 seconds because of fatigue, at a peak heart rate of 152 beats/min and peak systolic blood pressure of 200 mm Hg. The diastolic blood pressure declines by 5 mm Hg during exercise. During recovery, the systolic blood pressure decreases to 15 mm Hg below his preexercise pressure. There are no ischemic changes on the ECG during or after exercise. Which of the following is correct?

A. His peak systolic blood pressure during exercise exceeds that normally observed
B. The change in diastolic blood pressure during exercise is indicative of significant coronary artery disease
C. This test is nondiagnostic owing to an inadequate peak heart rate
D. These results are consistent with a low prognostic risk of a coronary event
E. The postexercise reduction in systolic blood pressure is suggestive of severe coronary artery disease

QUESTION 2

Which of the following statements regarding the second heart sound (S_2) is TRUE?

A. Earlier closure of the pulmonic valve with inspiration results in physiologic splitting of S_2
B. Right bundle branch block results in widened splitting of S_2
C. Paradoxical splitting of S_2 is the auscultatory hallmark of an ostium secundum atrial septal defect
D. Fixed splitting of S_2 is expected in patients with a right ventricular electronically paced rhythm
E. Severe pulmonic valvular stenosis is associated with a loud P_2

QUESTION 3

A state-of-the-art blood test has been developed for the rapid, noninvasive diagnosis of coronary artery disease. The assay has a sensitivity of 90% and a specificity of 90% for the detection of at least one coronary stenosis of >70%. In which of the following scenarios is the blood test likely to be of most value to the clinician?

A. A 29-year-old man with exertional chest pain who has no cardiac risk factors
B. A 41-year-old asymptomatic premenopausal woman
C. A 78-year-old diabetic woman with exertional chest pain who underwent two-vessel coronary stenting 6 weeks ago
D. A 62-year-old man with exertional chest pain who has hypertension, dyslipidemia, and a 2-pack-per-day smoking history
E. A 68-year-old man with chest discomfort at rest accompanied by 2 mm of ST-segment depression in the inferior leads on the ECG

QUESTION 4

A murmur is auscultated during routine examination of an 18-year-old asymptomatic college student, at the second left intercostal space, close to the sternum. The murmur is crescendo-decrescendo, is present throughout systole and diastole, and peaks simultaneously with S_2. It does not change with position or rotation of the head. Which of the following best describes this murmur?

A. This is a continuous murmur, most likely a venous hum commonly heard in adolescents
B. This is a continuous murmur resulting from mixed aortic valve disease
C. This is a continuous murmur due to a congenital shunt, likely a patent ductus arteriosus
D. Continuous murmurs of this type can only be congenital; murmurs due to acquired arteriovenous connections are purely systolic
E. This murmur, the result of left subclavian artery stenosis, is not considered continuous, because a continuous murmur can result only from an arteriovenous communication

QUESTION 5

Unequal upper extremity arterial pulsations are often found in each of the following disorders EXCEPT
A. Aortic dissection
B. Takayasu disease
C. Supravalvular aortic stenosis
D. Subclavian artery atherosclerosis
E. Subvalvular aortic stenosis

QUESTION 6

A 58-year-old woman with metastatic breast cancer presents with exertional dyspnea and is found to have a large circumferential pericardial effusion, jugular venous distention, and hypotension. Which of the following echocardiographic signs is likely present?
A. Collapse of the right ventricle throughout systole
B. Exaggerated decrease in tricuspid inflow velocity during inspiration
C. Exaggerated decrease in mitral inflow velocity during inspiration
D. Exaggerated increase in left ventricular outflow tract velocity during inspiration
E. Markedly increased E/A ratio of the transmitral Doppler velocity profile

QUESTION 7

Which of the following statements about pulsus paradoxus is correct?
A. Inspiration in normal individuals results in a decline of systolic arterial pressure of up to 18 mm Hg
B. Accurate determination of pulsus paradoxus requires intra-arterial pressure measurement
C. Pulsus paradoxus in tamponade is typically accompanied by the Kussmaul sign
D. Pulsus paradoxus is unlikely to be present in patients with significant aortic regurgitation, even in the presence of tamponade
E. Pulsus paradoxus is common in patients with hypertrophic cardiomyopathy

QUESTION 8

A 57-year-old man with a history of hypertension and elevated LDL cholesterol presents to the emergency room with the acute onset of substernal chest pressure, dyspnea, and diaphoresis. His blood pressure is 158/96 mm Hg and the heart rate is 92 beats/min. Physical examination reveals clear lung fields and no cardiac gallop or murmurs. The ECG shows sinus rhythm with a prominent R wave in lead V_2, 0.5 mm of ST elevation in lead III, and 2 mm of horizontal ST depression in leads V_1–V_3. Which of the following would be diagnostically useful to plan a course of action?
A. Repeat the ECG with right-sided precordial leads
B. Repeat the ECG with V_7–V_9 leads
C. Await results of serum cardiac biomarkers
D. Obtain a chest computed tomography (CT) to assess for pulmonary embolism

QUESTION 9

Which of the following combinations does NOT have the potential for significant pharmacologic interaction?
A. Simvastatin and erythromycin
B. Sildenafil and nitroglycerin
C. Pravastatin and ketoconazole
D. Cyclosporine and St. John's wort
E. Digoxin and verapamil

QUESTION 10

It would be reasonable and safe to order an exercise stress test for a patient with which of the following conditions?
A. Symptomatic hypertrophic obstructive cardiomyopathy
B. Advanced aortic stenosis
C. Acute myocarditis
D. Abdominal aortic aneurysm with transverse diameter of 5.5 cm
E. Unstable angina

QUESTION 11

A 42-year-old woman with hypertension and dyslipidemia underwent a 1-day rest-stress exercise myocardial perfusion single-photon emission computed tomography (SPECT) study with technetium-99m imaging to evaluate symptoms of "atypical" chest pain. Her resting ECG showed left ventricular hypertrophy. She exercised for 12 minutes 30 seconds on the standard Bruce protocol and attained a peak heart rate of 155 beats/min. She developed a brief sharp parasternal chest pain during the test that resolved quickly during recovery. Based on the images in Fig. 1.1, which of the following statements is correct?
A. The SPECT myocardial perfusion images are diagnostic of transmural myocardial scar in the distribution of the mid–left anterior descending coronary artery
B. The anterior wall defect on the SPECT images is likely an artifact due to breast tissue attenuation
C. Thallium-201 would have been a better choice of radiotracer to image this patient
D. Gated SPECT imaging cannot differentiate attenuation artifacts from a true perfusion defect
E. A transmural scar is associated with reduced wall motion but normal wall thickening on gated SPECT imaging

QUESTION 12

A 62-year-old man is noted to have an extra heart sound shortly after S_2. Which of the following is NOT a possible cause of that sound?
A. Opening snap
B. Third heart sound
C. Ejection click
D. Tumor plop
E. Pericardial knock

QUESTION 13

A 56-year-old asymptomatic man with a history of hypertension and cigarette smoking is referred for an exercise treadmill test. After 7 minutes on the standard Bruce protocol, he is noted to have 1 mm of flat ST-segment depression in leads II, III, and aVF. He stops exercising at 9 minutes because of leg fatigue and breathlessness. The peak heart rate is 85% of the maximum predicted for his age. The ST segments return to baseline by 1 minute into recovery. Which of the following statements is correct?

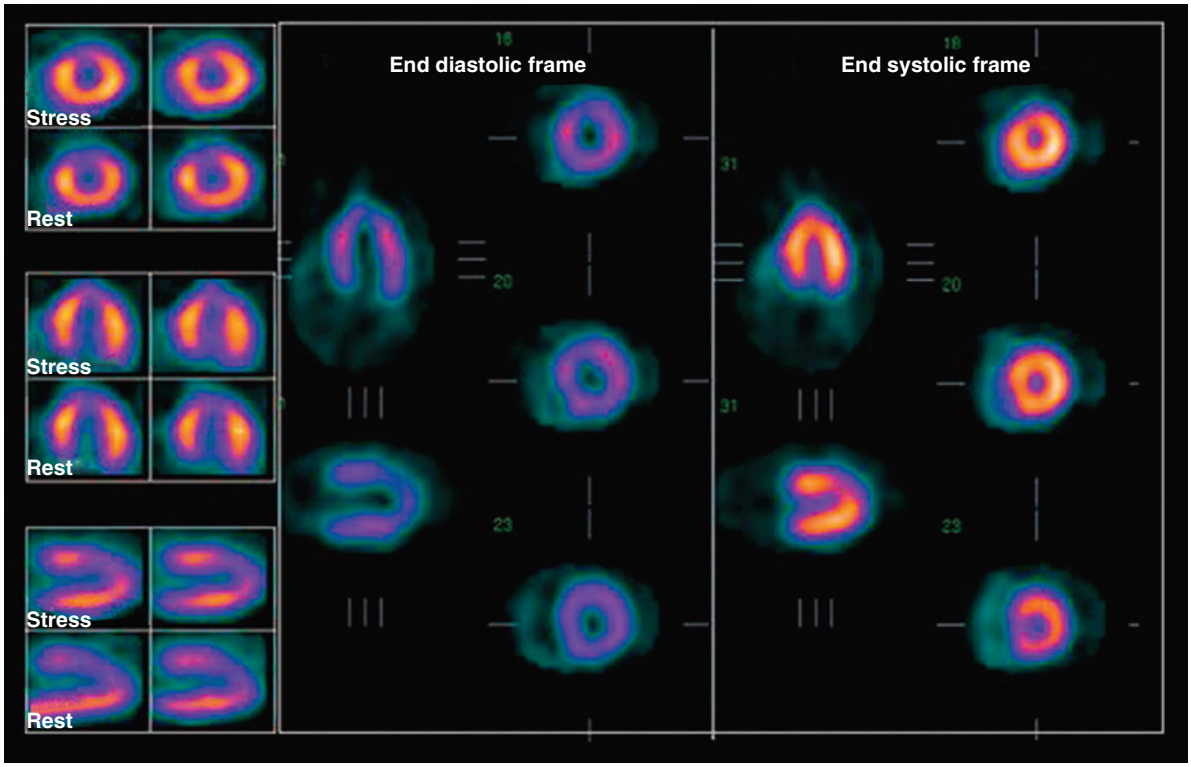


FIG. 1.1

A. This test is conclusive for severe stenosis of the proximal right coronary artery
B. His risk of death due to an acute myocardial infarction during the next year is >50%
C. He should proceed directly to coronary angiography
D. The test predicts a 25% risk of cardiac events over the next 5 years, most likely the development of angina
E. This is likely a false-positive test

QUESTION 14

In which of the following clinical scenarios do ST-segment depressions during standard exercise testing increase the diagnostic probability of significant coronary artery disease?
A. A 56-year-old man with left bundle branch block and a family history of premature coronary disease
B. A 45-year-old woman with diabetes and hypertension, with left ventricular hypertrophy on her baseline ECG
C. A 76-year-old woman with new exertional dyspnea, a history of cigarette smoking, and a normal baseline ECG
D. A 28-year-old woman with pleuritic left-sided chest pain after a gymnastics class
E. A 63-year-old man with exertional dyspnea on beta blocker, digoxin, and nitrate therapies

QUESTION 15

Which of the following statements regarding cardiac catheterization is TRUE?
A. The risk of a major complication from cardiac catheterization is 2.0% to 2.5%
B. The incidence of contrast-induced nephrotoxicity in patients with renal dysfunction is decreased with intravenous administration of mannitol before and after the procedure
C. High osmolar nonionic contrast agents demonstrate a reduced incidence of adverse hemodynamic reactions compared with low osmolar ionic contrast agents
D. One French unit (F), a measurement of catheter diameter, is equivalent to 0.33 mm
E. Retrograde left-sided heart catheterization is generally a safe procedure in patients with tilting-disc prosthetic aortic valves

QUESTION 16

A 75-year-old woman was brought urgently to the cardiac catheterization laboratory in the setting of an acute ST-elevation myocardial infarction. She had presented with chest pain, epigastric discomfort, and nausea. Physical examination was pertinent for diaphoresis, heart rate 52 beats/min, blood pressure 85/50 mm Hg, jugular venous distention, and slight bilateral pulmonary rales. Coronary angiography demonstrated ostial occlusion of a dominant right coronary artery, without significant left-sided coronary artery disease. Which of the following statements is correct?
A. Isolated infarction of the right ventricle, without left ventricular involvement, is likely
B. ST-segment elevation in leads V_1 and V_2 would be expected to accompany inferior ST elevation
C. The abnormal heart rate and blood pressure are likely a consequence of vagal stimulation
D. ST-segment depression is expected in lead V_4R

QUESTION 17

Using Doppler echocardiography, the following values are obtained in a patient with a restrictive ventricular septal defect (VSD) and mitral regurgitation: systolic transmitral

flow velocity = 5.8 m/s and systolic flow velocity at the site of the VSD = 5.1 m/s. The patient's blood pressure is 144/78 mm Hg. The estimated right ventricular systolic pressure is (choose the single best answer)

A. 20 mm Hg
B. 30 mm Hg
C. 40 mm Hg
D. 50 mm Hg
E. Not able to be determined from the provided information

QUESTION 18

A 68-year-old woman with a history of diabetes and cigarette smoking and previously normal cardiac examination is admitted to the hospital with the new onset of shortness of breath with exertion and orthopnea. She describes having experienced a "muscle ache" in her anterior chest 10 days earlier that lasted several hours and has not recurred. Her blood pressure is 109/88 mm Hg, the heart rate is 102 beats/min, and she is afebrile. Her examination reveals an elevated jugular venous pressure (JVP), bibasilar crackles, and 1+ pitting edema of both ankles. On auscultation, there is a II/VI early systolic murmur between the left sternal border and apex. The ECG reveals sinus tachycardia with inferior Q waves that were not present on a tracing 6 months earlier. The chest x-ray is consistent with pulmonary edema. She is admitted to the hospital and a transthoracic echocardiogram is obtained that is technically limited due to her body habitus. It reveals a left ventricular ejection fraction of 60% with inferior wall hypokinesis. The mitral valve is not well visualized but appears thickened and there is an anteriorly directed jet of mitral regurgitation that is difficult to quantitate. A diuretic is administered.

Which of the following is the next most reasonable approach in her management?

A. Urgent coronary angiography with planned percutaneous coronary intervention
B. Nuclear stress testing to evaluate for ongoing ischemia
C. Transesophageal echocardiography and surgical consultation
D. Initiate long-term management with aspirin, angiotensin-converting enzyme (ACE) inhibitor, and beta blocker therapies
E. Urgent right heart catheterization to evaluate for a left-to-right shunt

QUESTION 19

Which of the following statements regarding altered electrolytes and electrocardiographic abnormalities is TRUE?

A. Hypokalemia causes peaked T waves
B. Hyperkalemia causes QRS narrowing and increased P wave amplitude
C. Hypomagnesemia is associated with monomorphic ventricular tachycardia
D. Hypocalcemia causes prolongation of the QT interval
E. Severe hypocalcemia has been associated with the presence of a J wave (Osborn wave)

QUESTION 20

A 46-year-old woman with progressive exertional dyspnea was recently found to have bilateral hilar adenopathy on chest x-ray and first-degree atrioventricular (AV) block on her ECG. A transbronchial biopsy demonstrated noncaseating granulomas consistent with sarcoidosis and she is referred to you for assessment of cardiac involvement. Which of the following statements is TRUE regarding the diagnostic evaluation of cardiac sarcoidosis?

A. Left ventricular regional wall motion abnormalities in sarcoidosis are typically present in coronary distributions
B. An elevated serum angiotensin-converting enzyme level has low sensitivity, but high specificity, for the diagnosis of sarcoidosis
C. Sarcoid-associated late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging is usually localized to the endocardial border
D. CMR is not useful in the assessment of clinically silent cardiac sarcoidosis
E. ^{18}F-fluorodeoxyglucose (FDG) uptake on cardiac positron emission tomography (PET) differentiates active cardiac sarcoidosis from inactive scar tissue

QUESTION 21

Which of the following statements about the ECG depicted in Fig. 1.2 is correct?

A. The basic rhythm is wandering atrial pacemaker
B. The fifth QRS complex on the tracing is likely a premature ventricular beat
C. The Ashman phenomenon is present and it occurs because the refractory period is directly related to the length of the preceding RR interval
D. The bundle of His is the likely anatomic location of conduction delay in the fifth beat because it has the longest refractory period of conduction tissue

QUESTION 22

The timing of an "innocent" murmur is usually

A. Early systolic
B. Presystolic
C. Midsystolic
D. Holosystolic
E. Early diastolic

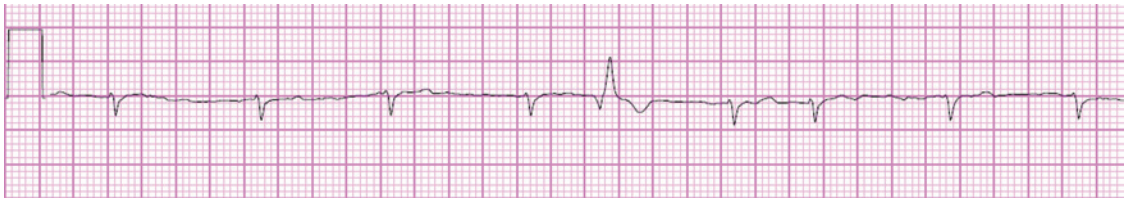


FIG. 1.2 *From Marriott HJL.* Rhythm Quizlets: Self Assessment. *Philadelphia: Lea & Febiger; 1987:14.*

QUESTION 23

Which of the following statements about the jugular venous wave form is correct?

A. The Kussmaul sign is pathognomonic for constrictive pericarditis
B. The *c* wave is a reflection of ventricular diastole and becomes visible in patients with diastolic dysfunction
C. The *x* descent is less prominent than the *y* descent in cardiac tamponade
D. Phasic declines in venous pressure (the *x* and *y* descents) are typically more prominent to the eye than the positive pressure waves (the *a*, *c*, and *v* waves)
E. Cannon *a* waves indicate intraventricular conduction delay

QUESTION 24

Which of the following statements regarding the measurement of cardiac output is correct?

A. In the thermodilution method, cardiac output is directly related to the area under the thermodilution curve
B. The thermodilution method tends to underestimate cardiac output in low-output states
C. In the presence of tricuspid regurgitation, the thermodilution method is preferred over the Fick technique for measuring cardiac output
D. A limitation of the Fick method is the necessity of measuring oxygen consumption in a steady state
E. Cardiac output is directly proportional to systemic vascular resistance

QUESTION 25

Which of the following conditions is associated with the Doppler transmitral inflow pattern shown in Fig. 1.3?

A. Gastrointestinal hemorrhage
B. Constrictive pericarditis
C. Normal aging
D. Restrictive cardiomyopathy
E. Hyperthyroidism

QUESTION 26

A 32-year-old woman, a native of India, is referred by her primary care physician for further evaluation of dyspnea on exertion. On examination, both an opening snap and mid-diastolic rumble are appreciated at the apex. An echocardiogram is obtained. Which of the following CANNOT be assessed from the transmitral Doppler tracing shown in Fig. 1.4?

A. The presence and severity of mitral stenosis
B. The presence of mitral regurgitation
C. The transmitral diastolic pressure gradient
D. The etiology of the valvular lesion
E. The mitral valve area

QUESTION 27

A 37-year-old woman with no significant past medical history presents to the emergency department with acute shortness of breath and pleuritic chest pain. Her only medication is an oral contraceptive. Her examination is notable for sinus tachycardia. A chest computed tomography (CT) shows subsegmental pulmonary emboli, and she is started on anticoagulation therapy. An echocardiogram is performed, which demonstrates the McConnell sign as well as mild tricuspid regurgitation with the following values:

Peak systolic velocity across the tricuspid valve = 3 m/s
Inferior vena cava (IVC) diameter = 1.9 cm with <50% collapse with inspiration

Which of the following statements is correct?

A. The McConnell sign refers to localized dyskinesis of the right ventricular apex in patients with acute pulmonary embolism
B. The Kussmaul sign may result from acute pulmonary embolism
C. This patient's estimated pulmonary artery systolic pressure is 64 mm Hg
D. This patient's right atrial pressure should be estimated as ~15 mm Hg

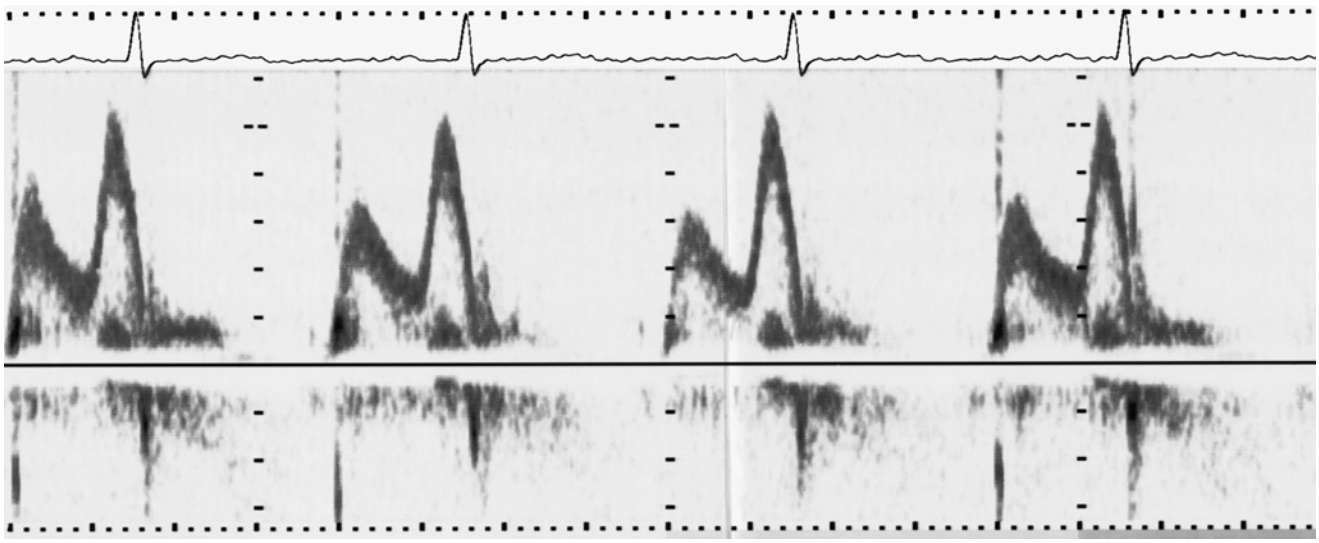


FIG. 1.3

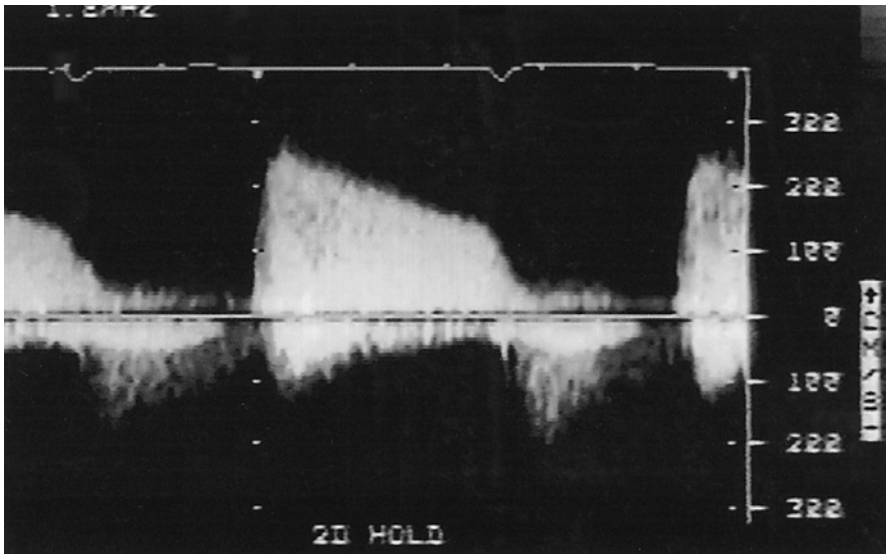


FIG. 1.4

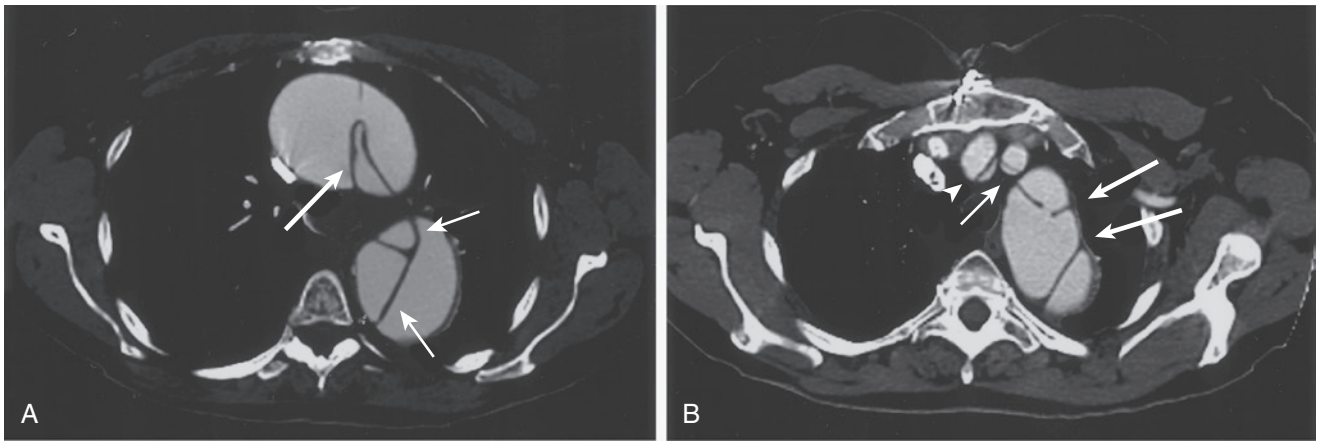


FIG. 1.5 *Courtesy of RC Gilkeson, MD, Case Western Reserve University, Cleveland, OH.*

QUESTION 28

Which of the following statements is TRUE regarding the response of healthy older adults to aerobic exercise?

A. Ventricular stroke volume decreases with age such that there is an age-related fall in cardiac output during exercise
B. Systolic and diastolic blood pressures each rise significantly during aerobic exercise
C. A decline in beta-adrenergic responsiveness contributes to a fall in the maximum heart rate in older individuals
D. A normal adult's cardiac output doubles during maximum aerobic exercise
E. Maximum aerobic capacity does not change significantly with age in sedentary individuals

QUESTION 29

Physiologic states and dynamic maneuvers alter the characteristics of heart murmurs. Which of the following statements is correct?

A. In acute mitral regurgitation, the left atrial pressure rises dramatically so that the murmur is heard only during late systole
B. Rising from a squatting to a standing position causes the murmur of mitral valve prolapse to begin later in systole
C. The diastolic rumble of mitral stenosis becomes more prominent during the strain phase of a Valsalva maneuver
D. The murmur of aortic stenosis, but not mitral regurgitation, becomes louder during the beat after a premature ventricular contraction
E. The murmur of acute aortic regurgitation can usually be heard throughout diastole

QUESTION 30

Which of the following statements regarding the computed tomograms of the chest shown in Fig. 1.5 is TRUE?

A. The patient's disorder should be managed medically, with surgical intervention considered only if there is evidence of secondary organ involvement
B. The left common carotid artery is spared by this process
C. The sensitivity of computed tomography for the diagnosis of this condition is >95%
D. Fewer than 50% of patients with this condition will report chest pain
E. Transesophageal echocardiography is necessary to confirm the diagnosis

QUESTION 31

Which of the following statements regarding ST-segment changes during exercise testing is TRUE?

A. The electrocardiographic localization of ST-segment depression predicts the anatomic territory of coronary obstructive disease
B. The J point is the proper isoelectric reference point on the ECG
C. J point depression during exercise is diagnostic for significant cardiac ischemia
D. Persistence of ST-segment depression for 60 to 80 milliseconds after the J point is necessary to interpret the electrocardiographic response as abnormal
E. ST-segment depression must be present both during exercise and in recovery to be interpreted as abnormal

QUESTION 32

An ECG is obtained as part of the routine preoperative evaluation of an asymptomatic 45-year-old man scheduled to undergo wrist surgery. The tracing is shown in Fig. 1.6 and is consistent with

A. Right ventricular hypertrophy
B. Left posterior fascicular block
C. Reversal of limb lead placement
D. Left anterior fascicular block and counterclockwise rotation
E. Dextrocardia with situs inversus

QUESTION 33

Which of the following statements is correct regarding exercise test protocols?

A. Regardless of the exercise protocol, the heart rate and systolic and diastolic blood pressures all must increase substantially to achieve a valid test
B. Bicycle, treadmill, and arm ergometry protocols all produce approximately equal heart rate and blood pressure responses
C. The standard Bruce protocol is characterized by only small increases in oxygen consumption between stages
D. A fall in systolic blood pressure during exercise is associated with severe coronary artery disease
E. An optimal graded treadmill exercise test rarely requires more than 5 minutes of exercise on the Bruce protocol

QUESTION 34

Which of the following patients is LEAST likely to have a cardiac cause of his/her recent onset of dyspnea?

A. An active 54-year-old man with a congenitally bicuspid aortic valve who has recently noticed shortness of breath walking his usual 18 holes of golf
B. A 70-year-old woman who sustained an anterior myocardial infarction 1 year ago with a left ventricular ejection fraction of 50% at that time. She has not had recurrent angina but has noted dyspnea during her usual housework over the past 2 months
C. A 46-year-old woman with a history of asymptomatic rheumatic mitral stenosis who recently noticed irregular palpitations and shortness of breath while climbing stairs
D. A 38-year-old woman with a previously asymptomatic ostium secundum atrial septal defect, now 8 months pregnant, who has noted shortness of breath during her usual weekly low-impact aerobics class
E. A 22-year-old man with trisomy 21 and a heart murmur who has described shortness of breath carrying grocery bundles over the past 3 months

QUESTION 35

A 68-year-old man with a history of diabetes, hypertension, and hyperlipidemia is transported to the hospital via ambulance, complaining of crushing substernal chest pain. Emergency medical services personnel report that ST segments are >2 mm elevated in multiple anterior leads. Which of the following electrocardiographic findings is LEAST likely in this patient?

A. Hyperacute T waves in the precordial leads
B. ST-segment depression in leads III and aVF
C. Shortened QT interval
D. New right bundle branch block

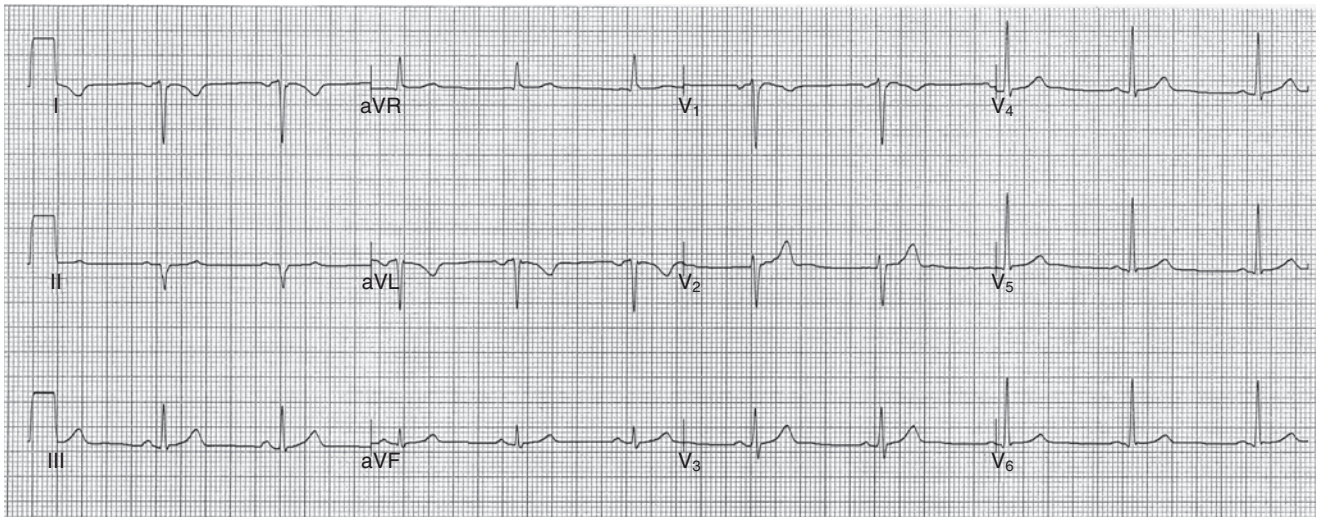


FIG. 1.6

QUESTION 36

Which of the following statements regarding nuclear imaging and acute myocardial infarction (MI) is TRUE?

A. The size of the resting myocardial perfusion defect after acute MI does not correlate with the patient's prognosis
B. Increased lung uptake of radioisotope at rest correlates with a favorable prognosis
C. Submaximal exercise imaging soon after MI is a better predictor of late complications than adenosine myocardial perfusion imaging
D. Technetium-99m sestamibi imaging is inaccurate in assessing the effectiveness of reperfusion therapy
E. Measuring infarct size by technetium-99m sestamibi imaging before discharge from the hospital is a reliable way to predict subsequent ventricular remodeling

QUESTION 37

A 61-year-old man presents for a treadmill exercise test because of intermittent chest pain. He believes he had a "small heart attack" in the past. He has a history of prior tobacco use and his father died of a myocardial infarction at age 68. His baseline ECG shows normal sinus rhythm with Q waves in the inferior leads. At 6 minutes into the Bruce protocol he develops mild anterior chest heaviness and the ECG demonstrates ST elevation in leads I, aVL, V_5, and V_6. Which of the following statements regarding ST-segment elevation during exercise testing is correct?

A. ST-segment elevation during exercise testing is a common finding in patients with coronary artery disease
B. ST-segment elevation in a lead that contains a pathologic Q wave at baseline indicates severe myocardial ischemia
C. The electrocardiographic leads that manifest ST-segment elevation during exercise localize the anatomic regions of ischemia
D. ST-segment elevation that develops during exercise is usually a manifestation of benign early repolarization
E. ST-segment elevation during exercise is commonly associated with the development of complete heart block

QUESTION 38

Which of the following statements regarding coronary calcium assessment by electron beam tomography (EBT) is TRUE?

A. The amount of calcium on EBT strongly correlates with the severity of coronary disease detected by angiography
B. Patients who benefit most from screening with EBT are those at a high risk for coronary events based on traditional risk factors
C. The absence of coronary calcium completely excludes the presence of severe obstructive coronary artery stenosis
D. Interpretation of the calcium score is independent of the patient's age and gender
E. A coronary calcium score higher than the median confers an increased risk of myocardial infarction and death

QUESTION 39

Which of the following statements is TRUE regarding prognosis as determined by myocardial perfusion imaging?

A. Patients with normal perfusion in the presence of angiographically documented coronary artery disease have very low rates of cardiac events (<1% per year)
B. Thallium imaging results in less breast attenuation artifact compared with technetium-99m sestamibi
C. Transient ischemic dilatation of the left ventricle and lung uptake of the nuclear tracer are common findings in normal individuals
D. The combination of clinical and cardiac catheterization data is more predictive of subsequent cardiac events than the combination of clinical and myocardial perfusion data
E. The risk of future cardiac events is unrelated to the number or extent of myocardial perfusion defects

QUESTION 40

A previously healthy 28-year-old man presented to the hospital because of 1 month of progressive exertional dyspnea, weakness, and weight loss. One day before hospitalization he was unable to climb one flight of stairs because of shortness of breath. On examination, he appeared fatigued with mild respiratory distress. His blood pressure was 110/70 mm Hg without pulsus paradoxus. His heart rate was 110 beats/min and regular. The jugular veins were distended without the Kussmaul sign. Pulmonary auscultation revealed scant bibasilar rales. The heart sounds were distant. There was mild bilateral ankle edema. As part of the evaluation during hospitalization, he underwent cardiac magnetic resonance imaging. A short-axis view at the midventricular level is shown in Fig. 1.7. Which of the following is the most likely diagnosis?

A. Pericardial malignancy
B. Chronic organized pericardial hematoma
C. Constrictive pericarditis
D. Extracardiac tumor compression of the heart
E. Congenital partial absence of the pericardium with cardiac herniation

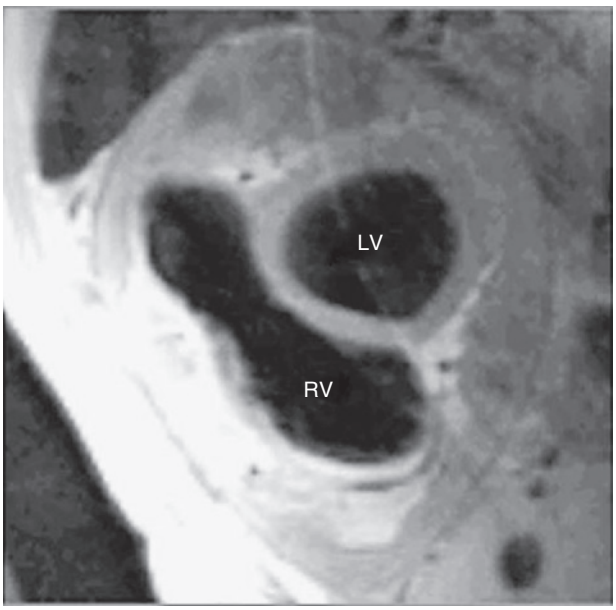


FIG. 1.7

QUESTION 41

Which of the following statements regarding intracardiac shunts is correct?

A. A left-to-right shunt should be suspected if the difference in oxygen saturation between the superior vena cava (SVC) and the pulmonary artery is 3% or more
B. Oxygen saturation in the SVC is normally higher than that in the inferior vena cava (IVC)
C. In a suspected atrial septal defect with left-to-right flow, mixed venous O_2 content should be measured at the level of the pulmonary artery
D. A pulmonic-to-systemic blood flow ratio (Q_p/Q_s) >1 indicates a net right-to-left shunt
E. Pulmonary artery oxygen saturation exceeding 80% should raise the suspicion of a left-to-right shunt

QUESTION 42

A 46-year-old man with dyspnea on exertion is noted to have a systolic ejection murmur along the left sternal border. An echocardiogram is obtained. Fig. 1.8 shows Doppler pulsed-wave interrogation of the left ventricular outflow tract, recorded from the apex. Which of the following recommendations would be most appropriate?

A. Strict fluid restriction
B. Avoid volume depletion
C. Aortic valve replacement
D. Bed rest

QUESTION 43

Which of the following statements regarding echocardiography in pericardial disease is correct?

A. Small pericardial effusions tend to accumulate anterior to the heart
B. Up to 100 mL of pericardial fluid is present in normal individuals
C. In cardiac tamponade, right ventricular diastolic collapse occurs less frequently if pulmonary hypertension is present
D. In the presence of a pericardial effusion, right atrial diastolic indentation is a more specific sign of cardiac tamponade than early diastolic collapse of the right ventricle
E. Transthoracic echocardiography is superior to chest computed tomography as a means to accurately measure pericardial thickness

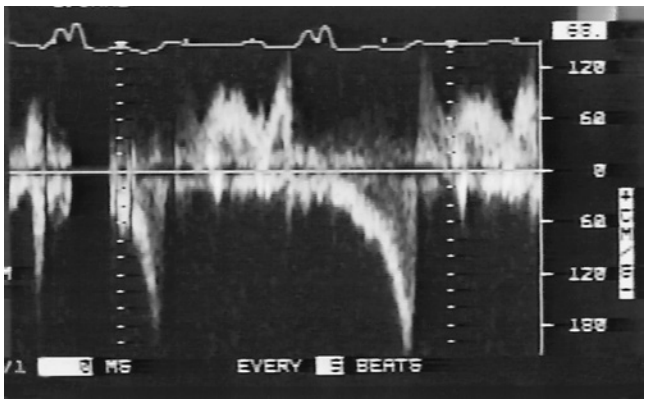


FIG. 1.8

QUESTION 44

Which of the following statements regarding nuclear imaging in cardiac disease is TRUE?

A. The use of single-photon emission computed tomography (SPECT) with electrocardiographic gating has no impact on the specificity of nuclear testing in women with attenuation artifacts
B. Exercise nuclear stress imaging, rather than pharmacologic stress testing, is the preferred diagnostic modality for patients with left bundle branch block
C. The presence of reversible defects on pharmacologic stress perfusion imaging before noncardiac surgery predicts an increased risk of perioperative cardiac events, but the magnitude of risk is not related to the extent of ischemia
D. Cardiovascular event rates are similar in diabetics compared with nondiabetics for any given myocardial perfusion abnormality
E. Viability of noncontracting myocardium can be accurately evaluated by thallium-201 imaging

QUESTION 45

A 45-year-old woman was referred for exercise echocardiography because of a history of intermittent chest pain. She has a strong family history of premature coronary artery disease but no other atherosclerotic risk factors. The exercise echocardiogram achieved the desired heart rate goal and demonstrated a focal wall motion abnormality of the left ventricular anterior wall at rest, which was unchanged at maximum exercise. A subsequent cardiac magnetic resonance study was performed to characterize the myocardial tissue in that region. A delayed image taken after intravenous administration of gadolinium is shown in Fig. 1.9. What is the most likely cause of the anterior wall motion abnormality?

A. Transient myocardial ischemia due to a significant coronary artery stenosis
B. Prior myocardial infarction
C. Myocarditis
D. Infiltrative cardiomyopathy
E. Breast attenuation artifact

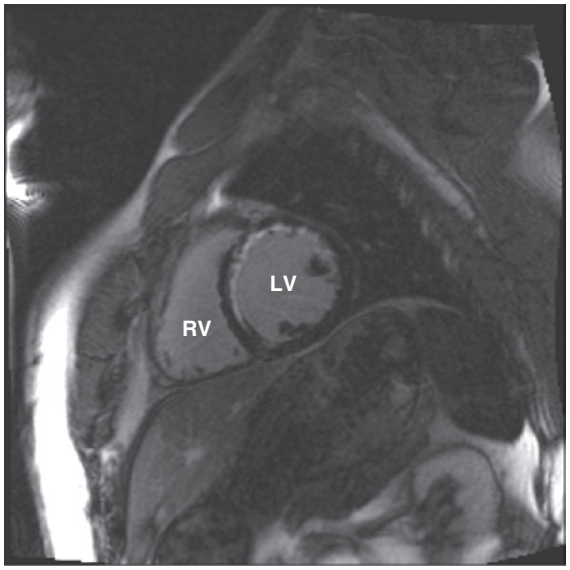


FIG. 1.9

QUESTION 46

Which of the following statements concerning the echocardiographic evaluation of aortic stenosis is TRUE?

A. The peak-to-peak gradient measured at cardiac catheterization routinely exceeds the peak instantaneous aortic valve pressure gradient assessed by Doppler echocardiography
B. Patients with impaired left ventricular function may have severe aortic stenosis, as determined by the continuity equation, despite a peak outflow velocity of only 2 to 3 m/s
C. Among Doppler techniques, the most accurate transaortic valve flow velocity in aortic stenosis is measured by pulsed-wave Doppler imaging
D. The greatest degree of error in the calculation of aortic valve area using the continuity equation resides in inaccurate measurement of the transaortic valve flow velocity
E. The mean aortic valve gradient measured by Doppler echocardiography is typically higher than the mean gradient measured by cardiac catheterization

QUESTION 47

Which of the following statements regarding the assessment for intracardiac shunts during cardiac catheterization is correct?

A. In normal subjects, there should be no difference in O_2 content in different portions of the right atrium
B. Atrial septal defect, anomalous pulmonary venous drainage, and ruptured sinus of Valsalva aneurysm all are associated with a significant step-up in O_2 saturation between the right atrium and the right ventricle
C. Because of the normal variability in O_2 saturation, shunts with pulmonary-to-systemic flow ratios (Q_p/Q_s) ≤1.3 at the level of the pulmonary artery or right ventricle may escape detection by oximetry run analyses
D. When a shunt is bidirectional, its magnitude can be calculated as the difference between the pulmonary and systemic blood flows ($Q_p - Q_s$) as determined using the Fick equation
E. In patients with a pure right-to-left shunt, the Q_p/Q_s ratio should be >1.0

QUESTION 48

Which of the following findings during an exercise test is NOT associated with multivessel (or left main) coronary artery disease?

A. Early onset of ST-segment depression
B. Persistence of ST-segment changes late into the recovery phase
C. ST-segment elevation in lead aVR
D. Sustained ventricular tachycardia
E. Failure to increase systolic blood pressure by at least 10 mm Hg

QUESTION 49

Which of the following statements regarding the auscultatory findings in aortic stenosis is TRUE?

A. Initial squatting decreases the intensity of the murmur
B. The murmur is increased in intensity during the strain phase of the Valsalva maneuver
C. In patients with premature ventricular contractions, aortic stenosis can be differentiated from mitral regurgitation because there is beat-to-beat variation in the intensity of the aortic stenosis murmur while the intensity of the mitral regurgitation remains constant
D. Respiration typically has a prominent effect on the intensity of the murmur

QUESTION 50

A 59-year-old business executive presents because of episodes of retrosternal chest discomfort that does not radiate. It is an aching, burning sensation, occurring most frequently at night, occasionally awakening the patient shortly after he has fallen asleep. It does not occur while walking or climbing stairs. His internist prescribed nitroglycerin, which he has taken infrequently. However, it does relieve his pain, usually within 10 to 20 minutes. The previous day during a luncheon meeting he had a severe episode while presenting a new financial plan; the discomfort seemed to lessen when he sat down and finished lunch. The most likely explanation for his chest discomfort is

A. Prinzmetal angina
B. Esophageal reflux and spasm
C. Pericarditis
D. Unstable angina pectoris
E. Biliary colic

QUESTION 51

A 44-year-old man with diabetes and a strong family history of premature coronary artery disease underwent cardiac evaluation because of episodes of exertional substernal chest pressure. His resting ECG demonstrated normal sinus rhythm and borderline left ventricular hypertrophy. During exercise myocardial perfusion imaging, he developed his typical chest discomfort and stopped at 03:20 minutes of the standard Bruce protocol, at a peak heart rate of 105 beats/min (60% of his age-predicted maximal heart rate). The systolic blood pressure decreased by 20 mm Hg at peak exercise. Based on the myocardial perfusion images in Fig. 1.10, which of the following statements is TRUE?

A. There is no evidence of reversible ischemia
B. Transient dilatation of the left ventricle after exercise stress is absent
C. The increased lung uptake of the radiotracer evident on stress imaging is a normal physiologic response
D. There is increased right ventricular tracer uptake on the post-stress images, which is a specific marker of multivessel or left main coronary disease
E. The test results are inconclusive owing to failure to achieve the target heart rate

QUESTION 52

Which of the following statements about the transaortic valve Doppler flow tracing shown in Fig. 1.11 is TRUE?

A. The probability of critical aortic stenosis in this patient is low
B. The estimated peak transaortic valvular gradient is 90 to 100 mm Hg
C. Aortic insufficiency is severe
D. Based on the Doppler findings, premature closure of the mitral valve is likely
E. The echocardiogram likely reveals normal left ventricular wall thickness

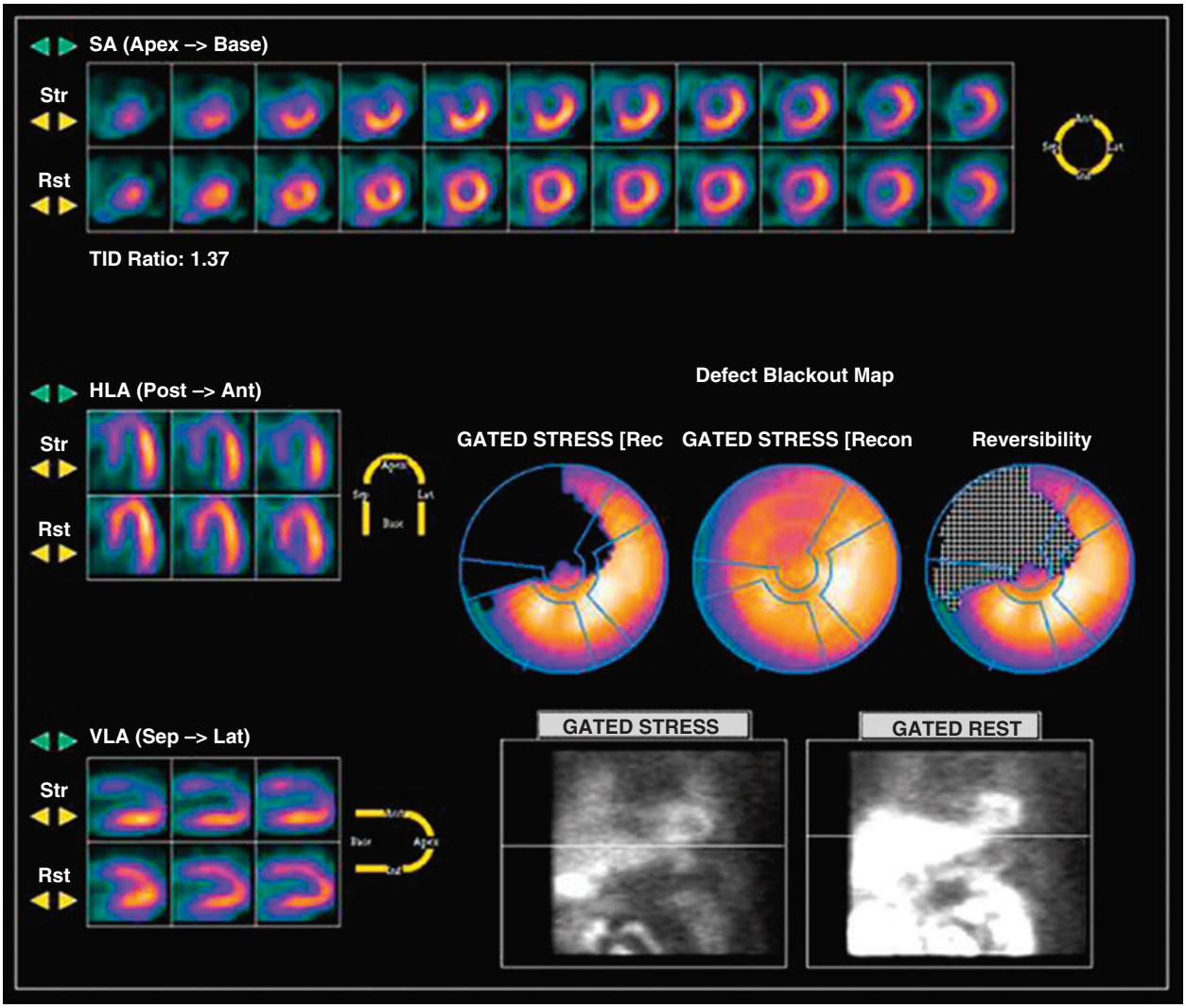


FIG. 1.10

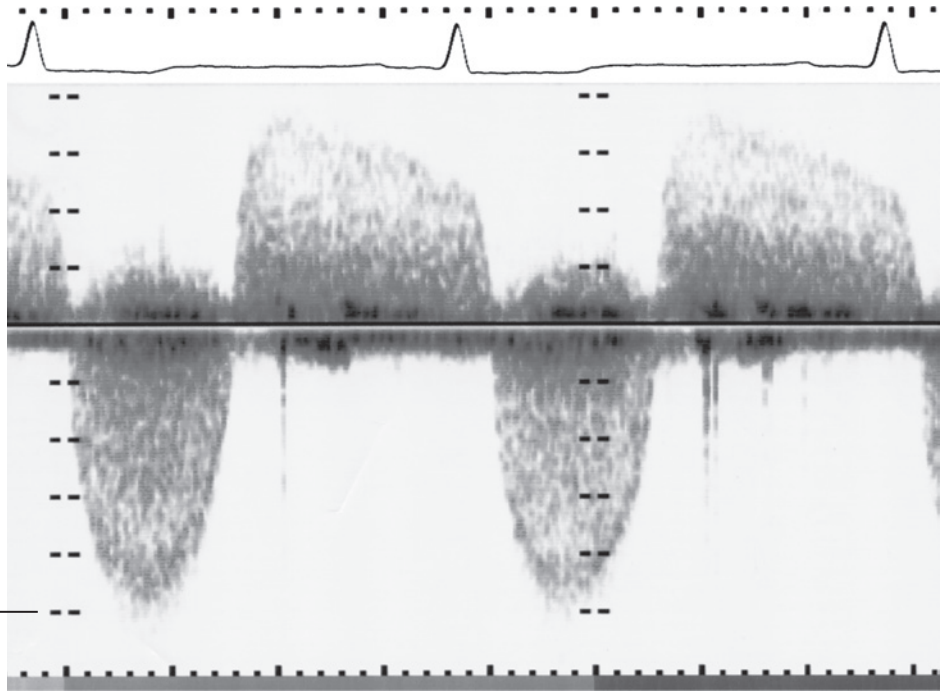


FIG. 1.11

QUESTION 53

Which of the following statements regarding abnormalities of the extremities in cardiac conditions is FALSE?
A. Arachnodactyly is associated with Marfan syndrome
B. A thumb with an extra phalanx commonly occurs in Turner syndrome
C. Quincke sign is typical of chronic aortic regurgitation
D. Osler nodes are tender, erythematous lesions of the fingers and toes in patients with infective endocarditis
E. Differential cyanosis is typical of patent ductus arteriosus with a reversed shunt

QUESTION 54

Which of the following is NOT commonly associated with the disorder illustrated in Fig. 1.12?
A. Tricuspid regurgitation
B. Patent foramen ovale
C. Wolff-Parkinson-White syndrome
D. Systemic hypertension
E. Atrial fibrillation

QUESTION 55

Which of the following statements is TRUE regarding the echocardiographic evaluation of suspected infective endocarditis?
A. Vegetations of the mitral valve typically appear on the ventricular aspect of the leaflets
B. The sensitivity of transthoracic echocardiography (TTE) for detection of vegetations is <70%
C. After successful antibiotic therapy, previously detected vegetations should not be visible by echocardiography
D. Functional and structural consequences of valvular infection are rarely observed by transthoracic echocardiographic evaluation, such that a transesophageal study (TEE) is always mandatory
E. TTE and TEE have similar sensitivities for detection of myocardial abscess formation

QUESTION 56

Which of the following statements is TRUE regarding examination of the arterial pulse?
A. A reduced-volume brachial pulse with a late systolic peak is the most characteristic arterial finding on physical examination in patients with severe aortic stenosis
B. A bisferious pulse is characterized by a systolic and then a diastolic peak and is typical of mixed mitral valve disease
C. The carotid artery is the blood vessel used to best appreciate the contour, volume, and consistency of the peripheral vessels
D. In coarctation of the aorta, the femoral pulse demonstrates a later peak than the brachial pulse.
E. The normal abdominal aorta is palpable both above and below the umbilicus

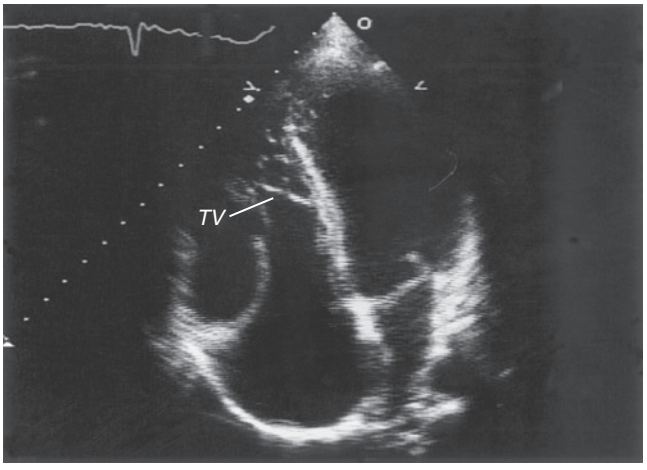


FIG. 1.12

QUESTION 57

Which of the following statements regarding cardiac catheterization is TRUE?
A. When catheterization is performed from the groin, the risk of retroperitoneal hemorrhage is decreased when the femoral artery puncture is made above the inguinal ligament
B. An international normalized ratio (INR) <2.2 is acceptable for radial artery catheterization
C. Patients with shellfish allergy are at greater risk of intravenous contrast reactions than patients with other food allergies
D. Pseudoaneurysm formation is more likely to occur if the femoral artery puncture is made above the bifurcation of the common femoral artery

QUESTION 58

Which of the following statements regarding the use of cardiopulmonary exercise testing in patients with congestive heart failure is TRUE?
A. A peak oxygen consumption <14 mL/kg/min identifies patients who would benefit from cardiac transplantation
B. Patients with ejection fractions <20% consistently have peak oxygen consumptions <10 mL/kg/min, and exercise testing is of little utility in this population
C. The exercise limitation in severe heart failure is due primarily to an inability to raise the heart rate
D. Exercise training in congestive heart failure patients improves functional capacity but has no effect on abnormalities of autonomic and ventilatory responsiveness or increased lactate production
E. Results of exercise testing are rarely useful when making clinical decisions about heart failure patients, such as timing of cardiac transplantation

QUESTION 59

In which of the following clinical scenarios is magnetic resonance imaging NOT a superior imaging modality for assessment?
A. Diagnosis of iron overload cardiomyopathy in a pediatric patient with beta-thalassemia major and congestive heart failure
B. Diagnosis of arrhythmogenic right ventricular cardiomyopathy in a 24-year-old man who recently survived a cardiac arrest
C. Diagnosis of aortic coarctation in a 17-year-old girl with hypertension and radial-femoral artery delay on physical examination

D. Serial evaluation of left ventricular function in a 54-year-old woman with metastatic breast cancer receiving doxorubicin chemotherapy
E. Diagnosis of renal artery stenosis in a 78-year-old man with refractory hypertension

QUESTION 60

Fig. 1.13 shows the post-test probability of coronary artery disease (CAD) as a function of the pretest probability of CAD and results of exercise electrocardiography—either a positive [(+) ST, red bars] or negative [(–) ST, blue bars] response. Four different patient examples are plotted. Which of the following statements is correct?

A. Stress testing should be pursued in the 45-year-old man with atypical chest pain because, if positive, the test will have the best positive predictive value of the cases shown
B. Stress testing should be pursued in the 55-year-old man with typical chest pain because, if negative, the test will have the best negative predictive value of the cases shown
C. The positive and negative predictive values cannot be determined for these patients from the given information
D. A 45-year-old asymptomatic man with a positive stress test is less likely to have CAD than is a man of the same age with atypical chest pain and a negative stress test
E. The pretest probability of coronary artery disease in a 45-year-old man depends solely on the presence of symptoms

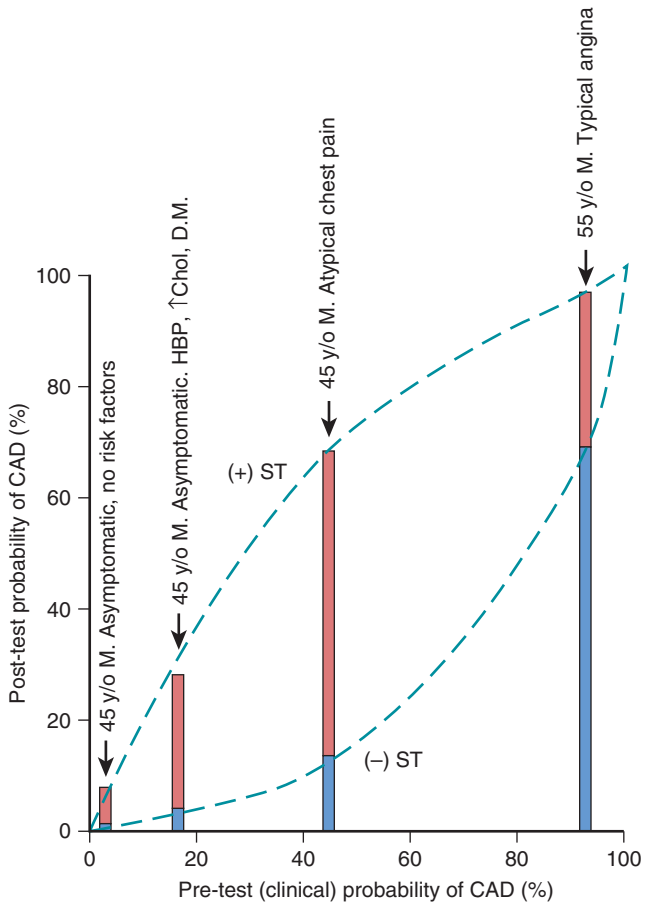


FIG. 1.13

QUESTION 61

Which of the following statements concerning imaging findings in hypertrophic cardiomyopathy (HCM) is TRUE?

A. The presence of systolic anterior motion of the mitral valve is consistent with dynamic outflow tract obstruction
B. Diastolic notching of the aortic valve on M-mode examination is typical in patients with outflow tract obstruction
C. Septal thickness is always abnormal in patients with HCM
D. Myocardial relaxation velocities measured by tissue Doppler imaging are typically normal

QUESTION 62

Each of the following statements regarding cardiac hemodynamics is true EXCEPT:

A. The *x* descent of the right atrial pressure wave form represents relaxation of the atrium and downward tugging of the tricuspid annulus by right ventricular contraction
B. In the left atrium, in contrast to the right atrium, the *v* wave is more prominent than the *a* wave
C. The *y* descent is blunted in cardiac tamponade
D. Tricuspid stenosis results in prominence of the *y* descent

QUESTION 63

Which of the following statements regarding the effects of maneuvers on the auscultation of cardiac murmurs is TRUE?

A. In patent ductus arteriosus, the diastolic phase of the murmur is softened by isometric handgrip
B. The murmur of hypertrophic obstructive cardiomyopathy becomes softer with standing or during a Valsalva strain maneuver
C. The murmur of a ventricular septal defect decreases with isometric handgrip
D. Isometric handgrip decreases the diastolic murmur of aortic regurgitation
E. The diastolic murmur of mitral stenosis becomes louder with exercise

QUESTION 64

A 62-year-old previously healthy man is brought to the emergency department because of severe headache and dizziness. He has no chest pain or dyspnea. He takes no medications. His blood pressure is 186/98 mm Hg; his heart rate is 56 beats/min and regular. The presenting ECG is shown in Fig. 1.14. Which of the following actions is appropriate?

A. Initiate antiplatelet therapy with aspirin and clopidogrel
B. Initiate antithrombotic therapy with heparin
C. Initiate anti-ischemic therapy with intravenous nitroglycerin and a beta blocker
D. Obtain a head computed tomographic scan
E. Proceed directly to cardiac catheterization if ST-segment/T wave abnormalities fail to quickly normalize with anti-ischemic therapy

QUESTION 65

Which of the following statements about diastolic murmurs is FALSE?

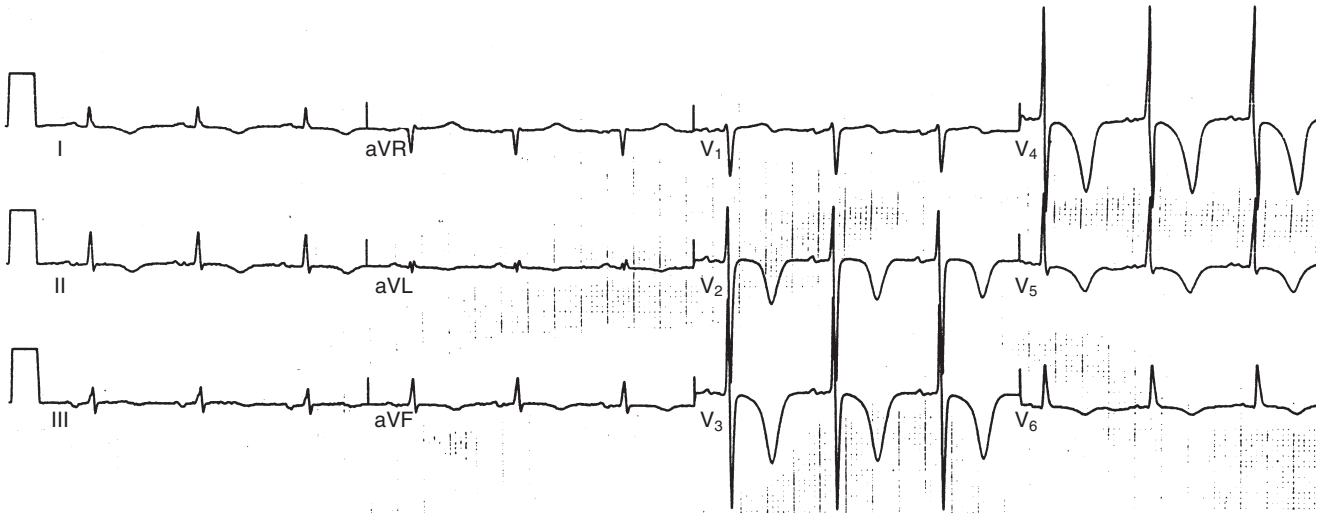


FIG. 1.14

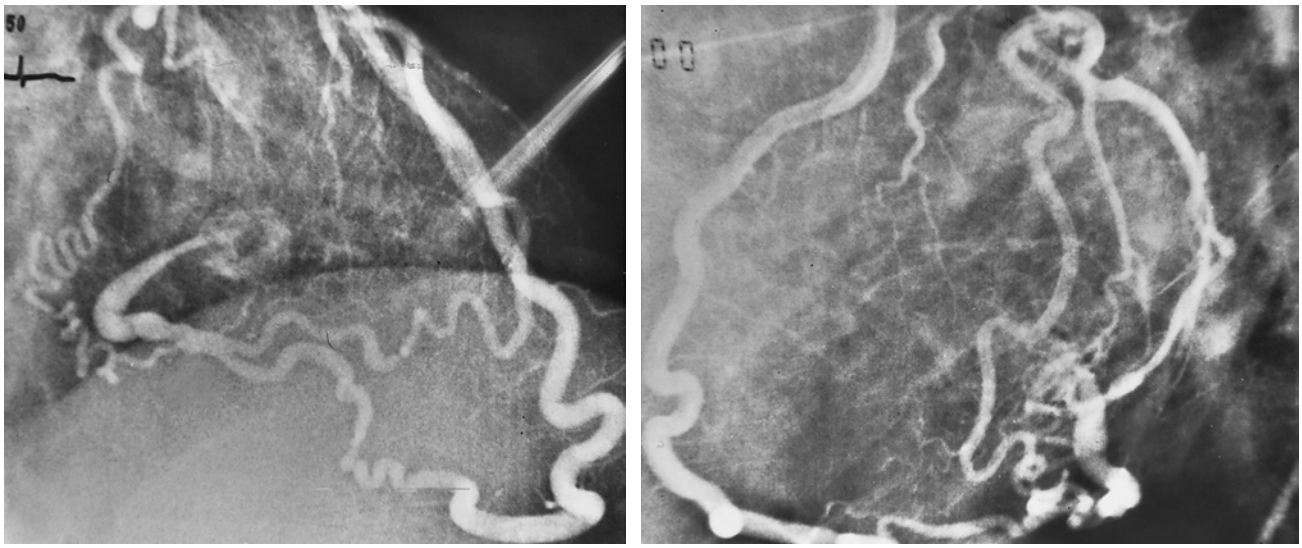


FIG. 1.15

A. Diastolic murmurs are classified according to their time of onset as early diastolic, mid-diastolic, or late diastolic
B. In aortic regurgitation due to aortic root dilatation, the murmur typically radiates to the right sternal border
C. It is possible to differentiate the murmur of acute severe aortic regurgitation from that of chronic aortic regurgitation at the bedside
D. Late diastolic (presystolic) accentuation of the murmur indicates that the patient is in atrial fibrillation.
E. The Graham Steell murmur begins in early diastole after a loud P_2

QUESTION 66

Which of the following statements regarding coronary artery anatomy is NOT correct?
A. At cardiac catheterization, the left main coronary artery is best visualized in the anteroposterior projection with slight caudal angulation
B. A ramus intermedius branch is present in more than 25% of people
C. The left circumflex artery is the dominant vessel in 45% of people
D. The most densely vascularized area of the heart is the interventricular septum
E. The abnormality shown in Fig. 1.15 is the most common type of coronary congenital abnormality that is hemodynamically significant

QUESTION 67

A 25-year-old asymptomatic man presents for routine physical examination with his new primary care physician. The physician notes that the patient is tall with unusually long limbs and pectus excavatum. There is no family history of Marfan syndrome. Which of the following is among the "major criteria" for the diagnosis of Marfan syndrome?
A. Mitral valve prolapse
B. Mild pectus excavatum
C. Joint hypermobility
D. Descending aortic aneurysm
E. Ectopia lentis

QUESTION 68

Which one of the following echocardiographic findings suggests that aortic regurgitation is severe?

A. Diastolic flow reversal in the descending thoracic aorta
B. Premature closure of the aortic valve
C. Pressure half-time of the aortic regurgitation Doppler spectrum of 500 milliseconds
D. A color Doppler regurgitant jet that extends to the tips of the papillary muscles
E. A left ventricular outflow tract systolic gradient of 64 mm Hg

QUESTION 69

Which of the following statements regarding pharmacologic agents used in myocardial perfusion stress testing is FALSE?

A. Patients who cannot perform exercise can be adequately evaluated for coronary artery disease (CAD) using vasodilating medications and nuclear scintigraphy
B. Dipyridamole blocks the cellular uptake of adenosine, an endogenous vasodilator
C. During perfusion stress testing, administration of adenosine or dipyridamole commonly provokes myocardial ischemia in patients with CAD
D. Radiopharmaceutical agents should be injected 1 to 2 minutes before the end of exercise
E. Dobutamine pharmacologic scintigraphy increases coronary blood flow less than adenosine

QUESTION 70

Which of the following statements regarding the auscultatory findings of mitral stenosis is correct?

A. The opening snap (OS) is a late diastolic sound
B. A long A_2-OS interval implies severe mitral stenosis
C. In atrial fibrillation, the A_2-OS interval does not vary with cycle length
D. The "snap" is generated by rapid reversal of the position of the posterior mitral leaflet
E. The presence of an opening snap implies a mobile body of the anterior mitral leaflet

QUESTION 71

Which of the following statements about digitalis-induced arrhythmias is FALSE?

A. Ventricular bigeminy with varying morphology and regular coupling is a sign of digitalis toxicity
B. Nonparoxysmal junctional tachycardia is a common digitalis-induced arrhythmia
C. Atrial tachycardia with block is diagnostic of digitalis toxicity
D. The development of atrioventricular dissociation in a patient taking digitalis is a likely indication of digitalis toxicity
E. Ventricular premature beats are common but are not highly specific for the presence of digitalis toxicity

QUESTION 72

An 82-year-old man presents after a recent non–ST-elevation myocardial infarction. Coronary angiography revealed severe three-vessel disease with 100% occlusion of the proximal left anterior descending (LAD) coronary artery, 100% mid–right coronary artery occlusion, and a 70% stenosis of the proximal left circumflex coronary artery. Echocardiography demonstrated akinesis of the entire anterior wall, septum, and mid- and apical anterolateral wall, with an estimated left ventricular ejection fraction of 20%. Myocardial viability was evaluated using cardiac positron emission tomography (PET) with rest rubidium-82 (^{82}Rb flow tracer) and ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG metabolism tracer) as shown in Fig. 1.16. The images show a large region of PET perfusion metabolism mismatch in the mid-LAD distribution. Which of the following statements about myocardial viability is FALSE?

A. This finding is consistent with the presence of hibernating (viable) myocardium
B. Radionuclide techniques are more sensitive than measurement of inotropic contractile reserve by dobutamine echocardiography for the detection of viable myocardium
C. Inotropic contractile reserve measured by dobutamine echocardiography is more specific than radionuclide techniques for predicting functional recovery after revascularization
D. Survival benefit associated with revascularization of hibernating myocardium has been demonstrated in randomized clinical trials
E. The transmural extent of myocardial scar can be assessed accurately using gadolinium-enhanced cardiac magnetic resonance imaging

QUESTION 73

Which of the following statements regarding physical findings that distinguish the murmur of aortic stenosis (AS) from the murmur of hypertrophic cardiomyopathy (HCM) is TRUE?

A. The strain phase of the Valsalva maneuver decreases the intensity of the murmurs of both AS and HCM
B. The carotid upstroke in HCM is more brisk than in AS
C. The murmurs of AS and HCM both radiate to the carotid arteries
D. If a systolic thrill is present, it is most often located in the second right intercostal space in HCM and at the apex in AS
E. Squatting increases the intensity of the murmur of HCM

QUESTION 74

Which of the following statements is correct regarding the oral anticoagulants dabigatran, rivaroxaban, and apixaban in the treatment of patients with atrial fibrillation?

A. These agents are as effective as warfarin for prevention of thromboemboli in patients with atrial fibrillation and mechanical heart valves
B. Each of these drugs can be used safely in patients with advanced renal disease
C. Intravenous idarucizumab rapidly reverses the anticoagulant effect of dabigatran
D. For patients whose INR levels on warfarin have varied due to noncompliance, rivaroxaban is an excellent alternative given its once-daily dosing

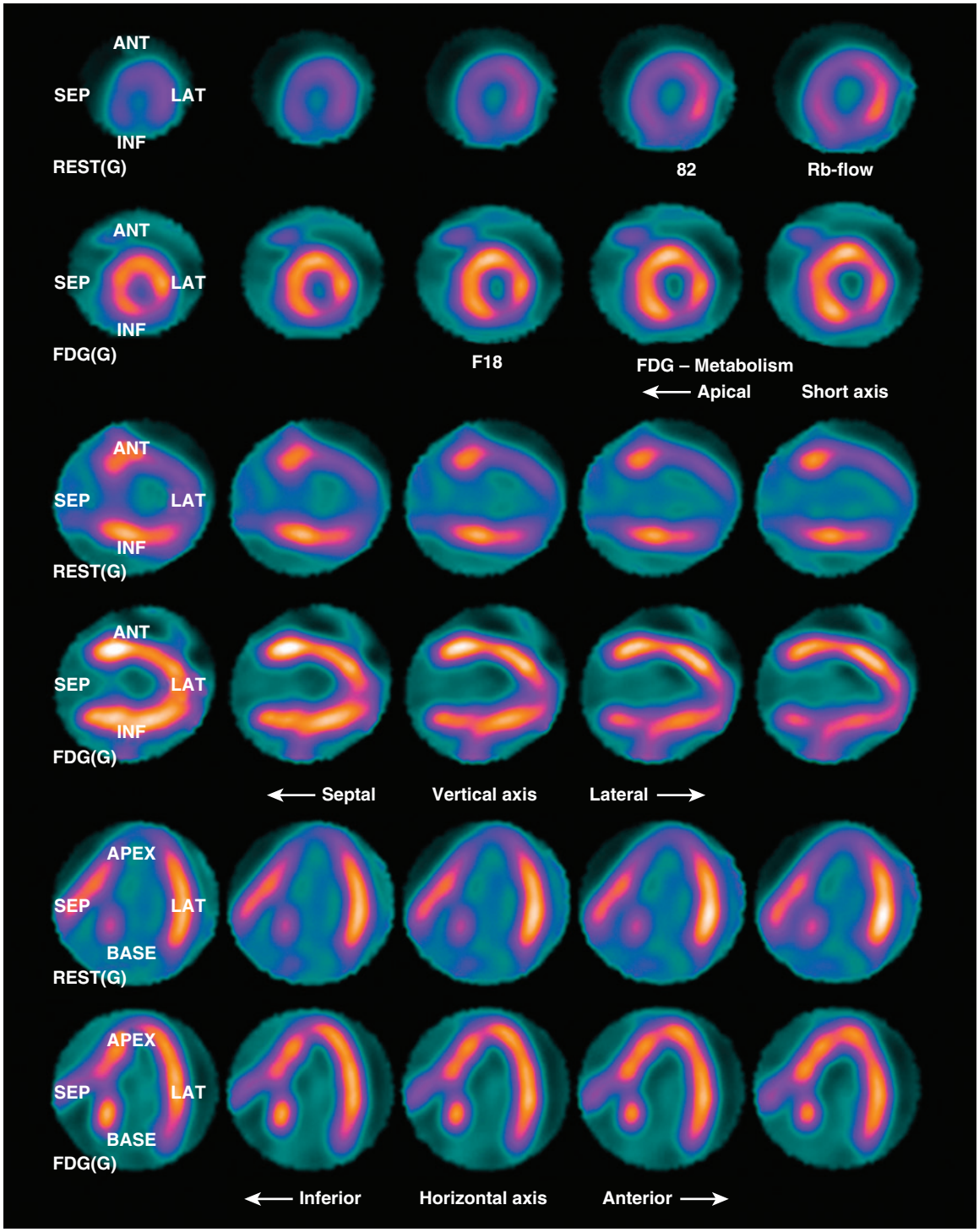

ANT
SEP
LAT
INF
REST(G)
82
Rb-flow
ANT
SEP
LAT
INF
FDG(G)
F18
FDG – Metabolism
Apical
Short axis
ANT
SEP
LAT
INF
REST(G)
ANT
SEP
LAT
INF
FDG(G)
Septal
Vertical axis
Lateral
APEX
SEP
LAT
BASE
REST(G)
APEX
SEP
LAT
BASE
FDG(G)
Inferior
Horizontal axis
Anterior

FIG. 1.16

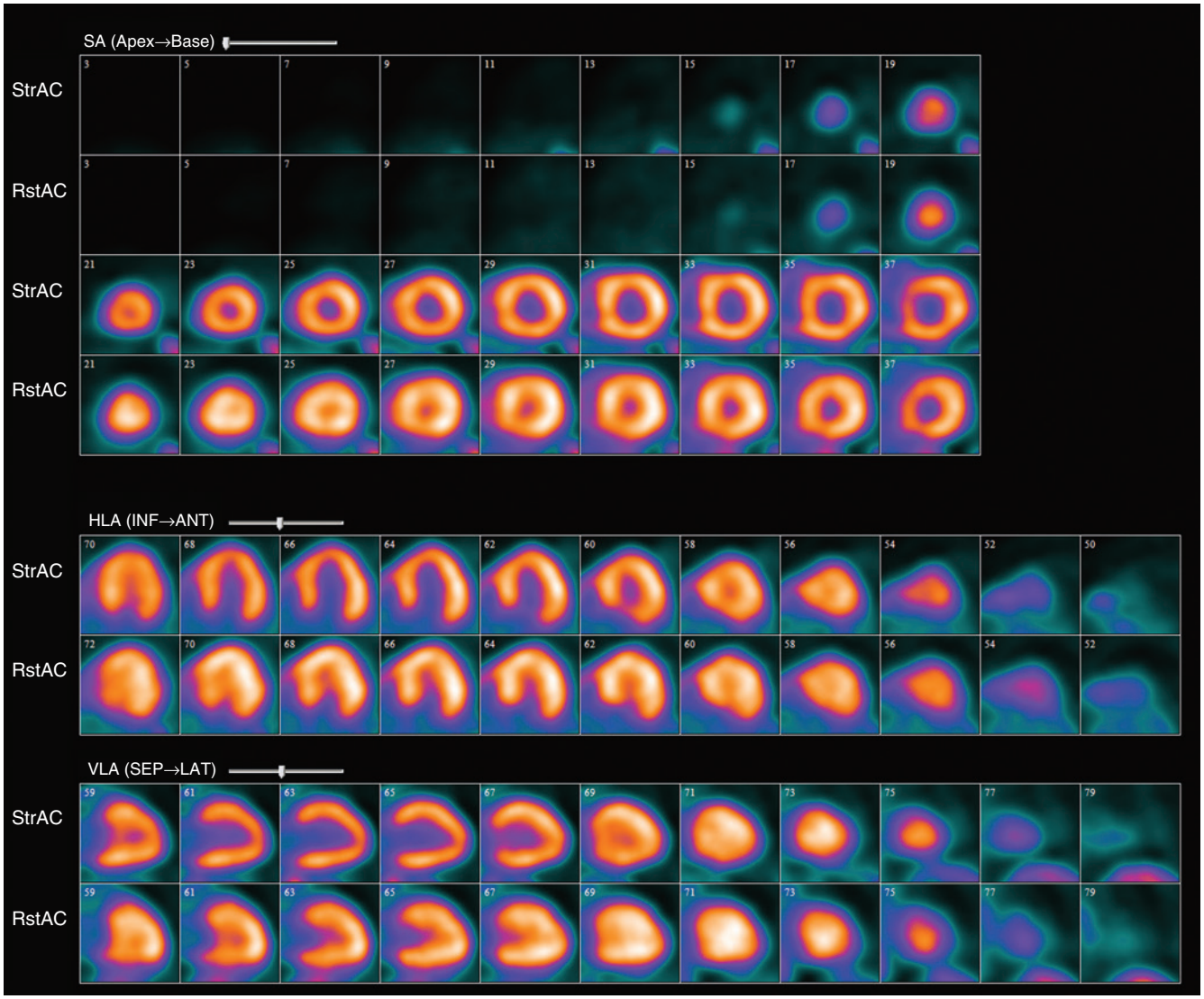


FIG. 1.17

QUESTION 75

A 73-year-old woman with exertional angina is referred for a standard Bruce protocol exercise tolerance test with thallium-201 single-photon emission computed tomography. Her nuclear images are shown in Fig. 1.17. What is the likely diagnosis?

A. Dilated cardiomyopathy
B. Single-vessel coronary artery disease involving the left circumflex artery
C. Prior inferior myocardial infarction with high-grade stenosis of the right coronary artery
D. Left main or severe multivessel coronary artery disease
E. Normal coronary arteries; the images demonstrate breast attenuation artifact

QUESTION 76

Which of the following statements regarding pulsus alternans in patients with marked LV dysfunction is true?

A. It is usually associated with electrical alternans of the QRS complex
B. It is less readily detected in the femoral as compared with radial arteries
C. It cannot be detected by noninvasive sphygmomanometry
D. It can be enhanced by the assumption of erect posture
E. It is uncommon for patients with pulsus alternans also to have an S_3 gallop

QUESTION 77

Which of the following statements regarding exercise testing is TRUE?

A. Frequent ventricular ectopy in the early postexercise phase predicts a worse long-term prognosis than ectopy that occurs only during exercise
B. Patients who develop QT interval prolongation during exercise testing are good candidates for class IA antiarrhythmic drugs

C. The appearance of sustained supraventricular tachycardia during exercise testing is diagnostic of underlying myocardial ischemia
D. Exercise-induced left bundle branch block is not predictive of subsequent cardiac morbidity and mortality
E. Tachyarrhythmias are commonly precipitated during exercise testing in patients with Wolff-Parkinson-White syndrome

QUESTION 78

Which of the following statements regarding extra systolic sounds is FALSE?
A. Ejection sounds are high-frequency "clicks" that occur early in systole
B. Ejection sounds due to a dilated aortic root have a similar timing as those associated with aortic valvular disease
C. The ejection sound associated with pulmonic stenosis decreases in intensity during inspiration
D. Aortic ejection sounds vary with respiration, occurring later in systole during inspiration
E. The bedside maneuver of standing from a squatting position causes the click of mitral valve prolapse to occur earlier in systole

QUESTION 79

Which of the following statements regarding the ECG in chronic obstructive lung disease with secondary right ventricular hypertrophy is correct?
A. The mean QRS axis is typically <15 degrees
B. The amplitude of the QRS complex is abnormally high in the precordial leads
C. Even mild right ventricular hypertrophy produces diagnostic electrocardiographic abnormalities
D. A deep S wave in V_6 is typical
E. Precordial lead transition is typically rotated in a counterclockwise fashion (early transition)

QUESTION 80

Which of the following statements regarding shunt detection is TRUE?
A. When an "anatomic" shunt is present, arterial oxygen saturation normalizes with administration of 100% oxygen
B. Methods of shunt detection include oximetry, echocardiography, and magnetic resonance imaging, but not radionuclide imaging
C. Among the sources of right atrial venous blood, the inferior vena cava (IVC) has the lowest oxygen saturation
D. Due to the low sensitivity of oximetry for shunt detection, most clinically relevant left-to-right shunts cannot be detected using this method
E. The Flamm formula is used to estimate mixed venous oxygen content proximal to a left-to-right shunt at the right atrial level

QUESTION 81

Which of the following conditions is NOT often associated with a prominent R wave in electrocardiographic lead V_1?
A. Right ventricular hypertrophy
B. Wolff-Parkinson-White syndrome
C. Duchenne muscular dystrophy
D. Left anterior fascicular block
E. Misplacement of the chest leads

QUESTION 82

The hemodynamic tracing illustrated in Fig. 1.18 is associated with which of the following features?
A. Advanced valvular aortic stenosis
B. A bifid aortic pulse contour
C. Normal left ventricular end-diastolic pressure
D. A delayed rise in the carotid artery pulsation
E. Expected clinical improvement with transcatheter aortic valve replacement

QUESTION 83

Which of the following statements regarding axis positions of the heart and findings on the ECG is FALSE?
A. A "horizontal" heart results in a tall R wave in lead aVL
B. "Clockwise rotation" refers to a delayed transition zone in the precordial leads
C. In patients with a "vertical" heart, the QRS complex is isoelectric in lead I
D. "Counterclockwise rotation" mimics left ventricular hypertrophy
E. When all six limb leads show isoelectric complexes, it is not possible to calculate the axis in the frontal plane

QUESTION 84

Which of the following statements concerning the cardiac catheterization evaluation of valve orifice areas is TRUE?
A. Valve area as calculated by the Gorlin formula is inversely proportional to the flow across the valve
B. Accompanying valvular regurgitation will result in a falsely high calculated valve area because actual flow across the valve is less than the flow calculated from the systemic cardiac output

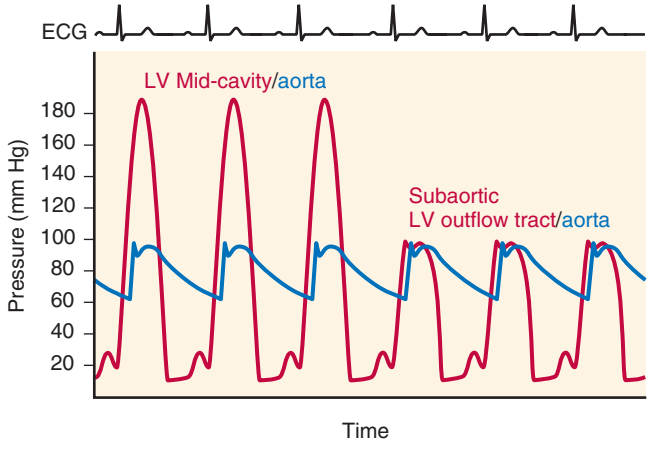


FIG. 1.18

C. Calculation of mitral valve area typically relies on substitution of a confirmed pulmonary capillary wedge pressure for left atrial pressure
D. Valve area calculation is more strongly influenced by errors in the pressure gradient measurement than by errors in cardiac output measurement

QUESTION 85

A 56-year-old man who underwent coronary artery bypass graft surgery 6 years ago has experienced exertional chest discomfort in recent months. He is not able to perform an exercise test because of chronic hip pain. He undergoes an adenosine positron emission tomography (PET) vasodilator stress test, images from which are shown in Fig. 1.19. What is the correct interpretation of this study?

A. No perfusion defects
B. A partially reversible defect of the entire inferior wall
C. A severe predominantly reversible defect of the anterior wall
D. A fixed defect of the anterior wall without reversibility
E. Fixed defects of the apex and lateral walls

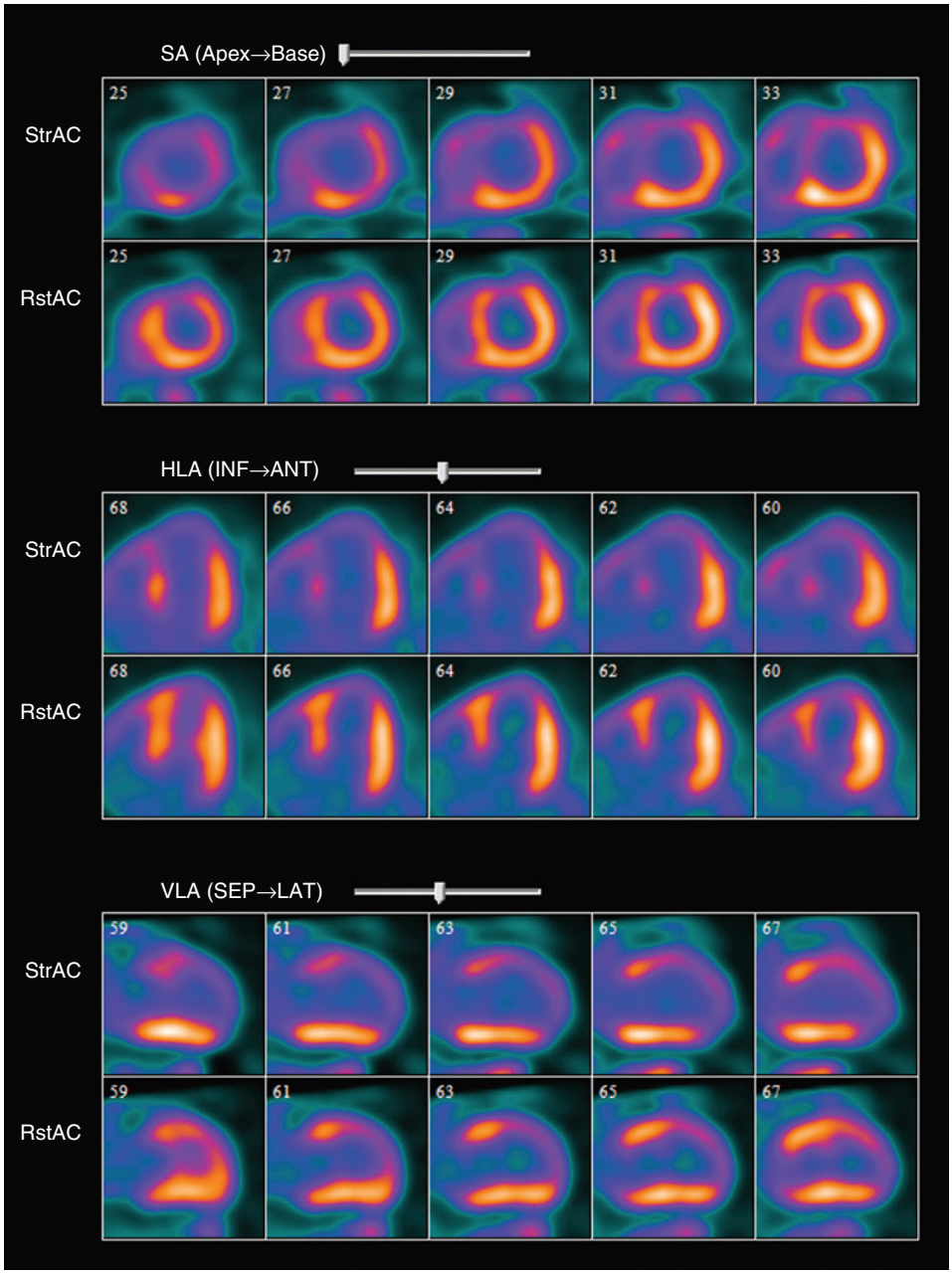


FIG. 1.19

QUESTION 86

A 40-year-old man presents to his physician with shortness of breath on exertion, peripheral edema, and arthritis of his hands. On examination, his vital signs are normal. His sclerae are icteric and his skin has a bronzed hue. Lung examination demonstrates rales at the bases; the carotids are of normal upstroke. The cardiac impulse is displaced laterally and there is an audible S_3. His abdomen is distended, with evidence of hepatosplenomegaly and ascites. There is peripheral pitting edema. Laboratory studies reveal a serum glucose level of 225 mg/dL and a transferrin saturation of 70%. Which of the following statements about this condition is TRUE?

A. It is inherited as an autosomal dominant condition
B. Cardiac involvement results in a mixed dilated and restrictive cardiomyopathy
C. Early cardiac death is common, due primarily to accelerated atherosclerosis
D. Ventricular hypertrophy with increased QRS voltages is the most common electrocardiographic finding
E. Echocardiography often shows a thickened ventricle with a "granular sparkling" appearance

QUESTION 87

A 56-year-old woman presents for routine evaluation. On examination, a systolic murmur is noted. Which of the following responses to maneuvers would be suggestive of mitral valve prolapse as the cause of the murmur?

A. With isometric handgrip, the murmur starts earlier in systole and becomes louder
B. With standing from a supine position, the murmur begins later in systole
C. Carotid sinus massage increases the intensity of the murmur
D. Valsalva maneuver causes the murmur to arise earlier in systole
E. Squatting from a standing position moves the onset of the murmur earlier in systole

QUESTION 88

Which of the following statements regarding the effect of the potassium concentration on the ECG is TRUE?

A. The earliest electrocardiographic sign of hyperkalemia is a reduction in P wave amplitude
B. Deep symmetric T wave inversions are characteristic of early hyperkalemia
C. Hyperkalemia predisposes to digitalis-induced tachyarrhythmias
D. Prominent U waves are a characteristic feature of hyperkalemia
E. QRS complex widening is common in severe hyperkalemia

QUESTION 89

Which of the following conditions does NOT result in significant electrocardiographic Q waves in the absence of infarction?

A. Left bundle branch block
B. Left ventricular dilatation with posterior rotation of the heart
C. Electrocardiographic lead misplacement
D. Acidosis
E. Wolff-Parkinson-White syndrome

QUESTION 90

Which of the following statements regarding the interpretation of exercise electrocardiography is TRUE?

A. The presence of right bundle branch block does not alter the sensitivity of exercise electrocardiography for the diagnosis of myocardial ischemia
B. ST-segment depressions in the inferior leads during exercise testing are specific for significant right coronary artery disease
C. The location of ST-segment elevations during exercise testing predicts the anatomic site of clinically advanced coronary stenosis
D. Digoxin therapy is not associated with false-positive findings on exercise electrocardiography if the baseline ST segments are normal

QUESTION 91

A patient underwent echocardiography as part of the evaluation of exertional dyspnea. Fig. 1.20 displays an image from the continuous-wave Doppler interrogation across the mitral valve, obtained from the apical long-axis view. Each of the statements below is true EXCEPT

A. The early diastolic peak velocity of 2.7 m/s is within the normal range
B. There is an abnormally delayed decline of the transmitral velocity signal during diastole
C. Significant mitral stenosis is present
D. Abnormal transmitral systolic blood flow is demonstrated
E. With color Doppler imaging, the extent of mitral regurgitation can be underestimated if the regurgitant jet is directed along the left atrial wall

QUESTION 92

Which of the following statements regarding commonly used quality improvement strategies is correct?

A. Iterative PDSA (Plan-Do-Study-Act) cycles are most successful when goals are subjective, allowing the quality improvement team to think creatively without being constrained by a discrete goal

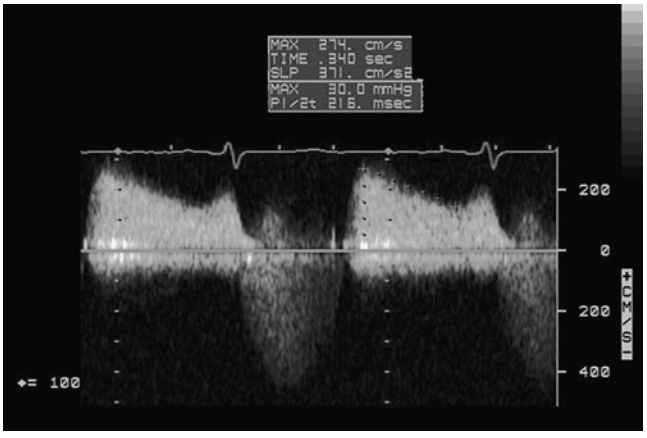


FIG. 1.20

B. The Lean approach focuses on high level concepts, avoiding getting bogged down in the details of a process
C. The Lean approach focuses on reducing unnecessary variation in a process
D. Six Sigma is an iterative process of Define, Measure, Analyze, Improve, and Control

QUESTION 93

A 25-year-old man died suddenly while jogging, and a postmortem examination was performed. A histologic section of left ventricular myocardium is shown in Fig. 1.21. Which of the following statements is TRUE?
A. The histologic findings are of normal myocardium subjected to chronic vigorous exercise
B. This condition is inherited as an autosomal dominant trait
C. This is a disease of plasma membrane protein synthesis
D. The greatest risk to affected patients is the development of complete heart block
E. One specific mutation has been identified that accurately predicts sudden cardiac death in the majority of patients with this disorder

QUESTION 94

A 28-year-old woman presents for evaluation after a syncopal episode. Her family history is notable for sudden death in an older sibling. Physical examination reveals woolly hair and palmar keratosis. Electrocardiography demonstrates T wave inversions in leads V_1–V_3. An ambulatory (Holter) electrocardiographic monitor captures runs of ventricular tachycardia with a left bundle morphology and superior axis. A signal-averaged ECG demonstrates late potentials. Echocardiography demonstrates a mildly dilated right ventricle with reduced systolic function; the left ventricle appears structurally normal. Which of the following statements is TRUE about this condition?
A. The majority of patients with this disorder have an abnormality of the ryanodine receptor
B. Endomyocardial biopsy establishes the diagnosis with high sensitivity
C. This patient likely has a mutation in the plakoglobin gene
D. This condition is transmitted in an autosomal dominant fashion
E. Noncaseating granulomas are likely present in the right ventricular myocardium

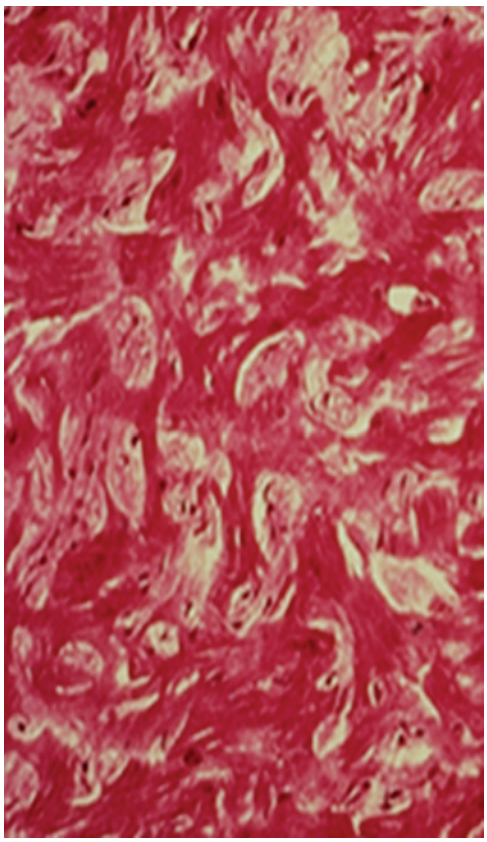


FIG. 1.21

QUESTION 95

A 72-year-old man with multiple myeloma presents with progressive exertional dyspnea, orthopnea, and peripheral edema. On examination the blood pressure is 118/62 mm Hg without pulsus paradoxus, but there is a 25 mm Hg systolic pressure postural decline. The jugular venous pressure is 12 cm, and there is periorbital purpura, macroglossia, hepatomegaly, and prominent symmetric pitting edema to the level of the mid-thighs. His electrocardiogram is remarkable for very low limb lead voltage. Which of the following echocardiographic findings is expected?
A. Increased right ventricular wall thickness with normal left ventricular thickness
B. Abnormal regional longitudinal strain on speckle tracking that spares the apex
C. Reversal of normal tissue Doppler mitral annular E′ velocity ratio (medial > lateral)
D. Very large pericardial effusion

Directions:

Each group of questions below consists of lettered headings followed by a set of numbered questions. For each question, select the ONE lettered heading with which it is most closely associated. Each lettered heading may be used once, more than once, or not at all.

QUESTIONS 96 TO 100

Match each of the following clinical scenarios to the most likely cause of syncope:
A. Ventricular tachycardia
B. High-degree atrioventricular block
C. Epilepsy
D. Neurocardiogenic syncope
E. Hysterical fainting

96. A 73-year-old man with a remote history of myocardial infarction feels the onset of palpitations while driving, then awakens having driven his car into a ditch, unaware of what has transpired
97. A 25-year-old woman on chronic antiseizure medication becomes warm, diaphoretic, and very pale after donating blood, then suffers frank syncope while seated upright in a chair. After being helped to the floor, she awakens embarrassed and alert

98. A 73-year-old woman with recent episodes of dizziness begins to feel lightheaded while seated at church, then within seconds turns pale and slumps to the floor with a few clonic jerks. She regains consciousness 1 minute later, completely aware of where she is and asks what has happened. When an ambulance arrives, her blood pressure is 108/70 mm Hg and the heart rate is 60 beats/min
99. A 32-year-old man with a history of prior syncope notices an odd odor, after which he falls to the ground. He awakens 3 minutes later, confused and disoriented, and is found to be incontinent of urine
100. An 18-year-old Army recruit falls to the ground while standing at attention for 20 minutes during his first week of basic training. He immediately awakens, feels a bit groggy, but quickly is able to rejoin his squad

QUESTIONS 101 TO 104

For each clinical scenario, select the most likely ECG from the four tracings shown in Fig. 1.22:

101. A 19-year-old male college student with exertional lightheadedness and a harsh systolic murmur that intensifies after standing from a squatting position
102. A 56-year-old woman with sudden onset of pleuritic chest discomfort and dyspnea
103. A 36-year-old man with sharp inspiratory precordial chest discomfort that radiates to the left shoulder
104. A 71-year-old alcoholic man with epigastric discomfort after 18 hours of intermittent vomiting

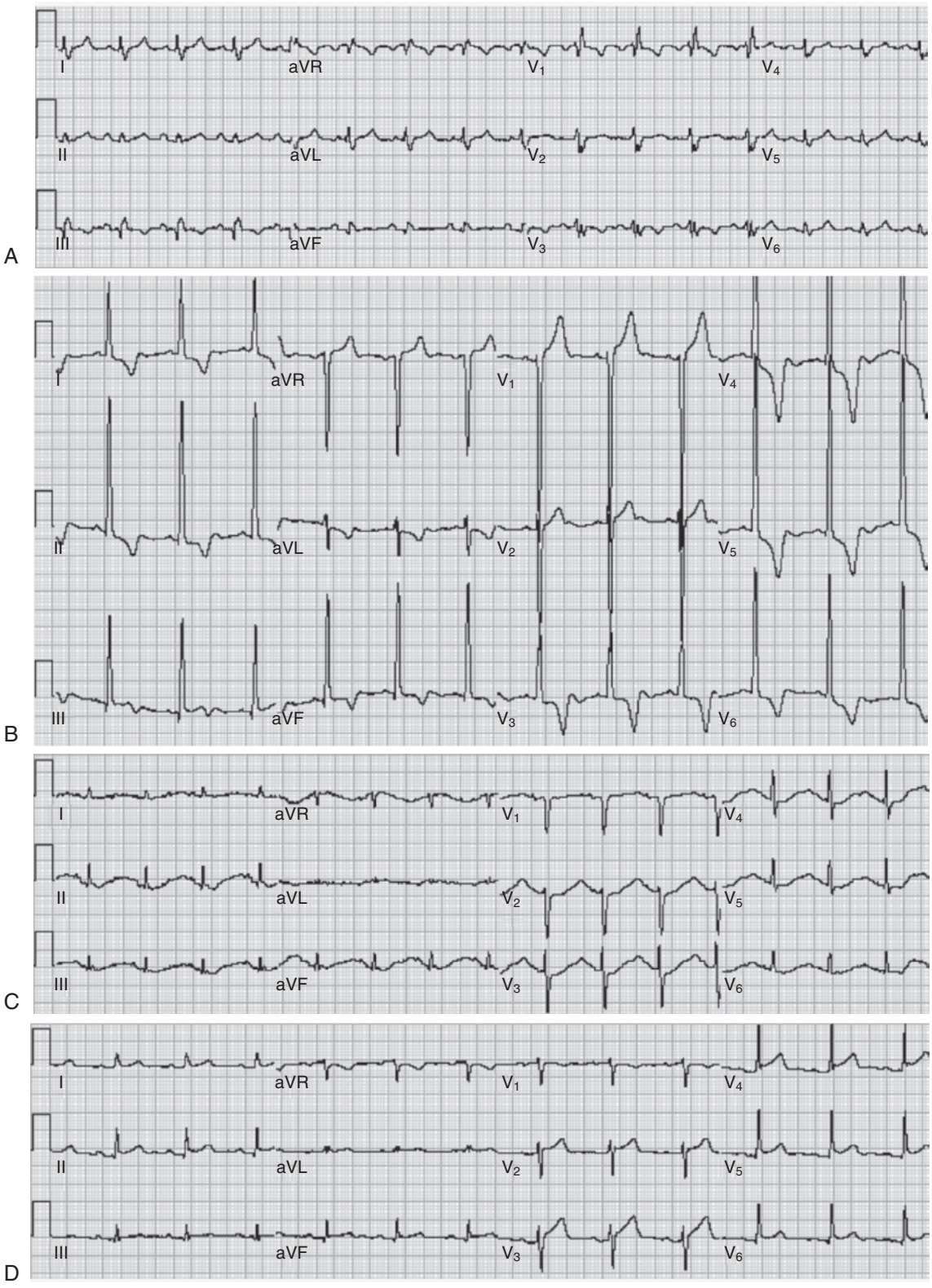

A
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
B
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
C
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
D
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

FIG. 1.22

QUESTIONS 105 TO 109

Match the most appropriate descriptive phrase to each angiogram shown in Fig. 1.23:

105. Right anterior oblique (RAO) projection: left anterior descending (LAD) artery, demonstrating myocardial bridging with narrowing in systole and near-normal caliber in diastole
106. Left anterior oblique (LAO) projection: right coronary arteriogram demonstrating anomalous origin of the left circumflex artery from the right coronary sinus
107. Collateral vessels arising from the distal right coronary artery (RCA) and supplying an occluded LAD artery
108. Right coronary arteriogram demonstrating diffuse coronary spasm and restoration of normal caliber with introduction of nitroglycerin
109. A dilated left circumflex artery and subsequent coronary sinus opacification due to a congenital coronary fistula

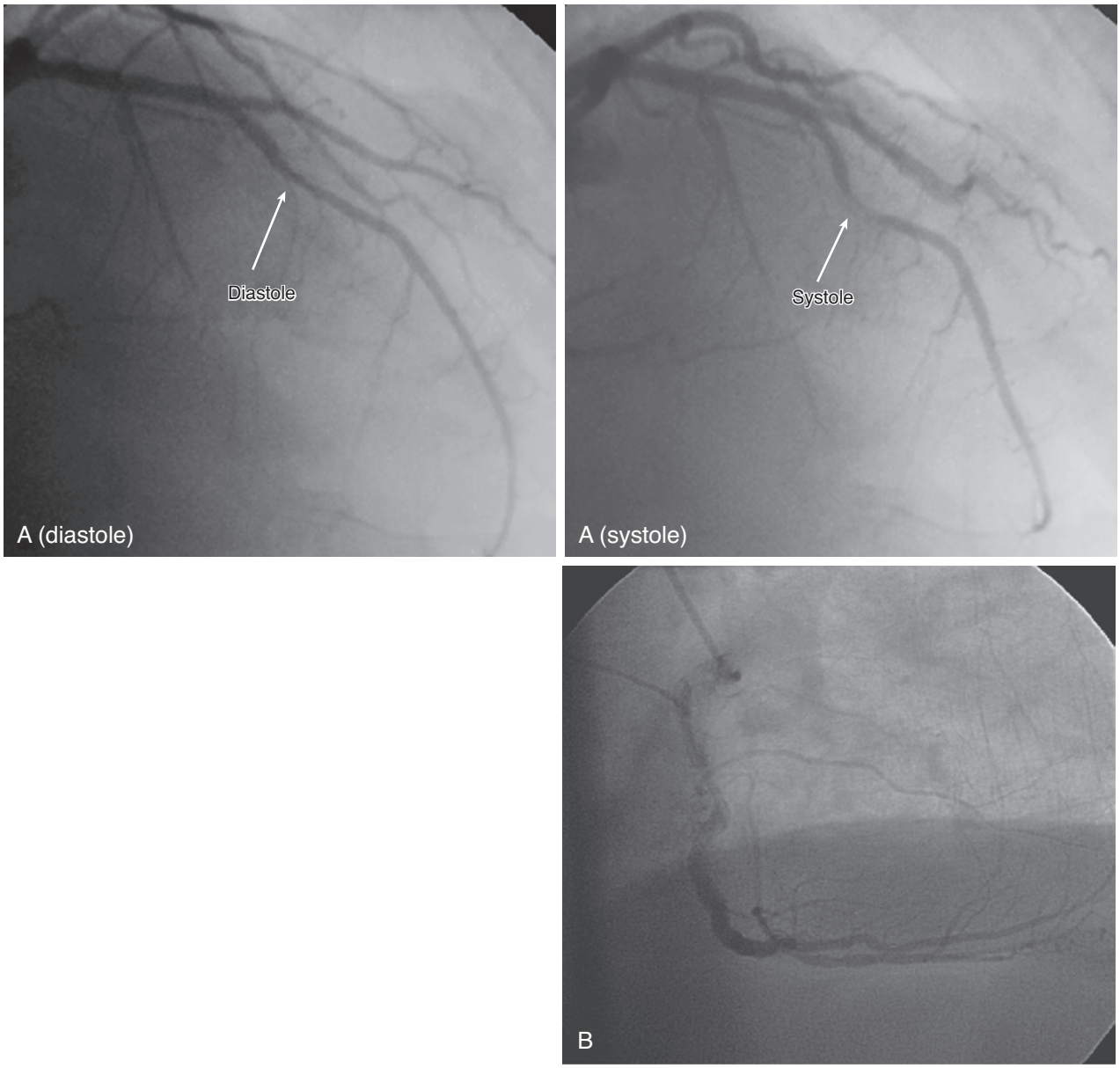


FIG. 1.23

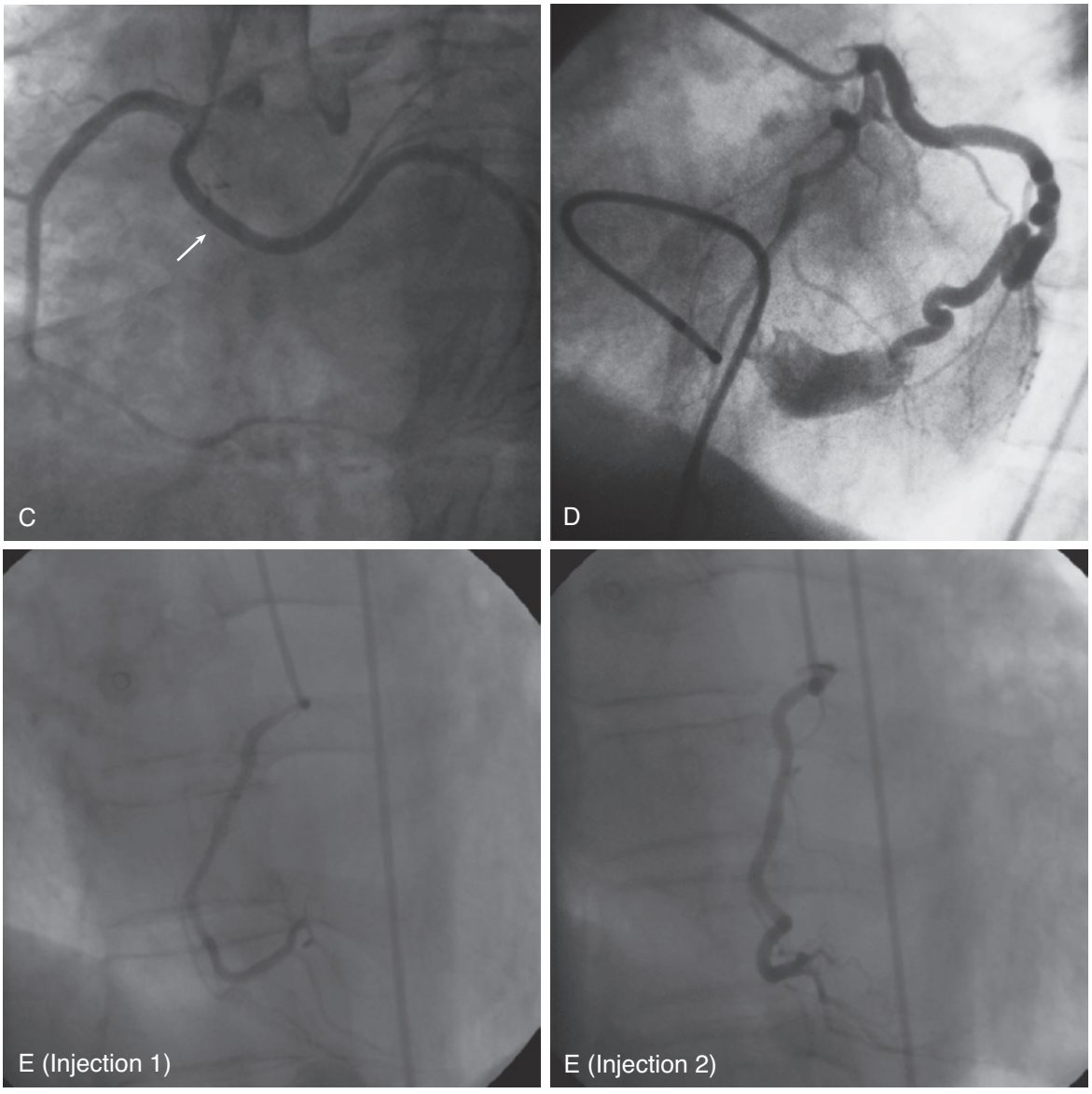


FIG. 1.23, cont'd

QUESTIONS 110 TO 113

For each clinical scenario, match the most likely computed tomogram in Fig. 1.24:

110. A 53-year-old woman with exertional dyspnea, recurrent transient ischemic attacks, lightheadedness with sudden changes in position, and a 15-pound weight loss over the past 6 months
111. A 21-year-old man with recurrent syncope
112. A 69-year-old woman with recent myocardial infarction and subsequent stroke
113. A 71-year-old man with jugular venous distention, ascites, and marked peripheral edema

QUESTIONS 114 TO 117

For each condition, match the appropriate pattern of left ventricular (LV) filling as recorded by Doppler of diastolic mitral flow velocities (E wave = early diastolic filling; A wave = period of atrial contraction; normal LV deceleration time in early diastole is >190 milliseconds):

A. E wave > A wave, LV deceleration time >190 milliseconds
B. E wave > A wave, LV deceleration time <190 milliseconds
C. E wave < A wave, LV deceleration time >200 milliseconds
D. E wave ≫ A wave, LV deceleration time <150 milliseconds

114. Restrictive cardiomyopathy
115. Normal pattern
116. Pseudonormalized pattern
117. Impaired LV diastolic relaxation

QUESTIONS 118 TO 121

For each of the chest radiographs shown in Fig. 1.25, match the most appropriate cardiac diagnosis:

118. Mitral stenosis
119. Aortic regurgitation
120. Atrial septal defect
121. Pericardial effusion

QUESTIONS 122 TO 125

Match each description below to the most appropriate cardiac rhythm:

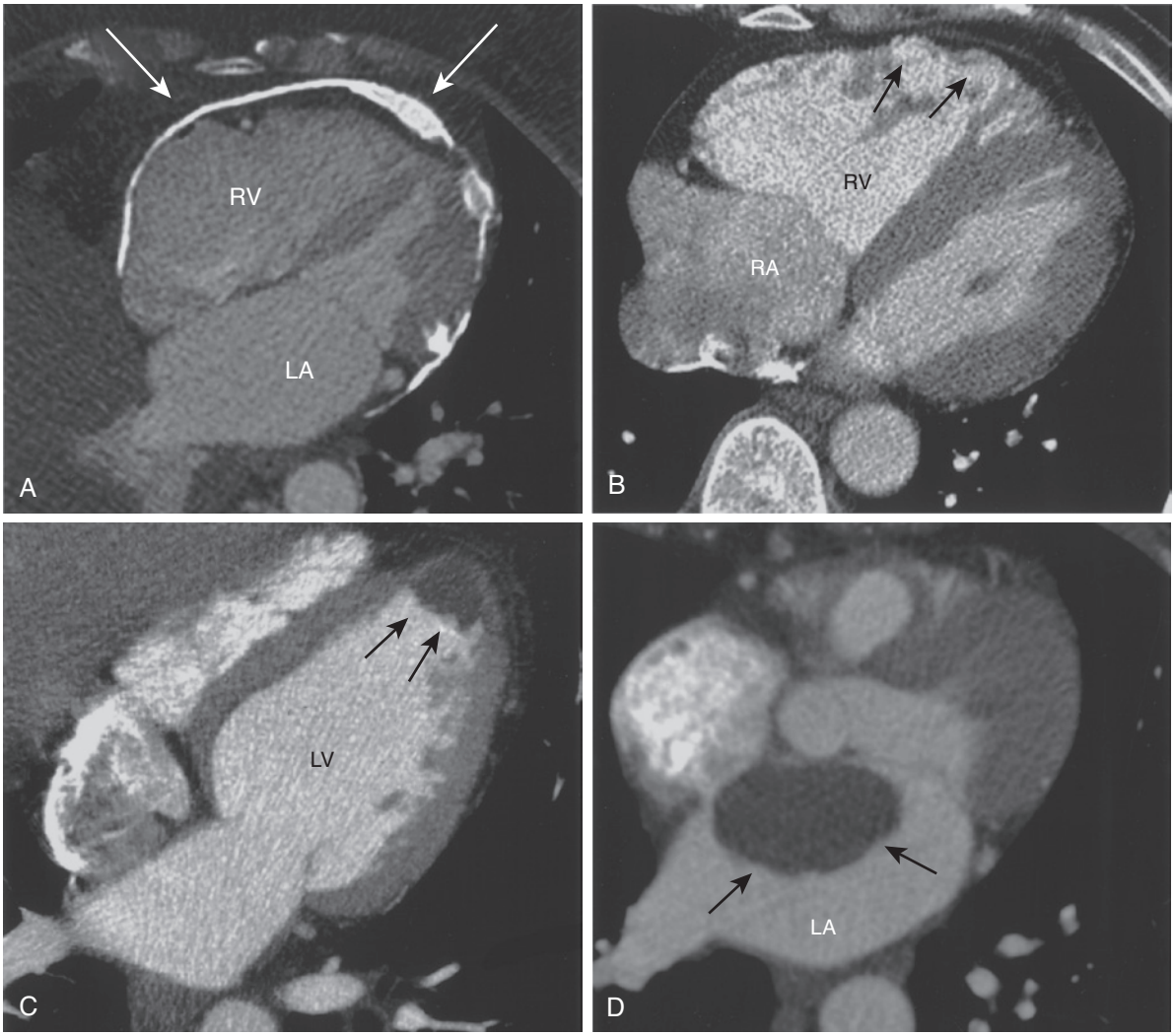


FIG. 1.24

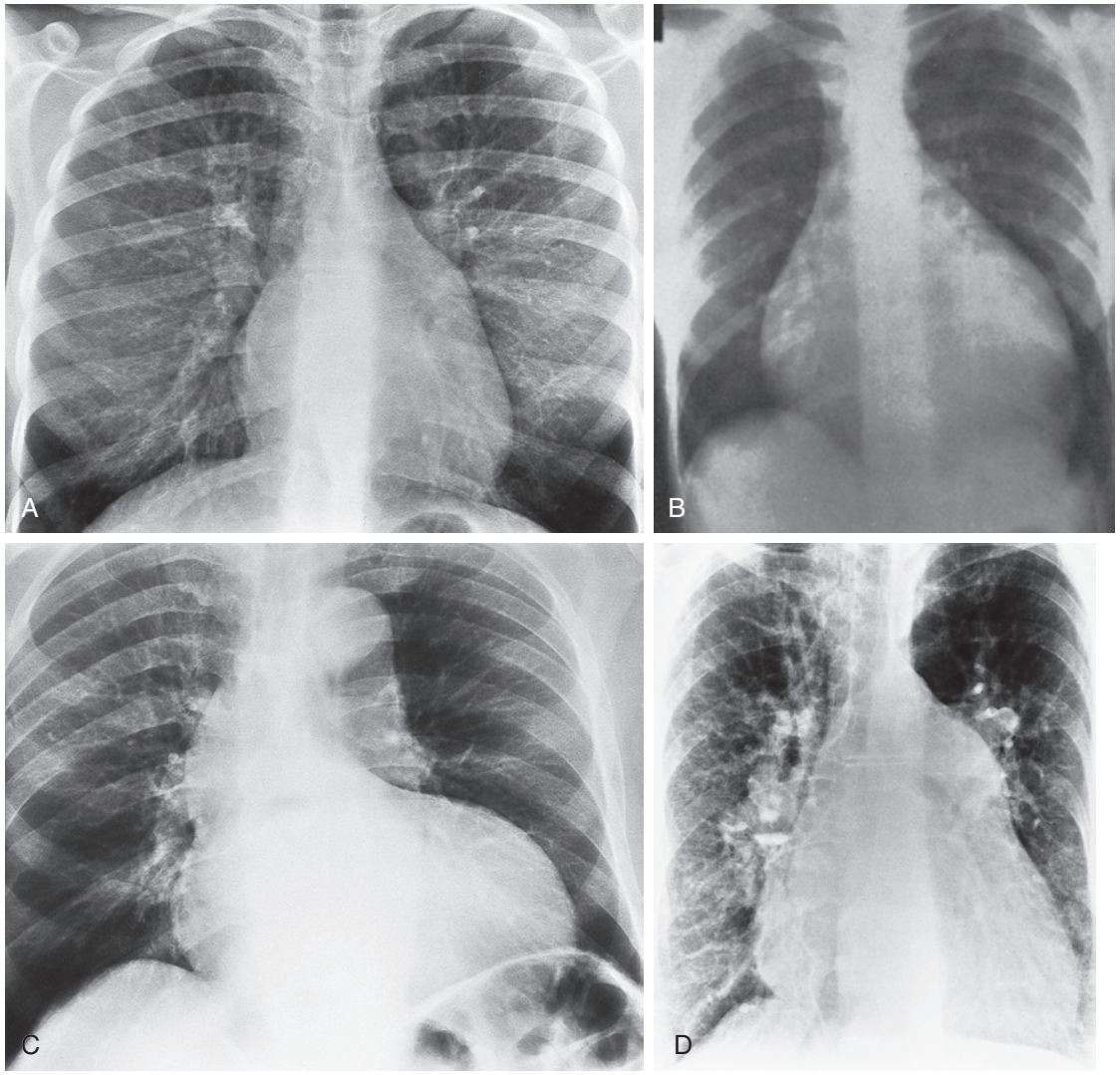


FIG. 1.25 *A, C, and D from Miller SW.* Cardiac Imaging: The Requisites. *2nd ed. Philadelphia: Elsevier; 2005. B, From Daves ML.* Cardiac Roentgenology. *Chicago: Year Book Publishers; 1981:470.*

A. Atrial tachycardia
B. Atrial flutter
C. Sinus rhythm
D. Atrioventricular nodal reentrant tachycardia
E. Atrial fibrillation

122. P waves are negative in lead aVR and upright in leads I, II, and aVF
123. Rhythm can be due to automaticity, reentry, or triggered mechanisms
124. Macroreentrant mechanism in the right atrium
125. The initial P wave of the tachycardia is usually different from the subsequent P waves

QUESTIONS 126 TO 129

For the receiver-operating curve (ROC) for two diagnostic tests shown in Fig. 1.26, match the following:

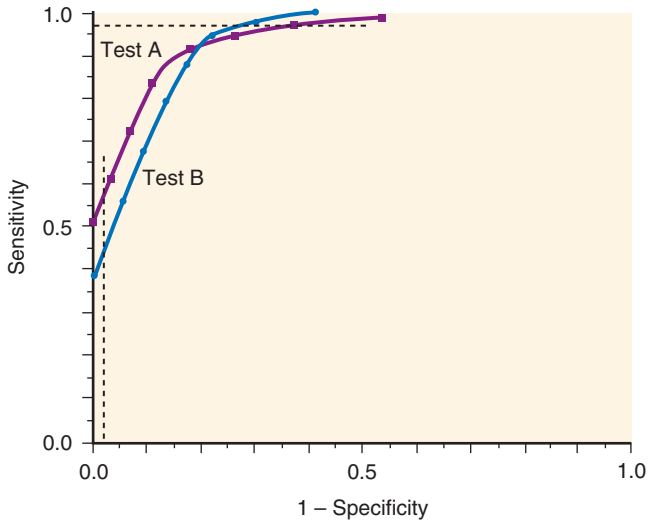


FIG. 1.26

A. 11%
B. 40%
C. 59%
D. 47%
E. Test A
F. Test B

126. The false-positive rate of Test A at a sensitivity of 98%
127. The sensitivity of Test A at a specificity of 98%
128. The positive predictive value of Test A with a sensitivity of 98%, for a population with disease prevalence of 50/1000
129. The superior screening test

QUESTIONS 130 TO 133

For each clinical scenario, select the appropriate ECG from those provided in Fig. 1.27:

130. A 49-year-old man with chronic renal failure and progressive fatigue
131. A 37-year-old man with a recent viral syndrome and sharp anterior chest pain that worsens when he changes position
132. A 59-year-old man with severe lightheadedness
133. A 38-year-old woman with perioral and peripheral cyanosis, digital clubbing, and a history of cardiac surgery as a child

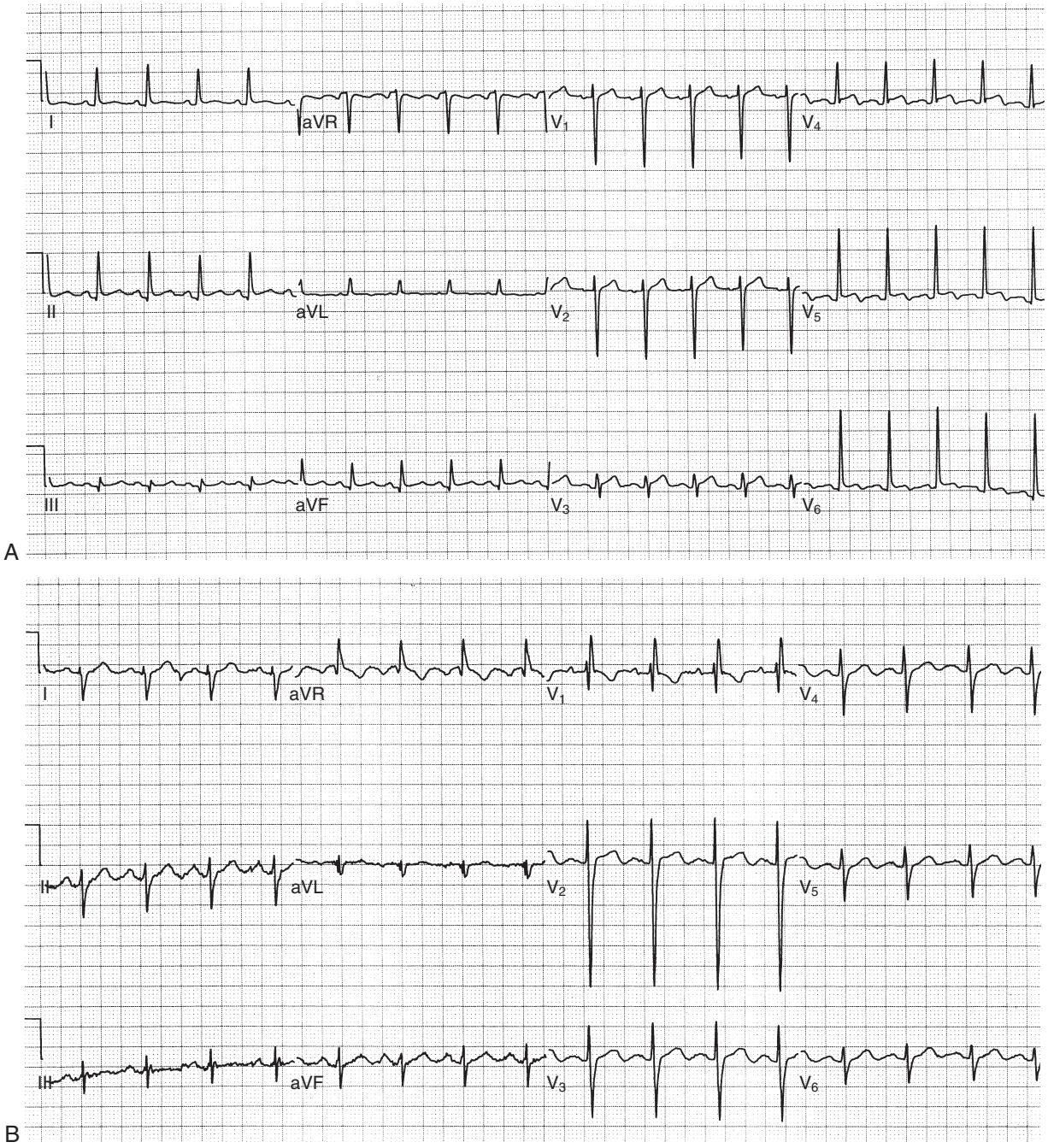
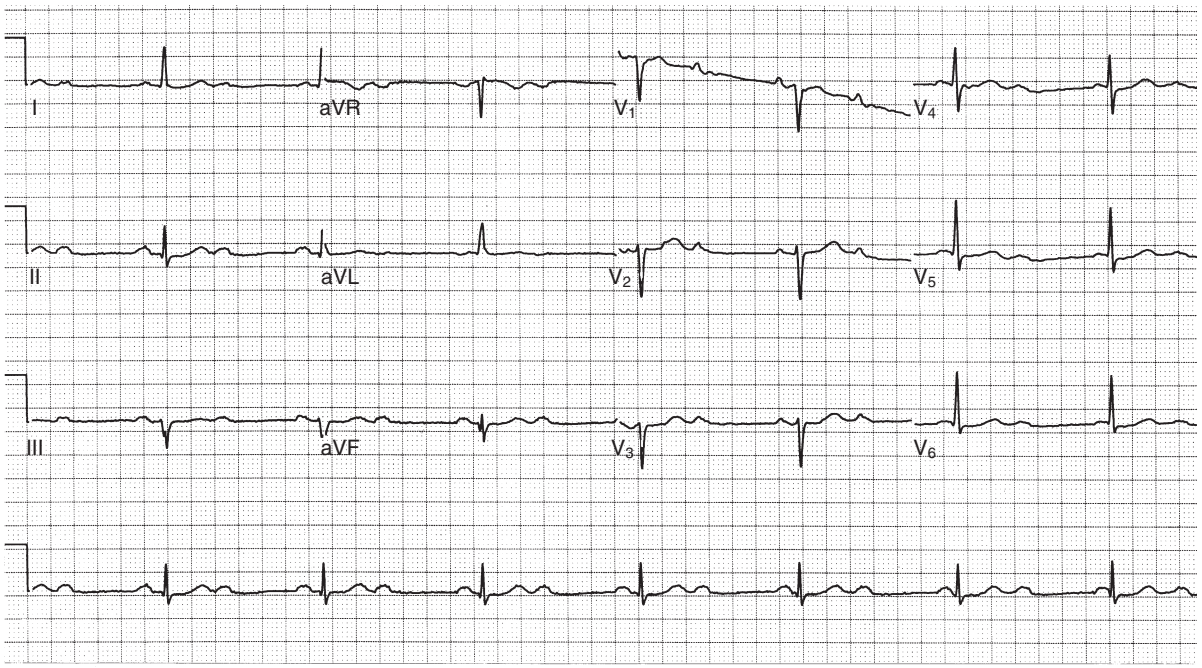
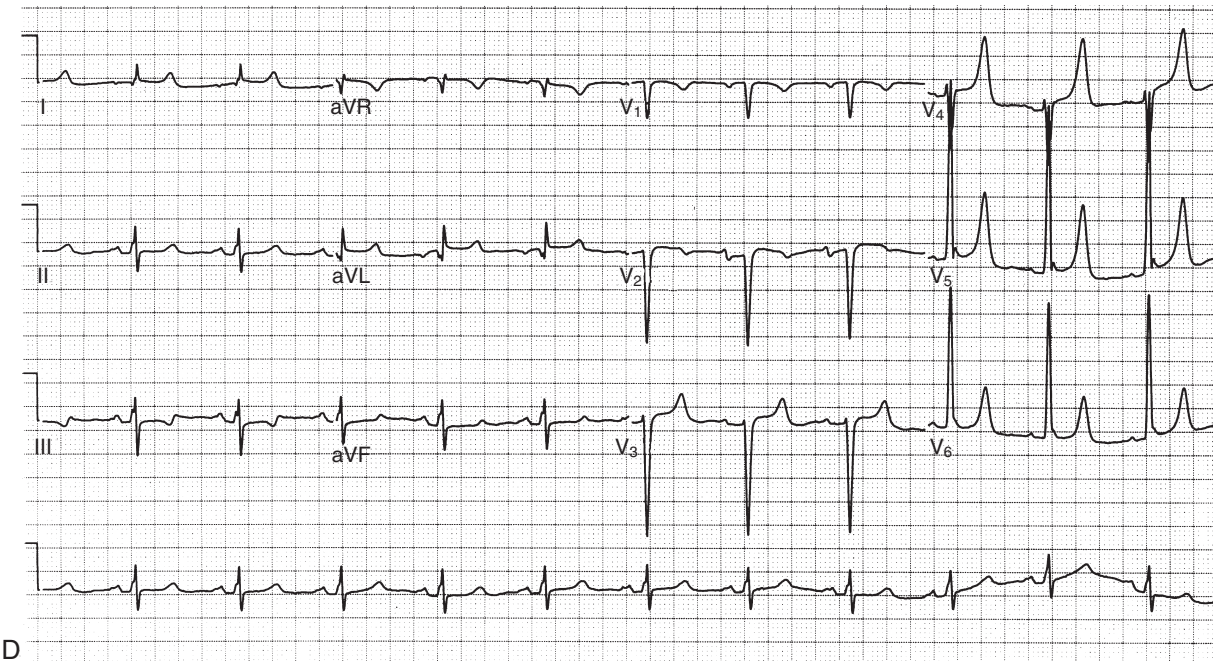


FIG. 1.27



C



D

FIG. 1.27, cont'd

ECHOCARDIOGRAMS (QUESTIONS 134–142)

Directions:

Each of the still-frame echocardiographic images below is introduced by a brief clinical scenario. For each image, comment on the major abnormal findings:

134. A 62-year-old man who sustained a myocardial infarction 1 month ago (Fig. 1.28)

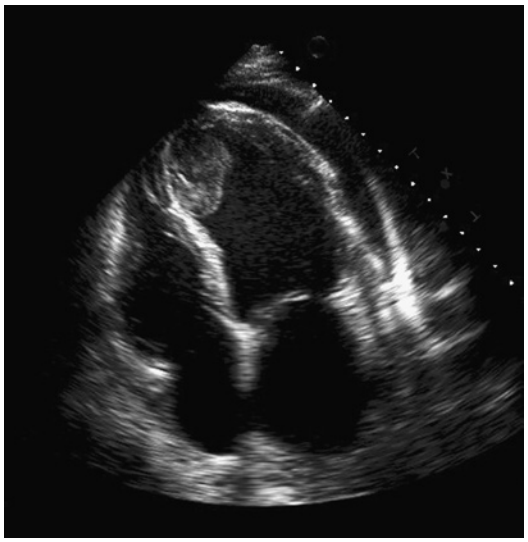


FIG. 1.28

135. A 33-year-old woman with an early systolic click (Fig. 1.29)

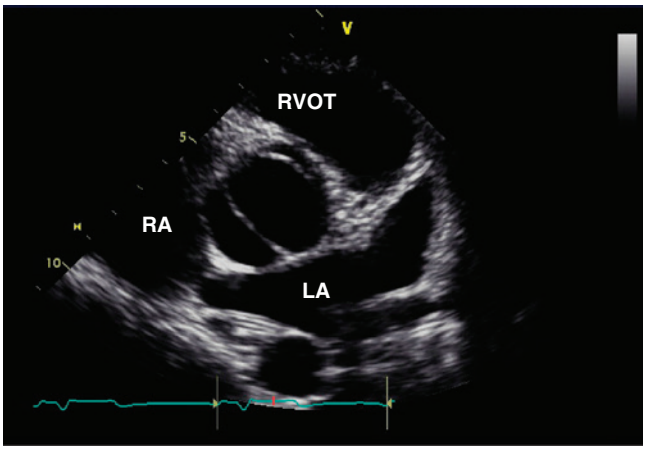


FIG. 1.29

136. A 26-year-old man with a loud asymptomatic systolic murmur (Fig. 1.30)

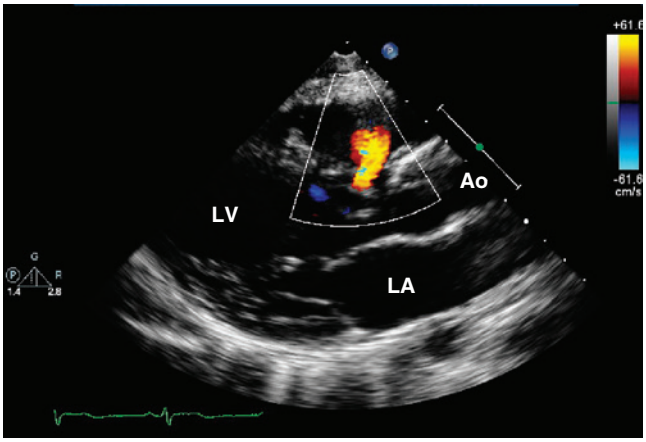


FIG. 1.30

137. A tall, thin 31-year-old woman with a diastolic murmur (Fig. 1.31)

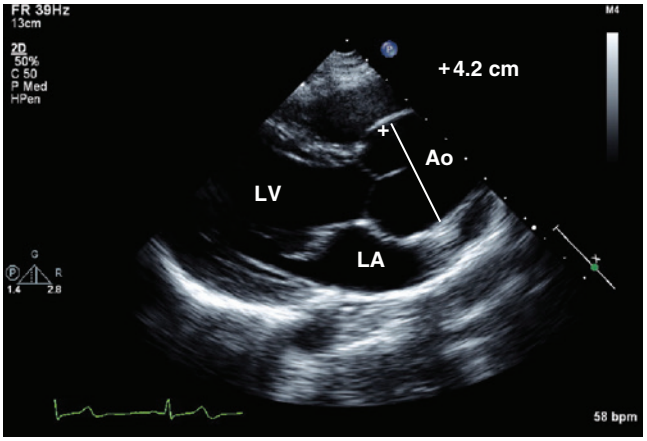


FIG. 1.31

138. A 59-year-old woman with a systolic murmur (Fig. 1.32)

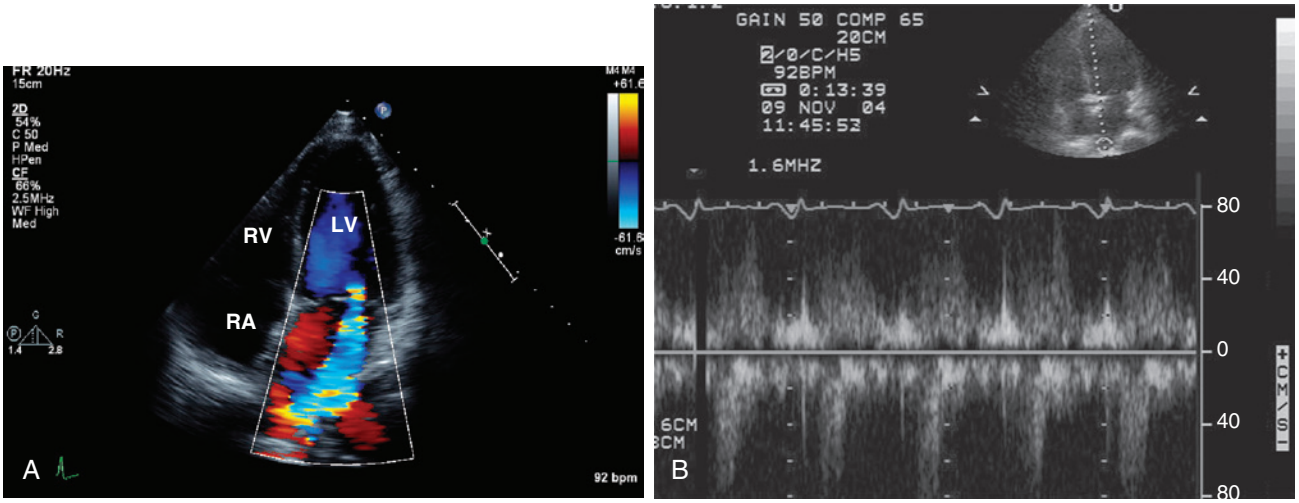


FIG. 1.32

139. Doppler tissue imaging in a 54-year-old man with multiple myeloma, exertional dyspnea, and peripheral edema (Fig. 1.33)

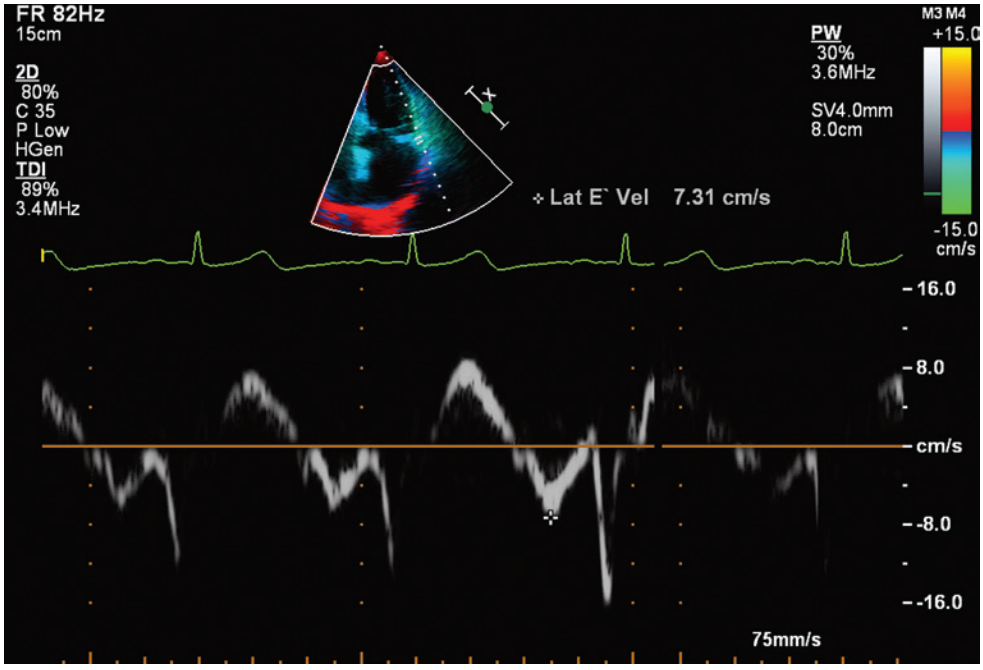


FIG. 1.33

140. A 44-year-old woman with an acute stroke (Fig. 1.34)

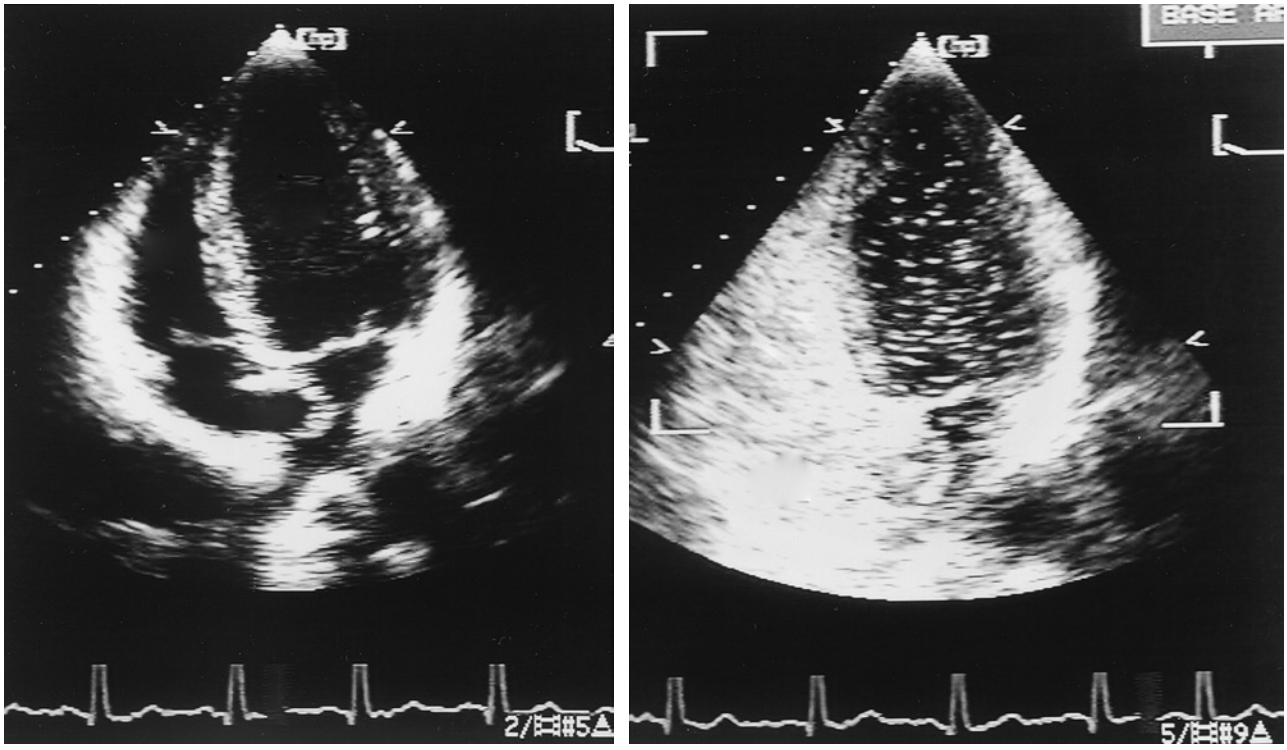


FIG. 1.34

141. A 78-year-old woman with atrial fibrillation (Fig. 1.35)

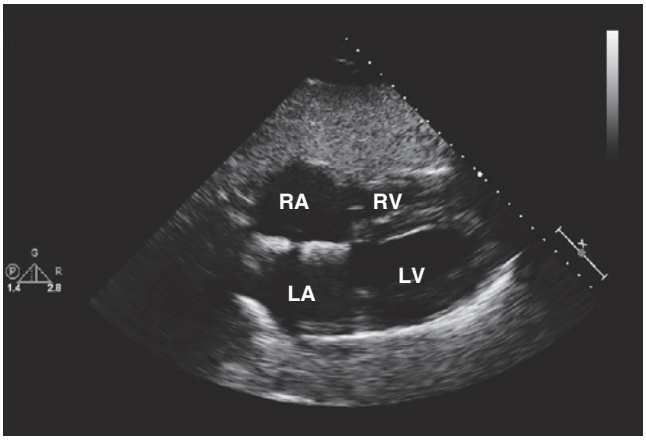


FIG. 1.35

142. A 66-year-old man with dyspnea (Fig. 1.36)

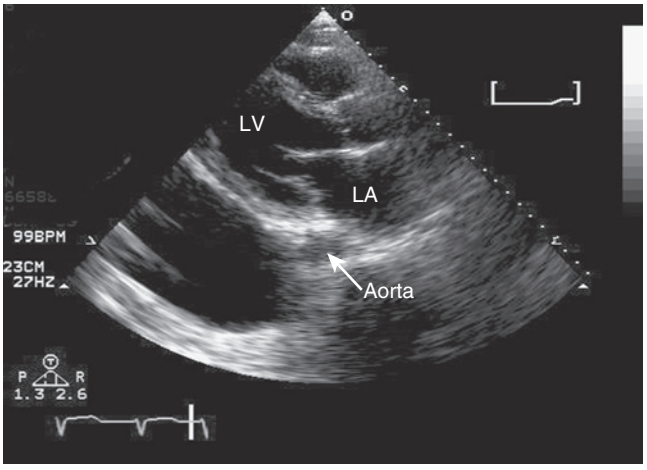


FIG. 1.36

ELECTROCARDIOGRAMS

Electrocardiogram Response Form (For Use With Questions 143–167)

General Features
- ☐ 1. Normal ECG
- ☐ 2. Normal variant
- ☐ 3. Incorrect electrode placement
- ☐ 4. Artifact

P Wave Abnormalities
- ☐ 5. Right atrial abnormality/enlargement
- ☐ 6. Left atrial abnormality/enlargement

Atrial Rhythms
- ☐ 7. Sinus rhythm
- ☐ 8. Sinus arrhythmia
- ☐ 9. Sinus bradycardia (<60)
- ☐ 10. Sinus tachycardia (>100)
- ☐ 11. Sinus pause or arrest
- ☐ 12. Sinoatrial exit block
- ☐ 13. Atrial premature complexes
- ☐ 14. Atrial parasystole
- ☐ 15. Atrial tachycardia
- ☐ 16. Atrial tachycardia, multifocal
- ☐ 17. Supraventricular tachycardia
- ☐ 18. Atrial flutter
- ☐ 19. Atrial fibrillation

AV Junctional Rhythms
- ☐ 20. AV junctional premature complexes
- ☐ 21. AV junctional escape complexes
- ☐ 22. AV junctional rhythm/tachycardia

Ventricular Rhythms
- ☐ 23. Ventricular premature complex(es)
- ☐ 24. Ventricular parasystole
- ☐ 25. Ventricular tachycardia (3 or more consecutive complexes)
- ☐ 26. Accelerated idioventricular rhythm
- ☐ 27. Ventricular escape complexes or rhythm
- ☐ 28. Ventricular fibrillation

AV Conduction
- ☐ 29. AV block, 1°
- ☐ 30. AV block, 2°—Mobitz type I (Wenckebach)
- ☐ 31. AV block, 2°—Mobitz type II
- ☐ 32. AV block, 2:1
- ☐ 33. AV block, 3°
- ☐ 34. Wolff-Parkinson-White pattern
- ☐ 35. AV dissociation

Abnormalities of QRS Voltage or Axis
- ☐ 36. Low voltage
- ☐ 37. Left axis deviation (>–30 degrees)
- ☐ 38. Right axis deviation (>+100 degrees)
- ☐ 39. Electrical alternans

Ventricular Hypertrophy
- ☐ 40. Left ventricular hypertrophy
- ☐ 41. Right ventricular hypertrophy
- ☐ 42. Combined ventricular hypertrophy

Intraventricular Conduction
- ☐ 43. right bundle branch block (RBBB), complete
- ☐ 44. RBBB, incomplete
- ☐ 45. Left anterior fascicular block
- ☐ 46. Left posterior fascicular block
- ☐ 47. left bundle branch block (LBBB), complete
- ☐ 48. LBBB, incomplete
- ☐ 49. Intraventricular conduction disturbance, nonspecific type
- ☐ 50. Functional (rate-related) aberrancy

Q Wave Myocardial Infarction

	AGE RECENT, OR PROBABLY ACUTE	AGE INDETERMINATE, OR PROBABLY OLD
Anterolateral	☐ 51	☐ 52
Anterior or anteroseptal	☐ 53	☐ 54
Lateral	☐ 55	☐ 56
Inferior	☐ 57	☐ 58
Posterior	☐ 59	☐ 60

ST, T, U Wave Abnormalities
- ☐ 61. Normal variant, early repolarization
- ☐ 62. Normal variant, juvenile T waves
- ☐ 63. Nonspecific ST and/or T wave abnormalities
- ☐ 64. ST and/or T wave abnormalities suggesting myocardial ischemia
- ☐ 65. ST and/or T wave abnormalities suggesting myocardial injury
- ☐ 66. ST and/or T wave abnormalities suggesting electrolyte disturbances
- ☐ 67. ST and/or T wave abnormalities secondary to hypertrophy
- ☐ 68. Prolonged QT interval
- ☐ 69. Prominent U waves

Clinical Disorders
- ☐ 70. Brugada syndrome
- ☐ 71. Digitalis toxicity
- ☐ 72. Torsades de pointes
- ☐ 73. Hyperkalemia
- ☐ 74. Hypokalemia
- ☐ 75. Hypercalcemia
- ☐ 76. Hypocalcemia
- ☐ 77. Dextrocardia, mirror image
- ☐ 78. Chronic lung disease
- ☐ 79. Acute cor pulmonale including pulmonary embolus
- ☐ 80. Pericardial effusion
- ☐ 81. Acute pericarditis
- ☐ 82. Hypertrophic cardiomyopathy
- ☐ 83. Central nervous system disorder
- ☐ 84. Hypothermia

Pacemaker Function
- ☐ 85. Atrial or coronary sinus pacing
- ☐ 86. Ventricular demand pacemaker (VVI), normally functioning
- ☐ 87. Dual-chamber pacemaker (DDD), normally functioning
- ☐ 88. Pacemaker malfunction, not constantly capturing (atrium or ventricle)
- ☐ 89. Pacemaker malfunction, not constantly sensing (atrium or ventricle)
- ☐ 90. Biventricular pacing or cardiac resynchronization therapy

Directions:

Each of the 12-lead ECGs below is introduced by a brief clinical description of the patient. For each ECG, perform a systematic reading. Consider the rhythm, rate, axis, and intervals and whether atrioventricular conduction disturbances are present. Then determine if criteria are met for atrial or ventricular hypertrophy, intraventricular conduction disturbances, or prior myocardial infarction. Continue by noting abnormalities of the ST segment and T waves. Conclude by suggesting a clinical diagnosis compatible with each tracing. You may use the electrocardiographic response form (p. 33) and its numerical codes, representative of that used by the American Board of Internal Medicine Cardiovascular Disease Certification Examination, as a framework.

143. A 70-year-old woman presents to the emergency department with severe chest pain and dyspnea (Fig. 1.37)

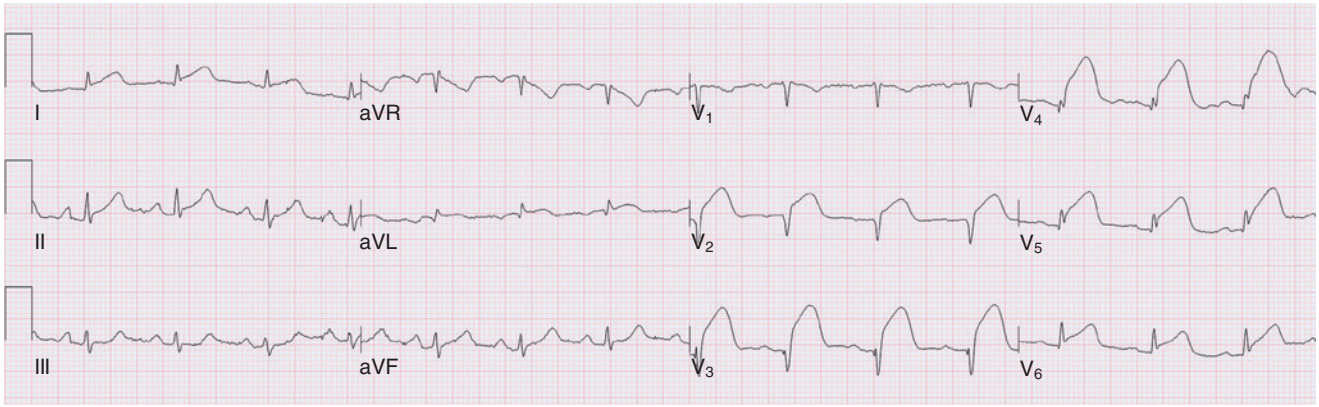


FIG. 1.37

144. A 66-year-old man with a history of cigarette smoking, who has not received medical care for many years, presents to his new primary care physician for a routine examination (Fig. 1.38)

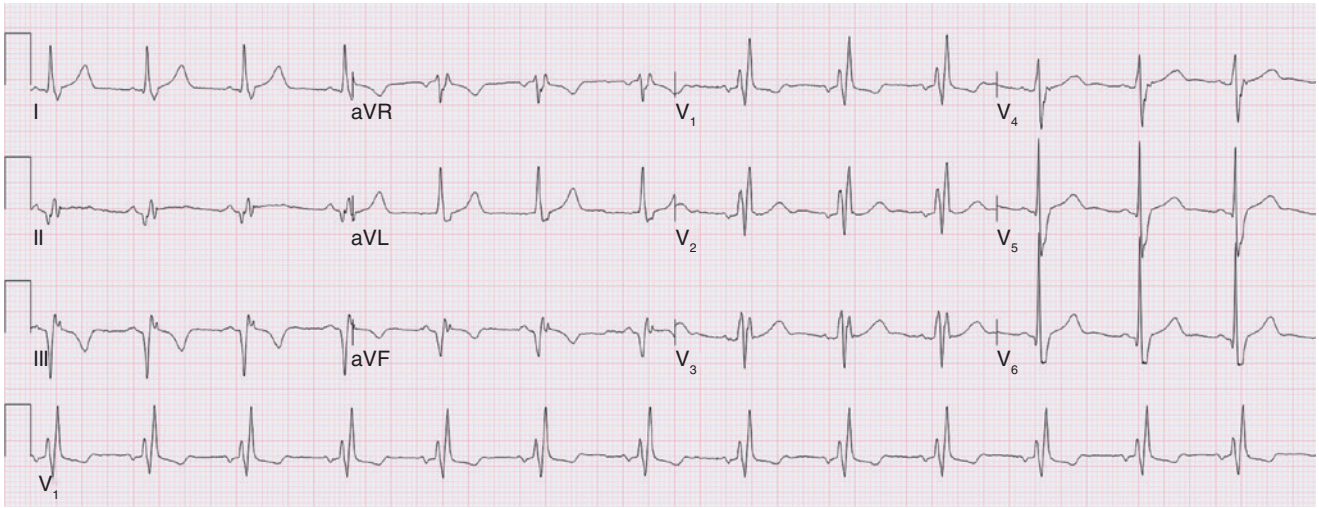


FIG. 1.38

145. A 28-year-old man with a lifelong heart murmur (Fig. 1.39)

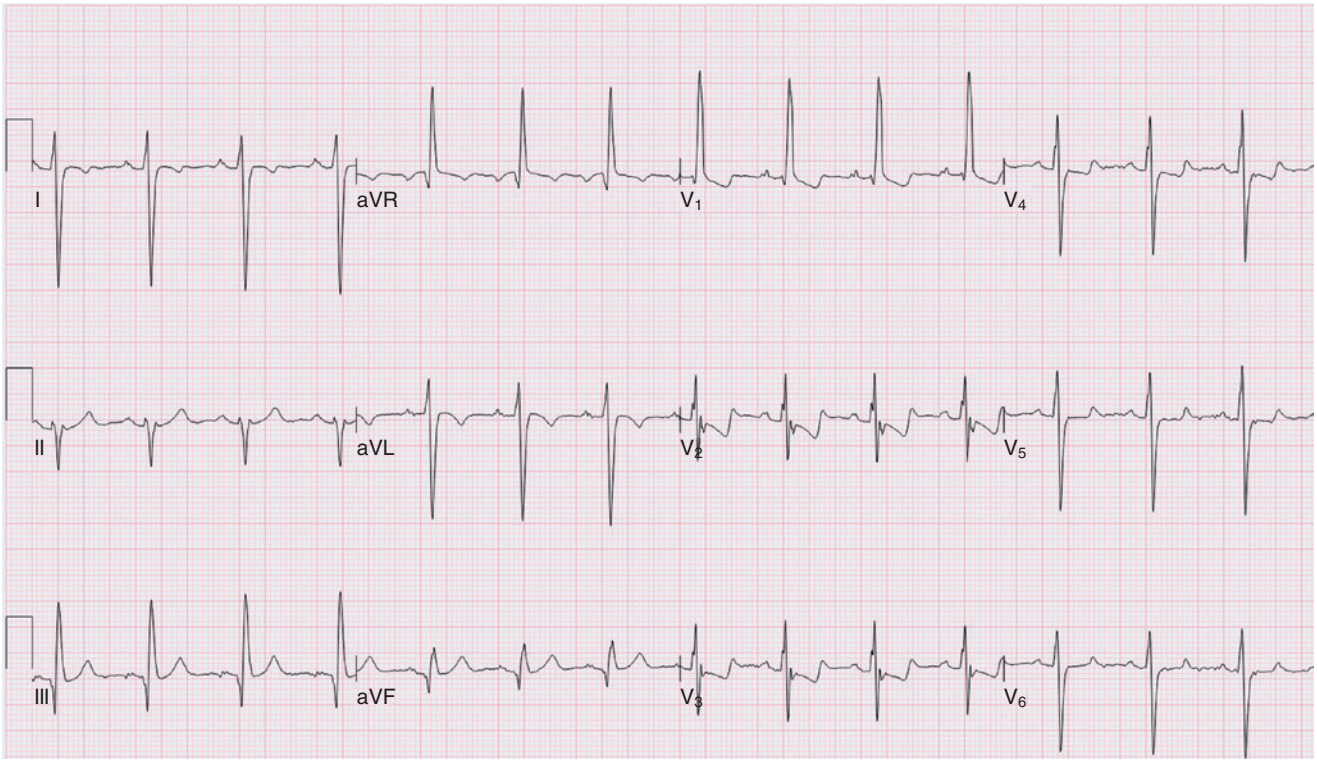


FIG. 1.39

146. An 85-year-old woman who comes for a routine appointment with her cardiologist (Fig. 1.40)

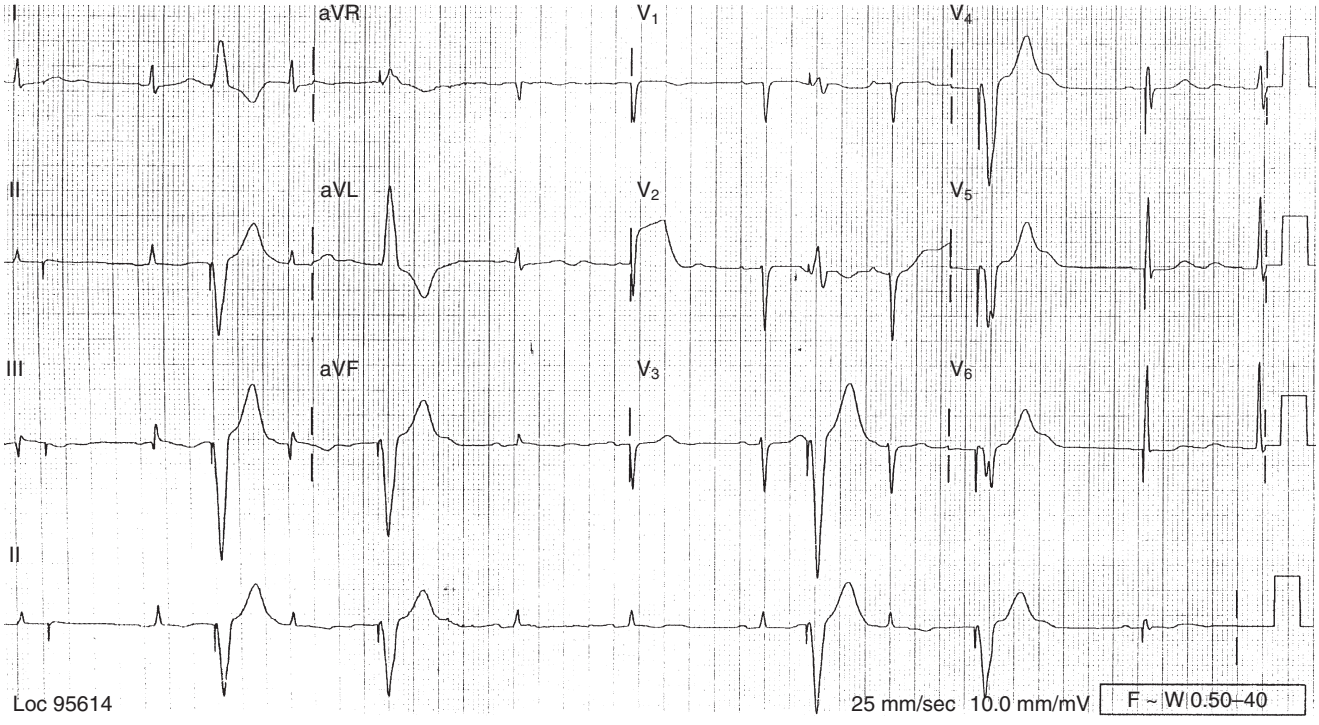


FIG. 1.40

147. A 47-year-old man with episodes of syncope (Fig. 1.41)

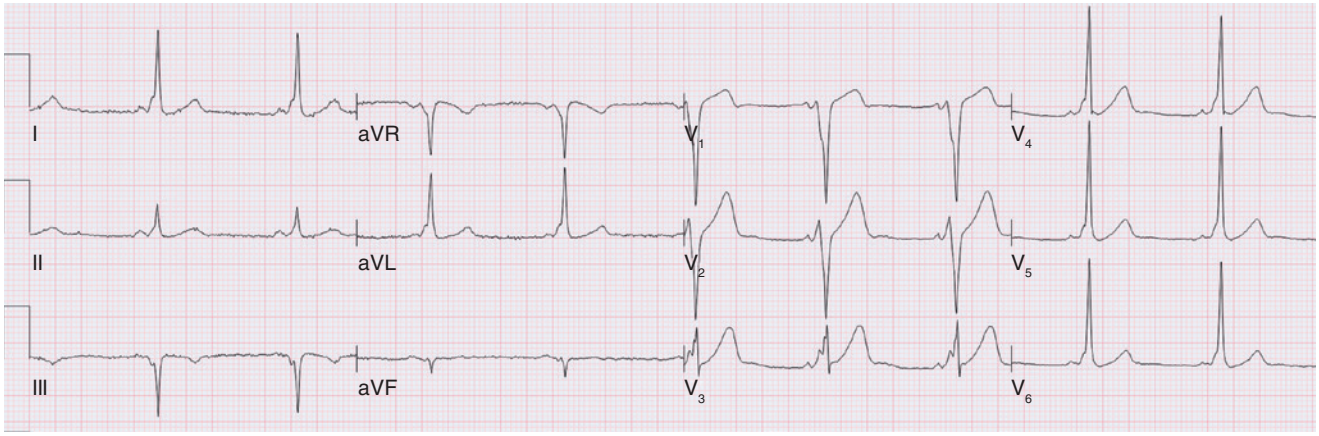


FIG. 1.41

148. A 63-year-old man with a rapid heart rate (Fig. 1.42)

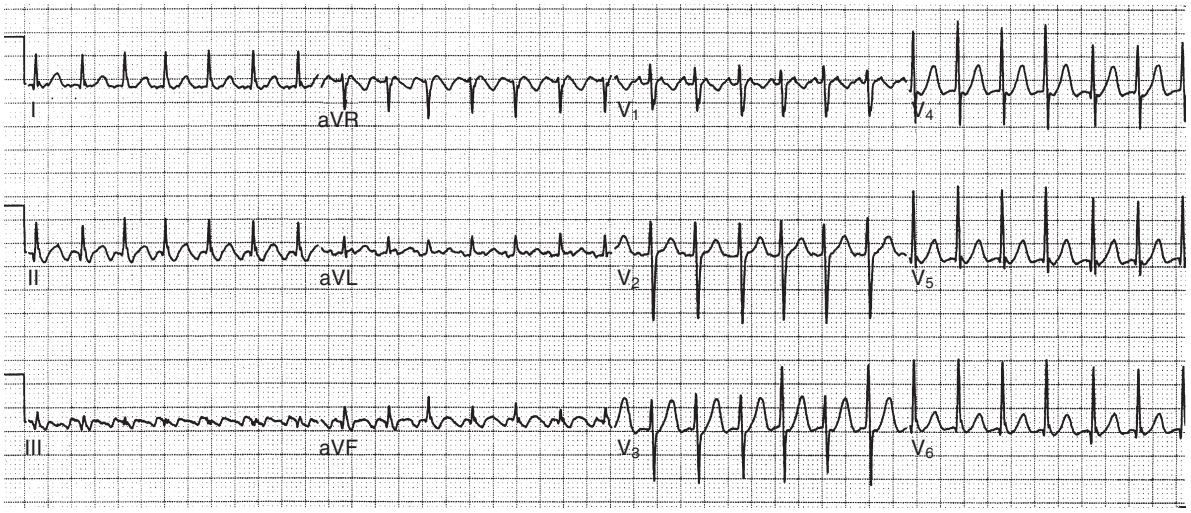


FIG. 1.42

149. A 78-year-old woman with a history of a heart murmur presents with intermittent dyspnea and lightheadedness (Fig. 1.43)

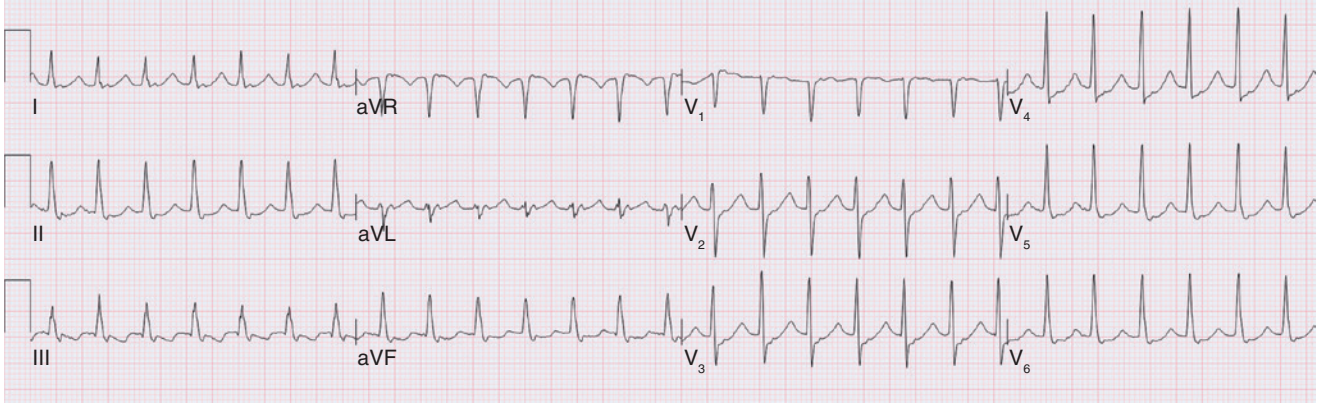


FIG. 1.43

150. A 21-year-old woman with palpitations and presyncope (Fig. 1.44)

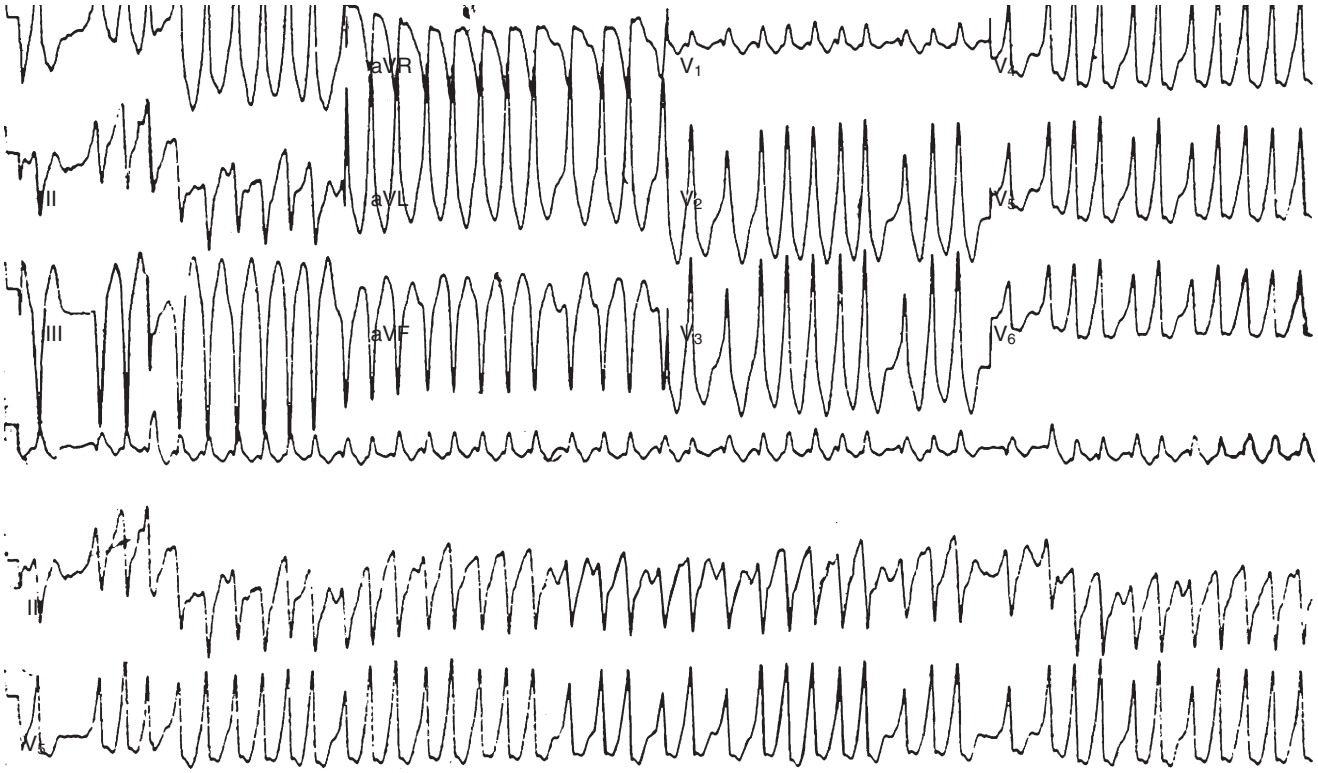


FIG. 1.44

151. A 48-year-old woman with nausea (Fig. 1.45)

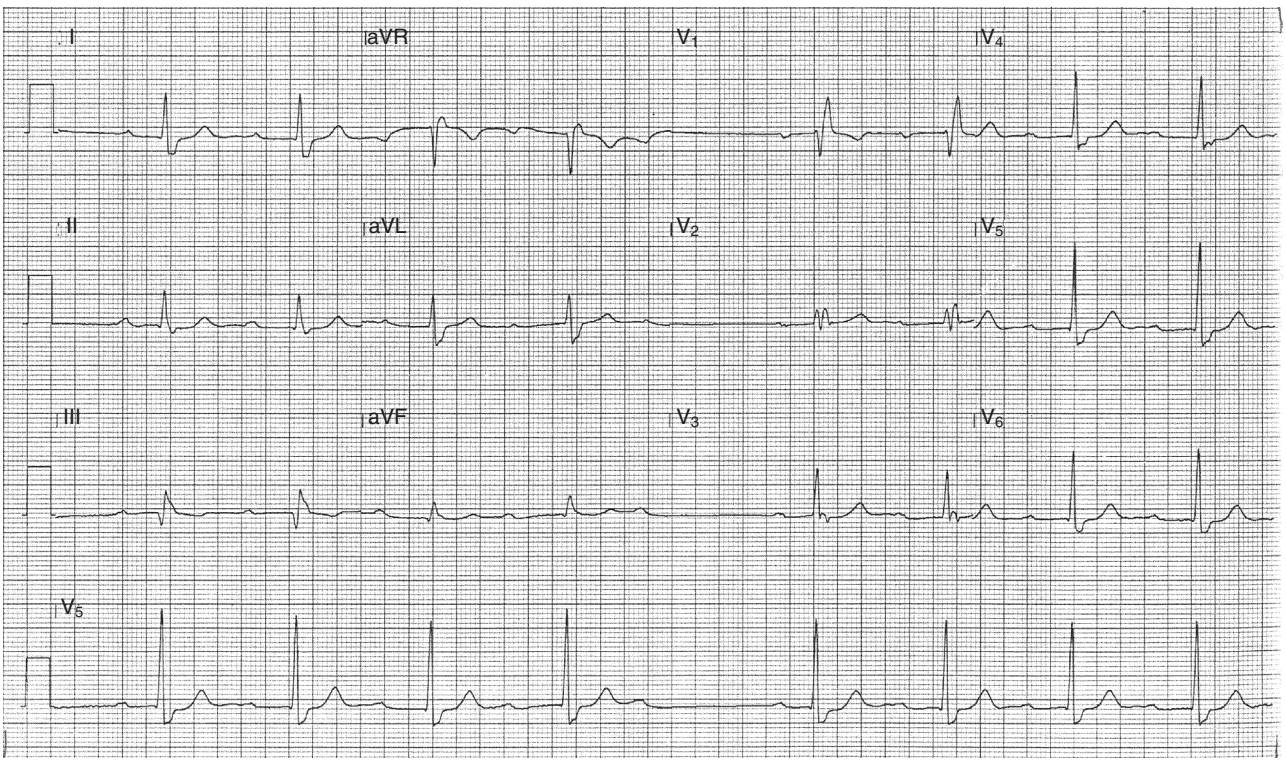


FIG. 1.45

152. A 61-year-old man admitted with frequent dizziness (Fig. 1.46)

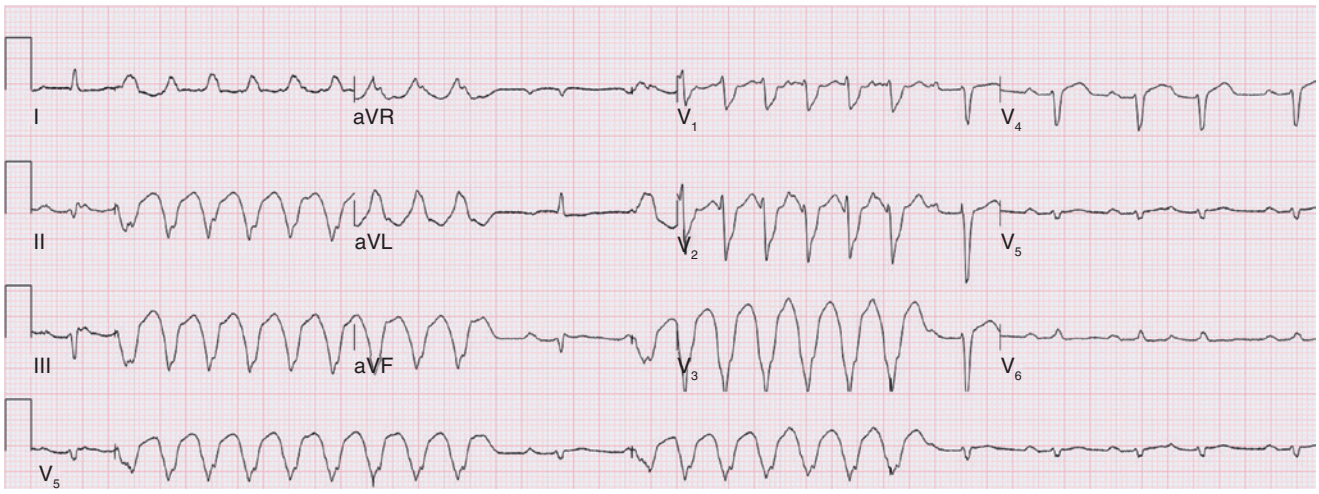


FIG. 1.46

153. A 65-year-old man who underwent coronary artery bypass graft surgery 24 hours ago (Fig. 1.47)

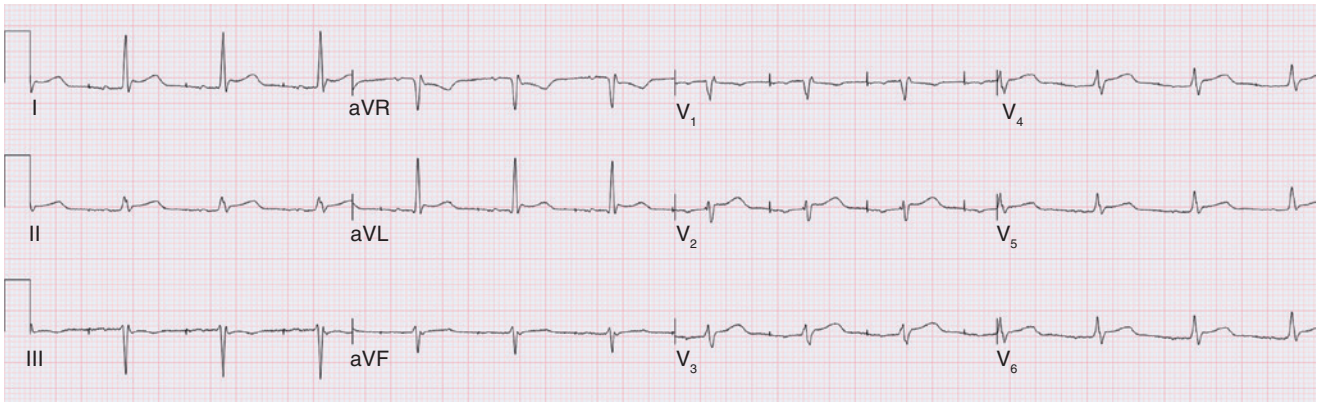


FIG. 1.47

154. A 74-year-old man with an irregular pulse (Fig. 1.48)

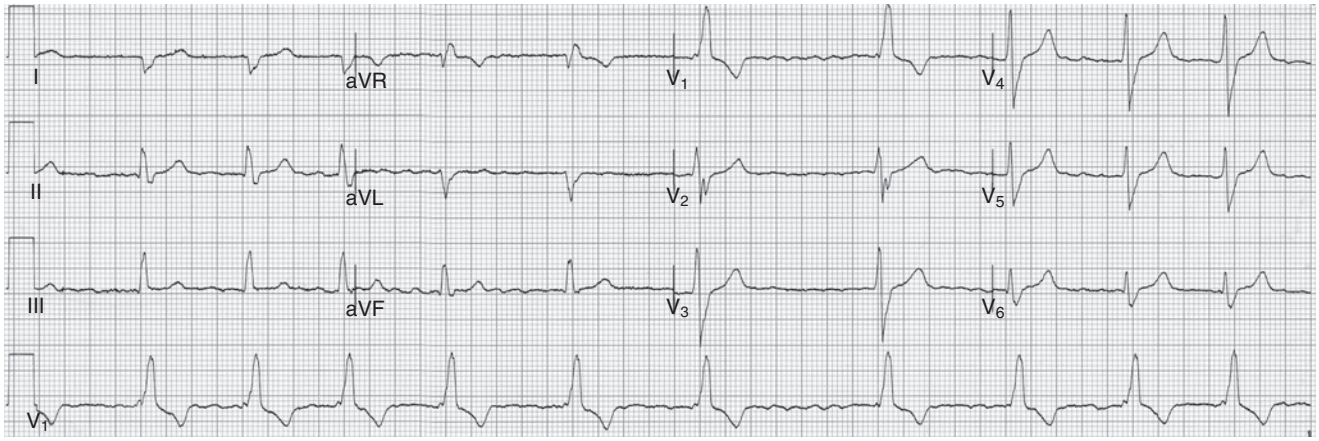


FIG. 1.48

155. A 28-year-old man presents for a pre-employment physical examination (Fig. 1.49)

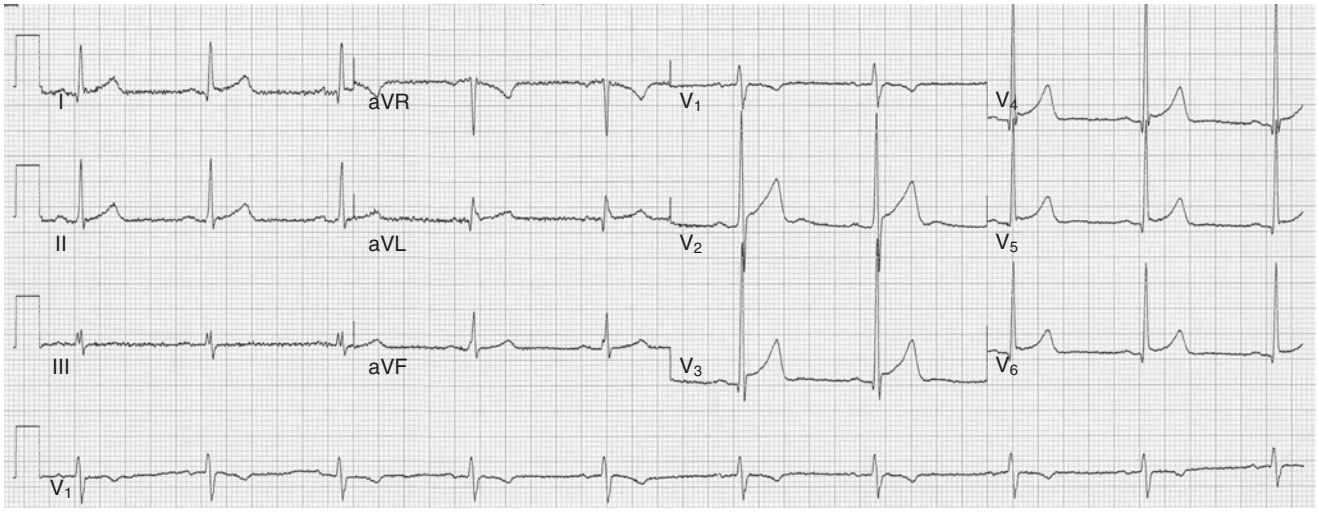


FIG. 1.49

156. A 66-year-old woman with renal failure, palpitations, and lightheadedness (Fig. 1.50)

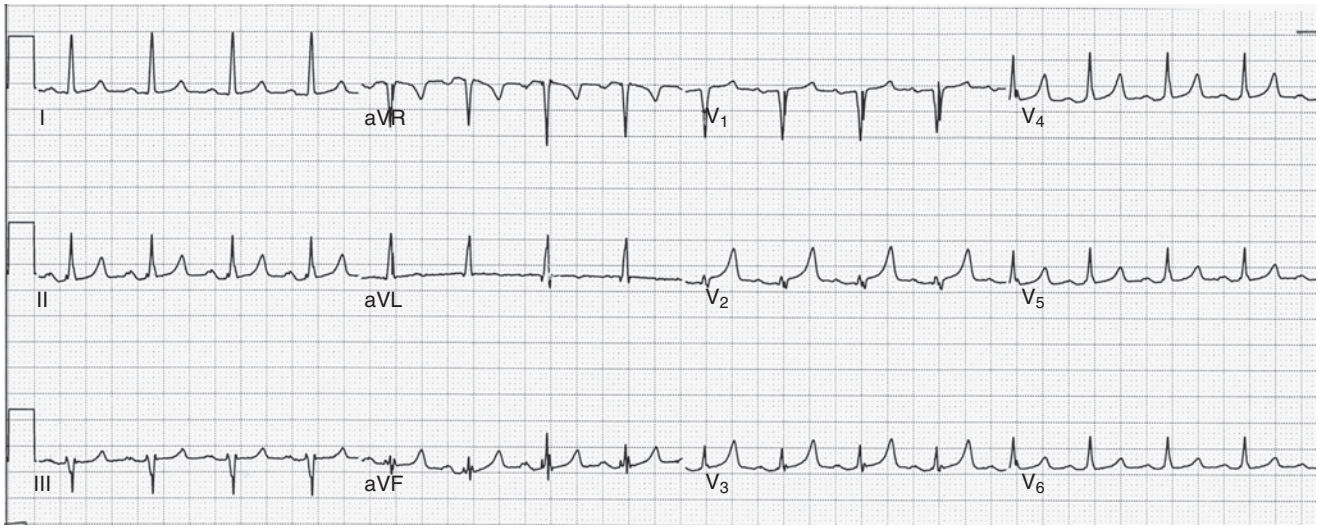


FIG. 1.50

157. A 63-year-old man admitted for elective orthopedic surgery (Fig. 1.51)

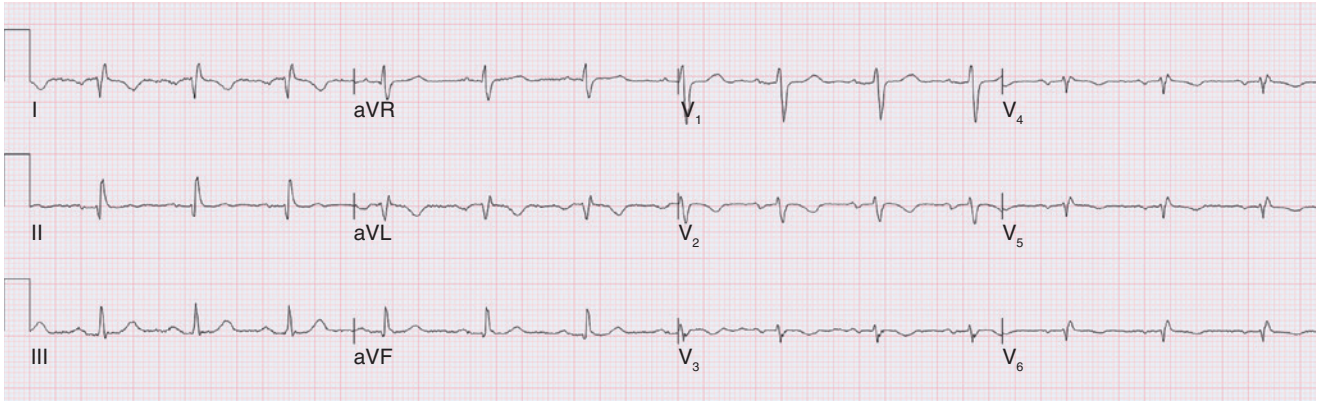


FIG. 1.51

158. A 54-year-old man with sudden lightheadedness (Fig. 1.52)

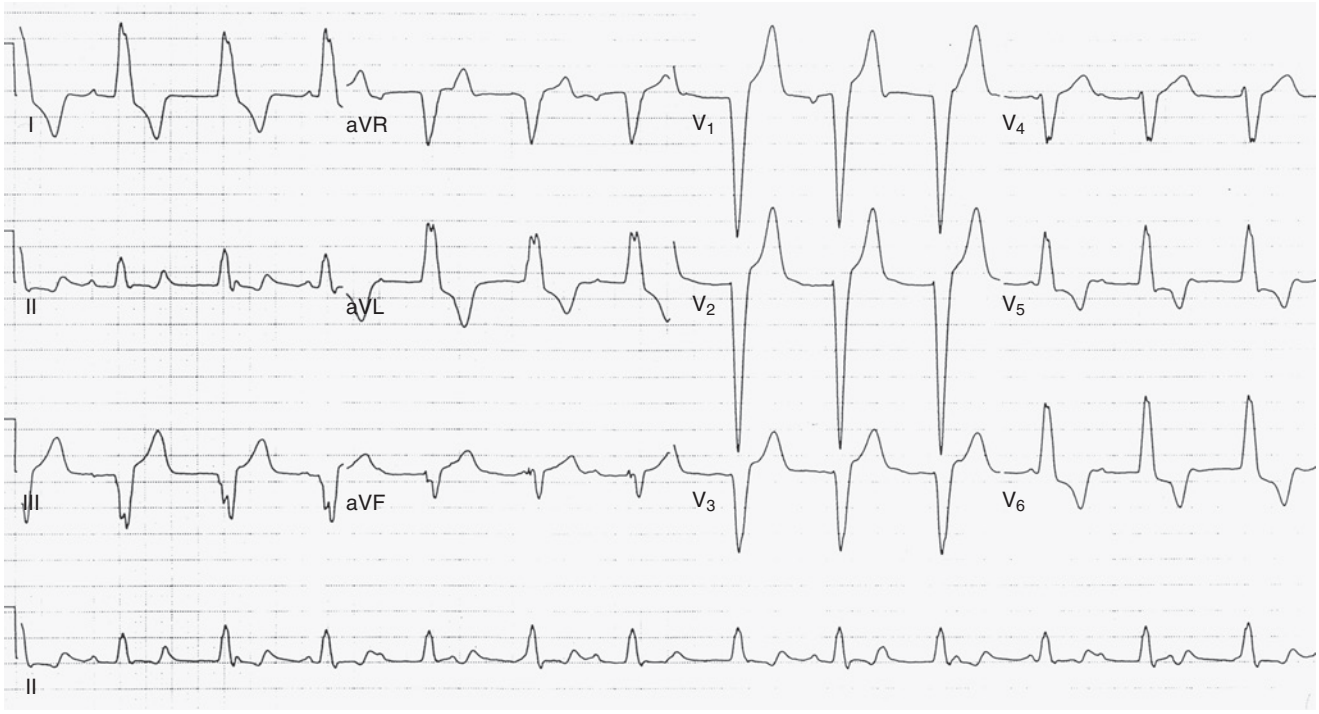


FIG. 1.52

159. A 64-year-old woman with profound nausea and diaphoresis (Fig. 1.53)

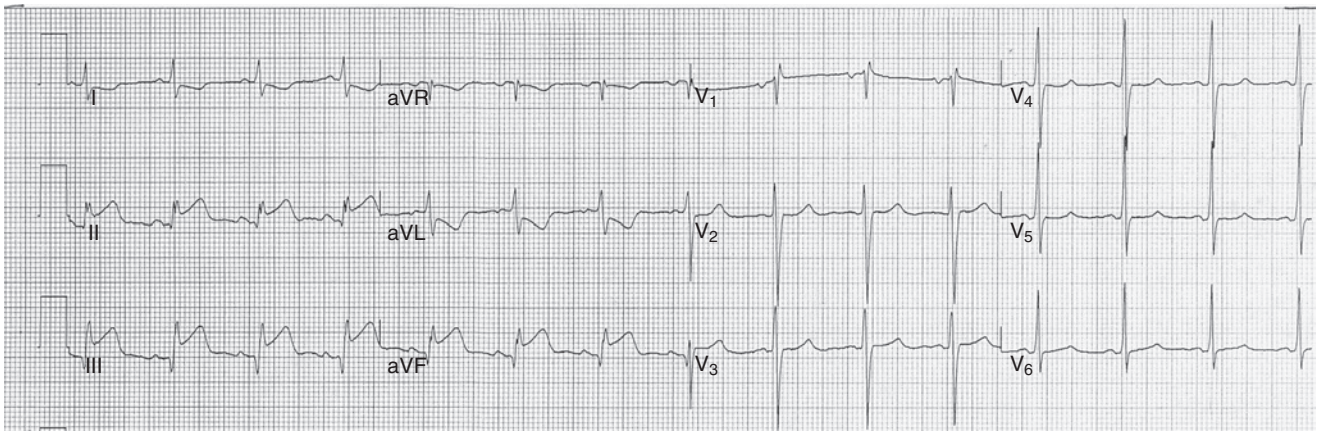


FIG. 1.53

160. A 55-year-old man with long-standing hypertension (Fig. 1.54)

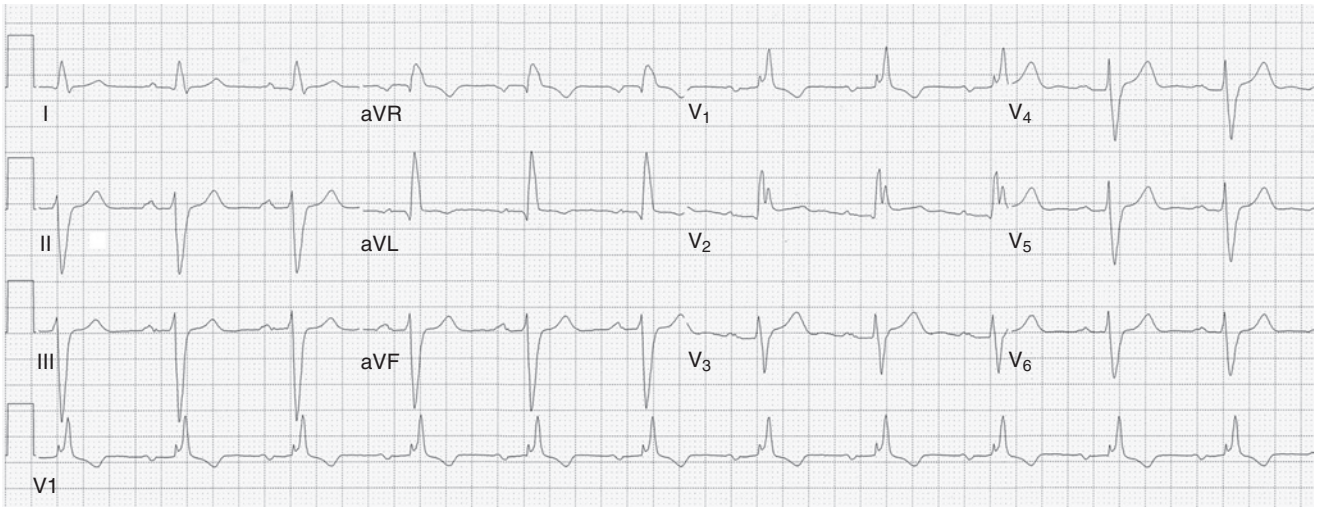


FIG. 1.54

161. An asymptomatic 36-year-old man presents for an insurance physical examination (Fig. 1.55)

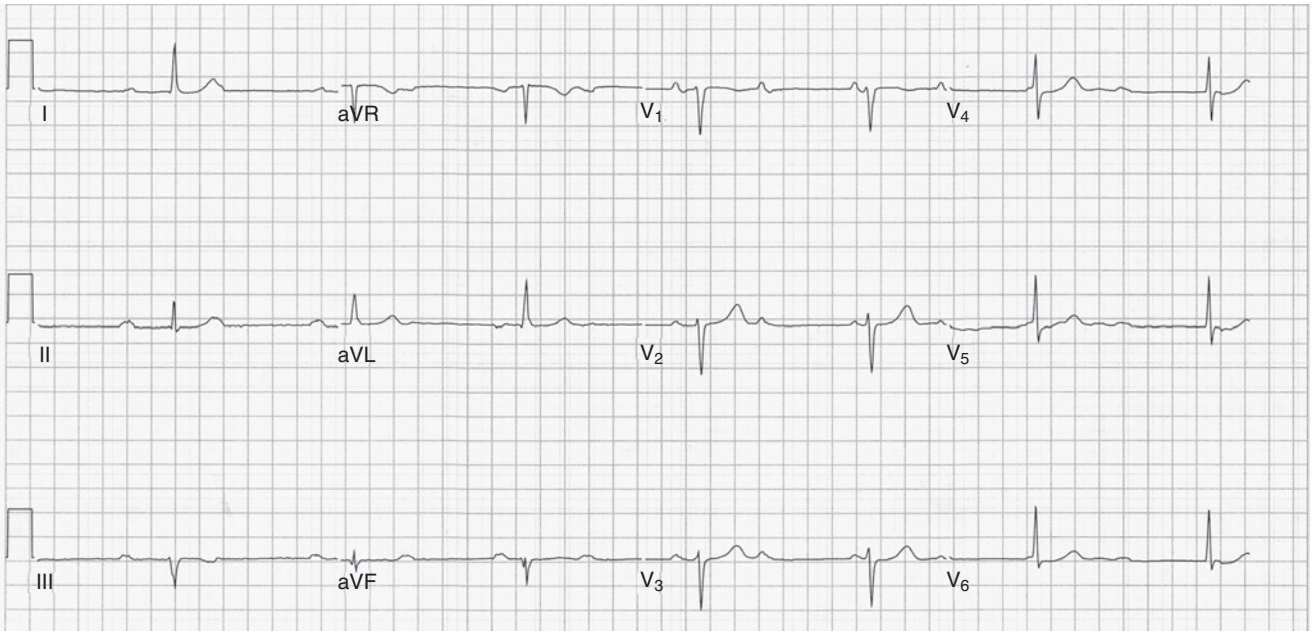


FIG. 1.55

162. A 23-year-old woman referred to the cardiology clinic because of a murmur and abnormal ECG (Fig. 1.56)

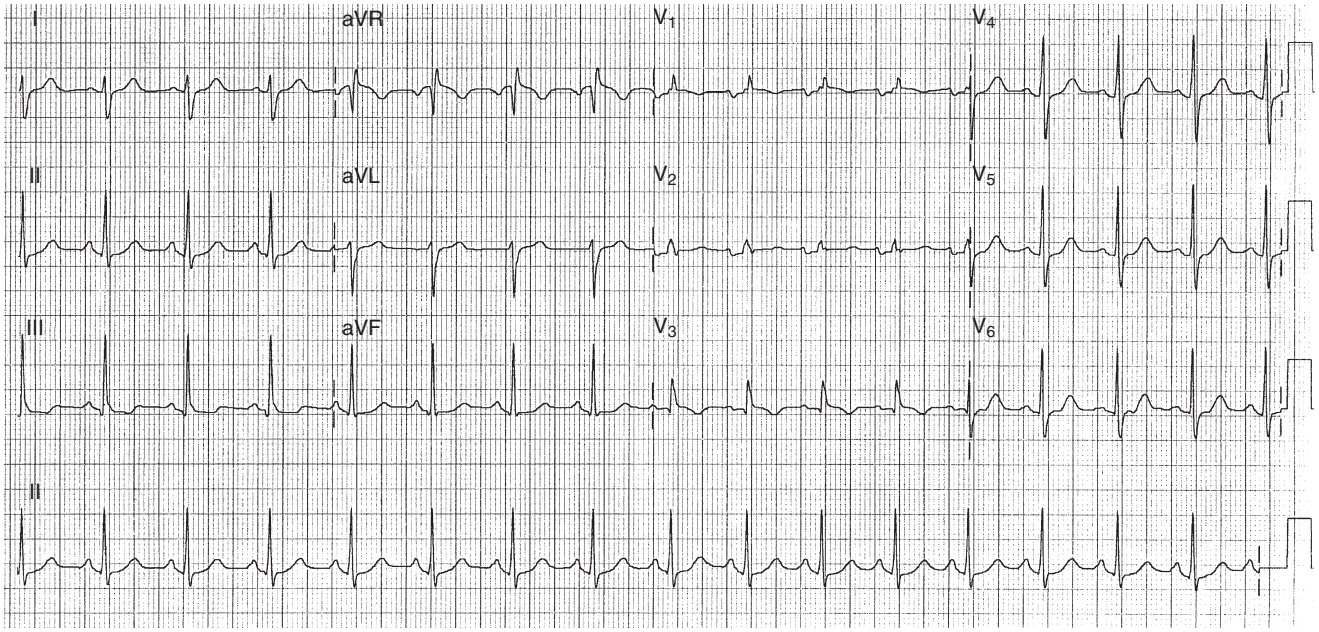


FIG. 1.56

163. A 51-year-old woman with discrete episodes of presyncope (Fig. 1.57)

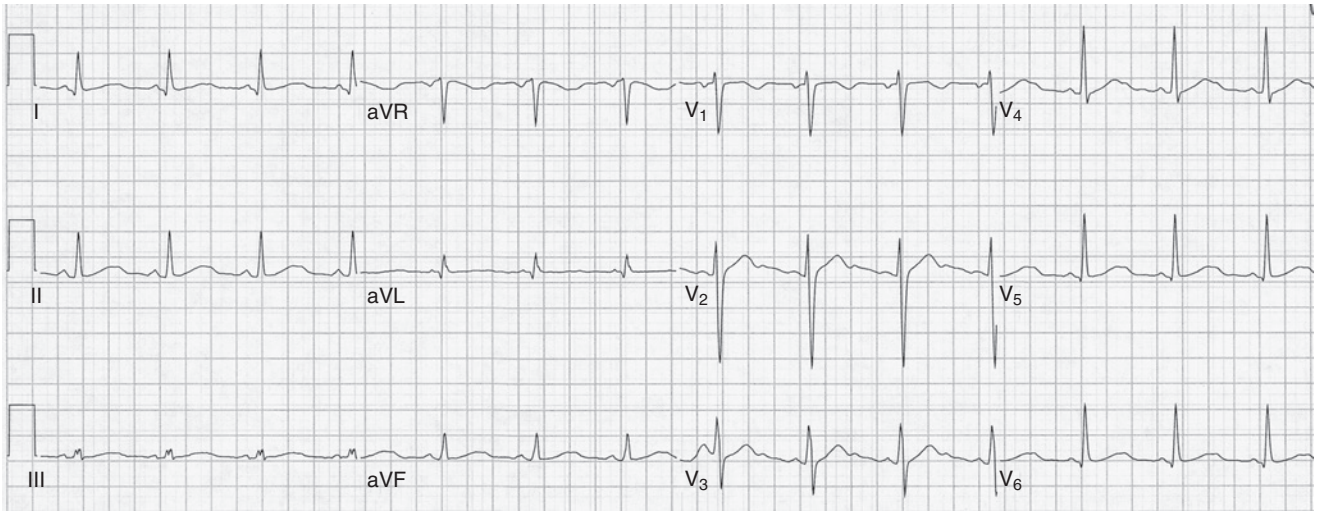


FIG. 1.57

164. A 72-year-old man with palpitations after coronary artery bypass surgery (Fig. 1.58)

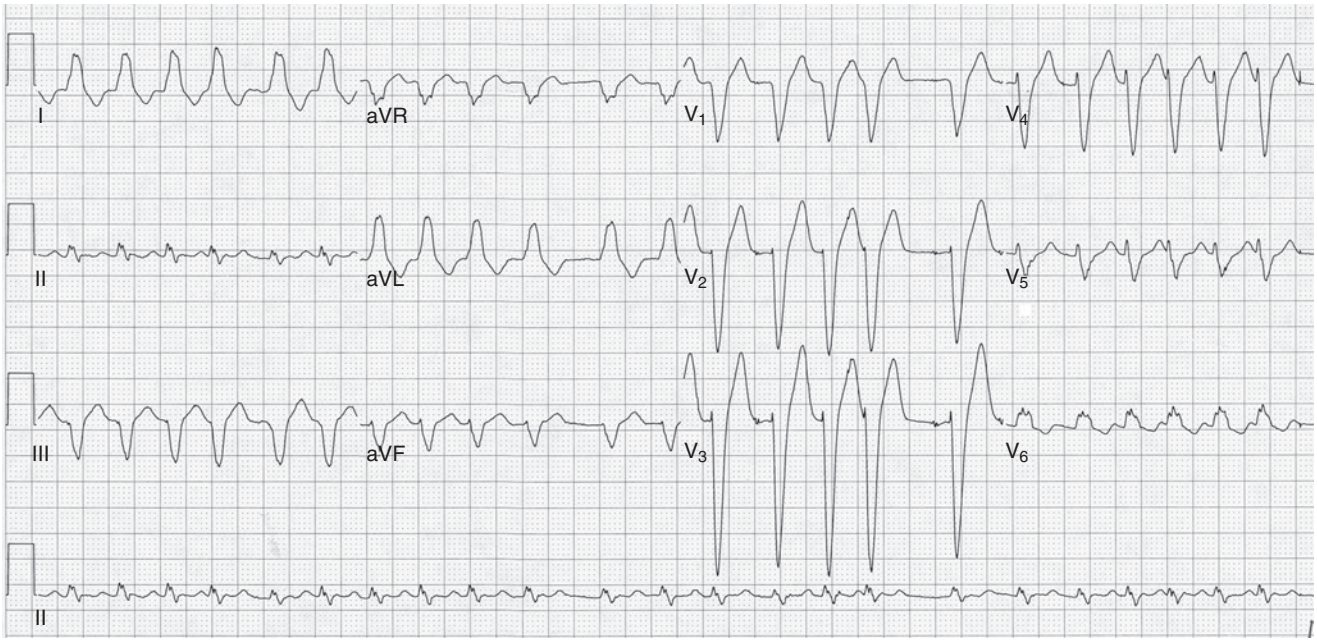


FIG. 1.58

165. A 78-year-old man with a long history of cigarette smoking and paroxysmal atrial fibrillation (Fig. 1.59)

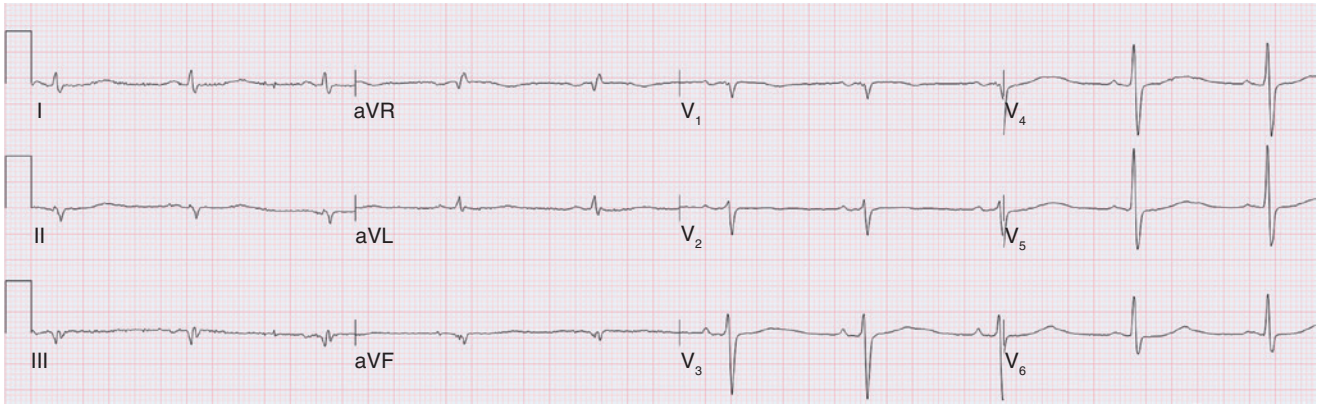


FIG. 1.59

166. A 69-year-old man with a history of dilated cardiomyopathy (Fig. 1.60)

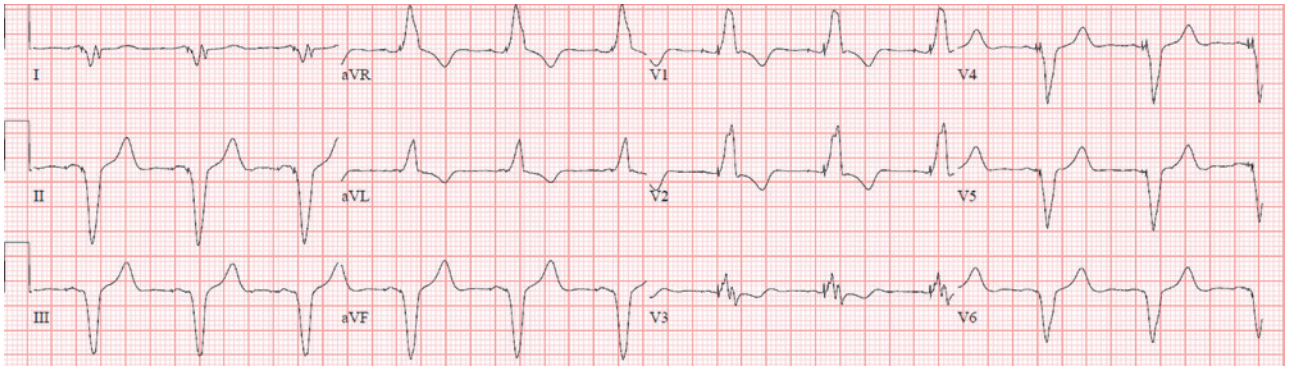


FIG. 1.60

167. An elderly nursing home resident with fatigue (Fig. 1.61)

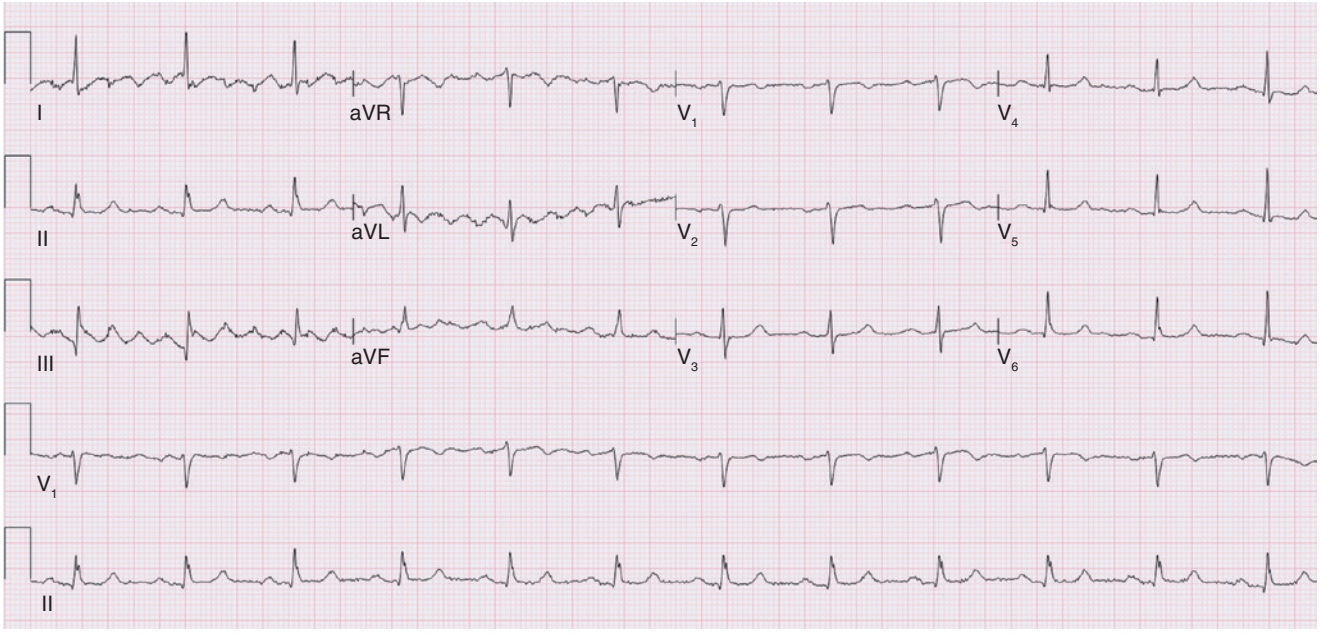


FIG. 1.61

SECTION I ANSWERS

(CHAPTERS 1 TO 20)

Fundamentals of Cardiovascular Disease; Genetics and Personalized Medicine; Evaluation of the Patient

ANSWER TO QUESTION 1

D (Braunwald, pp. 160–161)

The normal systolic blood pressure response during exercise is a progressive increase to a peak value between 160 and 200 mm Hg. The higher end of this range is more commonly observed in older patients; in general, black patients tend to have a higher systolic blood pressure response to exercise than white patients. A failure to increase systolic blood pressure to at least 120 mm Hg, or a decline in systolic blood pressure during exercise, is abnormal. Such exertional hypotension occurs in 3% to 9% of patients and is suggestive of underlying multivessel or left main coronary artery disease (CAD). Other causes of a decline in systolic blood pressure, or a failure to increase systolic blood pressure with exercise, include cardiomyopathy, vasovagal reactions, ventricular outflow obstruction, hypovolemia, arrhythmias, and prolonged vigorous exercise. Subjects who demonstrate hypotension in the *postexercise* period are much less likely to have advanced underlying CAD; about 3% of normal subjects younger than 55 years of age demonstrate such a response.

In normal subjects, diastolic blood pressure does not change significantly during exercise. A large change in diastolic blood pressure is uncommon and has not been shown to correlate with underlying CAD.

The age-related maximum predicted heart rate (MPHR) is estimated from the following formula:

$$\text{MPHR} = 220 - \text{age (in years)}$$

which in this patient would be 166 beats/min. The peak heart rate he achieved during the test was 152 beats/min, or 92% of the MPHR (i.e., 152/166 beats/min). An achieved heart rate of ≥85% MPHR is indicative of an adequate diagnostic workload.

Predictors of low prognostic coronary risk in his case include his very good functional capacity (having achieved stage IV of the Bruce protocol) and lack of cardiopulmonary symptoms or ST-segment changes during the test.

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ANSWER TO QUESTION 2

B (Braunwald, p. 91)

The normal second heart sound (S_2) consists of two parts, an earlier aortic component and a later pulmonic component. During inspiration, the increased filling of the right ventricle prolongs the ejection phase of the right side of the heart leading to *delayed* closure of the pulmonic valve. This is the predominant factor in normal inspiratory splitting of the S_2. Right bundle branch block delays right ventricular (RV) activation and ejection and is therefore associated with *widened* splitting of S_2. Conditions in which left ventricular activation is late, such as left bundle branch block or RV pacing, cause closure of the aortic valve to be delayed. In that setting, the pulmonic valve closure sound actually precedes that of the aortic valve. Then, during inspiration (and prolongation of RV ejection), the delayed closure of the pulmonic valve narrows the timing between the two sounds, a situation known as *paradoxical* splitting.

Fixed splitting of the S_2 is typical of an uncomplicated ostium secundum atrial septal defect. In this condition, closure of the pulmonic valve is delayed because of the increased flow through the right-sided cardiac chambers and an increase in pulmonary vascular capacitance, contributing to a widened split of S_2. On inspiration, augmentation of the systemic venous return is counterbalanced by a reciprocal decrease in the volume of the left-to-right shunt, such that RV filling and the timing of P_2 relative to A_2 do not change, resulting in the fixed splitting.

When valvular stenosis restricts opening of a cardiac valve, the decreased excursion of the leaflets *reduces* the intensity of the closure sound. Thus, in pulmonic stenosis, the pulmonic component of S_2 becomes softer.

ANSWER TO QUESTION 3

D (Braunwald, p. 26; Figs. 3.3–3.5)

In addition to accuracy and reliability, the performance of a diagnostic test depends on its ability to distinguish between the presence and absence of disease. Test performance depends on its sensitivity and specificity, as well as the

prevalence of disease in the population of patients to be studied or the pretest probability of disease in a particular patient. Sensitivity and specificity are characteristics of the diagnostic test that are not altered by disease prevalence or pretest probability. Sensitivity is the percentage of patients with disease who will be correctly identified by the test. Specificity is the percentage of patients without disease who will be correctly identified as disease free by the test. Positive predictive value is the probability that a positive test correctly identifies the presence of disease. Negative predictive value is the probability that a negative test correctly identifies the absence of disease. A perfect diagnostic test has a positive predictive value of 100% (no false-negative results) and a negative predictive value of 100% (no false-positive results).

For a diagnostic test with moderately high sensitivity and specificity, the test will perform best in a population of patients with an intermediate pretest probability of disease (patient D). In patients with a low pretest probability of disease (patients A and B), the positive predictive value of the test is low and there will be a large number of false-positive tests that may prompt unnecessary testing and procedures. In patients with an extremely high pretest probability of disease (patients C and E), the negative predictive value of the test is low and the possibility that a negative result represents a false negative is unacceptably high.

ANSWER TO QUESTION 4

C (Braunwald, pp. 92–93; Table 10.6; Fig. 10.8)

The term *continuous* applies to murmurs that begin in systole and continue without interruption into part or all of diastole. The murmur described here, that of a patent ductus arteriosus, is the classic continuous murmur, peaking in intensity just before or after S_2, then decreasing in intensity during diastole, sometimes disappearing before the subsequent first heart sound. Continuous murmurs may be congenital or acquired and can be caused by (1) an aortopulmonary shunt, such as patent ductus arteriosus; (2) an arteriovenous shunt, including arteriovenous fistulas, coronary artery fistulas, or rupture of an aortic sinus of Valsalva aneurysm into a right heart chamber; (3) constricted arterial vessels (e.g., a femoral arterial atherosclerotic stenosis); (4) turbulence in nonconstricted arteries (e.g., the "mammary souffle," an innocent flow murmur heard during late pregnancy and the puerperium over the lactating breast and augmented by light pressure with the stethoscope); or (5) venous murmurs, such as a cervical venous hum, an often "rough" sounding murmur present in healthy children and young adults. The cervical hum may be accentuated by deforming the internal jugular vein with rotation of the head. It is augmented during pregnancy and in disease states in which there is increased venous flow, such as thyrotoxicosis.

The combined murmurs of aortic stenosis and regurgitation have distinct systolic and diastolic components and do not constitute a continuous murmur.

ANSWER TO QUESTION 5

E (Braunwald, pp. 89–91; Fig. 10.5)

Reduced or unequal arterial pulsations may occur in the arms of patients with atherosclerosis affecting the subclavian arteries, aortic dissection, and uncommon arteritides such as Takayasu disease. In supravalvular aortic stenosis (AS), there may be selective streaming of the arterial jet toward the innominate artery and right arm, leading to higher pressures in that extremity. This is not the case, however, with subvalvular or valvular AS. Valvular AS leads to pulsus parvus et tardus, a slowly rising and weak pulse best appreciated by palpation of the carotid arteries. Coarctation of the aorta in adults usually involves the aorta distal to the origin of the left subclavian artery and leads to higher blood pressure in the upper extremities compared with the legs; the arm pulses and pressures are typically equal.

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ANSWER TO QUESTION 6

C (Braunwald, p. 219; Figs. 14.64 and 14.65)

This patient with metastatic breast cancer and a large pericardial effusion has clinical findings consistent with cardiac tamponade.[1] Tamponade physiology results when an accumulation of pericardial effusion causes equilibration of intrapericardial and intracardiac pressures.[2,3] In addition to the presence of an echo-free space surrounding the heart, characteristic echocardiographic and Doppler findings reflect the aberrant physiology of this disorder. Collapse of the right ventricle during early *diastole* occurs because the abnormally elevated pericardial pressure transiently exceeds right ventricular (RV) pressure at that phase of the cardiac cycle. Indentation of the right atrial wall during diastole is a more sensitive marker of increased pericardial pressure, but is less specific for tamponade physiology than RV collapse and tends to occur earlier in the course of hemodynamically significant pericardial effusion. Cardiac tamponade is associated with exaggerated ventricular interdependence, a phenomenon manifested at the bedside by pulsus paradoxus. The Doppler correlate of pulsus paradoxus is amplified respirophasic variation of flow across the right- and left-sided cardiac valves. This includes a prominent inspiratory decrease in flow velocity across the mitral and aortic valves (see the transmitral tracing in Fig. 1.62), whereas inspiration causes

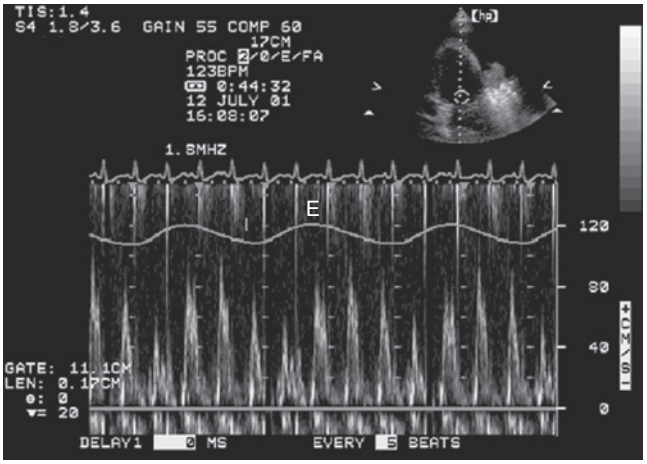

FIG. 1.62

a prominent reciprocal *increase* in flow velocity across the tricuspid and pulmonic valves.

A marked increase of the E/A ratio of the mitral valve inflow velocity is a finding typical of constrictive pericarditis, not cardiac tamponade.

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ANSWER TO QUESTION 7

D (Braunwald, pp. 88, 90)

Pulsus paradoxus is an exaggeration of the normal tendency for arterial pulse strength to fall with inspiration and can be measured easily and accurately at the bedside with a sphygmomanometer. A decline of more than 8 to 10 mm Hg with inspiration is considered abnormal and can be observed in a variety of conditions. Pulsus paradoxus is characteristic of patients with cardiac tamponade, is seen in approximately one-third of patients with chronic constrictive pericarditis, and is noted as well in patients with wide intrapleural pressure swings (e.g., bronchial asthma and emphysema), pulmonary embolism, pregnancy, extreme obesity, and hypovolemic shock.

Notably, aortic regurgitation augments left ventricular diastolic pressure and tends to prevent pulsus paradoxus even in the presence of tamponade.

The Kussmaul sign manifests as inappropriate augmentation of the jugular venous pressure during inspiration and implies the presence of constrictive pericarditis, not isolated cardiac tamponade.

ANSWER TO QUESTION 8

B (Braunwald, pp. 118, 136–138; Tables 12.1 and 12.9)

The clinical presentation is concerning for an acute coronary syndrome and rapid evaluation of the ECG is critical to detect whether an acute ST-segment elevation myocardial infarction (STEMI) is present, which would warrant prompt coronary revascularization. The ECG in this patient is not diagnostic for STEMI, with <1 mm of ST elevation in only one lead (III). However, the presence of ST depressions and a prominent R wave in the anterior precordial leads should raise suspicion for an acute ST elevation myocardial infarction in the *posterior* territory. Since standard leads are not placed on the patient's back, myocardial injury of the posterior wall is typically identified as mirror-image ECG findings in the opposite anatomic position, namely leads V_1–V_3. In this circumstance, posteriorly placed ECG leads (V_7–V_9) placed from the posterior axillary line to the left border of the spine would be helpful to evaluate for true posterior ST elevations.

Right-sided precordial leads are useful to detect right ventricular involvement in the setting of an inferior STEMI. Awaiting the results of cardiac biomarkers would delay care. Diagnostic tests should focus first on an acute coronary syndrome rather than pulmonary embolism, based on the presenting clinical symptoms.

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ANSWER TO QUESTION 9

C (Braunwald, Tables 8.1–8.3)

All drugs prescribed to achieve a particular clinical benefit also have the potential for toxicity. Many factors determine the likelihood of drug toxicity, including the pharmacokinetic and pharmacodynamic properties of the drug and its target, genetic variability in the patient's response to the drug, and drug-drug interactions.

Many medications are metabolized by isoforms of the cytochrome P-450 (CYP) enzyme system, which are expressed in the liver and other tissues. Ketoconazole, erythromycin, and clarithromycin (but not azithromycin) are examples of drugs that inhibit CYP3A4 and CYP3A5. Because these P-450 isoforms are responsible for metabolism of simvastatin, atorvastatin, and lovastatin, combined therapy with such inhibitors may increase the likelihood of myopathy due to these statins.[1,2] Pravastatin is not metabolized by the CYP3A system, and thus the risk of myopathy is not increased in the presence of CYP3A inhibitors.

St. John's wort induces activity of CYP3A and results in decreased cyclosporine levels.[3]

Sildenafil, a selective inhibitor of phosphodiesterase type 5 prescribed to treat erectile dysfunction, potentiates the vasodilatory effect of nitrates. Administration of nitrates within 24 hours of sildenafil use has been associated with profound hypotension.

Verapamil inhibits the P-glycoprotein-mediated efflux of digoxin into bile and urine and may contribute to digoxin toxicity.

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ANSWER TO QUESTION 10

D (Braunwald, p. 156; Table 13.1)

Treadmill exercise testing is a safe procedure with an associated mortality of <0.01% and risk of myocardial infarction of 0.04%.[1] The risk of a procedure-related complication is determined by the clinical characteristics of the patient to be studied. Patients with high-grade obstruction of the left ventricular outflow tract, such as those with hypertrophic obstructive cardiomyopathy or critical aortic stenosis, are at an increased risk of a procedural complication owing to the inability of cardiac output to compensate for peripheral vasodilatation during exercise. Patients with unstable angina should not be subjected to the high myocardial oxygen demands of exercise and should be referred

for coronary angiography instead. Acute myocarditis is associated with an increased risk of exercise-associated sudden death.

Despite the theoretical risk of aortic rupture due to increased wall stress, treadmill exercise testing may be safely performed in patients with an abdominal aortic aneurysm.[2] In contrast, aortic dissection is a contraindication to the stress of exercise testing.[3]

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ANSWER TO QUESTION 11

B (Braunwald, pp. 262–263, 266, 268; Table 16.1; Figs. 16.11 and 16.12)

The images show a fixed defect in the mid- and apical anterior wall segments with preserved wall motion and thickening as evident from the end-diastolic and end-systolic frames. These findings are most consistent with imaging artifact due to breast tissue attenuation.

Attenuation artifacts are a common source of error in single-photon emission computed tomography (SPECT). Regional wall motion and wall thickening should be assessed on the electrocardiographic-gated SPECT data in any region that shows a fixed perfusion defect. Although a transmural myocardial scar would be associated with reduced wall motion and wall thickening, attenuation artifact is more likely where there is a fixed perfusion defect with normal regional wall motion and wall thickening.

Thallium-201 is a lower-energy radiotracer that results in more attenuation artifacts than technetium-99m imaging, and hence would be an inferior choice in this case.

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ANSWER TO QUESTION 12

C (Braunwald, pp. 91–92; Figs. 10.4 and 10.8)

S_2 coincides with closure of the aortic and pulmonic valves and marks the onset of diastole at the bedside. Several abnormal heart sounds may follow S_2. The opening snap of mitral stenosis (MS) is a high-frequency sound that occurs shortly after S_2. It is generated when the superior bowing of the anterior mitral leaflet during systole rapidly reverses direction toward the left ventricle in early diastole, owing to the high left atrial (LA) pressure. The delay between the aortic component of S_2 and the opening snap corresponds to the left ventricular (LV) isovolumic relaxation time. As MS becomes more severe, this phase shortens because of the greater LA pressure, and the interval between S_2 and the opening snap decreases. Other sounds that occur shortly after S_2 are associated with the rapid filling phase of diastole. These include the third heart sound (S_3), which is a low-frequency sound thought to be caused by sudden limitation of LV expansion during brisk early diastolic filling. An S_3 is normal in children and young adults, but the presence of this sound beyond age 40 is abnormal and reflects flow into a dilated ventricle or an increased volume of flow in early diastole, as may occur in mitral regurgitation. A tumor "plop" may be auscultated when an atrial myxoma, attached to the interatrial septum by a long stalk, moves into and obstructs the mitral or tricuspid valve orifice during early diastole. In constrictive pericarditis, a pericardial "knock" may be heard during the rapid filling phase of early diastole as the high-pressure atria rapidly decompress into relatively noncompliant ventricles.

An ejection click is an early *systolic* sound that represents opening of an abnormal semilunar valve, characteristically a bicuspid aortic valve.

ANSWER TO QUESTION 13

D (Braunwald, pp. 161–163, 165–166)

Electrocardiographic changes during exertion in an asymptomatic patient must be interpreted in light of the pretest likelihood of coronary disease. An exercise-induced ST-segment abnormality is an independent predictor of future cardiac events in men with and without conventional risk factors for coronary disease, although the risk is greatest among the former. However, in over 5 years of follow-up, only one in four such patients will actually develop symptoms of cardiac disease, most commonly angina. Because the patient described in this question is asymptomatic and demonstrates good exercise capacity, there is no need for immediate aggressive intervention such as cardiac catheterization. Appropriate recommendations for this patient with asymptomatic coronary artery disease would include aggressive risk factor modification: smoking cessation, control of hypertension, the addition of aspirin, and statin therapy.

The distribution of ST-segment depressions during exercise testing correlates poorly with the location of coronary stenoses. Conversely, the location of ST-segment *elevations*, when present, does correlate well with the anatomic lesion causing ischemia.

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ANSWER TO QUESTION 14

C (Braunwald, pp. 126, 145; Fig. 12.44; pp. 164–165, 168, 172, 285)

Several clinical situations affect the ST segment and impair the diagnostic utility of the standard exercise ECG. These

include the presence of left bundle branch block (LBBB), left ventricular hypertrophy, ventricular preexcitation (Wolff-Parkinson-White syndrome), and digitalis therapy. In these situations, other aspects of the exercise test, such as exercise duration, presence or absence of symptoms, and abnormal blood pressure or heart rate responses, may still provide useful diagnostic information. However, in the presence of these baseline electrocardiographic abnormalities, concurrent imaging (e.g., nuclear scintigraphy or echocardiography) is frequently required when more specific diagnostic information is needed. In the case of LBBB, a vasodilator pharmacologic (e.g., adenosine or regadenoson) stress test with myocardial perfusion imaging helps to avoid artifactual septal perfusion defects compared with exercise protocols.

In patients with a low prior probability of significant coronary artery disease (CAD), such as a young woman without significant cardiac risk factors, the development of ST-segment depression on exercise testing is more often a nonspecific false-positive result than an indicator of previously undetected CAD.

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ANSWER TO QUESTION 15

D (Braunwald, pp. 350, 356; Table 19.1)

Diagnostic cardiac catheterization is a relatively safe procedure, with an overall risk of a major complication of 1%. Mortality rates related to the procedure depend on the population studied and range from 0.08% to 0.75%. The risk of myocardial infarction is approximately 0.05%, and neurologic complications occur in 0.03% to 0.2% of patients. The incidence of acute renal dysfunction in patients with baseline renal insufficiency can be most effectively decreased with intravenous saline administration before and after the procedure. The addition of mannitol or furosemide to saline infusion has been shown to *worsen* renal outcomes in patients receiving an intravenous contrast agent.

Nonionic low osmolar contrast agents reduce the likelihood of adverse hemodynamic and electrophysiologic reactions during angiography. They also reduce the incidence of contrast-induced nephropathy in patients with baseline renal insufficiency, with or without diabetes. Of note, in patients with normal renal function, there is no advantage of low osmolar agents over ionic agents in the prevention of nephrotoxicity.

Cardiac catheters are available in many sizes, shapes, and lengths. The outer diameter of the catheter is specified using French units (F), where 1 F is equal to 0.33 mm.

Patients with tilting-disc prosthetic aortic valves should not undergo retrograde left-sided heart catheterization because of the risk of catheter entrapment, occlusion of the valve, or possible dislodgement of the disc with embolization.

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ANSWER TO QUESTION 16

C (Braunwald, pp. 140–141; Fig. 12.37)

Proximal occlusion of a dominant right coronary artery (RCA) leads to infarction of the left ventricular (LV) inferior wall, but often also involves the posterior wall, the right ventricle, and portions of the conduction system, which are all supplied by branches of the RCA. ST-segment elevation in leads II, III, and aVF is the sine qua non of transmural infarction of the inferior wall. If the posterior wall is involved, ST-segment depression is usually evident in V_1 and V_2, reflecting a current of injury on the side of the heart opposite those leads (if unipolar leads were placed on the patient's back overlying the posterior wall, ST-segment elevation would be observed instead). Very proximal occlusion of the RCA is often accompanied by right ventricular (RV) infarction because the RV arterial branch arises near the origin of that vessel. If RV infarction is present, right-sided precordial electrocardiographic leads, particularly V_4R, often demonstrate ST-segment elevation as well (Fig. 1.63). Sinus bradycardia may occur, especially in inferior or posterior infarction. This arrhythmia, particularly when accompanied by hypotension, may arise from stimulation of cardiac vagal afferent fibers, which are prominent in the inferoposterior left ventricle. Sinus bradycardia may also be a vasovagal response to the severe chest pain in acute myocardial infarction or reflect ischemia of the sinoatrial artery, which arises from the RCA in 60% of the population. Another potential cause of bradycardia in this patient is the development of atrioventricular (AV) block because of either vagal stimulation or ischemia of the AV node. The AV node is supplied by the AV nodal artery, which arises from the RCA 85% of the time.

ANSWER TO QUESTION 17

C (Braunwald, pp. 178, 196; eFig. 14.2)

One of the most clinically important applications of Doppler technology is the estimation of pressure gradients across stenotic orifices or septal defects in the cardiovascular system. The Bernoulli equation relates the pressure difference across a narrowed area to the convective acceleration, flow acceleration, and viscous friction. By modifying the Bernoulli equation, a more clinically useful simplified formula is derived. The simplified Bernoulli equation states that the pressure difference across a flow-limiting orifice = $4V^2$, where V is the peak velocity distal to the obstruction. In this question, the patient's systolic blood pressure is 144 mm Hg, which,

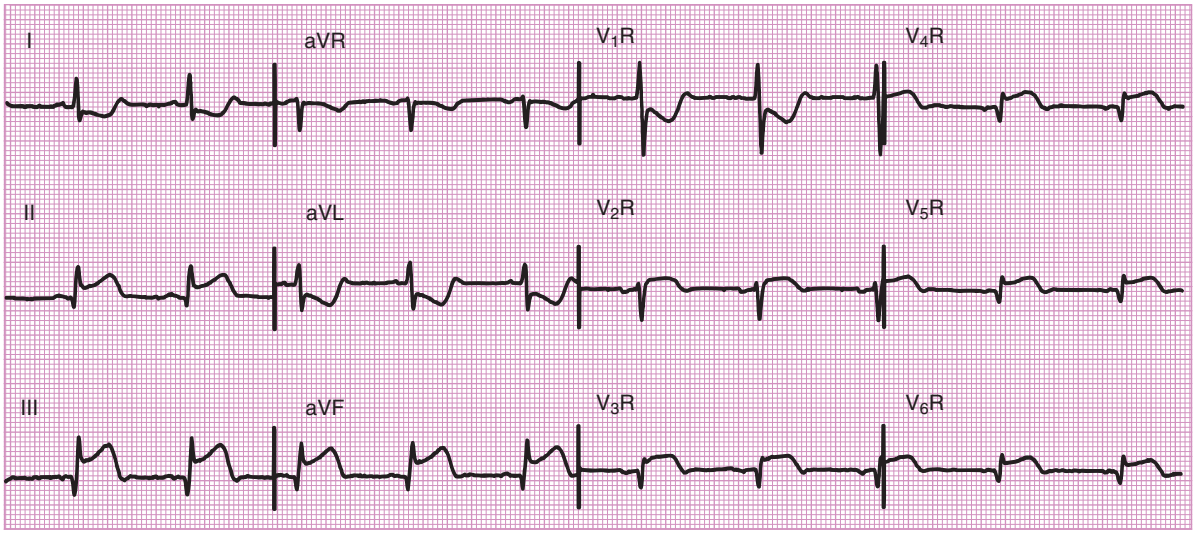

FIG. 1.63

in the absence of left ventricular (LV) outflow obstruction, is also the LV systolic pressure. If the ventricular septal defect (VSD) flow is 5.1 m/s, then using the modified Bernoulli equation, the pressure gradient across the VSD is $4 \times (5.1)^2 = 104$ mm Hg. The right ventricular systolic pressure can then be calculated by subtracting that gradient from the LV systolic pressure: 144 to 104, or 40 mm Hg. The transmitral flow velocity is not needed for this calculation.

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ANSWER TO QUESTION 18

C (Braunwald, pp. 92–93, 98–99; Table 10.6; p. 195; Fig. 14.30)

This patient's history is concerning for an undetected acute myocardial infarction (MI) 10 days earlier, including the prolonged chest "muscle ache," new Q waves in the inferior leads, and inferior wall motion abnormalities on echocardiography. The lack of acute intervention places the patient at risk for post-MI mechanical complications, including acute mitral regurgitation (MR) due to dysfunction or rupture of a papillary muscle, ventricular septal defect (VSD), and free wall rupture. The brief systolic murmur on examination in the setting of new-onset heart failure should raise suspicion for acute MR. Although chronic MR typically produces a holosystolic murmur at the apex, in acute MR there may only be a soft, early systolic murmur due to the rapid systolic increase in pressure in the unprepared and noncompliant left atrium (LA) that attenuates the pressure gradient between the left ventricle and LA responsible for the murmur.

The presumed recent right coronary artery occlusion in this patient would impair the blood supply to the posteromedial papillary muscle. Dysfunction or rupture of this papillary muscle often produces MR in an eccentric direction, which may be underestimated by transthoracic echocardiography, especially in this patient with poor acoustic windows. Given the high suspicion for papillary muscle involvement resulting in acute MR, a transesophageal echocardiogram would be appropriate, with cardiac surgical consultation for consideration of urgent valve repair. In most cases, coronary revascularization would be addressed with bypass grafting at the time of valve surgery rather than with percutaneous intervention.

A nuclear stress test would not address the urgent mechanical process in this patient's situation. The location of the murmur and echocardiographic findings are not consistent with a VSD such that urgent right heart catheterization alone would not be the best immediate approach.

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ANSWER TO QUESTION 19

D (Braunwald, pp. 146–147; Figs. 12.45 and 12.46)

Many electrolyte disturbances result in characteristic electrocardiographic manifestations. Decreased extracellular calcium in hypocalcemia prolongs phase 2 of the action potential (AP), thereby lengthening the AP duration and the QT interval. The long QT interval in hypocalcemia is characteristically flat (i.e., isoelectric), without the concave configuration of many drug-induced prolonged QT states. *Increased* extracellular calcium shortens the ventricular AP and the duration of the QT interval. The appearance of a J wave (also known as an Osborn wave—see arrow in Fig. 1.64), an extra deflection at the junction of the QRS complex and the ST segment that is typically observed in severe hypothermia, has been reported with severe *hyper*calcemia.[1]

Hyperkalemia causes a specific sequence of electrocardiographic changes depending on its severity. The earliest manifestation is narrow, peaked T waves. The QT interval is usually decreased at that time because of shortened AP duration. Progressive hyperkalemia reduces the resting membrane potentials in both the atria and ventricles, thus

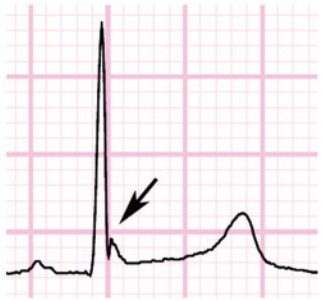

FIG. 1.64

inactivating sodium channels. The net result is to slow depolarization and reduce AP conduction velocity. The ECG shows widening of the QRS complex with a decrease in P wave amplitude. PR-segment prolongation may also occur. Very marked hyperkalemia leads to slow, undulating ventricular flutter (a "sine wave" appearance) followed by eventual asystole. Hypokalemia, in contrast, manifests primarily as ST-segment depressions with flattened T waves and U wave prominence. Because of prolongation of the QT interval, there is a propensity for polymorphic ventricular tachycardia (torsades de pointes).

The effects of magnesium on the surface ECG are not as well characterized. Magnesium deficiency may predispose to prolongation of the QT interval, primarily as a result of a prolonged U wave (QU interval), and *polymorphic* ventricular tachycardia.

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ANSWER TO QUESTION 20

E (Braunwald, pp. 199, 229; eFig. 14.27; pp. 293, 313, 1594–1595; Fig. 77.11)

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The lungs are affected in >90% of patients. Autopsy studies demonstrate cardiac involvement in at least 25% of patients who have pulmonary sarcoid. The three principal manifestations of cardiac sarcoidosis are conduction abnormalities, ventricular arrhythmias, and/or ventricular dysfunction. Several imaging modalities are useful in the diagnosis of cardiac sarcoidosis. Although echocardiography may show no abnormalities in clinically silent disease, systolic and/or diastolic ventricular dysfunction can be visualized in patients with active sarcoidosis. Discrete regional wall motion abnormalities typically appear in *non-coronary* distributions.

Cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) is sensitive for identifying abnormalities in sarcoidosis. LGE is usually patchy and nontransmural, with *sparing* of the endocardial border. LGE most commonly occurs in the basal septum and lateral wall and/or mid-myocardium. CMR is helpful in the assessment of clinically silent disease, as it can identify small regions of LGE, even in patients with normal systolic function. Of note, CMR cannot distinguish regions of active inflammation from permanent scar.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) which reveals regions of inflammation in active disease, is complementary to CMR in the diagnosis of cardiac sarcoidosis and in the monitoring of response to therapy. Focal FDG PET uptake identifies areas of active inflammation typical of active cardiac sarcoidosis; in distinction, areas of scarring without active inflammation do not show uptake by this technique.

Although angiotensin-converting enzyme levels are elevated in 60% of patients with sarcoidosis, the test has both low sensitivity and specificity for identifying the condition.

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ANSWER TO QUESTION 21

C (Braunwald, p. 135; Table 12.8)

The underlying rhythm is atrial fibrillation. The Ashman phenomenon (as exemplified by the fifth QRS complex in the tracing) represents conduction aberrancy caused by changes in the preceding cycle length. Because the duration of the refractory period is a function of the immediate preceding cycle length, the longer the preceding cycle, the longer the ensuing refractory period and the more likely that the next impulse will be conducted with delay. Normally the length of the refractory periods of the conduction system components are as follows: right bundle branch > left bundle branch = atrioventricular node ≫ His bundle. Therefore, it would be unusual for the bundle of His to be the site of conduction delay and, as is commonly the case, the aberrant beat on this tracing demonstrates right bundle branch block morphology in lead V_1.

ANSWER TO QUESTION 22

C (Braunwald, pp. 92–93; Table 10.6)

Innocent (normal) systolic murmurs are related to intracardiac flow rates and are usually loudest in midsystole. They may be caused by normal vibrations of the pulmonary leaflets, by exaggeration of normal ejection vibrations within the pulmonary artery, or may be associated with sclerosis at the base of the aortic valve leaflets in the absence of significant valvular stenosis. The mammary souffle, heard over the breasts of normal women in late pregnancy or during lactation, may also be midsystolic in timing or continuous. Careful auscultation usually reveals a time delay between S_1 and onset of this murmur.

ANSWER TO QUESTION 23

D (Braunwald, pp. 87–88; Figs. 10.3 and 10.4)

A great deal of information about right-sided heart hemodynamics can be ascertained from the jugular venous pressure waveforms. The *a* wave results from venous distention due to right atrial contraction; the *x* descent reflects atrial relaxation and downward descent of the base of the right atrium (RA) during right ventricular (RV) systole. The *c* wave is an inconstant positive deflection in the jugular venous pulse that interrupts the *x* descent and corresponds to ventricular contraction. The *v* wave results from right

atrial filling during ventricular systole when the tricuspid valve is closed, and the *y* descent occurs after the tricuspid valve opens and right atrial pressure declines. It is easier for an observer to see the *x* and *y* descents than the positive pressure waves (*a, c,* and *v* waves) in the neck because the former produce larger excursions. An elevated jugular venous pressure reflects increased right atrial pressure. During inspiration, the jugular venous pressure normally declines as intrathoracic pressure becomes more negative. The Kussmaul sign is a paradoxical rise in the height of the venous pressure during inspiration. It reflects an inability of the right-sided chambers to accept additional volume, typical of constrictive pericarditis, but may also be observed in patients with right-sided heart failure, severe cor pulmonale, or tricuspid stenosis.

The *a* wave becomes more prominent in conditions that increase the resistance to right atrial contraction, such as RV hypertrophy, pulmonary hypertension, or tricuspid stenosis. Amplified "cannon" *a* waves are evident during any situation that causes atrioventricular dissociation, because the RA intermittently contracts against a closed tricuspid valve.

In constrictive pericarditis, the *y* descent is rapid and deep because the very earliest phase of diastolic RV filling is unimpeded. In contrast, in cardiac tamponade, the *y* descent is blunted and it is the *x* descent that is more prominent.

ANSWER TO QUESTION 24

D (Braunwald, p. 360; Fig. 19.9; eFig. 19.11)

There is no completely accurate method for measuring cardiac output in the cardiac catheterization laboratory. Two commonly used methods are the thermodilution and the Fick techniques. The former involves injection of a bolus of fluid (i.e., saline or dextrose) into the proximal port of a right-sided balloon flotation (e.g., Swan-Ganz) catheter, after which alterations in temperature are measured at the distal end of the catheter. The change in the temperature over time is then plotted to derive the cardiac output, which is *inversely* related to the area under the thermodilution curve (Fig. 1.65). In low cardiac output states, there is a larger area under the curve owing to the longer time required for the temperature curve to return to its baseline. However, this technique tends to *overestimate* cardiac output in the setting of low output states, because the dissipation of the cooler temperature to the surrounding cardiac structures results in a reduction in the total area under the curve. In patients with severe tricuspid regurgitation, the back-and-forth flow across the tricuspid valve also creates significant error in measurement, producing a falsely low cardiac output by this technique.

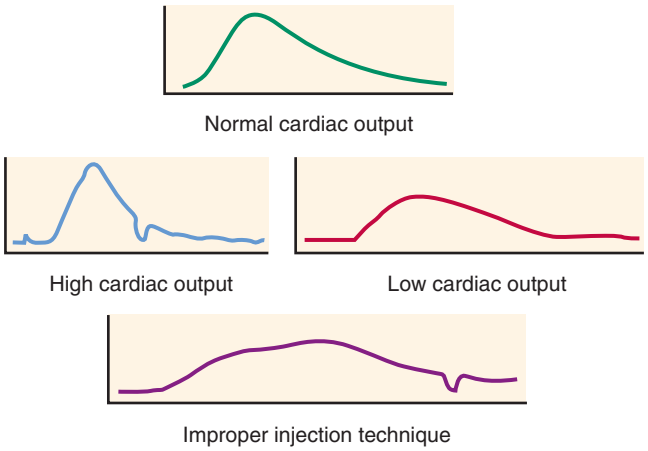

FIG. 1.65

The Fick technique is based on the principle that cardiac output is equal to the oxygen consumption divided by the difference in oxygen content between arterial and mixed venous blood. That is,

$$\text{Cardiac output} = \frac{\text{O}_2\ \text{Consumption}}{\text{A} - \text{VO}_2\ \text{Difference}}$$

The Fick technique is more accurate than thermodilution in patients with low cardiac outputs; however, its main limitation is in measuring true oxygen consumption in a steady state. Many laboratories use an "assumed" oxygen consumption by considering the patient's age, gender, and body surface area. Inaccuracy in the oxygen consumption measurement can result in substantial variability in reported cardiac outputs.

Systemic vascular resistance (SVR) is derived by dividing the difference between the mean aortic and right atrial (RA) pressures by the systemic cardiac output (and then multiplying by a constant to convert to the commonly used units of dynes·sec·cm^{-5}):

$$\text{SVR} = 80 \times \frac{\text{Mean Aortic Pressure} - \text{Mean RA Pressure}}{\text{Systemic cardiac output}}$$

The pulmonary vascular resistance (PVR) is obtained by dividing the difference between the mean pulmonary artery (PA) and left atrial (LA) pressures by the pulmonic cardiac output (then multiplying by the same constant). The pulmonary capillary wedge (PCW) pressure is commonly used as a surrogate for LA pressure:

$$\text{PVR} = 80 \times \frac{\text{Mean PA Pressure} - \text{Mean LA (or PCW) Pressure}}{\text{Pulmonic cardiac output}}$$

In the absence of intracardiac shunts, the systemic and pulmonic cardiac outputs should be the same.

ANSWER TO QUESTION 25

C (Braunwald, pp. 186–188; Fig. 14.18; eTable 14.1; Table 14.4)

Pulsed Doppler interrogation of mitral valve inflow is useful in identifying disorders of left ventricular (LV) diastolic function. In normal adults, the early (E wave) velocity exceeds the late (A wave) velocity such that the normal E/A ratio is >1.2. The figure accompanying this question illustrates an abnormal pattern of mitral inflow, with an E/A ratio <1.0. Although this pattern may be present in patients who have documented abnormalities of LV relaxation, it can also occur as a result of normal aging.[1] In fact, most people older than age 70 have an E/A ratio <1.0. In addition, the pattern of diastolic mitral inflow is load dependent. If a patient with the illustrated pattern of impaired relaxation were administered intravenous volume, the mitral inflow pattern could change to the "pseudonormalized" form, with an E/A ratio >1.0, without any alteration in the intrinsic relaxation properties of the

ventricle. Caution should thus be used when inferring a diastolic or relaxation abnormality from the mitral inflow pattern. Although none of the available echocardiographic indices of diastolic function is infallible, and even stepwise approaches using the mitral inflow pattern, Doppler tissue imaging, and assessment of pulmonary venous inflow can result in internally inconsistent results,[2] echocardiographic measures of diastolic function nonetheless provide clinically important diagnostic and prognostic information.[3]

Constrictive pericarditis and restrictive cardiomyopathy are clinical situations in which the bulk of ventricular filling occurs in early diastole. In these conditions there is a high E/A ratio, often >2.0. Hyperthyroidism and hemorrhage each result in hyperdynamic states in which diastolic relaxation is enhanced, such that reversal of the E/A ratio would be unusual.

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ANSWER TO QUESTION 26

D (Braunwald, pp. 206–207; Figs. 14.36–14.38)

The figure accompanying this question displays continuous Doppler interrogation of transmitral valvular flow obtained from the apical four-chamber transducer position. During diastole, the deceleration of transmitral inflow is prolonged, consistent with a persistent pressure gradient between the left atrium and left ventricle (i.e., mitral stenosis [MS]). In systole, a faint signal of mitral regurgitation (MR) is seen as a downward velocity spectrum. To determine the extent of MR noninvasively, simultaneous two-dimensional echocardiography and color Doppler interrogation would be required. However, the presented Doppler spectrum of mitral inflow is sufficient to determine the severity of MS, including the transmitral pressure gradient and the valve area, as described below.

The mitral valve area can be calculated noninvasively by three distinct noninvasive echo-Doppler methods. First, if an adequate two-dimensional short-axis image can be obtained in diastole, the valve orifice can be traced and the valve area measured directly using planimetry. The second method (which can be applied to the provided figure) utilizes the Doppler pressure half-time (PHT), which calculates the time in milliseconds required for the diastolic transmitral pressure gradient to decline to one-half of its peak value. Because of the relationship between velocity and pressure, this requires determining the time it takes for the peak diastolic velocity to fall to the peak velocity divided by the square root of 2. Most modern echocardiographic machines calculate the PHT automatically once the Doppler profile is traced on the screen, using the following equation:

$$\text{Mitral valve area} = 220 \div \text{PHT}$$

This relationship becomes less accurate when there is marked MR or aortic regurgitation, which interferes with the measured pressure gradient across the mitral valve. The third method to calculate the mitral valve area utilizes the continuity equation, which is based on the principle that the volume rate of flow through the heart is constant.

The cause of mitral stenosis (MS) in the vast majority of adults is rheumatic heart disease. Occasionally, other etiologies can be identified, such as congenital abnormalities of the valve or heavy calcification that restricts transvalvular flow. The transvalvular Doppler pattern cannot distinguish the etiology of MS, but two-dimensional echocardiographic imaging is usually diagnostic in this regard.

ANSWER TO QUESTION 27

B (Braunwald, pp. 88, 178, 206; eFig. 14.2; Fig. 14.76)

The McConnell sign is a distinct regional wall motion abnormality associated with acute pulmonary embolism in which the right ventricular (RV) *midwall* is dyskinetic, with sparing of the apex. The Kussmaul sign refers to a rise in jugular venous pressure (or its failure to decrease) with inspiration, which occurs in states of reduced RV compliance and right-sided volume overload. It is typically associated with constrictive pericarditis, but is also seen in pulmonary embolism, RV infarction, and restrictive cardiomyopathy.

The general calculation of a pressure gradient across a cardiac valve is determined by the simplified Bernoulli equation:

$$\Delta \text{ Pressure} = 4 \times \text{velocity}^2$$

In this patient, the pressure gradient between the RV and right atrium (RA) is 36 mm Hg (4×3^2). The RV pressure can then be calculated as this pressure gradient plus the RA pressure. The right atrial pressure can be estimated from the echocardiographic diameter of the inferior vena cava (IVC) and its respiratory variation (see Braunwald, Table 14.7). In this case, the IVC diameter is normal (<2.1 cm), but there is <50% inspiratory collapse, consistent with a right atrial pressure of 5 to 10 mm Hg. With a right atrial pressure of 5 to 10 mm Hg and a pressure gradient of 36 mm Hg between the RA and RV, the RV systolic pressure can then be estimated at 41 to 46 mm Hg. In the absence of pulmonic stenosis, the pulmonary artery (PA) systolic pressure is equal to the RV systolic pressure, such that the estimated PA systolic pressure in this patient is also 41 to 46 mm Hg.

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ANSWER TO QUESTION 28

C (Braunwald, pp. 154–155, 160; Figs. 13.1 and 13.2)

With normal aerobic exercise, the heart rate and systolic blood pressure both rise. Diastolic blood pressure, however, typically does not change significantly. During *isometric* exercise, both systolic and diastolic blood pressures may increase. In normal individuals, the cardiac output rises fourfold to sixfold above basal levels during maximum exercise. The physiologic response to physical activity often becomes attenuated as an individual ages. The heart rate response to exercise is blunted in the elderly, and the predicted maximum heart rate decreases with age (estimated by 220 minus age in years). This is due in part to decreased beta-adrenergic responsiveness in older individuals. The average stroke volume is preserved in normal older adults, and the observed decline in maximum cardiac output is due primarily to the blunted heart rate response. Maximal aerobic capacity ($\dot{V}O_2max$) declines 8% to 10% per decade in sedentary individuals, such that there is a 50% fall between ages 30 and 80. Thus, the exercise protocol chosen to test elderly individuals should take into account predicted limitations in exertional capacity.

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ANSWER TO QUESTION 29

D (Braunwald, pp. 91–93; Figs. 10.7 and 10.9; Tables 10.6 and 10.7)

The intensity of a heart murmur is related to the pressure gradient and rate of flow across the responsible orifice. Physiologic changes or bedside maneuvers that alter the driving pressure gradient or the rate of flow lead to audible changes in murmur intensity. In acute mitral regurgitation (MR), flow is directed backward from the left ventricle into a relatively noncompliant left atrium (LA), leading to a rapid increase in left atrial pressure during systole. Because this abolishes the pressure gradient between the left ventricle and LA in late systole, the murmur of acute MR is often present only in *early* systole. Similarly, in acute aortic regurgitation, the left ventricular (LV) diastolic pressure rises rapidly, leading to cessation of the diastolic murmur in mid- to late diastole, as LV and aortic pressures equalize. In patients with mitral valve prolapse, the auscultatory findings vary prominently with physiologic alterations. The valve physically prolapses into the LA, and the associated click/murmur commences when the reduction of LV volume during contraction reaches the point at which the mitral leaflets fail to coapt. Maneuvers that decrease LV volume, such as standing from a squatting position, cause the valve prolapse, the click, and the murmur to all occur earlier in systole. In mitral stenosis, the diastolic rumbling murmur increases with any maneuver that augments transvalvular flow and decreases in situations that reduce transmitral flow, such as the strain phase of the Valsalva maneuver.

The systolic murmurs of aortic valvular stenosis and MR are sometimes difficult to distinguish. However, the intensity of aortic stenosis varies from beat to beat when the duration of diastole is not constant, as in atrial fibrillation or after a premature contraction. The murmur of MR is not affected in this manner, because the changes in driving pressure between the left ventricle and the LA are smaller.

ANSWER TO QUESTION 30

C (Braunwald, pp. 222–225; Figs. 14.70 and 14.81; p. 357)

This computed tomogram demonstrates a type A aortic dissection involving the ascending (large arrow, A) and descending (small arrows, A) thoracic aorta. In addition, the dissection extends into the aortic arch vessels (large arrows, B), the left common carotid artery (small arrow, B), and the innominate artery (arrowhead, B). Dissection membranes are clearly visualized in the involved segments. Acute aortic dissection is often lethal; survival depends on prompt clinical recognition and definitive imaging of the aorta. Type A aortic dissections involve the ascending aorta. Type B aortic dissections do not involve the ascending aorta. The most common symptom of acute aortic dissection is chest or back pain, reported in up to 96% of patients. The pain is typically sudden in onset and severe, often with a "ripping" or "tearing" quality. The patient discussed in this question may have also presented with pulse deficits or neurologic symptoms, given the branch artery involvement demonstrated on the computed tomogram. Computed tomography (CT) and magnetic resonance imaging (MRI) have outstanding sensitivity for the diagnosis of aortic dissection, on the order of 96% to 100%. Transesophageal echocardiography is unnecessary in this case, but it is also an excellent imaging modality for the diagnosis of aortic dissection (sensitivity of ~98% and specificity of 94% to 97%), with the caveat that visualization of the distal ascending aorta and proximal aortic arch may be limited by interference by the trachea and bronchus. Conversely, the sensitivity of standard transthoracic echocardiography for aortic dissection is relatively poor (59% to 85%). Aortography is rarely necessary and has inferior diagnostic capabilities for aortic dissection compared with CT and MRI. Because of its rapid availability in most emergency departments, CT is the initial diagnostic test of choice for suspected aortic dissection in many centers.

All patients with acute aortic dissection should receive immediate parenteral therapy for hypertension, typically an intravenous beta blocker to additionally provide rate control and reduce aortic wall stress, after which vasodilators can be added as needed to further control blood pressure. Patients with acute type A aortic dissection should be referred for emergent surgery. Surgery is also the treatment of choice for patients with acute type B aortic dissection complicated by vital organ compromise, rupture or impending aortic rupture, retrograde extension into the ascending aorta, or Marfan syndrome. Patients with uncomplicated acute type B aortic dissections can typically be safely managed initially with parenteral agents for blood pressure control, in-hospital monitoring, and serial imaging of the aorta to assess for retrograde extension or other indications for surgery, and then conversion to oral antihypertensive therapy.

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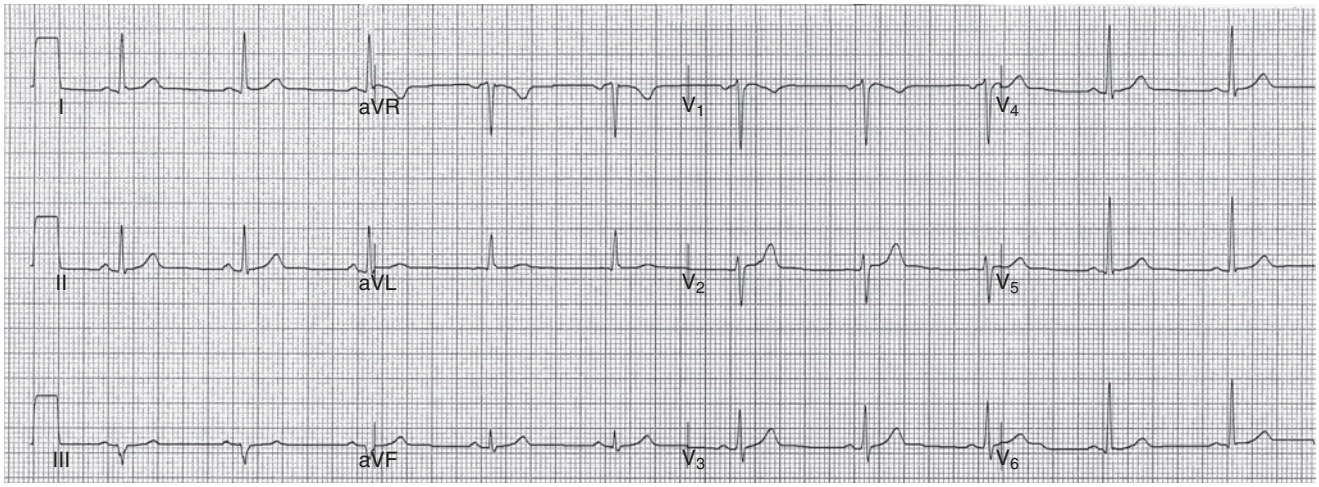

FIG. 1.66

ANSWER TO QUESTION 31

D (Braunwald, pp. 161–163; Fig. 13.14)

ST-segment displacement is the primary means by which ischemia is detected during standard exercise testing. ST-segment depression is the most common form of abnormal response, whereas ST-segment elevation in a lead without pathologic Q waves is found only in about 1% of patients with obstructive coronary disease. J point depressions with upsloping ST segments are a normal finding during exercise. Patients with ischemic heart disease usually display true ST-segment depression with a horizontal or downsloping configuration. The correct isoelectric reference point for the ST segment is the TP segment. However, because this segment is shortened during exercise, the PQ junction is typically chosen as the reference point instead. In normal individuals who have an early repolarization pattern on the resting ECG, the chronically elevated J point usually returns to baseline during exercise. In this setting, any ST-segment deviations during exercise should be referenced to the PQ junction, not to the original J point position. Ischemic ST-segment depressions may develop only during exercise or may occur during exercise and persist into recovery. In 10% of patients, ischemic changes are observed only during the recovery phase. The onset of ST-segment changes during recovery occurs more commonly in asymptomatic individuals compared with those with symptomatic coronary artery disease. An abnormal ST-segment response is considered to be 0.10 mV (1 mm) or greater of J point depression, with a flat or downsloping ST segment that remains depressed to 0.10 mV or greater at 80 milliseconds after the J point.

Although ST-segment *elevation* is helpful to localize ischemia to particular coronary territories, the location of ST-segment *depression* during exercise does not accurately predict the responsible coronary anatomy.

ANSWER TO QUESTION 32

C (Braunwald, pp. 118–121; Figs. 12.1–12.4; Table 12.1)

This ECG demonstrates extreme right-axis deviation of the QRS complex and an abnormally rightward P wave axis (the P waves are inverted in leads I and aVL). Although this pattern might suggest dextrocardia with situs inversus, the normal progression of the R waves in the precordial leads is not consistent with that diagnosis (in dextrocardia, R wave progression would be reversed). Rather, the tracing is most consistent with right and left arm lead reversal, a common error of lead placement. In this situation, the recordings from leads aVL and aVR are interchanged and the complexes in lead I are the mirror image of what would be expected in that lead had the limb leads been placed correctly. Fig. 1.66 shows the ECG from the same patient with the leads placed correctly.

ANSWER TO QUESTION 33

D (Braunwald, pp. 154–155, 157–159; Figs. 13.1 and 13.2; Tables 13.3, 13.6, 13.7)

An understanding of the differences between stress testing protocols is required to choose the appropriate study for a specific patient. Six to 12 minutes of progressive exercise, leading to a level of maximal oxygen consumption, provides the greatest diagnostic and prognostic information. An optimal exercise study is characterized by an appropriate rise in both heart rate and systolic blood pressure. The diastolic blood pressure may fall, rise, or stay the same, depending on the protocol used and the workload achieved. When systolic blood pressure falls during exercise, it is often indicative of severe underlying coronary artery disease (typically three-vessel or left main disease) or severe left ventricular (LV) contractile dysfunction. Other potential causes include LV outflow obstruction (e.g., advanced aortic stenosis or hypertrophic obstructive cardiomyopathy) and hypovolemia.

Treadmill protocols are the most commonly used form of stress testing and are characterized by achievement of high maximum heart rates and oxygen consumption. Bicycle protocols are sometimes better tolerated by deconditioned patients because of the ramped nature of the test and achieve maximum heart rates similar to, but maximal oxygen consumption less than, treadmill tests. Arm crank ergometry can be useful for patients who cannot perform leg exercise, such as patients with severe peripheral arterial disease. Arm

protocols typically produce a higher heart rate and blood pressure response for a given workload than leg exercise protocols; however, the maximum heart rate achieved during arm ergometry testing is typically only about 70% of that achieved during treadmill or bicycle tests. Maximal oxygen consumption and minute ventilation are also lower for arm cycling than for leg exercise. The standard treadmill Bruce protocol is the most commonly used, and a large diagnostic and prognostic database has been accumulated with this regimen. The primary limitation of the Bruce protocol is the large increase in oxygen consumption from one stage to the next, which limits the utility of this protocol in elderly, deconditioned, or ill individuals. In such patients a more gradual regimen, such as the Naughton or Weber protocol, using 1- to 2-minute stages with 1 metabolic equivalent (MET) increases per stage, or a ramped bicycle protocol with small increases in workload each minute, is typically better tolerated.

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ANSWER TO QUESTION 34

D (Braunwald, pp. 83–85, 95–97)

The development of new exertional dyspnea in a patient with cardiac disease may herald progression or a change in the clinical syndrome. Each of the patients in this question has a known, previously asymptomatic cardiac lesion and has recently developed shortness of breath with physical activities. A congenitally bicuspid aortic valve often becomes progressively stenotic with age, and symptoms associated with aortic stenosis (angina, syncope, heart failure) frequently develop in mid- to late adulthood. A patient with a history of myocardial infarction who presents with new dyspnea without recurrent angina is likely to have developed left ventricular (LV) dysfunction due to ventricular remodeling. Other potential contributing factors include dyspnea as an anginal equivalent or a superimposed arrhythmia. New irregular palpitations in a patient with a history of rheumatic heart disease may indicate superimposed atrial fibrillation. This is a poorly tolerated complication in patients with mitral stenosis because of the abbreviated LV diastolic filling period during rapid heart rates.

Most young adults with an uncomplicated ostium secundum atrial septal defect (ASD) have normal exercise tolerance. Previously asymptomatic ostium secundum ASDs, in the absence of pulmonary hypertension, are typically well tolerated during pregnancy. Although problems may arise because of paradoxical embolism in the setting of lower extremity venous thrombosis, symptoms of ventricular dysfunction or reversed shunting across the ASD are rare. Exertional dyspnea in the third trimester of pregnancy in such patients is more likely the result of impaired diaphragmatic excursion from the increasing size of the uterus.

The most common causes of morbidity and mortality in trisomy 21 (Down syndrome) are congenital heart defects, which are present in 40% to 50% of patients. The most characteristic abnormalities are endocardial cushion defects, such as ostium primum ASD and "cleft" mitral valve with mitral regurgitation. Approximately one-third of the congenital heart lesions are complex defects that are detected early, but simpler cardiac anomalies may remain unnoticed into adulthood. The onset of exertional dyspnea in a patient with trisomy 21 warrants evaluation for such lesions.

ANSWER TO QUESTION 35

C (Braunwald, pp. 136–143; Figs. 12.31, 12.32, 12.38–12.40)

Early recognition of myocardial infarction (MI) is critical to take full advantage of emergent percutaneous revascularization or fibrinolytic therapy. The earliest electrocardiographic finding in acute ST-elevation MI is ST-segment elevation and hyperacute (tall, positive) T waves overlying the affected region of myocardium. Reciprocal ST-segment depressions are often noted in leads overlying the opposite cardiac territories. In the absence of reperfusion therapy, T wave inversions become evident in the leads overlying the region of infarction over a matter of hours, accompanied by Q wave development. In the case of an anterior Q wave MI, the early ST-segment deflections become apparent in the anterior precordial leads, whereas ST-segment depressions are often present in the inferior leads. Acute infarction affecting portions of the conduction system may produce a new bundle branch block. The presence of a new right bundle branch block (RBBB) does not obscure the diagnosis of an acute MI, because the ST-segment elevations in the precordium should remain interpretable. However, the ST-segment and T wave changes that accompany a new left bundle branch block (LBBB) typically mask the ST-segment and T wave changes of acute infarction, making the diagnosis more difficult. In a patient with a convincing history of prolonged ischemic chest discomfort, a new LBBB is an acceptable criterion of acute infarction.

A shortened QT interval is typical of hypercalcemia, not acute MI.

ANSWER TO QUESTION 36

E (Braunwald, pp. 268–270, 290–292; Fig. 16.13; eFig. 16.15)

Myocardial perfusion imaging with either thallium-201- or technetium-99m-labeled compounds (e.g., technetium-99m sestamibi) is useful for the detection of myocardial ischemia and infarction (MI), to characterize infarct size (which predicts future ventricular remodeling), and to determine the effectiveness of acute revascularization. Nuclear imaging is also useful for early risk stratification after an acute MI. The size of the resting myocardial perfusion defect correlates with prognosis: the larger the defect, the worse the outcome. Certain resting image patterns seen after acute MI, such as increased lung uptake of radioisotope, have been associated with an unfavorable prognosis because they are indicative of impaired left ventricular (LV) function.

Pharmacologic stress testing with nuclear imaging after an acute MI has been shown to be safe and to predict in-hospital and late cardiac complications better than submaximal exercise stress imaging. Gated single-photon emission computed tomography myocardial perfusion imaging allows

for determination of LV function, which adds additional prognostic information in the management of the postinfarction patient.

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ANSWER TO QUESTION 37

C (Braunwald, pp. 161–163; Fig. 13.4; see also Answer to Question 31)

The development of ST-segment elevation during exercise testing is predictive of the presence of transmural ischemia owing to vasospasm or a high-grade coronary narrowing. It is very uncommon, occurring in only about 1% of patients with obstructive coronary artery disease. In contrast to ST-segment depression, the development of ST-segment elevation is useful in localizing the anatomic site of ischemia and typically correlates with a perfusion defect on imaging studies. In patients with early repolarization, the normal response is for elevated J points to return to baseline during exercise.

ST-segment elevation during exercise testing does not have predictive significance when it occurs in leads that contain pathologic Q waves. In that situation, it may represent a region of myocardial scar with a resting wall motion abnormality. There is no direct association between exercise-induced ST-segment elevation and the development of conduction system abnormalities.

ANSWER TO QUESTION 38

E (Braunwald, pp. 324–326; Figs. 18.4 and 18.5)

Assessment of coronary artery calcification by electron beam tomography (EBT) using electrocardiographic gating is a technique to screen for coronary artery disease (CAD). Although coronary artery calcification is a surrogate marker for coronary atherosclerotic plaque, the correlation between the amount of coronary calcium and the actual angiographic severity of the CAD is weak. The complete absence of coronary calcification on EBT has a strong negative predictive value for high-grade coronary stenosis, but does not completely rule out the presence of significant CAD. The Agatston score is the most frequently used system for reporting the severity of coronary artery calcifications, and reference data sets for interpretation are stratified by age and gender. Annual rates of myocardial infarction or cardiovascular death rise with increasing Agatston scores, even in patients with similar Framingham risk scores. Coronary EBT is of most clinical value for patients who are at *intermediate* risk for coronary events based on traditional cardiovascular risk factors and for whom an abnormal scan will have an impact on clinical management.

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ANSWER TO QUESTION 39

A (Braunwald, pp. 266–267, 283–289; Fig. 16.29; eFig. 16.11)

Myocardial perfusion imaging provides an important source of prognostic information in patients with coronary artery disease (CAD). Stress myocardial perfusion imaging has been shown to be a powerful predictor of subsequent cardiac events. The combination of clinical and myocardial perfusion data is more predictive than the combination of clinical and cardiac catheterization data. Indeed, even when angiographic CAD is present, a normal myocardial perfusion study confers a very low risk of a subsequent cardiovascular event (<1% per year).

Stress perfusion defects in multiple locations corresponding to multiple vascular territories are suggestive of left main or three-vessel CAD. Other indicators of high-risk CAD include large defects, transient pulmonary uptake of tracer, and left ventricular cavity dilatation with exercise. The severity of a myocardial perfusion defect can be assessed in terms of both its size and the extent of its reversibility. The severity of defects as well as their number and size are important indicators of prognosis. The predictive value of myocardial perfusion imaging is independent of the imaging technique (planar or single-photon emission computed tomography [SPECT]) and the imaging agent used (e.g., thallium-201- or technetium-99m-based compounds), with one important exception. There is a decreased likelihood of significant breast attenuation artifact with the use of technetium-99m-based agents with ECG-gated SPECT imaging.

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ANSWER TO QUESTION 40

A (Braunwald, p. 315)

Cardiac magnetic resonance (CMR) imaging is an excellent technique to define pericardial anatomy and abnormalities. It is highly sensitive for the detection of pericardial fluid, masses, and pericardial thickening. The T1-weighted spin-echo CMR image in this case demonstrates diffuse encasement of the heart by a structure within the pericardium that has intermediate signal intensity resembling myocardial tissue (labeled with asterisks in Fig. 1.67). The features are most consistent with pericardial malignancy.

Biopsy of the affected region demonstrated pericardial angiosarcoma. This is a rare primary pericardial malignancy that arises from the pericardial vasculature and typically does not metastasize. However, it usually proliferates widely throughout the pericardial cavity and may invade the myocardium. This case was considered inoperable at surgery and the patient died 4 days after presentation.

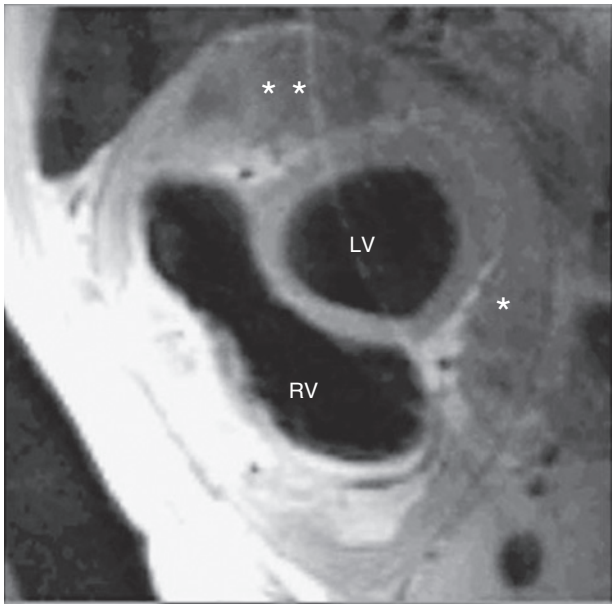

FIG. 1.67

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ANSWER TO QUESTION 41

E (Braunwald, pp. 364–366)

In a normal individual, systemic and pulmonary cardiac outputs are approximately equal. In the presence of an intracardiac shunt, blood flows abnormally between the pulmonary and systemic circulations. Although many shunts are detected by noninvasive means, certain findings during right and left heart catheterization may point to unexpected intracardiac communications. For example, suspicion for a left-to-right shunt should be raised if the pulmonary artery (PA) oxygen saturation exceeds 80% or if the difference in oxygen saturation between the superior vena cava (SVC) and the PA is 8% or more. A right-to-left shunt should be considered if the systemic arterial saturation is <93% without any other reason.

Normally, the oxygen saturation in the inferior vena cava (IVC) is higher than that in the SVC. Mixed venous saturation is most accurately determined in the PA, because complete mixing of venous return has occurred at that level. However, when assessing a transatrial shunt, the mixed venous saturation must be determined proximal to the shunt and can be estimated by the Flamm formula, measuring oxygen content in the SVC and IVC:

$$\text{Mixed venous oxygen content} = \frac{3(\text{SVC } O_2 \text{ content}) + 1(\text{IVC } O_2 \text{ content})}{4}$$

The ratio of pulmonic to systemic blood flow (Q_p/Q_s) is used to determine the significance of an intracardiac shunt. A Q_p/Q_s <1 indicates net right-to-left shunting. A Q_p/Q_s of 2.0 or more indicates a large left-to-right shunt that generally requires repair. A Q_p/Q_s of 1.0 to 1.5 indicates a small left-to-right shunt.

ANSWER TO QUESTION 42

B (Braunwald, p. 201; Fig. 14.32; p. 1606; Fig. 78.6)

The pulsed-wave Doppler spectrum in the illustration demonstrates late systolic acceleration of flow characteristic of left ventricular outflow tract (LVOT) obstruction, typically seen in patients with hypertrophic cardiomyopathy (HCM). This abnormal Doppler signal ("dagger" pattern) is detected in the LVOT and peaks significantly later than that of valvular aortic stenosis, owing to the dynamic nature of the obstruction. Because the disorder is at the subvalvular level, there is no therapeutic role for aortic valve surgery.

The LVOT obstruction may be worsened by any action that decreases left ventricular volume and narrows the distance between the interventricular septum and the anterior mitral leaflet, including volume depletion. Bed rest has no specific role in the management of HCM.

ANSWER TO QUESTION 43

C (Braunwald, pp. 218–221; Figs. 14.62, 14.64–14.66; p. 315)

Echocardiography is an excellent technique to detect and grossly quantify the volume of pericardial effusions. The normal pericardial space contains 35 to 50 mL of serous fluid between the visceral and parietal pericardial layers. Small pathologic effusions tend to accumulate posteriorly, external to the left ventricular free wall, because of the effects of gravity. Larger effusions tend to circumscribe the heart. Certain echocardiographic features are good indicators of the presence of cardiac tamponade physiology in patients with pericardial effusion. These include early diastolic collapse of the right ventricle, which indicates the presence of elevated intrapericardial pressure (see Braunwald, Fig. 14.64). However, right ventricular (RV) diastolic collapse may be absent in clinical tamponade if pulmonary hypertension or RV hypertrophy is present, because these forces oppose RV indentation. Diastolic invagination of the right atrium (see Braunwald, Fig. 14.64) is a more sensitive, but less specific, marker of tamponade physiology. Doppler interrogation can also provide clues to the presence of tamponade, including exaggerated respiratory variation of transvalvular velocities (see Answer to Question 6).

Transthoracic echocardiographic imaging is often inadequate in direct assessment of the thickness of the pericardium; transesophageal echocardiography, computed tomography, and magnetic resonance imaging are more accurate techniques for this purpose.

ANSWER TO QUESTION 44

E (Braunwald, pp. 266–270, 280, 285, 295; Fig. 16.13)

Although nuclear stress testing is commonly used in the evaluation of women with suspected coronary artery

disease (CAD), there is the possibility of breast attenuation artifact in female patients. The use of technetium-99m-based agents with single-photon emission computer tomography imaging and electrocardiographic gating reduce the likelihood of a false-positive study due to such artifact, thereby increasing the specificity of nuclear testing in women. Breast attenuation artifact typically appears as a fixed defect of the anterior or anterolateral wall. If this defect is due to artifact rather than prior infarction, the involved segment(s) will demonstrate normal wall motion on the gated images (see Answer to Question 11).

Patients with left bundle branch block (LBBB) may demonstrate artifactual exercise-induced perfusion defects, especially in the septal and anteroapical regions. Pharmacologic stress testing with adenosine, regadenoson, or dipyridamole minimizes the incidence of such artifacts. Thus, it is recommended that patients with complete LBBB on the ECG be evaluated by vasodilatory agents, rather than an exercise protocol, to avoid false-positive results.

Nuclear imaging is a useful modality for preoperative risk stratification before noncardiac surgery, especially for patients at intermediate clinical risk.[1] For example, dipyridamole stress testing with perfusion imaging is predictive of perioperative cardiac events and the magnitude of risk correlates with the extent of ischemia. Patients with diabetes are at increased risk for CAD and its complications, and perfusion defects during testing predict *higher* event rates in diabetics compared with nondiabetics.[2]

In patients with CAD, assessment of myocardial viability may be of importance in defining revascularization options. Modalities for the determination of myocardial viability include thallium-201 imaging, magnetic resonance imaging, dobutamine echocardiography, and positron emission tomography.[3]

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ANSWER TO QUESTION 45

B (Braunwald, pp. 302, 308–312)

In this delayed cardiac magnetic resonance (CMR) image, the midseptum and midanterior segments of the left ventricle demonstrate subendocardial late enhancement (the bright area indicated by the white arrows in Fig. 1.68) that involves approximately half of the transmural thickness of the myocardium. This finding, as well as the matching wall motion abnormality by echocardiography, is most consistent with a prior nontransmural myocardial infarction (MI). The presence of MI (acute or old) can be determined accurately using the protocol of late gadolinium enhancement (LGE). Gadolinium is an extracellular contrast agent that only minimally enters normal myocardial cells. However, disrupted myocardium after an MI allows expansion of the volume of distribution and delayed entry of the contrast agent into the affected region. A subendocardial distribution is indicative of MI. Both conventional CMR and LGE are useful in assessing myocardial viability, to help determine whether a segment of poorly contracting myocardium would benefit from mechanical revascularization. For example, improved wall thickening with low-dose dobutamine CMR correlates well with the presence of viable myocardium. Using LGE, a transmural extent of MI (i.e., region of late enhancement) of <50% is also predictive of functional recovery after revascularization.

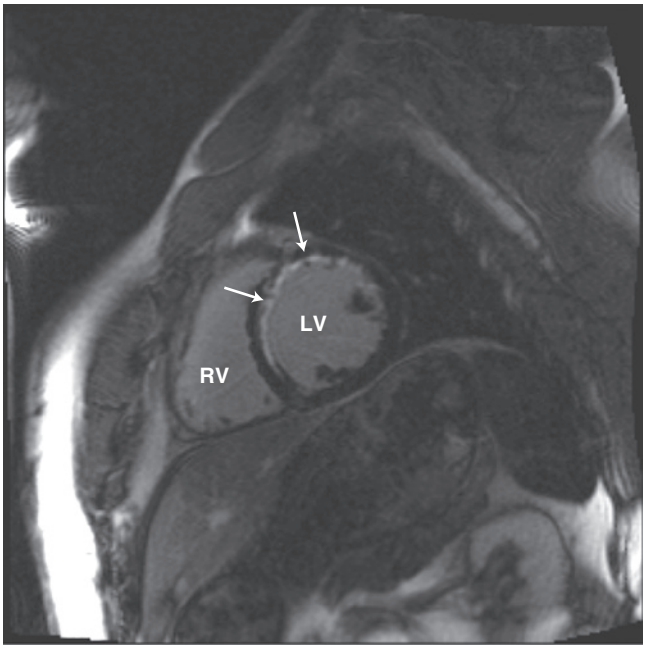

FIG. 1.68

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ANSWER TO QUESTION 46

B (Braunwald, pp. 210–212; Figs. 14.47 and 14.48; pp. 361–364; Figs. 19.10 and 19.11)

As with most stenotic valvular lesions, echocardiographic evaluation of aortic stenosis (AS) is accurate and clinically useful. The morphology of the valve can be examined by two-dimensional imaging to assess for congenital or rheumatic abnormalities or age-related changes of valvular architecture. The peak outflow velocity is then measured using continuous-wave Doppler imaging. Important AS usually results in outflow velocities of 3.5 m/s or greater, which is out of the range for accurate quantification by pulsed-wave Doppler imaging. From the continuous-wave Doppler measurement, both the peak and mean gradients can be determined. The peak instantaneous gradient measured by Doppler imaging reflects the true maximum pressure difference between the left ventricle and aorta. The peak-to-peak gradient measured

in the catheterization laboratory has no actual physiologic basis and does not directly correspond to the echocardiographically measured values—the peak instantaneous gradient routinely exceeds the peak-to-peak valve gradient. Conversely, the mean gradients determined noninvasively and in the catheterization laboratory show excellent agreement, because they both measure the difference in pressure between the left ventricular (LV) and aorta averaged throughout systole.

The aortic valve area can be calculated using the continuity equation (see Braunwald, Fig. 14.48), comparing the volume rate of flow across the left ventricular outflow tract (LVOT) with that through the aortic valve. The greatest potential error introduced into this calculation resides in inaccurate measurement of the *LVOT diameter*. In practice, a peak transaortic valvular gradient >50 mm Hg correlates with clinically significant AS. Similarly, a patient with normal LV contractile function and a low gradient is unlikely to have significant stenosis. However, in the presence of impaired LV function, a more modest gradient (corresponding to transvalvular velocities of 2 to 3 m/s) may be clinically important, and calculation of the aortic valve area by the continuity equation can be helpful in this case.

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ANSWER TO QUESTION 47

C (Braunwald, pp. 364–366)

Detection and localization of intracardiac shunts is possible at catheterization by a traditional oximetry run, in which samples are drawn at numerous sites in the right side of the heart and adjacent vessels. The technique involves measurement of O_2 saturations to identify a significant step-up between consecutive chambers. Using averaged samples, an O_2 saturation step-up of ≥8% is typically necessary to diagnose a left-to-right shunt at the atrial level, whereas one ≥5% suffices at the level of the right ventricle or pulmonary artery (PA; O_2 content in different portions of the right atrium may vary by as much as 2%, reflecting the streaming of blood that enters from the superior vena cava, the inferior vena cava, and the coronary sinus).

The data obtained in the course of an oximetry run may be used to quantify shunt size. Pulmonary and systemic blood flows can be calculated using the standard Fick equation. The ratio of pulmonary to systemic blood flow (Q_p/Q_s) is used to determine the significance of a shunt. A Q_p/Q_s of <1.5 indicates a small left-to-right shunt. A Q_p/Q_s of 2.0 or more indicates a large left-to-right shunt that generally warrants percutaneous or surgical closure. Because of normal variability in O_2 saturation, left-to-right shunts with Q_p/Q_s ≤1.3 at the PA or right ventricular levels and those with Q_p/Q_s <1.5 at the atrial level may not be detected. A Q_p/Q_s of <1 indicates a net right-to-left shunt. For *unidirectional* shunts, the magnitude of the shunt can also be expressed by the difference $Q_p - Q_s$. From this calculation, it can be deduced that a negative value will occur with pure right-to-left shunts.

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ANSWER TO QUESTION 48

C (Braunwald, pp. 159–164)

The exercise ECG is very likely to be abnormal in patients with severe coronary artery disease (CAD). There are several abnormalities that are suggestive of multivessel CAD and an adverse prognosis. These include the early onset of ischemic ST-segment depression, such as during the first stage of a standard Bruce protocol. In addition, ST-segment depression of ≥2 mm (0.20 mV) involving five or more leads, or persisting ≥5 minutes into recovery, is suggestive of more severe underlying coronary atherosclerosis. Exercise-induced ST-segment elevation is also consistent with multivessel CAD, except in lead aVR, which may demonstrate ST-segment elevation in a variety of circumstances, including less severe coronary disease. A failure to increase systolic blood pressure by 10 mm Hg, or a sustained decrease in systolic blood pressure of 10 mm Hg or more, is suggestive of multivessel (or left main) CAD and an adverse prognosis. Multifocal premature ventricular contractions occurring during exercise are not correlated with extensive disease, but reproducible, sustained, or symptomatic ventricular tachycardia is highly suggestive of multivessel CAD.

ANSWER TO QUESTION 49

C (Braunwald, pp. 91–92; Fig. 10.7; Tables 10.6 and 10.7)

Squatting increases venous return to the heart and ventricular stroke volume. The resultant augmented flow and turbulence across the stenotic aortic valve increase the intensity of the murmur. In distinction, during the early phase of the Valsalva maneuver, venous return (and therefore stroke volume) is decreased so that the intensity of the murmur of aortic stenosis (AS) lessens.

The systolic murmur of AS can be confused with mitral regurgitation (MR). However, if the patient has an irregular rhythm or premature ventricular contractions, beat-to-beat variations in diastolic filling of the left ventricle result in changes of the intensity of the AS murmur, whereas the murmur of MR does not demonstrate such variability. Respiration has little effect on the intensity of left-sided heart murmurs, including AS, but can accentuate most right-sided murmurs, including tricuspid regurgitation.

ANSWER TO QUESTION 50

B (Braunwald, pp. 83–85)

This man has classic findings of chest discomfort caused by esophageal reflux and spasm. Differentiation of esophageal disorders from ischemic heart disease can be difficult, because the sensations are often located in similar areas and both can be associated with emotional stress. However, although each condition may produce substernal burning, features in this case are more suggestive of an esophageal rather than cardiac origin. These include a prolonged

continuous ache, a discomfort that is primarily retrosternal but does not radiate toward the arms, and the fact the symptom is not precipitated by exercise but occurs while recumbent. Classically, esophageal disease associated with regurgitation causes "water brash," a taste in the mouth consistent with regurgitation of gastric contents. Frequently, patients with esophageal spasm experience some relief with nitroglycerin. Unlike angina due to myocardial ischemia, however, esophageal pain is often relieved by milk, antacids, or food. Biliary colic also may be confused with angina pectoris. It is usually caused by a rapid rise in biliary pressure due to obstruction of the cystic or bile ducts. Thus, the pain is usually abrupt in onset and steady in nature and lasts from minutes to hours. In many cases, the discomfort is described as colicky. It should be suspected when a history of dyspepsia, fatty food intolerance, and indigestion is present.

The chest discomfort of pericarditis is typically described as sharp, stabbing, or knife-like. Pain due to pericarditis is often localized in the substernal or apical areas and can radiate to the neck or left shoulder. The pain is often worsened by deep breathing or lying in a supine position. Patients may find relief from the chest discomfort of pericarditis by sitting up and leaning forward.

ANSWER TO QUESTION 51

D (Braunwald, pp. 161, 265–267; Fig. 16.9)

The perfusion images display a large region of reversible ischemia in the anteroseptal territory, in the distribution of the left anterior descending coronary artery. In addition, compared with the rest images, there are additional postexercise abnormalities, including dilatation of the left ventricular (LV) cavity (best seen on the short-axis images), increased right ventricular (RV) tracer uptake (most evident in the horizontal long-axis images), and increased lung uptake. Transient dilatation of the LV cavity after stress is associated with extensive and severe coronary artery disease (CAD). It is thought to represent diffuse subendocardial ischemia resulting in an apparent LV dilatation, rather than true cavity enlargement. Increased pulmonary radiotracer uptake after stress is a marker of elevated LV end-diastolic pressure and is predictive of a poor prognosis. It is usually associated with multivessel CAD, depressed LV function, and extensive ischemia. Increased RV tracer uptake on the post-stress images, compared with the rest images, is a specific marker of severe multivessel or left main disease. Finally, a fall in systolic blood pressure of 10 mm Hg or more during exercise is also predictive of left main or three-vessel CAD. In this case, all of these findings are present, along with a large and severe reversible perfusion defect, indicative of severe CAD despite failure to achieve the target heart rate.

ANSWER TO QUESTION 52

B (Braunwald, pp. 178, 210–213; Figs. 14.47–14.50)

The Doppler tracing was obtained across the left ventricular outflow tract of a patient with combined aortic stenosis (AS) and aortic insufficiency. The tracing shows a characteristic delayed onset of peak velocity, consistent with significant AS. The pressure gradient across the aortic valve can be calculated using the modified Bernoulli equation (pressure gradient = $4 \times V^2$). The peak velocity across the aortic valve of approximately 4.8 m/s in the figure corresponds to an instantaneous peak systolic gradient of 92 mm Hg. In general, when the aortic flow velocity is >4 m/s, the probability of critical AS is high. In contrast, an aortic flow velocity <3 m/s is usually associated with only mild AS. For aortic flow velocities that are intermediate, echocardiographic calculation of the aortic valve area or additional hemodynamic data are often needed.

The diastolic flow on this tracing represents aortic insufficiency. Severe aortic insufficiency is associated with a rapidly declining flow velocity, whereas mild aortic insufficiency demonstrates a gradually declining velocity. In this case, the decline in diastolic velocity is gradual and the degree of aortic insufficiency is likely mild. Premature diastolic closure of the mitral valve may be observed in patients with severe, acute aortic insufficiency owing to the greatly elevated diastolic left ventricular (LV) pressure; it would not be expected in this patient given the mild degree of aortic insufficiency present.

Additional findings on the echocardiogram that may help assess the severity of aortic valve disease include measurements of LV size and thickness. In this patient with severe AS, one would expect to find concentric LV hypertrophy.

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ANSWER TO QUESTION 53

B (Braunwald, pp. 85, 86, 99)

Many congenital and acquired cardiac diseases are associated with abnormalities of the extremities. Arachnodactyly—abnormally long and slender digits—is a manifestation of Marfan syndrome. A common finding in arachnodactyly is that when a clenched fist is made around the thumb, the latter extends beyond the ulnar side of the hand (the "thumb sign"). Characteristic extremity abnormalities associated with Turner syndrome include short stature and bowed arms. It is the Holt-Oram syndrome that consists of an atrial septal defect (ASD) and skeletal abnormalities, including deformities of the radius and ulna, and a "fingerized" thumb (i.e., the thumb has an extra phalanx).

Quincke sign, systolic flushing of the nail beds, is common in chronic aortic regurgitation and other conditions with a widened pulse pressure.

Osler nodes are small, tender erythematous skin lesions observed primarily on the pads of the fingers and toes but also on the palms of the hands and soles of the feet. They result from infective microemboli in patients with endocarditis. In contrast, Janeway lesions are slightly raised, nontender, hemorrhagic lesions on the palms of the hands and soles of the feet that may also appear in patients with infective endocarditis. Both types of lesions were more common in the pre-antibiotic era.

Differential cyanosis is the condition in which the hands and fingers are pink but the feet and toes are cyanotic. It is

typical of patent ductus arteriosus with pulmonary hypertension and a reversed shunt, in which case desaturated blood is directed to the lower body.

ANSWER TO QUESTION 54

D (Braunwald, Fig. 14.96; pp. 1565–1566; Fig. 75.42)

The echocardiographic image is an apical four-chamber view of a patient with Ebstein anomaly. Ebstein anomaly is a congenital malformation of the tricuspid valve characterized by elongation and tethering of the anterior leaflet ("sail-like" appearance) and apical displacement of a diminutive septal leaflet. This anomaly results in conversion of a portion of the right ventricle into an "atrialized" right ventricle. There is typically severe right atrial enlargement. Because of the structural deformity of the tricuspid valve, varying degrees of tricuspid regurgitation, and occasionally tricuspid stenosis, are present. The symptomatic presentation of patients with Ebstein anomaly depends on the severity of the valvular regurgitation and the presence of additional congenital heart lesions.

Ebstein anomaly is associated with a number of other congenital heart defects, including patent foramen ovale or ASD in approximately 50% of patients. Up to 25% of patients with Ebstein anomaly have an accessory conduction pathway (Wolff-Parkinson-White pattern on the ECG), which is typically right-sided. Atrial arrhythmias, particularly atrial fibrillation and atrial flutter, are common.

Although coarctation of the aorta can rarely be associated with Ebstein anomaly, systemic hypertension is not a common finding among patients with this disorder.

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ANSWER TO QUESTION 55

B (Braunwald, pp. 226–228; Fig. 14.77)

Echocardiography plays a key role in the diagnosis and evaluation of infective endocarditis. The echocardiographic hallmark is the presence of a valvular vegetation, which is a collection of thrombus, necrotic valvular debris, inflammatory material, and bacteria. Typically, vegetations are located on the atrial aspect of atrioventricular (mitral, tricuspid) valves and the ventricular aspect of the semilunar (aortic, pulmonic) valves; however, large and aggressive lesions may involve both surfaces of the involved valve. The sensitivity of transthoracic echocardiography for detection of vegetations is only ~63%. Transesophageal echocardiography (TEE) is more sensitive for detection of small vegetations (94% to 100% sensitive). However, there is little additional diagnostic yield of TEE when a high-quality transthoracic study is completely normal, without evidence of valve thickening or pathologic regurgitation. Echocardiography also plays a critical role in the identification of structural and functional impairments that result from endocarditis. The degree of valvular destruction and regurgitation can be assessed, particularly with TEE, but TEE is not mandatory if a high-quality transthoracic study provides all relevant information. TEE is more sensitive than transthoracic echocardiography for identification of myocardial abscess formation, valvular perforation, chordal rupture, and endocarditis of prosthetic valves.

Echocardiography can assist in determining whether corrective surgical intervention is appropriate in endocarditis, but the decision to operate should be made primarily on clinical grounds. Factors that predict poor outcome and favor earlier surgical intervention include a perivalvular abscess, intractable heart failure due to valve dysfunction, very large (>1 cm) and hypermobile vegetations, recurrent embolic events despite antibiotic therapy, infection by aggressive organisms, or persistent bacteremia.

It is not necessary to routinely repeat echocardiography in the presence of clinical improvement. Residual vegetation often is evident despite bacteriologic cure, and the patient's clinical status, as well as repeat blood cultures after completion of an appropriate antibiotic course, should dictate further clinical decision making.

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ANSWER TO QUESTION 56

D (Braunwald, p. 90; Figs. 10.5 and 10.6)

The volume and contour of the arterial pulse depend in part on the left ventricular stroke volume, the ejection velocity, and the compliance and capacity of the arterial system. Pulsus parvus et tardus—a small pulse with a delayed systolic peak—is characteristically seen in severe aortic stenosis (AS) and is best appreciated by palpating the carotid artery rather than a peripheral vessel such as the brachial artery. In patients with severe AS and congestive heart failure, the delayed upstroke is not usually evident, leaving only pulsus parvus.

Pulsus bisferiens, characterized by two systolic peaks, occurs when a large stroke volume is ejected rapidly from the ventricle. It is typical of pure aortic regurgitation (AR) and of AR combined with AS. It is also seen in hypertrophic cardiomyopathy with dynamic outflow obstruction.

The *peripheral* pulse rate of rise, contour, and volume is best appreciated by palpation of the brachial artery. The carotid pulse provides the most accurate representation of the *central* aortic pulse.

In coarctation of the aorta, the carotid and brachial pulses are usually bounding and rapidly rising and have large volumes. Conversely, the lower extremity pulses, such as at the femoral artery, have reduced systolic and pulse pressures with a slow rate of rise and a late peak. The femoral artery delay can be appreciated by palpating the brachial and femoral arteries simultaneously.

The normal aorta is often palpable only above the umbilicus. If the aorta is palpable below the umbilicus, an abdominal aortic aneurysm should be suspected.

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ANSWER TO QUESTION 57

B (Braunwald, pp. 350–351, 352–354; Fig. 19.2)

Over 1 million diagnostic cardiac catheterizations are performed annually in the United States.[1] Common vascular entry sites are the femoral, brachial, and radial artery approaches. To decrease the risk of retroperitoneal hemorrhage when using the femoral artery approach, the puncture of the common femoral artery should be made below the inguinal ligament but proximal to the bifurcation of the superficial femoral and profunda arterial branches. If the puncture site is proximal to the inguinal ligament, it may be difficult to establish hemostasis with manual compression. If the puncture site is distal to the bifurcation, there is an increased risk for the formation of a pseudoaneurysm after sheath removal.

For patients on anticoagulation, warfarin should generally be held for 3 days prior to catheterization and the international normalized ratio (INR) should be <1.8 at the time of the procedure to minimize bleeding when the femoral artery approach is used. An INR <2.2 is acceptable for radial artery access. Dabigatran should be held for 24 hours prior to the procedure in patients with normal renal function, and at least 48 hours before when the estimated glomerular filtration rate (GFR) is <50 mL/min. Rivaroxaban and apixaban should also be held the day prior to the procedure.

Contrary to common belief, patients with a history of shellfish allergy are not at higher risk of contrast media reactions than patients with other types of food allergies. The allergens in shellfish are non-iodine-containing proteins (e.g., tropomyosin).[2]

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ANSWER TO QUESTION 58

A (Braunwald, pp. 154–155)

Exercise testing and exercise training play a critical role in the care of patients with advanced congestive heart failure. It has been demonstrated that peak oxygen consumption and anaerobic threshold, measured during cardiopulmonary exercise testing, provide independent prognostic information in this population and are superior to measures such as ejection fraction or functional class in predicting outcome. Patients with severely depressed ejection fractions exhibit a wide range of exercise capacities, with some being near normal, and exercise testing can be critical to quantifying the true functional limitation. A peak oxygen consumption of <14 mL/kg/min has been shown to predict poor survival and to identify a population in whom mortality is improved by cardiac transplantation. Patients at this level of impairment demonstrate a profound exercise limitation, with maximal exercise capacity being required for activities such as walking, golf, or raking leaves. Such a patient would be unable to complete stage I on a standard Bruce protocol. Conversely, patients who achieve a peak oxygen consumption of >14 mL/kg/min have a mortality rate similar to patients who have undergone transplantation and would be less likely to benefit from that intervention.

The exercise limitation in patients with congestive heart failure is correlated most strongly with alterations in skeletal muscle metabolism. Abnormalities in autonomic and ventilatory responsiveness, increased lactate production, and inability to augment cardiac output are also contributing factors. All of these limitations improve with exercise training, and long-term moderate exercise has been shown to benefit functional capacity, reduce symptoms, and enhance quality of life.

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ANSWER TO QUESTION 59

D (Braunwald, pp. 308–317)

Cardiac magnetic resonance (CMR) imaging is a powerful noninvasive tool for the diagnosis of several heart and vascular disorders. There has been significant growth in the use of CMR for clinical and research applications due to a number of factors, including outstanding image quality, reproducibility, and attractive safety features (i.e., no need for ionizing radiation exposure or iodinated contrast). CMR is well suited for identification of congenital heart lesions and cardiac tumors, assessment of myocardial infarction and viability, and characterization of cardiomyopathies. CMR has been used to identify the presence of iron overload in patients with beta-thalassemia and to guide chelation therapy. CMR can define the structure and function of the right ventricle and is useful in the diagnosis of arrhythmogenic right ventricular cardiomyopathy. CMR can also be useful in the evaluation of stenotic and regurgitant valves when echocardiographic windows are inadequate. The use of CMR for pharmacologic myocardial perfusion imaging and dobutamine stress testing is another important clinical application. Compared with nuclear (single-photon emission computed tomography) imaging, CMR myocardial perfusion imaging is not limited by attenuation artifacts, does not require ionizing radiation, and has higher spatial resolution.

Although CMR can accurately measure global left ventricular function with excellent reproducibility, echocardiography (or radionuclide ventriculography) remains the superior option for the patient described in answer D, in light of cost and patient comfort issues (e.g., breath holding, confined space, and relatively lengthy scan times for CMR).

Magnetic resonance angiography (MRA) is an excellent imaging technique for assessment of the aorta and peripheral arteries, and coarctation of the aorta can be readily characterized by this technique. MRA has also been validated for the noninvasive diagnosis of renal artery stenosis and is the screening test of choice for this condition at many medical centers.

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ANSWER TO QUESTION 60

D (Braunwald, pp. 26–29, 164; eFig. 16.4)

The figure demonstrates the impact of pretest probability on prognostic information that can be determined from a positive or negative stress test. The test provides the greatest impact on patients whose pretest probability is in an intermediate range—in such patients, a negative test results in a much lower post-test probability than pretest probability, whereas a positive test results in a much higher post-test probability, relative to the pretest probability. For patients who have a high pretest probability, the post-test probability that disease is present remains high even if the test is negative (i.e., there is a high likelihood that the result is a false negative). In such patients, the negative predictive value of the test is low. Similarly, for patients who have a low pretest probability, the positive predictive value of the test is low.

ANSWER TO QUESTION 61

A (Braunwald, pp. 186–188, 201; Fig. 14.32)

In hypertrophic cardiomyopathy (HCM) with outflow tract obstruction, the anterior leaflet of the mitral valve is abnormally drawn toward the hypertrophied interventricular septum during systole. This systolic anterior motion of the valve can be readily identified by echocardiography (see Braunwald, Fig. 14.32) and plays an integral role in the development of outflow tract obstruction in this condition. In addition, characteristic systolic, not diastolic, notching of the aortic valve is often evident, particularly by M-mode recordings, owing to the dynamic nature of the obstruction. Asymmetric hypertrophy of the interventricular septum is common in HCM and is readily identifiable by echocardiography. However, pathologic localized hypertrophy in this condition can instead be confined to the apex, lateral, or inferior segments, typically without dynamic outflow obstruction. Cardiac magnetic resonance imaging is complementary to echocardiography by visualizing regions that are difficult to assess by echocardiography.

The Doppler spectral mitral inflow pattern in HCM can be variable, but usually reflects the abnormal diastolic filling of the hypertrophied ventricle. Usually there is evidence of a diminished E wave and prominent A wave. Abnormalities of diastolic function can also be identified by Doppler tissue imaging, which typically demonstrates reduced early diastolic mitral annular velocities (E′) as a measure of impaired myocardial relaxation.

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ANSWER TO QUESTION 62

D (Braunwald, pp. 359–360; eTable 19.2; Table 19.3; Fig. 19.8)

As summarized in the Answer to Question 23, the right atrial pressure waveform contains three positive deflections termed the *a, c,* and *v* waves. The *a* wave represents atrial systole and occurs after the P wave on the ECG. The *x* descent represents the relaxation of the atrium and downward tugging of the tricuspid annulus by right ventricular contraction. The *c* wave interrupts the *x* descent and represents the protrusion of the closed tricuspid valve into the right atrium (RA). The *v* wave represents the passive venous filling of the atrium, which occurs during ventricular systole. The height of the *v* wave reflects atrial compliance. In the left atrium, as opposed to the RA, the *v* wave is generally more prominent than the *a* wave. The *y* descent follows the *v* wave, and it represents right atrial emptying after the tricuspid valve opens.

Conditions that blunt the right atrial *y* descent include cardiac tamponade, ventricular ischemia, and tricuspid stenosis. Conversely, constrictive pericarditis is associated with prominence of the *y* descent, because the very earliest phase of diastolic ventricular filling is unimpeded in this condition.

Blunting of the *x* descent can be observed in the presence of atrial fibrillation or atrial ischemia.

ANSWER TO QUESTION 63

E (Braunwald, pp. 91–93; Figs. 10.7 and 10.8; Tables 10.6 and 10.7)

Dynamic auscultation is the technique of altering circulatory dynamics with physiologic maneuvers and then determining the effect on cardiac murmurs. Typical maneuvers include changes in respiration, the Valsalva maneuver, squatting or standing, and isometric exercise.

Patent ductus arteriosus causes a continuous murmur that is loudest at the second left intercostal space. The diastolic phase of this murmur is increased by isometric handgrip as a result of augmented systemic vascular resistance (SVR).

Hypertrophic obstructive cardiomyopathy is associated with a harsh, crescendo-decrescendo systolic murmur best heard between the apex and left sternal border. Actions that reduce left ventricular (LV) size, such as standing or the strain phase of a Valsalva maneuver, bring the anterior mitral leaflet and the interventricular septum into closer proximity, thus *intensifying* the murmur. These maneuvers are useful in differentiating hypertrophic obstructive cardiomyopathy from a fixed orifice obstruction (i.e., aortic stenosis), in which the murmur softens with standing or the Valsalva maneuver.

The murmur of an uncomplicated ventricular septal defect is holosystolic because LV systolic pressure and systemic resistance exceed right ventricular systolic pressure and pulmonary resistance from the beginning to the end of systole. Isometric handgrip increases SVR and may further intensify the murmur.

Aortic regurgitation is a diastolic murmur best heard with the patient sitting forward and holding a deep expiration. The murmur may be accentuated by maneuvers that increase the arterial pressure, such as isometric handgrip.

The diastolic murmur of mitral stenosis is a low-pitched, rumbling murmur best heard at the apex. Maneuvers that increase the rate of transmitral flow, including exercise, accentuate the murmur.

ANSWER TO QUESTION 64

D (Braunwald, p. 145; Fig. 14.43)

Although the ST-segment and T wave abnormalities on this ECG may suggest myocardial ischemia, the deeply inverted T waves are typical of acute cerebrovascular conditions, including subarachnoid hemorrhage. Given the presenting symptoms of headache, nausea, and dizziness, a cranial imaging study such as computed tomography should be obtained rapidly. In this scenario, antiplatelet agents and antithrombotic therapy should be withheld until intracranial bleeding has been excluded. In the absence of findings to suggest unstable myocardial ischemia, anti-ischemic therapies and cardiac catheterization are not initially appropriate. Electrocardiographic abnormalities are present in a large percentage of patients with acute cerebral events. These abnormalities may include tachyarrhythmias or bradyarrhythmias, conduction disturbances, repolarization abnormalities that resemble myocardial ischemia, prolongation of the QT interval, and prominent U waves. The mechanisms responsible for such electrocardiographic changes are unknown, but appear to be related to abnormal autonomic nervous system function. Myocardial damage with release of serum markers (cardiac-specific troponins, CK-MB) and subendocardial hemorrhage can actually occur in the setting of acute severe cerebrovascular disease, believed to be related to the release of excessive local myocardial catecholamines.

In the appropriate clinical situation, diffuse deep T wave inversions are also found in some patients with hypertrophic cardiomyopathy (HCM). Giant inverted T waves in the midprecordial leads are particularly characteristic of the apical form of HCM.

ANSWER TO QUESTION 65

D (Braunwald, p. 92; Fig. 10.8; Table 10.6)

Diastolic murmurs are classified according to their time of onset as early diastolic, mid-diastolic, or late diastolic. Early diastolic murmurs include aortic regurgitation (AR) and pulmonic regurgitation (PR). AR begins with the aortic component of the second heart sound (S_2) and PR starts with the pulmonic component of S_2. Mid- and late diastolic murmurs begin at a clear interval after S_2. When the murmur of AR radiates selectively to the right sternal border (and not the left sternal border), it implies that aortic root dilatation, rather than aortic valve disease, is the cause.

The murmur of acute severe AR differs importantly from the murmur of chronic severe AR. The high-pitched murmur of chronic AR begins with the aortic component of S_2 and has an early peak and a dominant decrescendo pattern throughout diastole. In contrast, in acute severe AR (e.g., caused by infective endocarditis or aortic dissection), the diastolic murmur is of short duration and tends to be soft, because the aortic diastolic pressure rapidly equilibrates with the steep rise in diastolic left ventricular pressure.

Presystolic accentuation of diastolic murmurs, owing to atrial activation and a transient increase in driving pressure, is typical of patients with mitral or tricuspid stenosis who are in sinus rhythm. Such accentuation is absent in atrial fibrillation because of the lack of organized atrial contraction.

When PR develops in the setting of pulmonary hypertension, the murmur begins with a loud P_2 and may last throughout diastole (the Graham Steell murmur).

ANSWER TO QUESTION 66

C (Braunwald, pp. 383–386; Fig. 20.1; Table 20.8)

The left main coronary artery arises from the superior portion of the left aortic sinus. It ranges from 3 to 6 mm in diameter and is up to 10 mm in length. This vessel is best visualized in the anteroposterior projection with slight caudal angulation. The left main coronary artery bifurcates into the left anterior descending (LAD) artery and the left circumflex (LCx) artery. In up to 37% of patients, however, the left main trifurcates into a third vessel known as the ramus intermedius, which lies between the LAD and the LCx. The right coronary artery is the dominant vessel in 85% of patients, supplying the posterior descending artery. The LCx artery is the dominant vessel 15% of the time. The interventricular septum is the most densely vascularized area of the heart. It is supplied by septal branches of the LAD that interconnect with septal branches from the posterior descending artery, producing a network of potential collateral channels. There are a number of congenital anomalies that can cause myocardial ischemia. Coronary artery fistulas (abnormal communications between a coronary artery and a cardiac chamber or major vessel) comprise the most common congenital coronary abnormality that is of hemodynamic significance. About half of the patients with such an anomaly are asymptomatic, but the remainder develop complications including heart failure, infective endocarditis, ischemia, or rupture of an aneurysm. The figure in this question demonstrates a congenital coronary fistula, arising from branches of the LAD and circumflex coronary arteries, that drains into the left ventricle (see right anterior oblique view in *A* and left anterior oblique view in *B*). Other congenital anomalies that may result in myocardial ischemia include anomalous origin of the left coronary artery from the pulmonary artery, congenital coronary stenosis, and anomalous origin of either coronary artery from the contralateral sinus of Valsalva.

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ANSWER TO QUESTION 67

E (Braunwald, pp. 85, 86, 90)

The clinical diagnosis of Marfan syndrome has historically depended on characteristic abnormalities of the skeletal, cardiovascular, and ocular systems. Genetic testing for mutations in the *FBN1* gene has not been required for routine assessment. Since 1996, the Ghent criteria have been the standard for diagnosis and rely on "major" and "minor" manifestations. Major criteria include the following:

Skeletal findings: at least four of the following: pectus carinatum, pectus excavatum requiring surgery, arm span/height ratio >1.05, positive thumb sign (distal phalanx

protrudes beyond clenched fist) and wrist sign (thumb and fifth finger overlap while encircling the wrist), scoliosis >20 degrees or spondylolisthesis, reduced elbow extension <170 degrees, pes planus (flat feet), and protrusio acetabulae

Cardiovascular findings: Dilation of sinuses of Valsalva and ascending aorta, or ascending aortic dissection

Ocular finding: Ectopia lentis (lens dislocation identified by slit lamp examination)

Central nervous system finding: Lumbosacral dural ectasia (identified by computed tomography or magnetic resonance imaging)

Family or genetic history: First-degree relative who meets diagnostic criteria or who has known Marfan mutation

Minor criteria include lesser skeletal abnormalities (joint hypermobility, nonsurgical pectus excavatum, high arched palate, and facial features such as malar hypoplasia), mitral valve prolapse, and dilation/dissection of the descending thoracic/abdominal aorta before age 50.

In the absence of a family history, the diagnosis of Marfan syndrome requires one major manifestation in two of the above organ systems, with involvement (major or minor criterion) in a third organ system, or if a mutation known to cause Marfan syndrome is found, the diagnosis is based on one major criterion plus involvement (major or minor criterion) in a second organ system.

In this patient's case, ectopia lentis is a major criterion, the other choices are minor criteria.

In 2010, an international expert committee proposed revised diagnostic nosology for Marfan syndrome that emphasizes the importance of the cardiovascular manifestations of this condition. By the new criteria, in the absence of a family history of Marfan syndrome, the combination of aortic root dilatation and ectopic lentis is sufficient to establish the diagnosis. In the absence of either of these findings, the identification of a known *FBN1* mutation or a combination of systemic findings is required for confirmation.

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ANSWER TO QUESTION 68

A (Braunwald, pp. 212–213; eFigs. 14.21–14.23; Fig. 14.50)

Assessment of the severity of regurgitant valvular lesions by Doppler echocardiography is less straightforward than assessment of stenotic conditions. Often a combination of findings must be visually integrated, because no one criterion has sufficient accuracy for quantification. In aortic regurgitation (AR), findings that suggest marked elevation of left ventricular (LV) end-diastolic pressure are among the more predictive indicators of lesion severity. Unlike mitral regurgitation, in which the overall jet size correlates with the degree of regurgitation, the size and depth of penetration of the AR color Doppler signal are less strongly correlated with the magnitude of the lesion. This is in part due to merging of the color jet signals of AR with normal mitral inflow into the left ventricle. Measurements of the jet width may also be misleading, because it may rapidly widen after passing through the more restricted valvular orifice, giving a falsely severe appearance. Careful imaging of the regurgitant signal in the parasternal short-axis view often gives the best sense of true jet width.

In the presence of severe AR, there is rapid elevation of LV diastolic pressure such that the velocity of retrograde flow into the left ventricle quickly decays, resulting in a shortened pressure half-time (PHT). A PHT < 250 milliseconds correlates with severe AR. In addition, the rapid rise of diastolic LV pressure can force the *mitral* valve to close prematurely. Such premature closure is often best visualized by M-mode imaging, in which the mitral leaflets coapt before the subsequent QRS complex appears.

Although the depth of the Doppler signal in the left ventricle correlates poorly with the severity of AR, in advanced AR such flow typically extends past the tips of the papillary muscles and into the apex. Finally, detection of diastolic flow reversal in the descending thoracic aorta, imaged from the suprasternal notch, is a sign of moderate-to-severe regurgitation.

Elevated LV outflow tract systolic gradients are a sign of systolic obstruction and do not provide direct information about the severity of AR.

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ANSWER TO QUESTION 69

C (Braunwald, pp. 277–279; Table 16.3)

Several pharmacologic stress-testing agents are available for patients who cannot exercise because of orthopedic limitations, neurologic conditions, or peripheral arterial disease. Dipyridamole acts by inhibiting the cellular uptake and intracellular breakdown of adenosine, increasing the concentration of the latter in the circulation. The subsequent increased activation of adenosine A_{2a} receptors results in vasodilatation and increased coronary blood flow in healthy coronary arteries. However, atherosclerotic vessels tend to be maximally dilated distal to the site of significant stenosis at baseline, such that adenosine does not cause further dilatation in those territories. Therefore, perfusion imaging with dipyridamole, adenosine, or the selective A_{2a} agonist regadenoson in a patient with clinically significant coronary artery disease (CAD) reveals regions of relatively hypoperfused myocardium adjacent to normal zones of increased myocardial blood flow, with little change in myocardial oxygen demand. As a result, in a "positive" test, the infusion of the pharmacologic agent results in heterogeneity of myocardial perfusion, but does not actually provoke myocardial ischemia in the majority of patients with CAD, unlike standard exercise stress testing. Ischemic ST-segment depression may occur in 10% to 15% of patients receiving these vasodilators and tends to correlate with the presence of multiple perfusion defects and extensive CAD. In contrast, chest pain without electrocardiographic changes is a common symptom after infusion of these agents, is likely due to stimulation of adenosine A_1 receptors, and is of no prognostic significance. Of note, xanthine derivatives (e.g., theophylline and caffeine) compete for adenosine receptors and consumption of substances that contain these agents (e.g., coffee) before the test can result in a false-negative study.

Dobutamine is an alternative pharmacologic agent when adenosine or dipyridamole should not be used, as in patients with bronchospastic pulmonary disease (because stimulation of the adenosine A_{2b} receptor can produce bronchospasm). Dobutamine increases myocardial oxygen demand by augmenting myocardial contractility, heart rate, and blood pressure. The increase in coronary blood flow is similar to that in physical exercise, but less than that caused by dipyridamole or adenosine.

In myocardial perfusion imaging, radiotracer agents such as technetium-99m sestamibi or thallium-201 should be injected 1 to 2 minutes before the end of exercise. It is important to maintain the elevated heart rate and blood pressure to allow accumulation of the radiotracer at a "steady" ischemic state.

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ANSWER TO QUESTION 70

E (Braunwald, pp. 90, 92–93, 98; Fig. 10.8)

In mitral stenosis (MS), the opening snap is an *early* diastolic sound generated when superior systolic bowing of the *anterior* mitral valve leaflet is rapidly reversed toward the left ventricle in early diastole, as a result of the high left atrial (LA) pressure. The presence of an opening snap implies a mobile body of the anterior mitral leaflet. The first heart sound tends to be quite loud in MS for a similar reason: it relates to the abrupt systolic movement of the body of the anterior mitral leaflet, which was recessed into the left ventricle throughout diastole because of the elevated LA pressure.

The timing of the A_2-OS interval relates to the severity of MS. When MS is advanced and LA pressure is therefore high, LA and left ventricular pressures equilibrate earlier in diastole, resulting in a *shorter* A_2-OS interval. This interval does vary in atrial fibrillation according to the previous cycle length. During relatively short cycles, LA pressure is higher (because less atrial emptying can occur) and the A_2-OS interval lessens.

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ANSWER TO QUESTION 71

C (Braunwald, p. 145; Fig. 12.44; p. 687)

A large number of arrhythmias may result from digitalis excess. These include bradyarrhythmias related to enhanced vagal tone (e.g., sinus bradycardia or arrest, or atrioventricular [AV] nodal blocks) and tachyarrhythmias attributed to delayed afterdepolarization-triggered activity (e.g., atrial, junctional, and ventricular tachycardias). One of the most common manifestations of excess digitalis is the appearance of ventricular premature beats (VPBs). However, because these are morphologically similar to VPBs of other causes, they are not highly specific for digitalis toxicity. When ventricular bigeminy occurs, varying morphology of the VPBs is suggestive of digitalis excess. Some forms of ventricular tachycardia are also more indicative of digitalis toxicity as the cause, including ventricular tachycardia with exit block and bidirectional ventricular tachycardia. Atrial tachycardia with block may be caused by excess digitalis but can also occur in the setting of structural heart disease without digitalis toxicity. The rhythm must be distinguished from atrial flutter, and because the amplitude of the atrial depolarization may be low, this rhythm is sometimes difficult to recognize. Nonparoxysmal junctional tachycardia is highly suggestive of digitalis excess, although other causes of this rhythm must be excluded, including myocardial ischemia, recent cardiac surgery, and myocarditis. The term *nonparoxysmal* refers to the gradual appearance and disappearance of the rhythm. The majority of patients with this arrhythmia demonstrate AV dissociation due to acceleration of the AV junctional pacemaker. AV dissociation that appears in the course of digitalis therapy should be considered a sign of digitalis intoxication until proven otherwise.

ANSWER TO QUESTION 72

D (Braunwald, pp. 262–263, 275, 277, 280–281, 291–292; Figs. 16.26, 16.28, 16.37, 16.38)

Myocardial perfusion and integrity of cell membranes can be assessed using thallium-201 or technetium-99m radiotracers. However, flow and metabolism can be simultaneously assessed with positron emission tomography using rubidium-82- or nitrogen-13-labeled ammonia as a flow tracer, and ^{18}F-fluorodeoxyglucose as a metabolic tracer. A mismatch pattern (preserved metabolic activity despite reduced flow), as in this case, is indicative of the presence of viable myocardium. Conversely, a true myocardial scar would demonstrate reduced flow and a matched reduction in metabolism (a perfusion-metabolism match). Additional modalities used to assess for viability include dobutamine echocardiography (which is more specific but less sensitive than radionuclide techniques) and delayed hyperenhancement assessed by gadolinium-enhanced magnetic resonance imaging, which has excellent resolution and can accurately estimate the transmural extent of myocardial scar.[1]

Observational studies have suggested that patients with ischemic cardiomyopathy and large areas of viable myocardium identified by noninvasive cardiac imaging have superior rates of survival, more substantial improvements in left ventricular function, a greater reduction in symptoms of heart failure, and better exercise tolerance after revascularization than patients with large areas of nonviable myocardium. However, the prospective, randomized STICH trial failed to show a difference in outcome with revascularization in patients with or without viable myocardium.[2]

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ANSWER TO QUESTION 73

B (Braunwald, pp. 90–93; Fig. 10.5; Tables 10.6 and 10.7)

Both aortic stenosis (AS) and hypertrophic cardiomyopathy (HCM) cause harsh systolic murmurs, but these conditions

frequently can be differentiated by careful physical examination. For example, the carotid upstroke quality is different (see Braunwald, Fig. 10.5). In AS, there is fixed outflow obstruction and the carotid upstrokes are diminished in amplitude and delayed (pulsus parvus et tardus). In contrast, the carotid upstroke in HCM is initially brisk, then diminishes in midsystole as the left ventricular (LV) outflow gradient becomes more pronounced. Another differentiating feature is the pattern of radiation of the murmur. In AS, the systolic murmur radiates to the carotid arteries, which is not the rule in HCM. If a systolic thrill is present, it is usually located in the second right intercostal space in AS, whereas it is more likely to be felt at the fourth left intercostal space in HCM. Dynamic bedside maneuvers are helpful to distinguish AS from HCM. Physiologic maneuvers that enhance contractility increase the intensity of both murmurs. Maneuvers that reduce LV filling (e.g., strain phase of Valsalva maneuver or standing from a squatting position) decrease the intensity of the AS murmur, but in HCM the decreased intraventricular volume causes LV dynamic outflow obstruction to intensify and the murmur of HCM becomes louder. The murmur of HCM diminishes in intensity with maneuvers that augment LV filling, such as sudden squatting from the standing position.

ANSWER TO QUESTION 74

C (Braunwald, pp. 1841–1843)

The direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban and apixaban, are non-vitamin K antagonist oral anticoagulants approved by the US Food and Drug Administration for the prevention of stroke in patients with nonvalvular atrial fibrillation. Each of these agents has been shown to be noninferior, or superior, to warfarin in efficacy and produce less serious bleeding than warfarin.[1] Additional advantages of these agents over warfarin include a fixed dosing regimen (no need to monitor laboratory tests to assess degree of anticoagulation), rapid onset of action such that bridging therapy with parenteral agents is not necessary, fewer drug interactions, and no important food interactions. Disadvantages compared to warfarin include higher cost and lack of a laboratory test to accurately monitor compliance.

The new oral anticoagulants are *not* approved for patients with prosthetic heart valves. Indeed, dabigatran resulted in more thromboembolic complications and greater bleeding risk compared to warfarin in the RE-ALIGN trial of patients with mechanical valves.[2]

The dose of each of these agents must be adjusted in patients with renal dysfunction, and should not be used in severe renal disease. Despite its once-daily dosing in patients with atrial fibrillation, rivaroxaban actually has a shorter half-life (5 to 9 hours) than do apixaban or dabigatran (10 to 16 hours), which are administered twice daily. All of these agents lose most of their anticoagulant effect after 24 hours of discontinuation, so they do not offer an advantage in patients with drug noncompliance.

The antibody fragment idarucizumab binds dabigatran with high affinity, forming an essentially irreversible complex that is cleared through the kidneys. It rapid reverses the anticoagulant effect of dabigatran.

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ANSWER TO QUESTION 75

D (Braunwald, pp. 265–267; Fig. 16.9; see also Answer to Question 51)

These single-photon emission computed tomographic images demonstrate transient ischemic dilatation of the left ventricle during stress. The size of the left ventricular (LV) cavity appears larger in the exercise images than in the rest images. This phenomenon is typically due to extensive exercise-induced ischemia with transient LV dysfunction and dilatation. In some patients, the appearance of LV chamber dilatation is actually due to the development of global subendocardial ischemia with reduced tracer uptake along the internal border of the left ventricle. As a result, there is the appearance of a larger chamber without true chamber dilatation. Regardless of the precise underlying mechanism, transient LV dilatation is a high-risk marker of severe ischemia and correlates with extensive coronary artery disease (CAD; i.e., multivessel or left main coronary artery) on angiography.[1] Similarly, increased lung uptake is another marker of extensive CAD and indicates increased risk for an adverse cardiac event.[1]

LV dilatation that is present both at rest and with exertion would be typical for dilated cardiomyopathy. Nuclear images of a patient with chest pain due to single-vessel disease of the left circumflex artery would likely demonstrate a reversible isolated perfusion defect at the lateral or posterior wall. For the patient with prior inferior myocardial infarction, a fixed inferior wall defect, with or without partial reversibility, would be expected. Breast attenuation artifact typically appears as a fixed defect of the anterior or anterolateral wall. A number of techniques have been developed to reduce the likelihood of a false-positive test due to breast attenuation artifact, including the use of technetium-99m-based agents and electrocardiographic gating.

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ANSWER TO QUESTION 76

D (Braunwald, pp. 90, 92; Fig. 10.6)

Pulsus alternans (Fig. 1.69) is a sign of marked left ventricular dysfunction characterized by alternating strong and weak ventricular contractions, which results in alternating intensity of the peripheral pulses. It is thought to reflect cyclic changes in intracellular calcium levels and action potential duration. It is more easily detectable in the femoral than in the brachial, radial, or carotid artery and can be observed with sphygmomanometry by slowly deflating the blood pressure cuff below the systolic level. When present, this sign can be enhanced with maneuvers that decrease venous return, such as assumption of erect posture. Because patients with pulsus alternans generally have markedly reduced ventricular contractile function, an S_3 gallop sound is common. Pulsus alternans would only rarely be accompanied by electrical

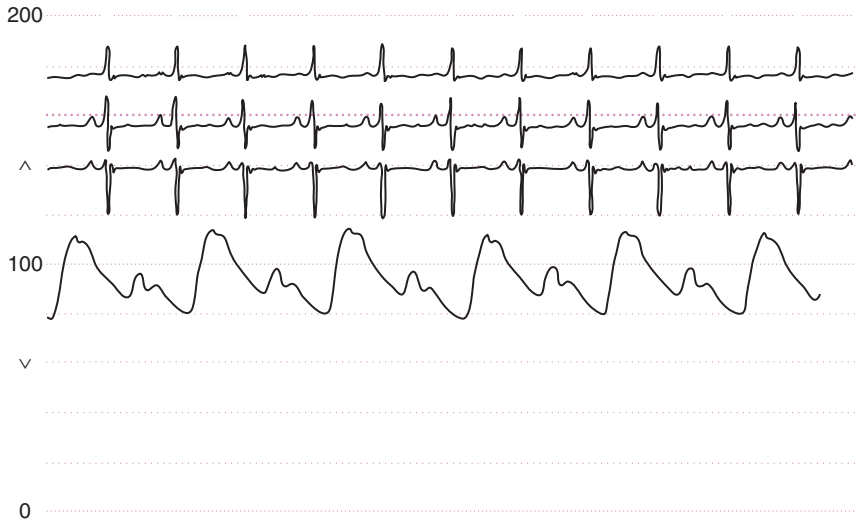

FIG. 1.69 *Pulsus alternans in a patient with severe left ventricular systolic dysfunction. The systolic pressure varies from beat to beat independently of the respiratory cycle. The rhythm is sinus throughout.*

alternans of the QRS complex on the ECG. The latter is more likely to be found in patients with large pericardial effusions.

ANSWER TO QUESTION 77

A (Braunwald, pp. 163, 168–169; Table 13.13)

Exercise testing is often helpful in the assessment of patients with known or suspected arrhythmias. In select patients, particularly those with exercise-induced palpitations, exercise testing is a crucial component of the evaluation. In others, exercise testing can be an important adjunct to ambulatory monitoring and invasive electrophysiologic testing. In association with exercise testing, ventricular arrhythmias may occur during the recovery period, in part because circulating catecholamines continue to increase for several minutes after exertion. In fact, frequent ventricular ectopy in the early postexercise phase predicts a worse long-term cardiac prognosis than ectopy that occurs only during exercise. Supraventricular tachycardia during exercise testing occurs in 4% to 10% of normal individuals and in up to 40% of patients with underlying heart disease. Sustained supraventricular tachycardia develops in only 1% to 2% of patients and is not diagnostic for underlying ischemic heart disease. Patients with known preexcitation, such as Wolff-Parkinson-White (WPW) syndrome, only rarely experience tachyarrhythmias during exercise testing, because antegrade conduction through the atrioventricular node is favored by the catecholamine response to exercise. As such, the delta wave disappears during exercise in 20% to 50% of patients with WPW syndrome.

Exercise testing is also useful to assess the response and risks of antiarrhythmic drug therapy. This is particularly important for patients on class IC antiarrhythmic agents, such as propafenone and flecainide, because QRS widening during exercise on such drugs is predictive of a proarrhythmic effect and reentrant ventricular tachycardia. In addition, prolongation of the QT interval of >10 milliseconds during exercise identifies patients at particularly high risk of a proarrhythmic effect on class IA antiarrhythmic agents.

The development of left bundle branch block (LBBB) during exercise is predictive of subsequent progression to permanent LBBB. Patients with exercise-induced LBBB also have a threefold increase in the risk of death or major cardiac events compared with patients without this abnormality.

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ANSWER TO QUESTION 78

D (Braunwald, pp. 91, 93; Figs. 10.7 and 10.8; Tables 10.6 and 10.7)

Ejection sounds are high-frequency "clicks" that occur in early systole. They may be either aortic or pulmonic in origin, require a mobile valve for their generation, and begin at the exact time of maximal opening of the semilunar valve in question. If the valve is structurally abnormal, the ejection sound is believed to be caused by the abrupt halting of valve opening at its maximum level of ascent in early systole. If the sound is associated with a structurally normal valve, it is called a "vascular" ejection sound (e.g., associated with a dilated aortic root), in which case the origin of the sound is not clearly defined. In valvular pulmonic stenosis, the ejection sound is loudest during expiration. With inspiration, increased venous return augments atrial systole and results in partial opening of the pulmonic valve before ventricular systole commences. In contrast, with expiration, the pulmonic valve is forced to open from a fully closed position, thus generating a louder ejection sound as the valve's systolic movement is suddenly halted. Aortic ejection sounds do not vary with respiration.

The click of mitral valve prolapse occurs in mid- or late systole and coincides with maximal systolic excursion of the prolapsed leaflet(s) into the left atrium. The generation of the click has been attributed to sudden tensing of the redundant leaflets and elongated chordae tendineae.

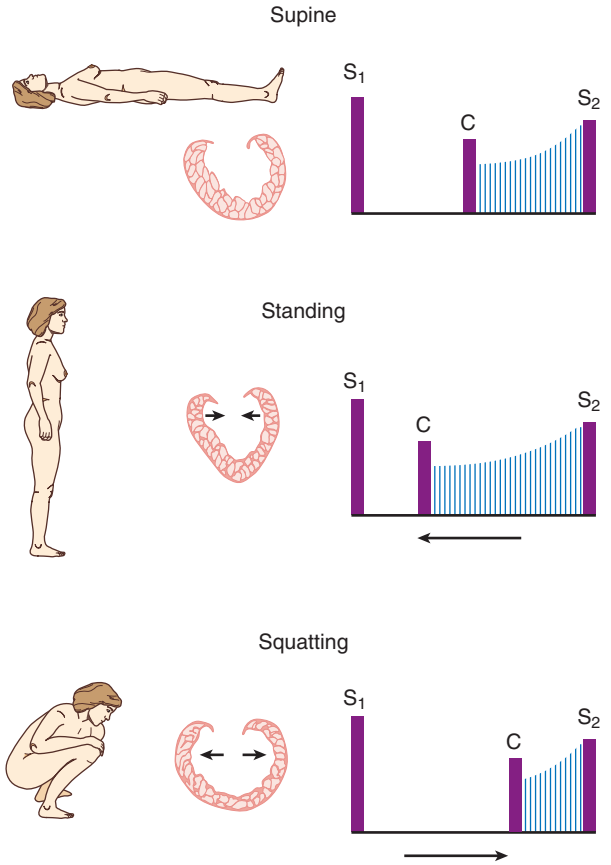

FIG. 1.70 *From Shaver JA, Leonard JJ, Leon DF.* Examination of the Heart: IV Auscultation of the Heart. *Dallas: American Heart Association; 1990:13.*

Maneuvers that decrease left ventricular volume, such as the strain phase of the Valsalva maneuver or standing from a squatting position, move the click earlier in systole (Fig. 1.70).

ANSWER TO QUESTION 79

D (Braunwald, pp. 124, 128, 132, 143, 147; Fig. 12.18; Table 12.10)

Chronic obstructive pulmonary disease (COPD) causes several electrocardiographic abnormalities related to changes of the position of the heart in the chest and hyperinflation of the lungs. These include reduced amplitude of the QRS complex, right-axis deviation, and *delayed* transition in the precordial leads, which may be sufficiently prominent to simulate anterior myocardial infarction (see Braunwald, Fig. 12.18).

For right ventricular hypertrophy (RVH) to be evident on the ECG, it must be severe enough to overcome the opposing effects of the larger left ventricular forces. In patients with COPD, additional electrocardiographic abnormalities that support the presence of true RVH include (1) marked right-axis deviation (>110 degrees); (2) deep S waves in the lateral precordial leads; and (3) an $S_1Q_3T_3$ pattern (S wave in lead I, prominent Q in lead III, inverted T waves in the inferior leads).

ANSWER TO QUESTION 80

E (Braunwald, p. 234; Fig. 14.83; pp. 315, 354–366; see also Answer to Question 41)

Detection and quantification of shunts within the cardiac chambers or great vessels can be accomplished by cardiac catheterization, echocardiography, magnetic resonance imaging, and radionuclide scintigraphy. Shunt evaluation by cardiac catheterization involves utilizing oximetry in multiple locations and calculation of pulmonary and systemic blood flow. Comparison of pulmonary and systemic blood flows helps to establish the presence and magnitude of the shunt, whereas oximetry in multiple locations helps to localize the site of abnormal flow. "Physiologic" shunting, such as occurs in hypoventilation, pulmonary edema, and cardiogenic shock, should be correctable with the administration of 100% oxygen. Failure to correct with 100% oxygen suggests an "anatomic" shunt.

A shortcoming of oximetric shunt detection is its lack of sensitivity, although most clinically relevant shunts *can* be detected using this method. When performing an oximetry run, multiple sites in the inferior vena cava (IVC), superior vena cava (SVC), and right atrium must be sampled because the oxygen saturation from these sites may vary widely. The IVC, because of the relatively low renal oxygen consumption, usually has the *highest* oxygen saturation. Conversely, the coronary sinus delivers venous blood with a very low oxygen saturation. The Flamm formula is used to estimate the mixed venous oxygen content (Mvo_2) proximal to a left-to-right shunt at the right atrial level:

$$Mvo_2 = \frac{3(\text{SVC } O_2 \text{ content}) + 1(\text{IVC } O_2 \text{ content})}{4}$$

ANSWER TO QUESTION 81

D (Braunwald, pp. 124, 130–132; Figs. 12.17 and 12.21; Tables 12.5, 12.6, 12.9)

The normal QRS complex in lead V_1 consists of a small R wave, representing initial septal depolarization, followed by an S wave, which is inscribed as the bulk of electrical forces swing in the direction of the left ventricle.

In right ventricular hypertrophy, the increased right-sided forces cause abnormally tall R waves in leads V_1 and V_2, deep S waves in the lateral precordial leads, and right-axis deviation. The Wolff-Parkinson-White (WPW) syndrome, a form of preexcitation, is characterized by a short PR interval and an initial slur (delta wave) with prolongation of the QRS complex. When WPW is caused by a posterior or lateral left ventricular (LV) accessory pathway, the delta wave is positive in lead V_1, associated with prominence of the R wave. A tall R wave in the right precordial leads is also typical of Duchenne muscular dystrophy. In that disorder, myocardial dystrophy of the posterobasal and contiguous lateral LV wall results in deep Q waves in leads I, aVL, and V_5 and V_6, with reciprocal changes (tall R waves) in leads V_1 and V_2. Accidental placement of the right precordial leads too low on the chest wall is a common technical error that results in prominent R waves in leads V_1 and V_2.

In left anterior fascicular block, the amplitude of the R waves in the right precordial leads is often *diminished* and deep S waves are present in leads V_5 and V_6 because of the anterosuperiorly directed late QRS forces.

ANSWER TO QUESTION 82

B (Braunwald, p. 90; Fig. 10.5; pp. 201, 364; Fig. 19.14)

The hemodynamic pressure tracing is consistent with hypertrophic obstructive cardiomyopathy (HCM). In the tracing, a large gradient exists between the midcavity of the left ventricle and the aorta as shown during the first three full beats. As the catheter is withdrawn into the subaortic left ventricular (LV) outflow tract, the gradient is no longer observed (last three beats). In patients with valvular aortic stenosis (AS), the pressure gradient would persist in the latter location.

A bifid aortic pulse contour is demonstrated in the tracing, with a notch on the upstroke ("spike-and-dome" configuration) characteristic of HCM. This is in contrast to delayed rise of the aortic pressure tracing (and therefore carotid artery pulsation) expected in patients with valvular AS. In addition, LV diastolic dysfunction is common in HCM, owing to impaired LV compliance, which leads to a prominent LV *a* wave and elevation of end-diastolic pressure, as shown on the tracing (~20 mm Hg in this example).

There is no role for aortic valve replacement in the treatment of HCM. In selected patients with HCM and severe symptomatic obstruction due to septal hypertrophy, surgical myomectomy or alcohol septal ablation may be beneficial.

ANSWER TO QUESTION 83

D (Braunwald, pp. 119–121, 123–124; Figs. 12.4 and 12.9)

The normal mean QRS complex in the frontal plane ranges from –30 degrees to +90 degrees. A mean axis more positive than +90 is referred to as *right-axis deviation*, whereas an axis more negative than –30 degrees is *left-axis deviation*. The axis is *indeterminate* (i.e., cannot be calculated in the frontal plane) if all six limb leads record isoelectric QRS complexes (i.e., equal positive and negative deflections).

The designation "vertical" heart is applied when the mean QRS complex is near +90 degrees, in which case the QRS recording in lead I would be isoelectric. A "horizontal" heart refers to a mean axis near 0 degrees, in which case there is a tall R wave in leads I and aVL and an isoelectric QRS complex in aVF.

The normal QRS complex in precordial leads V_1 and V_2 shows small R waves with more prominent S waves, reflecting early septal depolarization followed by activation of the posteriorly located left ventricle. Proceeding from V_1 to V_6, the R wave becomes gradually taller and the S wave less deep. The transition zone represents the lead in which the R wave height surpasses the depth of the S wave and is usually localized to lead V_3 or V_4. An early transition (termed *counterclockwise rotation* as viewed from under the diaphragm) is present when the height of the R wave is greater than the depth of the S wave prior to lead V_3 and would not be expected in left ventrocular hypertrophy. Conversely, a delayed transition *(clockwise rotation)* is present when the S wave depth exceeds the height of the R wave beyond lead V_4.

ANSWER TO QUESTION 84

C (Braunwald, pp. 362–363)

The pioneering work of Gorlin and Gorlin provided equations to calculate cardiac valve areas based on the measured transvalvular pressure gradient and blood flow. The valve area is proportional to

$$\frac{F}{K \times \sqrt{\Delta P}}$$

in which F represents flow across the valve, ΔP is the mean pressure gradient across the orifice, and K is an empiric constant for the valve in question. In the calculation of mitral valve area, a confirmed pulmonary capillary wedge pressure is typically substituted for the left atrial pressure.

There are assumptions and potential pitfalls in the determination of valve area by catheterization techniques. Because flow in the Gorlin equation is assumed to be systemic (forward) cardiac output, the presence of regurgitation across the valve in question results in a falsely *low* value for F in the Gorlin equation, and therefore the calculated valve area may be underestimated. In such cases, the calculated valve area actually represents the lower limit of the true valve area.

Accurate and simultaneous determinations of cardiac output and mean pressure gradient are essential in the determination of a stenotic orifice area. Both of these measurements are subject to error. Because it is the square root of the mean pressure gradient that is used in the Gorlin formula, errors in measurement of the cardiac output have a proportionately greater influence on the calculated valve area.

ANSWER TO QUESTION 85

C (Braunwald, pp. 275–279; Fig. 16.25; Table 16.3; see also Answer to Question 69)

Exercise testing is the preferred stress modality to evaluate for coronary artery disease because it allows a correlation between exertional symptoms and objective findings of ischemia and provides substantial prognostic information. However, many patients are not capable of attaining a sufficient level of exercise (because of physical limitations or poor conditioning) and undergo pharmacologic stress testing instead. The most widely used agents for pharmacologic stress testing are (1) coronary arteriolar vasodilators (adenosine, dipyridamole, and regadenoson) and (2) adrenergic agents such as dobutamine. During pharmacologic perfusion positron emission tomographic scintigraphy of a normal individual, there is homogeneous uptake of the radiotracer (e.g., rubidium-82) throughout the myocardium in both the exercise and resting states. The images in the case of this patient demonstrate severe vasodilator-induced ischemia (hypoperfusion) of the anterior and anteroseptal walls. That is, there is a large region of hypoperfusion on the stress images that is predominantly *reversible:* it almost completely fills in on the resting images. A *fixed* defect is one that is present and unchanged on both exercise and rest images and corresponds to a region of prior myocardial infarction or scar. This patient subsequently underwent cardiac catheterization. A 90% stenosis at the anastomosis of the left internal mammary artery to the left anterior descending artery was found, and successful percutaneous intervention was performed.

ANSWER TO QUESTION 86

B (Braunwald, pp. 85, 201)

This patient has an advanced form of hemochromatosis, a disease that leads to abnormal deposition of iron in tissues.

The most common form of hemochromatosis is *inherited* as an autosomal recessive disorder due to a mutation in the *HFE* gene that codes for a transmembrane protein responsible for regulating iron uptake in the intestine and liver. *Acquired* hemochromatosis is the result of excess iron load due to an underlying disease process (e.g., thalassemia) or increased ingestion of iron.

Normal body content of iron is maintained by the regulated absorption of iron in the intestines. In inherited hemochromatosis, mucosal absorption is inappropriately high, which leads to elevated plasma iron levels and increased transferrin saturation. The extra iron load is deposited in multiple organs, including the heart, pancreas, and liver. A classic presentation therefore is that of "bronze diabetes" due to excess iron deposition in the dermis and pancreas. Other findings include hypogonadism (impaired hypothalamic-pituitary function), arthropathy (often the small joints of the hands), and cirrhosis. The severity of cardiac involvement in hemochromatosis varies widely and may culminate in heart failure due to a mixed dilated and restrictive cardiomyopathy. Electrocardiographic findings may include supraventricular arrhythmias, varying degrees of atrioventricular block, and *low* QRS voltage. Diagnosis is based on the history, an elevated plasma iron level, normal or low total iron-binding capacity (TIBC), and markedly increased transferrin saturation (iron:TIBC ratio) and serum ferritin levels. Treatment options include phlebotomy and chelating agents (e.g., desferrioxamine).

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ANSWER TO QUESTION 87

D (Braunwald, pp. 91–93, 99; Fig. 10.7; Tables 10.6 and 10.7; see also Answer to Question 78)

Physiologic maneuvers that alter left ventricular (LV) filling can aid in the bedside diagnosis of mitral valve prolapse (MVP). Any maneuver that reduces LV volume, such as the Valsalva maneuver or standing from a supine position, causes the valve to prolapse into the left atrium sooner, such that the click and onset of the murmur occur earlier in systole and the murmur may become louder. Conversely, actions that augment impedance to LV emptying, such as isometric handgrip, increase the LV volume and thus delay the click and murmur. Squatting from a standing position will also delay the click and murmur due to the increased venous return and augmented LV volume.

Carotid sinus massage is not generally helpful in differentiating the murmur of MVP from other valvular abnormalities. This maneuver can be useful to slow the heart rate in a tachycardic patient to help characterize extra heart sounds.

ANSWER TO QUESTION 88

E (Braunwald, pp. 135, 143, 144, 146–147; Fig. 12.46; Tables 12.8, 12.10, 12.11; see also Answer to Question 19)

Hyperkalemia is associated with a distinctive sequence of electrocardiographic abnormalities, beginning with narrowing and peaking (tenting) of the T wave, with a shortened QT interval. Progressive hyperkalemia reduces atrial and ventricular resting membrane potentials, which inactivates sodium channels and decreases conduction velocity. At that stage, the QRS complex begins to widen and the P wave amplitude decreases. Complete loss of observed P waves may occur. In that situation, sinus rhythm typically persists but the P wave amplitude is so small that it is not recorded on the surface ECG. Very marked hyperkalemia leads to asystole, sometimes preceded by a slow undulatory (sinusoidal wave) pattern on the ECG caused by marked QRS widening.

Hypokalemia, in contrast, is associated with hyperpolarization of the resting membrane potential and increased action potential duration. This results in resting ST-segment depression and QT interval prolongation. The T waves often become flat, whereas U waves become prominent. The QT prolongation predisposes to torsades de pointes. Hypokalemia, not hyperkalemia, predisposes to digitalis-associated tachyarrhythmias.

ANSWER TO QUESTION 89

D (Braunwald, p. 143; Table 12.10)

Noninfarction Q waves can be produced by any condition that results in (1) abnormal heart position, (2) altered ventricular conduction, (3) ventricular enlargement, or (4) myocardial damage or replacement. Wolff-Parkinson-White syndrome is an example of altered ventricular conduction, in which early activation of the inferoposterior wall by a bypass tract results in inferior Q waves and a pseudoinfarction pattern. Similarly, left bundle branch block is frequently associated with noninfarction Q waves due to altered ventricular activation. Any condition that displaces the mass of the left ventricle posteriorly, such as cardiomyopathy with ventricular dilatation, or chronic obstructive pulmonary disease, is associated with Q waves in the right-sided chest leads and poor R wave progression across the precordium. Incorrect superior placement of the right precordial chest leads can also result in the appearance of Q waves in those leads.

Acidosis leads to hyperkalemia with the characteristic changes of that condition (see Answer to Question 88), but not to the development of Q waves.

ANSWER TO QUESTION 90

C (Braunwald, pp. 134, 145, 161–164; Fig. 13.4)

Several abnormalities on the baseline ECG limit the interpretation of standard exercise electrocardiography. These patterns include preexcitation syndromes, paced ventricular rhythms, left ventricular hypertrophy, and left bundle branch block. Digoxin can accentuate ischemic exercise-induced ST-segment changes, even if the resting ECG is without evidence of ST-segment depression.

Right bundle branch block (RBBB) is associated with T wave and ST-segment changes in the anterior precordial leads. Exercise-induced ST-segment depression in these leads (V_1 to V_4) is a common finding in patients with RBBB and is nondiagnostic for ischemia. Thus, RBBB decreases the sensitivity of the test; however, the ST segments in leads V_5 and V_6, and in leads II and aVF, remain interpretable in patients with this conduction disorder.

ST-segment *depressions* typically are not predictive of the anatomic site of ischemia. In contrast, ST-segment *elevations* in leads that do not contain pathologic Q waves *are* specific for exercise-induced ischemia and are predictive of the anatomic location of ischemia.

Certain findings on exercise electrocardiography are indicative of severe (left main or multivessel) coronary artery disease and should be considered "high risk" markers. These include ≥2-mm ST-segment depressions (particularly at low levels of exercise), ST-segment depressions in more than five leads, ST-segment depressions that persist more than 5 minutes during the recovery phase, ST-segment elevations, and hypotension during exercise (see Answer to Question 48).

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ANSWER TO QUESTION 91

A (Braunwald, pp. 205–209; Figs. 14.38, 14.39, 14.42, 14.43; eFig. 14.20)

The continuous-wave Doppler profile demonstrates combined mitral stenosis (MS) and mitral regurgitation (MR). In the figure, diastolic flow toward the transducer (into the left ventricle) is represented by velocities above the baseline while flow away from the transducer (into the left atrium [LA]) is indicated by velocities below the baseline. In a normal individual, there would be no flow across the valve during systole and the peak diastolic velocity would be <1.3 m/s. The presence of MS results in a high diastolic velocity (usually >1.5 m/s). In addition, the persistent diastolic pressure gradient between the LA and left ventricle in patients with MS results in an abnormally delayed decline of the transmitral velocity signal, as shown in this case. The severity of MS can be determined from Doppler measurements by calculating the pressure decline half-time (see Answer to Question 26).

Two-dimensional echocardiography and Doppler interrogation are also very useful techniques for assessing MR and determining its cause. The continuous-wave Doppler examination shown here demonstrates abnormal systolic flow directed retrograde into the LA. Doppler color flow imaging (not shown in this example) estimates the magnitude of MR, which can be estimated by the area of the visualized regurgitant jet. When MR is severe, Doppler interrogation demonstrates reversal of systolic flow in the pulmonary veins. MR jets that are peripherally directed along the left atrial wall, rather than centrally located, may underestimate the severity of MR as determined by Doppler techniques (Coanda effect).

ANSWER TO QUESTION 92

D (Braunwald, p. 37; Fig. 4.2)

Quality improvement initiatives are increasingly used in healthcare settings, employing several approaches. A commonly used model is PDSA (Plan-Do-Study-Act) in which goals, metrics, and changes to implement are set, and then tested in an iterative PDSA cycle (see Braunwald, Fig. 4.2). This model works best with goals that are measurable, allowing quantification of the effects of a given iteration. The Lean approach was developed at Toyota as a means to improve the efficiency of automobile production. Lean is focused on reducing wasteful processes (including overproduction, unnecessary motion, and uneven production). In healthcare, this approach relies on mapping the essential components of complex processes and empowering all team members to identify targets and areas of potential waste. Whereas Lean focuses on eliminating waste, Six Sigma focuses on reducing unnecessary variation in care delivery, and reducing error rates to less than six standard deviations below average. Six Sigma's iterative process (Define, Measure, Analyze, Improve, and Control) is a variation on the PDSA theme, adding the "control" element to underscore the need for continued monitoring of care processes after successfully reducing variability.

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ANSWER TO QUESTION 93

B (Braunwald, p. 1604; Fig. 78.1)

The microscopic specimen demonstrates marked myocyte disarray typical of hypertrophic cardiomyopathy (HCM). HCM is a genetic disorder caused by more than 900 mutations in genes that encode sarcomeric proteins. It is transmitted in an autosomal-dominant fashion, and specific mutations are often unique to affected families. More than 50% of all HCM mutations occur in genes that encode β-myosin heavy chain or cardiac myosin-binding protein C.

The risk of most concern for patients with HCM is sudden cardiac death. It results from ventricular tachycardia/fibrillation and may occur at any age, but is most often a complication in adolescents and young adults with HCM. The risk is greatest in those with specific clinical markers, for whom primary prevention with an implantable cardioverter-defibrillator is often appropriate, particularly in younger patients: (1) a family history of HCM-related death, especially if sudden; (2) unexplained syncope; (3) hypotensive or attenuated blood pressure response on exercise testing; (4) multiple, prolonged nonsustained bursts of ventricular tachycardia on ambulatory electrocardiographic monitoring; and (5) marked left ventricular hypertrophy (wall thickness ≥30 mm).

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ANSWER TO QUESTION 94

C (Braunwald, pp. 1586–1588)

This patient has a form of arrhythmogenic right ventricular cardiomyopathy (ARVC), a condition in which fibrofatty replacement of myocardium, most commonly of the right ventricle, leads to ventricular arrhythmias and sudden cardiac death. ARVC results from mutations in genes that encode

components of cardiac desmosomes, cell membrane structures that maintain structural and functional contacts between neighboring myocytes. ARVC can occur as an isolated cardiomyopathy or as a syndromic disorder. In *Naxos syndrome*, ARVC is accompanied by woolly, kinky hair and palmar-plantar keratosis. It arises from autosomal *recessive* mutations (in distinction to isolated ARVC, which is transmitted in an autosomal-dominant fashion) in the gene that encodes plakoglobin, a cytoplasmic desmosomal protein. Patients with *Carvajal syndrome* display similar hair and skin findings, but the cardiomyopathic findings predominantly affect the left ventricle. The patient in this question has predominantly right ventricular involvement and therefore has Naxos syndrome.

Major diagnostic criteria for ARVC include (1) RV enlargement and dysfunction visualized by echocardiography, cardiac magnetic resonance imaging, or angiography; (2) fibrofatty replacement of myocardium on endomyocardial biopsy (however, there is a high false-negative rate of diagnosis because of sampling error and because the RV septum [the region sampled by the bioptome] may not display characteristic changes); (3) electrocardiographic abnormalities including inverted T waves in V_1 to V_3, an epsilon wave between the QRS complex and the T wave in leads V_1 to V_3, late potentials on signal averaged electrocardiography, nonsustained or sustained ventricular tachycardia with a left bundle branch morphology, and superior axis; and (4) a confirmed family history of ARVC in a first-degree relative.

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ANSWER TO QUESTION 95

B (Braunwald, pp. 201, 1591–1594; Fig. 77.9)

The presented clinical scenario is most consistent with cardiac amyloidosis, an infiltrative cardiomyopathy in which amyloid fibrils (in this case, abnormal amyloid light-chains [AL] associated with multiple myeloma) expand the extracellular space of cardiac tissues. Clinical manifestations include progressive heart failure (often right-sided > left-sided), postural hypotension due to autonomic dysfunction, macroglossia, and periorbital purpura (in AL amyloidosis). This patient's electrocardiogram shows reduced limb lead voltage due to myocardial infiltration of amyloid fibrils.

The echocardiogram in cardiac amyloidosis typically demonstrates increased thickness of both ventricles with an echobright appearance of the myocardium, diffusely thickened valves, and biatrial enlargement. Diastolic dysfunction is common, as manifest by tissue Doppler imaging, with reduced early diastolic E′ velocities at both the lateral and medial mitral annular levels (note that medial > lateral mitral annular E′ ["annulus reversus"] in answer choice C is characteristic of constrictive pericarditis, not amyloidosis) (see Braunwald, p. 1673).

Although the LV ejection fraction may appear normal in patients with symptomatic cardiac amyloidosis, systolic dysfunction is often present by strain imaging (speckle-tracking), which characteristically reveals severely reduced longitudinal strain at the LV base, but preserved apical strain (Fig. 1.71).

While pericardial effusion is a common finding in cardiac amyloidosis, it is rarely large.

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ANSWERS TO QUESTIONS 96 TO 100

96–A, 97–D, 98–B, 99–C, 100–D (Braunwald, pp. 83–84)

Cardiac syncope is usually of rapid onset and is not preceded by an aura. Patients typically regain consciousness promptly with a clear sensorium. In any patient with a history of coronary artery disease (CAD), cardiac causes of syncope should be carefully investigated, even when the presenting history is somewhat atypical. Neurologic syncope is sometimes preceded by an aura, is more characteristically associated with incontinence and tongue biting, and is notable for a clouded sensorium with slow clearing after return of consciousness. Seizure-like activity may occur at any time cerebral perfusion is impaired and is not particularly helpful in distinguishing different types of syncope.

Distinguishing cardiac syncope due to tachyarrhythmias (usually ventricular tachycardia) from that due to bradyarrhythmias can be difficult on clinical grounds alone. Patients with a history of CAD are at increased risk for ventricular tachyarrhythmias. Bradyarrhythmias are more common in patients with a history of conduction abnormalities.

A neurocardiogenic (vasovagal) cause accounts for approximately 50% of syncopal episodes. It may be precipitated by emotional distress, fear, pain, or extreme fatigue or may occur in the setting of diminished venous return with a reduced stroke volume. Each of these situations results in high catecholamine activity with sympathetic stimulation of the heart. In susceptible individuals, the resultant hypercontractility excessively stimulates cardiac mechanoreceptors (vagal afferent C fibers), which then leads to sympathetic withdrawal, vasodilatation, and bradycardia. When extreme, this activation leads to frank syncope.

Hysterical fainting is typically not accompanied by a change in pulse, blood pressure, or skin color. It is often associated with paresthesias of the hands or face, hyperventilation, dyspnea, and other manifestations of acute anxiety.

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ANSWERS TO QUESTIONS 101 TO 104

101–B, 102–A, 103–D, 104–C (Braunwald, pp. 83–85, 92, 93, 100; Table 10.7; pp. 123, 128–130, 131, 134, 143, 144, 146–147; Figs. 12.14, 12.15, 12.19, 12.42, 12.46; Table 12.11)

The ECG of the young man with exertional chest discomfort and a systolic murmur demonstrates marked left ventricular (LV) hypertrophy with a "strain" pattern. In this case, the

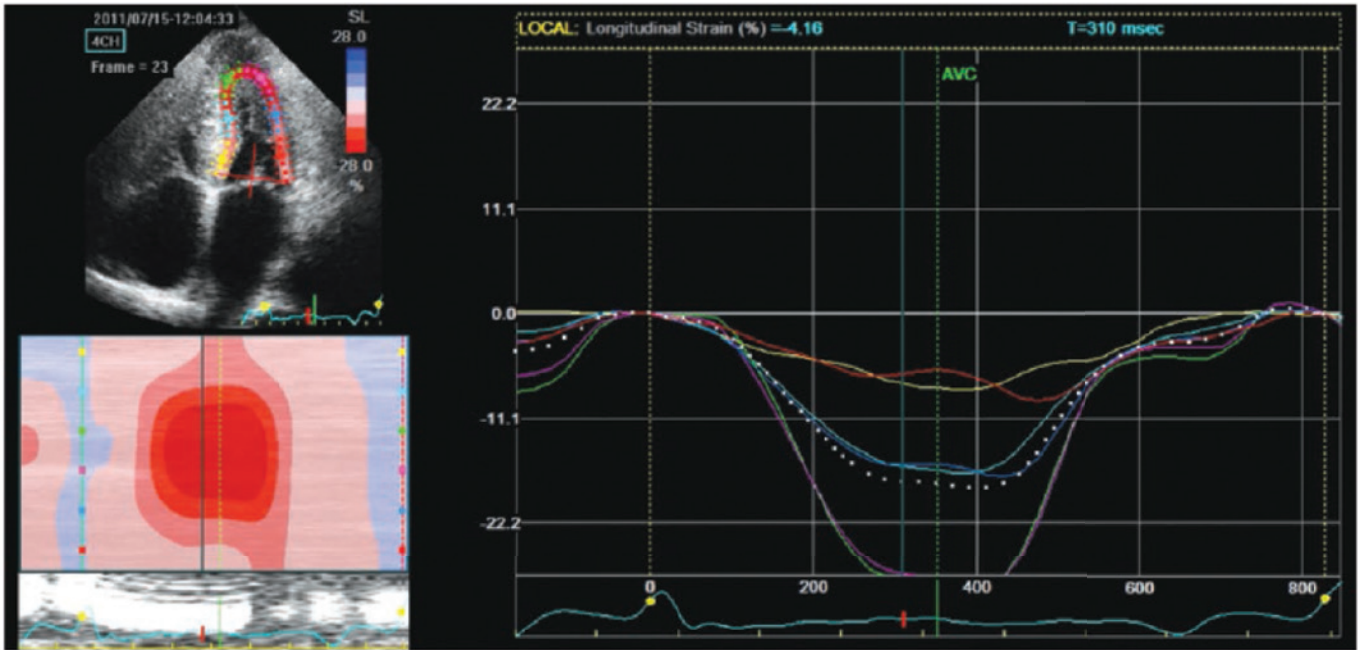

FIG. 1.71 *Echocardiographic strain imaging in amyloid cardiomyopathy. The "bulls-eye" appearance of the longitudinal strain pattern from an echocardiographic apical four-chamber view is shown in a patient with familial amyloid cardiomyopathy and a normal ejection fraction. The appearance represents a gradient of longitudinal strain from the apex to the base with relatively well-preserved apical strain and severely impaired basal strain. In contrast, normal subjects have no significant strain gradient from the apex to the base. This appearance, a useful diagnostic finding, is seen in more than 80% of patients with cardiac amyloidosis, regardless of the precursor amyloid protein.*

systolic murmur is due to dynamic LV outflow obstruction because of hypertrophic cardiomyopathy. Such a murmur becomes louder with maneuvers that decrease LV preload, such as standing from a squatting position or during the strain phase of the Valsalva maneuver. The 56-year-old woman with pleuritic chest discomfort and dyspnea has suffered a pulmonary embolism. Her ECG demonstrates borderline sinus tachycardia, an incomplete right bundle branch block, and an $S_1Q_3T_3$ pattern in the limb leads. The latter reflects a deep S wave in lead I, and a prominent Q wave with T wave inversion in lead III, a pattern that can be observed in individuals with hemodynamically significant pulmonary embolism. However, the sensitivity of this finding is low and it is observed in only a minority of such patients. The most common electrocardiographic findings of hemodynamically important pulmonary embolism are sinus tachycardia and T wave inversions in the anteroseptal leads that may mimic anterior myocardial ischemia. The 36-year-old man with sharp inspiratory chest discomfort has acute pericarditis. His ECG demonstrates diffuse ST-segment elevations. There is also subtle PR-segment depression in the limb leads (especially lead II) and slight PR-segment elevation in lead aVR. All are common findings in patients with acute pericarditis. The elderly alcoholic man with vomiting and epigastric discomfort has developed hypokalemia and hypomagnesemia. His ECG is consistent with these electrolyte derangements, including a prolonged QT (actually QU) interval and low-voltage T waves.

ANSWERS TO QUESTIONS 105 TO 109

105–A, 106–C, 107–B, 108–E, 109–D (Braunwald, pp. 384–386, 390; Figs. 20.15–20.19, 20.22, 20.23, 20.25, 20.26; Tables 20.7 and 20.8)

Coronary arteriography remains the benchmark to assess coronary anatomy. Coronary artery spasm (in the figure see *E*, Injections 1 & 2) may be due to organic vascular disease or may be induced by the mechanical stimulation of the artery by the catheter tip. In 1% to 3% of patients who do not receive vasodilators (e.g., nitroglycerin) before arteriography, spasm may be observed. Whereas the major coronary arteries usually pass along the epicardial surface of the heart, occasional short segments tunnel into the myocardium, leading to myocardial bridging, as demonstrated in the figure in *A* (diastole and systole). Such bridging has been identified in about 5% of human hearts at autopsy. Angiographic identification of a myocardial bridge usually is most common in the left anterior descending (LAD) artery.

Intercoronary collateral vessels in the interventricular septum are normally <1 mm in diameter, are characterized by moderate tortuosity, and tend to serve as connections between numerous septal branches of the LAD and smaller posterior septal branches that arise from the posterior descending artery. Recruitment and development of such collateral vessels due to occlusion of the LAD artery are shown in part *B* of the figure.

The most prevalent hemodynamically significant congenital coronary artery anomaly is the coronary arteriovenous fistula (see *D*). When the fistula drains into any of several areas—the coronary sinus, superior vena cava, pulmonary artery, or a right-sided cardiac chamber—a left-to-right shunt is created. When present in infancy and childhood, approximately half of such patients develop symptoms of congestive heart failure, but the majority of these patients come to attention because of the presence of a loud continuous murmur.

Anomalous coronary origins are present in 1% to 5% of patients undergoing coronary angiography. Ectopic origin of the right coronary artery is present in approximately 2% of patients. Ectopic origin of the left circumflex from the right coronary cusp (see *C*) occurs in <1% of patients. Other abnormal coronary origins occur even less frequently.

ANSWERS TO QUESTIONS 110 TO 113

110–D, 111–B, 112–C, 113–A (Braunwald, pp. 198, 201, 220–221, 231–234; Figs. 14.25, 14.26, 14.31, 14.65–14.67, 14.79; Table 14.11; pp. 312, 315, 317; Fig. 17.17; Tables 17.1 and 17.2; p. 337)

Computed tomography (CT) provides high-resolution morphologic imaging of the heart and is very useful in the diagnosis of a number of cardiovascular disorders. The 53-year-old woman with dyspnea, embolic events, positional lightheadedness, and weight loss has a left atrial (LA) myxoma, the most common primary cardiac tumor. In this case, the myxoma is identified as a large LA mass attached to the interatrial septum (arrows in *D* of the figure). CT and magnetic resonance imaging (MRI) can supplement echocardiography in the assessment of cardiac tumors because of excellent spatial resolution.[1] The young man with recurrent syncope has arrhythmogenic right ventricular (RV) cardiomyopathy. The computed tomogram in *B* demonstrates a dilated right ventricle and aneurysmal bulging of the RV free wall with a scalloped appearance (arrows). Fatty infiltration, fibrosis, and wall motion abnormalities may also be visualized on imaging studies.[2] The 69-year-old woman with prior myocardial infarction has suffered a cerebral thromboembolism due to the left ventricular apical thrombus demonstrated in *C*. The x-ray attenuation of the thrombus is markedly different from that of the surrounding myocardium.

The computed tomogram in *A* demonstrates a thickened pericardium with prominent calcification, typical of constrictive pericarditis, manifest by findings of right-sided heart failure in the clinical scenario presented. Diffuse or localized pericardial thickness >4 mm on cardiac CT is found in the majority of patients with pericardial constriction. Either CT or MRI may be used to image thickened pericardium in suspected constrictive disease; however, pericardial calcification cannot be directly visualized by MRI.[3]

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ANSWERS TO QUESTIONS 114 TO 117

114–D, 115–A, 116–B, 117–C (Braunwald, pp. 186–188; Figs. 14.17 and 14.18; eFig. 14.11; eTable 14.1; Table 14.4)

Normal left ventricular (LV) filling, as recorded by Doppler imaging of diastolic mitral flow velocities, is characterized by a rapid early diastolic phase (the E wave), followed by late additional filling during atrial contraction (the A wave). The relative contribution of early versus late filling is expressed as the E/A ratio. Normally this ratio is >1 and the time required for LV deceleration in early diastole is >190 milliseconds. These relationships are altered in states of abnormal LV filling.

When impaired LV diastolic relaxation is present, there is a reduced diastolic gradient between the left atrium and left ventricle, resulting in a decreased early LV filling (E wave) with a reversed E/A ratio of <1, and the early deceleration time may be prolonged.

The pseudonormalized pattern is observed in patients with more severe diastolic impairment. In this situation there is restoration of the normal early diastolic LV pressure gradient due to elevated left atrial (LA) pressure. Thus, the E wave is taller than the A wave, but the LV deceleration time is more rapid compared with normal (see Braunwald, Figs. 14.17 and 14.18).

The restrictive pattern of LV filling is seen in patients with infiltrative disease and other forms of restrictive cardiomyopathy. Because of the markedly elevated LA pressure, there is enhanced early filling of the left ventricle such that early mitral inflow (E wave) is much greater than the atrial (A wave) contribution to filling and the LV deceleration time is shortened. In this situation, atrial contraction often contributes little to LV filling and the A wave may be barely detected.

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ANSWERS TO QUESTIONS 118 TO 121

118–A, 119–C, 120–D, 121–B (Braunwald, pp. 253–258; Figs. 15.3, 15.5, 15.6; eFigs. 15.18 and 15.19; Table 15.2)

The chest radiograph in patients with abnormalities of the mitral valve commonly displays left atrial (LA) enlargement, whether the lesion is mitral stenosis (MS) or mitral regurgitation. The characteristic chest film in MS (see *A*) displays a heart that is often normal in size, except for the enlargement of the left atrium, which is even more prominent in patients with atrial fibrillation. Calcification of the mitral valve may also be visible. Severe MS is commonly accompanied by pulmonary hypertension, which may be associated with right ventricular dilatation on the chest radiograph. With advanced MS there may be pulmonary vascular redistribution or frank interstitial edema.

A number of findings may be present on the chest radiograph in patients with aortic regurgitation (see *C*). Enlargement of the left ventricle results in displacement of

the cardiac apex downward, to the left, and posteriorly. In addition, the ascending aorta may be dilated. In contrast, aortic stenosis (AS) tends to be more difficult to recognize on plain chest films. Abnormalities in the shape of the heart, although sometimes present, tend to be subtle. Significant left ventricular dilatation occurs only with myocardial failure in end-stage AS. Although calcification of the aortic valve is common in AS, it may not be appreciated on routine chest films. Similarly, routine views may not visualize the post-stenotic dilatation of the ascending aorta that often occurs in this condition.

The ostium secundum type of atrial septal defect (ASD; see *D*) is a congenital cardiac lesion that may be first identified in adulthood. Findings on the chest radiograph include dilatation of the main pulmonary artery, enlargement of the right ventricle, and a generalized increase in the pulmonary vascularity. Right atrial enlargement may be present. Although the chest film in a patient with a secundum ASD may be similar to that of the patient with MS, in the latter condition there is usually LA enlargement (as noted in image *A*) and redistribution of pulmonary blood flow with dilatation of upper lobe vessels and constriction of the vessels at the lung bases. In contrast, when significant left-to-right shunting is present in an ASD, all the pulmonary vessels—including those at the bases—are dilated.

The presence of pericardial effusion (see *B*) leads to a characteristic set of changes in the chest x-ray. With increasing volumes of pericardial fluid, enlargement of the cardiac silhouette with smoothing out and loss of the normal cardiac contours occurs, leading to a symmetrically distended, flask-shaped cardiac shadow. Although such a pattern may be seen with the generalized dilatation that occurs in heart failure, the appearance of the pulmonary hila distinguishes between these two conditions. In pericardial effusion, the pericardial sac tends to cover the shadows of the hilar vessels as it is further distended. In contrast, the failing heart is usually associated with abnormally prominent hilar vessels and pulmonary vascular congestion.

ANSWERS TO QUESTIONS 122 TO 125

122–C, 123–A, 124–B, 125–D (Braunwald, pp. 122–123, 126, 127)

Sinus rhythm is initiated by impulses from the sinus node at rates between 60 and 100 beats/min. Because the wave of depolarization spreads downward from the right atrium (RA) toward the left atrium and ventricles, the P wave is upright in leads I, II, and aVF and is negative in lead aVR. The rate of atrial tachycardia is generally 150 to 200 beats/min, with a P wave contour that is different from that of the normal sinus P wave. This rhythm occurs most commonly in patients with structural heart disease (coronary artery disease, cor pulmonale, digitalis intoxication), but can also occur in normal hearts. Potential mechanisms of atrial tachycardia include automaticity, triggered activity, and reentry. Focal atrial tachycardia due to automaticity generally accelerates after its initiation, but the initiating P wave has the same contour as subsequent ones. In contrast, in reentrant rhythms such as atrioventricular nodal reentrant tachycardia, the first P wave is usually different in shape compared with subsequent P waves because the tachycardia is initiated by a premature atrial complex, whereas subsequent P waves derive from retrograde atrial activation.

Atrial flutter is a macroreentrant atrial rhythm. In the typical form, the reentrant pathway circulates in a counterclockwise direction in the RA, constrained anteriorly by the tricuspid annulus and posteriorly by the crista terminalis and eustachian ridge. The atrial rate during typical atrial flutter is 250 to 350 beats/min. The ECG shows recurring regular sawtooth flutter waves often best visualized in leads II, III, and aVF. In typical counterclockwise flutter, the flutter waves are inverted (negative) in these leads.

ANSWERS TO QUESTIONS 126 TO 129

126–B, 127–C, 128–A, 129–F (Braunwald, pp. 26–29; Figs. 3.3–3.5; pp. 163–164; Table 13.10; pp. 264–265; eFig. 16.4)

Test selection depends in part on the goal of the test (i.e., is the test intended to select a subpopulation with increased probability of disease for further testing [a screening test], or is the purpose to definitively rule out the presence of disease [a confirmatory test])? Sensitivity quantifies a test's ability to detect disease when present, whereas specificity quantifies a test's ability to rule out disease. As demonstrated in the receiver operating curve, sensitivity and specificity are inversely related—as sensitivity increases, the specificity of the test decreases, and vice versa. Sensitivity and specificity can be derived from the graph: the dashed vertical line denotes 98% specificity, at which point Test A has a sensitivity of ~59%, but Test B has a sensitivity of only ~47%. Test A is thus a better test to confirm the presence of disease (i.e., better sensitivity at the high level of specificity required for a confirmatory test). In contrast, an ideal screening test has high sensitivity while minimizing false positives (i.e., maximizing specificity). In the high-sensitivity range, Test B has a higher specificity (specificity ~70% at a sensitivity of 98%, denoted by the dashed line) than does Test A (specificity ~60% at the same sensitivity of 98%), making Test B the better screening test.

$$\text{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}$$

$$\text{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}}$$

Sensitivity and specificity are specific to a test, whereas positive predictive value and negative predictive value reflect the characteristics not only of the test but also of the population in which the test is being used.

$$\text{Positive Predictive Value} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}} \times 100$$

$$\text{Negative Predictive Value} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}} \times 100$$

For the population in question with a disease prevalence of 50/1000,

True Positives = Number of people affected × Sensitivity = $50 \times 0.98 = 49$

False Negatives = Number affected − True Positives = $50 - 49 = 1$

True Negatives = Number unaffected × Specificity = 950 × 0.6 = 570

False Positives = Number unaffected − True Negatives = 950 − 570 = 380

$$\text{Positive Predictive Value} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}} \times 100 = \frac{49}{49+380} \times 100 = 11\%$$

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ANSWERS TO QUESTIONS 130 TO 133

130–D, 131–A, 132–C, 133–B (Braunwald, pp. 123, 130–131, 134–135, 144, 146–147; Figs. 12.17, 12.42, 12.46; Tables 12.5, 12.7, 12.11)

The patient with renal failure has developed hyperkalemia. The ECG was obtained when the serum potassium level was 7.2 and shows the characteristic narrow, peaked T waves of hyperkalemia (see *D* in the figure). The QT interval is shortened relative to the baseline, and there is mild QRS widening. The P wave amplitude is normal at this time, but would decrease with progressive, untreated hyperkalemia. The patient with positional, sharp chest discomfort has acute viral pericarditis, manifest on the ECG by diffuse ST-segment elevation, PR-segment depression, and a resting tachycardia (see *A*). The ECG of the man with lightheadedness demonstrates complete heart block. Although the initial portion of the rhythm may suggest 2:1 second-degree atrioventricular block (see *C*), there is actually no relationship between the P waves and QRS complexes (note that the PR interval varies). The 38-year-old woman has congenital heart disease with partially corrective surgery as a child and has subsequently developed pulmonary hypertension with a right-to-left shunt through an atrial septal defect, resulting in systemic oxygen desaturation. The ECG shows findings of right ventricular (RV) hypertrophy, including right-axis deviation in the frontal plane, deep S waves, and abnormally small R waves in the left-sided leads, with reversal of normal R wave progression across the precordium (see *B*). The rSR′ pattern in lead V_1 is consistent with RV conduction delay.

ANSWERS TO QUESTIONS 134 TO 142

(Braunwald, Chapter 14)

134. Transthoracic echocardiogram, apical four-chamber view in systole. There is left ventricular (LV) enlargement with a thinned region of the distal septum and apex, which bulges outward and contains a large thrombus. There is a pericardial effusion external to the left ventricle. *Diagnosis:* LV aneurysm with thrombus and pericardial effusion.
135. Transthoracic echocardiogram, parasternal short-axis view at the aortic valve level. A bicuspid aortic valve is present (10-o'clock to 4-o'clock orientation). *Diagnosis:* Congenital bicuspid aortic valve.
136. Transthoracic echocardiogram, parasternal long-axis view. Turbulent color flow across the interventricular septum is consistent with a left-to-right shunt through a perimembranous ventricular septal defect. *Diagnosis:* Congenital ventricular septal defect.
137. Transthoracic echocardiogram, parasternal long-axis view. There is dilatation of the aortic root. *Diagnosis:* Patient has aortic root dilatation because of Marfan syndrome.
138. Transthoracic echocardiogram, apical four-chamber view, with color Doppler interrogation (*A*). The blue (retrograde flow) color Doppler signal extends to the level of the pulmonary veins, consistent with severe mitral regurgitation. In *B*, pulsed Doppler interrogation of a pulmonary vein confirms reversed systolic flow at that level (the systolic Doppler signal below the baseline indicates flow from the left atrium into the pulmonary vein). *Diagnosis:* Severe mitral regurgitation.
139. Doppler tissue imaging (DTI) at the lateral mitral annulus. The early diastolic relaxation velocity (the deflection below the baseline after the electrocardiographic T wave) is recorded at 7.3 cm/s. Values <10 cm/s are consistent with impaired diastolic relaxation. An example of a normal DTI is shown in Fig. 1.72 (The arrow indicates the early diastolic relaxation velocity.). *Diagnosis:* Diastolic dysfunction, due in this case to cardiac amyloidosis.
140. Transthoracic echocardiogram, apical four-chamber view. Images are before (*left*) and after (*right*) injection of agitated saline into an antecubital vein (a "bubble study"). A redundant and mobile interatrial septum bulges into the left atrium. Passage of "bubbles" into the left side of the heart is consistent with a right-to-left shunt. *Diagnosis:* Atrial septal aneurysm with likely patent foramen ovale and right-to-left shunt (possible paradoxical embolism as the cause of the stroke).
141. Transthoracic echocardiogram, subcostal view. There is a thickened interatrial septum that spares the fossa ovalis. *Diagnosis:* Lipomatous hypertrophy of the atrial septum.
142. Transthoracic echocardiogram, parasternal long-axis view. There is a large left-sided pleural effusion posterior to the left ventricle (note that the effusion extends posterior to the descending aorta; pericardial effusions accumulate *anterior* to the descending aorta). *Diagnosis:* Dyspnea due to large pleural effusion.

ANSWERS TO QUESTIONS 143 TO 167

The numbers in brackets refer to features on the Electrocardiogram Response Form on page 32.

143. [7] Normal sinus rhythm (rate 89)
[36] Low voltage (borderline)
[53] Acute anterior Q wave myocardial infarction
[65] Anterior ST-segment elevation consistent with myocardial injury
(Patient presented with an acute anterior STEMI)
144. [7] Normal sinus rhythm (rate 74)
[6] Left atrial abnormality
[43] Right bundle branch block
[58] Inferior Q waves consistent with old MI
(The ECG suggests patient has had prior inferior MI, and right bundle branch block)
145. [7] Normal sinus rhythm (rate 83)
[38] Right-axis deviation

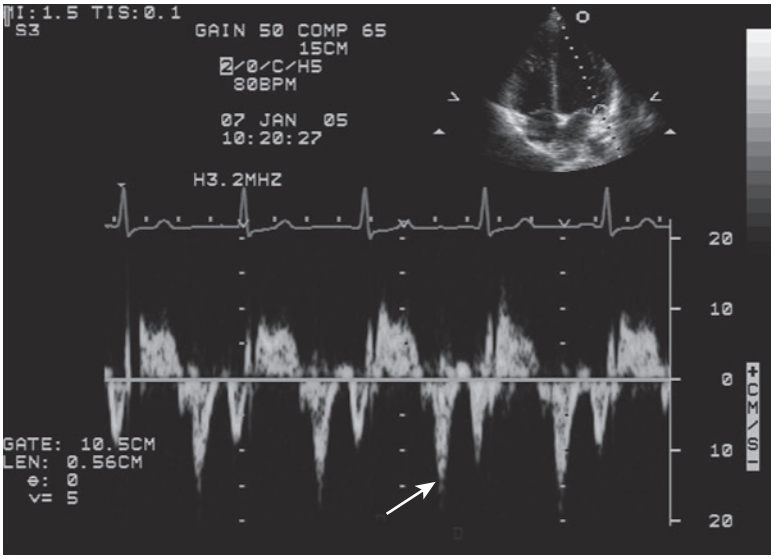

FIG. 1.72

[41] Right ventricular hypertrophy
[43] Right bundle branch block
(The patient has pulmonic stenosis with right ventricular hypertrophy)

146. [9] Sinus bradycardia (rate 55)
[89] Inappropriate ventricular paced beats (failure to sense [complex 11])
[63] Nonspecific inferior T wave abnormality
[69] Prominent U waves
(Pacemaker malfunction)

147. [7] Normal sinus rhythm (rate 67)
[34] Wolff-Parkinson-White syndrome (type B)

148. [18] Atrial flutter with 2:1 atrioventricular conduction, ventricular rate 160 (the flutter waves are seen best in the inferior leads)

149. [17] Supraventricular tachycardia
(Note retrograde P waves between QRS and T wave, best seen in leads V_3–V_6)

150. [19] Rapid atrial fibrillation (ventricular rate ~220)
[37] Left-axis deviation
[34] Wolff-Parkinson-White syndrome
(Patient has Wolff-Parkinson-White syndrome with atrial fibrillation and rapid conduction through the accessory pathway, which is probably located in the left posteroseptal region)

151. [8] Sinus arrhythmia
[30] Type I second-degree atrioventricular block (Wenckebach)
[43] Right bundle branch block
(Patient experienced a vagal reaction during an uncomfortable medical procedure)

152. [8] Sinus arrhythmia
[36] Low voltage of native beats
[37] Left-axis deviation (borderline)
[25] Nonsustained ventricular tachycardia
(He has bursts of nonsustained ventricular tachycardia triggered by paced beats)

153. [85] Atrial paced rhythm
[81] Diffuse ST elevation consistent with acute pericarditis
(Patient has findings of postoperative pericarditis)

154. [19] Atrial fibrillation (ventricular rate ~60)
[43] Right bundle branch block
[38] Right-axis deviation
[46] Left posterior fascicular block

155. [9] Sinus bradycardia (rate 58)
Counterclockwise rotation
[61] Early repolarization
(Diffuse ST-segment elevation is <25% height of the T wave and there is no PR-segment depression, which helps distinguish early repolarization from pericarditis)

156. [10] Borderline sinus tachycardia (rate 100)
[49] Intraventricular conduction delay
[66, 73] Peaked T waves consistent with hyperkalemia
(This patient with chronic renal failure presented with a serum potassium level of 7.5 mmol/L)

157. [7] Sinus rhythm (rate 78)
[77] Dextrocardia
(Patient has total situs inversus and is asymptomatic [note inverted P in I, aVL and reverse R wave progression across the chest leads])

158. [10] Sinus tachycardia (atrial rate 106)
[33, 27] Third-degree atrioventricular block with ventricular escape rhythm (or possibly AV junctional rhythm with left bundle branch block [22])

159. [7] Normal sinus rhythm (rate 84)
[44] Incomplete right bundle branch block
[57] Acute ST-elevation inferior myocardial infarction

160. [7] Normal sinus rhythm (rate 66)
[29] First-degree atrioventricular block
[43] Right bundle branch block
[45] Left anterior fascicular block
[40] Left ventricular hypertrophy

161. [7] Normal sinus rhythm (atrial rate ~84)
[33, 22] Third-degree atrioventricular block with junctional escape rhythm
(Patient has congenital complete heart block related to maternal systemic lupus erythematosus)

162. [7] Normal sinus rhythm (rate 90)
[38] Right-axis deviation
[6] Left atrial abnormality

[49] Right ventricular conduction delay
[41] Right ventricular hypertrophy
[63] Nonspecific ST-segment/T wave abnormality in anterior leads
(A 23-year-old woman with a secundum atrial septal defect)

163. [7] Normal sinus rhythm (rate 82)
[68] Prolonged QT interval
(Patient with congenital prolongation of the QT interval whose subsequent ambulatory monitor showed periods of polymorphic ventricular tachycardia as the cause of her presyncopal episodes)

164. [19] Atrial fibrillation with rapid ventricular response (ventricular rate ~140)
[37] Borderline left-axis deviation
[47] Left bundle branch block

165. [9] Sinus bradycardia (rate 58)
[36] Low voltage
[37] Left-axis deviation
[58] Inferior Q waves—old inferior MI
[68] Prolonged QT interval
(Patient has COPD, and QT interval is prolonged because of amiodarone therapy)

166. [90] Biventricular pacing (cardiac resynchronization therapy)

167. [4] Baseline artifact due to resting tremor
[7] Sinus rhythm (rate 70)
Otherwise normal tracing
(Patient has Parkinson disease.)

SECTION II QUESTIONS

(CHAPTERS 21 TO 43)

Heart Failure; Arrhythmias, Sudden Death, and Syncope

Akshay Desai, Garrick Stewart, and Leonard S. Lilly

Directions:

For each question below, select the ONE BEST response.

QUESTION 168

Based on current heart failure guidelines, switching from an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker to the angiotensin receptor neprilysin inhibitor sacubitril/valsartan would be appropriate for which of the following patients?

A. A 60-year-old woman with anthracycline-induced cardiomyopathy, left ventricular ejection fraction (LVEF) of 35%, New York Heart Association (NYHA) class IV symptoms, permanent atrial fibrillation (AF), heart rate 75 beats/min, and blood pressure 90/70 mm Hg, who currently takes lisinopril 5 mg daily, metoprolol succinate 25 mg daily, and spironolactone 25 mg daily
B. A 40-year-old man with ischemic cardiomyopathy, LVEF 40%, NYHA class II symptoms, heart rate 70 beats/min in sinus rhythm, blood pressure 105/70 mm Hg, and prior intolerance of ACE inhibitors due to angioedema, currently treated with carvedilol 25 mg twice daily, losartan 100 mg daily, furosemide 80 mg twice daily, and eplerenone 50 mg daily
C. A 75-year-old woman with heart failure and preserved ejection fraction, LVEF 50%, NYHA class III symptoms, heart rate 75 beats/min in sinus rhythm, blood pressure 120/80 mm Hg, treated with metoprolol succinate 100 mg daily and hydrochlorothiazide 25 mg daily, valsartan 160 mg twice daily, and spironolactone 25 mg daily
D. A 64-year-old man with nonischemic dilated cardiomyopathy, LVEF 35%, NYHA class III symptoms, permanent AF, heart rate 65 beats/min, blood pressure 104/70 mm Hg who is currently treated with bisoprolol 10 mg twice daily, candesartan 16 mg daily, spironolactone 25 mg daily, and torsemide 40 mg daily

QUESTION 169

Which of the following statements about natriuretic peptides is NOT correct?

A. Circulating levels of both atrial natriuretic peptide and brain natriuretic peptide (BNP) are elevated in patients with heart failure
B. Plasma BNP level is useful in distinguishing cardiac from noncardiac causes of dyspnea in the emergency department setting
C. Elevated plasma BNP levels predict adverse outcomes in patients with acute coronary syndromes
D. Prohormone BNP is cleaved into the biologically inactive N-terminal (NT) proBNP and biologically active BNP
E. Circulating levels of NT-proBNP levels decrease with age

QUESTION 170

Which of the following conditions is likely to precipitate symptomatic heart failure in patients with previously compensated left ventricular contractile dysfunction?

A. Atrial fibrillation
B. Marked sinus bradycardia
C. Atrioventricular dissociation
D. Right ventricular apical pacing
E. All of the above

QUESTION 171

An 80-year-old woman with a history of hypertension and type 2 diabetes is hospitalized because of progressive exertional dyspnea and orthopnea. Her examination is notable for an elevated jugular venous pressure (JVP) to the angle of the jaw, pitting peripheral edema with warm extremities, normal blood pressure, and clear mental status. The admission chest radiograph is shown in Fig. 2.1, demonstrating cardiomegaly, small bilateral pleural effusions, and vascular engorgement. After 4 days of treatment with a loop diuretic, she appears clinically euvolemic with a JVP of 7 cm H_2O. However, the serum creatinine value has risen from 1.6 mg/dL at the time of admission to 2.3 mg/dL. Which of the following statements about this patient's condition is NOT correct?

A. Diabetes and hypertension predispose to the development of cardiorenal syndrome
B. Worsening renal function during hospitalization for acute heart failure is an important predictor of early hospital readmission and mortality
C. Decreased renal venous pressure contributes to the cardiorenal syndrome

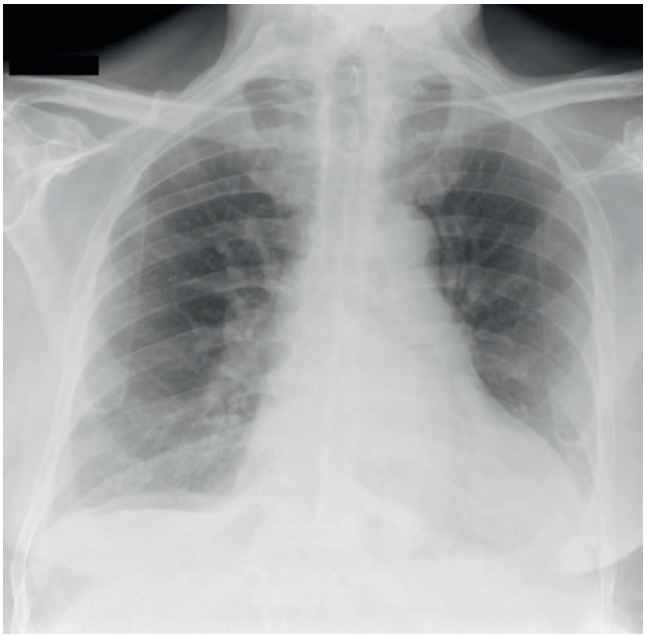

FIG. 2.1

D. High-dose loop diuretic therapy activates neurohormones that contribute to the cardiorenal syndrome
E. A disproportionate rise in blood urea nitrogen compared with serum creatinine is a sign of renal hypoperfusion

QUESTION 172

Which of the following statements regarding therapy for heart failure with reduced ejection fraction is NOT correct?
A. Angiotensin-converting enzyme (ACE) inhibitors improve survival in heart failure more than the combination of hydralazine plus isosorbide dinitrate
B. Digoxin therapy decreases hospitalizations and mortality in patients with chronic heart failure
C. Angiotensin II receptor blockers provide morbidity and mortality benefits comparable with ACE inhibitors in patients with heart failure
D. Spironolactone reduces mortality in patients with class III to IV heart failure symptoms
E. The aldosterone antagonist eplerenone reduces mortality in patients with class II to III heart failure

QUESTION 173

Which of the following statements about cardiac transplantation is NOT true?
A. Use of the immunosuppressant agent cyclosporine improves long-term outcomes after cardiac transplantation
B. Younger patients have better survival rates than older patients after cardiac transplantation
C. Cardiac transplant patients lack the chronotropic response necessary to support the hemodynamic demands of exercise
D. Endomyocardial biopsy is the most reliable current technique to assess allograft rejection
E. Risk of death from malignancy rises with time after transplantation, whereas mortality from infection declines

QUESTION 174

Which of the following statements about diuretics in heart failure is TRUE?
A. Mannitol is an effective diuretic in cardiac surgical patients with decompensated heart failure
B. Aldosterone receptor antagonists lessen the tendency of angiotensin-converting enzyme inhibitors to cause hyperkalemia
C. Loop diuretics often result in hypokalemia and metabolic acidosis
D. The effectiveness of loop diuretic agents is reduced by nonsteroidal anti-inflammatory drugs

QUESTION 175

Which of the following statements about laboratory findings in heart failure is NOT correct?
A. Serum electrolyte values are usually normal in patients with untreated heart failure of short duration
B. Contributors to hyponatremia in heart failure include dietary sodium restriction, diuretic therapy, and an elevated circulating vasopressin level
C. Elevated serum aspartate aminotransferase levels may accompany congestive hepatomegaly due to heart failure
D. Acute hepatic venous congestion due to heart failure may produce a syndrome that closely resembles viral hepatitis
E. Pulmonary capillary wedge pressures of 13 to 17 mm Hg are commonly responsible for pulmonary vascular redistribution and interstitial edema on the chest radiograph

QUESTION 176

Each of the following statements about myocardial contraction is true EXCEPT
A. $Beta_1$-adrenergic stimulation increases the concentration of intracellular calcium
B. $Beta_1$-adrenergic stimulation promotes production of intracellular cyclic guanosine monophosphate
C. Interaction of calcium with troponin C is essential for myocyte contraction
D. Myosin molecules are tethered to the Z line by the protein titin
E. The sarcoplasmic reticulum plays a key role in the release and uptake of calcium

QUESTION 177

A 45-year-old woman who underwent orthotopic cardiac transplantation because of a familial dilated cardiomyopathy presents 2 months later for routine post-transplant surveillance. An endomyocardial biopsy is obtained (Fig. 2.2). Which of the following statements is NOT correct?
A. Endomyocardial biopsy is the most reliable technique to assess for this complication
B. This disorder is caused by preexisting recipient antibodies to allogeneic antigens on the vascular endothelium of the donor organ
C. Lymphocyte infiltration and myocyte necrosis are the most important biopsy features in the diagnosis of this disorder

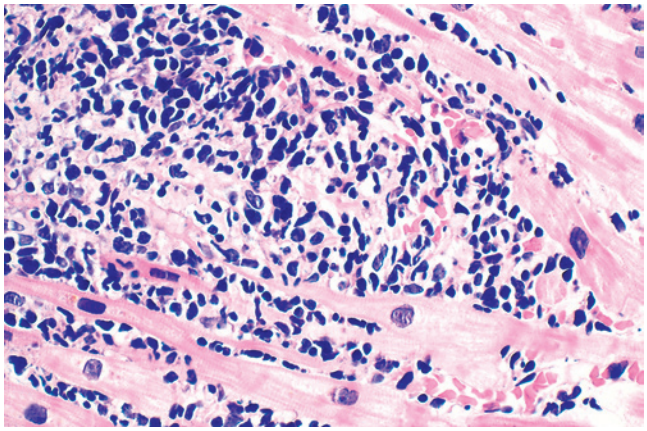

FIG. 2.2 *From Kumar V, Abbas AK, Fausto N, eds.* Robbins and Cotran Pathologic Basis of Disease. *7th ed. Philadelphia: Elsevier; 2005:615.*

D. Most episodes of this complication arise <6 months after transplantation
E. Pulsed corticosteroid therapy is the treatment of choice for this finding

QUESTION 178

Which of the following statements is NOT correct?
A. Major determinants of cardiac output are heart rate and ventricular stroke volume
B. The myocardium extracts oxygen from blood nearly maximally at rest such that the coronary sinus oxygen saturation is <40%
C. During strenuous exercise, O_2 consumption can increase up to 18-fold
D. The peak O_2 consumption and the anaerobic threshold as measured by cardiopulmonary exercise testing are highly reproducible when measured days or weeks apart
E. A measured peak O_2 consumption of 20 mL/min/kg at exercise testing indicates severe functional impairment

QUESTION 179

Which of the following statements regarding structural and hemodynamic left ventricular (LV) parameters in chronic pressure- and volume-overload states is correct?
A. LV systolic stress is proportional to intracavitary pressure and chamber radius
B. Eccentric hypertrophy is characteristic of pressure overload
C. Concentric hypertrophy is characteristic of volume overload
D. LV wall thickness is greater in volume-overload states than in pressure-overload states

QUESTION 180

Which of the following statements concerning therapy of patients with left ventricular (LV) dysfunction is NOT correct?
A. Amiodarone reduces mortality in patients with class II or III heart failure who have a left ventricular ejection fraction <35%
B. Implantation of a cardioverter-defibrillator is indicated in patients with the combination of LV dysfunction and unexplained syncope or resuscitated cardiac arrest
C. Patients with LV dysfunction and a transient or correctable cause of ventricular tachycardia remain at high risk for sudden death
D. Prophylactic implantation of a cardioverter-defibrillator is effective in reducing mortality in patients with coronary artery disease and severe LV dysfunction
E. Use of dronedarone in patients with moderate or severe heart failure is associated with increased mortality

QUESTION 181

A 56-year-old man with ischemic cardiomyopathy and a left ventricular ejection fraction of 25% comes for an outpatient clinic visit complaining of dyspnea and fatigue with minimal exertion (New York Heart Association class III). His medical regimen includes lisinopril, carvedilol, eplerenone, and furosemide, as well as aspirin and atorvastatin. Resting electrocardiography reveals sinus rhythm with a QRS complex duration of 160 milliseconds and left bundle branch morphology. He is being considered for implantation of a biventricular pacemaker. Which of the following statements about cardiac resynchronization therapy (CRT) is correct?
A. CRT reduces mortality in patients with class III or IV heart failure only when combined with an implantable cardioverter-defibrillator
B. A patient with right bundle branch block is as likely to respond to CRT as a patient with left bundle branch block and similar QRS duration
C. CRT improves myocardial performance without increasing myocardial oxygen consumption
D. Echocardiographic measures of dyssynchrony are part of the standard selection criteria for CRT

QUESTION 182

A 35-year-old woman with peripartum cardiomyopathy, left ventricular ejection fraction 25%, and a dual chamber implantable cardioverter-defibrillator (ICD) comes to see you for a routine clinic evaluation. She is able to perform most of her daily activities without limitation, but becomes short of breath walking one flight of stairs. She is currently treated with metoprolol succinate 50 mg daily, candesartan 32 mg daily, furosemide 40 mg daily, and spironolactone 25 mg daily. On examination the heart rate is 84 beats/min, blood pressure 110/70 mm Hg, jugular venous pressure 7 cm, the lungs are clear to auscultation, and there is no peripheral edema. The electrocardiogram shows sinus rhythm with right bundle branch block and QRS duration of 120 ms. Which of the following is the most appropriate next step in her heart failure management?
A. Increase metoprolol succinate to 100 mg once daily
B. Add ivabradine 5 mg twice daily
C. Substitute candesartan with sacubitril/valsartan 24/26 mg twice daily
D. Upgrade her ICD to a device that also provides cardiac resynchronization therapy (biventricular pacing)
E. Her symptoms are stable; make no changes to the regimen

QUESTION 183

A 52-year-old businessman presents to the office complaining of increasing fatigue and shortness of breath. He has also recently noticed that he is more comfortable sleeping on three pillows. He denies chest discomfort or pleuritic pain. His only

medications are hydrochlorothiazide 25 mg daily and atenolol 50 mg daily for hypertension of 10 years' duration with good control. His past medical history includes an appendectomy. He smokes ½ pack of cigarettes per day. He drinks whiskey socially and admits to two martinis at lunchtime each day. There is no family history of heart disease.

On examination, his heart rate is 104 beats/min, respirations are 20 breaths/min, and blood pressure is 134/84 mm Hg. There are no hypertensive changes in the fundi. There are bibasilar rales over the lower third of the lung fields; the carotid upstrokes are normal. The apical impulse is laterally displaced and sustained. S_1 and S_2 are normal. There is both a loud S_4 and S_3. There is a grade 2/6 holosystolic murmur that radiates to the axilla. The remainder of the examination findings are normal except for a trace of pedal edema. The chest radiograph shows left ventricular (LV) enlargement. The ECG is consistent with LV hypertrophy. The most likely cause for this man's heart failure is

A. Hypertension
B. Alcoholic cardiomyopathy
C. Coronary atherosclerosis
D. Hypertrophic cardiomyopathy
E. Excessive beta blocker dosage

QUESTION 184

A 68-year-old woman with long-standing hypertension presents to the emergency department because of progressive exertional dyspnea and fatigue over the past several months. She notes that it is increasingly difficult to put on her shoes because of ankle edema and is uncomfortable sleeping on one pillow due to a cough while recumbent. She denies chest discomfort or palpitations. Her medications include atenolol and hydrochlorothiazide.

On examination, she is an overweight woman with heart rate of 70 beats/min, respirations of 20 breaths/min, and blood pressure of 170/90 mm Hg. The jugular venous pressure is 14 cm H_2O. Examination of the chest is notable for bibasilar rales. The cardiovascular examination reveals a normal S_1, physiologically split S_2, and S_4 gallop. There is no audible murmur. The extremities demonstrate pitting edema to the midcalf bilaterally.

The ECG reveals sinus rhythm with voltage criteria for left ventricular (LV) hypertrophy. The chest radiograph shows a normal cardiac silhouette with bilateral pleural effusions with mild interstitial pulmonary edema. Echocardiography demonstrates concentric LV hypertrophy. The estimated ejection fraction is 70%.

Which of the following pharmacologic agents has been shown to consistently improve survival in this condition?

A. Digoxin
B. Perindopril
C. Spironolactone
D. Candesartan
E. None of the above

QUESTION 185

A 40-year-old man is admitted to the hospital with progressive exertional dyspnea, fatigue, and palpitations. He has no significant past medical history and was well until 4 weeks ago, when he developed flu-like symptoms with low-grade fever, myalgias, pharyngitis, and cough. Clinical examination is consistent with decompensated heart failure. The electrocardiogram shows first-degree atrioventricular block and T wave inversions in the anterior precordial leads. Echocardiography at the time of admission reveals normal left ventricular (LV) size, global hypokinesis with an ejection fraction (EF) of 40%, and no valve abnormalities.

Viral myocarditis is suspected and lisinopril, metoprolol, and furosemide are administered. However, the patient's symptoms rapidly progress, accompanied by frequent episodes of nonsustained ventricular tachycardia (VT). IV amiodarone is initiated, but VT episodes continue. His blood pressure is 88/40 mm Hg, the heart rate is 115 beats/min. Echocardiogram is repeated on the third hospital day: LV contractile function is now severely decreased, with an estimated EF of 15%.

Which of the following management strategies would be most appropriate?

A. Place an implantable cardioverter-defibrillator
B. Treat with high-dose methylprednisolone
C. Add intravenous milrinone
D. Administer intravenous immune globulin
E. Perform an endomyocardial biopsy and consult cardiac surgery regarding mechanical circulatory support

QUESTION 186

A 72-year-old diabetic man with long-standing dilated cardiomyopathy presents for evaluation of dyspnea at rest. He has been hospitalized three times within the past year for decompensated heart failure and recently underwent a cardiopulmonary exercise test showing a peak oxygen consumption of 10 mL/kg/min during maximal effort. His past medical history is notable for prior placement of an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death, and prostatectomy 1 year earlier for adenocarcinoma. For the past 6 months he has been intolerant of beta-adrenergic blockers because of hypotension. He has a supportive family, adheres to therapeutic recommendations, and does not use tobacco.

Physical examination reveals a blood pressure of 92/78 mm Hg, resting heart rate of 106 beats/min, body mass index of 26 kg/m^2, jugular venous pressure of 10 cm H_2O, clear lungs, an S_3 apical gallop, and cool extremities but no evidence of hepatomegaly or ascites. Laboratory studies are notable for the following: sodium 126 mEq/L; potassium 4.6 mEq/L; blood urea nitrogen 34 mg/dL; and creatinine 2.5 mg/dL. Liver function tests and the complete blood cell count are normal. Electrocardiography shows sinus tachycardia and a QRS complex duration of 96 milliseconds. Echocardiography demonstrates a dilated left ventricle with an ejection fraction of 20%, mild mitral regurgitation, and normal right ventricular size and function.

Which of the following is the most appropriate consideration for this patient?

A. Cardiac resynchronization therapy
B. Urgent listing for cardiac transplantation
C. Listing for combined heart-kidney transplantation
D. Implantation of a left ventricular assist device
E. Implantation of a biventricular assist device

QUESTION 187

Which of the following statements regarding the cardiac cycle is NOT correct?

A. The third heart sound (S_3) corresponds to rapid early diastolic filling of the ventricles

B. The absence of an *a* wave on the right atrial pressure tracing is typical of atrial fibrillation
C. Isovolumic ventricular contraction corresponds to the period between mitral valve closure and aortic valve opening
D. The *v* wave on the right or left atrial pressure tracing occurs before the T wave on the electrocardiogram
E. The mitral valve opens in diastole when the left ventricular pressure falls below the left atrial pressure

QUESTION 188

Which of the following statements about physical findings in heart failure is TRUE?
A. Hydrothorax in heart failure is most often bilateral, but when unilateral it is usually confined to the right side of the chest
B. The absence of pulmonary rales on examination excludes the presence of an elevated pulmonary capillary pressure
C. Hepatomegaly typically follows the development of overt peripheral edema
D. The absence of peripheral edema indicates the lack of volume overload and systemic venous congestion
E. In left ventricular failure, P_2 is often reduced in intensity

QUESTION 189

A 66-year-old man with a history of diabetes and hypertension presents for evaluation of exertional dyspnea. He denies associated chest discomfort, but frequently awakens from sleep with shortness of breath. On examination, he has prominent jugular venous distention, a regular heart rhythm with an apical S_4 gallop, bibasilar rales, hepatomegaly, and mild bilateral pedal edema. Electrocardiography reveals sinus rhythm at a rate of 94 beats/min without ST-segment deviations or pathologic Q waves. Echocardiography is notable for a left ventricular ejection fraction of 25% and akinesis of the anterior wall. Subsequent coronary angiography reveals severe three-vessel coronary artery disease with distal targets suitable for surgical revascularization. Which of the following statements about this patient's ischemic cardiomyopathy is correct?
A. Coronary artery bypass grafting (CABG) is superior to medical therapy only if angina is present
B. In this patient's case, dobutamine echocardiography could be used to differentiate anterior wall infarction from hibernating myocardium
C. CABG improves quality of life and survival more than medical therapy only if >50% of the myocardium is shown to be viable
D. Stunned myocardium refers to persistent contractile dysfunction caused by chronically reduced coronary blood flow
E. Surgical ventricular reconstruction should be performed along with CABG because the anterior wall is akinetic

QUESTION 190

Which of the following statements about digitalis toxicity is NOT correct?
A. Lidocaine is a useful agent for treating arrhythmias due to digitalis excess
B. Second- and third-degree atrioventricular blocks in this setting often respond to atropine
C. Recurrence of digitalis toxicity may occur 24 to 48 hours after the administration of antidigoxin immunotherapy
D. Direct-current cardioversion may precipitate ventricular arrhythmias in patients with digitalis intoxication and should be avoided
E. Dialysis is effective in cases of massive overdose

QUESTION 191

A 57-year-old man is admitted to the hospital with 2 hours of severe chest pain. His initial electrocardiogram shows 3-mm ST-segment elevations and small Q waves in leads V_1–V_4. Emergency coronary angiography reveals occlusion of the proximal left anterior descending artery (LAD) without collateral vessel flow. The left circumflex and right coronary arteries are patent without significant obstruction. Primary percutaneous coronary intervention of the LAD restores Thrombolysis in Myocardial Infarction grade 3 flow.

Following coronary intervention, his physical examination reveals a blood pressure of 120/70 mm Hg and heart rate of 70 beats/min. The jugular venous pressure is not elevated. On lung auscultation, bibasilar crackles are audible without wheezes. Cardiac examination reveals a normal apical impulse, a prominent fourth heart sound, and a grade II/VI apical holosystolic murmur. His extremities are warm and peripheral pulses are symmetric and full. The chest radiograph shows a normal cardiac silhouette with interstitial pulmonary edema.

Echocardiography reveals a reduced left ventricular ejection fraction of 34% with anteroapical akinesis. No apical thrombus is visualized. Moderate mitral regurgitation is present. Brief runs of nonsustained ventricular tachycardia are noted on the first hospital day.

His current regimen includes aspirin 81 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily, metoprolol succinate 50 mg daily, and lisinopril 10 mg daily.

Which of the following interventions prior to discharge would further reduce his mortality risk?
A. Implantation of a defibrillator
B. Valsartan 80 mg daily
C. Eplerenone 25 mg daily
D. Amiodarone 200 mg daily
E. Warfarin adjusted to an international normalized ratio of 2.0 to 3.0

QUESTION 192

The circulatory support device seen in the radiograph in Fig. 2.3 has been shown to significantly improve survival and quality of life in select patients with advanced heart failure. Common adverse events associated with this therapy include all of the following EXCEPT
A. Stroke
B. Driveline infection
C. Pump rotor failure
D. Gastrointestinal bleeding
E. Right ventricular failure

QUESTION 193

A 56-year-old woman with atrial fibrillation and nonischemic dilated cardiomyopathy is admitted to the hospital with acute decompensated heart failure. Her past medical history is notable for type 2 diabetes, chronic renal insufficiency, and

gout. Her admission blood pressure is 90/76 mm Hg with an irregular heart rate of 94 beats/min and her examination is notable for pulmonary and systemic congestion. Treatment is initiated with a continuous IV furosemide infusion at 10 mg/h after an intravenous bolus. However, her urine output remains <70 mL/h and her serum creatinine increases from 1.4 mg/dL to 2.1 mg/dL over the first 48 hours of hospitalization. Short runs of nonsustained ventricular tachycardia are noted on telemetry.

Which of the following would be most appropriate in the management of this patient?

A. Addition of dopamine 2 mcg/kg/min by continuous IV infusion
B. Addition of milrinone 0.25 mcg/kg/min by continuous IV infusion
C. Addition of sodium nitroprusside 20 mcg/min by continuous IV infusion
D. Insertion of a pulmonary artery catheter for assessment of central hemodynamics
E. Initiation of bedside ultrafiltration

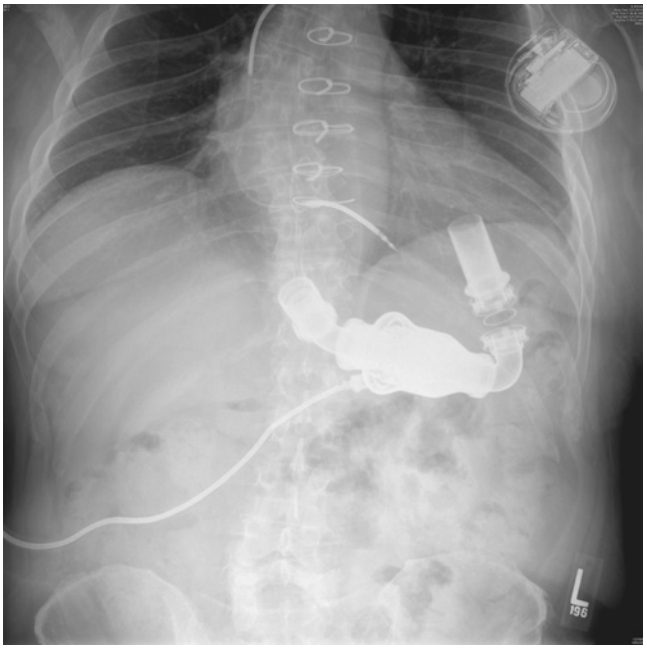

FIG. 2.3

QUESTION 194

Fig. 2.4 displays posteroanterior and lateral chest radiographs of a patient with an idiopathic cardiomyopathy, symptomatic heart failure, left ventricular ejection fraction <0.35, and left bundle branch block on the ECG. Which of the following statements about the pictured device is NOT correct?

A. Implantation of this device reduces left ventricular dimensions and mitral regurgitation
B. Placement of this type of device is associated with improved survival
C. A complication of device implantation is phrenic nerve stimulation with diaphragmatic pacing
D. Minimization of this form of ventricular pacing is important to prevent progressive heart failure
E. QRS duration on the surface ECG is an important predictor of clinical benefit

QUESTION 195

Which of the following conditions is NOT associated with the development of pulmonary edema?

A. Increased pulmonary venous pressure
B. High altitude
C. Increased plasma oncotic pressure
D. Eclampsia
E. Heroin overdose

QUESTION 196

True statements about cardiac physical findings in patients with heart failure include all of the following EXCEPT

A. Cardiomegaly is usually absent in primary restrictive cardiomyopathy
B. Elevated jugular venous pressure and an S_4 gallop in patients with heart failure are each associated with a poor prognosis
C. Pulsus alternans results from variation of the stroke volume, likely owing to incomplete recovery of contracting myocardial cells

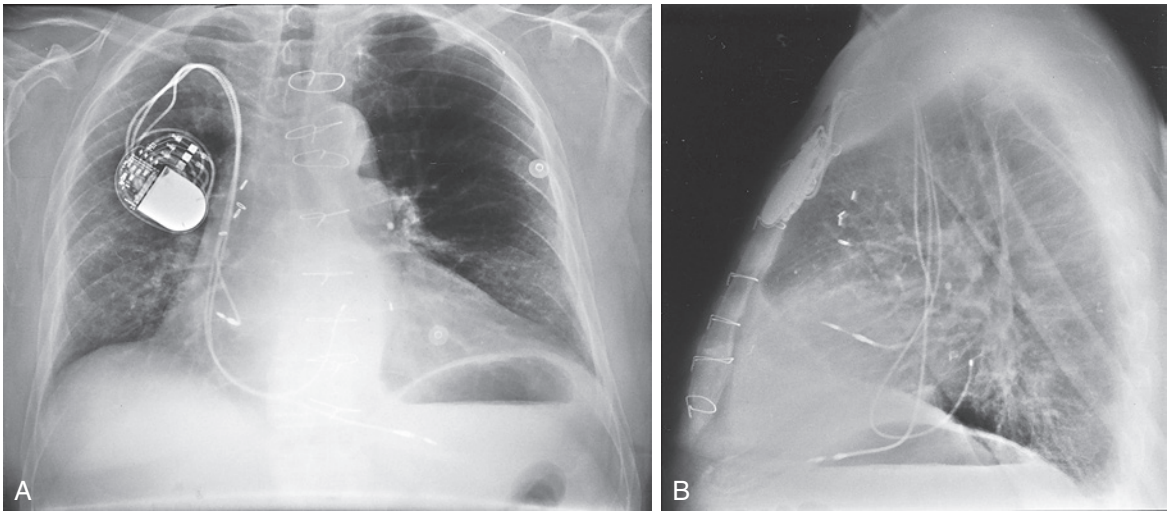

FIG. 2.4

D. Low-grade fever may occur in advanced heart failure in the absence of underlying infection
E. Sleep-disordered breathing is common in patients with heart failure

QUESTION 197

Which of these statements regarding the relationship between perfusion pressure and airway pressure in the upright lung is NOT correct?
A. Pulmonary artery pressure is greater than alveolar pressure at the lung apices
B. Pulmonary venous pressure exceeds alveolar pressure at the lung bases
C. Measurement of pulmonary capillary wedge pressure is most meaningful in lung zones in which pulmonary venous and arterial pressures exceed alveolar pressure
D. Pulmonary vascular redistribution on the chest radiograph occurs when there is a relative reduction in perfusion of the bases with a relative increase in apical perfusion

QUESTION 198

Which of the following is NOT likely to be a complication of cyclosporine therapy in the cardiac transplant recipient?
A. Gingival hyperplasia
B. Myelosuppression
C. Hypertension
D. Tremor
E. Hirsutism

QUESTION 199

Which of the following statements about acute heart failure is NOT correct?
A. Most patients with acute heart failure present with normal or elevated blood pressure
B. Milrinone does not improve in-hospital mortality
C. Serum vasopressin levels are elevated in acute heart failure and contribute to hyponatremia, a marker of poor prognosis
D. Tolvaptan, a vasopressin receptor antagonist, reduces the risk of death and heart failure re-hospitalization
E. Noninvasive ventilation in patients with acute pulmonary edema does not reduce short-term mortality compared with oxygen alone

QUESTION 200

Which of the following statements about patients with symptomatic heart failure is NOT correct?
A. Plasma norepinephrine level is usually elevated
B. Serum B-type natriuretic peptide is elevated
C. Cardiac beta-adrenergic receptor density is increased
D. Serum aldosterone level is elevated
E. The circulating level of tumor necrosis factor-alpha is increased

QUESTION 201

Which of the following statements regarding post-cardiac transplantation complications is NOT true?
A. Infectious complications are responsible for approximately 20% of deaths during the year after transplantation
B. Allograft coronary artery disease is the most significant factor limiting long-term survival
C. The propensity for allograft rejection decreases with time
D. Cytomegalovirus infection is associated with development of post-transplantation lymphoproliferative disorder
E. Transplant recipients have an increased incidence of cancer compared with age-matched controls

QUESTION 202

Which of the following statements regarding intra-aortic balloon (IAB) counterpulsation is NOT correct?
A. The tip of the IAB should be positioned just distal to the left subclavian artery
B. The IAB should be timed to deflate during the isovolumetric phase of left ventricular contraction
C. Inflation of the IAB should be timed with aortic valve closure on the arterial pressure waveform
D. Aortic valve stenosis is a strict contraindication to the use of an IAB
E. In the SHOCK II trial, IAB therapy did not reduce 30-day mortality in comparison to medical therapy among patients with acute myocardial infarction complicated by cardiogenic shock for whom early revascularization was planned

QUESTION 203

Which of the following statements regarding therapy for patients with heart failure is NOT correct?
A. Angiotensin receptor blocking drugs are less effective than angiotensin-converting enzyme (ACE) inhibitors in the reduction of mortality in patients with heart failure
B. ACE inhibitors are indicated in patients with heart failure and left ventricular dysfunction, irrespective of the functional New York Heart Association classification
C. Digoxin has been shown to decrease heart failure hospitalizations
D. Spironolactone has been shown to decrease mortality in patients with class III to IV symptoms
E. Regular physical exercise does not reduce mortality in patients with chronic heart failure

QUESTION 204

Which of the following statements about the use of adenosine in the management of cardiac arrhythmias is NOT correct?
A. Adenosine administration aids in the diagnosis of wide QRS complex tachycardias
B. Slow, peripheral intravenous administration of 6 to 12 mg of adenosine terminates supraventricular tachycardias involving the atrioventricular node
C. Patients with heart transplants demonstrate an exaggerated response to adenosine
D. Adenosine may be ineffective in patients who have recently consumed caffeine
E. Flushing, dyspnea, and chest pressure are common side effects of adenosine

QUESTION 205

Which of the following statements regarding dysrhythmias is NOT correct?
A. The prevalence of premature ventricular complexes increases with age

B. In the absence of structural heart disease, detection of premature ventricular complexes has no impact on survival
C. Class IC antiarrhythmic agents are the drugs of choice for suppression of premature ventricular complexes after myocardial infarction
D. Most concealed accessory pathways are located between the left ventricle and the left atrium
E. A concealed accessory pathway should be suspected in narrow-complex tachycardias when the retrograde P wave occurs after completion of the QRS complex

QUESTION 206

A 56-year-old man with a history of hypercholesterolemia and smoking is referred to the cardiology clinic for preoperative risk assessment before an orthopedic procedure. He denies any cardiovascular symptoms and exercises regularly. His ECG is shown in Fig. 2.5. Which of the following statements is NOT correct?

A. This syndrome is thought to account for 40% to 60% of all cases of idiopathic ventricular fibrillation
B. Genetic mutations in the sodium channel have been identified in some families with this syndrome
C. An implantable cardioverter-defibrillator is appropriate therapy for some patients with this syndrome to prevent sudden death
D. Antiarrhythmic therapy with procainamide reliably prevents ventricular arrhythmias in this syndrome
E. Screening of family members for this condition is recommended

QUESTION 207

True statements regarding the prevention of sudden cardiac death (SCD) include all of the following EXCEPT

A. The therapy of choice for survivors of SCD is implantation of a cardioverter-defibrillator
B. Defibrillators reduce the risk of sudden death from arrhythmia in patients with nonischemic cardiomyopathy and left ventricular ejection fraction (LVEF) ≤35%
C. For survivors of out-of-hospital cardiac arrest not associated with a myocardial infarction, the risk of recurrent cardiac arrest at 1 year is about 30%
D. Prophylactic defibrillator implantation is appropriate for prevention of sudden death in patients with left ventricular dysfunction (LVEF ≤ 30%) and prior myocardial infarction
E. Amiodarone is the most appropriate long-term prophylactic strategy for patients with hypertrophic cardiomyopathy and a prior history of syncope

QUESTION 208

Which of the following statements regarding atrioventricular (AV) block is NOT correct?

A. In first-degree AV block, the intensity of the first heart sound is increased
B. The conduction abnormality in Mobitz type I second-degree heart block with normal QRS complex duration is almost always at the level of the AV node, proximal to the His bundle
C. In typical Mobitz type I second-degree heart block, the RR interval progressively shortens over consecutive beats until a beat is dropped
D. In Mobitz type II second-degree heart block, the PR intervals are constant prior to the nonconducted P wave
E. The ventricular escape rate in acquired complete heart block is usually <40 beats/min

QUESTION 209

Which of the following statements about the use of ambulatory electrocardiographic monitoring for the detection of cardiac arrhythmias is NOT correct?

A. A long-term loop recorder is frequently useful for diagnosis in patients with frequent symptoms and an unrevealing Holter recording
B. Type I second-degree atrioventricular block is commonly present in normal subjects

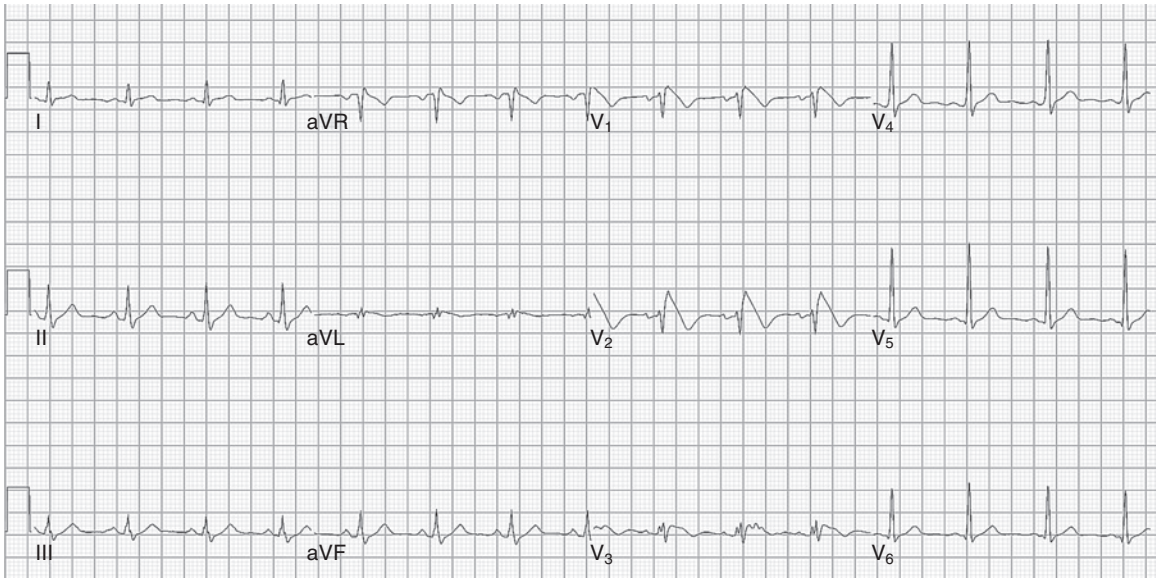

FIG. 2.5

C. Sinus bradycardia with rates as low as 35 beats/min and sinoatrial exit block may be found in persons without cardiac disease
D. Long-term monitoring of patients with a history of atrial fibrillation (AF) indicates that symptomatic AF episodes occur more commonly than asymptomatic episodes
E. The frequency of ventricular premature beats after myocardial infarction increases over the first several weeks

QUESTION 210

Which of the following statements regarding syncope is NOT correct?
A. Cardiac causes account for 10% to 20% of syncopal episodes
B. Syncope of cardiac origin is associated with a 30% 1-year mortality
C. The most common causes of syncope are vascular in origin, including reflex-mediated syncope and orthostatic hypotension
D. Supraventricular tachycardia has been identified as a common cause of syncope
E. The cause of syncope can be identified in a large percentage of patients based on history and physical examination alone

QUESTION 211

Which of the following statements about permanent pacemakers is NOT correct?
A. AAIR pacing is appropriate for patients with sinus node dysfunction and intact atrioventricular (AV) conduction
B. Symptomatic Wenckebach AV block is an indication for permanent pacing
C. Pacemaker syndrome can be manifest in any pacing mode in which there is AV dissociation
D. Medically refractory hypertrophic cardiomyopathy is a class I indication for the placement of a permanent dual-chamber pacemaker
E. A pacemaker mode-switching option is beneficial for patients with paroxysmal supraventricular rhythm disturbances

QUESTION 212

Which of the following statements regarding pacemaker-mediated tachycardia (PMT) is NOT correct?
A. A dual-chamber system must be present to cause PMT
B. Intact atrial sensing is required for PMT
C. Premature ventricular contractions frequently initiate PMT
D. Shortening the postventricular atrial refractory period will prevent PMT
E. Retrograde P waves are typically present

QUESTION 213

A 76-year-old man with diabetes mellitus and exertional angina is found to have three-vessel coronary artery disease and a left ventricular ejection fraction of 40%. He undergoes successful coronary artery bypass grafting surgery. A rhythm strip obtained on the second postoperative day is shown in Fig. 2.6. Preoperative administration of each of the following therapies has been shown to prevent this dysrhythmia after cardiac surgery EXCEPT
A. Amiodarone
B. Atorvastatin
C. Sotalol
D. Digoxin
E. Metoprolol

QUESTION 214

Which of the following statements about procainamide is NOT correct?
A. At therapeutic concentrations, procainamide prolongs the QRS complex duration on the surface ECG
B. Procainamide may accelerate the ventricular rate in patients with atrial flutter
C. Procainamide suppresses conduction in the accessory pathway of patients with Wolff-Parkinson-White syndrome
D. A positive antinuclear antibody in procainamide-treated patients signals a drug-induced lupus syndrome
E. Rapid intravenous administration of procainamide may precipitate hypotension

QUESTION 215

Each of the following statements about invasive cardiac electrophysiologic study is true EXCEPT
A. Of the common arrhythmic causes of syncope, tachyarrhythmias are most reliably initiated in the electrophysiology laboratory, followed by sinus node abnormalities and His-Purkinje block
B. Supraventricular tachycardias are characterized by a His-ventricular interval that is shorter than that recorded during normal sinus rhythm

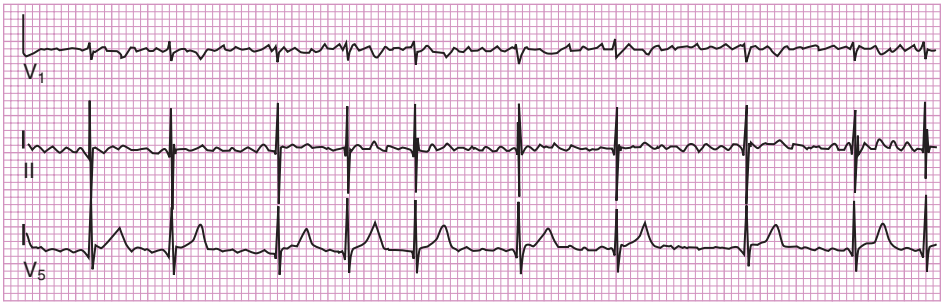

FIG. 2.6

C. Patients with sinus node dysfunction often have atrioventricular nodal conduction abnormalities
D. Sinus node recovery time is defined as the difference between the spontaneous sinus node cycle length prior to pacing and the duration to the first spontaneous sinus response after termination of pacing
E. Accessory pathways are most commonly left lateral in location

QUESTION 216

Which of the following statements regarding the antiarrhythmic drug dronedarone is NOT correct?
A. Its electrophysiologic properties are similar to amiodarone
B. It is safe for use in patients with heart failure symptoms
C. The prevalence of thyroid toxicity is low
D. QT prolongation is typical during use, but only rarely results in proarrhythmia
E. Mortality is increased when it is prescribed to patients with permanent atrial fibrillation

QUESTION 217

A 34-year-old teacher is referred for consultation because of intermittent palpitations and is found to have paroxysmal atrial fibrillation (AF) on ambulatory electrocardiography. His pertinent co-morbid conditions include mild obesity, controlled hypertension, and untreated obstructive sleep apnea. Ethanol and caffeine consumptions are minimal. Echocardiography demonstrates normal left ventricular size and contractile function and mild left atrial enlargement. Exercise treadmill testing reveals no evidence of ischemia. Despite initiation of metoprolol and flecainide, symptomatic paroxysmal AF continues and the patient is referred for catheter ablation. Which of the following statements about ablation for AF is correct?
A. A trial of suppressive antiarrhythmic drug therapy is mandatory before proceeding to AF ablation
B. The efficacy of catheter ablation for paroxysmal AF is higher than for persistent AF
C. A successful procedure requires focal ablation of premature atrial beats originating deep within the pulmonary veins
D. Radiofrequency ablation in the posterior left atrium is associated with a risk of atrial-tracheal fistula
E. Catheter ablation eliminates the need for chronic anticoagulation in subsequently asymptomatic individuals

QUESTION 218

A 76-year-old woman is evaluated by her cardiologist because of recently recognized paroxysmal atrial fibrillation. She has a history of hypertension, diabetes, obesity (current weight is 80 kg), and chronic kidney disease with a serum creatinine of 1.3 mg/dL. She does not have a contraindication to antithrombotic therapy. Which of the following would be the most appropriate antithrombotic regimen for this patient?
A. Aspirin 325 mg daily
B. Aspirin 162 mg plus clopidogrel 75 mg daily
C. Warfarin, dose adjusted to achieve international normalized ratio 2.5 to 3.5
D. Apixaban 5 mg twice daily
E. Apixaban 2.5 mg twice daily

QUESTION 219

Which of the following statements concerning atrial fibrillation (AF) is correct?
A. AF develops in 10% to 20% of patients after cardiac surgery
B. Patients who have been in AF for less than 72 hours can be safely cardioverted without the need for prolonged anticoagulation
C. Restoration of sinus rhythm results in superior clinical outcomes compared with chronic rate control and anticoagulation in patients with asymptomatic AF
D. A chronically rapid ventricular response rate in AF results in impaired left ventricular systolic function
E. The incidence of AF declines after age 60

QUESTION 220

Which of the following statements regarding the cardiac conduction system is NOT correct?
A. The sinus node is innervated with postganglionic adrenergic and cholinergic nerve terminals
B. In 60% of people, the arterial supply to the atrioventricular node is derived from a branch of the left circumflex artery
C. The conduction system in the upper muscular interventricular septum receives its blood supply from branches of the anterior and posterior descending arteries
D. Inhibition of the delayed rectifier K^+ current (I_{kr}) has been implicated in the acquired form of the long QT syndrome
E. The resting transmembrane potential of the cardiac myocyte is close to the equilibrium potential of potassium

QUESTION 221

Which of the following statements regarding amiodarone for the treatment of cardiac arrhythmias is correct?
A. The mean terminal half-life of amiodarone is 6 months
B. Among patients with systolic heart failure, amiodarone is of comparable efficacy as implantable cardioverter-defibrillator therapy in the prevention of sudden cardiac death
C. Corneal deposits develop in <10% of patients who are treated with amiodarone for more than 6 months
D. Hyperparathyroidism is a known complication of long-term amiodarone therapy
E. Amiodarone-induced pulmonary toxicity may develop within the first week of therapy

QUESTION 222

Which of the following statements regarding the mechanisms of cardiac arrhythmias is correct?
A. In the common form of atrioventricular (AV) nodal reentrant tachycardia, anterograde conduction occurs down the "fast" pathway
B. In orthodromic AV reentrant tachycardia, the activation wave travels via the accessory pathway to the ventricles, then retrograde via the AV node to the atria
C. In most patients with Wolff-Parkinson-White syndrome, the accessory pathway conducts more rapidly than the normal AV node but takes longer to recover excitability
D. Abnormal automaticity is the most common mechanism of atrial flutter
E. All forms of ventricular tachycardia arise from abnormal automaticity

QUESTION 223

A 14-year-old boy suffers two episodes of sudden syncope during gym class while jogging and is referred for further evaluation. His paternal uncle had died suddenly during physical exercise at age 20. Laboratory evaluation includes an ECG that shows normal sinus rhythm with a normal QTc interval. Cardiac magnetic resonance imaging reveals a structurally normal heart. Computed tomography angiography demonstrates normal coronary anatomy. He undergoes treadmill exercise testing, and the rhythm displayed in Fig. 2.7 is noted after 3 minutes of exercise. What is the first-line treatment for this condition?

A. Magnesium
B. Dual-chamber pacemaker
C. Beta blocker and an implantable cardioverter-defibrillator
D. Exercise training with adequate hydration
E. Cardiac sympathectomy

QUESTION 224

A 72-year-old man with nonischemic dilated cardiomyopathy, left ventricular ejection fraction 38%, New York Heart Association class III symptoms, and chronic kidney disease (creatinine = 2.8 mg/dL) presents with symptomatic paroxysmal atrial fibrillation. Electrocardiography (ECG) when in sinus rhythm shows a corrected QT interval of 442 milliseconds. Which of the following is the most appropriate initial oral antiarrhythmic regimen to maintain sinus rhythm in this patient?

A. Outpatient initiation of dofetilide 250 mcg twice daily
B. Outpatient initiation of sotalol 120 mg twice daily
C. Inpatient initiation of disopyramide extended release 200 mg every 12 hours
D. Inpatient initiation of dronedarone 400 mg twice daily with close ECG monitoring
E. Outpatient oral amiodarone 200 mg three times daily for 2 weeks followed by 200 mg daily

QUESTION 225

A sample tracing from an electrophysiologic study in a patient with a narrow-complex tachycardia is displayed in Fig. 2.8. What is the diagnosis?

A. Sinus tachycardia
B. Atrial flutter
C. Typical (slow-fast) atrioventricular (AV) nodal reentrant tachycardia
D. Orthodromic AV reentrant tachycardia using an accessory pathway
E. Atrial tachycardia

QUESTION 226

A 75-year-old woman presents following an episode of syncope. She was watching television with her husband when she suddenly lost consciousness and was unresponsive for approximately 20 seconds. She awoke slightly confused, but otherwise felt well. Her past medical history is unremarkable. The baseline ECG demonstrates right bundle branch block and left anterior fascicular block. An electrophysiologic study was performed, and a panel from that procedure is shown in Fig. 2.9. Which of the following is the most appropriate recommendation?

A. Catheter ablation for atrioventricular nodal reentrant tachycardia
B. Beta blocker therapy
C. Neurologic consultation
D. Permanent pacemaker implantation
E. Coronary angiography with anticipated percutaneous revascularization

QUESTION 227

All of the following statements about distinguishing ventricular tachycardia (VT) from a supraventricular tachycardia (SVT) with aberrant conduction in a patient with a wide-complex rapid rhythm are true EXCEPT

A. The presence of fusion beats supports the diagnosis of VT
B. Termination of the tachycardia by vagal maneuvers is consistent with an SVT
C. The presence of atrioventricular dissociation implies VT
D. Concordance of the QRS complexes in the precordial leads is more suggestive of SVT than VT
E. A past history of myocardial infarction makes the diagnosis of VT significantly more likely

QUESTION 228

A 53-year-old man with symptomatic atrial fibrillation (AF) presents for elective outpatient cardioversion. For the past 3 months he has been taking appropriately dosed rivaroxaban as an anticoagulant, and diltiazem for rate control. Which of the following statements about external electrical cardioversion is correct?

A. Administration of intravenous ibutilide before electrical cardioversion facilitates successful conversion of AF to normal sinus rhythm
B. Electrical cardioversion is most effective at terminating tachycardias that arise from enhanced automaticity
C. Repeated shocks at the same energy level increase chest wall impedance
D. Rivaroxaban can be safely discontinued 7 days after successful cardioversion if sinus rhythm is achieved

QUESTION 229

Each of the following predisposes to the arrhythmia shown in Fig. 2.10 EXCEPT

A. Congenital severe bradycardia
B. Hypokalemia
C. Loss of function mutation in the *SCN5A* gene
D. Tricyclic antidepressant overdose
E. Disopyramide

QUESTION 230

A 60-year-old man presents with presyncope and is found to have a wide-complex tachycardia at 140 beats/min. An electrophysiologic study is performed and tachycardia is induced, as shown in Fig. 2.11. The mechanism of this tachycardia is

A. Atrioventricular reciprocating tachycardia utilizing an accessory pathway
B. Atrioventricular nodal reentrant tachycardia with aberrant ventricular conduction
C. Ventricular tachycardia
D. Atrial flutter with aberrant ventricular conduction
E. Sinus tachycardia

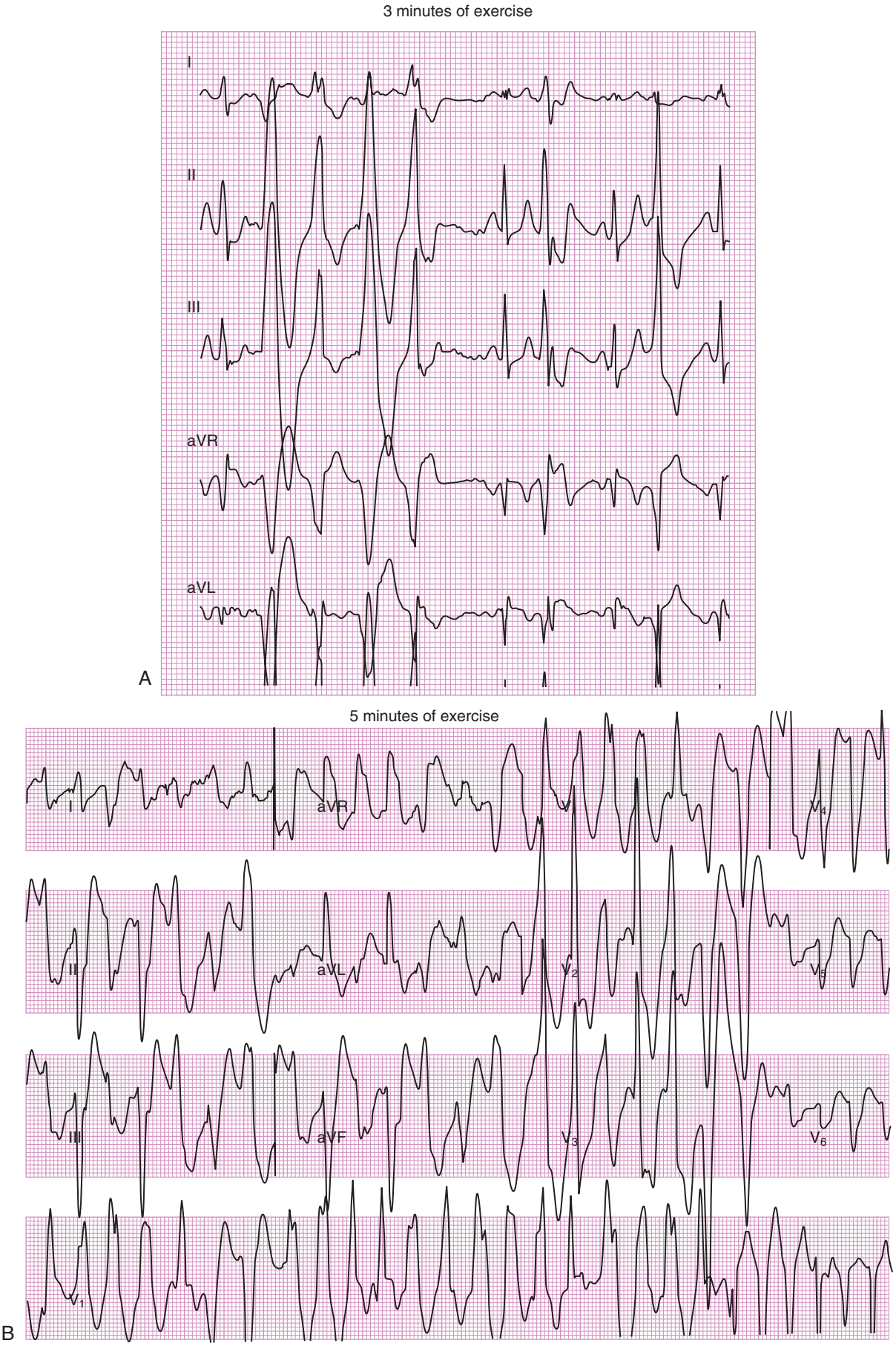
3 minutes of exercise
I
II
III
aVR
aVL
A
5 minutes of exercise
I
aVR
V1
II
aVL
V2
V5
III
aVF
V3
V6
V1
B

FIG. 2.7

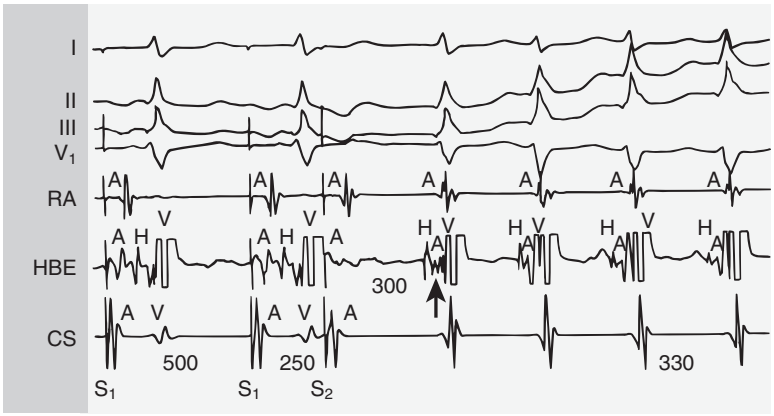

FIG. 2.8

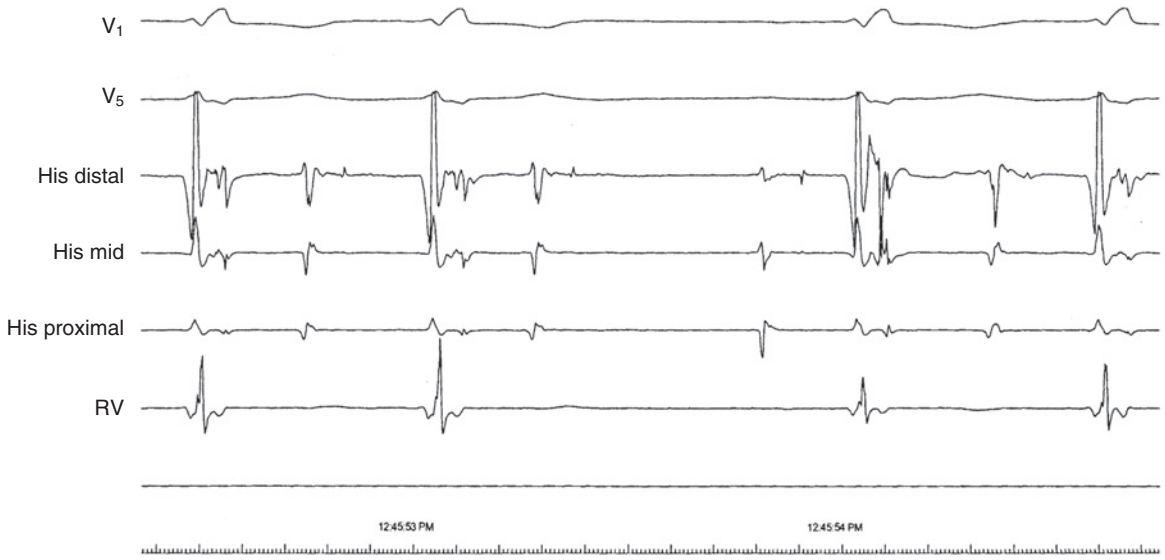

FIG. 2.9

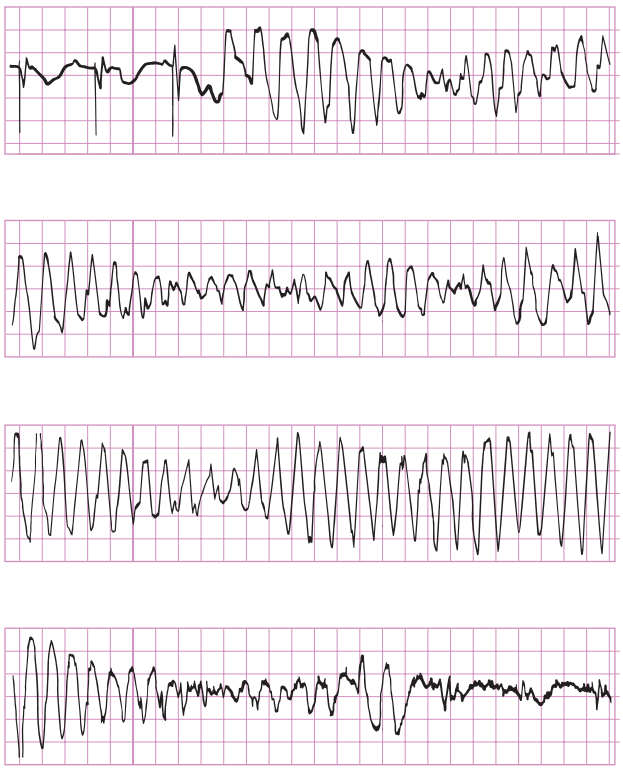

FIG. 2.10

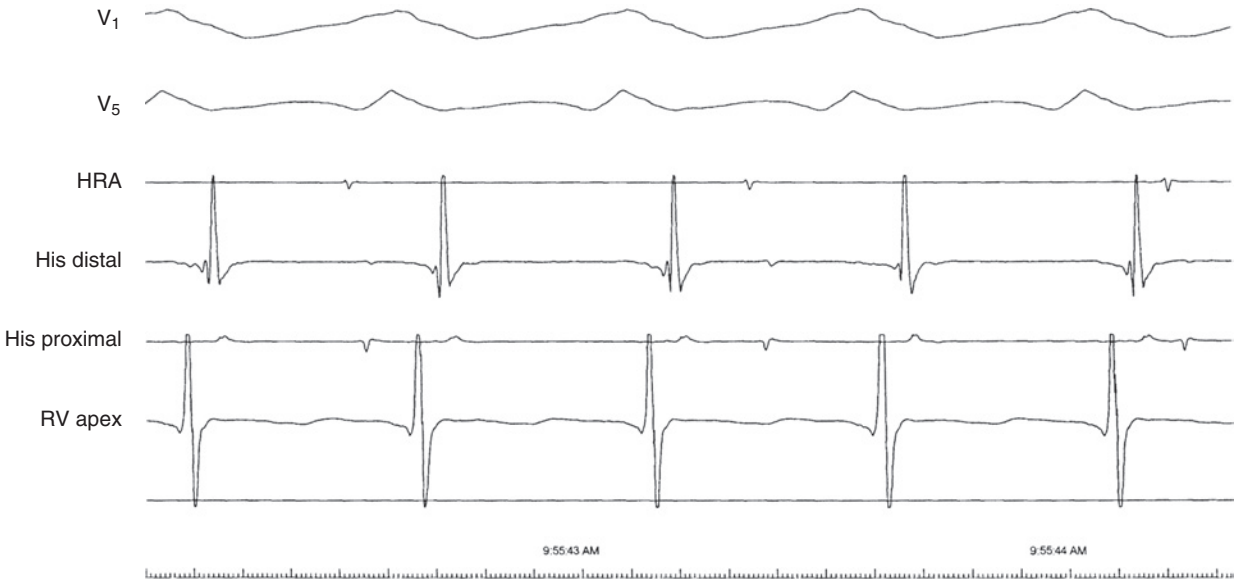

FIG. 2.11

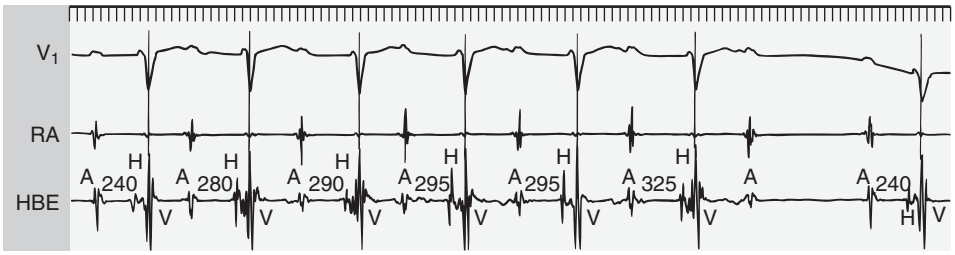

FIG. 2.12

QUESTION 231

Which of the following statements is correct regarding the electrophysiologic abnormality depicted in Fig. 2.12?

A. It is associated with syncope and sudden death
B. When present with an inferior myocardial infarction, it is an indication for temporary pacing
C. It typically reflects block at the level of the atrioventricular node, proximal to the His bundle
D. Carotid sinus massage typically abolishes this abnormality

QUESTION 232

For which of the following patients is permanent cardiac pacing NOT reasonable therapy?

A. A 35-year-old man with asymptomatic type II second-degree atrioventricular (AV) block and sinus bradycardia at 38 beats/min
B. A 70-year-old man with left ventricular hypertrophy, persistent fatigue, and lightheadedness, with marked first-degree AV block (PR interval = 0.36 second)
C. A 57-year-old man with acquired asymptomatic third-degree AV block
D. A 40-year-old woman with asymptomatic congenital complete AV block
E. A 56-year-old marathon runner with calf cramps and 3.4-second pauses during sleep

QUESTION 233

A 62-year-old man underwent pacemaker insertion 4 years ago because of marked bradycardia. As part of his exercise program, he has been using a rowing machine. Recently, he has had several episodes of near-syncope that have occurred only during such exercise. An ambulatory ECG (Holter monitor) demonstrated the rhythm strip shown in Fig. 2.13 during one near-syncopal episode while rowing. Which of the following is correct?

A. There is evidence of a single-chamber pacing system
B. There is inappropriate inhibition of ventricular pacing
C. There is undersensing of atrial activity
D. There is lack of capture of the ventricles
E. There is lack of capture of the atria

QUESTION 234

The ECG in Fig. 2.14 is compatible with all of the following diagnoses EXCEPT

A. Lead insulation breach
B. Hyperkalemia
C. Lead dislodgment
D. Loose set screw
E. Impending battery depletion

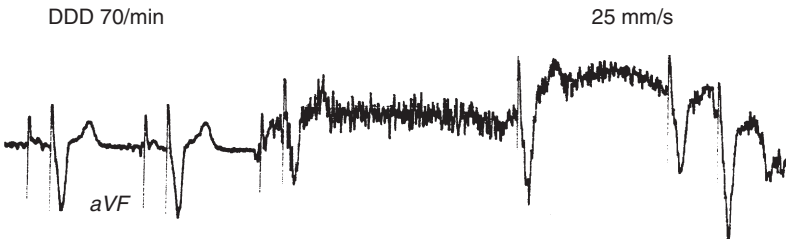

FIG. 2.13

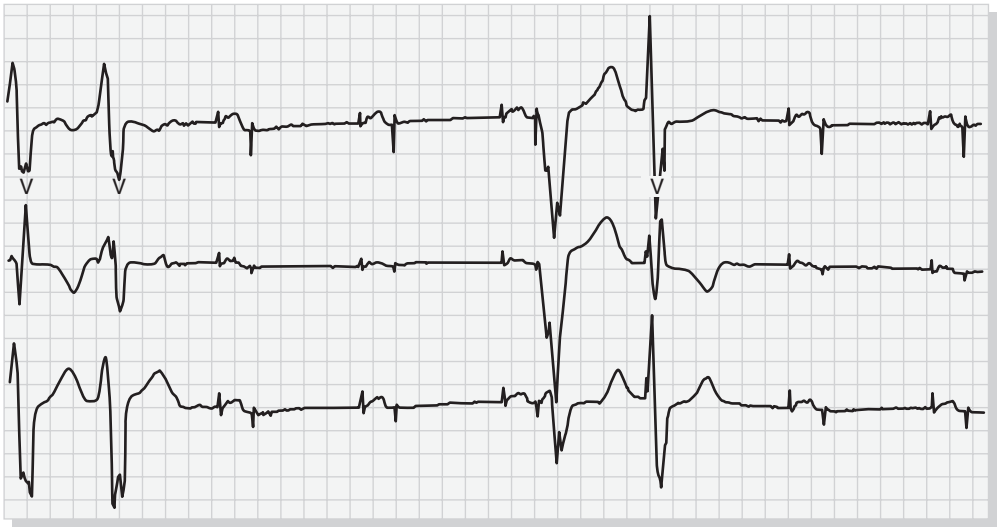

FIG. 2.14

QUESTION 235

Which of the following statements regarding sinus node function is correct?

A. Atropine enhances cardioinhibitory input to the sinus node
B. Sinus arrest is defined as a pause that is an exact multiple of the PP interval of the underlying rhythm
C. Vasodepressor carotid sinus hypersensitivity is defined as asystole exceeding 2 seconds during carotid sinus massage
D. In the respiratory form of sinus arrhythmia, the PP interval cyclically shortens during inspiration

QUESTION 236

Which of the following statements regarding arrhythmogenic right ventricular cardiomyopathy (ARVC) is correct?

A. Ventricular tachycardia (VT) in patients with ARVC typically has a right bundle branch block morphology
B. ARVC is more common in women
C. Fatty or fibrofatty infiltration of the right ventricle is the pathologic hallmark
D. Pathologic changes do not occur in the left ventricle
E. Radiofrequency ablation is successful at preventing VT

QUESTION 237

A 62-year-old man with ischemic cardiomyopathy underwent routine generator change of his implanted cardioverter-defibrillator 2 weeks ago. He now presents with mildly tender erythema and scant purulent drainage at the defibrillator pocket. He is afebrile, otherwise feels well, and blood cultures grow no organisms. The defibrillator leads were implanted 11 years prior. Which of the following would be the best approach to management?

A. The generator should be explanted. A new generator should be implanted, using the old leads, after a period of antibiotic therapy
B. The generator should be explanted. After a period of antibiotic therapy, a new system should be implanted on the contralateral side, leaving the abandoned leads in place
C. The entire generator and lead system should be removed, and a new system implanted on the contralateral side after a period of antibiotic therapy
D. Since the infection appears localized, a course of intravenous antibiotic therapy alone should be attempted; if evidence of infection recurs after antibiotics, then device extraction should be considered
E. Needle aspiration of the pocket should be performed to isolate the organism responsible for the apparent infection prior to treatment decisions

QUESTION 238

An 80-year-old man with permanent rate-controlled atrial fibrillation, hypertension, diabetes, chronic kidney disease (serum creatinine 2.5 mg/dL), and spinal stenosis has sustained three mechanical falls over the past year, without serious injury. He has a history of occasional lower gastrointestinal bleeding without a source of blood loss identified

by upper, lower, and capsule endoscopy. Of the following, which is the most appropriate method for stroke prevention in this patient?
A. Aspirin 325 mg daily
B. Enoxaparin 80 mg twice daily
C. Apixaban 5 mg twice daily
D. Ablation of the atrioventricular node
E. Implantation of a left atrial appendage closure device

QUESTION 239

A 30-year-old woman presents because of recurrent episodes of paroxysmal tachycardia with dyspnea and presyncope. A maternal uncle died suddenly at age 27. An electrophysiologic study is performed. The intracardiac electrograms at baseline (*A*) and during tachycardia (*B*) are shown in Fig. 2.15. Of the following choices, the most appropriate therapy is
A. Ablation of the atrioventricular nodal slow pathway
B. Ablation of an accessory pathway
C. Implantation of an automatic cardioverter-defibrillator
D. Direct-current cardioversion followed by long-term anticoagulation with warfarin
E. No further therapy is required

QUESTION 240

Which of the following statements about congenital long QT syndromes (LQTS) is TRUE?
A. Most forms of LQTS result from mutations in genes that code for proteins in cardiac calcium channels

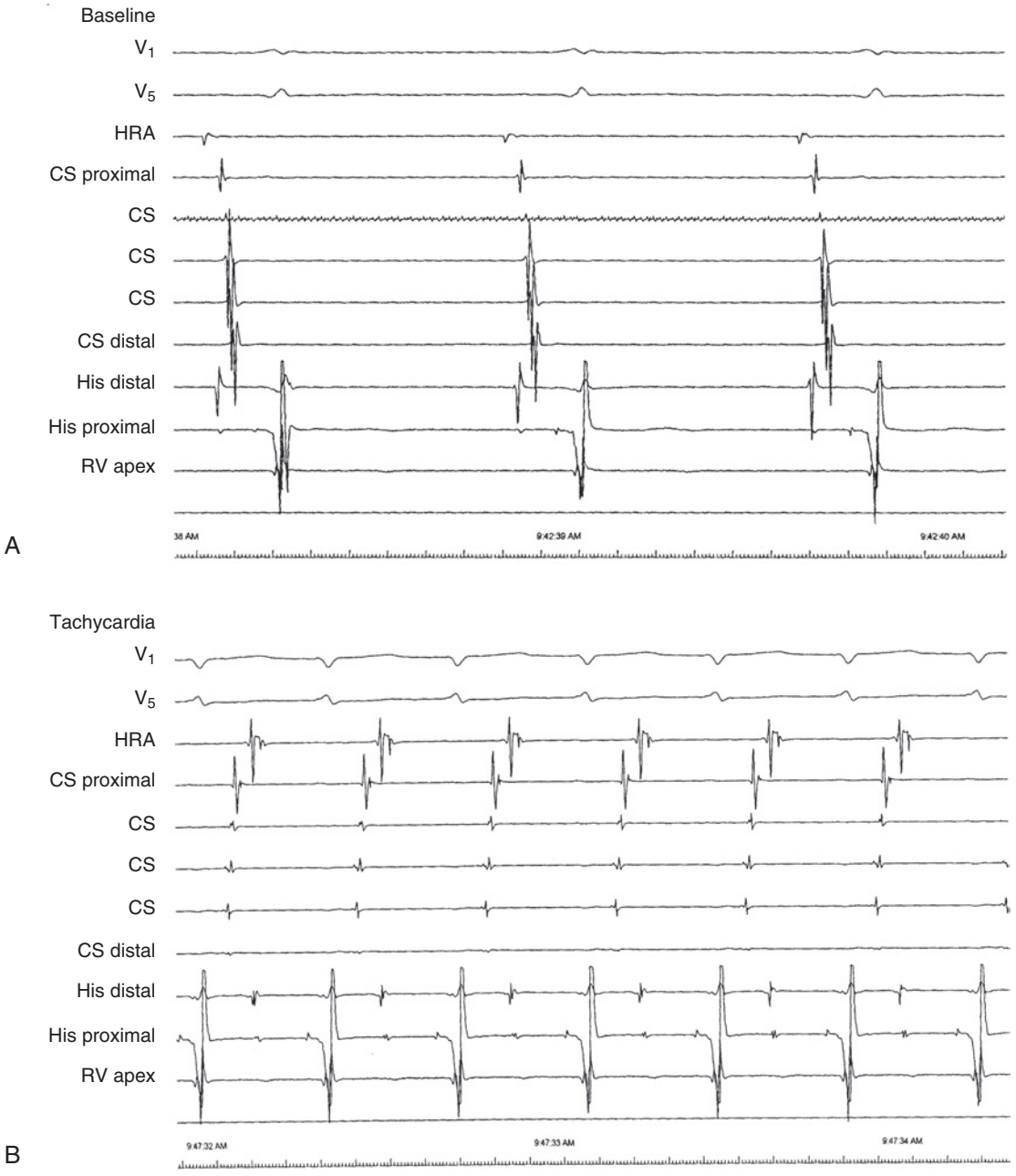

FIG. 2.15

B. LQT1 patients experience a high frequency of cardiac events during swimming
C. Sudden loud acoustic events are a common trigger of syncope in LQT3 patients
D. Cardiac events during sleep are common in patients with LQT2

QUESTION 241

All of the following statements regarding sudden cardiac death (SCD) are true EXCEPT
A. There are over 350,000 SCDs annually in the United States
B. The peak incidence of SCD among adults is between the ages of 45 and 75 years
C. Hereditary causes of SCD include hypertrophic cardiomyopathy, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, and the Brugada syndrome
D. SCD is more common in women than in men
E. An intraventricular conduction abnormality on the ECG is a stronger predictor of SCD than findings of left ventricular hypertrophy

QUESTION 242

All of the following are likely in a patient with the ECG shown in Fig. 2.16 EXCEPT
A. A gradual increase in atrial rate with the administration of digoxin
B. An irregular atrial rate
C. Precipitation of the arrhythmia by hypokalemia
D. Absence of underlying cardiac disease
E. Frequent ventricular premature beats

QUESTION 243

Which of the following statements regarding sudden cardiac death (SCD) in patients with coronary artery disease is correct?
A. SCD accounts for 10% of all coronary artery disease-related deaths
B. Compared with Caucasians, African Americans have a higher age-adjusted incidence of SCD
C. The most common mechanism of cardiac arrest is asystole
D. The outcome of patients with bradycardic/asystolic out-of-hospital cardiac arrest is better than if ventricular tachycardia is the initial arrhythmia
E. Successfully resuscitated ventricular fibrillation during the first 48 hours of an acute MI identifies individuals at increased risk of future SCD and warrants implantable cardioverter-defibrillator therapy

QUESTION 244

A 62-year-old woman with permanent atrial fibrillation takes dabigatran 150 mg twice daily for stroke prevention. Thirty minutes ago she sustained trauma in a motor vehicle collision on her way to work, was stabilized at the scene, then rapidly transported to the nearby emergency department. Upon arrival, she is unresponsive, intubated, and hypotensive. Computed tomography imaging demonstrates a small intracranial subdural hematoma and a retroperitoneal hemorrhage that requires urgent exploratory laparotomy. Which of the following is the most appropriate method to reverse anticoagulation in this patient with life-threatening bleeding in need of emergency surgery?
A. Vitamin K 10 mg intravenously
B. Oral activated charcoal
C. Idarucizumab 5 g intravenously
D. 4-factor prothrombin complex concentrate 25 U/kg intravenously
E. Hemodialysis

QUESTION 245

Which of the following patients is the most appropriate candidate for placement of an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death?
A. 45-year-old man 1 week after acute anterior myocardial infarction with left ventricular ejection fraction (LVEF) 35% and New York Heart Association (NYHA) class III symptoms
B. 66-year-old woman with a history of nonischemic dilated cardiomyopathy and LVEF 30% despite medical therapy with an angiotensin-converting enzyme-inhibitor and beta blocker for the past 6 months
C. 22-year-old man who presents with chest pain and reduced LVEF of 50% who has a normal surface ECG but evidence of myocarditis on cardiac MR imaging
D. 78-year-old man with history of ischemic cardiomyopathy, LVEF 30%, end-stage renal disease on dialysis, and recently diagnosed metastatic non-small cell lung cancer
E. 52-year-old man with history of alcoholism with newly recognized LVEF of 20% and NYHA class II symptoms

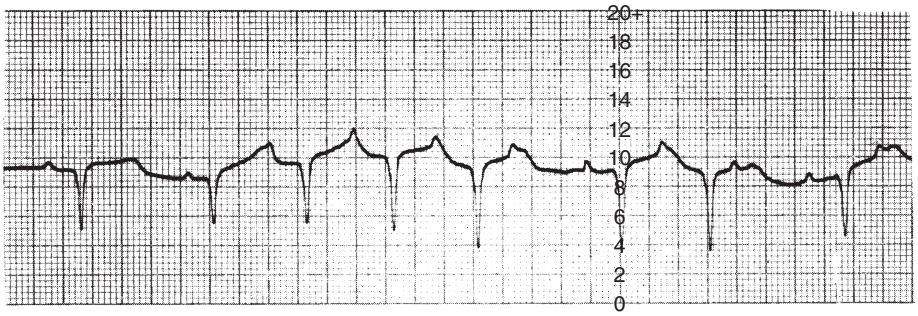

FIG. 2.16

QUESTION 246

Which of the following statements regarding cardiac pacing modes is correct?

A. Ventricular inhibited pacing (VVI) restores and maintains atrioventricular (AV) synchrony
B. VVI pacing provides rate responsiveness in the chronotropically incompetent patient
C. Single-chamber triggered pacing (AAT or VVT) increases the drain on the pacemaker battery
D. Atrial inhibited pacing is an appropriate mode of pacing for patients with AV nodal dysfunction
E. Dual-chamber pacing and sensing with inhibition and tracking (DDD) is the preferred mode of pacing for patients in atrial fibrillation

QUESTION 247

Which of the following statements regarding cardiac pacemakers is NOT correct?

A. Hyperkalemia results in pacing and sensing threshold abnormalities
B. Lead dislodgement or inadequate initial lead placement should be suspected if true undersensing is present
C. Cellular telephones do not cause clinically important pacemaker interference during normal use
D. Right bundle branch block is the expected electrocardiographic pattern during right ventricular pacing
E. Pseudofusion on the surface ECG is identified by an appropriately timed pacing stimulus that does not alter the morphology of a superimposed intrinsic QRS

QUESTION 248

The finding on the chest radiograph shown in Fig. 2.17 would be associated with which of the following measurements on device interrogation?

A. High-voltage threshold, high lead impedance
B. Low-voltage threshold, high lead impedance
C. High-voltage threshold, low lead impedance
D. Low-voltage threshold, low lead impedance
E. High-voltage threshold, normal lead impedance

QUESTION 249

The electrocardiographic abnormality displayed in Fig. 2.18 is associated with all of the following EXCEPT

A. An absence of underlying structural heart disease in most adults
B. Beneficial response to treatment with verapamil
C. An association with Ebstein anomaly
D. A higher prevalence in men
E. A right posteroseptal pathway

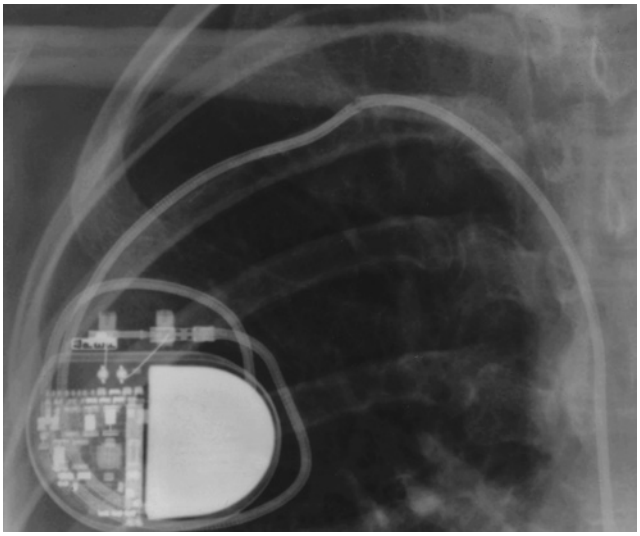

FIG. 2.17

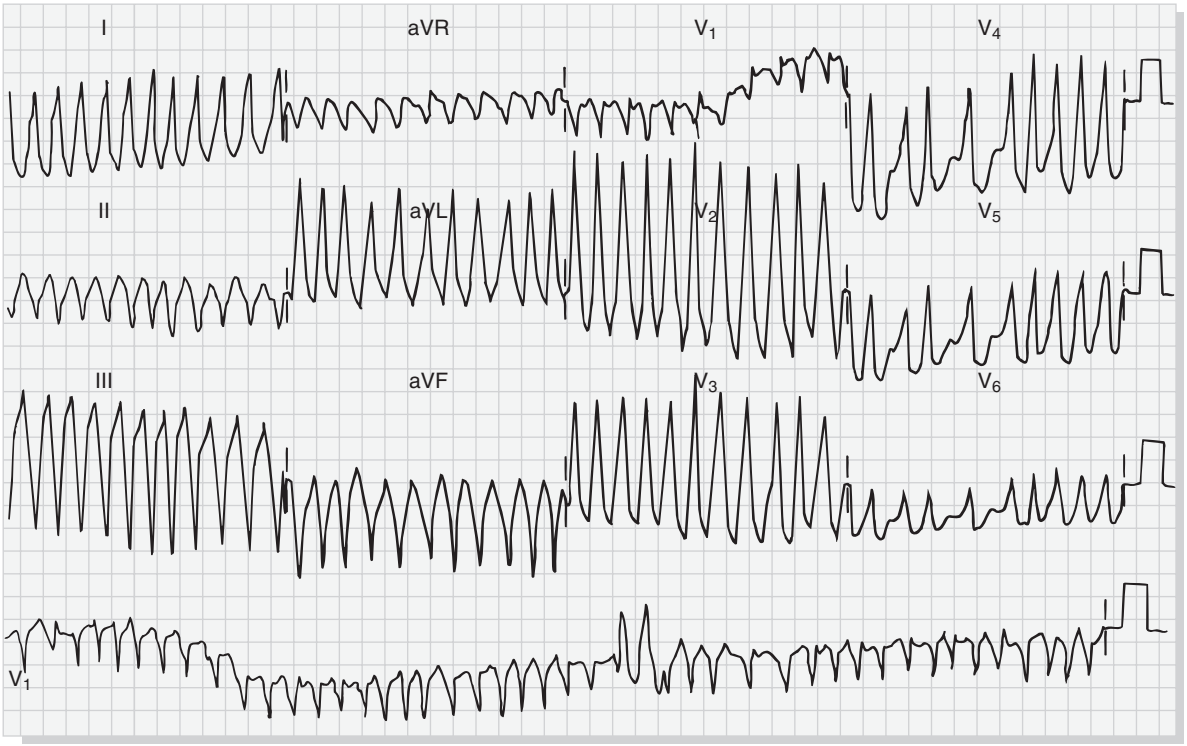

FIG. 2.18

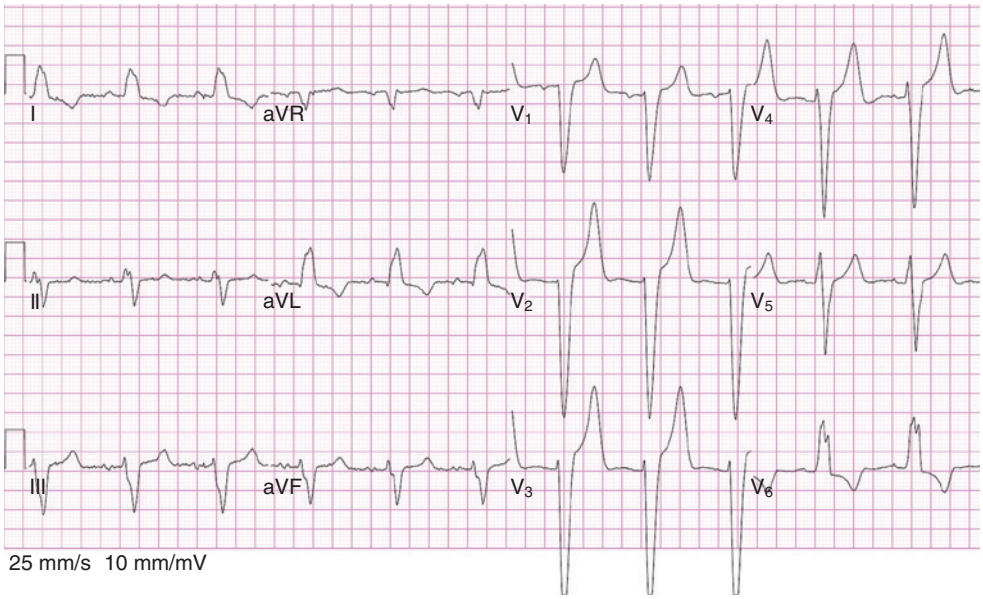

FIG. 2.19

QUESTION 250

A 65-year-old diabetic man with a history of myocardial infarction presents to your office for evaluation. He is known to have a left ventricular ejection fraction of 30% with anterior wall hypokinesis. He is comfortable at rest, but reports dyspnea with simple household activities and cannot ascend a flight of stairs without stopping to catch his breath. He does not describe chest discomfort and there is no evidence of reversible ischemia by exercise scintigraphy. His current medical regimen includes carvedilol 25 mg twice daily; lisinopril 20 mg daily; furosemide 40 mg daily; and spironolactone 25 mg daily. His physical examination reveals blood pressure of 90/50 mm Hg, heart rate of 70 beats/min, normal jugular venous pressure, and clear lungs to auscultation. The apical cardiac impulse is laterally displaced toward the anterior axillary line. On auscultation there is a normal S_1, paradoxically split S_2, an apical S_3 gallop, and a grade 3/6 holosystolic murmur at the apex that radiates to the axilla. There is no peripheral edema. His ECG is shown in Fig. 2.19. Which of the following is the most appropriate approach to device therapy in this patient?

A. No device implantation is indicated
B. Implantation of a cardioverter-defibrillator is warranted
C. Implantation of a combined cardiac resynchronization-defibrillator system is appropriate
D. Refer the patient for echocardiography to assess dyssynchrony and, if present, implant a cardiac resynchronization-defibrillator
E. Implantation of a cardiac-resynchronization pacemaker without defibrillation capability is most appropriate

QUESTION 251

The electrophysiologic study tracing in Fig. 2.20 is obtained from a 28-year-old man with palpitations, recurrent syncope, and a structurally normal heart. Which of the following is the most appropriate therapy?

A. Atenolol
B. Verapamil

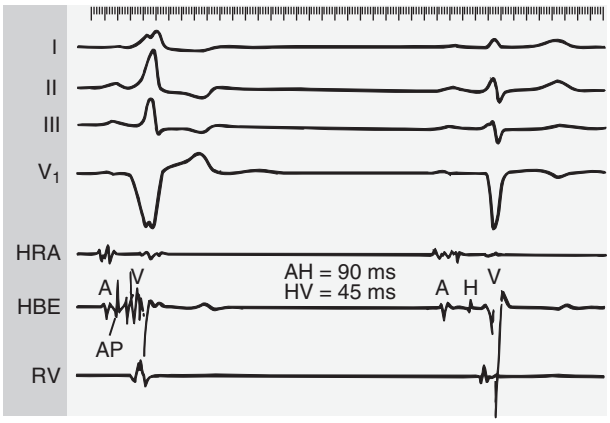

FIG. 2.20 *From Prystowsky EN, Browne KF, Zipes DP. Intracardiac recording by catheter electrode of accessory pathway depolarization.* J Am Coll Cardiol. *1983;1:468.*

C. Pacemaker implantation
D. Radiofrequency catheter ablation
E. Defibrillator implantation

QUESTION 252

Which of the following statements about the antiarrhythmic drug dofetilide is NOT correct?

A. It has significant renal excretion
B. It prolongs the QT interval in a dose-dependent fashion
C. It is unsafe in patients with prior myocardial infarction
D. Patients must be admitted to hospital for drug initiation
E. It should not be used in patients taking verapamil

QUESTION 253

A 26-year-old construction worker comes to the emergency department on the morning of January 2 in atrial fibrillation. He states that for the past few months he has had occasional episodes of palpitations, almost always on Mondays. His vital signs include heart rate of 140 beats/min, respirations of 16 breaths/min, and blood pressure of 160/95 mm Hg.

His physical examination is unremarkable. While being observed in the hospital, he spontaneously reverts to normal sinus rhythm. The most likely precipitating cause is
A. Caffeine
B. Cocaine
C. Alcohol
D. Hypertension
E. Mitral valve prolapse

QUESTIONS 254 TO 257

For each of the following descriptions, match the appropriate disorders:
A. Jervell and Lange-Nielsen syndrome
B. Romano-Ward syndrome
C. Right ventricular outflow tract ventricular tachycardia
D. Brugada syndrome

254. Autosomal recessive disorder associated with sensorineural deafness
255. ECG shows right bundle branch block morphology with ST-segment elevation in the anterior precordial leads
256. Autosomal dominant long QT syndrome with normal hearing
257. Left bundle branch block with an inferior axis

QUESTIONS 258 TO 261

Match the following antiarrhythmic drug actions with the appropriate Vaughan-Williams drug classification:
A. Predominantly block potassium channels and prolong repolarization
B. Predominantly block beta-adrenergic receptors
C. Predominantly block slow calcium channels ($I_{Ca.L}$)
D. Reduce the rate of rise of the action potential upstroke (V_{max}) and prolong the action potential duration
E. Block sodium channels, but shorten the action potential duration and do not reduce V_{max}

258. Class IA drugs
259. Class II drugs
260. Class III drugs
261. Class IV drugs

QUESTIONS 262 TO 265

Assume that you have decided to prescribe antiarrhythmic drug therapy to prevent recurrent episodes of atrial fibrillation for each of the patients described below. Match each patient with the most appropriate antiarrhythmic from the provided list:
A. Flecainide
B. Sotalol
C. Amiodarone
D. Mexiletine

262. A 64-year-old man with remote history of anterior myocardial infarction and left ventricular ejection fraction of 50%
263. A 74-year-old woman with long-standing hypertension and left ventricular hypertrophy (wall thickness = 1.6 cm)
264. A 58-year-old man with nonischemic cardiomyopathy and class III congestive heart failure
265. A 46-year-old otherwise healthy man with no structural heart disease

QUESTIONS 266 TO 269

For each of the following diuretic agents, match the appropriate adverse effect:
A. Ototoxicity
B. Gynecomastia
C. Metabolic acidosis
D. Hypercalcemia
E. Hyperkalemia

266. Acetazolamide
267. Metolazone
268. Torsemide
269. Eplerenone

QUESTIONS 270 TO 273

For each clinical condition, match the most appropriate pacemaker mode:
A. VAT
B. VVIR
C. DDD
D. DDDR
E. AAIR

270. A 58-year-old man with tachycardia-bradycardia syndrome who develops symptomatic sinus bradycardia with beta-blocker therapy
271. A 70-year-old woman with long-standing atrial fibrillation who complains of dizziness and is found on examination to have a ventricular rate of 30 beats/min
272. A 62-year-old man with complete heart block after aortic valve surgery
273. A 45-year-old man with symptomatic sinoatrial exit block and an appropriate junctional escape rhythm

QUESTIONS 274 TO 277

For each clinical description, match the corresponding etiology of dilated cardiomyopathy with electric instability:
A. Cardiac sarcoidosis
B. Giant cell myocarditis
C. Chagas disease
D. Arrhythmogenic right ventricular cardiomyopathy
E. Cardiolaminopathy

274. A 30-year-old man with a history of syncope who is found to have low-amplitude deflections on the ST segment in the right precordial leads and abnormal desmosomes on cardiac immunohistochemistry
275. A 38-year-old man with gastrointestinal dysmotility, complete heart block, and an apical aneurysm
276. A 50-year-old woman with a history of restrictive lung disease who presents with syncope in the setting of first-degree atrioventricular block and right bundle branch block
277. A 42-year-old woman with rapidly deteriorating cardiac function, frequent bursts of ventricular tachycardia, and widespread myocyte necrosis on endomyocardial biopsy

QUESTIONS 278 TO 282

For each of the following conditions, match the corresponding clinical presentations of syncope:
A. A 20-year-old woman "blacked out" during phlebotomy for a routine blood test

B. A 65-year-old woman lost consciousness after arm exercises
C. A 35-year-old man sustained syncope during exercise and has a systolic murmur that intensifies on standing upright
D. A 74-year-old man experiences sudden syncope while shaving
E. A 28-year-old woman with recurrent episodes of breathlessness, lightheadedness, and syncope after changes in body position

278. Hypertrophic cardiomyopathy
279. Subclavian steal syndrome
280. Vasovagal syncope
281. Carotid sinus hypersensitivity
282. Left atrial myxoma

QUESTIONS 283 TO 286

For each condition capable of precipitating high-output cardiac failure, match the appropriate physical findings:

A. Hyperthyroidism
B. Beriberi
C. Arteriovenous fistula
D. Carcinoid syndrome
E. Osler-Weber-Rendu syndrome

283. Nicoladoni-Branham sign
284. Hepatomegaly and abdominal bruits
285. Means-Lerman scratch
286. Paresthesias and painful glossitis

QUESTIONS 287 TO 290

For each of the following descriptions, match the appropriate medication:

A. One of the least lipid-soluble beta blockers
B. Cardioselective beta blocker with intrinsic sympathomimetic activity
C. Beta blocker with alpha-blocking activity
D. Noncardioselective beta blocker with intrinsic sympathomimetic activity

287. Atenolol
288. Carvedilol
289. Acebutolol
290. Pindolol

QUESTIONS 291 TO 294

	END-DIASTOLIC VOLUME (mL/m^2)	STROKE VOLUME (mL/m^2)	LV MASS (g/m^2)
Normal =	70	45	92
A.	84	44	172
B.	193	92	200
C.	199	37	145
D.	70	40	80

For each disease state, match the appropriate left ventricular volume and mass data:

291. Aortic valve stenosis with peak systolic gradient >30 mm Hg
292. Myocardial disease (primary dilated cardiomyopathy)
293. Aortic regurgitation with regurgitant flow >30 mL per beat
294. Mitral valve regurgitation with regurgitant flow >20 mL per beat

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Section II Answers

(CHAPTERS 21 TO 43)

Heart Failure; Arrhythmias, Sudden Death, and Syncope

ANSWER TO QUESTION 168

D (Braunwald, pp. 560–507; Fig. 25.13)

Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that combines the effects of the angiotensin receptor blocker (ARB) valsartan with those of the neprilysin inhibitor sacubitril. Neprilysin inhibition augments the circulating levels of several vasoactive peptides, including the natriuretic peptides, bradykinin, and adrenomedullin resulting in vasodilatory, natriuretic, antifibrotic, and antihypertrophic effects in patients with heart failure. The incremental benefits of ARNI over angiotensin-converting enzyme (ACE) inhibition were studied in the PARADIGM-HF trial, in which 8399 subjects with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤40%), New York Heart Association (NYHA) II to IV symptoms, and elevated natriuretic peptides were randomized to treatment with sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily after a run-in period designed to ensure tolerability of both drugs at target doses.[1] In this trial, which enrolled predominantly NYHA II and III subjects, treatment with sacubitril/valsartan resulted in a 20% reduction in the composite outcome of cardiovascular death or heart failure hospitalization and a 16% reduction in overall mortality compared with enalapril.

Heart failure guidelines have accordingly been updated to recommend that for patients with heart failure and reduced ejection fraction and NYHA II to III functional capacity, substitution of an ARNI for ACE inhibitor or ARB therapy should be considered to reduce morbidity and mortality.[2] ARNIs are not currently indicated for patients with heart failure and preserved ejection fraction or those with acute decompensated heart failure. In addition, like ACE inhibitors, there is a risk of angioedema with this agent. Thus, ARNIs should not be administered to patients with a history of angioedema or to those who have received an ACE inhibitor dose within the prior 36 hours.

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ANSWER TO QUESTION 169

E (Braunwald, pp. 446–447; Fig. 23.6)

Natriuretic peptides are of importance in the diagnosis, and assessment of prognosis, in patients with heart failure. The natriuretic peptide system consists of five structurally similar peptide hormones: atrial natriuretic peptide (ANP), urodilatin (an isoform of ANP), brain-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP). ANP is released by atrial myocytes in response to acute increases in atrial pressure. Prohormone BNP is released in response to hemodynamic stress from ventricular dilatation, hypertrophy, or increased wall tension. Prohormone BNP is cleaved by a circulating endoprotease into two polypeptides: the inactive N-terminal proBNP (NT-proBNP), 76 amino acids in length, and the biologically active peptide BNP, 32 amino acids in length.

Circulating levels of ANP and BNP are elevated in patients with heart failure. Both ANP and BNP promote vasodilatation and natriuresis, thereby counteracting the salt- and water-retaining effects of the adrenergic, renin-angiotensin-aldosterone, and vasopressin systems. BNP and NT-proBNP levels *rise* with increasing age and worsening renal function. In contrast, BNP levels have an inverse relationship with body mass index.

CNP is derived predominantly from endothelial cells in the peripheral vasculature. The precise roles of CNP, urodilatin, and DNP in cardiovascular physiology are unclear.

A large, multicenter study of patients in the emergency department undergoing evaluation for acute dyspnea showed that a BNP level of >100 pg/mL is 90% sensitive and 76% specific in identifying a cardiac etiology. A BNP level >400 pg/mL rendered the diagnosis of heart failure likely. Analogous results were found for NT-proBNP—patients in acute heart failure had mean levels >4000 pg/mL compared with 130 pg/mL in those without heart failure.

A substudy of the TACTICS-TIMI 18 trial demonstrated that an elevated BNP level in patients presenting with acute

coronary syndromes is associated with a higher risk of subsequent congestive heart failure and death.

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ANSWER TO QUESTION 170

E (Braunwald, p. 469; Fig. 24.5; p. 543)

Cardiac arrhythmias are common in patients with structural heart disease, can contribute to worsening intracardiac hemodynamics, and may precipitate acute decompensated heart failure.[1] Cardiac output (CO) is dependent on maintenance of adequate stroke volume (SV) and heart rate. Tachyarrhythmias increase myocardial oxygen demand and reduce the time available for ventricular filling in diastole, compromising ventricular SV and CO.

Since SV is compromised in patients with left ventricular (LV) dysfunction, maintenance of CO is largely dependent on an adequate heart rate. Thus, excessive heart rate slowing (i.e., bradyarrhythmias) may also depress CO.

Dissociation between atrial and ventricular contraction (as in high-grade atrioventricular block) reduces the atrial contribution to ventricular filling, impairing subsequent SV and CO in patients with systolic or diastolic dysfunction. Abnormal intraventricular conduction, as in ventricular tachycardia or right ventricular apical pacing, may impair myocardial performance because of the loss of synchronized ventricular contraction.[2] Optimization of atrioventricular and ventriculoventricular synchrony is the primary mechanism of benefit from cardiac resynchronization therapy (biventricular pacing) in patients with LV dysfunction and heart failure.[3]

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ANSWER TO QUESTION 171

C (Braunwald, pp. 472, 1922–1923; Figs. 98.12 and 98.13)

The cardiorenal syndrome is characterized by worsening renal function during a heart failure hospitalization, or soon after discharge, despite symptomatic improvement with diuretic therapy and maintenance of adequate intravascular volume. Underlying chronic kidney disease (e.g., associated with diabetes or hypertension) increases the risk of cardiorenal syndrome, as does neurohormonal activation resulting from impaired cardiac output (CO) and excessive loop diuretic therapy.

Renal function is an important prognostic indicator in patients with acute heart failure syndromes. Impaired baseline renal function and worsening renal function, during hospitalization or early after discharge, are potent predictors of adverse outcomes, including early readmission rates and mortality. *Elevated*, not reduced, systemic venous pressure appears to be an important contributing factor to the development of cardiorenal syndrome, because venous congestion contributes to elevated intra-abdominal pressure that can impair glomerular filtration.

An increase in blood urea nitrogen (BUN) out of proportion to serum creatinine is a sign of renal hypoperfusion, resulting from low forward CO or intravascular volume depletion because of high doses of intravenous diuretics. The neurohormonal activation accompanying renal hypoperfusion increases proximal sodium and urea reabsorption, while creatinine handling is unaffected, leading to an elevated BUN/creatinine ratio.

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ANSWER TO QUESTION 172

B (Braunwald, pp. 504–509; Table 25.8)

The effectiveness of digoxin was studied in the Digitalis Investigators Group trial, which enrolled 6800 patients with class I to III heart failure, with a mean left ventricular ejection fraction (LVEF) of 28%.[1] Over 37 months of follow-up, there was a significant decrease in heart failure hospitalizations but no significant improvement in total mortality with digoxin therapy compared with placebo.

Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of therapy for patients with chronic heart failure with reduced ejection fraction or asymptomatic left ventricular (LV) dysfunction because of their favorable hemodynamic effects and unsurpassed benefit on long-term mortality. The Vasodilator Heart Failure Trial II (V-HEFT II) compared the ACE inhibitor enalapril with the combination of hydralazine plus isosorbide dinitrate in the treatment of chronic moderate congestive heart failure. Survival in the enalapril-treated group proved superior.[2]

Aggregate clinical data indicate that angiotensin receptor blockers (ARBs) are as effective as ACE inhibitors in reducing HF-related morbidity and mortality. Candesartan significantly reduced the primary composite of cardiovascular death or hospital admission for heart failure among ACE-inhibitor intolerant patients enrolled in the CHARM-Alternative Trial.[3] The VALIANT trial randomized patients with LV dysfunction after myocardial infarction to valsartan, captopril, or both and found similar benefit with the ACE inhibitor or ARB in reducing mortality.[4] Thus, ARBs are currently accepted as appropriate substitutes for patients with LV dysfunction who are intolerant of ACE inhibitors.[5] The incremental benefit of ARBs in patients already treated with ACE inhibitors is less clear.

In the RALES trial, the aldosterone antagonist spironolactone was shown to reduce mortality when added to standard heart failure therapy in patients with class III to IV heart failure with an ejection fraction <35%.[6] In the EMPHASIS trial, eplerenone, a selective aldosterone antagonist, significantly reduced mortality compared with placebo when added to standard heart failure therapy in patients with class II or III systolic heart failure.[7]

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ANSWER TO QUESTION 173

C (Braunwald, pp. 560–566; Fig. 28.9)

Long-term outcomes after transplantation improved dramatically with the introduction of the calcineurin inhibitor cyclosporine as the cornerstone of immunosuppression. The median survival of all cardiac transplant patients is now >10 years, with a median survival of 13 years among those patients who are alive 1 year after transplant.[1] By the first year after transplantation, 90% of surviving patients report no functional limitations.[2]

The selection of candidates for transplantation is a complex process that integrates assessment of hemodynamics, comorbidities that might limit post-transplantation survival, and psychosocial factors that may impair compliance. Optimal candidates for heart transplantation are younger patients with advanced heart failure, minimal comorbid illness or end-organ damage, a history of adherence to prescribed medical therapy, and a strong family and social network.

The transplanted heart is denervated and relies on atypical adaptive mechanisms to meet varying demands for cardiac output (CO). As a result of increased venous return at the onset of exercise, the transplanted heart responds with the intrinsic Frank-Starling mechanism to augment CO. Circulating catecholamine levels rise as exercise ensues, providing a delayed chronotropic response. This mechanism allows near-normal hemodynamic function at rest, and the capacity to support at least moderate exercise in a large majority of long-term survivors. Of note, beta blockers may impair the heart rate response and should be used cautiously after heart transplantation.

As no reliable serologic markers for allograft rejection have been identified, right ventricular endomyocardial biopsy remains the gold standard for this diagnosis. Biopsies are typically performed through a transjugular vein approach and are carried out on a routine schedule during the post-transplantation period and over the life of the transplant. High-grade rejection may be signaled by the development of clinical heart failure, atrial arrhythmias, low QRS voltage on the ECG, or echocardiographic evidence of left ventricular dysfunction; however, definitive diagnosis or identification of early or subtle lower-grade rejection requires histologic examination of the myocardium.

Allograft rejection and infection are the most common causes of death early after transplant. The risk of infection diminishes with time as the intensity of immunosuppression therapy is reduced. In contrast, the risk of fatal malignancy increases progressively in the years thereafter. The most common fatal early malignancies are post-transplant lymphoproliferative disorders and lung cancer.

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ANSWER TO QUESTION 174

D (Braunwald, pp. 496–498, 501; Fig. 25.7; Table 25.6)

Mannitol is an inert osmotic agent that expands the extracellular fluid volume; its use is *contraindicated* in patients with decompensated heart failure.

Mineralocorticoid receptor antagonists (spironolactone and eplerenone) act at the renal distal convoluted tubule and cortical collecting tubule to reduce sodium reabsorption and inhibit K^+ and H^+ excretion. Although only weak diuretics, they have been shown to reduce morbidity and mortality in systolic heart failure.[1] However, aldosterone receptor antagonists may contribute to clinically significant hyperkalemia, particularly when used in combination with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers.[2]

Loop diuretics, such as furosemide, torsemide, and bumetanide, are inhibitors of the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle. Inhibition of this cotransporter markedly increases the fractional excretion of sodium and chloride. However, the delivery of large amounts of sodium and fluid to the distal nephron increases K^+ and H^+ secretion, leading to hypokalemia and metabolic *alkalosis*.

Nonsteroidal anti-inflammatory agents (NSAIDs) may impair renal function and diminish the action of diuretics by inhibiting the production of vasodilating prostaglandins. All NSAIDs, including aspirin, have this potential effect, which can contribute to diuretic resistance in individuals with an initially favorable diuretic response.[3]

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ANSWER TO QUESTION 175

E (Braunwald, pp. 407–408)

A variety of laboratory abnormalities may be noted in patients with congestive heart failure. Alterations in serum electrolyte values usually occur only after patients have begun treatment or in more long-standing, severe cases of heart failure. Hyponatremia is seen in up to 25% of patients with acute heart failure decompensation and is an important negative prognostic indicator.[1] It may be present for a variety of reasons, including sodium restriction, intensive diuretic therapy, a decrease in the ability to excrete water related to reductions in renal blood flow and glomerular filtration rate (GFR), and elevations in the concentration of circulating vasopressin.[2] Hypokalemia may result from aggressive diuretic therapy. Conversely, hyperkalemia may occasionally occur in patients with severe heart failure who have marked reductions in GFR or who are receiving aldosterone receptor antagonists (spironolactone or eplerenone).

Congestive hepatomegaly due to "backward" failure and cardiac cirrhosis from long-standing heart failure is often accompanied by impaired hepatic function, reflected by abnormal circulating liver enzymes. In acute hepatic venous congestion, jaundice may result, with bilirubin levels as high as 15 to 20 mg/dL, dramatic elevations of serum aspartate aminotransferase levels, and prolongation of the prothrombin time. Although the clinical and laboratory profiles of such an event may resemble viral hepatitis, the diagnosis of hepatic congestion is confirmed by rapid normalization of these values with successful treatment of heart failure. In patients with long-standing heart failure and secondary severe hepatic damage, albumin synthesis may become impaired. Rarely, more severe sequelae may occur, including hepatic hypoglycemia, fulminant hepatic failure, and hepatic coma.

Elevations in pulmonary capillary pressure are reflected by the appearance of the vasculature on the chest radiograph. With minimal elevations (i.e., ~13 to 17 mm Hg), early equalization in the size of the vessels in the apices and bases is first discernible. It is not until greater pressure elevations occur (~18 to 20 mm Hg) that actual pulmonary vascular redistribution occurs. When pressure exceeds 20 to 25 mm Hg, frank interstitial pulmonary edema is usually observed. Importantly, however, in patients with *chronic* left ventricular failure, higher pulmonary pressures can be accommodated with few clinical and radiologic signs of congestion due to enhanced lymphatic drainage.

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ANSWER TO QUESTION 176

B (Braunwald, pp. 421–422, 430–431, 432–433; Figs. 22.12 and 22.13)

The binding of a beta-adrenergic agonist to its myocyte receptor initiates a complex system of messengers within the sarcolemma and cytosol of the cell. The $beta_1$ receptor is coupled, via G-proteins, to activation of adenylate cyclase and formation of cyclic *adenosine* monophosphate (cAMP). This molecule acts via protein kinases to phosphorylate proteins and enzymes within the cell. Such action stimulates enhanced entry of calcium ions through voltage-dependent L-type calcium channels, followed by additional calcium-induced calcium release from the sarcoplasmic reticulum. The rise in cytosolic calcium increases calcium-troponin C interaction, a necessary step for subsequent contraction. The activated troponin C binds tightly to the inhibitory molecule troponin I, thus removing inhibition of actin-myosin cross-bridge formation, and contraction ensues.

Whereas cAMP is a second messenger for the beta-adrenergic system, another cyclic nucleotide, cyclic guanosine monophosphate (cGMP), acts as a second messenger during cholinergic stimulation. In vascular smooth muscle, cGMP acts as an intracellular messenger after nitric oxide stimulation.

Titin is a large protein that provides elasticity and supports the myosin molecule by tethering it to the myocyte Z line.

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ANSWER TO QUESTION 177

B (Braunwald, p. 563; Table 28.4)

Rejection is a ubiquitous concern after solid organ transplantation. It results from cell- or antibody-mediated allograft injury owing to recognition of the allograft as non-self tissue. Three major types of rejection have been identified: hyperacute, acute, and chronic. *Hyperacute* rejection occurs within minutes to hours after heart transplantation and is mediated by preexisting antibodies to allogeneic antigens on the vascular endothelium that fix complement. This results in occlusion of graft vasculature and overwhelming graft failure. In contrast, the biopsy specimen in this question shows a dense lymphocytic infiltrate and myocyte damage typical of *acute* cellular allograft rejection. Acute cellular rejection is a T-cell-mediated process that develops in the first weeks to 6 months after transplantation. *Chronic* rejection, or late graft failure, is an irreversible deterioration of graft function years after transplant mediated by antibodies or progressive graft loss from ischemia.

Risk factors for rejection include female gender, black recipient race, recipient-positive cytomegalovirus serology, prior infections, and the number of human leukocyte antigen (HLA) mismatches.[1] Patients who do not experience acute rejection within the first 6 months after transplantation have a lower incidence of late rejection.

Although progress has been made in novel noninvasive serologic approaches, such as gene expression profiling, to identify acute rejection,[2] endomyocardial biopsy remains the diagnostic gold standard. The procedure is performed under fluoroscopic or echocardiographic guidance using a bioptome inserted percutaneously via the right internal jugular vein. Potential complications include pneumothorax, transient rhythm disturbances, myocardial perforation, and tricuspid regurgitation.

The most important feature of the post-transplant biopsy specimen is the detection of lymphocyte infiltration and the presence of myocyte necrosis. A revised continuum scale

has been established for grading cardiac biopsies from no rejection (grade OR) to diffuse damaging inflammatory cell infiltrates with encroachment of myocytes and disruption of normal cell architecture (grade 3R).[3] Appropriate therapy for acute cellular rejection depends on the timing and severity of the rejection episode. Episodes that occur within the first 3 months, or episodes that are moderate to severe, are initially treated with pulsed-dose methylprednisolone. If steroid therapy is ineffective, then more aggressive therapy with OKT3 monoclonal antibody or ATGAM (horse antithymocyte globulin) may be necessary.[4]

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ANSWER TO QUESTION 178

E (Braunwald, pp. 435, 438–439, 411)

The four primary determinants of cardiac output (CO) are (1) heart rate; (2) preload, which is closely related to left ventricular (LV) end-diastolic volume; (3) afterload, which is closely related to aortic impedance (i.e., the sum of the external factors that oppose ventricular ejection); and (4) contractility, a fundamental property of cardiac muscle that reflects the level of activation of cross-bridge formation. Preload, afterload, and contractility determine the ventricular stroke volume (SV), and CO = Heart rate × SV.

Unlike other organs, the myocardium extracts oxygen from blood nearly maximally. Thus, even at rest, the oxygen saturation in coronary venous blood (measured at the coronary sinus) is quite low, usually <40%.

The body's oxygen consumption at peak exercise is an indirect measure of the CO. The peak oxygen uptake ($\dot{V}O_2$ max) is defined as the value achieved when $\dot{V}O_2$ plateaus despite a continued increase in the intensity of exercise. The anaerobic threshold is indicated by the $\dot{V}O_2$ at which carbon dioxide production starts to rise, resulting in an increase in the $\dot{V}CO_2/\dot{V}O_2$ ratio. Both the peak oxygen consumption and the anaerobic threshold are reproducible when measured days or weeks apart. During exercise, the CO of a normal heart increases up to sixfold and the body's oxygen consumption can increase up to 18-fold.

In patients with LV dysfunction, cardiopulmonary exercise tests are often performed to determine functional capacity. A peak oxygen consumption of >20 mL/kg/min reflects mild or no functional impairment. Conversely, a peak oxygen consumption of <12 mL/kg/min indicates severe impairment and a poor prognosis. Serial tests can be performed over time to assess the response to pharmacologic therapies in patients with heart failure and can help guide the need for aggressive interventions such as cardiac transplantation or placement of a ventricular assist device.

ANSWER TO QUESTION 179

A (Braunwald, pp. 436–437; Fig. 22.18)

By the law of Laplace, left ventricular (LV) wall stress (σ) is directly proportional to intracavitary pressure and chamber radius and inversely proportional to wall thickness. Ventricular hypertrophy is therefore an adaptive mechanism that serves to reduce ventricular wall stress. Myocardial hypertrophy and remodeling proceed in different patterns based on the timing and nature of the provocative stimulus. When the primary stimulus is pressure overload (as in aortic stenosis or hypertension), an increase in wall stress during ventricular systole triggers the addition of new myofibrils in parallel, leading to wall thickening at the expense of chamber size, in a pattern of *concentric* hypertrophy. When the primary stimulus is volume overload (as in chronic mitral regurgitation), increased wall stress during ventricular diastole triggers the replication of sarcomeres in series, elongation of myocytes, and ventricular cavity dilatation, in a pattern of *eccentric* hypertrophy. Therefore, although both chronic pressure and volume overload are associated with a compensatory increase in LV mass, the pattern of hypertrophy is distinct in each case.

With the use of echocardiography, concentric hypertrophy can be distinguished from eccentric hypertrophy visually, or on the basis of the ratio between wall thickness and the LV internal diameter during diastole (i.e., the relative wall thickness = [2 × posterior wall thickness]/LV internal dimension). A relative wall thickness <0.45 suggests eccentric hypertrophy, whereas a higher ratio is more consistent with concentric hypertrophy.

ANSWER TO QUESTION 180

A (Braunwald, pp. 547–548, 551; Table 27G.2; pp. 681–683)

Amiodarone has been studied extensively in patients with left ventricular (LV) dysfunction. It effectively suppresses ventricular and supraventricular arrhythmias and appears to be safe for use in this subset of patients. However, convincing evidence of mortality reduction has not been shown. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study of patients with class II to III heart failure and a left ventricular ejection fraction (LVEF) of 35% or less, amiodarone did not improve survival compared with placebo.[1]

Dronedarone is a derivative of amiodarone that shares its electrophysiologic properties, but does not contain iodine and is associated with lower rates of lung and thyroid toxicity. Dronedarone is approved to facilitate maintenance of sinus rhythm in patients with atrial fibrillation or atrial flutter. It should not be prescribed in class III to IV heart failure because its use was associated with increased mortality in such patients in the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Heart Failure Evaluating Morbidity Decrease trial.[2]

The results of several randomized, controlled clinical trials support the benefit of implantable cardioverter-defibrillator (ICD) therapy in reducing mortality among patients with LV dysfunction. The Antiarrhythmics Versus Implantable Defibrillators study randomized patients with reduced LVEF and prior resuscitated cardiac arrest, or symptomatic sustained ventricular tachycardia (VT), to therapy with amiodarone or an ICD. ICD therapy was associated with a 29% reduction

in all-cause mortality compared with amiodarone. A concurrent registry of patients with transient or correctable causes of VT or ventricular fibrillation not enrolled in the primary trial revealed that the risk of mortality in these patients remains comparable with those with primary VT or ventricular fibrillation.[3] ICD therapy is therefore recommended as the standard of care for secondary prevention of sudden cardiac death or symptomatic ventricular tachyarrhythmias in patients with LV dysfunction.

The data for ICD efficacy in primary prevention of sudden cardiac death are also compelling. The results of the Multicenter Automatic Defibrillator Implantation II Trial confirm that, in patients with coronary artery disease, prior myocardial infarction, and LVEF ≤30%, prophylactic implantation of a defibrillator reduces mortality by 31% relative to conventional medical therapy.[4] The results of the SCD-HeFT extended the benefits of ICD therapy to patients with nonischemic cardiomyopathy.[1] Thus, current American College of Cardiology/American Heart Association guidelines recommend that patients with mild to moderate heart failure and an LV ejection function ≤35% on optimal medical therapy are potential candidates for ICD implantation.[5]

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ANSWER TO QUESTION 181

C (Braunwald, pp. 543–547)

Ventricular dyssynchrony is defined as a QRS duration >120 milliseconds on the surface ECG regardless of the QRS morphology. Ventricular conduction delay alters the timing of ventricular activation and places an already failing ventricle under further mechanical disadvantage by reducing contractility and ventricular filling and prolonging the duration of mitral regurgitation.[1] Cardiac resynchronization therapy (CRT), also known as biventricular pacing, serves to better coordinate left ventricular (LV) contraction, leading to improved ventricular performance and reduced LV filling pressures.

CRT improves ventricular function without increasing myocardial energy consumption, in contrast to the effects of inotropic agents such as dobutamine. CRT may also reverse LV remodeling over time, reducing LV mass and end-diastolic dimension while increasing the ejection fraction.

The CARE-HF trial demonstrated that CRT alone, without a defibrillator, reduces mortality in patients with classes III and IV heart failure, left ventricular ejection fraction ≤35%, and ventricular dyssynchrony.[2] CRT combined with an implantable cardioverter-defibrillator (CRT-D) has been shown to reduce death and hospitalization rates in patients with classes II and III heart failure and LV systolic dysfunction.[3] The benefit of CRT has more recently been extended to patients with less severe (class I to II) heart failure, left ventricular dysfunction, and QRS widening based on the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy trial.[4]

Approximately 25% of patients receiving CRT under current indications are nonresponders. Contributing factors to nonresponse include coronary venous anatomy that precludes optimal LV lead placement, the presence of ventricular scar, or suboptimal atrioventricular or ventriculo-ventricular activation timing. The greatest benefit of CRT appears to accrue to patients with QRS widening >150 milliseconds and left bundle branch block morphology, compared with those with lesser QRS widening or with right bundle branch block or nonspecific intraventricular conduction delay.[5]

Echocardiography can identify mechanical dyssynchrony, but has not proved useful in selecting patients for successful CRT.[6]

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ANSWER TO QUESTION 182

A (Braunwald, pp. 507–609, 510; Fig. 25.15; pp. 545–546)

This patient has heart failure with reduced ejection fraction and New York Heart Association (NYHA) II symptomatology on a pharmacologic regimen that includes a beta blocker, angiotensin receptor blocker, and mineralocorticoid receptor antagonist. Although she has only mild heart failure symptoms, treatment guidelines recommend further medical optimization for additional clinical benefit.[1] Notably, her heart rate is 84 beats/min in sinus rhythm, and the beta blocker dosage is below guideline-recommended targets (i.e., up to 200 mg daily for metoprolol succinate). The appropriate next step is therefore to upwardly titrate the beta blocker. If she does not tolerate augmentation of the beta blocker, then consideration of the I_f channel inhibitor, ivabradine, would be appropriate for heart rate reduction. In the SHIFT trial, patients with symptomatic heart failure, left ventricular ejection fraction (LVEF) ≤35%, and heart rate ≥70 beats/min in sinus rhythm, who were receiving standard heart failure therapy (including beta blockers)

were randomized to treatment with ivabradine or placebo. Patients assigned to ivabradine experienced an 18% reduction in the composite of cardiovascular death or heart failure hospitalization, driven principally by a reduction in the latter.[2] This result led to a class IIa indication for the addition of ivabradine in patients meeting the SHIFT inclusion criteria.

Although replacement of candesartan with the angiotensin receptor neprilysin inhibitor sacubitril/valsartan would also be a reasonable consideration for this patient, this step should follow optimization of the beta blocker dosage, and for a patient tolerating candesartan 32 mg daily, the appropriate starting dose of sacubitril would be 49/51 mg twice daily, not the 24/26 mg twice daily listed in the question.

By current heart failure guidelines, cardiac resynchronization therapy is indicated in NYHA II to IV heart failure patients with LVEF ≤35% who are in sinus rhythm with *left* bundle branch block and QRS duration ≥120 milliseconds (a class IIa indication; QRS ≥150 milliseconds would be a class I indication), and would be less beneficial for this patient with right bundle branch block and QRS duration of 120 milliseconds.

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ANSWER TO QUESTION 183

B (Braunwald, pp. 1631–1632)

This 52-year-old man has symptoms and signs of heart failure. There are several possible contributors to his left ventricular (LV) dysfunction based on the clinical history. The history of smoking and hypertension put him at high risk for coronary artery disease, but there is no evidence of angina or prior myocardial infarction by history or ECG. Long-standing, severe, uncontrolled hypertension may ultimately lead to heart failure owing to progressive LV hypertrophy and diastolic dysfunction; however, this patient's hypertension has been well controlled in recent years. The evidence by chest radiograph and physical examination for an enlarged heart with decompensated heart failure is most consistent with a dilated cardiomyopathy. His confessed alcohol use is moderate; however, patients with excessive alcohol intake may underreport their true consumption. Of the choices presented, the best unifying diagnosis is alcoholic cardiomyopathy.

Heavy alcohol consumption is the leading cause of nonischemic dilated cardiomyopathy in the United States for both men and women. In general, alcoholic cardiomyopathy is associated with heavy alcohol consumption, although the precise amount of alcohol that is "safe" for any given individual is variable. Excessive alcohol consumption causes abnormalities of both systolic and diastolic function as well as progressive LV cavity enlargement. Frequently, individuals with alcoholic cardiomyopathy develop atrial fibrillation or ventricular arrhythmias.

There is no definitive diagnostic test for alcoholic cardiomyopathy. As a result, it is often recommended that patients with dilated cardiomyopathy abstain completely from alcohol consumption. Total cessation in the early stages of the disease frequently leads to resolution of the manifestations of congestive heart failure and the return of the heart size to normal. Continued alcohol consumption leads to further myocardial damage and fibrosis, with the development of refractory heart failure. Patients with alcoholic cardiomyopathy benefit from treatment with standard medical therapies for heart failure with reduced ejection fraction. Because nutritional deficiencies are common in alcoholics and may contribute to myocardial dysfunction, vitamin supplementation (in particular, thiamine) should be considered.

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ANSWER TO QUESTION 184

E (Braunwald, pp. 536–538; Fig. 26.10)

This patient's presentation is most consistent with the syndrome of heart failure with preserved ejection fraction (HFpEF). She exhibits many of the typical demographic features including advanced age, a history of hypertension, and elevated body mass index, as well as clinical signs and symptoms of decompensated heart failure.

In contrast to heart failure with reduced ejection fraction, there are only limited data from prospective, randomized clinical trials to guide appropriate management of this large population of patients. Although aggressive management of hypertension in this disorder is beneficial,[1] no specific therapy has been clearly associated with a survival benefit. In the subgroup of HFpEF patients enrolled in the Digitalis Investigators Group trial, digoxin did not improve the composite primary endpoint of heart failure hospitalization or cardiovascular mortality.[2]

The Perindopril in Elderly People with Chronic Heart Failure[3] trial randomized a population of patients with heart failure, normal or near-normal EF, and age >70 years to treatment with the angiotensin-converting enzyme inhibitor perindopril or placebo and failed to demonstrate a benefit in the primary endpoint of all-cause mortality or unplanned heart failure hospitalizations.

The Candesartan Heart Failure: Assessment of Reduction in Mortality and Morbidity-Preserved trial randomized patients with chronic heart failure and ejection fraction >40% to treatment with the angiotensin receptor blocker candesartan or placebo.[4] Fewer hospitalizations for heart failure occurred in the candesartan group, but cardiovascular survival was not improved. The I-PRESERVE trial studied patients >60 years old with symptomatic heart failure and ejection fraction ≥45%. After randomization to irbesartan or placebo, there was no significant effect on mortality or hospitalizations from a cardiovascular cause.[5]

The Treatment of Preserved Cardiac Function with an Aldosterone Antagonist trial examined the role of spironolactone in patients with HFpEF and found no impact on the composite of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest relative to placebo; there was a statistically significant reduction in heart failure

hospitalizations, however, with spironolactone treatment.[6] In addition, post hoc analysis suggested geographic differences in results in that patients from the Americas with HFpEF benefited from spironolactone, but those from the countries of Russia and Georgia did not, possibly reflecting variation in clinical characteristics of the patients or in technical performance of the study.[7] Accordingly, in the absence of other evidence-based therapy, current guidelines suggest consideration of spironolactone for selected patients with HFpEF to decrease hospitalizations.[8]

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ANSWER TO QUESTION 185

E (Braunwald, p. 1626)

The clinical presentation of new-onset heart failure in the context of a viral prodrome suggests myocarditis. While most cases of myocarditis with antecedent viral infection are related to lymphocytic myocarditis, the rapid and fulminant progression of disease with worsening ventricular function, hypotension, ventricular arrhythmias, and hypoperfusion in this case suggest giant cell myocarditis (GCM). In patients with suspected GCM, endomyocardial biopsy is indicated to clarify the pathologic diagnosis.

Fulminant lymphocytic myocarditis generally carries a favorable prognosis if the patient can be supported through the period of acute illness. Immune suppression has generally not been effective in facilitating myocardial recovery. GCM, by contrast, carries a very poor prognosis with a mean transplant-free survival of only 5.5 months. Combination immunosuppressive therapy including cyclosporine, azathioprine, and corticosteroids has been demonstrated to prolong the time to transplantation or death once the diagnosis is confirmed. However, due to the rapid progression and poor survival, urgent mechanical circulatory support as a bridge to cardiac transplantation is the treatment of choice.

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ANSWER TO QUESTION 186

D (Braunwald, pp. 515, 568, 570–573)

The patient in this vignette has New York Heart Association (NYHA) class IV and American College of Cardiology/American Heart Association stage D congestive heart failure. He is not a candidate for cardiac resynchronization therapy because the QRS complex duration is normal (see Answer to Question 181). Repeated hospitalizations for heart failure, hyponatremia, intolerance to beta-adrenergic blockade, and a markedly reduced peak oxygen uptake of 10 mL/kg/min are all markers of poor prognosis and, taken together, predict mortality >50% in the next year. Such a patient should be considered for advanced therapies, including heart transplantation and mechanical circulatory support. Given the limitations of donor supply, cardiac transplantation is generally reserved for younger patients with few comorbid conditions. In addition, because of renal insufficiency and the recent diagnosis of cancer, this patient is unlikely to be eligible for transplantation (either heart alone or combined heart-kidney). Furthermore, the typically long waiting time for a donor heart renders transplantation an impractical immediate solution for this patient with a very limited predicted short-term survival.

Durable mechanical circulatory devices (i.e., ventricular assist devices) can extend survival and enhance the quality of life in patients with advanced heart failure. Mechanical support can be used as a "bridge to transplantation" and also as permanent "destination therapy" in patients for whom cardiac transplantation is not feasible. Such devices may also be used as a "bridge to recovery" in rare cases of an identifiable, potentially reversible cause of cardiac decompensation, such as acute myocarditis, postcardiotomy syndrome, or peripartum cardiomyopathy. Because this patient is ineligible for transplantation, destination therapy would be the most appropriate mechanical support strategy.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial evaluated patients with NYHA class IV symptoms and left ventricular ejection fraction <25%, most of whom were on continuous intravenous inotropes.[1] REMATCH demonstrated the superiority of an early-generation pulsatile left ventricular assist device (LVAD) compared with medical therapy, but by 2 years of follow-up only 23% of the patients with the assist devices were still alive.

The HeartMate II, an axial flow LVAD providing continuous blood flow, is approved by the US Food and Drug Administration both as a bridge to transplantation and as destination therapy. Continuous-flow pumps are relatively low profile devices that allow implantation in smaller patients and offer mechanical durability but do expose patients to the risk of stroke, infection, and bleeding. The HeartMate II LVAD confers an actuarial survival of 68% at 1 year and 58% at 2 years, while dramatically improving the quality of life in the majority of patients.[2,3]

The Heartware ventricular assist device is a smaller, intrapericardial, continuous-flow pump that is an alternative to the HeartMate II for use as a bridge to cardiac transplant, but is currently not approved for destination therapy.[4] More recently, data from the MOMENTUM 3 trial suggested improved clinical outcomes with implantation of a fully magnetically levitated centrifugal flow pump (HeartMate 3) compared with an axial flow pump (HeartMate II), driven largely by the lesser need for reoperation for pump malfunction.[5] Of note, patients being considered for destination LVAD therapy must have adequate native right ventricular (RV) function, because postoperative RV failure is associated with high mortality.

Although mechanical biventricular support is also available as a bridge to transplantation, it is not currently approved as destination therapy. Because this patient has adequate right ventricular function by echocardiography, he should be well supported by an isolated LVAD.

Finally, palliative and hospice level care play important roles in the care of stage D heart failure patients for whom these advanced options are not practical and there are no reasonable prospects for improvement in quality or length of life.

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ANSWER TO QUESTION 187

D (Braunwald, pp. 433–435; Fig. 22.16)

The Wiggers diagram of the cardiac cycle graphically demonstrates the important temporal relationships between the electrical and mechanical events of cardiac contraction and relaxation (Fig. 2.21). Nearly simultaneous events occur in the right and left sides of the heart during the cardiac cycle; here we concentrate on the left-sided events. Filling of the left ventricle begins in early diastole when the left ventricular (LV) pressure falls below left atrial pressure and the mitral valve opens. The subsequent early phase of rapid ventricular filling corresponds to the timing of the third heart sound (S_3), which may be audible when filling pressures are increased (as in patients with heart failure).

As the pressures in the left atrium and ventricle equalize, ventricular filling slows. Filling is then augmented at the end of diastole owing to atrial contraction, which generates the *a* wave on the left atrial pressure tracing. Temporally, the *a* wave occurs just after the P wave on the surface ECG and coincides with the fourth heart sound (S_4). In atrial fibrillation, organized atrial contraction is absent and a discrete *a* wave is usually not evident.

With the onset of the QRS complex on the surface ECG, ventricular systole begins and the LV pressure begins to rise. When LV pressure exceeds that in the left atrium, the mitral valve closes, producing the first heart sound (S_1). Ventricular pressure continues to rise at constant ventricular volume (isovolumic contraction) until it exceeds aortic pressure. At this point, the aortic valve opens and rapid ejection begins. After contraction, as the pressure in the left ventricle falls below the aortic pressure, ejection ceases and the aortic valve closes, generating the second heart sound (S_2). Isovolumic relaxation then occurs, beginning ventricular diastole again.

The *v* waves on the right and left atrial pressure tracings correspond to venous return to the atria when the tricuspid and mitral valves are closed. The peak of the *v* wave is usually inscribed after electrical repolarization of the ventricles, so that it *follows* the T wave on the ECG.

ANSWER TO QUESTION 188

A (Braunwald, pp. 406–407; Table 21.4)

Because the pleural veins drain into both the systemic and pulmonary venous beds, hydrothorax (pleural effusion) may develop when there is marked elevation of pressure in either venous system. Heart failure-related pleural effusions are usually bilateral, but when they are unilateral they are usually present on the right side. When hydrothorax develops, dyspnea becomes more marked because of a further reduction in vital capacity. The absence of pulmonary rales does not exclude considerable elevation of the pulmonary capillary pressure, especially in patients with chronic heart failure who may have well-developed lymphatic drainage.

Hepatomegaly is often present in patients with heart failure *before* the development of overt peripheral edema. When it develops rapidly with acute congestion, the liver may be tender as a result of rapid capsular distention.

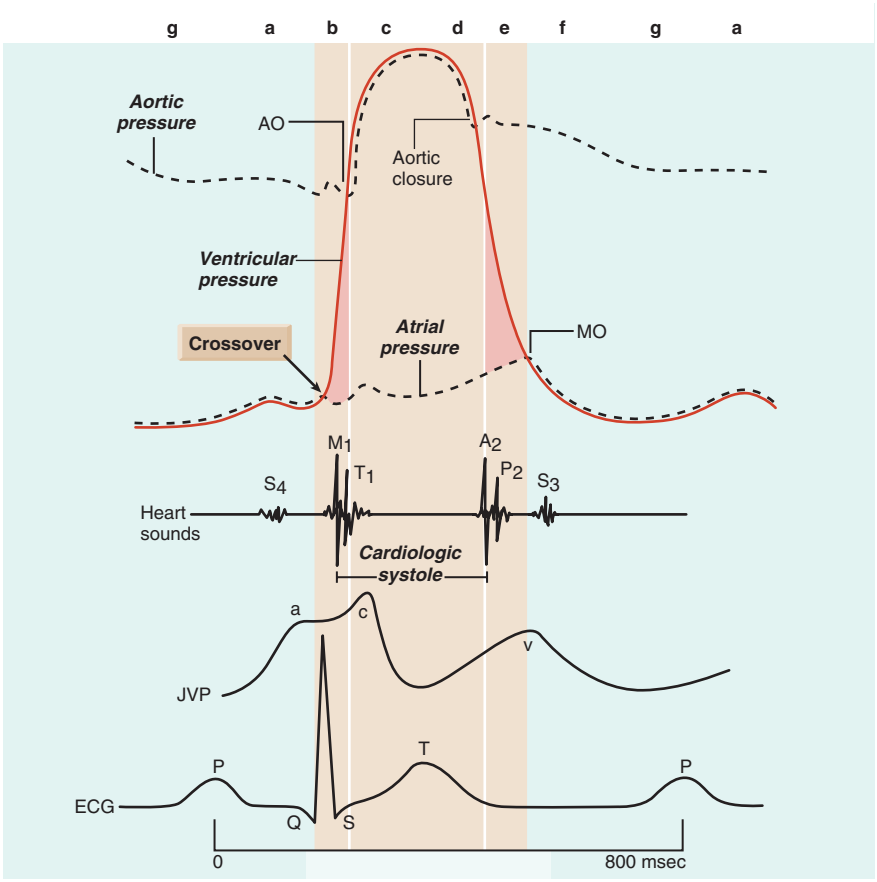
Peripheral edema often does not correlate well with the degree of systemic venous congestion. Usually, a substantial gain of extracellular fluid volume (>4 L in adults) must occur before peripheral edema develops.

With the development of left ventricular failure, pulmonary artery pressures rise and the pulmonic component of the second heart sound is *accentuated*. A systolic murmur of mitral regurgitation may also be audible owing to ventricular cavity dilatation.

ANSWER TO QUESTION 189

B (Braunwald, pp. 553–555; Figs. 28.1 and 28.2; Table 28.1)

This patient has ischemic cardiomyopathy due to multivessel obstructive coronary artery disease (CAD). Patients with left ventricular (LV) dysfunction and heart failure due to CAD may benefit from coronary artery bypass grafting (CABG) regardless of whether angina is present. Although the primary results of the STICH trial did not demonstrate a difference in the primary endpoint of all-cause mortality between medical therapy and surgical revascularization of patients with LV dysfunction and CAD amenable to CABG, secondary outcomes were improved in the revascularization group.[1] The recently published 10-year follow up of the STICH cohort



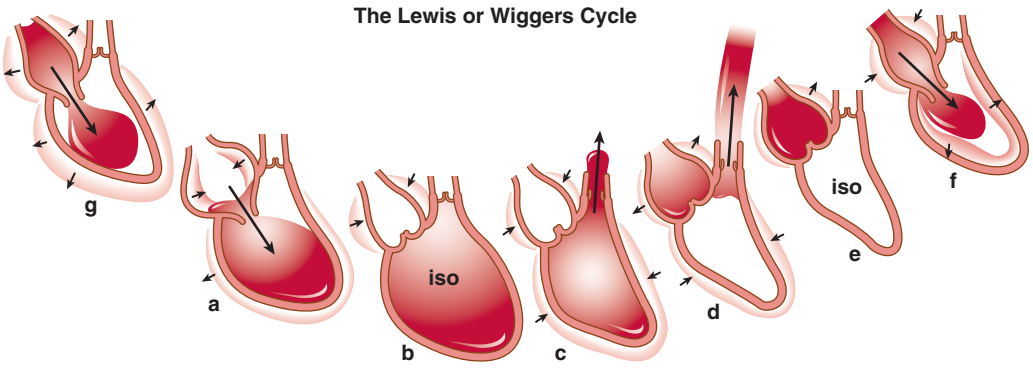


FIG. 2.21 *From Opie LH.* Heart Physiology: From Cell to Circulation. *Philadelphia: Lippincott Williams & Wilkins; 2004; copyright L.H. Opie, 2004.*

confirms the benefits of CABG over medical therapy, with improved median survival observed in subjects allocated to revascularization.[2] Many factors should be considered before referring such a patient for CABG, including the coronary anatomy, the degree of LV dysfunction, the severity of heart failure symptoms, and the magnitude of comorbid medical conditions. Because the benefits of revascularization are thought to result in part from improvement in blood flow to previously underperfused but still viable myocardium, testing to assess cellular viability has been utilized to identify patients likely to derive greatest benefit from CABG.[3] In patients with ischemic cardiomyopathy, the weight of evidence has suggested that significant myocardial viability (≥25%) predicts improvement in survival and quality of life with CABG over medical therapy alone. The myocardial viability substudy of the STICH trial called this conclusion into question, as assessment of viability did not identify patients with a survival benefit with CABG compared with medical therapy alone (i.e., the presence of viable myocardium in patients with CAD and LV dysfunction was associated with greater survival regardless of the treatment approach). Thus, the role of testing for viability is still evolving.[4]

Segments of markedly hypokinetic or akinetic myocardium identified by resting echocardiography may contain substantially viable myocardium if those areas are simply hibernating or stunned. Myocardial *hibernation* refers to persistent contractile dysfunction caused by a chronically reduced blood supply, usually a result of multivessel CAD. In such regions, irreversible damage has not occurred and ventricular function can improve with restoration of adequate blood flow through revascularization.[5] Myocardial *stunning* refers to reversible postischemic contractile dysfunction that

persists for a prolonged period after reperfusion. It is thought to be caused by the generation of oxygen-derived free radicals or the transient loss of contractile filament sensitivity to calcium. This patient's anterior wall akinesis may have resulted from cell death due to prior infarction, or it may represent hibernating myocardium. Viability testing with thallium perfusion imaging, positron emission tomography, or dobutamine echocardiography can confirm whether the anterior wall is viable or permanently scarred.

Surgical ventricular reconstruction (SVR) involves the resection of an aneurysmal or akinetic segment after transmural myocardial infarction and reconstruction with a patch. The exclusion of thinned, scarred myocardium restores an elliptical shape to the left ventricle with the goal of diminishing wall stress, mitral regurgitation, and residual ischemia. However, the results of the SVR portion of the STICH trial indicate that routine performance of SVR at the time of coronary artery bypass surgery is not associated with improved clinical outcomes.[6]

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ANSWER TO QUESTION 190

E (Braunwald, pp. 510–511)

Disturbances of cardiac rhythm are important and potentially life-threatening complications of cardiac glycoside administration. Side effects can be minimized by maintaining therapeutic levels of digoxin between 0.5 and 1.0 ng/mL. Although overt digitalis toxicity is usually manifest at serum levels >2.0 ng/mL, adverse drug effects may occur at lower levels, particularly if hypokalemia or hypomagnesemia is present. Digitalis toxicity may be manifest by neurologic symptoms (visual abnormalities, confusion), gastrointestinal disturbance (nausea, vomiting) or ventricular or supraventricular tachycardias and bradyarrhythmias. Common rhythm disturbances include junctional or ventricular ectopic beats, varying grades of atrioventricular (AV) block, accelerated AV junctional rhythm, paroxysmal atrial tachycardia with block, excessively slow ventricular response to atrial fibrillation, or bidirectional ventricular tachycardia. The class IB antiarrhythmic lidocaine may be helpful in managing ventricular arrhythmias due to digoxin toxicity, and vagally mediated AV block in this setting often responds to atropine. Conversely, direct-current cardioversion can precipitate serious ventricular arrhythmias in patients with overt digitalis toxicity.

Owing to its significant binding to plasma proteins and its large volume of distribution, digoxin is not efficiently removed by dialysis. Conversely, in cases of life-threatening overdose, antidigoxin immunotherapy can prove lifesaving. Doses of purified antidigoxin antigen-binding fragments (Fab) are administered on the basis of estimated dose of digoxin ingested, or total body burden. Although rare, recurrence of toxicity can occur, usually 24 to 48 hours after administration of antidigoxin immunotherapy.

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ANSWER TO QUESTION 191

C (Braunwald, pp. 1142–1143, 1166, 1167–1168; Fig. 59.19)

Current American College of Cardiology/American Heart Association guidelines for the management of ST elevation myocardial infarction (MI) recommend a number of predischarge pharmacologic interventions to reduce mortality risk, including antiplatelet agents (aspirin plus a platelet $P2Y_{12}$ receptor antagonist), a beta blocker, a high-dose HMG-CoA reductase inhibitor, and an angiotensin-converting enzyme (ACE) inhibitor, especially when left ventricular dysfunction is present.[1] For acute MI patients with left ventricular ejection fraction ≤40% and clinical heart failure or diabetes, the addition of a mineralocorticoid receptor antagonist is recommended based on the results of the EPHESUS trial.[2] This study showed that compared with placebo, the mineralocorticoid antagonist eplerenone resulted in a 15% decrease in death from any cause and reduced hospitalizations for cardiovascular events.

Implantation of a defibrillator prophylactically for a low ejection fraction should be deferred until 40 days after a MI based on the results of the DINAMIT trial.[3] The other answer choices (amiodarone, warfarin, or supplementing an ACE inhibitor with the angiotensin receptor antagonist valsartan) have not demonstrated mortality benefits in the post-MI setting.

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ANSWER TO QUESTION 192

C (Braunwald, pp. 575–577; eTable 29.1)

This radiograph displays a continuous-flow left ventricular assist device (LVAD) in the center of the figure. This rotary, axial-flow pump is implanted below the diaphragm, with an inflow cannula inserted in the left ventricular apex and

an outflow cannula connected to the ascending aorta. Continuous-flow LVADs have a smaller profile, lower weight, and greater durability than earlier-generation pulsatile LVADs and very low mechanical failure rates. The HeartMate II continuous-flow LVAD is approved by the US Food and Drug Administration for use both as a bridge to cardiac transplantation and as permanent destination therapy in patients not eligible for transplantation. In a pivotal destination therapy trial, patients with a HeartMate II had an actuarial survival of 68% at 1 year and 58% at 2 years, a significant improvement over the earlier-generation pulsatile device.[1] As indicated in the Answer to Question 186, data from the recent MOMENTUM 3 trial indicates even better clinical outcomes with implantation of a fully magnetically levitated centrifugal flow pump (HeartMate 3) compared with an axial flow pump (HeartMate II), driven largely by the lesser need for reoperation for pump malfunction.

Despite improved pump design and survival, disabling strokes remain a common complication of continuous-flow LVAD therapy, with rates approaching 10% per year. Device-related infections are the second leading cause of death after cardiac failure. Bacterial pathogens dominate and are found most commonly in the blood or the percutaneous driveline. Device endocarditis requires systemic antibiotics and device explantation. Gastrointestinal bleeding is more common with continuous-flow LVADs compared with earlier-generation pulsatile pumps and may be related to either an acquired von Willebrand factor defect (secondary to shear-related damage of high-molecular-weight von Willebrand factor multimers) or to enhanced development of gastrointestinal arteriovenous malformations (possibly as a consequence of low pulse pressure). Bleeding complications may be further exacerbated by the requirement for both antiplatelet and anticoagulant therapy to prevent pump thrombosis and device-related thromboembolism.[2] Rates of pump thrombosis appear to be lower with the newest generation centrifugal flow pump (HeartMate 3).[3]

LVAD therapy is associated with a high rate of right-sided heart failure, which may prolong hospitalization and reduce survival. Right-sided heart failure may be the consequence of underlying right-sided heart disease and LVAD-related hemodynamic alterations. A continuous-flow LVAD generates increased right-sided venous return and can produce interventricular septal shifts that can further impair right ventricular performance.[4] Therefore, patients with preoperative right ventricular dysfunction may not be candidates for isolated left-sided mechanical support.

The device in the upper left chest in the radiograph is an implantable cardioverter-defibrillator.

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ANSWER TO QUESTION 193

D (Braunwald, pp. 1922–1923; see also Answer to Question 171)

Cardiorenal syndrome, or coexistent cardiac and renal dysfunction, is common in patients with heart failure.[1] Furthermore, 15% to 30% of patients develop worsening renal insufficiency during a heart failure hospitalization. This patient has several risk factors for deterioration of renal function with heart failure treatment including older age, diabetes, and baseline renal dysfunction. Management of her apparent diuretic resistance would be aided by delineation of her intravascular hemodynamics with a pulmonary artery (PA) catheter. While there is no role for routine PA catheterization in the management of acute decompensated heart failure (ADHF), current guidelines recommend consideration of hemodynamic assessment in patients who are refractory to initial therapy, including high-dose or combination diuretics.[2]

Adding a low-dose inotrope has not been shown to improve short-term outcomes in heart failure and may exacerbate this patient's ventricular arrhythmia. Empiric administration of nitroprusside without arterial monitoring is inadvisable given the patient's hypotension. Ultrafiltration as a rescue strategy in this context would not be a preferred option based on the results of the CARESS study.[3] This randomized trial of patients with ADHF, worsened renal function, and congestion compared a strategy of ultrafiltration with stepped pharmacologic therapy. Compared with patients treated pharmacologically, those randomized to ultrafiltration showed higher creatinine levels, no significant change in weight, and more adverse effects (e.g., renal failure, bleeding, and IV catheter complications).

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ANSWER TO QUESTION 194

D (Braunwald, pp. 543–546)

The chest radiographs illustrate a biventricular pacing system, implanted for the purpose of cardiac resynchronization therapy (CRT). Three pacing leads are present, including standard leads in the right atrium and right ventricle and a third lead placed via the coronary sinus (CS) into a lateral marginal vein for left ventricular (LV) pacing. For patients with left ventricular ejection fraction (LVEF) ≤0.35, prolonged QRS duration on the surface ECG, and symptomatic heart failure (class II to IV) despite optimal medical therapy, there is compelling evidence that CRT, either alone or with defibrillator capability, is associated with improvements in functional capacity, quality of life, and mortality. For example, the RAFT trial of CRT in patients with class II to III heart failure, ejection fraction ≤0.30, and prolonged QRS complex demonstrated a 25% reduction in all-cause mortality and a 32% reduction in heart failure hospitalizations, confirming the results previously shown in Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy.[1]

Improvements in ventricular mechanical delay with CRT are associated with reductions in the end-systolic volume index and mitral regurgitation and an augmented LVEF. These data support a potential "reverse remodeling" benefit of CRT in patients with heart failure and reduced ejection fraction.

To date, the QRS complex duration (a marker of delayed electrical activation) is the most extensively validated criterion in selection of patients for CRT. Although it is an imperfect surrogate for mechanical ventricular dyssynchrony, QRS complex duration predicts acute hemodynamic improvement after CRT, especially among patients with left bundle branch block in sinus rhythm.

Because the LV lead is typically placed over the surface of the left ventricle via a CS branch, inadvertent phrenic nerve stimulation and diaphragmatic pacing may complicate device implantation.

To achieve the clinical and hemodynamic benefits of CRT, biventricular pacing must be continuous. This is in distinction to isolated right ventricular apical pacing, a mode that can *contribute* to dyssynchrony and a higher risk of heart failure symptoms.[2]

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ANSWER TO QUESTION 195

C (Braunwald, pp. 464–465, 467–468)

Pulmonary edema is initiated by an imbalance of Starling forces. Such an imbalance results from (1) increased pulmonary capillary pressure, (2) *decreased* plasma oncotic pressure, (3) increased negativity of interstitial pressure, or (4) increased interstitial oncotic pressure. An increased pulmonary venous pressure (e.g., due to mitral stenosis or left ventricular failure) raises the pulmonary capillary pressure and can result in pulmonary edema.

High-altitude pulmonary edema may occur in individuals who rapidly ascend to altitudes >2500 meters and then perform strenuous physical exercise before they have become acclimated.[1] The pathogenesis appears to involve hypoxic pulmonary vasoconstriction leading to increased capillary pressure. Symptoms respond quickly to descent to a lower altitude or to administration of a high inspiratory concentration of oxygen.

Acute pulmonary edema may develop in women with preeclampsia or eclampsia, most commonly in the postpartum period.[2] Multiple factors likely contribute, including the increased afterload of acute systemic hypertension, hypervolemia, hypoalbuminemia, and increased vascular permeability.

Heroin overdose is a recognized cause of pulmonary edema. The mechanism is not known, but may relate to an alveolar-capillary membrane leak induced by the drug.

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ANSWER TO QUESTION 196

B (Braunwald, pp. 406–407; Table 21.4; pp. 468–469, 1731–1732)

Systolic dysfunction sets into motion a cascade of neurohormonal events that promote ventricular remodeling and progressive left ventricular cavity enlargement. As a consequence, cardiomegaly is common in patients with heart failure and reduced systolic function. However, many patients develop heart failure without systolic dysfunction. This group of patients with heart failure and preserved ejection fraction comprises a diverse group of patients with primary diastolic heart failure, pericardial disease, valvular heart disease, hypertrophic heart disease, or primary restrictive cardiomyopathy. These syndromes present with signs and symptoms of heart failure typically in the absence of cardiomegaly.

Analysis of the Studies of Left Ventricular Dysfunction treatment trial has demonstrated that the physical examination carries important prognostic information in patients with heart failure. In particular, elevated jugular venous pressure and a *third* heart sound are each independently associated with adverse outcomes, including progression of heart failure.[1]

Pulsus alternans is characterized by a regular rhythm with an alternating strong and weak peripheral pulse. It signifies advanced myocardial disease and is likely the result of cyclic alteration in left ventricular stroke volume due to incomplete myocardial recovery after contraction. It often disappears with successful treatment of heart failure.

The presence of fever in heart failure should always raise the possibility of underlying infection, pulmonary infarction, or infective endocarditis. In severe heart failure, low-grade fever may be seen as a consequence of cutaneous vasoconstriction and impairment of heat loss from sustained adrenergic nervous system activation. Sleep-disordered breathing is common in heart failure and is an independent risk factor for death and need for cardiac transplantation. *Central* sleep apnea, commonly manifested by Cheyne-Stokes breathing, is present in approximately 40% of patients with a reduced left ventricular ejection fraction, whereas *obstructive* sleep apnea is present in another 10%. Sleep-disordered breathing causes recurrent apnea-related hypoxemia and sleep arousal, contributing to chronic neurohormonal activation, peripheral vasoconstriction, and reduced cardiac performance.[2]

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ANSWER TO QUESTION 197

A (Braunwald, pp. 357–358)

The lung can be divided into three zones on the basis of the relationship between pulmonary arterial, alveolar, and pulmonary venous pressures. In zone 1 (at the apex), the alveolar pressure exceeds both pulmonary arterial and pulmonary venous pressures, so that there is ventilation without perfusion (dead space). In zone 2, alveolar pressure

exceeds the venous but not the arterial pressure at some stage of the respiratory cycle. In zone 3, the alveolar pressure does not exceed either arterial or venous pressures. Zone 3 alveoli are therefore the best perfused and in the upright patient are situated in the dependent areas of the lung.

Measurement of the pulmonary capillary wedge pressure using a balloon-tipped catheter will be misleading if the catheter tip is wedged in a zone 1 or zone 2 arterial branch. In these zones, the wedge pressure measures alveolar pressure rather than the true left atrial pressure. In most spontaneously breathing patients, a flow-directed balloon-tipped catheter is naturally directed to zone 3 (because these areas are best perfused) and the pulmonary artery occlusion pressure is a truer estimate of the left atrial pressure.

Pulmonary vascular redistribution on the chest radiograph reflects a relative reduction of perfusion of the bases and a relative increase in apical perfusion. This phenomenon is likely due to compression of vessels at the lung bases owing to dependent edema in that zone.

ANSWER TO QUESTION 198

B (Braunwald, p. 562)

The calcineurin inhibitors (cyclosporine and tacrolimus) interfere with T-cell activation and have become the cornerstone of immunosuppression in solid organ transplantation. Despite reducing episodes of rejection and prolonging survival after transplantation, cyclosporine use is associated with a number of potential complications. Hypertension and nephrotoxicity are common, and cyclosporine levels must be monitored carefully to limit progressive renal failure. Adverse gastrointestinal tract side effects include hepatotoxicity and cholelithiasis, leading to dose-dependent abnormalities in liver function tests. Fine tremors, paresthesias, and occasionally seizures are potential neurologic side effects of cyclosporine therapy. Many patients who receive cyclosporine develop hypertrichosis (hirsutism) or gingival hyperplasia. The latter complication is reported to occur more frequently in those treated simultaneously with nifedipine. Myelosuppression in transplant patients is most commonly associated with azathioprine, not cyclosporine.

Tacrolimus has a different side-effect profile. Hirsutism and gingival hyperplasia do not occur with tacrolimus, and this drug is associated with a lower incidence of hypertension and dyslipidemia than cyclosporine. However, hyperglycemia and neurologic toxicity may be more common with tacrolimus.

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ANSWER TO QUESTION 199

D (Braunwald, pp. 470–472, 479–481; Fig. 24.6)

Acute heart failure syndromes (AHFS) are responsible for >1 million hospitalizations annually in the United States. Systolic blood pressure is usually normal or high (≥180 mm Hg) in patients with AHFS regardless of ejection fraction, likely related to enhanced sympathetic tone. Fewer than 10% of patients are hypotensive (<90 mm Hg), usually in association with advanced left ventricular (LV) systolic dysfunction and reduced cardiac output (CO). Patients with low CO may benefit hemodynamically from infusion of intravenous inotropes with vasodilating properties, such as the phosphodiesterase-3 inhibitor milrinone for short-term support. However, milrinone use has not been shown to improve hospital mortality rates and can be associated with hypotension, arrhythmias, and myocardial ischemia. It should be used only for patients who do not respond to diuretics and noninotropic vasodilators.[1]

Vasopressin (antidiuretic hormone) mediates (1) vasoconstriction via binding to the V_{1a} receptor on vascular smooth muscle, and (2) free water retention via the V_2 receptor at the renal collecting duct. Vasopressin levels are elevated in both acute and chronic heart failure and are thought to be a major contributor to hyponatremia, an adverse prognostic marker. Tolvaptan, an orally available V_2 receptor antagonist, has been shown to improve the pulmonary capillary wedge pressure and to normalize serum sodium concentrations. However, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial failed to demonstrate a reduction in mortality or re-hospitalizations for heart failure with use of this agent.[2]

Initial management of AHFS with noninvasive ventilation reduces respiratory distress and improves LV function by lowering afterload. Noninvasive mask ventilation may be administered by continuous positive airway pressure or noninvasive intermittent positive-pressure ventilation. The Three Interventions in Cardiogenic Pulmonary Oedema trial demonstrated that noninvasive ventilation improves dyspnea, hypercapnia, and acidosis compared with standard therapy, but does not reduce mortality or the need for intubation in patients with pulmonary edema.[3]

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ANSWER TO QUESTION 200

C (Braunwald, pp. 442–444; Fig. 23.1)

Neurohormonal activation is an important aspect of heart failure syndromes.[1] Although initially a beneficial compensatory response to falling cardiac output (CO), sustained neurohormonal activation ultimately contributes to ventricular remodeling and heart failure progression. Neurohormonal modulation is consequently a cornerstone of heart failure treatment.

Reduced CO in patients with heart failure triggers adrenergic nervous system stimulation and increased norepinephrine (NE) release. The degree of elevation in the plasma NE concentration correlates with the severity of left ventricular dysfunction, and plasma NE levels are a potent predictor of mortality in heart failure patients. Low forward CO also activates the renin-angiotensin system,

increasing circulating levels of angiotensin II and aldosterone and promoting salt and water retention. Increased preload and afterload in the failing heart contribute to mechanical atrial and ventricular stretch, which triggers the release of natriuretic peptides. These peptides, in particular atrial natriuretic peptide and B-type natriuretic peptide, promote compensatory vasodilatation and natriuresis. Circulating levels of inflammatory cytokines, including tumor necrosis factor-alpha, are also increased in heart failure and may contribute to the cachexia seen in patients with end-stage disease.[2]

In typical patients with heart failure, there is progressive *downregulation* of cardiac beta-adrenergic receptors, proportional to disease severity, likely mediated by increased circulating NE levels.

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ANSWER TO QUESTION 201

D (Braunwald, pp. 563–566)

Mortality from infection accounts for approximately 20% of deaths over the first year after transplantation.[1] Infections in the first postoperative month tend to involve nosocomial bacterial and fungal pathogens. Later post-transplantation infections are more diverse and involve opportunistic infections such as cytomegalovirus (CMV), herpes simplex, *Candida, Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), *Nocardia*, and *Toxoplasma gondii*.

CMV infection is one of the most frequent post-transplantation infections. CMV-negative recipients who receive a CMV-positive allograft are at highest risk, but prior seropositivity does not fully protect against this complication. Prophylactic therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) is prescribed to prevent infections by *Pneumocystis* and *T. gondii*. For patients allergic to TMP-SMZ, oral atovaquone prophylaxis against *Pneumocystis* pneumonia is commonly prescribed.

Allograft rejection is a very important potential complication of heart transplantation, but the likelihood is substantially reduced with effective immunosuppression. Immunologic tolerance to the donor organ develops in the recipient over time, making rejection less likely, which permits a gradual decrease in the intensity of immunosuppressive drugs.

More than 1 year from heart transplantation, the leading cause of death is the development of coronary artery disease in the allograft. It is pathologically distinct from typical atherosclerosis and is associated with intimal hyperplasia and smooth muscle cell proliferation that lead to progressive obliteration of the vessel lumen and loss of tertiary branching.[2] Patients with CMV infection appear to be at higher risk. The diagnosis of this complication is established by surveillance angiography, which is typically performed on an annual basis in patients after transplantation.

Transplant recipients have a markedly increased incidence of various cancers compared with age-matched controls. This increased risk is related to the intensity and chronicity of immunosuppression therapy. Skin cancers are the most common malignancy after transplantation, followed by lymphoproliferative disorders (which are associated with Epstein-Barr virus infection, not CMV). Other common malignancies after transplantation include adenocarcinomas of the prostate, lung, bladder, and kidney.

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ANSWER TO QUESTION 202

D (Braunwald, pp. 573–574; Fig. 29.1)

The intra-aortic balloon (IAB) is a catheter-mounted counterpulsation device that is most commonly inserted percutaneously through the common femoral artery and positioned in the descending aorta just distal to the left subclavian artery. The balloon timing should be adjusted such that inflation occurs at the dicrotic notch of the arterial pressure waveform, which coincides with the timing of aortic valve closure. The resultant diastolic rise in aortic pressure increases coronary blood flow. The IAB is timed to deflate during the isovolumic phase of left ventricular (LV) contraction. That relative reduction of afterload decreases peak LV pressure and myocardial oxygen consumption.

IAB counterpulsation improves aberrant hemodynamics in cardiogenic shock after cardiac surgery, acute myocardial infarction (MI), or during high-risk coronary interventions.[1] IAB therapy is indicated for stabilization of patients compromised by mechanical complications of acute MI such as mitral regurgitation or ventricular septal defect. IAB may also be useful as a treatment of refractory angina or ventricular arrhythmias and as a means to stabilize critically ill patients awaiting cardiac transplantation before insertion of a ventricular assist device. Of note, the SHOCK II trial showed that IAB therapy did not reduce 30-day mortality in comparison to medical therapy among patients with acute MI complicated by cardiogenic shock for whom early revascularization was planned.[2] Whether IAB therapy reduces mortality of cardiogenic shock in conditions other than acute MI remains unanswered. Absolute contraindications to the use of an IAB include aortic valve *insufficiency* and aortic dissection. An IAB should not be inserted via the femoral artery in patients with an abdominal aortic aneurysm or severe calcific aortoiliac or femoral arterial disease.

Major complications of IAB therapy include limb ischemia, aortic dissection, aortoiliac laceration or perforation, and deep wound infection.

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ANSWER TO QUESTION 203

A (Braunwald, pp. 504–511)

The annual mortality rate of patients with ventricular dysfunction and heart failure ranges from 2% to 5% in asymptomatic patients (class I) to greater than 25% in those who are severely symptomatic (class IV).

Many clinical trials have confirmed that angiotensin-converting enzyme (ACE) inhibitors should be the mainstay of treatment for patients with left ventricular (LV) dysfunction. In patients with asymptomatic LV dysfunction (class I), ACE inhibitors slow progression to symptomatic heart failure. In patients who have established symptomatic heart failure (class II to IV), ACE inhibitors significantly reduce mortality. For individuals who are intolerant of ACE inhibitors, an angiotensin receptor blocker (ARB) or the combination of hydralazine plus long-acting nitrates should be considered, because both of these strategies have shown outcome benefits in patients with symptomatic heart failure. The CHARM trial demonstrated that ARB therapy results in comparable outcomes as ACE inhibition in patients with chronic heart failure.[1] The use of a combined ARB and neprilysin inhibitor, sacubitril/valsartan, has been shown to reduce mortality more than enalapril in patients with heart failure and reduced ejection fraction, and this combination is now recommended to replace ACE inhibitors or ARBs in selected patients with heart failure and reduced ejection fraction.[2] In heart failure patients of African American descent, data from the A-HeFT trial show that addition of hydralazine plus isosorbide dinitrate to standard therapy results in improved clinical endpoints.[3] Beta blockers (in particular, carvedilol or metoprolol succinate) should also be prescribed to heart failure patients in stable condition (those without substantial fluid retention or recent episodes of acute decompensation requiring inotropic therapy).

The Digitalis Investigation Group trial demonstrated that digoxin decreases hospitalizations for heart failure in patients with class II to IV symptoms, but has no effect on overall mortality. The RALES trial showed that the addition of spironolactone to standard heart failure therapy decreases mortality in patients with advanced (class III to IV) symptoms.[4]

Historically, patients with chronic heart failure were instructed to avoid physical exercise and to rest in bed. This practice is no longer recommended because regular exercise has been shown to improve functional capacity. In addition, exercise may improve excessive neurohormonal activation and quality of life. However, moderate levels of exercise have not been demonstrated to improve the natural history of heart failure.[5]

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ANSWER TO QUESTION 204

B (Braunwald, pp. 686–687; Tables 36.1, 36.3, 36.4)

Intravenous administration of adenosine slows the sinus rate and conduction through the atrioventricular (AV) node, causing transient AV block. Its AV nodal effects, in combination with its extremely short half-life (1.5 seconds), make adenosine a safe and effective drug for the diagnosis and treatment of reentrant supraventricular tachycardias (SVTs) involving the AV node. Atrioventricular nodal reentrant tachycardia and atrioventricular reentrant tachycardia nearly always terminate after adenosine administration. In addition, the transient AV block induced by adenosine may help to unmask other underlying supraventricular arrhythmias such as atrial tachycardia or atrial flutter. Because of its short half-life, adenosine must be administered as a *rapid* intravenous bolus to achieve adequate blood and tissue levels. Short duration of action also implies a brief period of side effects, which differentiates adenosine from other drugs (e.g., beta blockers, calcium channel blockers) that are used to treat SVTs.

Adenosine may also be helpful in the differentiation of wide-QRS complex tachycardias. Ventricular tachycardia (VT) is usually unaffected by adenosine (except rare forms of RV outflow VT), whereas SVT with aberrant conduction will either terminate or be exposed by transient AV block after adenosine. However, a theoretical risk of adenosine use in these patients is acceleration of conduction through an accessory pathway, if one is present, as in patients with Wolff-Parkinson-White syndrome. Transient side effects are common with adenosine, occurring in up to 40% of patients. The most common are dyspnea, chest pressure, and flushing, all of which are fleeting and generally resolve within 1 minute. Adenosine may provoke bronchospasm in patients with severe asthma or obstructive lung disease. Patients after heart transplantation are particularly sensitive to the effects of adenosine, and appropriate caution should be exercised in this population. Since caffeine and theophylline antagonize the adenosine receptor, adenosine is less likely to be effective in patients with recent exposure to these substances.

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ANSWER TO QUESTION 205

C (Braunwald, pp. 719–721, 753–754)

Premature ventricular complexes (PVCs) are common and their prevalence increases with age. Their frequency may be exacerbated by a variety of factors, including electrolyte imbalances (especially hypokalemia and hypomagnesemia), infection, hypoxia, and excessive use of tobacco, caffeine, or alcohol. In the absence of structural heart disease, isolated

PVCs have no impact on survival. Conversely, after myocardial infarction (MI), PVCs identify patients who are at increased risk for ventricular tachycardia or sudden death. In the Cardiac Arrhythmia Suppression trial, the use of class IC antiarrhythmic drugs (encainide and flecainide) to suppress asymptomatic ventricular arrhythmias after acute MI was associated with an *increased* rate of death, and such agents should not be used in the setting of coronary artery disease.

Approximately 30% of patients with paroxysmal supraventricular tachycardias referred for electrophysiologic study are found to have a concealed accessory pathway, most commonly between the left ventricle and the left atrium. These concealed pathways conduct unidirectionally from the ventricles to the atria, but not in the opposite direction. Thus, the ventricle is not preexcited and the ECG does not demonstrate a delta wave during normal sinus rhythm. Nonetheless, concealed pathways may participate in reentrant AV tachycardias. This mechanism should be suspected during tachycardias when the QRS complex is of normal width (due to anterograde conduction down the atrioventricular node) and the retrograde P wave occurs after completion of the QRS complex, in the ST segment or T wave.

ANSWER TO QUESTION 206

D (Braunwald, pp. 767–768; Fig. 39.11; eFig. 39.1; pp. 820–821)

The ECG demonstrates right bundle branch block with prominent ST-segment elevation in the anterior precordial leads, typical of Brugada syndrome. This condition can lead to sudden cardiac death due to ventricular fibrillation despite the fact that the heart is structurally normal.[1] The clinical presentation is distinguished by male predominance and appearance of arrhythmic events at an average age of 40 years. It is believed that this syndrome accounts for 40% to 60% of cases of idiopathic ventricular fibrillation. In many families the syndrome segregates in an autosomal dominant fashion and is associated with loss of function mutations in the sodium channel *SCN5A*.[2] Screening of family members, including an ECG, is therefore important. Pharmacologic therapies are not effective in treating ventricular arrhythmias associated with Brugada syndrome. Administration of procainamide may be useful in bringing out the typical electrocardiographic phenotype in patients with a history of aborted sudden cardiac death (SCD) and an equivocal ECG. Implantation of a defibrillator is the therapy of choice for patients with Brugada syndrome with a history of aborted SCD or spontaneous ventricular tachycardia/ventricular fibrillation (VT/VF) (class I indication) or history of syncope (class IIa indication). ICD implantation can also be considered for patients with a Brugada pattern on the ECG and inducible VT/VF with ≤2 extra stimuli at electrophysiologic testing.[3]

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ANSWER TO QUESTION 207

E (Braunwald, pp. 787, 803–805; see also Answer to Question 180)

The preferred therapy for survivors of cardiac arrest at risk for recurrence is an implantable cardioverter-defibrillator (ICD), rather than antiarrhythmic drug therapy.[1] Among survivors of out-of-hospital cardiac arrest not associated with a myocardial infarction (MI), the risk of recurrent cardiac arrest after 1 year is 30% and after 2 years it is about 45%. In the Antiarrhythmics Versus Implantable Defibrillators trial, ICD implantation resulted in a 27% relative risk reduction in total mortality over 2 years of follow-up.

A number of studies directed at the primary prevention of sudden cardiac death (SCD) in high-risk patients have been reported. In patients with left ventricular (LV) dysfunction (ejection fraction ≤30%) and prior history of MI, prophylactic ICD implantation is associated with a reduction in all-cause mortality.[2] Defibrillator implantation also reduces death rates in patients with symptomatic systolic heart failure from nonischemic causes. In the Sudden Cardiac Death in Heart Failure Trial of patients with class II to III heart failure and left ventricular ejection fraction ≤35%, ICD implantation reduced overall mortality by 23% and was superior to amiodarone therapy.[2]

ICDs are also an appropriate consideration in primary and secondary prevention of SCD in high-risk individuals with hypertrophic cardiomyopathy. High-risk features include a history of syncope, a family history of SCD, the presence of marked LV hypertrophy (wall thickness >30 mm), and the finding of nonsustained ventricular tachycardia on noninvasive monitoring.[3]

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ANSWER TO QUESTION 208

A (Braunwald, pp. 775–779)

Atrioventricular (AV) block is present when atrial impulses are conducted to the ventricles with abnormal delay or are not conducted at all. There are three categories. *First-degree AV block* is present when the PR interval is prolonged (>0.20 second) in a constant fashion and every atrial impulse conducts to the ventricle. In *second-degree heart block*, some impulses fail to conduct from the atria to the ventricles. Second-degree block is divided into two groups: *Mobitz type I* and *Mobitz type II*. In the former type (also termed *Wenckebach block*), the PR interval progressively increases (and the RR interval usually progressively shortens) until an atrial impulse fails to conduct to the ventricles. In Mobitz type II block, the PR intervals are constant and without warning there is intermittent failure of an atrial impulse to conduct to the ventricles. *Third-degree heart block* is present when

all atrial impulses fail to conduct to the ventricles such that the atrial and the ventricular rhythms are independent of one another.

In first-degree heart block, the delay between atrial and ventricular contraction allows the leaflets of the mitral and tricuspid valves to drift toward a partially closed position prior to ventricular systole. Therefore, the intensity of the first heart sound is *diminished*. First-degree heart block and Mobitz type I second-degree heart block often arise in normal healthy adults and well-trained athletes, owing to increased vagal tone.

Mobitz type I second-degree heart block with a normal QRS duration almost always occurs at the level of the AV node, proximal to the His bundle. Conversely, type II second-degree heart block, especially when accompanied by a bundle branch block QRS morphology, usually reflects a more serious abnormality in the His-Purkinje system.

In third-degree heart block there is complete AV dissociation. As a result, the ventricular rate is governed not by the atrial rate but by an independent ventricular escape pacemaker. In acquired forms of third-degree heart block, the ventricular rate is usually <40 beats/min. The ventricular rate tends to be faster in patients with congenital complete heart block, about 50 beats/min.

ANSWER TO QUESTION 209

D (Braunwald, pp. 652–654)

Prolonged ambulatory electrocardiographic (Holter) monitoring of patients engaged in normal daily activity is useful to document the nature and frequency of underlying cardiac arrhythmias and to correlate a patient's symptoms with rhythm disturbances. Although significant rhythm disturbances are uncommon in healthy persons, a variety of arrhythmias, including sinus bradycardia (with rates as low as 35 beats/min), sinus arrhythmia, sinoatrial exit block, type I second-degree atrioventricular block (especially during sleep), and junctional escape complexes may be seen in normal persons. In addition, the prevalence of arrhythmias in normal subjects increases with older age. Persons with ischemic heart disease, especially those recovering from acute myocardial infarction (MI), exhibit ventricular premature beats (VPBs) when long-term recordings of the heart rhythm are obtained. The frequency of VPBs increases over the first several weeks after infarction and decreases about 6 months after infarction. Frequent and complex ventricular ectopy is associated with a twofold to fivefold increased risk of sudden cardiac death after MI.

Long-term electrocardiographic recordings are useful for the detection of underlying rhythm disturbances in patients with hypertrophic cardiomyopathy and mitral valve prolapse, as well as in patients who have unexplained syncope or transient cerebrovascular symptoms. In normal subjects and in patients with underlying rhythm disturbances, the cardiac rhythm may vary dramatically from one long-term recording period to the next.

On many occasions, the relatively brief period of recording provided by standard Holter monitoring (24 to 48 hours) may be inadequate to identify an abnormal rhythm responsible for a patient's symptoms. Longer-term monitoring in such patients, using an external event recorder, may help to establish a diagnosis. For patients with very infrequent symptoms, implantable loop recorders may be appropriate as they can remain in place for months or years. These devices have proven useful in establishing a diagnosis in patients with recurrent syncope and prior unrevealing evaluations.

Long-term monitoring has demonstrated a high frequency of asymptomatic recurrences of atrial fibrillation in patients treated for that condition. The frequency of asymptomatic episodes exceeds that of symptomatic episodes, which has important implications for the risk of discontinuing anticoagulant medications.

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ANSWER TO QUESTION 210

D (Braunwald, pp. 848–851)

Syncope may result from vascular, cardiac, neurologic, and metabolic causes. Vascular causes of syncope are the most common, accounting for about one-third of all episodes. Vascular causes include orthostatic hypotension and reflex-mediated syncope, such as carotid sinus hypersensitivity and neurocardiogenic (vasovagal) syncope.

Cardiac abnormalities, especially tachyarrhythmias and bradyarrhythmias, represent the second most common causes of syncope, accounting for 10% to 20% of episodes. Ventricular tachycardia is the rhythm disorder that most frequently causes loss of consciousness. Bradyarrhythmias such as sick sinus syndrome and advanced atrioventricular blocks can also result in syncope, but less commonly. Supraventricular tachycardias are much more likely to present as less severe symptoms such as palpitations or light-headedness rather than loss of consciousness. Although the prognosis of patients with noncardiac causes of syncope tends to be benign, those who have syncope of cardiac origin have a 30% mortality rate over the next year.

The history and physical examination are the most important part of the evaluation of patients presenting with syncope. Studies estimate that, in up to one-fourth of cases, an accurate diagnosis can be made on the basis of history and physical examination alone. The ECG is the most useful initial diagnostic test; any abnormality of the baseline ECG in patients with syncope is an independent predictor of mortality and indicates the need to pursue a cardiac etiology.

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ANSWER TO QUESTION 211

D (Braunwald, pp. 783–784; Table 41.1)

The most common nomenclature for pacemaker coding uses a four-letter code. The first position reflects the chamber

that is being paced (O = none, A = atrium, V = ventricle, D = dual [both atrium and ventricle are paced]); the second position reflects the chamber being sensed (O, A, V, and D as above); the third position corresponds to the response to sensing (O = none, T = triggered, I = inhibited, D = dual); and the fourth position reflects programmability and rate modulation (e.g., O = none, R = rate modulation). As an example, a patient with a dual-chamber, rate-adaptive pacemaker would have a DDDR code.

Rate-adaptive pacemakers incorporate a sensor that can modulate the pacing rate independently of intrinsic cardiac activity by monitoring physiologic processes such as physical activity or minute ventilation. Mode switching is a useful feature in which the pacemaker mode automatically changes (e.g., from DDDR to DDIR) in response to inappropriate rapid atrial rhythms. This is particularly beneficial for patients with paroxysmal supraventricular tachyarrhythmias, such as atrial fibrillation or flutter, to avoid rapid ventricular pacing during those episodes.

"Pacemaker syndrome" refers to the deterioration of hemodynamics with associated patient symptoms, or a limitation of optimal functional status, despite a normally functioning pacing system. This is observed most commonly with ventricular inhibited pacing, but may occur in any pacing mode in which atrioventricular (AV) synchrony is lost. Patients may experience a sensation of fullness in the head and neck, syncope or presyncope, hypotension, cough, dyspnea, congestive heart failure, or weakness. Physical findings include cannon *a* waves in the jugular venous pulsations and a fall in blood pressure during pacing compared with normal sinus rhythm (Fig. 2.22). Symptomatic AV block of any kind (including Wenckebach) is an indication for permanent pacing. In patients with hypertrophic cardiomyopathy, dual-chamber pacing has been shown to reduce the left ventricular outflow tract gradient and lead to symptomatic improvement in some trials. There is, however, a significant placebo effect from pacing, and other studies have not confirmed clinical benefit. Thus, the American College of Cardiology/American Heart Association guidelines consider pacemaker placement a class IIb indication in patients with medically refractory hypertrophic cardiomyopathy and significant outflow tract obstruction.

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ANSWER TO QUESTION 212

D (Braunwald, p. 787; eFig. 41.9)

Pacemaker-mediated tachycardia (PMT), or endless loop tachycardia, is a syndrome of upper rate behavior that occurs when there is intact ventriculoatrial conduction resulting in retrograde P waves. If these retrograde P waves are sensed by the atrial sensing circuit, the pacemaker atrioventricular interval is initiated and a paced ventricular contraction follows, which generates another retrograde P, and so on, generating a perpetual "loop." The diagnosis should be suspected in patients with a dual-chamber device who present with a paced tachycardia near the maximum tracking limit of the device. It is managed by *increasing* the postventricular atrial refractory period, which prevents atrial sensing of the retrograde P wave. Because episodes of PMT are often triggered by a premature ventricular complex (PVC), some commercially available devices offer automatic extension of the postventricular refractory period after a PVC.

ANSWER TO QUESTION 213

D (Braunwald, pp. 742–743)

Postoperative atrial fibrillation (AF) occurs in up to 40% of patients undergoing coronary artery bypass grafting or valvular surgery. This dysrhythmia is associated with an increased stroke risk in this setting and is the most common cause of prolonged hospitalization after cardiac surgery.[1] Risk factors for postoperative AF include advanced age (>70 years), male gender, diabetes, obesity, chronic lung disease, and left ventricular dysfunction. Several antiarrhythmic drugs have been shown to reduce the risk of developing AF after cardiac surgery. Oral beta blockers such as metoprolol lower the risk by 31%.[2] Other effective prophylactic antiarrhythmic agents are the class III agents amiodarone and sotalol. Digoxin may have a role in rate control of AF when it occurs, but has not been shown to prevent postoperative AF. Atrial pacing using temporary electrodes attached to either the right atrium or both atria reduces the probability of postoperative AF.

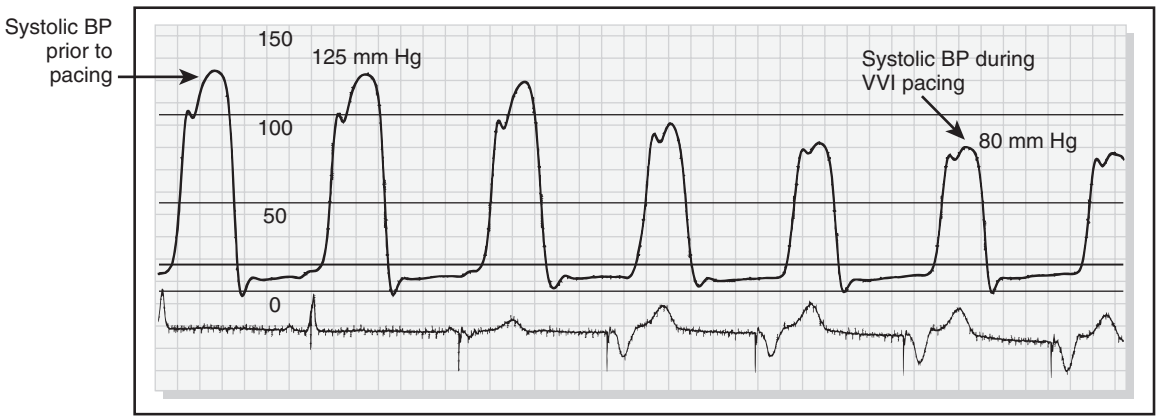

FIG. 2.22

Atorvastatin, an HMG-CoA reductase inhibitor, has been shown to reduce postoperative AF by 62%, an effect that is likely independent of its lipid-lowering properties.[3] Other agents that have also been shown in randomized trials to reduce the incidence of postoperative AF are hydrocortisone and colchicine (in patients who tolerate and continue the drug), presumably through their anti-inflammatory effects.[4,5]

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ANSWER TO QUESTION 214

D (Braunwald, pp. 676–677)

Procainamide, a class IA antiarrhythmic agent, is effective in the management of both supraventricular and ventricular arrhythmias. As a sodium channel-blocking agent, it acts to depress phase 0 depolarization, thereby slowing conduction. In addition, it has moderate potassium channel-blocking activity (largely owing to the action of its metabolite *N*-acetyl-procainamide), which leads to slowing of repolarization and prolongation of the action potential duration. A widened QRS complex duration is seen at therapeutic concentrations owing to slowing of conduction in the Purkinje system and ventricular muscle. QT interval prolongation occurs with rising serum concentrations and may precipitate ventricular arrhythmias.

In patients with atrial fibrillation (AF) or flutter, procainamide may lead to chemical cardioversion to normal sinus rhythm. Otherwise, since procainamide slows the atrial rate, it may facilitate rapid 1:1 conduction through the atrioventricular node and increase the ventricular response rate in atrial flutter or fibrillation unless a nodal blocking agent (e.g., a beta blocker) is co-administered. In patients with AF and Wolff-Parkinson-White syndrome, procainamide is effective at prolonging the effective refractory period of the bypass tract and suppresses extranodal atrioventricular conduction.

Multiple noncardiac side effects of procainamide have been reported, including rashes, myalgias, digital vasculitis, Raynaud phenomenon, gastrointestinal side effects, and central nervous system toxicity. Higher doses of the drug may depress myocardial contractility and diminish myocardial performance; rapid intravenous administration has been associated with hypotension due to a reduction in systemic vascular resistance. Chronic administration of procainamide is associated with a positive antinuclear antibody in almost all patients, particularly slow acetylators. However, symptoms of drug-induced lupus (arthritis, arthralgias, pleuritis) occur only in 15% to 20% of patients. Many of these patients exhibit positive antihistone antibodies, and the syndrome resolves after drug discontinuation.

ANSWER TO QUESTION 215

B (Braunwald, pp. 656–659)

Invasive electrophysiologic study (EPS) is employed for the evaluation of patients with disturbances of cardiac rhythm and conduction. It provides information about the type of rhythm abnormality and its electrophysiologic mechanism. Therapeutically, it is possible during EPS to terminate tachycardias by electrical stimulation, to evaluate the effects of antiarrhythmic therapies, and to ablate myocardium responsible for tachycardias.

EPS is the gold standard for evaluation of arrhythmic causes of syncope, including the three most common: sinus node dysfunction, His-Purkinje block, and tachyarrhythmias. Of the three, tachyarrhythmias are most reliably initiated in the electrophysiology laboratory, followed by sinus node abnormalities and His-Purkinje block.

EPS allows the measurement of intracardiac conduction times and the sequence of myocardial activation using catheter electrodes capable of sensing and pacing. In patients with acquired atrioventricular (AV) block and related symptoms, EPS evaluates the length of the His-ventricular (HV) interval, in order to assess infranodal conduction abnormalities that might prompt pacemaker implantation. HV intervals >55 milliseconds are associated with organic heart disease, a greater likelihood of developing trifascicular block, and higher mortality.

EPS is helpful in the management of patients with suspected sinus node dysfunction. The sinus node recovery time (SNRT) is used to assess the effects of overdrive suppression on sinus node automaticity. The SNRT is measured by subtracting the spontaneous sinus node cycle length before pacing from the time delay to the first spontaneous sinus response after termination of pacing. Normal values are generally <525 milliseconds, and prolongation of the SNRT suggests abnormal sinus node function. Because many patients with impaired sinus node function also exhibit abnormal AV conduction, it is important also to evaluate AV nodal and His-Purkinje function in this population.

In patients with wide-QRS complex tachycardias, EPS may be used to differentiate supraventricular tachycardia (SVT) with aberrancy from ventricular tachycardia, because the sequence of, and relation between, atrial and ventricular activation can be determined. SVTs are characterized in part by the presence of an HV interval during tachycardia equal to or greater than that recorded during normal sinus rhythm. Shortening of the HV interval during tachycardia suggests either VT or the presence of an accessory pathway. EPS is also used to locate and ablate accessory pathways in preexcitation syndromes. Left lateral accessory pathways are most common (~50%), followed by posteroseptal, right anteroseptal, and right lateral locations.

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ANSWER TO QUESTION 216

B (Braunwald, p. 683)

Dronedarone is an antiarrhythmic drug derived from amiodarone and the two agents share electrophysiologic properties, including blockade of the delayed rectifier potassium current (class III effect), inhibition of the rapid sodium and L-type calcium currents, and antiadrenergic effects. However, unlike amiodarone, dronedarone does not contain iodine molecules, a property that likely accounts for its much lower rate of thyroid and pulmonary toxicity.

Dronedarone is indicated for maintenance of sinus rhythm in patients with a history of atrial fibrillation (AF) or flutter.[1] It is orally absorbed, is hepatically metabolized, and has a much shorter elimination half-life than amiodarone (only 13 to 19 hours). Like amiodarone, the QT interval may become prolonged, but the risk of proarrhythmia is small.

In the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Heart Failure Evaluating Morbidity Decrease, patients on dronedarone had *increased* mortality compared with those taking a placebo (8.1% vs. 3.8%); thus, the drug should *not* be used in patients with recent or current heart failure.[2] In addition, in distinction to patients who maintain sinus rhythm on the drug, dronedarone is associated with increased mortality when prescribed to patients who have permanent atrial fibrillation (e.g., for rate control).[3]

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ANSWER TO QUESTION 217

B (Braunwald, pp. 738–741)

Early techniques of AF ablation were aimed at eliminating sites of initiating premature atrial contractions at their origin deep within the pulmonary veins, the site of origin of AF in many patients. However, only a small number of patients have sufficient atrial premature beats to serve as such a target, and ablation deep within these veins can result in pulmonary vein stenosis. Subsequently, techniques shifted to electrical isolation of the pulmonary veins by creating a circumferential line of block encircling the venous ostia, so as to prevent spread of impulses from the site of initiation to the remainder of the atria. At high-volume centers, single-procedure success rates (freedom from recurrences after 1 year) are 70% to 75% in patients with paroxysmal AF and 50% to 60% in patients with persistent AF. These success rates improve with additional follow-up ablation procedures. Success rates appear to be similar independent of the ablation technique used (radiofrequency catheter or cryoballoon).

Candidates for AF ablation are those without significant structural heart disease in whom AF interferes with quality of life. Catheter ablation is usually not appropriate for patients with AF who are asymptomatic. For symptomatic patients, it is usually appropriate to attempt AF control with at least one antiarrhythmic agent before proceeding to ablation. However, ablation may be appropriate first-line therapy for young individuals with symptomatic AF, those with sinus node dysfunction for whom antiarrhythmic drugs may cause significant bradycardia, and for patients who decline to take pharmacologic therapy. Since AF can recur after a successful ablation procedure, the need for ongoing anticoagulation is determined by the risk of stroke as estimated by the CHA_2DS_2-VASc score (summarized in the answer to question 218), rather than the presence or absence of symptoms.

Major complications occur in 5% to 6% of patients after catheter ablation for AF. The most common are cardiac tamponade, pulmonary vein stenosis, and cerebral thromboembolism, each of which occurs in approximately 1% of patients. Left atrial-esophageal fistula (not atrial-tracheal fistula) has been reported as a rare, but potentially lethal, complication of ablation in the posterior left atrium.

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ANSWER TO QUESTION 218

D (Braunwald, pp. 734–735; Fig. 38.6)

Stroke prevention is a major goal of therapy in patients with atrial fibrillation (AF). Because of the risk of hemorrhage, anticoagulants are reserved for patients with a risk of thromboembolism greater than that of bleeding. Thus, risk estimators have been developed for nonvalvular AF on the basis of clinical history, including the CHA_2DS_2-VASc score, which accurately discriminates between low-risk and intermediate-risk patients.[1,2] In this scoring system, the presence of congestive heart failure, hypertension, diabetes, female gender, vascular disease, and age ≥65 years are each assigned 1 point, while age ≥75 years and prior stroke (or transient ischemic attack) are assigned 2 points each. The higher the number of total points, the greater the stroke risk, and in general a score >1 warrants anticoagulation therapy.[1] The patient in this case vignette has a CHA_2DS_2-VASc score of 5 (hypertension, age ≥75 years, diabetes, and female gender), which corresponds to an annual stroke rate of ~4% (Fig. 2.23) such that prescription of therapeutic anticoagulation is appropriate.

If warfarin were chosen as the anticoagulant, the target INR for this patient would be 2.0 to 3.0. A higher target range of 2.5 to 3.5 for a patient in AF would be recommended in the presence of a mechanical mitral or aortic valve prosthesis. Antithrombotic therapy with either single- or dual -antiplatelet therapy is insufficient to prevent stroke in this high-risk patient.

The non-vitamin K antagonist oral anticoagulants (the direct thrombin inhibitor dabigatran and factor Xa inhibitors, including apixaban, rivaroxaban, and edoxaban) have several advantages over vitamin K antagonists, including fixed dosing regimens that eliminate the need for frequent laboratory testing. Novel oral anticoagulants have been shown to be

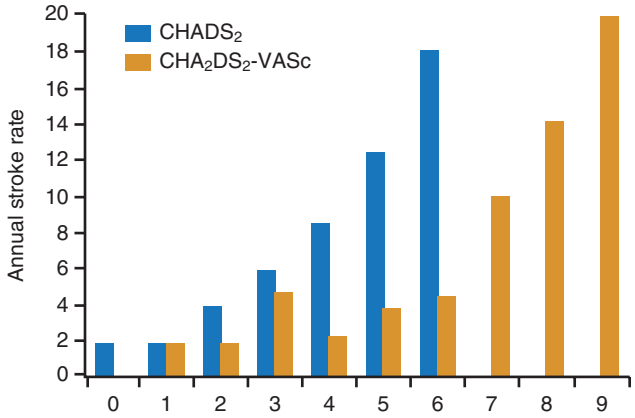

FIG. 2.23 *The annual risk of stroke (percent risk/year) based on the $CHADS_2$ and CHA_2DS_2-VASc scores. Based on data from Lip GY. Implications of the CHA(2) DS(2)-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation.* Am J Med. *2011;124:111–114.*

noninferior or superior to warfarin in efficacy for stroke prevention and have a lower rate on intracranial hemorrhage. Risk factors for bleeding while on oral factor Xa inhibitors include small body size, renal dysfunction, and advanced age. For the direct factor Xa inhibitor apixaban, the appropriate dose for prevention stroke in nonvalvular AF is 5 mg twice daily. Apixaban 2.5 mg twice daily is recommended for patients with at least two of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

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ANSWER TO QUESTION 219

D (Braunwald, pp. 731, 736–737, 742)

Atrial fibrillation (AF) commonly occurs in patients with hypertensive heart disease, hyperthyroidism, rheumatic heart disease, cardiomyopathy, coronary artery disease, or after cardiac surgery (in up to 40% of patients). The incidence of AF approximately doubles with each decade of adult life. It is an independent risk factor for mortality, after adjustment for other risk factors, including age, diabetes, hypertension, congestive heart failure, rheumatic and non-rheumatic valvular disease, and myocardial infarction. The presence of AF increases the risk of stroke by threefold to fivefold.

Treatment of AF varies depending on the clinical presentation, but includes three components: (1) assessment of the need for, proper timing of, and appropriate method for the restoration of sinus rhythm; (2) anticoagulation to prevent embolic stroke; and (3) medication to control the ventricular rate (to reduce symptoms and prevent the development of tachycardia-related cardiomyopathy).[1] Several randomized studies have demonstrated that a strategy of sinus rhythm maintenance with antiarrhythmic drugs offers no survival advantage over a strategy of long-term rate control in patients with AF and that long-term anticoagulation is imperative in all high-risk patients to prevent thromboembolic complications.[2]

In patients presenting with AF of <48 hours' duration, electrical or chemical cardioversion for restoration of sinus rhythm can be performed without the need for prolonged anticoagulation. In those presenting with AF of longer duration, anticoagulation for at least 3 weeks is advised before cardioversion, given the potential for dislodging formed thrombus within the left atrial appendage. If intra-atrial thrombus is first excluded by transesophageal echocardiography, more expeditious cardioversion may be safely performed in these patients.

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ANSWER TO QUESTION 220

B (Braunwald, pp. 619–621, 624–625, 631–632; Table 34.1; Fig. 34.2)

The sinus node is composed of nodal cells, transitional cells, and atrial muscle cells and is richly innervated by both postganglionic adrenergic and cholinergic nerve terminals. Vagal stimulation releases acetylcholine and slows the discharge rate of the sinus node, whereas adrenergic stimulation releases norepinephrine and speeds the discharge rate.

The arterial supply to the atrioventricular node arises from a branch of the right coronary artery in 85% to 90% of human hearts and from a branch of the circumflex in 10% to 15%. The upper muscular interventricular septum is supplied by both the anterior and posterior descending arteries.

Phase 3 (final rapid depolarization) of the cardiac action potential results from activation of repolarizing K^+ currents and inactivation of the inward calcium current. Interference with potassium currents by genetic mutation or drugs can result in prolongation of the QT interval. For example, a number of medications, including erythromycin, terfenadine, and ketoconazole, can inhibit the delayed rectifier K^+ current (I_{Kr}), resulting in an acquired form of the long QT syndrome, thereby predisposing to the ventricular arrhythmia torsades de pointes.

Phase 4 of the action potential represents the resting membrane potential in cardiac myocytes. During this phase, a set of potassium membrane channels are open, while other ionic channels are essentially impermeable to flow, such that the resting transmembrane potential of a ventricular myocyte is primarily determined by the equilibrium potential of potassium, at approximately –91 mV.

ANSWER TO QUESTION 221

E (Braunwald, pp. 681–683; Tables 36.1, 36.3, 36.4)

Amiodarone is a class III antiarrhythmic agent that is used to treat and suppress a wide spectrum of supraventricular

and ventricular arrhythmias. The onset of action of the intravenous form is within 1 to 2 hours. After oral administration, the onset of action is delayed by days or weeks but is shortened by large loading doses. Elimination is primarily by hepatic excretion into bile with some enterohepatic recirculation. Renal elimination of amiodarone is negligible and the dose does not need to be adjusted in the presence of renal insufficiency. Amiodarone's elimination half-life is multiphasic, with an initial 50% reduction in plasma concentration 3 to 10 days after drug cessation, followed by a terminal half-life ranging from 26 to 107 days, with a mean of ~53 days.

Unlike many other antiarrhythmic drugs, amiodarone is tolerated by patients with left ventricular dysfunction and it is not associated with increased mortality in patients with heart failure. However, all prospective, randomized comparisons have shown that implanted defibrillators are superior for the prevention of sudden cardiac death in this population.

Amiodarone is associated with a number of significant extracardiac toxicities. Of great significance is the development of pulmonary toxicity, which may reflect a hypersensitivity reaction. This complication can occur as early as 6 days after amiodarone's initiation or may appear after long-term use.

Additional adverse effects of amiodarone include hepatic toxicity, neurologic dysfunction, photosensitivity, and bluish skin discoloration. Both hypothyroidism (2% to 4%) and hyperthyroidism (1% to 2%) have been reported with the use of this drug. Amiodarone is not associated with hyperparathyroidism or disturbances of calcium homeostasis. Corneal deposits, visualized by slit lamp examination, occur in almost all patients who are treated with amiodarone for more than 6 months, but resultant visual impairment is unusual. Optic neuritis is a more serious potential adverse ophthalmic effect, but is very rare.

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ANSWER TO QUESTION 222

C (Braunwald, pp. 636–641, 643–646; Table 34.3; Fig. 34.14)

Mechanisms of cardiac arrhythmias can be classified into those of disordered impulse formation (e.g., abnormal automaticity, triggered activity) and those of disordered impulse conduction (e.g., conduction blocks, reentry). Common examples of reentry include atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and atrial flutter.

AVNRT arises from reentry involving dual AV nodal pathways. In the *common* form of AVNRT, the anterograde conduction occurs down the "slow" pathway and retrograde conduction occurs up the "fast" pathway. As a result, retrograde P waves on the ECG are typically superimposed on the terminal portion of the QRS complex. In the *uncommon* form of AVNRT, anterograde conduction occurs down the "fast" pathway and retrograde conduction is delayed as it proceeds up the "slow" pathway. Thus, in this form, retrograde P waves occur later, after the QRS complex.

In most cases of AVRT due to preexcitation, such as those in Wolff-Parkinson-White syndrome, the accessory pathway conducts more rapidly than the normal AV node, but takes a longer time to recover excitability (i.e., the accessory pathway has a longer anterograde refractory period than the AV node). The consequence is that a premature atrial complex may be blocked in the accessory pathway, continue to the ventricle over the normal AV node and His bundle, and return to the atrium retrograde via the accessory pathway. This creates a continuous conduction loop for generation of a narrow-complex, *orthodromic* AVRT. In *antidromic* AVRT, anterograde conduction to the ventricles occurs down the accessory pathway with retrograde conduction up the AV node, resulting in a wide-QRS complex tachycardia.

The typical form of atrial flutter ("counterclockwise" flutter) is due to *reentry* within the right atrium. Radiofrequency ablation of the cavotricuspid isthmus often interrupts the reentrant pathway and eliminates recurrences of the arrhythmia.

Ventricular tachycardias can be caused by numerous mechanisms, including reentry (e.g., bundle branch reentry), triggered activity (e.g., right ventricular outflow tachycardias), or abnormal automaticity.

ANSWER TO QUESTION 223

C (Braunwald, pp. 612–613; Fig. 33.5; pp. 762–763; Fig. 39.9)

In the absence of structural heart disease or coronary artery anomalies, a history of recurrent, exertionally related syncope in a young person is of concern for a predisposition to ventricular dysrhythmias. His ECG during exercise confirms the likely cause of syncope with the onset of polymorphic ventricular tachycardia. This constellation of findings, the family history of sudden cardiac death during exertion, and the normal corrected QTc interval at rest suggests the diagnosis of *catecholaminergic polymorphic ventricular tachycardia (CPVT)*, an inherited form of ventricular tachycardia. CPVT is triggered by stress, which first induces sinus tachycardia, followed by ventricular premature beats, then by polymorphic or bidirectional VT, as shown in the figure. Approximately 30% of CPVT patients have a family history of sudden death or stress-induced syncope. Mutations in the ryanodine receptor gene have been linked to an autosomal dominant form of CPVT that accounts for half of all cases.[1]

The treatment of choice for CPVT is beta blocker therapy (to blunt the impact of catecholamine surges) along with an implantable cardioverter-defibrillator for prevention of sudden death. Patients with CPVT should be counseled to avoid vigorous exercise. Cardiac sympathectomy has been reported to be effective in some cases, but is not considered first-line therapy. Magnesium has not been shown to be effective in patients with CPVT.[2]

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ANSWER TO QUESTION 224

E (Braunwald, pp. 681–684; Tables 36.1, 36.3, 36.4; p. 737)

Before initiating antiarrhythmic drug therapy to maintain sinus rhythm, precipitating or reversible causes of atrial fibrillation should be considered and addressed. The selection of an antiarrhythmic drug must take into account the underlying heart condition and comorbidities that may increase specific drug toxicities.

Dofetilide, an oral class III agent approved for the treatment of atrial flutter and fibrillation, acts by blocking the rapid component of the delayed rectifier potassium current (I_{Kr}), thereby prolonging repolarization. The most important adverse effect is torsades de pointes, which occurs in 2% to 4% of patients. The greatest risk of torsades is at the time of drug initiation, so drug loading must occur in a hospitalized setting with continuous electrocardiographic monitoring. The risk of torsades can be reduced by calculating the drug's appropriate dose based on the patient's creatinine clearance and by carefully monitoring the QT interval.

Sotalol is a nonspecific beta blocker that also prolongs repolarization. It should be used cautiously in patients with reduced contractile function because its negative inotropic effect may cause a further decline in cardiac index and precipitate heart failure. The most common and serious cardiac side effect of sotalol use is proarrhythmia; new or worsened ventricular tachyarrhythmias occur in about 4% of cases, and this complication is due to torsades de pointes in ~2.5%. Sotalol is primarily eliminated via the kidney and should be avoided in patients with chronic renal insufficiency.

Disopyramide, a class IA drug, is a negative inotrope that can exacerbate heart failure symptoms and is *contraindicated* in patients with systolic left ventricular dysfunction.

Dronedarone is a class III agent similar to amiodarone but with fewer extracardiac side effects. However, dronedarone should not be prescribed to patients with symptomatic systolic heart failure, as it has been associated with increased mortality in this population.

Despite the many potential extracardiac side effects of amiodarone (as described in the Answer to Question 221), it is generally well tolerated in patients with systolic dysfunction, does not require dose adjustment in patients with renal insufficiency, and unlike other class III antiarrhythmic drugs can typically be initiated in an outpatient setting, since torsades de pointes rarely occurs with this agent. Monitoring of thyroid function, liver function tests, and pulmonary symptoms is required during long-term amiodarone administration. The lowest effective maintenance dose of amiodarone should be used to minimize adverse effects.

ANSWER TO QUESTION 225

C (Braunwald, pp. 715–719; Figs. 37.8 and 37.10)

The figure depicts the initiation of a narrow-complex tachycardia during electrophysiologic study by rapid atrial pacing from the coronary sinus (CS). A train of stimuli is delivered at a cycle length of 500 milliseconds (S_1), followed by a premature stimulus (S_2) at an S_1–S_2 interval of 250 milliseconds. The effects of this premature stimulus on intracardiac conduction are seen in the His bundle recording (HBE). The AH interval, reflecting the conduction time from the atrium to the His bundle, is markedly prolonged after the premature stimulus, increasing to 300 milliseconds. This occurs because, in this patient with dual atrioventricular (AV) nodal pathways, the premature atrial stimulus encounters a refractory *fast* pathway and conducts anterograde through the *slow* pathway instead. In a patient without such dual AV nodal pathways, the premature stimulus would merely extinguish in the AV node. In this case, the slowed conduction through the AV node initiates a narrow-complex tachycardia. Such a "jump" in the AH interval during rapid atrial pacing is the electrophysiologic signature of dual AV nodal physiology. Examination of the sequence of atrial activation in the subsequent tachycardia reveals that the earliest atrial activation is in the His bundle recording (low right atrium, HBE lead), later progressing to the high right atrium and CS, (reflecting left atrial activation). These features identify this rhythm as an AV nodal reentrant tachycardia.

ANSWER TO QUESTION 226

D (Braunwald, pp. 775–777; p. 801; Table 41G.2)

The electrogram depicted demonstrates spontaneous infrahisian block, consistent with infrahisian conduction disease. Four QRS complexes are shown, with two surface electrocardiographic leads (V_1 and V_5), three His catheter electrograms (proximal, mid-, and distal pole), and a right ventricular electrogram. The surface ECG shows right bundle branch block and sinus rhythm with a single dropped beat after the second QRS complex. After the second QRS complex, deflections are present on the three His catheter channels, representing atrial depolarization. This event is followed by a small, sharp deflection evident only on the distal His channel, representing the His electrogram. That His bundle deflection fails to conduct to the ventricles because there is no QRS complex immediately following it. Together with bifascicular block evident on the surface ECG, this is a class I indication for permanent pacing.

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ANSWER TO QUESTION 227

D (Braunwald, pp. 757–759; Table 39.2; Fig. 39.6)

The differential diagnosis of wide-QRS complex tachycardia includes ventricular tachycardia (VT) and supraventricular tachycardia (SVT) with aberrancy. Several features of the clinical history and surface ECG may assist in this differentiation, although none is absolute. The clinical scenario is important, because a history of myocardial infarction makes the diagnosis of VT more likely. On the ECG, the presence of fusion beats (which indicate activation of the ventricle from two different foci, one of ventricular origin), capture

beats (intermittent narrow-complex QRS at an interval shorter than the rate of tachycardia), or atrioventricular dissociation all support the diagnosis of VT. Concordance of the QRS complex in the precordial leads (all complexes are positively directed or all are negatively directed) favors VT over SVT. Slowing or termination of the tachycardia by vagal maneuvers is consistent with SVT. Hemodynamic stability is not a useful criterion for differentiating SVT from VT.

Specific QRS contours are also helpful. For example, a triphasic QRS complex (rSR′) in lead V_1 supports the presence of SVT. Conversely, monophasic or biphasic QRS complexes in lead V_1 are more consistent with VT. VT with a left bundle branch block configuration typically demonstrates a small Q-large R (qR) or QS pattern in lead V_6 and a broad, prolonged (>40 milliseconds) R wave in lead V_1. VT with a right bundle branch pattern demonstrates a monophasic or biphasic QRS in lead V_1 and small R-large S waves or QS complexes in lead V_6.

ANSWER TO QUESTION 228

A (Braunwald, pp. 688–690; Fig. 36.1)

Electrical cardioversion is very effective for termination of supraventricular and ventricular tachyarrhythmias, particularly those due to reentry. The cardioversion of tachycardias caused by disorders of enhanced automaticity is less successful. For example, ectopic atrial tachycardia and other arrhythmias caused by disorders of impulse formation typically recur within seconds after the electrical discharge.

Except in patients with ventricular fibrillation or rapid ventricular flutter, a synchronized shock (delivered during the QRS complex) should be used to minimize the risk of firing on the ST segment or T wave, which might precipitate ventricular fibrillation. The minimal effective energy should be employed initially to reduce the risk of myocardial damage, with upward titration as required. If the "maximum" energy level of the electrical cardioverter fails to terminate the abnormal rhythm, repeated shocks at the same energy level can *decrease* the chest wall impedance and may succeed. Treatment with the class III intravenous agent ibutilide may convert atrial fibrillation to sinus rhythm, and when used as pretreatment also enhances the success of subsequent electrical cardioversion. Direct-current cardioversion is contraindicated in suspected digitalis-induced tachyarrhythmias because of the potential of inducing ventricular proarrhythmia.

After successful cardioversion, anticoagulation should be continued for an additional 3 to 4 weeks because full recovery of atrial mechanical activity often lags behind the return of normal electrical function and persistent blood stasis could permit thrombus formation.

ANSWER TO QUESTION 229

C (Braunwald, pp. 763–765; Fig. 39.10)

The arrhythmia in the figure is *torsades de pointes*, a form of polymorphic ventricular tachycardia that may develop in patients with delayed ventricular repolarization, manifest by a prolonged QT interval on the ECG. Torsades de pointes is thought to be triggered by early afterdepolarizations during the vulnerable period of ventricular repolarization, producing QRS complexes of changing amplitude twisting around the isoelectric line at a rate of 200 to 250 beats/min.

A prolonged corrected QT interval on the surface ECG is defined as >0.46 millisecond in men or >0.47 millisecond in women. A long QT interval, the electrocardiographic substrate for torsades de pointes, can be either congenital or acquired. Congenital forms include those associated with congenital severe bradycardia or loss of function mutations in the *KCNQ1* (LQT1) and *KCNQ2* (LQT2) potassium channel genes or a *gain* of function mutation in the *SCN5A* sodium channel gene, which is responsible for LTQ3. Loss of function mutations in the *SNC5A* gene (which result in accelerated sodium channel recovery or inactivated sodium channels) are associated with Brugada syndrome (and ventricular fibrillation) rather than prolongation of the QT interval and torsades de pointes.

Multiple drugs, both in toxic and therapeutic doses, can result in prolongation of the QT interval and an increased risk of torsades de pointes, including commonly used agents such as tricyclic antidepressants, phenothiazines, and erythromycin. Antiarrhythmic drugs that prolong the QT interval and predispose to torsades de pointes include quinidine, procainamide, disopyramide, sotalol, and dofetilide. Electrolyte disturbances, including hypokalemia or hypomagnesemia, may also contribute to a long QT interval and torsades de pointes.

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ANSWER TO QUESTION 230

C (Braunwald, pp. 756–759)

Intracardiac electrograms are shown depicting electrical activity in the high right atrium (HRA), in the bundle of His (His proximal and His distal), and at the right ventricular apex. The surface electrocardiographic leads V_1 and V_5 also are shown. The surface ECG demonstrates a wide-complex tachycardia at approximately 140 beats/min with a right bundle branch block morphology. The His distal and RV apical electrograms show deflections corresponding to each QRS complex, which represent ventricular depolarization. Smaller, periodic deflections at a slower rate are evident on the HRA and His proximal electrograms that represent atrial depolarizations. The lack of relationship between the atrial and ventricular depolarizations confirms the presence of atrioventricular dissociation. Thus, this rhythm represents ventricular tachycardia.

ANSWER TO QUESTION 231

C (Braunwald, pp. 775–777; Fig. 40.7)

The electrophysiologic tracing in the figure depicts Mobitz type I (Wenckebach) second-degree atrioventricular (AV) block. This is evident both in the surface electrocardiographic channel, which demonstrates progressive PR interval prolongation followed by a nonconducted P wave, and in the His bundle tracing (HBE), which shows progressive AH interval prolongation followed by block within the AV node. In contrast, in patients with Mobitz type II second-degree

heart block, there would be sudden block of impulse conduction (a P wave not followed by a QRS complex) without prior lengthening of the PR interval.

Type I second-degree AV block with normal QRS duration almost always reflects block at the level of the AV node proximal to the His bundle, typically portends a benign clinical course, and no specific intervention is indicated in the absence of symptoms. When type I AV block occurs in acute myocardial infarction (MI), it is usually in the setting of an inferior wall infarction. Such occurrences are usually transient and do not typically require therapy. The presence of higher degrees of AV block, including type II second-degree block, in acute MI indicates greater myocardial damage and predicts higher mortality.

Vagal maneuvers, such as carotid sinus massage, may *enhance* type I AV block by further prolonging AV nodal conduction and may therefore be useful in differentiating type I from type II AV block.

ANSWER TO QUESTION 232

E (Braunwald, p. 800; Tables 41G.1 and 41G.2)

Acquired atrioventricular (AV) blocks are most commonly idiopathic and related to aging. However, many defined conditions can impair AV conduction, including coronary artery disease, infections (e.g., Lyme disease, Chagas disease, endocarditis), collagen vascular diseases (e.g., rheumatoid arthritis, scleroderma, dermatomyositis), infiltrative diseases (e.g., sarcoid, amyloid), neuromuscular disorders, and drug effects.

Indications for permanent pacing in AV conduction disorders include (1) permanent or intermittent complete (third-degree) heart block, (2) permanent or intermittent type II second-degree AV block, and (3) type I second-degree AV block if accompanied by symptoms or evidence of block at, or inferior to, the bundle of His.

Pacing is not indicated in asymptomatic first-degree AV block or type I second-degree AV block proximal to the bundle of His. Occasionally, patients with first-degree AV block with marked prolongation of the PR interval (>300 milliseconds) are hemodynamically symptomatic because of the loss of effective AV synchrony. In that case, consideration of a pacemaker is appropriate if reversible contributors to the AV block are not identified. Because of vagal influences, many normal persons (particularly those with high resting vagal tone, such as conditioned athletes) may exhibit pauses significantly longer than 3 seconds during sleep; in and of itself, therefore, this finding is not sufficient to warrant permanent pacemaker implantation.

Controversy exists about the appropriateness of permanent pacing in adults with asymptomatic congenital complete heart block. Because of the high incidence of unpredictable syncope, the tendency is to implant permanent pacemakers in adults with this condition (class IIb indication).

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ANSWER TO QUESTION 233

B (Braunwald, p. 786; Fig. 41.13; Table 41.2)

Some dual-chamber pacemakers operate with unipolar leads, as in this case. The metal capsule of the generator serves as the indifferent electrode. This can result in oversensing, in which skeletal muscle potentials result in inappropriate inhibition or triggering of pacing.

The first two beats in the tracing show appropriate dual-chamber atrial and ventricular sensing and pacing at a rate of 70 beats/min. There is no evidence of lack of capture (all pacing stimuli cause myocardial depolarizations) or undersensing (because there are no native atrial or ventricular complexes).

After the third complex there is a long pause during which no pacemaker activity is observed. There is significant baseline artifact (due to muscle contractions) during this period. The lack of pacemaker activity during the pause indicates that the ventricular lead has sensed the electrical activity generated by the arm and chest muscles and has inappropriately inhibited pacemaker output.

In cases of suspected oversensing, placing the pacemaker in an asynchronous mode (with application of a magnet) will abolish the symptoms caused by pacemaker malfunction and aid in the diagnosis. Conversion of the lead system to a bipolar configuration frequently eliminates oversensing of myopotentials.

ANSWER TO QUESTION 234

D (Braunwald, p. 786; Fig. 41.12; Table 41.2)

The figure is an electrocardiographic tracing from a patient with a dual-chamber pacemaker. Atrial pacing artifacts with effective atrial depolarization are seen throughout the tracing. However, all but one ventricular pacing artifact (complex 5) fail to result in ventricular depolarization. Because the pacemaker generates appropriate output but not consistent, effective ventricular depolarization, this is an example of intermittent failure to capture of the ventricular lead.

Failure to capture most commonly occurs due to dislodgment of the pacemaker lead from the endocardial surface, a complication that usually occurs within the first few weeks after implantation. Modern designs for active and passive fixation of pacemaker leads are associated with a low frequency of lead dislodgement. Failure to capture may also occur due to a lead insulation break, which allows some of the electrode current to dissipate into the surrounding tissues. Even if the lead system is intact and in contact with the myocardium, failure to capture may occur if the pacing threshold required to depolarize the myocardium exceeds the programmed voltage amplitude and pulse duration. This can occur in the setting of exit block, in which an inflammatory reaction or fibrosis at the electrode-myocardium interface raises the depolarization threshold; the risk of this complication is greatly reduced through the use of a steroid-eluting lead. Pacing thresholds (and the likelihood of failure to capture) may also be increased in the setting of marked metabolic abnormalities (e.g., hyperkalemia) or therapy with antiarrhythmic drugs (e.g., flecainide).

Impending total battery depletion may also result in a subthreshold pacing stimulus and failure to capture. Total battery depletion usually results in complete failure to output, which is not the case here, because consistent atrial and

ventricular pacing and atrial capture are seen. In patients with a unipolar pacemaker, air in the pacemaker pocket may act as an insulator and reduce the effective pacemaker output, resulting in noncapture.

A loose set screw (which helps secure the lead to the generator) is a cause of failure to output, but not failure to capture. That diagnosis is inconsistent with this tracing, because consistent ventricular pacing artifacts are seen.

ANSWER TO QUESTION 235

D (Braunwald, pp. 772–774; eFigs. 40.1 and 40.2; Fig. 40.2)

There are several forms of bradycardia related to sinus node function. *Sinus bradycardia* is defined as a sinus node discharge <60 beats/min. It is generally a benign arrhythmia and well tolerated in most patients. It can result from excessive vagal stimulation or decreased sympathetic discharge and is common in well-trained athletes. During sleep, the heart rate in normal individuals can decrease to 35 to 40 beats/min and pauses of 2 to 3 seconds or even longer are not uncommon. Asymptomatic sinus bradycardia does not require specific therapy. Symptomatic patients can be treated acutely with intravenous atropine (which increases the sinus node discharge rate) or sympathetic stimulants. For chronic, symptomatic sinus bradycardia, electronic pacing may be required.

Carotid sinus hypersensitivity can be cardioinhibitory (ventricular asystole >3 seconds during carotid sinus stimulation) or vasodepressor (defined as a decrease in systolic blood pressure more than 50 mm Hg). Atropine is a competitive muscarinic acetylcholine receptor antagonist that *blocks* cardioinhibitory input to the sinus node. Atropine transiently abolishes cardioinhibitory carotid sinus hypersensitivity, but most symptomatic patients require permanent pacemaker placement.

Sick sinus syndrome encompasses a number of sinus node abnormalities including persistent spontaneous sinus bradycardia, sinus arrest or exit block, combinations of SA and AV conduction disturbances, and alternations of paroxysmal rapid atrial tachyarrhythmias with periods of slow atrial rates. *Sinus arrest* (which is distinct from sinus exit block) is identified by a pause in the sinus rhythm and a PP interval surrounding the pause that *is not* a multiple of the underlying PP rate. Sinus arrest can be due to sinus node ischemia during an acute myocardial infarction, degenerative fibrotic changes, digitalis toxicity, or excessive vagal tone. A large proportion of patients with sleep apnea have periods of sinus arrest as well as atrioventricular block.

Sinus arrhythmia is defined as phasic variations in the sinus cycle length, and it can appear in two forms: respiratory and nonrespiratory. In the respiratory form, the PP interval shortens in a cyclical fashion during inspiration owing to inhibition of vagal tone. In the nonrespiratory form, as seen in digitalis toxicity, the phasic variation is unrelated to the respiratory cycle. Symptoms are uncommon, and therapy is generally not necessary.

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ANSWER TO QUESTION 236

C (Braunwald, p. 762; Fig. 39.8; Table 39.4)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is depicted by fatty or fibrofatty infiltration of the right ventricular (RV) wall. Clinically, the disease is characterized by life-threatening ventricular arrhythmias in otherwise healthy-appearing young people, afflicting males most commonly. The prevalence is estimated at 1 in 5000 individuals, although the difficulty of diagnosis makes the true prevalence difficult to estimate. In its familial form, mutations have been identified in genes that encode desmosomal proteins (e.g., plakoglobin, desmoplakin, and others). Immunohistochemistry of desmosomal proteins in endomyocardial biopsy samples has been shown to be a sensitive and specific diagnostic test for ARVC. Most patients with ARVC demonstrate RV abnormalities by echocardiography, computed tomography, RV angiography, or magnetic resonance imaging. In advanced forms, the left ventricle may be involved.

The ECG in patients with ARVC in sinus rhythm may demonstrate a complete or incomplete right bundle branch block, with a terminal notch in the QRS complex, known as an *epsilon wave* (see arrowheads in Fig. 2.24). Ventricular tachycardia (VT) occurs commonly in patients with ARVC, usually with a *left* bundle branch block morphology due to its RV origin.

Because of the progressive nature of this disease and the multiple morphologies of the VT it produces, radiofrequency catheter ablation is not often successful. Use of an implantable cardioverter-defibrillator is usually the treatment of choice, even in asymptomatic patients.

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ANSWER TO QUESTION 237

C (Braunwald, p. 798)

Cardiac implanted electronic device (CIED) infections are increasing in incidence and are more common after a generator change than at the time of initial implantation. The organisms responsible for early infections are typically gram-positive cocci derived from the skin, predominantly staphylococcal species. Pocket infections can present with pain, erythema, purulent discharge, and/or generator or lead erosion. Septic pulmonary emboli may be the first manifestation. Patients with evidence of an infection of a CIED, including localized pocket infections without evidence of systemic involvement, should undergo complete removal of the system hardware (generator and leads). The risk of transvenous lead extraction increases the longer the lead has been in place. However, when performed by an experienced operator, this procedure can be performed with low morbidity rates.

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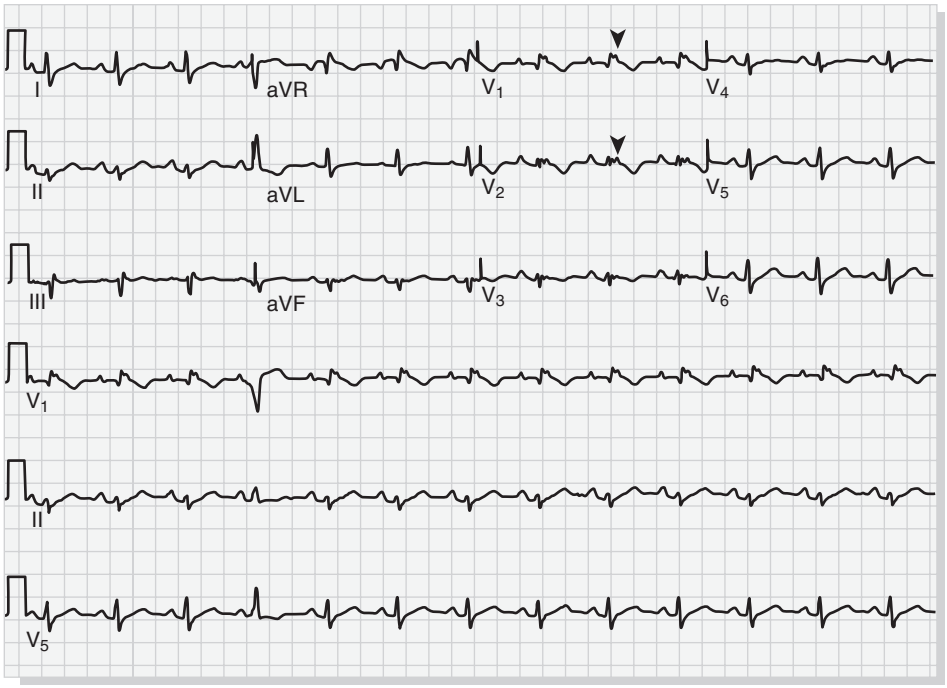

FIG. 2.24

scientific statement from the American Heart Association. *Circulation.* 2010;121:458.

Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. *J Antimicrob Chemother.* 2015;70:325–359.

ANSWER TO QUESTION 238

E (Braunwald, p. 753)

Nearly all left atrial thrombi form in the left atrial appendage (LAA). Surgical or percutaneous device exclusion of the LAA may reduce thromboembolic complications in patients with atrial fibrillation (AF), especially in those who are not candidates for long-term anticoagulation. A US Food and Drug Administration-approved LAA percutaneous occlusion device (WATCHMAN, a fenestrated fabric-covered nitinol plug implanted via the femoral vein with transseptal catheterization) was demonstrated to be noninferior to warfarin for stroke prevention, with a lower risk of hemorrhagic stroke, in long-term follow-up.[1] At present, implantation of this device requires short-term anticoagulation for 45 days, followed by transesophageal echocardiographic-confirmation that there is no residual peri-device flow. Approximately 95% of patients are able to discontinue anticoagulation at that time.

This patient is at high risk for stroke (CHA_2DS_2-VASc score is 4, with 1 point for hypertension, 1 point for diabetes, and 2 points for age ≥75 years) such that aspirin alone would be insufficient to reduce stroke risk. The patient has also had recurrent falls and repetitive gastrointestinal bleeding that increase the risk for bleeding events on anticoagulation, such that implantation of an LAA closure device is a reasonable option.[2]

Enoxaparin is typically used as a temporary bridge for some patients during warfarin interruption. In chronic kidney disease, the elimination of enoxaparin is prolonged, the bleeding risk is increased, and it would not be an appropriate choice for this patient's chronic anticoagulation. Like other novel oral anticoagulants, the factor Xa inhibitor apixaban is noninferior or superior to warfarin for prevention of thromboemboli in patients with nonvalvular AF, while causing less major bleeding. It would be a safer option than warfarin for this patient, but the appropriate dose would be 2.5 mg twice daily (age ≥80 years, creatinine ≥1.5 mg/dL). AV nodal ablation is useful for symptomatic patients with AF and persistently rapid ventricular rates, but the procedure does not reduce the risk of stroke.

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ANSWER TO QUESTION 239

B (Braunwald, pp. 721–726; Figs. 37.13–37.15, 37.18; Table 37.5)

The two intracardiac electrograms include surface electrocardiographic leads V_1 and V_5, a recording from a catheter in the high right atrium, a series of five recordings from a multiple-pole catheter placed in the coronary sinus (CS; displayed from the proximal to distal CS), recordings from a bundle of His position catheter (His proximal and His distal), and a recording from a catheter at the right ventricular (RV) apex.

The baseline electrogram demonstrates preexcitation: the surface ECG shows that the QRS complex occurs nearly simultaneously with the small, sharp His potential deflection on the His distal electrogram. This implies that ventricular activation occurs well before depolarization of the His-Purkinje system.

In the electrogram recorded during tachycardia, the surface ECG leads show a narrow-complex rhythm at approximately 160 beats/min. The intracardiac electrograms demonstrate ventricular depolarizations at the His and RV apical catheters corresponding to the QRS complex on each surface ECG. Each ventricular depolarization is preceded by a His depolarization. Atrial depolarization is apparent in the His catheter positions and throughout the CS electrograms. The sequence of atrial activation begins at the distal CS electrogram and proceeds to the proximal and His catheters. These observations are consistent with orthodromic AV reentrant tachycardia via an accessory pathway. Specifically, the location of the accessory pathway is likely to be left lateral based on the sequence of atrial activation.

ANSWER TO QUESTION 240

B (Braunwald, pp. 604–609; Figs. 33.2 and 33.3; Table 33.1)

Congenital long QT syndromes (LQTS) are inherited disorders characterized by delayed repolarization of the myocardium (QTc >480 milliseconds) and susceptibility to life-threatening ventricular arrhythmias (torsades de pointes). Hundreds of causal mutations have been identified in at least 12 LQTS susceptibility genes.

Approximately 75% of disease-causing mutations occur in three genes, comprising the most common forms of this condition: LQT1 (mutations in the *KCNQ1* gene, which encodes the alpha subunit of the I_{Ks} potassium channel, causing loss of function), LQT2 (mutations in *KCNH2*, the gene that encodes the alpha subunit of the I_{Kr} potassium channel, causing loss of function), and LQT3 (mutations in the *SCN5A* gene, which encodes the cardiac sodium channel, causing gain of function).

Clinical symptomatology in LQTS is highly variable and is related in part to the genetic locus that is affected. LQT1 patients experience the majority of cardiac events during physical (especially swimming) or emotional stress, suggesting a connection with sympathetic nervous system activation. In contrast, LQT2 patients are at highest risk for lethal events by auditory triggers or during the postpartum period. Cardiac events during sleep or at rest are most common in LQT3.

For patients who have congenital LQTS but no history of syncope, ventricular arrhythmias, or family history of sudden cardiac death, generally no therapy or treatment with a beta blocker (to reduce triggered activity) is appropriate. Permanent pacing is indicated in select patients with atrioventricular block or pause-dependent torsades de pointes. In patients deemed at high risk for sudden death (e.g., those with a history of syncope or resuscitated cardiac arrest), an implantable cardioverter-defibrillator is the therapy of choice.

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ANSWER TO QUESTION 241

D (Braunwald, pp. 807–815; Figs. 42.1–42.3; Tables 42.1 and 42.3)

Sudden cardiac death (SCD) is defined as a natural death due to cardiac causes, in which abrupt loss of consciousness occurs within 1 hour of the onset of acute symptoms. An estimated 390,000 out-of-hospital cases occur in the United States annually. There are two peak age distributions of sudden death: (1) from birth to 6 months of age (i.e., sudden infant death syndrome) and (2) between 45 and 75 years of age. Coronary artery disease is the structural basis for ~80% of SCDs.

SCD is more common in men than woman, with a fourfold to sevenfold excess of SCD in men compared with women before age 65. At older ages, the difference decreases to 2:1 or less. A number of hereditary conditions can result in SCD, including hypertrophic cardiomyopathy, the long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, and Brugada syndrome. This observation allows potential screening and preventive therapy for individuals at high risk.

Hypertension and cigarette smoking, but not hypercholesterolemia, have been established as risk factors for SCD. Interestingly, in the Framingham study, intraventricular conduction abnormalities on the ECG (but not left ventricular hypertrophy or nonspecific ST-segment T wave abnormalities) were associated with an increased risk of SCD. Psychosocial factors such as social isolation and a high level of life stress were also found to increase the risk of sudden death.

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ANSWER TO QUESTION 242

D (Braunwald, pp. 687, 715; Fig. 37.6)

The ECG illustrated shows atrial tachycardia with block. In this condition, an atrial rate of 130 to 200 beats/min, with a ventricular response less than or equal to the atrial rate, is present. Digitalis toxicity accounts for this rhythm in 50% to 75% of cases, and in such instances the atrial rate may show a gradual increase if digoxin is continued. Other signs of digitalis excess are often present, including frequent premature ventricular complexes.

In nearly one-half of all patients with atrial tachycardia with block, the atrial rate is irregular and demonstrates a characteristic isoelectric interval between each P wave, in contrast to the morphology of atrial flutter waves. Most instances of this rhythm occur in patients with significant organic heart disease. Causes other than digitalis toxicity include ischemic heart disease, myocardial infarction, and cor pulmonale. In patients taking digitalis, potassium depletion may precipitate the arrhythmia, and the oral administration of potassium and the withholding of digoxin often will allow reversal to sinus rhythm. Because atrial tachycardia with block is seen primarily in patients with serious underlying heart disease, its onset may lead to significant clinical deterioration.

ANSWER TO QUESTION 243

B (Braunwald, pp. 808–809, 815; Fig. 42.7)

Approximately 50% of deaths caused by coronary artery disease (CAD) are sudden and unexpected, and ~80% of all sudden cardiac deaths in Western countries are related to CAD. Such events may complicate either an acute coronary syndrome or previously stable coronary disease, and in the

latter case, often relate to myocardial scar from prior infarction. The extent of left ventricular dysfunction and the presence of premature ventricular complexes in convalescence after myocardial infarction (MI) are both powerful predictors of sudden cardiac death (SCD). However, the occurrence of ventricular fibrillation in the earliest stages of acute MI (within the first 48 hours) does not identify long-term risk and is not an indication for implantable cardioverter-defibrillator therapy.

The arrhythmias that most commonly cause cardiac arrest, in decreasing order of frequency, are ventricular fibrillation, bradyarrhythmias/asystole or pulseless electrical activity, and sustained ventricular tachycardia (VT). Survival after an out-of-hospital cardiac arrest is best for those patients in whom sustained VT was the initial recorded rhythm. Patients with bradycardic/asystolic cardiac arrest have the worst prognosis.

There are racial differences in the incidence of SCD throughout adulthood: compared with Caucasians, African Americans display a higher incidence of sudden cardiac death (Fig. 2.25).

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ANSWER TO QUESTION 244

C (Braunwald, pp. 734–735, 1842)

Non-vitamin K-dependent oral anticoagulants (NOACs) include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, rivaroxaban, edoxaban, and betrixaban. Compared with warfarin, these agents produce predictable anticoagulation, are more convenient to administer, and do not require routine blood test monitoring of coagulation. They are at least as effective as warfarin and cause fewer serious bleeding complications, especially less intracranial hemorrhage.[1]

NOACs have short half-lives so that minor bleeding complications can usually be managed by simply withholding the drug. More extensive measures are necessary for serious hemorrhage, but unlike for bleeding caused by warfarin, vitamin K administration is ineffective. Idarucizumab is a humanized monoclonal antibody fragment indicated for reversal of dabigatran in the case of life-threatening bleeding and/or when emergency surgery is necessary, and would be the most appropriate choice for this patient. The RE-VERSE AD trial confirmed the effectiveness of idarucizumab for rapid and safe reversal of dabigatran in 503 patients with uncontrolled bleeding or who were about to undergo an urgent invasive procedure.[2] Hemodialysis may also be used to remove active dabigatran from the circulation in patients with renal failure, but is better suited for less severe bleeding because of its delayed effect compared with idarucizumab.[3]

In 2018, andexanet alfa was approved for use in the United States to rapidly reverse the anticoagulant effect of the factor Xa inhibitors apixaban and rivaroxaban. An alternative approach to reverse the anticoagulant effect of current NOACs is 4-factor prothrombin complex concentrate.[4]

Oral activated charcoal may help prevent absorption of NOACs ingested within the prior 4 hours and can be useful in the case of drug overdose.

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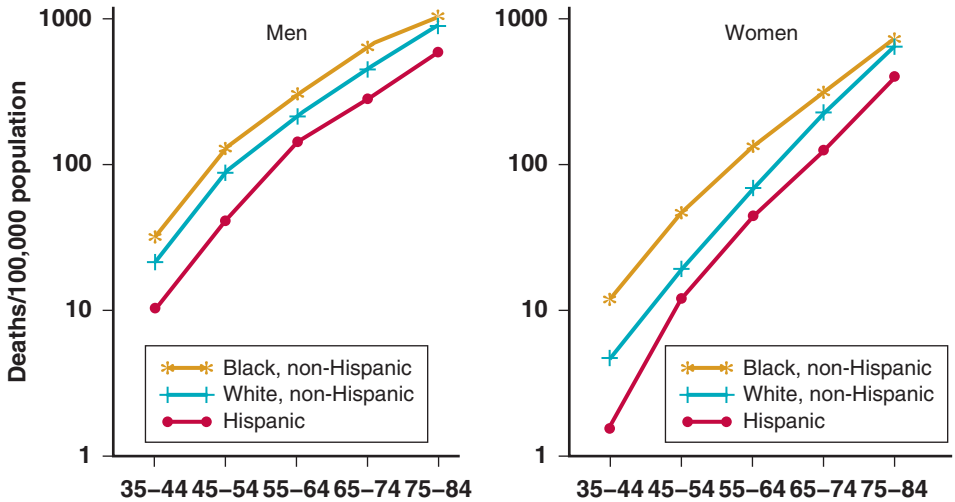

FIG. 2.25 *Age-, sex-, and race-specific risks for sudden cardiac death (SCD). Data modified from Gillum RF. Sudden cardiac death in Hispanic Americans and African Americans.* Am J Public Health. *1997;87:1461.*

ANSWER TO QUESTION 245

B (Braunwald, pp. 787–791; Table 41G.11; Answer to Question 207)

Implantable cardioverter-defibrillators (ICDs) are indicated to prevent sudden death due to ventricular tachyarrhythmias. The strongest evidence for their use is for secondary prevention in patients with reduced left ventricular (LV) function and resuscitated cardiac arrest or unstable sustained ventricular tachyarrhythmias. There is also strong evidence for ICDs as beneficial in primary prevention of sudden death, a therapy that has changed the approach to chronic heart failure care in patients with systolic dysfunction and left ventricular ejection fraction (LVEF) from chronically <30% to 40%.

Patients with ischemic cardiomyopathy who have been shown to derive benefit from ICD therapy are those at least 40 days after acute myocardial infarction. In patients with nonischemic cardiomyopathy and LVEF ≤35%, a trial of optimal heart failure therapy, with reassessment of the LVEF, is appropriate prior to ICD placement since systolic dysfunction may improve in the interim. Patients with identifiable reversible causes of cardiomyopathy (e.g., tachycardia-mediated, alcoholic) should not receive an ICD until reassessment of ventricular function after correction of those contributors.

Patients with significant comorbid conditions that would limit survival with acceptable functional status (e.g., metastatic cancer and end-stage renal disease) to <1 year are generally not appropriate candidates for an ICD.

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ANSWER TO QUESTION 246

C (Braunwald, pp. 783–785; Fig. 41.9; Table 41.1; see also Answer to Question 211)

Selection of the appropriate mode of cardiac pacing depends on many factors, including the underlying rhythm disturbance, the patient's exercise capacity, and the chronotropic response to exercise. Ventricular inhibited pacing (VVI) inhibits ventricular pacemaker output if a ventricular event is sensed, but it does not sense or pace the atrium. This mode protects against bradycardias, but does not restore or maintain atrioventricular (AV) synchrony, so that AV dissociation is common. In addition, in chronotropically incompetent patients in whom the sinus heart rate does not increase with exercise, this mode does not provide rate responsiveness. These deficiencies may result in the "pacemaker syndrome" of reduced functional capacity, shortness of breath, dizziness, and fatigue, which can occur in up to 20% of patients with normally functioning VVI pacing.

Single-chamber triggered pacing (AAT or VVT) generates an output pulse every time a native event is sensed. As a result, it accelerates the rate of battery depletion. This mode of pacing is not frequently used.

Atrial inhibited pacing inhibits atrial pacemaker output if an atrial event is sensed. It does not sense or pace the ventricle. It is an appropriate mode for patients with sinus node dysfunction who have normal AV conduction, but should not be used in individuals with AV nodal disease. Dual-chamber pacing and sensing with inhibition and tracking (DDD) is typically the preferred mode of pacing for patients with combined sinus and AV node dysfunction, because physiologic pacing reduces the frequency of the pacemaker syndrome and may reduce the incidence of atrial fibrillation (AF). However, no randomized trial has demonstrated any effect of pacing mode choice (DDD vs. VVI) on mortality in patients with sinus node dysfunction.

In patients with AF, standard DDD or DDDR is not desirable because P-synchronous pacing is not possible and sensing of the chaotic atrial rhythm could trigger an accelerated ventricular pacing response. To compensate for this deficiency, DDD and DDDR devices commonly have an automatic mode switching feature that, when AF develops, inhibits atrial-sensed ventricular pacing.

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ANSWER TO QUESTION 247

D (Braunwald, pp. 785–787; eTable 41.2)

Pacemaker malfunction may be manifested by impaired pacemaker output or failure to capture or sense the appropriate cardiac chamber. On the ECG, failure to capture is identified when a pacing "spike" is present without evidence of subsequent myocardial depolarization (a P wave or QRS complex). This condition can result from an abnormally elevated electrical threshold, lead dislodgement or perforation, impending battery depletion, or circuit failure. Threshold alterations may be due to medications (e.g., class IC antiarrhythmic agents) or electrolyte and metabolic abnormalities, including hyperkalemia, severe acidosis and alkalosis, hypercapnia, hypoxemia, and myxedema. Failure to sense can result from lead dislodgement or inadequate initial lead placement, lead insulation or circuit failure, electromagnetic radiation, or battery depletion.

Patients with pacemakers should be cautioned about electromagnetic interference that could result in malfunction. An example is industrial-strength welding equipment; close contact should be avoided. Patients with pacemakers should be warned not to lean on or linger near electronic antitheft devices (situated at the exits of many stores) because pacemaker malfunction has been reported in that setting; simply walking past or through such devices is not problematic. Cellular telephones rarely interfere with the function of cardiac pacemakers; when they are placed in the normal position over the ear, rather than over the device,

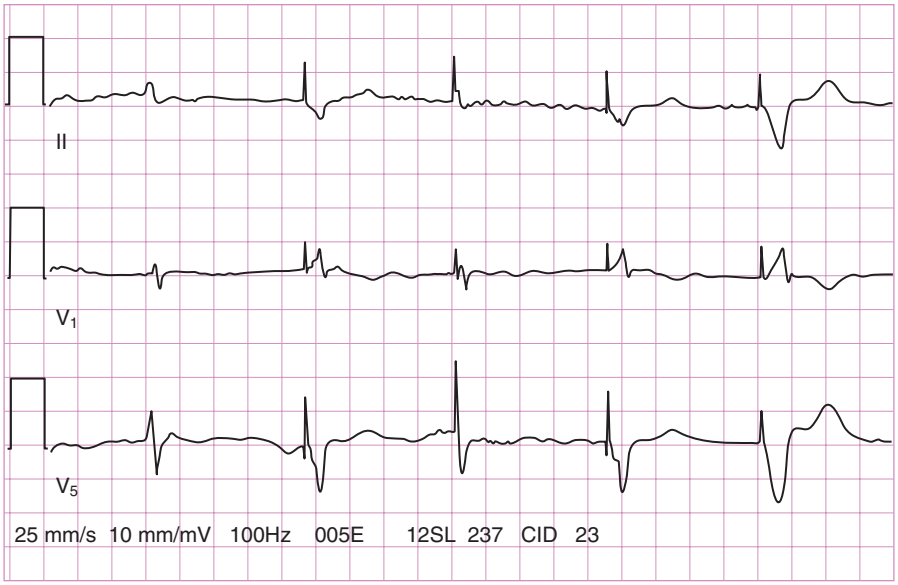

FIG. 2.26 *Three-channel tracing from an ambulatory monitor. The first QRS is intrinsic. The second and fourth beats represent fusion; the third beat is pseudofusion, that is, the underlying morphology is nearly identical to the intrinsic QRS; and the final QRS represents paced depolarization.*

they do not pose a significant risk. As a general rule, they should not be carried in the breast pocket ipsilateral to the pacemaker.

Left bundle branch block morphology is the expected electrocardiographic pattern during standard right ventricular pacing owing to the delay in depolarization of left ventricular myocardium. The presence of right bundle branch block after right ventricular pacemaker implantation is suggestive of accidental lead placement or migration into the left ventricle.

Pseudofusion is present on the surface ECG when a pacing spike does not alter the normal morphology of a superimposed intrinsic QRS complex (Fig. 2.26). This results when a pacing impulse is delivered at the appropriate escape interval into myocardium whose action potentials are in the absolute refractory period owing to slightly earlier intrinsic activation. Pseudofusion can be distinguished from a *fusion beat*, in which the QRS complex represents the combination of intrinsic ventricular activation and *effective* pacemaker depolarization, producing a morphology intermediate between intrinsic and paced beats.

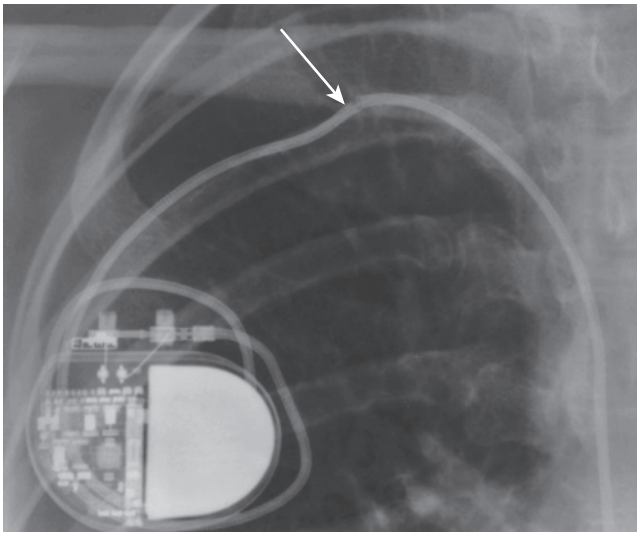

FIG. 2.27

ANSWER TO QUESTION 248

A (Braunwald, pp. 795–798; Fig. 41.25; eFig. 41.18)

The figure depicts a close-up view of a chest radiograph in a patient with a single-chamber pacemaker. The finding of note is a fracture at the point where the lead dives below the clavicle (*arrow* in Fig. 2.27). The patient presented with intermittent failure to capture and intermittent failure to output on the ventricular lead. Lead impedance was greatly elevated.

The telemetric measurement of voltage and current thresholds, lead impedance, and electrograms is very helpful in differentiating the causes of pacemaker malfunction. When a pacemaker wire has fractured, both the voltage threshold and the lead impedance are high. In the case of an insulation break, the voltage threshold and the lead impedance are low. In the setting of a dislodged lead, the voltage threshold is high but the lead impedance is normal. Exit block may occur as the result of an inflammatory reaction at the point of contact between the pacemaker lead and the myocardium. When this occurs, the measured voltage and current thresholds are high but lead impedance is normal.

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ANSWER TO QUESTION 249

B (Braunwald, pp. 721–722; Figs. 37.13–37.15; Table 37.5)

The ECG in the figure depicts atrial fibrillation (AF) with rapid ventricular rate and aberrant conduction in a patient

with Wolff-Parkinson-White (WPW) syndrome and a right posteroseptal accessory pathway. The latter localization is possible because of the negative initial deflections in leads II, III, aVF, and V_1, with upright initial forces in leads I and aVL. Acute treatment of this dysrhythmia should include agents that prolong refractoriness in the accessory pathway, such as intravenous procainamide or amiodarone. In hemodynamically unstable patients, direct-current cardioversion is the treatment of choice. Intravenous verapamil prolongs conduction time in the atrioventricular node without affecting conduction through the accessory pathway. Thus the administration of verapamil to a patient with WPW in AF may *accelerate* conduction through the bypass tract and precipitate ventricular fibrillation, such that it should not be used in this setting.

Electrocardiographic evidence of WPW syndrome is present in approximately 0.25% of healthy individuals. Three basic features characterize the electrocardiographic abnormalities of the syndrome: the presence of a PR interval <120 milliseconds during sinus rhythm; a QRS duration >120 milliseconds with a slurred, slowly rising onset of the QRS in some leads (the delta wave); and secondary ST-segment/T wave changes generally directed opposite to the major QRS vector. The axis of the delta waves on the surface ECG can be used to localize the position of the accessory pathway in the heart. Left free wall accessory pathways are the most common, followed by posteroseptal, right free wall, and anteroseptal locations.

The prevalence of WPW is higher in men and decreases with age. Most associated dysrhythmias are reciprocating (reentrant) tachycardias (80%), with 15% to 30% presenting as AF and 5% as atrial flutter. Although most adults with WPW syndrome have normal hearts, a number of cardiac defects are occasionally associated with this syndrome, including Ebstein anomaly. In patients with Ebstein anomaly, multiple accessory pathways are often present and are located on the right side of the heart, with preexcitation localized to the atrialized ventricle.

ANSWER TO QUESTION 250

C (Braunwald, pp. 543–547; Table 27G.1)

This patient has ischemic cardiomyopathy with a reduced left ventricular ejection fraction of 30% and left bundle branch block with a QRS complex duration of ~190 milliseconds. He is on optimal medical therapy with apparently normal filling pressures by physical examination and has persistent class III symptoms. Accordingly, he meets the guideline-based criteria for cardiac resynchronization therapy (CRT).[1] In addition, based on the reduced ejection fraction and persistent symptoms, he qualifies for implantation of a cardioverter-defibrillator for primary prevention of sudden cardiac death. The results of the COMPANION trial suggest incremental mortality benefit from a device capable of combined cardiac resynchronization and defibrillation over cardiac resynchronization alone in this population. The PROSPECT study did not support the use of echocardiographic measures of dyssynchrony as selection criteria for CRT in patients with a QRS duration ≥120 milliseconds. Patients with systolic heart failure who are most likely to respond to CRT are those in sinus rhythm, with typical left bundle branch block, QRS duration ≥150 milliseconds, and NYHA class II to IV symptoms despite optimal guideline-based medical therapy.

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ANSWER TO QUESTION 251

D (Braunwald, pp. 691–692; Figs. 36.4 and 36.5)

The electrophysiologic tracing depicts a recording of ventricular depolarization over an accessory pathway. The first QRS complex is preexcited, with a short PR interval and delta wave on the surface ECG. The His bundle activation is buried within the ventricular complex (see lead His bundle recording). During the second beat, the accessory pathway is refractory and normal conduction over the atrioventricular (AV) node ensues, generating a normal QRS complex. In this normal complex, His bundle activation clearly precedes ventricular activation, with a measurable His-ventricular interval of 45 milliseconds. Ventricular preexcitation in association with a delta wave is consistent with a diagnosis of Wolff-Parkinson-White (WPW) syndrome.

Patients with ventricular preexcitation and symptomatic tachyarrhythmia require therapy. Options for management include pharmacologic therapy with class IA or IC antiarrhythmic drugs (which prolong the refractory period in the accessory pathway) and invasive treatment with radiofrequency catheter ablation. Both atenolol and verapamil prolong AV nodal conduction time, but do not directly affect conduction through the accessory pathway. As a result, in patients with WPW syndrome and atrial fibrillation, these drugs may actually *enhance* ventricular response and precipitate ventricular fibrillation, and therefore they should be avoided. Radiofrequency catheter ablation in patients with WPW syndrome has a high success rate, a low frequency of complications, and is cost effective. It is the therapy of choice in this symptomatic young patient.

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ANSWER TO QUESTION 252

C (Braunwald, p. 684; Tables 36.1 and 36.4)

Dofetilide is a class III antiarrhythmic drug whose sole electrophysiologic effect appears to be blockade of the rapid component of the delayed rectifier potassium current (I_{Kr}). Its effect is most pronounced in the atria, and the drug is approved for the acute conversion of atrial fibrillation (AF) to sinus rhythm as well as chronic suppression of recurrent AF. Its role in therapy for ventricular arrhythmias is not well established. Dofetilide has a neutral effect on mortality (i.e., it does not increase it) in patients after myocardial infarction.

Dofetilide is well absorbed orally, with over 90% bioavailability. Fifty percent to 60% of the drug is excreted in the urine, whereas the remainder undergoes hepatic metabolism to inert compounds. The drug's dosage must be carefully adjusted based on the creatinine clearance (Ccr), and it should not be administered to patients with a Ccr <20 mL/min. The most important adverse effect of dofetilide is QT interval prolongation with development of torsades de pointes, occurring in 2% to 4% of patients receiving the drug. The risk is highest in patients with hypokalemia, those taking other drugs that prolong repolarization, and when there is baseline QT interval prolongation. For this reason, dofetilide is approved only for inpatient initiation so that the QT interval can be closely monitored. Patients with a corrected baseline QT interval >440 milliseconds are not candidates for dofetilide therapy. Verapamil, ketoconazole, and trimethoprim all increase the serum dofetilide concentration and should not be used concurrently with this drug.

ANSWER TO QUESTION 253

C (Braunwald, pp. 731–732)

This 26-year-old man presents with atrial fibrillation (AF) after the New Year holiday, and most of his prior episodes of AF have occurred following weekends. These facts should prompt consideration of the "holiday heart syndrome," which is the occurrence of palpitations, chest discomfort, and syncope after a binge of alcohol consumption.

The most common arrhythmia associated with this syndrome is AF, followed by atrial flutter and frequent ventricular premature beats. Electrophysiologic testing in subjects without heart disease suggests that alcohol enhances the vulnerability of the heart to induction of atrial arrhythmias. AF in this situation usually occurs several hours after the last drink and may also be related to the onset of early withdrawal symptoms, especially sympathetic hyperactivity. Treatment is typically focused on abstinence from alcohol.

Regular excess alcohol consumption is also an important cause of hypertension and left ventricular (LV) systolic dysfunction. In fact, ethanol abuse is a leading cause of nonischemic dilated cardiomyopathy in industrialized nations. The likelihood of developing cardiomyopathy appears to correlate with the amount and duration of daily alcohol consumption, but there are wide variations in the susceptibility of individual patients to myocardial toxicity. With abstinence from alcohol, LV systolic and diastolic dysfunctions often improve.

Cocaine is associated with multiple cardiovascular complications, most commonly myocardial ischemia and infarction due to coronary artery vasoconstriction and cocaine-enhanced platelet aggregation. Long-term cocaine use is also associated with left ventricular hypertrophy and systolic dysfunction, perhaps the sequelae of repeated, profound sympathetic stimulation. The direct arrhythmogenic potential of cocaine is not well established.

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ANSWERS TO QUESTIONS 254 TO 257

254–A, 255–D, 256–B, 257–C (Braunwald, pp. 604–609, 613; Figs. 33.1 and 33.3; Table 33.1; see also Answers to Questions 206, 229, and 240)

Many specific syndromes associated with ventricular tachycardia (VT) have been identified. The *long QT syndromes*, either familial or acquired, can result in ventricular arrhythmias (torsades de pointes) and sudden death. The *familial* phenotypes include (1) the autosomal recessive Jervell and Lange-Nielsen syndrome and (2) the autosomal dominant Romano-Ward syndrome. The former is associated with sensorineural deafness, whereas patients with the latter condition have normal hearing. Genetic abnormalities in potassium and sodium channels cause the familial long QT syndromes, and specific mutations carry varying degrees of risk for the development of ventricular arrhythmias. The *acquired* form of long QT syndrome can result from many medications, including quinidine, procainamide, sotalol, tricyclic antidepressants, erythromycin, and ketoconazole. Electrolyte abnormalities, including hypokalemia, hypomagnesemia, and hypocalcemia, can also result in significant prolongation of the QT interval and predispose to ventricular arrhythmias.

Right ventricular outflow tract VT is a type of idiopathic VT with a characteristic left bundle branch block morphology and inferior axis. Vagal maneuvers and adenosine administration may terminate this type of VT, whereas exercise or isoproterenol infusion can initiate it. Beta blockers and verapamil may suppress VT in this disorder, and catheter ablation can be curative. The prognosis is generally good.

Brugada syndrome is a form of idiopathic ventricular fibrillation (VF) associated with characteristic abnormalities on the surface ECG and a high risk of sudden cardiac death. The ECG in sinus rhythm typically demonstrates a right bundle branch block morphology with unusual ST-segment elevation in the anterior precordial leads. Loss of function mutations in the gene that encodes the cardiac sodium channel *(SCN5A)* have been identified in some families with this syndrome. Implantable cardioverter-defibrillator implantation is warranted in patients with Brugada syndrome with spontaneous VT/VF or history of aborted sudden cardiac death (class I indication) or history of syncope (class IIa).

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ANSWERS TO QUESTIONS 258 TO 261

258–D, 259–B, 260–A, 261–C (Braunwald, pp. 670–673; Table 36.1)

The Vaughan-Williams classification is a commonly used system for grouping similarly acting antiarrhythmic agents. Not all drugs within a class have identical effects, and drug actions are more complex than those depicted by this classification scheme.

Class I drugs predominantly block the fast sodium channels and are divided into three subgroups. Class IA drugs (e.g., quinidine, procainamide, disopyramide) reduce the rate of rise of the action potential upstroke (V_{max}) and prolong the

action potential duration. Class IB drugs (e.g., lidocaine, mexiletine, phenytoin) reduce V_{max} to only a minimal degree and *shorten* the action potential duration. Class IC drugs (e.g., flecainide, propafenone) reduce V_{max}, slow conduction, and minimally prolong refractoriness.

Class II drugs are beta-adrenergic receptor blockers (e.g., metoprolol, timolol, propranolol). Class III drugs (e.g., sotalol, amiodarone, dronedarone, ibutilide, dofetilide) primarily block potassium channels and prolong repolarization. Class IV drugs are slow calcium channel ($I_{Ca.L}$) blockers (e.g., verapamil, diltiazem).

ANSWERS TO QUESTIONS 262 TO 265

262–B, 263–C, 264–C, 265–A (Braunwald, p. 737)

Many antiarrhythmic drugs are available to maintain sinus rhythm in patients with a history of atrial fibrillation (AF). Standard beta blockers are sometimes useful for this purpose and are generally well tolerated. Conversely, when more potent antiarrhythmic agents are required, the benefit of the drug must be weighed against the risk of potentially dangerous adverse effects. Such risk can be minimized by choosing a drug that is appropriate for the patient's underlying cardiac disease (Table 2.1). For example, Vaughan-Williams class IC drugs (e.g., flecainide or propafenone) are well tolerated and are reasonably safe drugs for patients without ischemic or structural heart disease, but are associated with increased morbidity and mortality in patients with these conditions. Similarly, class IA agents (e.g., quinidine) and the class III drug sotalol should not be used in patients with a prolonged QT interval or left ventricular hypertrophy (e.g., wall thickness >1.3 cm) because of the risk of precipitating torsades de pointes. The class III drug amiodarone is the most potent agent available to prevent recurrent AF. It is only rarely proarrhythmic, even in patients with underlying structural heart disease. It is, however, associated with significant noncardiac toxicities (especially affecting the lungs, liver, and thyroid), and therefore therapy with this drug must be monitored carefully.

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TABLE 2.1

CARDIAC CONDITION	FIRST-LINE DRUG	SECOND-LINE DRUG
Structurally normal heart without coronary disease	Class IC agent (e.g., flecainide, propafenone), sotalol, dronedarone	Amiodarone
Hypertension with LV wall thickness >1.3 cm	Amiodarone	
Coronary artery disease with preserved LV function	Sotalol, dofetilide, dronedarone	Amiodarone
Heart failure	Amiodarone, dofetilide	

LV, Left ventricular.

ANSWERS TO QUESTIONS 266 TO 269

266–C, 267–D, 268–A, 269–E (Braunwald, pp. 496–498; Fig. 25.7)

Diuretics are frequently used in the management of heart failure and hypertension. Collectively, they act to lower plasma volume by increasing excretion of sodium and water. Diuretics can be classified into four categories based on mechanism and site of action in the nephron: (1) carbonic anhydrase inhibitors (e.g., acetazolamide), which act at the proximal tubule; (2) loop diuretics, which inhibit the $Na^+/K^+/Cl^-$ transporter in the thick ascending limb of the loop of Henle (e.g., furosemide, torsemide, bumetanide, and ethacrynic acid); (3) thiazide-like diuretics, which inhibit the Na^+/Cl^- cotransporter in the distal convoluted tubule (e.g., chlorothiazide, hydrochlorothiazide, metolazone, indapamide, and chlorthalidone); and (4) potassium-sparing diuretics, which block sodium reabsorption in the collecting duct. Potassium-sparing diuretics are available in two classes: (1) those that directly inhibit epithelial sodium channels (e.g., triamterene, amiloride) and (2) those that antagonize the mineralocorticoid type I receptor, inhibiting the effects of aldosterone (spironolactone and eplerenone).

Each type of diuretic is associated with potential adverse effects. For example, acetazolamide, a carbonic anhydrase inhibitor, may result in increased urinary excretion of sodium, potassium, and bicarbonate, leading to metabolic acidosis. As a result of this "adverse effect," it can be useful in treating alkalemia caused by other diuretics.

Metolazone is a thiazide-like diuretic that can elevate the serum calcium and uric acid levels. It can also result in hypokalemia and hypomagnesemia, particularly when utilized in combination with loop diuretics. Hydrochlorothiazide, which is in the same family as metolazone, can cause elevations in serum low-density lipoproteins and triglyceride levels.

Torsemide, like other loop diuretics, may cause ototoxicity. High doses of loop diuretics should be used cautiously in combination with aminoglycoside antibiotics due to an additive ototoxic effect.

The aldosterone antagonists may be associated with hyperkalemia, particularly in patients with renal insufficiency, owing to their inhibition of potassium excretion in the collecting duct. This side effect can be favorably exploited to help limit potassium wasting caused by loop diuretics. Spironolactone, in contrast to eplerenone, has potent antiandrogenic side effects and may be associated with gynecomastia in male patients.

ANSWERS TO QUESTIONS 270 TO 273

270–D, 271–B, 272–C, 273–E (Braunwald, pp. 783–785; Fig. 41.9; Table 41.1; see also Answer to Question 246)

The listed examples are all class I indications for pacing, as recommended by the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines. In general, dual-chamber pacemakers should be used in patients who require sensing or pacing of both the atria and the ventricles. Rate-modulating pacemakers should be used in patients with chronotropic incompetence due to abnormal or absent sinus node function.

In the 58-year-old man with tachycardia-bradycardia syndrome who developed symptomatic sinus bradycardia with beta blocker therapy, the most appropriate pacemaker mode would be DDDR. Ventricular pacing is necessary here because there is a risk of atrioventricular block due to beta blockers, and the rate-modulating function is important because of the abnormal sinus node function. Use of a non–rate-responsive (DDD) pacemaker in this patient would most likely result in lower rate pacing most of the time, with inappropriate response to physical activity.

In the 70-year-old woman with atrial fibrillation (AF) who complains of dizziness and is found on examination to have a ventricular rate of 30 beats/min, VVIR pacing is most appropriate. Atrial sensing or pacing is not possible because of chronic AF, and the rate-modulating function is necessary because of the evident chronotropic dysfunction.

In the 62-year-old man with complete heart block after aortic valve surgery, there is no indication of sinus node disease and DDD pacing should be sufficient.

In the 45-year-old man with symptomatic sinoatrial exit block and junctional escape rhythm, loss of sinus mechanism requires atrial pacing and rate modulation. There is no evidence of AV block and ventricular pacing support is therefore not necessary, so the AAIR pacing mode is appropriate.

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ANSWERS TO QUESTIONS 274 TO 277

274–D, 275–C, 276–A, 277–B (Braunwald, pp. 1586–1588, 1594–1595; eTable 77.2; pp. 1621–1622)

Multiple disease processes produce a clinical phenotype of dilated cardiomyopathy (DCM) with electrical instability. Sarcoidosis is a systemic inflammatory disease of unknown etiology that most often causes thoracic lymphadenopathy and interstitial lung disease; cardiac involvement can be identified by imaging studies in at least 25% of patients with pulmonary sarcoidosis. Clinical cardiac sarcoid findings include cardiomyopathy of variable severity accompanied by heart block and/or ventricular tachycardia (VT). Although the identification of noncaseating granulomas by endomyocardial biopsy is consistent with cardiac sarcoid, the false-negative rate is high because of the patchy nature of the disease. Cardiac magnetic resonance imaging with gadolinium enhancement is sensitive for detecting abnormalities in cardiac sarcoid; ^{18}F-fluorodeoxyglucose positron emission tomography is complementary to magnetic resonance imaging, and serial studies are helpful in monitoring the response to therapy.

Giant cell myocarditis is notable for its rapidly progressive clinical course, widespread necrosis with giant cells on histology, and association with autoimmune disease and thymoma. Prompt diagnosis via endomyocardial biopsy along with early institution of mechanical circulatory support and immunosuppression is critical, because the prognosis is generally poor, with many cases progressing to cardiac transplant or death.

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* endemic to Central and South America. A common noncardiac manifestation of Chagas disease is gastrointestinal dysmotility. Cardiac involvement is notable for conduction disease, apical aneurysm formation often with mural thrombus, and VT. Chagas disease is a common cause of heart failure leading to transplantation in South America.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable disorder of cardiac desmosomes characterized by fibrofatty infiltration of the right ventricular myocardium (see Answer to Question 236). The hallmark of ARVC on the surface ECG (apparent in ~50% of cases) is a low-amplitude "notch" in the ST segment near the terminal portion of the QRS complex in the right precordial leads V_1 to V_3 (termed an *epsilon wave*). Additional electrocardiographic findings include right-sided T wave inversions and ventricular tachycardia with a left bundle branch block morphology indicating its origin in the right ventricle. The cardinal pathologic feature of ARVC, typically apparent on immunohistochemistry, is evidence of disruption in the desmosomes connecting cardiomyocytes, leading to abnormal cell-to-cell signaling and loss of structural integrity.

Cardiolaminopathy is a cause of autosomal dominant familial DCM resulting from a mutation in the *LMNA* gene, encoding the nuclear envelope protein lamin A/C. The clinical course is highly variable, with typically subtle initial manifestations of conduction system disease (e.g., first-degree atrioventricular block) frequently delaying recognition until adulthood when more significant heart block, arrhythmias, or ventricular dysfunction become apparent.

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ANSWERS TO QUESTIONS 278 TO 282

278–C, 279–B, 280–A, 281–D, 282–E (Braunwald, pp. 848–851; Tables 43.1 and 43.2)

The approach to the patient with syncope begins with a careful clinical history and physical examination, which can often suggest a specific cause. For example, syncope in patients with hypertrophic cardiomyopathy typically occurs with exertion, and examination may demonstrate the typical murmur associated with dynamic left ventricular outflow tract obstruction. Syncope with exertion is also typical of patients with the long QT syndrome (LQT1 in particular), aortic stenosis, pulmonary hypertension, mitral stenosis, coronary artery disease, and idiopathic ventricular tachycardia.

Patients with the subclavian steal syndrome may present with syncope after arm exercises. In this condition, atherosclerotic stenosis of a subclavian artery is present proximal to the origin of the vertebral artery. Retrograde blood flow through the ipsilateral vertebral artery, enhanced by exercise

involving the affected arm, can induce cerebral ischemia. Auscultation over the supraclavicular fossa may demonstrate a bruit caused by the subclavian stenosis, and the blood pressure is usually diminished in the affected arm.

Vasovagal (neurocardiogenic) syncope occurs after a sudden unexpected pain; an unpleasant sight, sound, or smell; prolonged standing; or a stressful situation. This common form of syncope is characterized by the abrupt onset of hypotension with or without bradycardia.

Carotid sinus hypersensitivity is manifest during stimulation of the carotid sinus baroreceptors and syncopal events in patients with this disorder may be associated with head rotation or application of pressure to the carotid sinus with shaving or wearing tight shirt collars. The physiologic response to carotid hypersensitivity syndrome can be cardioinhibitory (e.g., marked bradycardia), vasodepressor (e.g., decrease in blood pressure in the absence of bradycardia), or mixed.

Left atrial myxoma is a rare cause of syncope. Symptoms may be positional as the tumor shifts and transiently obstructs the mitral orifice.

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ANSWERS TO QUESTIONS 283 TO 286

283–C, 284–E, 285–A, 286–B (Braunwald, p. 1598; pp. 1815–1817)

Each of the conditions listed is associated with sustained increases in cardiac output (CO) that may ultimately precipitate heart failure symptoms. Clinical findings in hyperthyroidism include constitutional changes such as nervousness, diaphoresis, heat intolerance, and fatigue, as well as cardiovascular manifestations such as palpitations, atrial fibrillation, and sinus tachycardia with a hyperkinetic heart action. Cardiovascular examination may reveal tachycardia, widened pulse pressure, brisk arterial pulsations, and a variety of findings associated with the hyperkinetic state. These may include a prominent S_1, the presence of an S_3 or S_4 or both, and a midsystolic murmur along the left sternal border secondary to increased flow. When a particularly hyperdynamic cardiac effect is seen, this murmur may have a scratching component known as the *Means-Lerman scratch.* This is thought to be caused by the rubbing together of normal pleural and pericardial surfaces.

Systemic arteriovenous (AV) fistulas may be acquired as a result of trauma, or they may be congenital. The increase in CO that such lesions create is related to the size of the communication and the resultant reduction in the systemic vascular resistance that it promotes. In general, systemic AV fistulas lead to a widened pulse pressure, brisk arterial pulsations, and mild tachycardia. The *Nicoladoni-Branham sign,* defined as the slowing of heart rate after manual compression of the fistula, is commonly present. The maneuver may also raise arterial and lower venous pressure.

Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, is an inherited condition that may include AV fistulas, especially in the liver and the lungs. The disease may produce a hyperkinetic circulation with abdominal bruits and hepatomegaly due to intrahepatic AV connections.

Beriberi heart disease is a rare condition caused by severe thiamine deficiency that leads to impaired oxidative metabolism. It occurs most frequently in the Far East; in Western society, alcoholic cardiomyopathy may contribute to, or overlap with, this syndrome because of the tendency for alcoholics to become vitamin deficient. Patients with beriberi may present with a high-output state due to vasodilation and increased blood volume, followed by eventual impairment of contractile function. Typical findings include peripheral neuropathy with paresthesias of the extremities, decreased or absent knee and ankle jerks, hyperkeratinized skin lesions, and painful glossitis. The presence of edema characterizes "wet beriberi" and differentiates this condition from the "dry" form.

Carcinoid syndrome is an uncommon disease that results from the release of serotonin and other vasoactive substances by carcinoid tumors. Physical findings may include cutaneous flushing, telangiectasia, diarrhea, and bronchial constriction due to release of humoral mediators.

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ANSWERS TO QUESTIONS 287 TO 290

287–A, 288–C, 289–B, 290–D (Braunwald, pp. 680–681)

Beta blockers can be classified by their degree of cardioselectivity, that is, their ability to block the $beta_1$-adrenergic receptors in the heart compared with the $beta_2$-adrenergic receptors in the bronchi, peripheral blood vessels, and other sites. Beta blockers can be further classified into those that possess intrinsic sympathomimetic activity (ISA) versus those that do not. Beta blockers with ISA induce an agonist response, but at the same time block the greater agonist effects of endogenous catecholamines. The result is to lower blood pressure similar to other beta blockers but to cause less bradycardia.

Acebutolol is a selective beta blocker with ISA. Atenolol, metoprolol, and esmolol are examples of selective beta blockers without ISA. Atenolol and nadolol are less lipid soluble than other beta blockers; as a result, they may cause fewer central nervous system side effects.

Pindolol, carteolol, and penbutolol are nonselective beta blockers with ISA. Nadolol, propranolol and timolol are examples of nonselective beta blockers without ISA.

Carvedilol is a minimally $beta_1$-receptor selective agent that also expresses high affinity for $alpha_1$-adrenergic receptors and is used primarily in patients with heart failure. Because of its vasodilating property, orthostatic symptoms can occur and upward dose titration must be undertaken carefully.

ANSWERS TO QUESTIONS 291 TO 294

291–A, 292–C, 293–B, 294–B (Braunwald, Fig. 23.7; eFig. 23.9; Fig. 68.14)

Left ventricular mass increases in response to chronic pressure or volume overload or secondary to primary myocardial

disease. With predominant pressure overload, as in aortic stenosis, there is an increase in mass with little change in chamber volume (concentric hypertrophy, as exemplified by patient A). In contrast, chronic volume overload (as in aortic or mitral regurgitation), or primary dilated cardiomyopathy, results in ventricular dilatation with only a small increase in wall thickness (eccentric hypertrophy). In chronic regurgitant disease (patient B), there is usually an increased stroke volume in the compensated state, whereas in cardiomyopathy there is impaired systolic function and a reduced stroke volume (patient C).

SECTION III QUESTIONS

(CHAPTERS 44 TO 66)

Preventive Cardiology; Atherosclerotic Cardiovascular Disease

Brian A. Bergmark and Leonard S. Lilly

Directions:

For each below, select the ONE BEST response.

QUESTION 295

A 48-year-old man with elevated low-density lipoprotein (LDL) cholesterol, hypertension, and a family history of premature coronary disease presents to his physician's office for routine evaluation. He does not have diabetes. He smokes one pack of cigarettes per day and is exploring means to quit. His 10-year risk of atherosclerotic cardiovascular disease using the ACC/AHA Pooled Cohort Equations was recently calculated to be 18.8%, compared with a 1.7% risk in a similarly aged man with optimal risk factors. He also has a history of supraventricular tachycardia that has been successfully suppressed by verapamil, after not tolerating a beta blocker. He is currently taking simvastatin 20 mg daily, verapamil sustained-release 180 mg daily, and aspirin 81 mg daily. His blood pressure is 138/70 mm Hg. Laboratory studies include total cholesterol 250 mg/dL; high-density lipoprotein cholesterol 42 mg/dL; LDL cholesterol 166 mg dL; and triglycerides 210 mg/dL. The hepatic transaminase levels are normal. Which of the following is the most appropriate recommendation regarding lipid-altering therapy?

A. He does not have active coronary artery disease—no further adjustment in medication is required
B. Simvastatin should be increased to 40 mg daily
C. Simvastatin should be increased to 80 mg daily
D. Replace simvastatin with atorvastatin 20 mg daily or rosuvastatin 10 mg daily
E. Gemfibrozil 150 mg twice daily should be added

QUESTION 296

Which one of the following interventions does not have a blood pressure–lowering effect?

A. A diet that reduces caloric intake by 1000 calories per day
B. Reduction of dietary sodium
C. Daily magnesium and calcium supplements
D. Reduction of ethanol consumption to less than 1 oz (30 mL)/day

QUESTION 297

With respect to renovascular hypertension, which of the following statements is correct?

A. Worsening renal function with angiotensin-converting enzyme inhibitor therapy suggests unilateral renovascular disease
B. Atherosclerotic disease most commonly involves the proximal third of the main renal artery
C. Fibromuscular renovascular disease arises primarily in women aged >60 years
D. When atherosclerotic renal artery stenosis is found, mechanical revascularization is the treatment of choice
E. Patients with severe, accelerated hypertension are unlikely to have renovascular disease as the cause

QUESTION 298

Which of the following statements regarding hypertension is TRUE?

A. Pure "white coat" hypertension is found in 5% of patients
B. Renal parenchymal disease is the most common cause of secondary hypertension
C. Inaccurately low blood pressure is typically recorded in patients with sclerotic brachial arteries
D. When measuring the blood pressure, an inappropriately small cuff size results in a spuriously low systolic measurement
E. Coarctation of the aorta, Cushing disease, and pheochromocytoma together account for ~10% of hypertensive patients

QUESTION 299

A 76-year-old man with type 2 diabetes and hypertension sustained an inferior non-ST-elevation myocardial infarction 3 years ago. A right coronary artery drug-eluting stent was placed and he has been free of angina since. His left ventricular ejection fraction is 45% with inferior wall hypokinesis. He experiences intermittent peripheral edema, particularly after salty meals, relieved by furosemide. He has stable claudication of the right calf that develops after walking two blocks. Review of systems is notable for obstructive sleep apnea and

recurrent urinary tract infections. His current medications are aspirin 81 mg daily, atorvastatin 80 mg daily, metoprolol succinate 25 mg daily, lisinopril 20 mg daily, furosemide 20 mg daily, and metformin 500 mg twice daily. The serum creatinine is 1.14 mg/dL and hemoglobin A1c is 9.4%.

Which of the following would be most appropriate to prescribe to improve this patient's glycemic control and reduce his risk of future cardiac events?

A. Pioglitazone (a thiazolidinedione)
B. Liraglutide (a glucagon-like peptide [GLP]-1 receptor agonist)
C. Empagliflozin (a sodium/glucose co-transporter [SGLT]-2 inhibitor)
D. Linagliptin (a dipeptidyl peptidase [DPP]-4 inhibitor)

QUESTION 300

Which of the following statements regarding the association of oral contraceptives (OCs) and hypertension is NOT correct?

A. Among OC users, the likelihood of developing hypertension is increased by alcohol consumption
B. The likelihood of developing hypertension is independent of the age of the user
C. Elevated blood pressure normalizes within 6 months of initiating OC therapy in 50% of patients
D. The mechanism for contraceptive-induced hypertension likely involves renin-aldosterone-mediated volume expansion

QUESTION 301

A 57-year-old black businessman visits his primary physician for follow-up of dyslipidemia, for which he takes atorvastatin 10 mg daily. His blood pressure is 138/84 mm Hg, similar to measurements at other recent office visits and on a home sphygmomanometer (range: 134 to 138/78 to 86 mm Hg). He does not smoke. He consumes three to four alcoholic beverages per week. His body mass index is 28. His predicted 10-year risk for a first atherosclerotic cardiovascular event is 12% using the ACC/AHA pooled cohort risk assessment equations. Which of the following statements is consistent with current ACC/AHA hypertension guidelines?

A. His blood pressure is not in a range that requires intervention; only serial monitoring of blood pressure is needed
B. He should follow lifestyle modifications, including cessation of alcohol intake and weight loss, but drug therapy should not be initiated at this point
C. He should follow lifestyle modifications and begin antihypertensive drug therapy using a beta blocker or angiotensin-converting enzyme inhibitor
D. His target on-therapy blood pressure is <130/80 mm Hg

QUESTION 302

Which of the following statements regarding adverse effects of antihypertensive agents is correct?

A. Cough resulting from angiotensin-converting enzyme (ACE) inhibitors arises more commonly in Caucasians than in Asians
B. ACE inhibitor–induced cough reliably resolves within 5 days after discontinuation of the drug
C. Gingival hyperplasia is a recognized adverse effect of calcium channel blockers
D. Bradycardia is a common side effect of hydralazine
E. Volume depletion and alopecia are established side effects of minoxidil therapy

QUESTION 303

Which of the following abnormalities is NOT associated with the use of thiazide-type diuretics?

A. Hypomagnesemia
B. Hypouricemia
C. Hypercalcemia
D. Hypertriglyceridemia
E. Hyponatremia

QUESTION 304

Which of the following statements regarding the effects of HMG-CoA reductase inhibitors ("statins") is correct?

A. Expression of hepatic low-density lipoprotein receptors is decreased
B. Hepatic production of very-low-density lipoprotein is increased
C. Myonecrosis with muscle symptoms and elevated serum creatine kinase (CK) >10 times normal occurs in 5% of patients
D. Concurrent administration of erythromycin increases the risk of myositis

QUESTION 305

Which statement regarding the effect of medications on the serum lipid profile is correct?

A. Nonselective beta blockers increase high-density lipoprotein (HDL) levels
B. Thiazide diuretics decrease triglyceride levels
C. Estrogen replacement therapy decreases HDL and triglyceride levels
D. Protease inhibitors raise total cholesterol and triglyceride levels
E. Corticosteroids reduce triglyceride levels

QUESTION 306

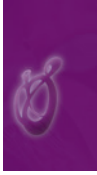
Which of the following statements regarding genetic lipoprotein disorders is correct?

A. Familial hypercholesterolemia (FH) results from mutations in the gene that encodes the enzyme HMG-CoA reductase
B. Mutations in the apo B gene results in a form of hypercholesterolemia that is indistinguishable from FH
C. Patients with familial hypertriglyceridemia typically develop xanthomas or xanthelasmas
D. Gain-of-function mutations in the *PCSK9* gene result in decreased low-density lipoprotein (LDL) cholesterol levels and a reduction in coronary events
E. Patients with familial combined hyperlipidemia have elevations of both LDL and high-density lipoprotein cholesterol levels and a rate of coronary events similar to populations with normal lipid levels

QUESTION 307

Which of the following statements regarding niacin is correct?

A. It acts primarily via upregulation of the hepatic low-density lipoprotein (LDL) receptor
B. It raises plasma high-density lipoprotein cholesterol levels, but has no effect on LDL levels
C. It reduces the circulating level of lipoprotein (a)
D. Niacin added to statin therapy reduces coronary event rates



QUESTION 308

Which of the following statements about apolipoproteins is correct?

A. Apo AI is a major component of low-density lipoprotein cholesterol
B. Apo B48, synthesized by the small intestine, and apo B100, secreted by the liver, are synthesized by two distinct genes
C. Apo B48 is the major apoprotein in high-density lipoprotein cholesterol
D. Type III hyperlipoproteinemia (also termed dysbetalipoproteinemia) is a disorder of apoprotein E

QUESTION 309

Which of the following statements regarding hypertriglyceridemia is NOT correct?

A. Hypertriglyceridemia is associated with diabetes mellitus, chronic renal failure, and obesity
B. Cigarette smoking and excessive alcohol consumption are associated with secondary hypertriglyceridemia
C. In epidemiologic studies, adjustment for high-density lipoprotein levels and other factors diminishes the role of hypertriglyceridemia as an independent predictor of coronary artery disease
D. There is a stronger relationship between hypertriglyceridemia and cardiovascular risk in women than in men
E. The addition of fenofibrate to simvastatin lowers triglyceride levels and has been shown to reduce coronary events in type 2 diabetic patients, compared with simvastatin alone

QUESTION 310

Which of the following statements regarding lipoprotein (a) [Lp(a)] is NOT correct?

A. One component of Lp(a) is structurally identical to low-density lipoprotein and another is similar to plasminogen
B. Lp(a) levels do not vary significantly between racial groups
C. Lp(a) levels vary little with changes in dietary fat intake
D. Observational studies have associated elevated Lp(a) levels with cardiovascular events

QUESTION 311

Which statement regarding lipid-lowering medications is NOT correct?

A. Fibric acid derivatives lower triglycerides, raise high-density lipoprotein levels, and may increase low-density lipoprotein cholesterol levels
B. Fish oil therapy raises triglyceride levels
C. Other medications should not be taken within 1 hour before or within 3 hours after taking a bile acid–binding resin
D. Ezetimibe added to statin therapy in patients with a recent acute coronary syndrome reduces subsequent coronary event rates more than statin therapy alone

QUESTION 312

A 70-year-old businessman presented to the emergency department (ED) of a university medical center with multiple episodes of anterior substernal chest discomfort over the prior 2 days, each lasting 5 to 10 minutes in duration. He has a history of hypertension, elevated low-density lipoprotein-cholesterol, and had been a regular cigarette smoker until stopping 4 months ago. He experienced a single transient ischemic attack 1 year ago. His home medications included aspirin 81 mg daily, atorvastatin 10 mg daily, and lisinopril 10 mg daily. The initial ECG was unremarkable, but while being evaluated in the ED he experienced another 5-minute episode of chest discomfort, during which the ECG demonstrated transient 1-mm ST depression in leads II, III, aVF, V_5, and V_6. The initial cardiac troponin T was 0.06 ng/mL (reference range <0.01). He received aspirin, IV unfractionated heparin, beta blocker, and high-dose (80 mg) atorvastatin therapies and suffered no further episodes of chest discomfort.

On examination, the blood pressure is 116/82, heart rate 72 beats/min, jugular venous pressure 6 cm water, the chest is clear, cardiac examination shows an apical S_4 and no murmur, the abdomen is benign, and there is no peripheral edema. No arrhythmias are observed on telemetry. Three hours after presentation, the cardiac troponin T is 0.08 ng/mL. The serum creatinine is 1.11 mg/dL.

Of the following approaches, which would be most appropriate?

A. Add prasugrel and pursue an ischemia-guided (i.e., "conservative") strategy
B. Add clopidogrel and pursue an ischemia-guided strategy
C. Add either ticagrelor or clopidogrel and pursue an early invasive strategy
D. Add prasugrel and pursue an early invasive strategy
E. Do not add additional antiplatelet therapy at this time and pursue an ischemia-guided strategy

QUESTION 313

Which of the following statements regarding the secondary prevention of atherothrombotic stroke is correct?

A. Clopidogrel monotherapy is superior to aspirin plus dipyridamole for secondary prevention of noncardioembolic stroke
B. Hypertension should not be a target of secondary prevention after an ischemic stroke because elevated blood pressure is necessary to maintain adequate cerebral perfusion
C. Treatment with HMG-CoA reductase inhibitors reduces the risk of recurrent stroke
D. The combination of aspirin plus clopidogrel is superior to aspirin alone for prevention of recurrent stroke
E. Compared with aspirin, chronic warfarin therapy reduces the risk of recurrent stroke

QUESTION 314

Which of the following statements regarding the relationship between alcohol and coronary artery disease is NOT correct?

A. Moderate alcohol intake (1 or 2 drinks daily) is associated with a lower incidence of coronary heart disease than is no alcohol intake
B. Alcohol consumption reduces platelet aggregation
C. Heavy alcohol intake is associated with increased cardiovascular mortality
D. Alcohol lowers low-density lipoprotein levels
E. Alcohol raises high-density lipoprotein levels

QUESTION 315

Which of the following statements regarding smoking cessation is NOT correct?
A. Smoking cessation reduces the risk of a coronary event by 50% within 2 years
B. Patients who continue to smoke after a myocardial infarction have twice the mortality rate of those who stop smoking
C. Patients who successfully quit usually do so after five or more unsuccessful attempts
D. Physician counseling is as effective as pharmacologic aids in achieving smoking cessation

QUESTION 316

Which of the following statements regarding exercise training and rehabilitation of patients with coronary artery disease is TRUE?
A. Home programs should emphasize bursts of exercise to the onset of marked dyspnea
B. Augmented cardiac output during exercise is due more to an increase in stroke volume than in heart rate
C. During exercise, increased myocardial oxygen consumption is provided more by a rise in augmented oxygen extraction than by coronary blood flow
D. Exercise-based cardiac rehabilitation participation is associated with lower mortality rates
E. Approximately 80% of the improvement in exercise performance with physical training is due to increased cardiac output and 20% to peripheral adaptations that improve tissue oxygen extraction

QUESTION 317

Which of the following statements regarding homocysteine is NOT correct?
A. Inherited defects of methionine metabolism may cause extremely high serum levels of homocysteine and premature atherothrombosis
B. Polymorphisms in the methylene tetrahydrofolate reductase gene are associated with elevated homocysteine levels
C. Epidemiologic studies have linked mild hyperhomocysteinemia with an increased risk of coronary events
D. Folic acid and other vitamin B supplements reduce serum homocysteine levels
E. Dietary supplementation with a combination of B vitamins (folic acid, B_6, and B_{12}) reduces the risk of atherothrombotic events

QUESTION 318

Which of the following is NOT a component of the atherogenic "metabolic syndrome"?
A. Hyperglycemia
B. Elevated serum triglycerides
C. Abdominal obesity
D. Serum low-density lipoprotein >140 mg/dL
E. Hypertension

QUESTION 319

A 52-year-old woman presents for routine outpatient management. She is interested in nonpharmacologic approaches to blood pressure reduction. Which of the following statements is TRUE?
A. Acupuncture is an effective modality to achieve long-term blood pressure reduction
B. Biofeedback methods that teach individuals to breathe more rapidly are effective for lowering blood pressure
C. Garlic supplementation stimulates angiotensin II production and raises blood pressure
D. The DASH diet can lead to a sustained 10 mm Hg decline in systolic blood pressure

QUESTION 320

Clinical trials of which of the following dietary interventions have NOT shown significant improvements in coronary artery disease endpoints?
A. Mediterranean-style diet supplemented with alpha-linolenic acid
B. Mediterranean-style diet supplemented with extra-virgin olive oil or nuts
C. Low-carbohydrate, high-protein, high-fat diet (e.g., Atkins-style diet)
D. Regular fatty fish or fish oil consumption

QUESTION 321

Which of the following statements about pharmacologic therapy for secondary prevention of coronary artery disease is NOT correct?
A. Long-term aspirin use after myocardial infarction (MI) reduces cardiovascular mortality, re-infarction, and stroke rates
B. After MI, beta blocker therapy significantly reduces mortality over the next 2 to 3 years
C. Angiotensin-converting enzyme inhibitors administered after MI confer an early mortality reduction only in patients with left ventricular dysfunction
D. Administration of HMG-CoA reductase inhibitors reduces cardiovascular deaths after MI in patients with average cholesterol levels
E. After an acute MI, intensive lipid lowering with a high-dose statin confers better clinical outcomes compared with only moderate lipid lowering

QUESTION 322

Which of the following statements regarding heterozygous familial hypercholesterolemia is correct?
A. It is a relatively common disorder with a gene frequency of at least 1 in 500 persons in the population
B. Tendon xanthomas are rare
C. It is inherited as a recessive trait
D. Cutaneous planar xanthomas are common
E. The fundamental defect is the presence of only one-quarter of the normal number of low-density lipoprotein surface receptors

QUESTION 323

Which of the following is characteristic of familial hypertriglyceridemia?
A. Plasma low-density lipoprotein is usually high
B. Plasma triglyceride levels can rise as high as 1000 mg/dL after a meal

C. Plasma high-density lipoprotein cholesterol is usually increased
D. It is accompanied by a threefold increased incidence of atherosclerosis
E. Hypertriglyceridemia is usually manifest in childhood

QUESTION 324

Which of the following statements about coronary stent thrombosis is NOT correct?
A. The strongest predictor of late stent thrombosis is premature discontinuation of dual antiplatelet therapy
B. The risk of bare metal stent thrombosis is greatest 2 to 6 months following implantation
C. Stent thrombosis has been reported to occur more than a year after the placement of drug-eluting stents
D. Late-stent thrombosis is more likely to occur in individuals with diabetes or renal failure than in patients without these conditions

QUESTION 325

A 60-year-old man was admitted to the hospital with an acute anterior myocardial infarction (MI). He underwent urgent cardiac catheterization and successful reperfusion was achieved after a complex coronary angioplasty with stent placement. His hospital course was complicated by rising serum creatinine and urea nitrogen levels. In addition, a purple, net-like discoloration developed on his lower extremities (Fig. 3.1). Which of the following statements is correct?
A. These findings likely resulted from the presenting MI rather than from the catheterization procedure
B. The urinalysis likely reveals an active sediment with cells and casts
C. A high serum complement level is likely
D. Transient eosinophilia is often part of this syndrome
E. Recovery of renal function within a few days is expected

QUESTION 326

Which of the following statements about low-density lipoprotein (LDL) is correct?
A. Apo AI comprises 25% of LDL mass
B. LDL is derived from metabolism of high-density lipoprotein
C. The predominant lipid components of LDL are esterified cholesterol and triglyceride

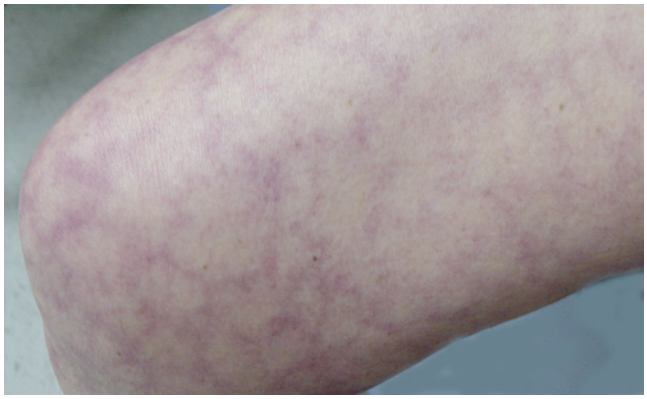


FIG. 3.1 *From Firestein.* Kelley's Textbook of Rheumatology. *8th ed. Philadelphia: Elsevier; 2008.*

D. The majority of patients with plasma LDL >190 mg/dL carry a familial hypercholesterolemia mutation

QUESTION 327

Which of the following statements regarding high-sensitivity C-reactive protein (hsCRP) is NOT correct?
A. Statins reduce hsCRP in a manner directly related to their low-density lipoprotein-lowering effect
B. An hsCRP level >3 mg/L in a patient with unstable angina is associated with an increased risk of recurrent coronary events
C. An elevated level of hsCRP is predictive of the onset of type 2 diabetes mellitus
D. Statin therapy has been shown to reduce cardiovascular events in apparently healthy individuals with elevated hsCRP even if the baseline LDL-C is <130 mg/dL
E. The cardiovascular benefit of aspirin therapy appears to be greatest in patients with elevated hsCRP levels

QUESTION 328

Which of the following is a feature of renovascular hypertension due to atherosclerosis as opposed to fibromuscular hyperplasia?
A. Age <60 years
B. Female gender
C. No family history of hypertension
D. Progression more likely to complete renal artery occlusion
E. Absence of carotid bruits

QUESTION 329

A newly diagnosed diabetic patient presents with multiple blood pressure (BP) readings that are 150/90 mm Hg or higher. Which of following statements about treatment of this patient's hypertension is NOT correct?
A. Current guidelines recommend a BP target of <130/80 mm Hg in diabetics
B. Control of BP reduces cardiovascular event rates more in diabetics than in nondiabetics
C. Pharmacologic blockade of the renin-angiotensin system reduces the risk of both microvascular and macrovascular events
D. Antihypertensive therapy with dihydropyridine calcium channel blockers reduces cardiovascular event rates
E. Aggressive BP control (target systolic BP <120 mm Hg) in diabetics has been shown to reduce cardiovascular event rates more than a target systolic BP <140 mm Hg

QUESTION 330

Which of the following statements regarding the use of percutaneous coronary intervention (PCI) as primary therapy in acute ST-segment elevation myocardial infarction (STEMI) is NOT correct?
A. PCI is associated with lower rates of intracranial hemorrhage than fibrinolysis
B. The primary success rate for PCI during acute STEMI is approximately 90%
C. In trials comparing primary PCI with fibrinolysis, patients randomized to primary PCI had a lower incidence of death or re-infarction by hospital discharge and at 6-month follow-up

D. Primary PCI does not improve survival in patients with acute STEMI who present with cardiogenic shock
E. When performed in experienced centers, hospital length of stay and follow-up costs are significantly less than for patients treated with fibrinolysis

QUESTION 331

A 67-year-old man with hypertension, elevated low-density lipoprotein cholesterol, chronic obstructive lung disease, and gastroesophageal reflux presents to the emergency department (ED) with 1 hour of 8/10 substernal chest pressure that radiates to the left arm. He had previously been healthy with no known history of coronary disease, though he led a sedentary lifestyle with little physical activity. His medications are aspirin 81 mg daily, lisinopril 40 mg daily, atorvastatin 40 mg daily, albuterol inhaler as needed, and omeprazole 20 mg daily.

Vital signs in the ED include a temperature of 37.2°C, heart rate 92 beats/min, blood pressure 160/93 mm Hg, respirations 20 breaths/min, and oxygen saturation 98% on room air. Physical examination reveals a well-developed man in moderate distress with jugular venous pulsation at 8 cm H_2O, clear lungs to auscultation, regular heart rhythm with no murmurs or gallops, and warm extremities with no peripheral edema.

The electrocardiogram shows normal sinus rhythm with normal intervals and axis and 3 mm ST elevations in leads V_1–V_4.

Aspirin 325 mg and ticagrelor 180 mg orally are administered and he is taken emergently to the cardiac catheterization laboratory. Two angiographic views are shown in Fig. 3.2. Which of the following interventions would be most appropriate?

A. Percutaneous coronary intervention (PCI) of left anterior descending (LAD) coronary artery now, and consideration of PCI of the left circumflex (LCX) and/or right coronary artery (RCA) at the same time, or as a staged procedure later
B. PCI of LAD now. Additional PCI of LCX and/or RCA should be avoided now
C. PCI of LCX first now. Additional PCI of LAD and/or RCA to follow at same setting or as staged procedure later
D. PCI of LCX only. Additional PCI of LAD and/or RCA should be avoided
E. Proceed to coronary artery bypass surgery now

QUESTION 332

Which statement about atrial infarction is FALSE?

A. Atrial infarction is found in <20% of autopsy-proven cases of myocardial infarction
B. Atrial infarction typically occurs in conjunction with left ventricular infarction
C. Rupture of the atrial wall is a recognized complication
D. Atrial infarction commonly leads to supraventricular arrhythmias
E. Infarction of the left atrium occurs more commonly than infarction of the right atrium

QUESTION 333

Which statement regarding ventricular free wall rupture complicating myocardial infarction (MI) is NOT correct?

A. It is more likely to occur in patients with a history of prior MI
B. It occurs most commonly within the first 48 hours after infarction
C. It occurs in 1% to 2% of patients after MI
D. It is more common in elderly patients and in women
E. A history of hypertension is a risk factor for free wall rupture

QUESTION 334

Which statement about right ventricular infarction (RVI) is FALSE?

A. RVI is a cause of the Kussmaul sign
B. ST-segment elevation in lead V_4 is commonly present
C. Echocardiography typically demonstrates right ventricular enlargement and hypokinesis

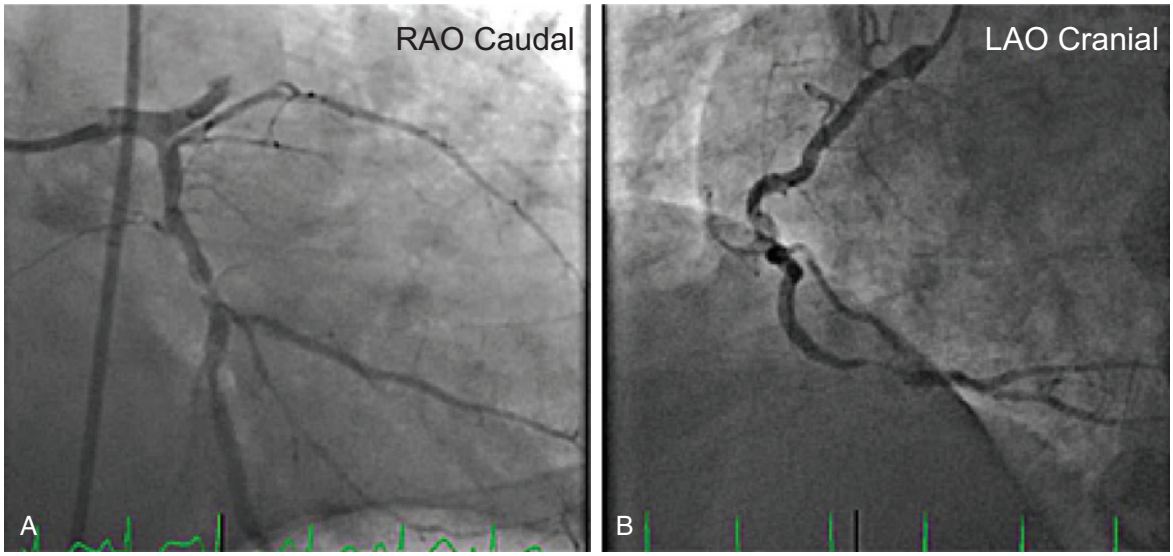
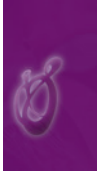


FIG. 3.2



D. A marked hypotensive response to nitroglycerin administration is consistent with this diagnosis
E. Atrioventricular sequential pacing offers greater hemodynamic benefit than single-chamber ventricular pacing in patients with RVI

QUESTION 335

A 60-year-old man is admitted to the coronary care unit after 14 hours of chest pain that had resolved by the time of hospital presentation. The initial ECG reveals 0.5-mm ST-segment elevations with T wave inversions and pathologic Q waves in leads II, III, and aVF. The initial cardiac examination is unremarkable. On the second day, a faint late systolic murmur is heard at the apex, and by the third day this murmur has increased to grade III/VI. The patient has mild dyspnea, and a chest radiogram shows pulmonary vascular redistribution. The most likely explanation for the murmur is
A. Ruptured posterior papillary muscle
B. Ruptured anterior papillary muscle
C. Infarcted posterior papillary muscle
D. Infarcted anterior papillary muscle
E. Ruptured chordae tendineae

QUESTION 336

Which statement about pericarditis and pericardial effusion in the setting of acute myocardial infarction (MI) is FALSE?
A. Post-MI pericardial effusions are found most often in patients with larger infarcts, in those with congestive heart failure, and in the setting of an anterior wall MI
B. Early post-MI pericarditis should be treated with nonsteroidal anti-inflammatory therapy (e.g., ibuprofen) plus colchicine
C. When present, Dressler syndrome manifests 1 to 8 weeks after infarction
D. Tamponade due to pericarditis in the setting of acute MI is rare

QUESTION 337

Which statement about conduction disturbances in acute myocardial infarction (MI) is FALSE?
A. Most patients with acute MI and first-degree atrioventricular (AV) block have an intranodal conduction disturbance
B. Sinus bradycardia in acute MI often results from increased vagal tone
C. Of patients with acute MI and second-degree AV block, the majority have Mobitz type I (Wenckebach) block
D. Mobitz type II second-degree AV block occurs more commonly in anterior infarction than in inferior infarction
E. In patients with anterior infarction who develop third-degree AV block, the conduction disturbance almost always appears without prior intraventricular conduction abnormalities

QUESTION 338

Which statement regarding the use of fibrinolytic therapy in acute myocardial infarction (MI) is TRUE?
A. Fibrinolytic therapy reduces the mortality of ST-segment elevation MI by 70% at 35 days after the event
B. Compared with patients with anterior ST-segment elevation, those who present with left bundle branch block have a similar risk reduction with fibrinolytic therapy
C. Compared with patients with anterior ST-segment elevation, patients with inferior ST-segment elevation demonstrate a greater risk reduction with fibrinolytic therapy
D. Clinical trial data demonstrate no mortality benefit of fibrinolysis administered more than 6 hours after the onset of symptoms
E. Patients older than age 75 years experience a greater relative reduction in mortality than patients younger than 55 years

QUESTION 339

Which statement regarding acute coronary syndromes is FALSE?
A. Occlusive coronary thrombosis is typically responsible for ST-segment elevations
B. Q waves develop in approximately 75% of patients with ST-segment elevation myocardial infarction who do not undergo acute reperfusion interventions
C. The presence of pathologic Q waves reliably indicates the transmural involvement of myocardial infarction
D. Nonocclusive coronary thrombosis typically results in ST-segment depressions and/or T wave inversions

QUESTION 340

Which statement regarding primary percutaneous coronary intervention (PCI) performed by experienced operators in acute ST-segment elevation myocardial infarction is FALSE?
A. PCI results in higher coronary artery patency rates than fibrinolysis
B. PCI results in lower mortality than fibrinolysis
C. PCI results in lower stroke rates than fibrinolysis
D. Radial artery access and femoral artery access in primary PCI result in similar rates of mortality and bleeding complications

QUESTION 341

Each of the following statements about left ventricular (LV) aneurysm after myocardial infarction is correct EXCEPT
A. Aneurysms typically range from 1 to 8 cm in diameter
B. Inferoposterior aneurysms are more common than apical aneurysms
C. The presence of an aneurysm increases the mortality rate compared with patients with similar ejection fractions without an aneurysm
D. Persistent ST-segment elevation on the ECG does not necessarily indicate aneurysm formation
E. True LV aneurysms rarely rupture

QUESTION 342

The rhythm shown in Fig. 3.3 developed in a 72-year-old man on the second day of hospitalization for an acute ST-segment elevation myocardial infarction (STEMI). Which statement is NOT correct?
A. The presence of this rhythm in STEMI is associated with increased mortality
B. This rhythm tends to be persistent, rather than transient, in the setting of acute STEMI
C. This rhythm may result from left ventricular failure, pericarditis, or left atrial ischemia in the setting of STEMI
D. If associated with hemodynamic compromise, it should be treated by immediate electrical conversion

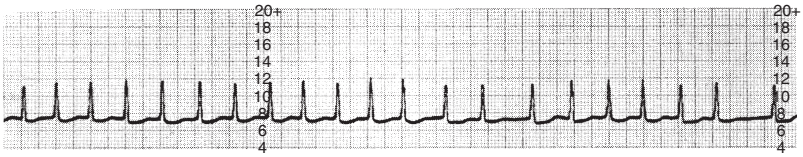


FIG. 3.3

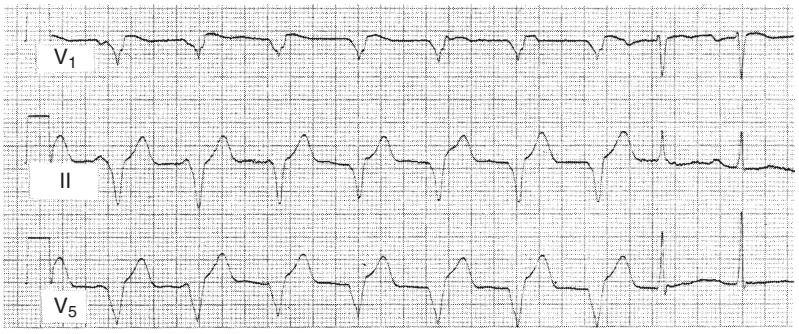


FIG. 3.4

QUESTION 343

Which of the following statements about the arrhythmia illustrated in Fig. 3.4, observed in the setting of an acute myocardial infarction (MI), is NOT correct?

A. This rhythm is associated with increased mortality
B. This rhythm is observed in up to 20% of patients with acute MI
C. It often occurs as a result of slowing of the sinus rhythm
D. Approximately 50% of such episodes are initiated by a premature beat
E. This is the most common arrhythmia after reperfusion with fibrinolytic therapy

QUESTION 344

Which of the following statements concerning the utility of cardiac biomarkers in patients with acute coronary syndromes is FALSE?

A. Levels of C-reactive protein (CRP) are greatly elevated in patients with an acute coronary syndrome (ACS) compared with patients with stable coronary disease
B. CRP and cardiac-specific troponin levels offer complementary information in the prognosis of patients with ACS
C. In patients with unstable angina, an elevated myeloperoxidase level is associated with increased risk of death
D. Patients with elevated levels of B-type natriuretic peptide have a twofold to threefold increased risk of adverse events
E. Patients with non–ST-elevation MI and elevated white blood cell (WBC) counts have similar mortality rates as those with normal WBC counts

QUESTION 345

A 76-year-old woman with permanent nonvalvular atrial fibrillation, hypertension, and peripheral artery disease presents to the emergency department with anterior chest pressure of two hours' duration. Her medications include apixaban 5 mg BID, metoprolol succinate 100 mg daily, indapamide 2.5 mg daily, and atorvastatin 80 mg daily. Initial vital signs are heart rate 84 beats/min, blood pressure 149/86 mm Hg, respiratory rate 18 breaths/min, and oxygen saturation 97% on ambient air. The ECG shows atrial fibrillation with a ventricular rate of 84 beats/min. There are 2 mm ST-segment depressions in leads II, III, and aVF, which are new when compared with a tracing 6 months earlier. Serum cardiac troponin-T is elevated at 1.3 ng/mL. At coronary angiography there is a 95% stenosis of the mid-right coronary artery, which is treated with a drug-eluting stent. In consideration of subsequent medications, which of the following statements about combined anticoagulant and antiplatelet therapy is correct?

A. Oral anticoagulation therapy plus clopidogrel, without aspirin ("double therapy") significantly reduces bleeding rates compared to "triple therapy" (anticoagulation plus aspirin and clopidogrel) in patients with a need for long-term anticoagulation who undergo percutaneous coronary intervention (PCI)
B. Rivaroxaban 15 mg daily plus a $P2Y_{12}$ receptor inhibitor has been shown to be as beneficial as the combination of warfarin plus dual antiplatelet therapy (aspirin + $P2Y_{12}$ inhibitor) for prevention of ischemic events in patients undergoing PCI
C. After an acute coronary syndrome (ACS), the addition of very low-dose rivaroxaban (2.5 or 5 mg twice daily) to aspirin plus a $P2Y_{12}$ inhibitor reduces the risk of cardiovascular death, nonfatal myocardial infarction, or stroke, without increasing the bleeding risk
D. Substituting rivaroxaban 2.5 mg BID for low-dose aspirin following a recent ACS reduces the rate of cardiovascular death, but increases the bleeding risk

QUESTION 346

Which statement about the progression of atherosclerosis after coronary artery bypass graft (CABG) surgery is FALSE?

A. Between 15% and 30% of vein grafts occlude by the end of the first year after CABG
B. The annual rate of saphenous vein graft occlusion between years 2 through 5 after CABG is about 2%
C. At 10 years, the overall occlusion rate for a saphenous vein graft approaches 50%
D. The atherosclerotic process that occurs in venous grafts is histologically distinct from that which occurs in native arterial vessels

QUESTION 347

Which of the following statements regarding myocardial stunning is NOT correct?
A. Stunning is a state of depressed myocardial function due to chronic hypoperfusion
B. Stunning can be global or regional
C. Stunning can follow cardiac surgery with cardiopulmonary bypass
D. Oxygen free radicals and excess intracellular calcium likely contribute to stunning
E. Stunning affects both systolic and diastolic function

QUESTION 348

Which of the following statements regarding antithrombotic therapies in the treatment of unstable angina or non–ST-segment elevation MI is FALSE?
A. The early beneficial cardiac outcome effects of clopidogrel in acute coronary syndromes persist for 12 months after hospital discharge
B. The combination of aspirin and an anticoagulant is superior to aspirin alone in prevention of death and nonfatal MI
C. Anticoagulation with the low-molecular-weight heparin enoxaparin is superior to unfractionated heparin in reducing the rate of death, nonfatal MI, and recurrent ischemia
D. Compared with enoxaparin, treatment of acute coronary syndromes with the factor Xa inhibitor fondaparinux results in excess major bleeding
E. Bivalirudin therapy alone is noninferior to the combination of low-molecular-weight heparin plus a glycoprotein IIb/IIIa inhibitor for prevention of ischemic endpoints in patients for whom an invasive strategy is planned, but results in less bleeding

QUESTION 349

Which statement regarding coronary collateral circulation is FALSE?
A. Preexisting collateral vessels open immediately after coronary occlusion
B. Increased flow through preexisting collateral vessels triggers a maturation process that produces a vessel nearly indistinguishable structurally from a normal coronary artery
C. Exercise does not increase coronary collateral circulation formation
D. Collateral vessels can provide nearly as much blood flow as the native coronary circulation
E. In the setting of an acute myocardial infarction, the presence of preexisting collateral vessels decreases infarct size and improves survival

QUESTION 350

Which of the following statements regarding medical therapy versus percutaneous coronary intervention (PCI) for chronic stable angina is correct?
A. PCI reduces the risk of future myocardial infarction compared with optimal medical therapy
B. In patients with stable coronary disease, fractional flow reserve-guided PCI plus optimal medical therapy reduces anginal episodes, but not the need for future urgent revascularization, compared with optimal medical therapy alone
C. PCI is superior to medical therapy alone in reducing cardiovascular mortality in patients with chronic stable angina
D. In the COURAGE trial, patients treated with PCI experienced less angina after 1 year, but not after 5 years of follow-up, compared with optimal medical therapy alone

QUESTION 351

Which of the following statements regarding the surgical management of abdominal aortic aneurysms (AAA) is correct?
A. Small aneurysms enlarge faster than larger ones
B. Aortic aneurysms grow and rupture at greater rates in men than in women
C. It is generally safe to wait until an AAA is ≥6.0 cm in diameter before proceeding with surgical repair
D. With aneurysm rupture, 60% of patients die before reaching the hospital
E. In men, surgical repair of aneurysms with diameters of 4.0 to 5.5 cm offers a mortality benefit over continued surveillance

QUESTION 352

Which of the following statements regarding the abnormality in Fig. 3.5 is correct?
A. Without treatment, expected mortality is approximately 5% in the first 24 hours
B. Outcomes with pharmacologic therapy are equivalent to surgical repair in the management of this condition when it occurs proximally

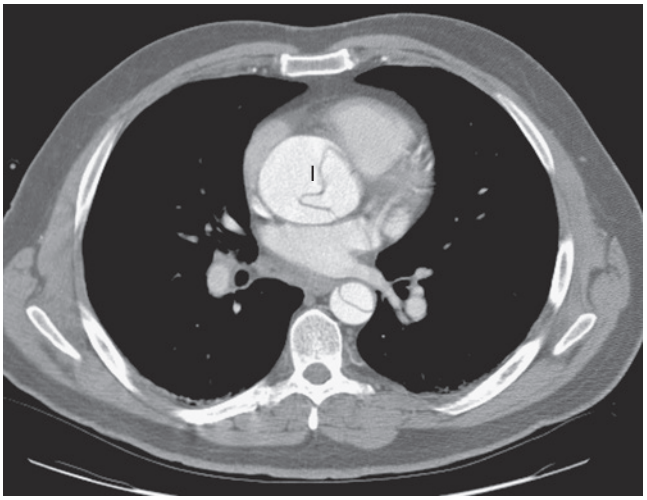


FIG. 3.5 *From Isselbacher EM. Aortic dissection. In: Creager MA, ed.* Atlas of Vascular Disease. *2nd ed. Philadelphia: Current Medicine; 2003.*

C. Initial pharmacologic therapy without surgery is recommended when this condition is distal in location and uncomplicated
D. Aortic valve replacement is universally required when there is accompanying aortic regurgitation
E. Labetalol should be avoided in patients with this condition

QUESTION 353

A 65-year-old man with cirrhosis and chronic stable angina presents to the cardiovascular clinic for evaluation. He describes his typical angina climbing one flight of stairs, despite beta blocker and long-acting nitrate therapies. Stress testing with nuclear perfusion imaging confirms exercise-induced reversible ischemia of the anterior left ventricular wall; the left ventricular ejection fraction is 50%. Coronary angiography reveals a long occlusion of the left anterior descending artery in its mid-segment with collateral perfusion to the distal vessel from the right coronary artery. The lesion is not amenable to percutaneous intervention. You are hesitant to increase the beta blocker and nitrate dosages because his resting heart rate is 50 beats/min and the blood pressure is 102/78 mm Hg. Which of the following statements is correct?

A. Ranolazine would decrease the blood pressure and heart rate further and should be avoided
B. Ranolazine does not offer incremental antianginal benefit to patients already taking beta blocker, long-acting nitrate, or calcium channel blocker therapies
C. Compared with placebo, ranolazine increases the risk of torsades de pointes
D. Ranolazine is metabolized in the liver and it should be avoided in this patient
E. The most common side effect of ranolazine is diarrhea

QUESTION 354

Which statement regarding the abnormality labeled "A" in Fig. 3.6 is correct?

A. The majority are symptomatic
B. Physical examination tends to underestimate the size
C. Imaging by ultrasonography is usually not sufficient to plan surgical repair
D. Although magnetic resonance angiography can define the size, it cannot accurately determine the proximal extent of disease

QUESTION 355

Which of the following statements regarding the use of platelet glycoprotein (GP) IIb/IIIa inhibitors in percutaneous coronary intervention procedures is NOT correct?

A. They decrease the need for urgent revascularization over the next 30 days
B. They decrease the rate of subsequent myocardial infarction
C. The major reduction of clinical events with GP IIb/IIIa inhibitors occurs within the first 48 hours
D. For patients with acute non–ST-segment elevation myocardial infarction, routine early administration of a GP IIb/IIIa inhibitor at initial encounter improves 30-day mortality rates without a significant increase in bleeding

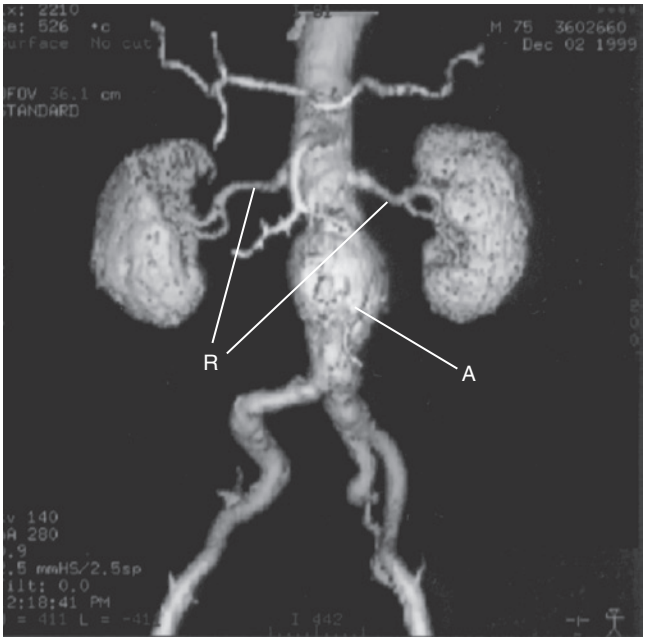


FIG. 3.6 *Courtesy of John A. Kaufman, MD, Division of vascular radiology, Massachusetts General Hospital, Boston.*

QUESTION 356

Which of the following statements regarding Prinzmetal (variant) angina is FALSE?

A. The majority of coronary sites that manifest focal vasospasm have evidence of underlying atherosclerosis
B. It can be precipitated by administration of 5-fluorouracil
C. Calcium channel blockers and nitrates are useful in treating and preventing attacks of Prinzmetal angina
D. Provocative testing is indicated in patients with nonobstructive lesions on coronary angiography, a clinical picture consistent with vasospasm, and documented transient ST-segment elevations on electrocardiography
E. Patients with isolated Prinzmetal angina have a low rate of sudden cardiac death

QUESTION 357

Which statement about the condition shown in Fig. 3.7 is NOT correct?

A. The most common cause is surgical manipulation of an atherosclerotic aorta
B. Cardiac catheterization may lead to this condition
C. Angiography is the definitive test to diagnose this condition
D. Stigmata of this disorder may be visible on direct inspection of the retinal arteries
E. Livedo reticularis is a recognized manifestation

QUESTION 358

Which statement regarding nitric oxide (NO) is FALSE?

A. NO production by endothelial cells is augmented by hypoxia, thrombin, and adenosine diphosphate
B. In atherosclerotic vessels, acetylcholine causes unopposed smooth muscle constriction
C. NO is formed in endothelial cells by the actions of NO synthase on the substrate L-arginine

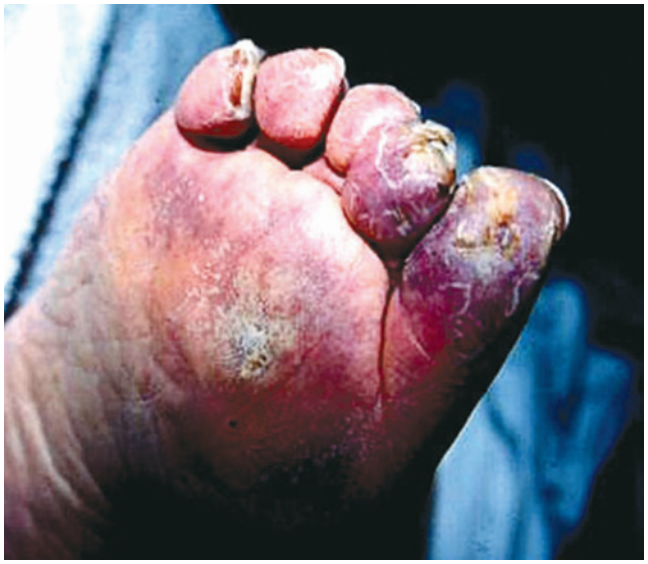


FIG. 3.7 *Modified from Beckman JA, Creager MA. In: Creager MA, Dzau VJ, Loscalzo J, eds.* Vascular Medicine: A Companion to Braunwald' s Heart Disease. *Philadelphia: Elsevier; 2006:259.*

D. NO stimulates increased cyclic adenosine monophosphate formation in vascular smooth muscle cells
E. The vasodilatory effects of nitroglycerin and prostacyclin are independent of endothelial NO production

QUESTION 359

Which of the following statements regarding aortic intramural hematoma is TRUE?
A. Symptoms are indistinguishable from those of classic aortic dissection
B. This condition results from an intimal tear in the aorta
C. A history of hypertension or aortic atherosclerosis is unusual
D. Computed tomography is less sensitive than aortography for diagnosis

QUESTION 360

Which of the following statements regarding low-molecular-weight heparins is correct?
A. They possess greater anti–factor IIa activity than anti–factor Xa activity
B. They are contraindicated in patients with type II heparin-induced thrombocytopenia
C. They cause significant elevations in the activated partial thromboplastin time, which is useful for monitoring the anticoagulant effect
D. Their clearance is minimally affected by renal impairment

QUESTION 361

All of the following are independent adverse risk predictors in patients who present with unstable angina or non–ST-segment elevation myocardial infarction EXCEPT:
A. Increased cardiac troponin level
B. ST-segment deviation ≥0.05 mV
C. Diabetes mellitus
D. Lack of prior aspirin use
E. Increased C-reactive protein level

QUESTION 362

Which of the following statements regarding peripheral arterial disease (PAD) is correct?
A. The prevalence of PAD is 5% in patients older than 75 years
B. Hypercholesterolemia is a more powerful risk factor than cigarette smoking
C. Claudication symptoms are present in only 10% to 30% of patients with PAD
D. The earliest aortic site of fatty streak and atheroma development is in the ascending thoracic aorta

QUESTION 363

Which of the following statements about the clinical manifestations of aortic dissection is FALSE?
A. Men are more frequently affected than women
B. Severe pain is the most common presenting symptom
C. Patients with aortic dissection usually present with hypotension
D. Pulse deficits are more common in proximal than in distal aortic dissection

QUESTION 364

Which of the following statements about patients with peripheral arterial disease (PAD) is NOT correct?
A. Intermittent claudication is characterized by pain precipitated by walking as well as by standing upright for several minutes
B. On examination, arterial bruits and hair loss of the affected extremity are common
C. Segmental pressure measurements demonstrate gradients of >20 mm Hg in the lower extremities or >10 mm Hg in the upper extremities
D. The ankle/brachial index is typically <1.0
E. Magnetic resonance angiography is >90% sensitive and specific for the diagnosis of PAD in the aorta, iliac, femoral-popliteal, and tibial-peroneal arteries

QUESTION 365

Which of the following statements regarding anticoagulation therapy in percutaneous coronary intervention (PCI) procedures is FALSE?
A. Clinical outcomes are similar for patients treated with fixed-dose unfractionated heparin (UFH) or weight-adjusted UFH during PCI
B. In patients pretreated with clopidogrel, bivalirudin is associated with a lower rate of major bleeding complications than UFH
C. Routine administration of intravenous UFH after PCI procedures results in a reduced number of ischemic complications
D. In conjunction with platelet glycoprotein IIb/IIIa inhibitor therapy, standard-dose UFH results in a similar rate of ischemic complications, but a higher rate of hemorrhagic complications when compared with low-dose weight-adjusted UFH
E. No additional anticoagulation is required during PCI if a patient has received a dose of the low-molecular-weight heparin enoxaparin within the previous 8 hours

QUESTION 366

Which of the following statements regarding nitrates in ischemic heart disease is FALSE?
A. Nitrates directly relax vascular smooth muscle
B. The vasodilator effects of nitrates predominate in the venous circulation
C. Coronary arteries containing significant atherosclerotic plaque often dilate in response to nitrates
D. An intact endothelium is required for nitrate-induced vasodilatation
E. Nitrates reduce left ventricular wall tension

QUESTION 367

Which of the following statements regarding glycoprotein (GP) IIb/IIIa inhibitors is NOT correct?
A. Abciximab administration before transport to the cardiac catheterization laboratory reduces ischemic complications in patients with ST-segment elevation myocardial infarction pretreated with clopidogrel who undergo percutaneous intervention
B. Administration of eptifibatide immediately before percutaneous coronary intervention (PCI) is as efficacious as early upstream therapy prior to PCI in patients presenting with acute coronary syndrome
C. Tirofiban has a half-life of approximately 2 hours
D. Long-term benefits of GP IIb/IIIa inhibitors are greater when administered with heparin
E. Human antichimeric antibodies develop in approximately 5% of patients treated with abciximab

QUESTION 368

Which of the following statements about atherosclerotic renal artery stenosis (RAS) and percutaneous renal artery intervention is correct?
A. Renal percutaneous transluminal angioplasty has a technical success rate of 60% for nonostial lesions
B. Compared with surgical revascularization, percutaneous renal artery interventions result in similar blood pressure control and stabilization of renal function
C. Stenting of hemodynamically significant RAS allows discontinuation of antihypertensive medications in the majority of patients
D. Compared to medical therapy alone, percutaneous treatment of atherosclerotic RAS results in fewer subsequent cardiovascular events

QUESTION 369

Which of the following statements regarding patients with the syndrome of recurrent angina-like chest pain and normal coronary angiograms is correct?
A. During stress testing, such patients do not develop chest pain or scintigraphic evidence of ischemia
B. During periods of increased myocardial oxygen demand, patients with this syndrome consistently produce elevated myocardial lactate
C. The prognosis is similar to patients with obstructive coronary artery disease
D. Endothelial and microvascular coronary dysfunction and enhanced pain sensitivity have been associated with this syndrome
E. The incidence of coronary calcification by multislice computed tomography is the same as normal subjects

QUESTION 370

Which of the following statements regarding endovascular repair of abdominal aortic aneurysms is FALSE?
A. Anatomic constraints limit the use of endografts
B. Primary success rates for aneurysm exclusion are >75%
C. Endoleaks are a serious complication after implantation
D. Thirty-day mortality rates are lower with endovascular repair compared with open surgical repair
E. Long-term outcomes are better with endografts than with open surgical repair

QUESTION 371

Which of the following statements regarding treatment of peripheral arterial disease is NOT correct?
A. Pentoxifylline's actions are mediated through its hemorheologic properties
B. Cilostazol's benefits arise via calcium channel blockade
C. Supervised exercise training programs improve maximum walking distances by 50% to 200%
D. Percutaneous transluminal angioplasty of the iliac artery results in 4-year patency rates of 60% to 80%
E. Aortobifemoral bypass results in 10-year patency rates of nearly 90%

QUESTION 372

Which of the following steps is NOT appropriate in the management of patients with acute aortic dissection?
A. Intravenous sodium nitroprusside
B. Intravenous beta blocker therapy
C. Emergent surgical repair for uncomplicated type B dissection
D. Use of narcotics for pain relief

QUESTION 373

Which of the following statements regarding diabetes mellitus as a cardiovascular risk factor is correct?
A. The prevalence of diabetes is decreasing in the developed world
B. A glycosylated hemoglobin (hemoglobin A1c) level >7.0% is required to make a diagnosis of diabetes
C. Statin therapy reduces coronary events only in diabetics with abnormal cholesterol levels
D. Fibric acid therapy, added to a statin, improves cardiovascular outcomes in type 2 diabetics
E. Lifestyle modifications significantly reduce the rate of diabetes development in at-risk individuals

QUESTION 374

Which of the following statements regarding blood flow in the subendocardium as compared with the subepicardium is correct?
A. Systolic flow is greater in the subendocardium
B. Under normal conditions, total subepicardial flow is equal to or greater than subendocardial flow

C. An elevation of ventricular end-diastolic pressure will reduce subendocardial flow to a greater extent than subepicardial flow
D. The reserve for vasodilatation in the subendocardium is greater than in the subepicardium

QUESTION 375

Which of the following statements regarding myocardial stunning and hibernation is NOT correct?
A. Stunning refers to myocardial dysfunction that persists after periods of severe ischemia
B. Molecular contributors to stunning include oxygen-derived free radicals, calcium overload, and reduced sensitivity of myofilaments to calcium
C. Stunned myocardium does not respond to inotropic agents
D. Hibernating myocardium reflects decreased myocardial function due to chronically decreased coronary blood flow that can be reversed with revascularization
E. Histopathologic studies of hibernating myocardium reveal dedifferentiation and apoptosis

QUESTION 376

Which of the following statements regarding atherosclerotic plaque in unstable angina is FALSE?
A. Approximately 15% of patients presenting with unstable angina have no significant coronary artery disease on angiography
B. The culprit lesion in unstable angina typically exhibits an eccentric stenosis
C. Patients with unstable angina due to coronary microvascular dysfunction have a poor short-term prognosis
D. Intravascular ultrasonography often reveals vulnerable plaques in unstable angina to be echolucent, consistent with a lipid-rich core with a thin fibrous cap

QUESTION 377

In patients with stable coronary artery disease, each of the following statements about the role of percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery is correct EXCEPT
A. In the majority of patients there is no mortality advantage of one treatment strategy compared with the other
B. CABG is consistently associated with a lower rate of subsequent myocardial infarction
C. PCI is associated with a higher rate of recurrent angina
D. Patients with diabetes and severe multivessel disease demonstrate a greater reduction in mortality with CABG
E. In patients with single-vessel disease (>70% stenosis) of the left anterior descending coronary artery, there is no difference between PCI and CABG in the rates of subsequent myocardial infarction or cardiovascular death

QUESTION 378

Which of the following statements regarding high-dose statin therapy (e.g., 80 mg/day) is NOT correct?
A. High-dose simvastatin results in a greater degree of skeletal myopathy compared with low-dose (20 mg/day) therapy
B. High-dose atorvastatin results in measurable regression of atherosclerotic coronary stenosis
C. High-dose simvastatin has been shown to reduce coronary events after an acute coronary syndrome compared with less intensive therapy
D. Compared with less intensive statin therapy, high-dose atorvastatin reduces subsequent mortality in patients after an acute coronary syndrome

QUESTION 379

Which of the following statements regarding oral antiplatelet agents is correct?
A. Aspirin's principal antiplatelet action is via inhibition of the PAR-1 thrombin receptor
B. Clopidogrel and prasugrel are irreversible inhibitors of the platelet $P2Y_{12}$ adenosine diphosphate receptor
C. Prasugrel displays a slower onset of action than clopidogrel
D. Nonsteroidal anti-inflammatory drugs such as ibuprofen enhance the antiplatelet effect of aspirin
E. Cilostazol's mechanism of action is via activation of nitric oxide synthesis

QUESTION 380

Which of the following statements regarding pharmacologic inhibition of the renin-angiotensin system in patients with ST-segment elevation myocardial infarction (STEMI) is FALSE?
A. Oral angiotensin-converting enzyme (ACE) inhibitors reduce mortality in patients with STEMI
B. In patients with STEMI and left ventricular dysfunction, an angiotensin receptor blocker in combination with an ACE inhibitor results in better cardiovascular outcomes than an ACE inhibitor alone
C. In short-term trials, one-third of the mortality benefit of ACE inhibitors in STEMI occurs within the first 2 days of therapy
D. Oral administration of the selective aldosterone inhibitor eplerenone is associated with reduced mortality in patients with STEMI and left ventricular dysfunction

QUESTION 381

A 42-year-old man with a long smoking history presents with claudication and rest pain of his right calf and foot. An angiogram of his posterior tibial artery is shown in Fig. 3.8. Which of the following statements about this condition is correct?
A. It affects primarily the large vessels of the arms and legs
B. High-dose statin therapy improves symptoms
C. Smoking cessation improves clinical outcomes
D. Vascular surgery is usually required emergently
E. More than 75% of patients with this condition are women

QUESTION 382

Which of the following characteristics is typical of a hypertensive crisis?
A. Central retinal artery occlusion
B. Constriction of cerebral arterioles with decreased vascular permeability
C. Renal insufficiency without proteinuria
D. Microangiopathic hemolytic anemia

QUESTION 383

Which of the following conditions has NOT been associated with the abnormality demonstrated in the transesophageal echocardiogram image in Fig. 3.9?
A. Heroin use
B. Hypertension
C. Marfan syndrome
D. Bicuspid aortic valve
E. Pregnancy

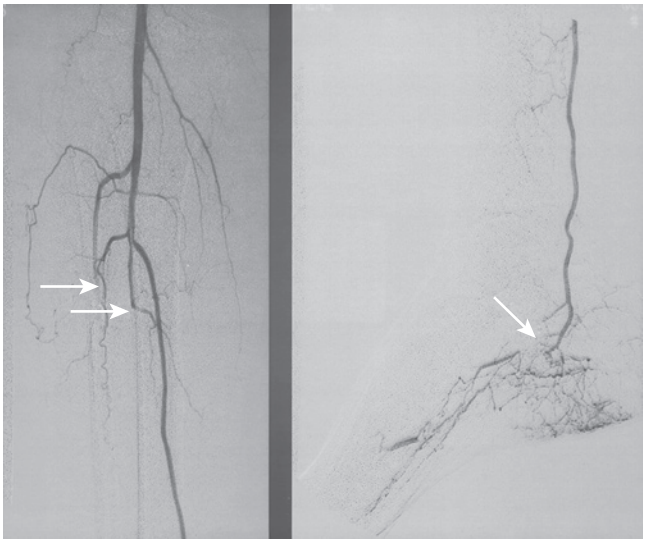


FIG. 3.8

QUESTION 384

Which of the following would NOT be an appropriate intervention for a patient with acute ST-segment elevation myocardial infarction and cardiogenic shock?
A. Percutaneous left ventricular assist device
B. Fibrinolytic therapy
C. Urgent percutaneous coronary intervention
D. Vasopressor drugs
E. Coronary artery bypass surgery

QUESTION 385

Which statement about the diagnosis and treatment of right ventricular infarction (RVI) is NOT correct?
A. Hypotension in response to small doses of nitroglycerin in patients with inferior infarction suggests RVI
B. Unexplained systemic hypoxemia in RVI raises the possibility of a patent foramen ovale
C. Hemodynamic parameters in RVI often resemble those of patients with pericardial disease
D. Loop diuretics are usually the preferred initial therapy for patients with RVI and intact left ventricular contractile function
E. ST-segment elevation in lead V_4R is a sensitive and specific sign of RVI

QUESTION 386

A 65-year-old man presents with several months of right lower extremity discomfort and fatigue while walking. Segmental pressure measurements were obtained as shown in Fig. 3.10. Which of the following statements is TRUE?

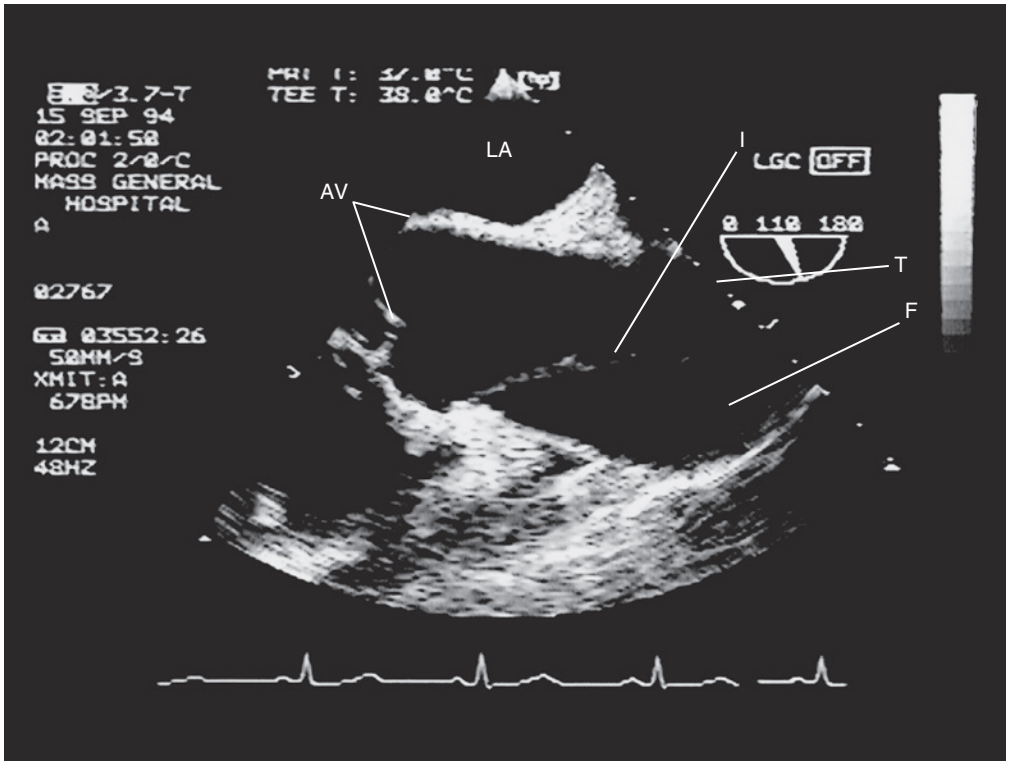


FIG. 3.9

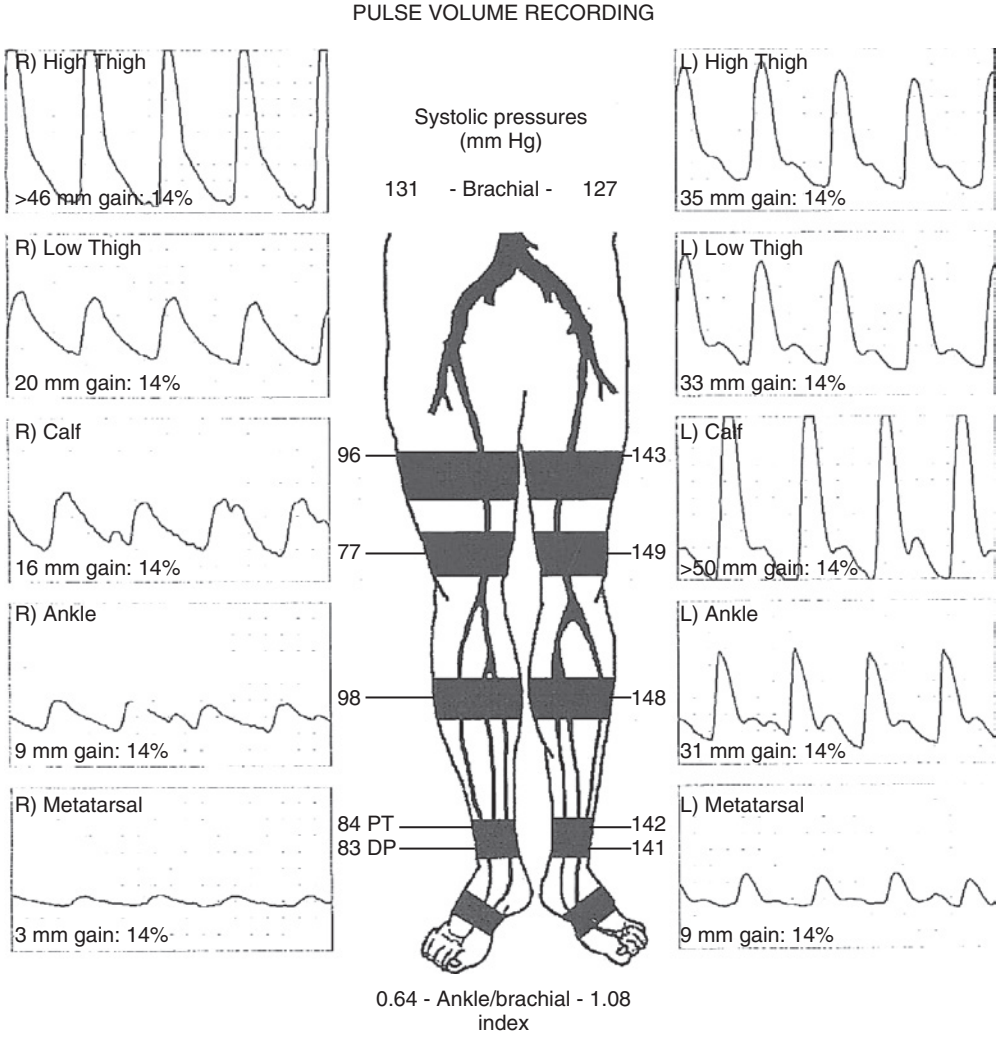


FIG. 3.10

A. An ankle/brachial index >0.85 is considered normal
B. A pressure difference >20 mm Hg between successive cuffs is evidence of significant arterial stenosis
C. Critical limb ischemia is associated with an ankle/brachial index of 0.8 or less
D. The sensitivity of the ankle/brachial index for the diagnosis of peripheral arterial disease is increased in severely calcified arteries
E. This patient's main abnormality is right tibial artery stenosis

QUESTION 387

Which of the following statements regarding bare metal stents (BMSs) is correct?
A. BMSs have a 5% to 10% rate of angiographic in-stent restenosis
B. BMS in-stent restenosis is more likely to occur in diabetics
C. Direct coronary atherectomy and rotational atherectomy are the preferred therapies for in-stent restenosis
D. Brachytherapy is more effective than placement of a drug-eluting stent for BMS in-stent restenosis

QUESTION 388

Which of the following statements regarding drug-eluting stents (DES) is correct?
A. DES stimulate local neointimal proliferation
B. The rate of angiographic restenosis after DES implantation is 10% to 15%
C. Paclitaxel stabilizes microtubules and prevents cell division
D. DES that incorporate everolimus are less effective at preventing target lesion failure compared with stents that incorporate paclitaxel
E. Zotarolimus-eluting stents significantly reduce the frequency of late-stent thrombosis compared with sirolimus DES

QUESTION 389

Which of the following is an effect of regular exercise?
A. Favorable changes in the fibrinolytic system
B. Decreased heart rate variability
C. Decreased expression of nitric oxide synthase
D. Decreased HDL levels
E. Increased systolic and diastolic blood pressures

QUESTION 390

Each of the following is a major determinant of myocardial oxygen demand (MVO_2) EXCEPT
A. Ventricular wall tension
B. Plasma hemoglobin level
C. Myocardial contractile state
D. Heart rate
E. Left ventricular volume

QUESTION 391

A 63-year-old man with long-standing insulin-requiring diabetes presented to his physician's office 2 weeks ago for management of hypertension. His blood pressure was 160/94 mm Hg. The serum creatinine was 1.6 mg/dL and blood urea nitrogen (BUN) was 30 mg/dL, with otherwise normal serum chemistries. A potassium-sparing diuretic (triamterene plus hydrochlorothiazide) was prescribed. When he returns 2 weeks later, the serum potassium level is 6.8 mmol/L with no significant change in BUN or creatinine level. The most likely contributing mechanism is
A. Excessive consumption of bananas and tomatoes
B. A recent urinary tract infection
C. Primary hyperaldosteronism
D. Hyporeninemic hypoaldosteronism
E. Cushing syndrome

QUESTION 392

Which of the following statements about the use of prasugrel is NOT correct?
A. Compared with clopidogrel, platelet aggregation is more effectively inhibited by prasugrel
B. Compared with clopidogrel, prasugrel reduces the risk of stent thrombosis
C. Compared with clopidogrel, bleeding complications associated with prasugrel are lower
D. Prasugrel is contraindicated in patients with a history of stroke
E. The risk of bleeding with prasugrel is higher in patients >75 years of age

Directions:

For each below, select the ONE BEST response.

QUESTIONS 393 TO 396

Match the following cell types potentially involved in atherogenesis with the appropriate descriptive phrase:
A. Endothelial cell
B. Smooth muscle cells
C. Macrophage
D. Platelet

393. Demonstrate(s) proliferation in the intima in atherosclerosis
394. Is (are) the principal cell(s) of the fatty streak
395. Secrete(s) prostacyclin
396. Is (are) capable of little or no protein synthesis

QUESTIONS 397 TO 400

For each statement, match the corresponding beta blocker:
A. Atenolol
B. Carvedilol
C. Propranolol
D. Acebutolol

397. Has alpha- and beta-receptor blocking activity
398. Is most hydrophilic
399. Has inherent sympathomimetic activity
400. Has shortest half-life

QUESTIONS 401 TO 405

For each statement, match the most appropriate complication following myocardial infarction:
A. Aneurysm
B. Pseudoaneurysm
C. Both
D. Neither

401. Low risk of rupture
402. Narrow base
403. Due to true myocardial rupture
404. Associated thrombus is common
405. Surgical repair is usually required

QUESTIONS 406 TO 409

For each statement, match the corresponding anticoagulant(s):
A. Unfractionated heparin (UFH)
B. Low-molecular-weight heparin (LMWH)
C. Bivalirudin
D. UFH and bivalirudin
E. LMWH and bivalirudin

406. Binds directly to thrombin, independent of antithrombin
407. Dose(s) should be adjusted if creatinine clearance is <30 mL/min
408. Degree of anticoagulation can be monitored using the activated partial thromboplastin time
409. Least likely to trigger type II heparin-induced thrombocytopenia

QUESTIONS 410 TO 414

Match the descriptions with the appropriate cell type:
A. Monocytes
B. Smooth muscle cells
C. Both
D. Neither

410. Migrate into the arterial intima from the media in response to chemoattractants
411. Primary constituent(s) of fibrous plaques
412. Require low-density lipoprotein receptor to become foam cells
413. Rely on chemoattractants to enter into developing atherosclerotic intimal lesions
414. Adhesion molecules, including vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, regulate adherence to endothelial cells

QUESTIONS 415 TO 418

For each statement, match the most appropriate fibrinolytic agent:

A. Streptokinase
B. Alteplase
C. Reteplase
D. Tenecteplase

415. Shortest half-life
416. Most fibrin-specific
417. Administered as a single bolus
418. Lowest intracranial hemorrhagic risk

QUESTIONS 419 TO 422

For each statement, match the most likely complication following acute myocardial infarction:

A. Acute ventricular septal rupture
B. Acute mitral regurgitation
C. Both
D. Neither

419. The murmur may decrease in intensity as arterial pressure falls
420. Pulmonary artery wedge pressure tracing demonstrates large *v* waves
421. Associated with the pathologic process shown in Fig. 3.11
422. Occurs primarily with large infarctions

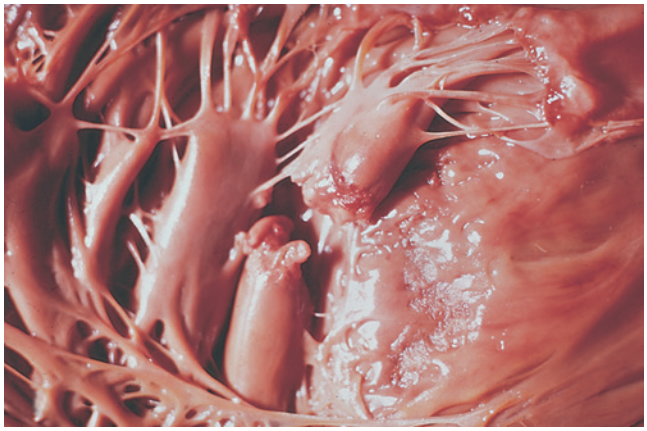


FIG. 3.11 *From Schoen FJ. The heart. In: Kumar V, Abbas AK, Fausto N, eds.* Robbins & Cotran Pathologic Basis of Disease. *8th ed. Philadelphia: Elsevier; 2010:529–587.*

QUESTIONS 423 TO 427

For each of the following prospective lipid-lowering trials, match the most appropriate statement.

A. Statistically significant reduction in nonfatal myocardial infarction
B. Statistically significant reduction in overall mortality
C. Both
D. Neither

423. Scandinavian Simvastatin Survival Study (4S)
424. The Heart Protection Study (HPS)
425. Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA)
426. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER)
427. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)

QUESTIONS 428 TO 431

For each pharmacologic agent, match the associated lipoprotein effect:

A. Elevate(s) high-density lipoprotein (HDL) cholesterol
B. Elevate(s) low-density lipoprotein (LDL) cholesterol
C. Have (has) no significant effect on lipoproteins
D. Lower(s) HDL cholesterol
E. Lower(s) very-LDL cholesterol

428. Corticosteroids
429. Propranolol
430. Second-generation antipsychotic medications (e.g., olanzapine)
431. Calcium channel antagonists

QUESTIONS 432 TO 435

For each clinical feature in Fig. 3.12, match the appropriate condition:

A. Familial hypercholesterolemia
B. Type III hyperlipoproteinemia (familial dysbetalipoproteinemia)
C. Both
D. Neither

432. See part A
433. See part B
434. See part C
435. See part D

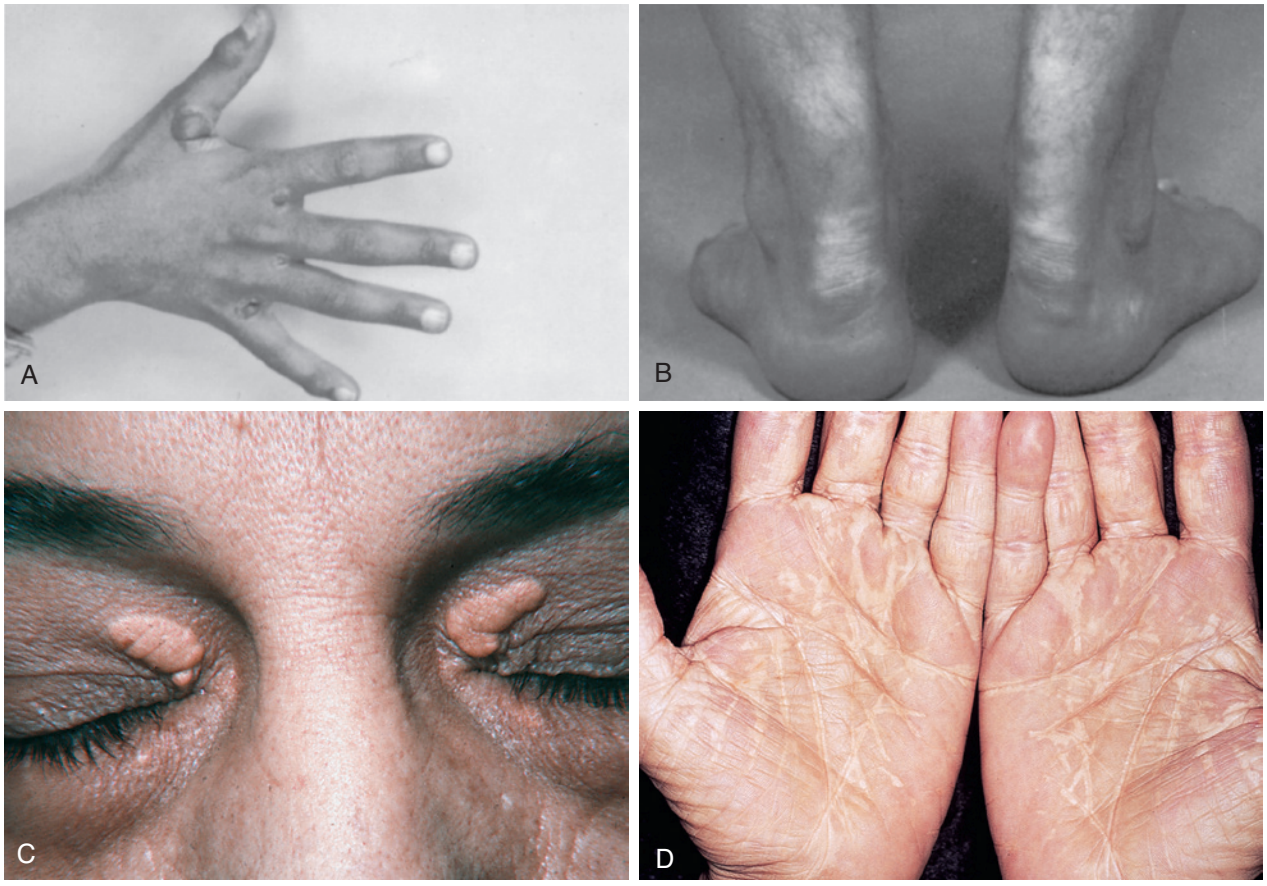


FIG. 3.12 *(A and B) From Gotto A.* Cholesterol Education Program: Clinician's Manual. *Dallas: American Heart Association; 1991:34–36. By permission of the American Heart Association, Inc; (C and D) From* Habif: Clinical Dermatology. *5th ed. St. Louis: Elsevier; 2009.*

Section III Answers

(CHAPTERS 44 TO 66)

Preventive Cardiology; Atherosclerotic Cardiovascular Disease

ANSWER TO QUESTION 295

D (Braunwald, pp. 971–974; Tables 48.8 and 48.9; Fig. 48.7)

This patient has multiple coronary risk factors and his 10-year risk of cardiovascular (CV) disease is significantly elevated. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines recommend moderate- or high-intensity statin therapy for primary prevention of CV disease for individuals with an estimated 10-year risk ≥7.5%.[1]

Because each doubling of statin dosage results in only another approximately 6% decline in low-density lipoprotein (LDL) cholesterol, this patient would require a substantial increase in the dose of simvastatin to achieve further desired LDL reduction. However, the US Food and Drug Administration (FDA) has issued an advisory against augmenting simvastatin to 80 mg daily because of an increased risk of muscle injury compared with patients taking lower doses.[2] Furthermore, simvastatin is metabolized primarily by cytochrome P-450 CYP3A4, which if inhibited by other medications leads to an augmented serum simvastatin level and the potential for increased toxicity, including myositis and rhabdomyolysis. Among commonly used CV medications, such impaired simvastatin metabolism can result from verapamil (which this patient takes), diltiazem, gemfibrozil, and amiodarone.[3] The FDA advises that gemfibrozil not be prescribed concurrently with simvastatin, and that the dosage of simvastatin should not exceed 10 mg daily for patients who also take verapamil, diltiazem, or amiodarone.[2]

As a reasonable next step, this patient could be switched to an alternate, higher-potency statin. For primary prevention for this patient at ≥7.5% 10-year atherosclerotic risk, moderate intensity regimens recommended by the 2013 ACC/AHA guidelines include atorvastatin 10 to 20 mg daily or rosuvastatin 5 to 10 mg daily. Optional high-intensity regimens include atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily.

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2. U.S. Food and Drug Administration. FDA Drug Safety Communication: new restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Available at: www.fda.gov/Drugs/DrugSafety/ucm256581.htm. Accessed January 2, 2018.
3. Kellick KA, Bottorff M, Toth PP. A clinician's guide to statin drug-drug interactions. *J Clin Lipidol*. 2014;8:S30.

ANSWER TO QUESTION 296

C (Braunwald, p. 897; Figs. 45.20 and 45.21)

Lifestyle modifications benefit most individuals with hypertension.[1] Obesity contributes to elevated blood pressure (BP) and even small degrees of weight loss can lower it, no matter what type of diet is employed.[2]

Modest sodium restriction can also improve hypertension. Reduction of dietary sodium intake to <100 mmol/day (2.4 g of sodium or 6 g sodium chloride) decreases systolic BP approximately 2 to 8 mm Hg. Not all hypertensive individuals respond to lower salt intake, and some patients (African Americans and the elderly) may be particularly sensitive to sodium reduction.[3] Adoption of the DASH (Dietary Approaches to Stop Hypertension) eating plan—rich in fruits, vegetables, and low-fat dairy products and low in total and saturated fat—has been shown to reduce BP by 11.4/5.5 mm Hg. Even greater reductions are manifest by combining the DASH diet with reduced sodium intake.[3] Magnesium and calcium supplements have not been demonstrated to significantly reduce BP.

Ethanol consumption of no more than 1 oz/day (24 oz beer, 10 oz wine, 3 oz 80-proof liquor for a normal-size man and less for a woman) is associated with decreased cardiac mortality, but excessive alcohol intake exerts a pressor effect, so that alcohol abuse is actually a cause of reversible hypertension.

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panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2013;311:507.
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ANSWER TO QUESTION 297

B (Braunwald, pp. 922–923; Fig. 46.16; Table 46.65)

Renovascular disease is one of the most common causes of secondary hypertension and has two main etiologies. The most common cause (80% to 90% of cases) is atherosclerotic disease affecting the proximal third of the main renal artery, typically seen in older men. The prevalence of atherosclerotic renovascular disease is higher with advanced age, diabetes, and evidence of atherosclerosis in other arterial beds.

The second, and less common, form of renal artery stenosis is fibromuscular dysplasia, which primarily afflicts women aged 20 to 60 years. It involves mainly the distal two-thirds of the main renal artery, and, although all layers of the vessel may be affected, involvement of the media is most common. A renovascular etiology of hypertension should be suspected in patients who develop high blood pressure before age 30, or after age 50 with the abrupt onset of severe and resistant hypertension and signs of atherosclerosis elsewhere, or in patients with recurrent sudden unexplained pulmonary edema. *Bilateral* renal artery stenosis should be suspected if renal insufficiency is present, especially if renal function worsens following initiation of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy.[1]

The treatment of choice for renal fibromuscular dysplasia is balloon angioplasty of the affected segment. However, the cornerstone of therapy for patients with atherosclerotic renovascular disease is pharmacologic control of blood pressure and other atherosclerotic risk factors such as dyslipidemia. Mechanical intervention should be reserved for patients with refractory hypertension or progressive renal insufficiency.[2]

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ANSWER TO QUESTION 298

B (Braunwald, pp. 910–926; Fig. 46.2 and eFig. 46.5; Tables 46.1 and 46.2)

Essential hypertension accounts for approximately 90% of patients with elevated blood pressure.[1] Renal parenchymal disease is the second most common cause, responsible for approximately 5%. Grouped together, coarctation of the aorta, Cushing disease, and pheochromocytoma contribute to <1%. Primary aldosteronism accounts for ~1% of hypertension in the general population, but a higher percentage (~11%) in patients with resistant hypertension.[2]

Pure "white coat" hypertension, in which blood pressures taken in the office are persistently elevated but out-of-office readings are not, is found in 20% to 30% of patients. Most patients with white coat hypertension are found to be free of target organ damage and have an excellent 10-year prognosis with respect to cardiovascular disease.

When measuring the blood pressure, the correct cuff size should be used. The cuff bladder should encircle and cover two-thirds of the length of the arm. If the cuff bladder is too small, blood pressure readings may be spuriously *high*.[3]

In elderly patients, the brachial arteries are often sclerotic and may not become occluded until the blood pressure cuff is inflated to a very high pressure. As a result, the recorded cuff pressure may be much higher than that measured intra-arterially, resulting in "pseudohypertension."

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ANSWER TO QUESTION 299

B (Braunwald, pp. 1012–1018; Tables 51.3 and 51.4)

The goal of glucose-lowering therapy for most type 2 diabetic patients is to achieve a hemoglobin A1c level <7.0%, which reduces microvascular complications including diabetic neuropathy, nephropathy, and retinopathy. More recent attention has focused on the cardiovascular safety of these agents, including their effects on macrovascular events (i.e., myocardial infarction [MI], stroke). Notably, recent clinical trials have demonstrated significant cardiovascular outcomes benefits with specific glucagon-like peptide (GLP)-1 receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors.[1]

The LEADER trial randomized 9340 patients with type 2 diabetes at high risk of cardiovascular disease to the GLP-1 receptor agonist liraglutide or placebo, in addition to standard therapy.[2] After a median follow-up of 3.8 years, the composite endpoint of cardiovascular death, nonfatal MI, and stroke was significantly reduced in the liraglutide group (hazard ratio 0.87; 95% confidence interval [CI], 0.78 to 0.97, $P = .01$ for superiority). In the SUSTAIN-6 trial, the GLP-1 receptor antagonist semaglutide (not yet approved for use in the United States) was randomized versus placebo in 3297 patients with type 2 diabetes and high cardiovascular risk.[3] After 104 weeks, the composite of cardiovascular death, nonfatal MI, and stroke was significantly reduced in those receiving the GLP-1 receptor antagonist (hazard ratio 0.74; 95% CI, 0.58 to 0.95, $P = .02$ for superiority).

In the EMPA-REG OUTCOME trial, the SGLT2 inhibitor empagliflozin was randomly assigned versus placebo to 7020 patients with type 2 diabetes and known cardiovascular disease.[4] After a median of 3.1 years, there were fewer events (cardiovascular death, nonfatal MI, or stroke) in those

randomized to empagliflozin (hazard ratio 0.86; 95% CI, 0.74 to 0.99, $P = .04$ for superiority). In the CANVAS trials, patients randomized to the SGLT2 inhibitor canagliflozin also demonstrated a reduced composite outcome of cardiovascular death, nonfatal MI, and stroke compared with placebo, but patients treated with this drug experienced a higher incidence of lower extremity amputations.[5] The patient presented in this question has a history of claudication and presumed peripheral vascular disease, so canagliflozin should be avoided in his case. Other potential side effects of SGLT2 inhibitors include volume depletion and recurrent urinary tract infections.

The thiazolidinedione pioglitazone was studied in a placebo-controlled randomized trial of 5238 patients with type 2 diabetes and cardiovascular disease in the PROactive trial.[6] There was a lower incidence of a secondary endpoint (death, nonfatal MI, stroke) with pioglitazone. However, like other thiazolidinediones, it is associated with a higher incidence of heart failure in diabetics and should be avoided in this patient with a history of heart failure symptoms.

An analysis of 19 trials of patients with type 2 diabetes concluded that the dipeptidyl peptidase 4 inhibitor linagliptan does not increase the composite outcome of cardiovascular death, MI, or stroke, but unlike other agents described above, it is not associated with a reduction of these adverse cardiovascular events.

As of this writing (mid 2018), the American Diabetes Association recommends that empagliflozin or liraglutide be considered as preferred agents to add to standard therapy (e.g., metformin) to reduce mortality and major cardiovascular events in suboptimally controlled type 2 diabetics with established cardiovascular disease.[1] For the patient presented in this question, liraglutide is the preferred answer. His history of urinary tract infections makes empagliflozin an inferior choice.

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ANSWER TO QUESTION 300

B (Braunwald, pp. 915–916; Fig. 46.9; eFig. 46.4)

The use of oral contraceptives (OCs) is a cause of secondary hypertension in young women. The risk of such patients developing hypertension is increased by alcohol consumption, age >35 years, and obesity and is likely related to the estrogen content of the agent. Because estrogen increases the hepatic production of angiotensinogen, a probable mechanism for hypertension induced by OCs is activation of the renin-angiotensin system with subsequent sodium retention and volume expansion. Nonetheless, angiotensin-converting enzyme inhibitors do not influence blood pressure to a greater degree in women with contraceptive-induced hypertension than in those with primary essential hypertension. Of note, blood pressure normalizes within 6 months of initiating OC therapy in approximately 50% of patients.

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ANSWER TO QUESTION 301

D (Braunwald, pp. 952–953)

Per the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines, this patient has stage 1 hypertension (Table 3.1) with a consistent systolic pressure 130 to 139 mm Hg.[1] The Guideline recommends that his target blood pressure should be <130/80 mm Hg. This endorsement is based in part on the Systolic Blood Pressure Intervention Trial (SPRINT) trial, which randomized 9361 hypertensives with high cardiovascular risk to a systolic pressure target of either <120 mm Hg or <140 mm Hg.[2] The trial was stopped early at 3.3 years when the lower blood pressure target group demonstrated superior outcomes, namely lower rates of acute coronary syndromes, stroke, heart failure, or cardiovascular death. Since blood pressure measurements taken in practice are generally higher than in the careful experimental setting of the SPRINT trial, the Hypertension Guideline relaxed the target systolic pressure to <130 mm Hg.

All patients with elevated blood pressure or stage 1 or stage 2 hypertension (defined in Table 3.1) should follow lifestyle modifications that can improve blood pressure (e.g., a Dietary Approach to Stop Hypertension [DASH] diet, reduced sodium intake, weight loss if overweight, increased exercise, and moderation of ethanol intake [≤2 drinks day for men, ≤1 drink day for women]). Furthermore, the Guideline recommends that antihypertensive drug therapy be initiated for patients with stage 2 hypertension, and for those with stage 1 hypertension who have a 10-year predicted cardiovascular risk >10% using the ACC/AHA pooled cohort risk assessment equations (http://tools.acc.org/ASCVD-Risk-Estimator).

Recommended initial drugs are those that have been shown to reduce cardiovascular risk in hypertensive patients, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and thiazide-type diuretics.[1] Beta blockers are not recommended for initial therapy, as clinical trials have not shown a mortality

TABLE 3.1 Blood Pressure Categories

CATEGORY	SYSTOLIC PRESSURE (MM HG)		DIASTOLIC PRESSURE (MM HG)
Normal	<120	and	<80
Elevated	120–129	and	<80
Stage 1 Hypertension	130–139	or	80–89
Stage 2 Hypertension	≥140	or	≥90

benefit when used for hypertension (possibly in part because the key trials used inadequately dosed atenolol). In addition, for black patients, thiazide-type diuretics and calcium channel blockers are more effective at lowering blood pressure then are beta blockers or drugs that interfere with the renin-angiotensin system.

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ANSWER TO QUESTION 302

C (Braunwald, pp. 932–937; Tables 47.5–47.7)

All antihypertensive medications have potential side effects that may limit their use. Angiotensin-converting enzyme (ACE) inhibitors lower blood pressure by blocking the formation of angiotensin II and by increasing the circulating concentration of the vasodilator bradykinin. The most common side effect is an annoying dry cough that occurs in in 5% to 20% of patients taking ACE inhibitors, likely related to increased bradykinin.[1] Its incidence is higher in African American and Asian patients compared with Caucasians. The cough may persist for more than 3 weeks after discontinuation of the medication. Substitution with an angiotensin receptor blocker results in a similar antihypertensive effect, without producing cough in the majority of affected patients.

Calcium channel blockers vasodilate and lower blood pressure by interacting with plasma membrane L-type calcium channels in vascular smooth muscle and cardiac myocytes. A common side effect is ankle edema (which arises because of arterial > venous vasodilation). Less common adverse effects include headache, flushing, and gingival hyperplasia. Verapamil and diltiazem can also impair cardiac conduction and cause bradycardia.

Hydralazine is a direct vasodilator with potential adverse effects that include *tachycardia*, flushing, and headaches. These side effects can be prevented, and the antihypertensive effect increased, by co-administration of a beta blocker.

Minoxidil is a direct vasodilator that is occasionally used in patients with renal failure and severe hypertension. Its side effects include a reflex increase in cardiac output, fluid *retention*, and *hirsutism*. Approximately 3% of patients who take minoxidil develop a pericardial effusion, even in the absence of renal or cardiac dysfunction.

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ANSWER TO QUESTION 303

B (Braunwald, p. 935; Table 47.6)

Thiazide diuretics are among the most frequently prescribed first-line agents for the treatment of hypertension. They have a number of important side effects. The most common metabolic disturbance is hypokalemia; the hazard ratio for moderate or severe hypokalemia (≤3.0 mmol/L) with any thiazide exposure is 2.41 (95% confidence interval [CI] 1.28 to 4.53) after adjustment for age, sex, renal function, and use of RAS inhibitors.[1] The serum potassium level falls an average 0.7 mmol/L after institution of 50 mg/day of hydrochlorothiazide, and 0.4 mmol/L with 25 mg/day, but there is almost no decline with 12.5 mg/day.[2] Hypomagnesemia is usually mild but may prevent the restoration of an intracellular deficit of potassium and it should be corrected.

*Hyper*uricemia is present in one-third of untreated hypertensive persons, and it develops in another third during therapy with thiazide diuretics. This is likely a result of increased proximal tubular reabsorption of urate.[2] There may also be a rise in serum calcium (usually <0.5 mg/dL) on thiazide therapy, which is probably secondary to increased proximal tubular reabsorption. Hyponatremia may occur with thiazide therapy, especially in the elderly. Thiazides in higher dosages (≥50 mg daily) may increase the total blood cholesterol, low-density lipoprotein, and triglyceride levels in a dose-related fashion.[3]

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ANSWER TO QUESTION 304

D (Braunwald, pp. 971–974; Tables 48.8 and 48.9; Fig. 48.7)

The HMG-CoA reductase inhibitors (statins) are competitive inhibitors of the rate-limiting enzyme in cholesterol synthesis, primarily in the liver. By reducing the intracellular cholesterol concentration, the expression of cell-surface low-density lipoprotein (LDL) receptors is *increased* (resulting in enhanced removal of LDL particles from the circulation) and the hepatic production of very-low-density lipoprotein (VLDL), the precursor of LDL cholesterol, is *reduced*. As a result of these actions, total and LDL cholesterol levels fall, as do triglycerides, the major component of VLDL particles. Statins are very well tolerated. Reversible elevations of hepatic transaminases (alanine transaminase [ALT], aspartate transaminase [AST]) are almost always asymptomatic and rarely require stopping the drug. Myonecrosis, consisting of muscle aching or weakness in association with a serum creatine kinase level >10 times normal, occurs in <0.5% of patients. This adverse effect mandates immediate discontinuation of the statin. The risk of myopathy is increased when there is concurrent therapy with other drugs that interfere with cytochrome P-450 metabolism of many of the statins. Examples of such drugs include erythromycin, cyclosporine, and antifungal agents.

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ANSWER TO QUESTION 305

D (Braunwald, p. 971; Table 48.7; p. 1651)

Many medications have the potential to alter a patient's lipid profile. Beta blockers, particularly non–beta$_1$-selective agents, increase triglyceride levels and *lower* high-density lipoprotein (HDL) levels. Thiazides tend to *increase* triglyceride levels.

Hormonal replacement therapy with estrogen increases both HDL and triglyceride levels. Despite the augmented HDL effect, the use of estrogen to improve the lipid profile is not recommended because of an associated increase in cardiovascular events.[1] Immunosuppressive drugs and corticosteroids tend to raise triglyceride levels.

Protease inhibitors, for patients with human immunodeficiency virus infection, can induce a dyslipidemic syndrome characterized by elevated triglyceride and total cholesterol levels with decreased HDL levels. Chronic use of protease inhibitors has been associated with an increased risk of myocardial infarction compared with antiretroviral regimens that do not include a protease inhibitor.[2,3]

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ANSWER TO QUESTION 306

B (Braunwald, pp. 965–971; Tables 48.4 and 48.5)

Most clinically encountered lipoprotein disorders arise from an interaction between diet, lack of exercise, excessive weight, and an individual's genetic composition. Genetic lipoprotein disorders may affect low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, lipoprotein (a), and remnant lipoprotein molecules.

Familial hypercholesterolemia (FH) is an autosomal co-dominant disorder that results from defects in the LDL receptor gene.[1] More than 1000 different mutations of the LDL receptor gene have been described. Patients with FH have LDL levels > the 95th percentile for age and gender. Corneal arcus, tendinous xanthomas, and xanthelasmas are common. Men with heterozygous FH usually develop coronary artery disease (CAD) by the third or fourth decade. Affected women present 8 to 10 years later. Familial defective apolipoprotein B, which results from mutations in the apo B gene, is clinically indistinguishable from FH. It results in a reduced affinity of affected LDL particles for the LDL receptor.

Familial combined hyperlipidemia (FCH) is one of the most common familial lipoprotein disorders. It is a polygenic condition with abnormalities that include elevations of LDL and/or triglycerides, a *reduction* in HDL, and elevated apo B levels.[2] Patients with FCH have an *increased* risk of CAD, and there can be considerable clinical overlap between FCH and the insulin-resistance metabolic syndrome. Physical findings such as corneal arcus or xanthomas are rare.

Familial hypertriglyceridemia (type IV hyperlipoproteinemia) is also a polygenic disorder and is characterized by elevated triglycerides with normal or low LDL levels and reduced HDL. Patients do not develop xanthomas or xanthelasmas, and the relationship with CAD is not as strong or consistent as with FCH.

The proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*) encodes a protease that binds to the LDL receptor and targets it for lysosomal degradation. Gain-of-function mutations in this gene decrease the availability of the LDL receptor, which causes *higher* plasma LDL cholesterol levels and an *increased* risk of ischemic heart disease.[3] Loss-of-function mutations in this gene result in lower LDL-cholesterol and coronary event rates.

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ANSWER TO QUESTION 307

C (Braunwald, p. 975; Table 48.8)

Niacin (nicotinic acid) is a B vitamin with lipid-lowering effects when taken at pharmacologic doses. Its primary action is to reduce very-low-density lipoprotein secretion from the liver, which causes a subsequent reduction in intermediate-density lipoprotein and low-density lipoprotein (LDL) levels. In addition, niacin decreases the release of free fatty acids from adipocytes (which are used by the liver for triglyceride synthesis), thus reducing triglyceride levels. In therapeutic doses, niacin reduces LDL cholesterol by 10% to 25% and triglycerides by 20% to 50%, and increases high-density lipoprotein (HDL) cholesterol by 15% to 35%. The increase in HDL cholesterol is caused by decreased catabolism of HDL and apo AI.[1] Niacin also reduces circulating levels of lipoprotein (a). Despite these effects on the lipid profile, its widespread use has been limited historically because of side effects, including flushing, hepatotoxicity, hyperuricemia, hyperglycemia, and gastritis.

In the Coronary Drug Project, a trial of patients with prior MI performed before the statin era, 15-year mortality was reduced in patients randomized to niacin therapy. However, in more recent trials of patients treated aggressively with statin therapy (AIM-HIGH,[2] HPS2-THRIVE[3]), the addition of niacin did not further lower cardiovascular risk compared with the statin alone.

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ANSWER TO QUESTION 308

D (Braunwald, pp. 960–966; Tables 48.1–48.3; Figs. 48.2–48.6)

The apoprotein components of lipoproteins serve several functions, including structural support, receptor recognition, and, in some cases, enzymatic activity. Apo AI is the major protein in high-density lipoprotein (HDL) and its concentration is inversely correlated with angiographic evidence of coronary disease.[1] Circulating apo AI interacts with the ABCA1 transporter on peripheral cell membranes, initiating lipidation of HDL particles. Apo AI also activates the plasma enzyme lecithin-cholesterol acyltransferase, which esterifies free cholesterol, an important step in the reverse cholesterol transport pathway.

The two forms of apoprotein B (apo B48 and apo B100) arise from a *single* gene that displays a unique editing mechanism that allows for synthesis of both proteins.[2] Apo B100 is the primary apoprotein of low-density lipoprotein (LDL), allowing recognition of the particle by the LDL receptor on cell surfaces.

Apoprotein E is found in very-low-density lipoproteins (VLDL) particles as well as in chylomicrons, in intermediate-density lipoprotein (IDL) particles, and, to a small extent, in HDL. Most patients with type III hyperlipoproteinemia (also termed *dysbetalipoproteinemia* or *broad beta disease*) are homozygous for the apoprotein E2/2 genotype. This disorder is characterized by premature atherosclerosis and is notable for both hypercholesterolemia and hypertriglyceridemia owing to an increase in IDL and/or VLDL particle populations.

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ANSWER TO QUESTION 309

E (Braunwald, pp. 968–969 and 974–975)

The relation between triglyceride levels and coronary artery disease (CAD) remains controversial.[1] Although hypertriglyceridemia has been shown to be a risk factor for CAD in univariate analyses, its significance has typically been weakened in multivariable analyses. This is likely due to the association of elevated triglyceride levels with other degenerative conditions, such as diabetes mellitus, chronic renal failure, obesity, cigarette smoking, and excessive alcohol consumption. In addition, it would be difficult to design a trial to isolate the benefits of triglyceride reduction because most antilipidemic agents have multiple effects on the lipid profile. The association between hypertriglyceridemia and cardiovascular risk appears to be stronger in women than in men.[2]

In the ACCORD trial, type 2 diabetic patients already treated with simvastatin achieved a marked reduction in triglycerides with the addition of fenofibrate. However, compared with placebo, clinical outcomes (fatal cardiovascular events, nonfatal myocardial infarction, or stroke) were not reduced by the addition of fenofibrate.[3]

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ANSWER TO QUESTION 310

B (Braunwald, p. 968)

Lipoprotein (a) [Lp(a)] consists of a low-density lipoprotein particle with its apo B100 component linked by a disulfide bridge to apolipoprotein (a) [apo(a)]. Apo(a) is a complex molecule that has sequence homology with plasminogen. The latter structural feature has raised the possibility that Lp(a) may inhibit endogenous fibrinolysis by competing with plasminogen for binding at the endothelial surface.

The primary determinant of Lp(a) levels is genetic; changes in diet and physical activity have no significant impact. In addition, Lp(a) levels vary widely across racial groups and are higher in African Americans compared with whites. In several studies, Lp(a) has been shown to be an independent risk factor for vascular risk. A meta-analysis of 36 prospective studies including more than 12,000 patients found that the adjusted risk ratio of cardiovascular events is 1.13 for each standard deviation increase in Lp(a). Niacin is one of the few interventions that can significantly reduce Lp(a); statin drugs do not. However, no study yet has shown that targeted pharmacologic reduction of Lp(a) improves cardiovascular outcomes.

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ANSWER TO QUESTION 311

B (Braunwald, pp. 974–975)

Fibric acid derivatives (e.g., gemfibrozil, fenofibrate) are used primarily to reduce elevated triglyceride levels. These agents interact with a nuclear transcription factor (PPAR-alpha) that regulates the transcription of the lipoprotein lipase, apo CII, and apo AI genes. The resultant increase in lipoprotein lipase augments hydrolysis of triglycerides from very-low-density lipoproteins (VLDL) at peripheral tissues, which decreases VLDL and plasma triglyceride levels. However, this action may cause low-density lipoprotein (LDL) levels to rise. A meta-analysis of fibrate trials has shown a modest reduction in rates of myocardial infarction but no reduction in mortality.[1]

Fish oils are rich in omega-3 polyunsaturated fatty acids. They *decrease* plasma triglyceride levels by reducing VLDL synthesis and have antithrombotic effects. Such therapy is recommended in cases of hypertriglyceridemia refractory to other conventional therapies. Robust clinical trials to evaluate the efficacy of fish oil in reducing myocardial infarction and stroke are lacking.[2]

Bile acid–binding resins prevent the reabsorption of bile acids from the small intestine, thereby reducing the return of cholesterol to the liver through the enterohepatic circulation, with subsequent upregulation of hepatic LDL receptors.

The latter action enhances removal of LDL from the circulation. Resins are used occasionally as an adjunct to statins in patients with severe elevations of LDL cholesterol. Side effects include constipation, abdominal fullness, and hypertriglyceridemia. In addition, resins can interfere with the absorption of other medications, which therefore should be ingested at least 1 hour before or 3 hours after the resin.

Ezetimibe selectively inhibits cholesterol uptake by intestinal epithelial cells and reduces LDL cholesterol when used alone or in combination with statins. The IMPROVE-IT trial compared the effect of ezetimibe plus simvastatin to simvastatin alone in 18,144 patients with a recent acute coronary syndrome. Patients assigned to combined therapy achieved a median LDL cholesterol of 53.7 mg/dL compared to 69.5 mg/dL in those who received simvastatin alone. The primary outcome (cardiovascular death, acute coronary syndrome, stroke, or need for coronary revascularization) was significantly lower in the ezetimibe plus simvastatin group (32.7% vs. 34.7%, hazard ratio 0.94, $P = .016$).[3]

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ANSWER TO QUESTION 312

C (Braunwald, pp. 1189–1192, 1195; Table 60.5; Figs. 60.8 and 60.9)

This patient's clinical presentation, ECG abnormalities, and troponin elevation are consistent with a non–ST-segment elevation myocardial infarction (NSTEMI). Acute therapy of NSTEMI is directed at clinical symptoms and stabilization of the culprit lesion. Antiplatelet therapy should include aspirin and a $P2Y_{12}$ platelet receptor inhibitor, whether an early invasive or ischemia-guided strategy is pursued.[1] $P2Y_{12}$ inhibitor options for all NSTEMI patients include clopidogrel and ticagrelor. Compared with clopidogrel, ticagrelor has a more rapid onset of action and a faster recovery of platelet function once the drug is stopped. In the PLATO trial, ticagrelor reduced the risk of vascular death, myocardial infarction (MI), or stroke compared with clopidogrel, without an increase in major bleeding.[2] As a result, a class IIa recommendation of the 2016 American College of Cardiology/American Heart Association (AHA/ACC) dual antiplatelet therapy guidelines is that it is reasonable to prescribe ticagrelor in preference to clopidogrel for NSTEMI patients.[3] A potential disadvantage of ticagrelor compared with clopidogrel is a shorter half-life, necessitating twice daily dosage. Of note, ticagrelor's advantage over clopidogrel in the PLATO trial was found only in patients taking ≤100 mg aspirin daily, such that ticagrelor-treated patients should not take higher doses of aspirin. For patients directed to an early invasive strategy, a third $P2Y_{12}$ inhibitor option is prasugrel, which, like clopidogrel, is a thienopyridine drug and an irreversible antagonist of the platelet $P2Y_{12}$ receptor. Prasugrel's onset of action is more rapid than that of clopidogrel, and in the TRITON-TIMI 38 trial of acute coronary syndrome patients for whom percutaneous coronary intervention was planned, prasugrel reduced the incidence of cardiovascular death, MI, or stroke by 19%, but at a cost of significantly increased bleeding.[4] The bleeding risk was greatest in patients ≥age 75 and in those with reduced body weight (≤60 kg), such that those populations derived no net benefit from prasugrel, and patients with a history of stroke or transient ischemic attack (TIA) actually experienced net harm. The patient in this vignette has a history of TIA and he should not receive prasugrel.

The two general treatment pathways of patients with NSTEMI are (1) an early invasive strategy (coronary angiography with revascularization as appropriate) and (2) a more conservative ischemia-guided strategy in which patients proceed to invasive evaluation only if they develop recurrent ischemic symptoms despite medical therapy, either spontaneously or on noninvasive stress testing. AHA/ACC guidelines recommend an early invasive strategy for initially stabilized patients who are at high risk for clinical events, using risk stratification models such as the TIMI (Table 3.2) or GRACE risk scores.[1] The patient presented in this vignette has high TIMI and GRACE scores (calculated at 6 and 176, respectively), such that proceeding to an early invasive strategy would be appropriate.

TABLE 3.2 TIMI Risk Factors and Risk of Cardiovascular Endpoint

TIMI Risk Factors
Age 65 years or older ≥3 CAD risk factors Known CAD (>50% stenosis) Previous aspirin use ≥2 anginal episodes in previous 24 h ST deviation ≥0.5 mm on initial ECG Elevated cardiac biomarkers

NUMBER OF TIMI RISK FACTORS	RISK OF CARDIOVASCULAR ENDPOINT[a] AT 14 DAYS (%)
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

[a]Cardiovascular endpoints are death, myocardial infarction, or urgent revascularization.

CAD, Coronary artery disease.

Data from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. *2000;284:835.*

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ANSWER TO QUESTION 313

C (Braunwald, pp. 1352–1357; eFigs. 65.1–65.6, 65.8; Figs. 65.1–65.3, 65.6, 65.7)

In the United States, stroke is the third leading cause of death; only heart disease and cancer are more common. Each year, more than 795,000 strokes occur, and of these, ~185,000 are recurrent events in patients with a history of stroke. Treatable risk factors for ischemic stroke include hypertension, diabetes, and cigarette smoking.[1]

Blood pressure lowering is safe and beneficial in the period after an ischemic stroke, and the American Stroke Association recommends such therapy. For example, in the PROGRESS trial,[2] 6105 stable patients with a recent stroke were randomized to placebo or antihypertensive therapy with an angiotensin-converting enzyme inhibitor and diuretic. After 4 years, the relative risk of a new stroke declined by 28% in the patients randomized to the medical regimen compared with placebo.

Although data relating hypercholesterolemia to stroke risk have been equivocal, statins have been shown to reduce the incidence of stroke in patients at increased risk of vascular disease. A meta-analysis of 90,000 patients in cholesterol-lowering trials showed that each 10% reduction in low-density lipoprotein (LDL) level reduced the risk of stroke by 15.6%. In the Heart Protection Study (see Answer to Question 424), treatment with simvastatin was associated with a highly significant reduction in stroke rates. In the SPARCL study, 4731 patients with a history of cerebrovascular disease (recent stroke or transient ischemic attack [TIA]) and baseline LDL 100 to 190 mg/dL, but no known coronary disease, were randomized to atorvastatin 80 mg daily or placebo. After a mean follow-up of 4.9 years, there was a 16% reduction in subsequent stroke rates.[3]

Aspirin, or the combination of aspirin plus dipyridamole, has been shown to be effective for secondary prevention of ischemic stroke. In the MATCH trial, the combination of aspirin plus clopidogrel was compared with aspirin alone in 7599 patients who had sustained an ischemic stroke or TIA.[4] After 18 months, there was a nonsignificant reduction in the primary outcome (a composite of ischemic stroke, TIA, myocardial infarction, or vascular death) without a difference in all-cause mortality; life-threatening bleeding was higher in the combination group. Thus, dual antiplatelet therapy with aspirin and clopidogrel is not routinely recommended for secondary prevention after ischemic stroke.

In the PRoFESS study, aspirin plus dipyridamole was comparable with clopidogrel monotherapy for secondary stroke prevention in patients with noncardioembolic stroke; however, there were more major hemorrhages in the aspirin plus dipyridamole group.[5]

In three large trials of aspirin versus vitamin K antagonists (VKAs), VKAs did not reduce ischemic events but they increased the risk of intracranial hemorrhage.[2]

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ANSWER TO QUESTION 314

D (Braunwald, pp. 901–903)

Alcohol's interaction with the cardiovascular system is complex. Heavy alcohol intake is associated with increased cardiovascular and total mortality rates. However, several primary and secondary prevention studies have found that the relation between alcohol intake and cardiovascular disease is J-shaped, in that moderate (1 to 2 drinks) daily intake of alcohol is associated with lower risk compared with individuals who do not drink any alcoholic beverages.[1] Alcohol's beneficial effects may be a result of its ability to raise high-density lipoprotein levels, improve fibrinolysis, and reduce platelet aggregation. Alcohol intake is not associated with decreased low-density lipoprotein levels.

REFERENCE

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ANSWER TO QUESTION 315

D (Braunwald, pp. 878–880; Fig. 45.4)

Cigarette smoking is one of the strongest risk factors for coronary artery disease but is also one of the hardest to modify.[1] Among its deleterious effects, smoking increases platelet aggregation, serum fibrinogen, and oxidation of low-density lipoprotein cholesterol. Patients who continue to smoke after a myocardial infarction have twice the mortality rate of those who stop.

Observational studies show that smoking cessation reduces the risk of a coronary event by 50% within 2 years, compared with patients who continue to smoke. The cardiovascular risk approaches a person who never smoked after 3 to 5 years of smoking cessation.

Addiction to nicotine can be intense. Patients who successfully quit smoking usually do so after five or more unsuccessful attempts. Physician counseling alone carries a poor success rate, with only 6% of patients achieving 1 year of abstinence. Greater success is achieved when pharmacologic aids are included in the treatment program, along with counseling. Agents approved by the US Food and Drug Administration for smoking cessation include (1) nicotine replacement therapy (available as patches, gums, lozenges, nasal spray, and an inhaler), (2) the psychoactive drug bupropion, and (3) varenicline, a partial nicotinic acetylcholine receptor agonist.

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ANSWER TO QUESTION 316

D (Braunwald, pp. 897–899, 1046–1049; Fig. 54.2)

Comprehensive rehabilitation for patients with coronary disease includes physical exercise training, which benefits the cardiovascular system and skeletal muscle in ways that improve work performance. Different formats for outpatient physical activity include supervised and unsupervised programs. In supervised programs, the aerobic training goal is typically exercising to 70% to 80% of the maximum predicted heart rate; some patients may require lower intensities. In unsupervised home programs, patients are encouraged to exercise to the onset of mild dyspnea, which eliminates the need for monitoring the pulse rate.

Several meta-analyses have studied the relation between exercise-based cardiac rehabilitation and clinical outcomes and have come to similar conclusions: mortality rates are lower among exercise-program participants compared with patients who did not participate.[1] Most of the studies included in these meta-analyses were performed before the current era of aggressive revascularization and may overestimate the expected mortality results in current practice.

During exercise, an increase in heart rate accounts for a greater percentage of the augmented cardiac output than does the rise in stroke volume. In addition, at rest, the heart extracts about 75% of oxygen in the coronary flow. Because of the limited reserve, any increase in myocardial oxygen demand must be met by augmentation of coronary blood flow. With physical training, half the improvement in exercise performance is due to increased cardiac output and half to peripheral adaptations that actually improve oxygen extraction.

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ANSWER TO QUESTION 317

E (Braunwald, p. 902)

Homocysteine is an amino acid derived from the demethylation of dietary methionine. Inherited disorders of methionine metabolism cause extremely high levels of homocysteine as well as homocystinuria. The most common cause of severe hyperhomocystinemia is cystathionine beta-synthase deficiency. Patients with this genetic defect present with atherothrombosis as early as the first decade of life. In contrast, mild to moderate elevations in homocysteine (>15 µmol/L) are common in the general population. Such elevations are often due to insufficient dietary intake of folate, use of folate antagonists such as methotrexate, polymorphisms in the methylene tetrahydrofolate reductase gene, hypothyroidism, or renal insufficiency.

A large number of epidemiologic studies have shown a link between mildly elevated homocysteine levels and atherosclerosis.[1] Folic acid supplementation can decrease homocysteine levels by approximately 25%. Additional vitamin B_{12} supplementation typically reduces levels by another 7%. Nevertheless, clinical studies that have included over 37,000 subjects have shown that reduction in plasma homocysteine concentration with B-vitamin supplements does not reduce the risk of atherothrombotic events.[2]

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ANSWER TO QUESTION 318

D (Braunwald, pp. 998–1002)

Metabolic syndrome is a common constellation of risk factors that greatly increases the risk of cardiovascular disease. Insulin resistance, the underlying abnormality in metabolic syndrome, may in part explain the association between hyperglycemia and atherosclerosis. Because it precedes overt diabetes mellitus, insulin resistance may also explain why many patients with newly diagnosed type 2 diabetes already have extensive vascular disease. The severity of insulin resistance correlates with the rates of myocardial infarction, stroke, and peripheral arterial disease, whereas decreasing insulin resistance pharmacologically may reduce vascular events.[1]

Early study of metabolic syndrome was hampered by the absence of a universal definition of this process. In 2009, a joint definition of metabolic syndrome was published by the International Diabetes Federation, the U.S. National Heart, Lung and Blood Institute, and the American Heart Association. According to this definition, metabolic syndrome exists when three or more of the following are present: fasting serum glucose ≥110 mg/dL, abdominal obesity (waist circumference above a region/ethnicity-specific threshold, generally >85 to 102 cm in men or >80 to 90 cm in women), serum triglycerides ≥150 mg/dL, low serum high-density lipoprotein cholesterol (<40 mg/dL in men or <50 mg/dL in women), and hypertension (systolic BP ≥130 and/or diastolic BP ≥85 mm Hg).[2]

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ANSWER TO QUESTION 319

D (Braunwald, pp. 928–930; Fig. 47.1; Tables 47.1–47.4)

Many nonpharmacologic approaches have been proposed for treatment of hypertension. In addition to dietary approaches, commonly used complementary and alternative medicine practices are hypnotherapy, relaxation, meditation, music therapy, acupuncture, yoga, and biofeedback. The Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes consumption of fruit, vegetables, and low-fat dairy products, with low intake of saturated fat, reduced systolic blood pressure by ~10 mm Hg and diastolic blood pressure by 5 mm Hg among hypertensives.[1] Garlic contains a compound (allicin) that *inhibits* angiotensin II, thus inducing

vasodilation and blood pressure reduction. A meta-analysis of garlic ingestion in hypertensives showed a blood pressure reduction of 9.1 mm Hg systolic and 3.8 mm Hg diastolic at a daily dose of approximately 600 to 900 mg.[2] There was a high degree of heterogeneity and overall low quality of evidence in this meta-analysis.

Slow breathing has been shown to increase parasympathetic activity and reduce sympathetic activation. Use of a device-guided biofeedback program of slow breathing has been shown to be associated with a significant blood pressure reduction in a meta-analysis of eight studies, though there was significant variation in the study results.[3] Although a small number of studies have suggested a possible acute, nonsustained improvement in blood pressure with acupuncture, the overall data quality is poor and two meta-analyses concluded that the current evidence is inconclusive.[4]

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ANSWER TO QUESTION 320

C (Braunwald, p. 991; Tables 49.1 and 49.2)

Several clinical trials have examined the effects of diet on reducing cardiovascular events. The Lyon Diet Heart study randomized patients with coronary artery disease to either a Mediterranean-style diet (rich in fruits, legumes, vegetables, and fiber and reduced meat, butter, and cream), supplemented with alpha-linolenic acid–enriched margarine, or a control diet. Despite a similar percentage of total fat in each diet and similar lipid profiles, there was a significant reduction in all-cause mortality and nonfatal myocardial infarction in the Mediterranean-style diet group compared with the control group.[1] In the primary prevention PREDIMED study, individuals without known cardiovascular disease, but who were at increased risk, were randomized to a Mediterranean-style diet (supplemented with extra-virgin olive oil or mixed nuts) or a control diet with advice to reduce dietary fat intake. After a median follow-up of 4.8 years, there were fewer cardiac events in the patients randomized to the Mediterranean diets (hazard ratio [HR] ~0.7).[2]

A pooled estimate of two randomized controlled trials of either regular fatty fish consumption (200 to 400 g/week) or fish oil supplementation (~900 EPA and DHA per day) in coronary artery disease patients showed a reduction in mortality (HR 0.77; 95% confidence interval [CI] 0.66 to 0.89).[3]

A diet of reduced-carbohydrate, high-protein, and high-fat content was shown to result in greater weight loss at 12 months, increased high-density lipoprotein, and reduced triglycerides when compared with a low-calorie, high-carbohydrate, low-fat diet, but has not been shown in controlled trials to reduce cardiovascular events.[4]

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ANSWER TO QUESTION 321

C (Braunwald, pp. 1123–1168; Fig. 59.34, eFig. 59.10)

Aspirin has proven efficacy in acute treatment and secondary prevention of myocardial infarction (MI).[1] Clinical trials support the administration of 325 mg in the acute setting and 81 to 162 mg/day in chronic usage.[1] Studies prior to the acute reperfusion era showed that beta blocker therapy initiated during the convalescent phase of ST-elevation MI (STEMI) reduced long-term mortality by 23%. Observational studies in patients who have undergone primary percutaneous coronary intervention for STEMI also generally support the use of beta blocker therapy for secondary prevention.[2] In the absence of contraindications, AHA/ACC guidelines recommend oral beta blocker therapy for at least 2 to 3 years post-MI.[1]

Angiotensin-converting enzyme (ACE) inhibition is another important therapy during and after hospitalization for MI. In large clinical trials, more than 120,000 patients have been randomized to an ACE inhibitor or placebo in the setting of acute MI (regardless of left ventricular [LV] function), and the results are consistent: ACE inhibitors reduce morbidity and mortality during and after the acute event. The greatest benefit accrues during the first week post-MI, especially in the highest-risk patients. Putative beneficial effects include vasodilatation, increased production of nitric oxide, decreased aldosterone secretion, lowered sympathetic tone, and reduced adverse LV remodeling. In addition, in patients with documented LV dysfunction after MI, ACE inhibitor use has been associated with a 20% to 30% relative risk reduction in mortality over approximately 3 years of follow-up.[3]

Many studies support the benefit of statin therapy for secondary prevention after MI.[4] The 4S and CARE trials examined the effects of statins after MI among patients with elevated and average cholesterol levels, respectively. Each demonstrated a marked reduction in cardiovascular death and MI in patients randomized to the cholesterol-lowering regimen. The PROVE IT—TIMI 22 trial of patients with an acute coronary syndrome showed superior long-term outcomes with a high-intensity statin (atorvastatin 80 mg daily) compared with less intense therapy (pravastatin 40 mg daily), such that higher-dose regimens are the standard of care.[5,6]

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ANSWER TO QUESTION 322

A (Braunwald, pp. 967–968; Tables 48.5 and 48.6)

Inherited mutations in familial hypercholesterolemia (FH) occur in the gene that codes for the low-density lipoprotein (LDL) receptor. Heterozygotes inherit one mutant gene and one normal gene and therefore produce only half the normal number of receptors. Heterozygote FH affects about 1 in 500 persons, with an even higher frequency in populations with a founder effect. Homozygotes inherit two mutant alleles and so have virtually no LDL receptors. Physicians rarely see homozygotes, whose frequency in the population is 1 in 1 million.

FH heterozygotes commonly present with tendon xanthomas, which are nodules that may involve the Achilles tendon and various extensor tendons of the forearm and leg. They consist of deposits of cholesterol derived from LDL particles. Cutaneous planar xanthomas occur only in homozygotes and usually manifest within the first 6 years of life. These xanthomas are yellow to bright orange and occur over areas of trauma. Both the heterozygous and homozygous forms of FH are associated with an increased incidence of coronary artery disease, the homozygous form far more severely than the heterozygous form. The presence of FH may be verified by assaying the density of functional LDL receptors on circulating lymphocytes or by genetic testing, although this is rarely clinically necessary.

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ANSWER TO QUESTION 323

B (Braunwald, pp. 968–969)

Familial hypertriglyceridemia is a relatively common disorder in which the concentration of very-low-density lipoprotein is elevated in the plasma.[1] The prevalence is between 1 in 100 and 1 in 50. Affected patients do not usually exhibit hypertriglyceridemia until puberty or early adulthood, at which time plasma triglyceride levels are moderately elevated, in the range of 200 to 500 mg/dL. Both low-density lipoprotein and high-density lipoprotein (HDL) cholesterol levels are usually reduced. These individuals exhibit only a slightly increased incidence of atherosclerosis, and it is unclear whether this is caused by the hypertriglyceridemia, by accompanying decreases in HDL cholesterol, or by associated illnesses. Patients with hypertriglyceridemia can experience severe exacerbations, with plasma triglyceride levels as high as 1000 mg/dL, when exposed to a variety of precipitating factors (e.g., excessive alcohol ingestion, poorly controlled diabetes, use of birth control pills containing estrogen, or hypothyroidism), or even after a meal. Such high triglyceride levels may lead to pancreatitis and eruptive xanthomas.

The disorder appears to be genetically heterogeneous in that patients from different families may have different mutations. No consistent abnormalities of lipoprotein structure or receptor function have been described. Lipoprotein electrophoresis shows an increase in the prebeta fraction (type IV lipoprotein pattern). Affected individuals can often be treated by controlling the exacerbating conditions, such as obesity, and restricting the intake of fats and alcohol.[2]

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ANSWER TO QUESTION 324

B (Braunwald, pp. 1283–1284; Table 62.2; see also Answer to Question 388)

Stent thrombosis is an uncommon, but potentially devastating complication of coronary stenting. Stent thrombosis that occurs immediately after stent implantation is referred to as *acute thrombosis*, an occurrence within the first month is termed *subacute thrombosis*, and *late thrombosis* denotes cases that occur thereafter. Stent thrombosis is effectively prevented by the combination of aspirin and an inhibitor of the platelet $P2Y_{12}$ receptor (e.g., clopidogrel, prasugrel, or ticagrelor). In the case of bare metal stents, the risk of thrombosis becomes negligible after 1 month of such therapy. However, drug-eluting stents (DES) retard the development of neointima such that there is a more prolonged exposure of the thrombogenic surface to circulating blood elements, necessitating a longer duration of dual antiplatelet medications. While newer-generation DES appear to manifest lower rates of stent thrombosis than first-generation devices, the current recommendation is that at least 12 months of dual antiplatelet therapy be administered following DES placement.[1] Clinical decision tools are currently under study to clarify which patients would be expected to benefit from

even longer duration of $P2Y_{12}$ inhibitor therapy,[2] versus shorter duration for those at high bleeding risk.

The strongest predictor for stent thrombosis is premature cessation of antiplatelet therapies. Other factors that increase this risk include stent placement in small vessels, long stents, overlapping stents, multiple lesions, ostial or bifurcation lesions, prior brachytherapy, a suboptimal stent result (e.g., under-expansion or residual dissection), low ejection fraction, diabetes mellitus, and renal failure.

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ANSWER TO QUESTION 325

D (Braunwald, pp. 1344–1346)

The patient described in this question has likely experienced renal atheroembolism, triggered by the catheterization procedure. Atheroemboli can be produced by mechanical manipulation of the aorta via catheters or surgery, and the kidneys are common targets for such embolism. This complication can result in acute renal failure with a stepwise decline in function. Some patients may progress to end-stage renal disease, whereas others recover full kidney function. The emboli may lodge in terminal arteries of the kidney, causing localized glomerular ischemia, or may compromise the large arteries and result in the loss of entire renal function.[1,2]

The urinalysis is often unremarkable, with only mild proteinuria and a bland sediment. Rarely, lipid droplets in the urine can be observed. Peripheral eosinophilia and low serum complement levels may be present. Livedo reticularis, the purple discoloration described in this patient and shown in the figure, occurs in 50% of patients and is due to areas of impaired perfusion, most often in the lower extremities. Other cutaneous manifestations of atheroembolic disease include purple toes, purpura, and gangrene. Often, the diagnosis of renal embolization can be made on clinical grounds alone. If there is cutaneous involvement, biopsy of the skin and muscle may be helpful. Renal biopsy may provide useful information, but carries a significant complication rate. The management of atheroemboli centers on supportive care, which may include hemodialysis. Large emboli may be amenable to surgical or catheter removal.

Contrast nephropathy after angiographic procedures can also result in renal insufficiency. Findings that point to atheroemboli rather than a contrast effect as the cause of renal dysfunction include: (1) evidence of peripheral emboli to other sites (e.g., the cutaneous manifestations described in the previous paragraph), (2) the presence of eosinophilia and reduced complement levels, and (3) prolonged renal dysfunction (e.g., >1 week).

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ANSWER TO QUESTION 326

C (Braunwald, pp. 961–967; Figs. 48.4–48.6)

Low-density lipoprotein (LDL) is the major cholesterol-carrying component of the plasma. It is formed mainly from metabolism of hepatic-derived very-low-density lipoprotein (VLDL) in the circulation: VLDL undergoes hydrolysis by lipoprotein lipase to form intermediate-density lipoprotein, which is then further delipidated by hepatic lipase to form LDL. The major lipid components of LDL are esterified cholesterol and triglyceride. Apo *B100* is the predominant protein present in LDL and comprises approximately 25% of LDL mass. Cells internalize LDL after it binds to cell surface LDL receptors.

Familial hypercholesterolemia is an autosomal dominant disorder caused predominantly by mutations in one of three genes (the LDL receptor gene, the apolipoprotein B gene, and the *PCSK9* gene) resulting in plasma LDL cholesterol levels >190 mg/dL and often premature coronary artery disease. Approximately 7% of American adults have a plasma LDL ≥190 mg/dL, but fewer than 2% of such individuals actually have a familial hypercholesterolemia mutation.[1]

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ANSWER TO QUESTION 327

A (Braunwald, pp. 872, 890–893; Figs. 45.13–45.15)

C-reactive protein (CRP), a circulating member of the pentraxin family, plays an important role in innate immunity. It is formed primarily in the liver, but is also elaborated from coronary arteries, especially atherosclerotic intima. Levels of CRP are elevated in inflammatory states and multiple epidemiologic studies have demonstrated that CRP measured by high-sensitivity assays (hsCRP) is strongly associated with myocardial infarction, stroke, peripheral arterial disease, and sudden death.[1] hsCRP levels can be classified as low (<1 mg/L), intermediate (1 to 3 mg/L), or high (>3 mg/L). In patients with acute coronary events, high hsCRP levels are associated with worse outcomes, including increased mortality.[2]

An elevated level of hsCRP also predicts the onset of type 2 diabetes, perhaps because it correlates with insulin sensitivity, endothelial dysfunction, and hypofibrinolysis. Many medications lower hsCRP levels, in particular statins, fibrates, and niacin. Statin therapy reduces hsCRP levels largely unrelated to the low-density lipoprotein-lowering effect.[3] Furthermore, statin therapy has been shown to benefit patients with relatively normal LDL, if the hsCRP is elevated. In the JUPITER trial, rosuvastatin resulted in a 44% reduction in vascular events in apparently healthy individuals with baseline LDL <130 mg/dL and hsCRP >2 mg/L.[4,5]

Aspirin does not directly lower hsCRP levels, but appears to have the greatest cardiovascular benefit in patients with elevated baseline hsCRP.

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ANSWER TO QUESTION 328

D (Braunwald, pp. 922–923; Fig. 46.6; Table 46.6)

As reviewed in the Answer to Question 297, there are two major forms of renovascular disease—atherosclerosis and fibromuscular dysplasia. Atherosclerotic patients are older and have higher systolic blood pressure, greater target organ damage, and evidence of atherosclerotic disease elsewhere. Patients with fibromuscular hyperplasia are younger, are more often female, have no family history of hypertension, and have less evidence of target organ damage. Patients with fibromuscular dysplasia are less likely to progress to complete renal artery occlusion or develop ischemic nephropathy compared with patients with atherosclerotic renal artery stenosis.

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ANSWER TO QUESTION 329

E (Braunwald, pp. 930–931; Table 47.11)

Hypertension frequently accompanies diabetes and greatly augments the risk of cardiovascular events in this population. Control of hypertension reduces future cardiovascular events in diabetics even more than in nondiabetics, and all diabetics with a persistent blood pressure (BP) >130/80 mm Hg should be on antihypertensive therapy.[1] Many BP lowering agents, including diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta blockers, have been shown to improve blood pressure control in diabetics, and there has been much controversy about whether one group is superior to others in reducing cardiovascular morbidity and mortality. Early small studies suggested that ACE inhibitors were superior to dihydropyridine calcium channel blockers in this regard. However, the United Kingdom Prospective Diabetes Study (UKPDS), Systolic Hypertension in Europe (Sys-Eur), and HOT trials found that the degree of blood pressure control is more important than the agents used to achieve it; the antihypertensives captopril, atenolol, and the dihydropyridine calcium channel blockers felodipine and nitrendipine all led to beneficial reductions in cardiovascular events.

Drugs that interfere with the renin-angiotensin system do appear to have a special place in the treatment of diabetic patients, especially with renal disease.[2] In patients with type 1 diabetes, ACE inhibitors slow the progression of diabetic nephropathy and end-stage renal disease, and several studies have demonstrated that ARBs provide similar benefit in patients with type 2 diabetes. Furthermore, in the Heart Outcomes and Prevention Evaluation study, the ACE inhibitor ramipril reduced cardiac events, stroke risk, and death in diabetic patients.[3] The Losartan Intervention For Endpoint study randomized 1195 diabetic patients with hypertension and left ventricular hypertrophy to the ARB losartan or atenolol therapy.[4] Although blood pressure control was similar in both groups, those who received the ARB had reduced all-cause mortality.

In the ACCORD trial, very aggressive reduction of BP, targeting systolic BP <120 mm Hg, was compared with "standard" therapy at the time (target systolic BP <140 mm Hg) in 4733 type 2 diabetics without advanced renal dysfunction.[5] The more aggressive blood pressure lowering *failed* to reduce the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes over a mean follow-up of 4.7 years. While intensive therapy led to a reduction of the prespecified secondary outcome endpoint of stroke, it also caused significantly more serious adverse effects, including hypotension, bradycardia, hyperkalemia, syncope, and renal failure.

Based on results from major trials, the 2017 American hypertension practice guideline recommends a treatment BP goal of <130/80 mm Hg in diabetics.

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ANSWER TO QUESTION 330

D (Braunwald, pp. 1128–1134; Tables 59.4 and 59.5; Figs. 59.5, 59.9, 59.11; eFigs. 59.3 and 59.5)

Primary percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction has several important differences and advantages when compared with pharmacologic fibrinolysis. The safety and success rate in establishing reperfusion (>90%) is superior to that of fibrinolytic agents, and there is less likelihood of developing complications such as reocclusion, re-infarction, and stroke with primary PCI. Multiple studies have demonstrated that primary PCI, when performed at experienced centers, results in a significant reduction in the rates of death (7% vs. 9%), reinfarction (3% vs. 9%), stroke (1% vs. 2%), and hemorrhagic

stroke (0.05% vs. 1%) compared with fibrinolysis.[1–3] In addition, primary angioplasty has been associated with shorter hospital stays and lower follow-up costs. Patients presenting with an acute myocardial infarction and cardiogenic shock are at the highest risk of death and cardiovascular complications. The SHOCK trial randomized 302 patients with cardiogenic shock to early revascularization or medical management. Early revascularization with primary PCI or urgent bypass surgery was associated with improved survival at 6 months (49.7% vs. 36.9%, P = .027) and 1 year (46.7 vs. 33.6%, P = .025).[4]

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ANSWER TO QUESTION 331

A (Braunwald, pp. 1151–1162; Fig. 59.24)

Part *A* of the image is a right anterior oblique caudal view of the left coronary artery showing total proximal occlusion of the left anterior descending (LAD), the presumed culprit lesion. Within the mid-left circumflex (LCx) there is an 80% stenosis. Part *B* is a left anterior oblique view of the right coronary artery (RCA) showing a 60% stenosis of the mid-vessel and 90% stenosis of the distal vessel.

Approximately half of patients who undergo coronary angiography for ST-segment elevation myocardial infarction (STEMI) have multivessel disease.[1] Historically, percutaneous coronary intervention (PCI) of a non-infarct related artery at the time of primary PCI for STEMI in hemodynamically stable patients was a class III (considered harmful) recommendation of American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[2] This caution was based on the combination of observational data and safety concerns, including increased contrast exposure and longer procedure times, as well as concern for a possibly increased risk of stent thrombosis during the heightened inflammatory state of the acute STEMI.

Subsequent to the 2013 ACC/AHA STEMI guidelines, four randomized controlled trials of multivessel PCI at the time of primary PCI, or as a planned, staged procedure, have been reported and have led to reconsideration of this recomendation.[1] These trials were PRAMI,[3] CvLPRIT,[4] DANAMI-3-PRIMULTI,[5] and PRAGUE-13.[6] In three of these trials, a strategy of multivessel PCI (at the time of primary PCI or a later planned, staged procedure) was shown to be safe and to benefit composite cardiovascular outcomes (PRAMI: hazard ratio [HR] 0.35 [95% confidence interval (CI) 0.21 to 0.58], P < .001; CvLPRIT: HR 0.49 [95% CI 0.24 to 0.84], P = .009; DANAMI-3-PRIMULT: HR 0.56 [95% CI 0.38 to 0.83], P = .004). However, in the PRAGUE-13 trial, randomization to revascularization of all ≥70% diameter non-infarct stenoses did not result in improved cardiovascular outcomes (death, nonfatal MI, stroke) compared with culprit-only PCI.

As a result of these newer trials, the 2016 focused update STEMI guidelines upgraded the recommendation of multivessel PCI at the time of primary culprit vessel PCI, or as a subsequent staged procedure, in hemodynamically stable patients, to class IIb ("may be reasonable").[1]

The patient in this question presents with an acute anterior STEMI with proximal occlusion of the LAD, the culprit vessel, as well as high-grade lesions within the LCx and RCA. The LAD should be reperfused expeditiously. Consideration may be given to PCI of the LCx and/or RCA at the time of the LAD PCI or as a staged procedure in this hemodynamically stable patient.

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ANSWER TO QUESTION 332

E (Braunwald, p. 1083)

Studies have revealed that atrial infarction occurs in 7% to 17% of autopsy-proven cases of myocardial infarction. Atrial infarction is often seen in conjunction with left ventricular infarction and more commonly involves the right atrium than the left. This difference may reflect the presence of well-oxygenated blood in the left atrium, which could help nourish an ischemic atrial wall. Atrial infarction is frequently accompanied by supraventricular arrhythmias, including atrial fibrillation, sinus arrhythmia, and wandering atrial pacemaker. In addition, atrial infarction may be complicated by rupture of the atrial wall.

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ANSWER TO QUESTION 333

A (Braunwald, pp. 1155–1159; Table 59.11; Figs. 59.27–59.30; eFig. 59.8)

Free wall rupture is one of the most lethal complications of acute myocardial infarction (MI) because it usually leads to hemopericardium and cardiac tamponade. Rupture typically arises after a large MI in the left anterior descending artery territory at the junction of infarcted and normal muscle. Whereas older series have quoted an incidence of free wall rupture of approximately 5%, occurring within 3 to 6 days after MI, more recent observations implicate an incidence of 1% to 2%, occurring primarily within the first 48 hours.[1] Patients with free wall rupture tend to have had greater delays to hospitalization and are more likely to have been physically active after the onset of MI. Additional risk factors include advanced age, female gender, a history of hypertension, and the *absence* of previous infarction. It is thought that patients with prior MI are "protected" against rupture, because previous scars may reduce the magnitude of the shear forces between the fresh infarct and the healthy myocardium.[1] The rate of free wall rupture is lower after primary percutaneous coronary intervention than after fibrinolytic therapy.[2]

The frequency of free wall rupture has decreased over the past 30 years, and survival has improved but remains poor.[2]

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ANSWER TO QUESTION 334

B (Braunwald, pp. 1153–1154; Fig. 59.26)

Patients with right ventricular infarction (RVI) may have a hemodynamic profile that resembles that of patients with pericardial disease. For example, elevations in right atrial (RA) and right ventricle (RV) filling pressures, as well as a rapid RA *y* descent and an early diastolic dip-and-plateau ("square root sign") may occur. In addition, the Kussmaul sign may be present in patients with RVI and is highly predictive for RV involvement in the setting of inferior wall infarction.[1,2] Patients who present with inferior wall infarction who are suspected of having RV involvement should have an ECG obtained with precordial leads placed on the right side of the chest: most patients with RVI demonstrate ST-segment elevation of 1 mm or more in lead V_4R (not standard lead V_4).[3] Echocardiography can confirm the presence of RV dilatation and depression of systolic function and is able to distinguish RVI from other hemodynamically similar conditions, including pericardial tamponade and constrictive pericarditis.

From a hemodynamic standpoint, treatment is typically aimed at increasing RA and RV filling pressures through administration of intravenous fluids, so as to maintain normal left-sided preload. A marked hypotensive response to nitroglycerin may be a clinical clue to the presence of RVI, reflecting the impact of RV filling pressure in this condition. Similarly, the contribution of atrial contraction to RV filling is important in patients with RVI. Thus, patients who require pacemaker therapy benefit from atrioventricular sequential pacing, which has been shown to improve hemodynamic parameters in this condition.

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ANSWER TO QUESTION 335

C (Braunwald, pp. 1156–1158; Fig. 59.31)

The progressive development of mitral regurgitation (MR) in this 60-year-old patient after an inferior myocardial infarction (MI) is most consistent with infarction of the posterior papillary muscle. Because papillary muscles are perfused via terminal portions of the coronary vascular bed, they are particularly vulnerable to ischemia. The posterior papillary muscle, supplied usually by only the posterior descending branch of the right coronary artery, is more susceptible to ischemia and infarction than the anterolateral papillary muscle, which has a dual blood supply from the diagonal branches of the left anterior descending artery and the marginal branches from the left circumflex artery. Although necrosis of a papillary muscle is a potential complication of MI, particularly of inferior infarction, frank rupture is far less common. Total papillary muscle rupture is usually fatal because of the extremely severe and rapid-onset MR that it produces. MR may also develop later after MI, in which case it usually results from left ventricular dilatation. In that case, dyskinesis of the left ventricle results in an abnormal spatial relationship between the papillary muscles and the chordae tendineae, hence promoting MR.

Rupture of chordae tendineae is also an important cause of MR, although such an event bears no special relation to MI. Common causes of chordal rupture include congenitally abnormal chordae, infective endocarditis, trauma, rheumatic fever, and myxomatous degeneration. Posterior chordae rupture spontaneously more frequently than do anterior chordae.

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ANSWER TO QUESTION 336

B (Braunwald, p. 1163)

Post-myocardial infarction (MI) pericarditis has become uncommon in the era of acute coronary reperfusion therapies, likely because current pharmacologic and mechanical interventions limit infarct size. In a modern series, the incidence of early post-MI pericarditis in 743 patients with acute ST-segment elevation myocardial infarctions treated with primary percutaneous coronary intervention was 4.2%, with an increasing prevalence in patients with longer delays to hospital presentation.[1] Post-MI pericarditis can develop as early as the first day after the infarction. The diagnosis is often based on the presence of pleuritic, positional chest pain that may radiate to the trapezius ridge and/or a pericardial friction rub; typical ECG changes of pericarditis are

less common. Post-MI pericardial effusions are found most often in patients with larger infarcts, when congestive heart failure is present, and in the setting of an anterior MI; progression to tamponade is rare. Early post-MI pericarditis is best treated with high-dose aspirin (e.g., 650 mg 4 to 6 times daily); other nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids should be avoided, as they may interfere with healing of the infarct.[2,3] Colchicine therapy has not been formally studied for this type of pericarditis. Anticoagulation should be avoided if possible in the setting of post-MI pericarditis to avoid the uncommon complication of hemorrhagic tamponade.

Dressler syndrome is a form of pericarditis that may occur 1 to 8 weeks after infarction. Patients present with malaise, fever, pericardial pain, leukocytosis, elevated inflammatory markers, and pericardial effusion. Like early post-MI pericarditis, Dressler syndrome has become infrequent, likely related to limitation of infarct size by current reperfusion therapies. When it develops within the first month after MI, aspirin therapy is advised, rather than other NSAIDs, to prevent interference with scar formation, as indicated in the previous paragraph.

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ANSWER TO QUESTION 337

E (Braunwald, pp. 1160–1162; Table 59.13)

A variety of conduction disturbances can occur in acute myocardial infarction (MI). In almost all patients with first-degree atrioventricular (AV) block, the disturbance is intranodal (above the bundle of His) and generally does not require specific treatment. First-degree AV block may also be a manifestation of increased vagal tone in the setting of acute MI. Other manifestations of increased vagal tone include sinus bradycardia and hypotension that are generally responsive to atropine.

Approximately 90% of patients with second-degree AV block admitted to coronary care units have Mobitz type I (Wenckebach) block. Mobitz type I block occurs most commonly in patients with inferior MI, is usually transient, and rarely progresses to complete AV block. It usually resolves within 72 hours after infarction and does not require specific therapy. In contrast, Mobitz type II block typically reflects conduction disease below the bundle of His, is associated with a widened QRS complex, and almost always occurs in the setting of anterior infarction. Mobitz type II block may progress to complete heart block and therefore generally justifies pacemaker placement.

Complete AV block (third-degree AV block) may occur in either anterior or inferior infarction. Its prognosis relates to the location of the infarction. In inferior infarction, complete heart block usually evolves from first-degree and type I second-degree AV block, typically has a stable escape rhythm, and is most often transient, with spontaneous resolution. Patients with anterior infarction may develop third-degree AV block without warning; however, it is usually preceded by less advanced conduction abnormalities such as Mobitz type II block. In general, patients in this setting have unstable escape rhythms, wide QRS complexes, and a high mortality rate.

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ANSWER TO QUESTION 338

B (Braunwald, pp. 1130–1134; Table 59.4; eFig. 59.3)

Overall, fibrinolytic therapy in ST-segment elevation myocardial infarction is associated with a 15% to 20% reduction in mortality at 35 days. The Fibrinolytic Therapy Trialists' Collaborative Group performed an overview of nine major fibrinolytic trials that each randomized more than 1000 patients. Among patients stratified by presenting ECG, patients with left bundle branch block (LBBB) had the highest overall mortality, followed by patients with anterior ST-segment elevations, and then patients with inferior ST-segment elevations.[1] The relative risk reductions with fibrinolytic therapy in patients with LBBB and anterior ST-segment elevation were both approximately 21%. Compared with patients with anterior ST-segment elevation, patients with inferior ST-segment elevation had less of a risk reduction.

The benefits of fibrinolysis are time dependent, and there is a stepwise decrease in improvement with later therapy over the first 24 hours. Two trials (LATE and EMERAS) showed a mortality reduction in patients treated with fibrinolytic therapy 6 to 12 hours after the onset of ischemic symptoms. However, there was no benefit for individuals treated beyond that time. Patients treated within 1 to 2 hours after onset of symptoms gained the most benefit.

Fibrinolytic trials have demonstrated that patients older than 75 years have a more modest relative risk reduction compared with individuals younger than 55 years. However, because the risk of adverse outcomes is so high for older patients, the absolute risk reductions are comparable between the age groups.[2]

The STREAM trial compared fibrinolysis followed by timely coronary angiography with primary percutaneous coronary intervention (PCI) in patients early in STEMI who were not able to undergo PCI within 1 hour of first medical contact. The fibrinolytic strategy resulted in effective reperfusion and comparable 30-day outcomes as the primary PCI group, but was associated with a slightly increased risk of intracranial bleeding.[3]

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ANSWER TO QUESTION 339

C (Braunwald, pp. 1097–1105; Figs. 58.1 and 58.4; eFig. 58.2)

Plaque rupture and plaque erosion are mechanisms that lead to coronary thrombosis and acute coronary syndromes.[1] When the resulting intracoronary thrombus is only partially occlusive, ST-segment depressions or T wave inversions (or both) commonly develop. When the thrombus is completely occlusive, ST-segment elevations typically occur. In the latter setting, Q waves subsequently form in approximately 75% of patients who are not treated with fibrinolysis or acute mechanical coronary revascularization.[2] In the remaining 25%, other ECG manifestations may develop, including reduction of the R wave height or notching of the QRS complex.

In the pre-fibrinolytic era, it was common to divide patients with myocardial infarction (MI) into those experiencing either a "Q wave MI" (now called "ST-segment elevation MI") or a "non–Q wave" MI (now called "non–ST-segment elevation MI") based on the evolution of the ECG over several days. Q wave infarction was considered to be synonymous with the pathology of a transmural infarction, whereas non–Q wave infarctions were considered to involve only the subendocardial layer. However, contemporary studies using cardiac magnetic resonance imaging indicate that the development of a Q wave on the ECG is determined more by the size of the infarct than the depth of mural involvement.[3]

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ANSWER TO QUESTION 340

D (Braunwald, pp. 1128–1134; Table 59.5; Figs. 59.10 and 59.11; eFig. 59.5)

Percutaneous coronary intervention (PCI) in acute ST-segment elevation myocardial infarction has been shown in large registries and randomized trials to result in higher patency rates (93% to 98% vs. 54%) and lower 30-day mortality rates (5% vs. 7%) than fibrinolytic therapy.[1] An additional advantage of PCI over fibrinolysis is a significant reduction in bleeding complications and strokes.

When performing primary PCI, radial artery access now tends to be preferred over femoral artery access based on the European Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX trial, which showed a reduction in bleeding and all-cause mortality when radial access was used.[2]

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ANSWER TO QUESTION 341

B (Braunwald, pp. 1163–1164; eFig. 59.8)

Left ventricular (LV) aneurysms arise in <5% of patients who survive acute ST-segment elevation myocardial infarction (MI). Formation of the aneurysm is presumed to occur when intraventricular tension leads to expansion of the noncontracting, infarcted myocardial tissue. An anterior MI complicated by LV aneurysm occurs due to total occlusion of a poorly collateralized left anterior descending artery. The presence of multivessel disease, extensive collateral vessels, or a nonoccluded left anterior descending artery makes the development of an aneurysm much less likely. Aneurysms occur approximately four times more often at the apex and in the anterior wall than in the inferoposterior wall and, in general, range from 1 to 8 cm in diameter.

True LV aneurysms, in contrast to pseudoaneurysms, rarely rupture. However, even when compared with mortality in patients having comparable LV ejection fractions, the presence of an LV aneurysm leads to a mortality that is up to six times higher than that of patients without aneurysm. Death in such patients is often sudden and presumed to be secondary to a high incidence of associated ventricular tachyarrhythmias. The diagnosis of an aneurysm is best made by echocardiography, magnetic resonance imaging, computed tomography, or left ventriculography. The "classic" evidence of aneurysm on the ECG—persistent ST-segment elevation in the area of the infarction—actually indicates a large infarct, but does not necessarily imply an aneurysmal segment.[1]

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ANSWER TO QUESTION 342

B (Braunwald, pp. 1158–1159, 1162; Table 59.12)

The ECG demonstrates atrial fibrillation with a rapid ventricular rate. Atrial fibrillation in acute myocardial infarction is usually transient and occurs more commonly in patients with left ventricular failure, infarct-associated pericarditis, or ischemic injury to the atria. Atrial fibrillation is more common during the first 24 hours after infarction than later. It is associated with increased mortality, in part because it occurs more frequently with extensive anterior wall infarctions.[1–3] The rapid ventricular response and loss of atrial contribution to ventricular filling may lead to an important reduction in cardiac output.

In patients who are hemodynamically stable, the use of a negative chronotropic drug (usually a beta blocker) is appropriate to slow the ventricular rate. However, cardioversion is the treatment of choice in patients with evidence of hemodynamic decompensation. Patients with recurrent episodes of atrial fibrillation should be anticoagulated.

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ANSWER TO QUESTION 343

A (Braunwald, p. 1159; Table 59.12)

The rhythm displayed is accelerated idioventricular rhythm (AIVR), which is defined as a ventricular escape rhythm with a rate between 60 and 100 beats/min. This rhythm is frequently referred to as "slow ventricular tachycardia" and appears in up to 20% of patients with acute myocardial infarction (MI), most commonly in the first 2 days after presentation. In addition, AIVR is the most common arrhythmia noted after reperfusion of an occluded coronary artery by fibrinolytic therapy. Approximately 50% of all episodes of AIVR are initiated by a premature beat; the rest emerge during periods of sinus slowing. In general, episodes of AIVR are of short duration and may show variation in rate. Unlike more rapid forms of ventricular tachycardia, episodes of AIVR have not been found to affect prognosis in acute MI and usually do not require intervention. If AIVR is accompanied by hemodynamic compromise, treatment with atropine or atrial pacing will often suppress the rhythm.

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ANSWER TO QUESTION 344

E (Braunwald, pp. 1115–1118; eFig. 58.4; Figs. 58.17 and 58.18)

Several cardiac biomarkers have been found to have prognostic value in patients with acute coronary syndrome (ACS), independent of more established markers of cardiac necrosis such as cardiac-specific troponins. The level of C-reactive protein (CRP), an acute-phase reactant, is approximately five times higher in patients with an ACS compared with those with stable coronary disease, and patients with the highest levels of CRP have an increased risk of death, even if cardiac troponin levels are not elevated.[1] The white blood cell count is a simpler but nonspecific marker of inflammation. Patients with unstable angina/non-ST-segment elevation myocardial infarction (MI) and elevated white blood cell counts have higher mortality and recurrent MI rates. This association is independent of CRP levels.[2]

Myeloperoxidase, a hemoprotein expressed by neutrophils, is a potent pro-oxidant that is associated with the presence of angiographic coronary artery disease. In patients with an ACS, myeloperoxidase levels have been associated with increased rates of death or recurrent MI, independent of other cardiac markers.[3]

Elevated levels of B-type natriuretic peptide, a neurohormone released in response to ventricular wall stress, are associated with a twofold to threefold higher risk of death by 10 months.[4]

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ANSWER TO QUESTION 345

A (Braunwald, pp. 1194–1195; Fig. 60.10)

This patient has an indication for long-term oral anticoagulation (OAC) because of atrial fibrillation with an elevated stroke risk (CHA_2DS_2-VASc score is at least 5—see Answer to Question 218). Additionally, she has a new indication for dual antiplatelet therapy (DAPT), having just undergone drug-eluting stent placement following an non-ST-segment elevation myocardial infarction. Managing patients with indications for "triple" antithrombotic therapy presents a dilemma because of the elevated bleeding risk and uncertainty about the ischemic consequences of reducing the OAC dose, or eliminating one of the antiplatelet agents. In addition, recent studies have evaluated the role of low-dose OAC in reducing future ischemic events in patients with recent myocardial infarction (MI) who do not have a separate indication for anticoagulation. How antiplatelet therapy should be modified in such patients remains an open question.

The WOEST trial randomized 573 patients undergoing percutaneous coronary intervention (PCI), who also required long-term OAC therapy, to OAC plus clopidogrel alone ("double" therapy), or OAC plus DAPT with clopidogrel and aspirin ("triple" therapy).[1] At 1 year, there was a significant reduction in bleeding events with "double" therapy (hazard ratio [HR] 0.36; 95% confidence interval [CI] 0.26 to 0.50); $P < .0001$). There was no increased risk of ischemic events in the "double" therapy group, though this small trial was not powered for ischemic outcomes.

The PIONEER AF trial randomized 2124 patients with atrial fibrillation undergoing PCI to one of three regimens: (1) "triple" therapy with warfarin (target international normalized ratio [INR] 2.0 to 3.0) plus DAPT; (2) low-dose rivaroxaban (15 mg daily) plus a $P2Y_{12}$ inhibitor without aspirin; or (3) very low-dose rivaroxaban (2.5 mg twice daily) plus a $P2Y_{12}$ inhibitor without aspirin.[2] Patients who received reduced doses of rivaroxaban and only one antiplatelet agent had less bleeding at 12 months compared with patients receiving

"triple" therapy. Importantly, the trial participants had preexisting atrial fibrillation and were not treated with approved doses of rivaroxaban for stroke prevention. The trial was not powered for ischemic events, but there were numerically more strokes in the two rivaroxaban arms than the warfarin arm. Thus, as in WOEST, the data from this trial showed reduced bleeding with "double" therapy, but do not clarify whether "double" and "triple" therapies are equally effective for reduction of ischemic events.

Two recent trials have assessed the role of anticoagulation in the post-acute coronary syndrome (ACS) setting in patients without a separate indication for long-term OAC therapy. ATLAS ACS 2-TIMI 513 randomized 15,526 patients with a recent ACS to very low-dose rivaroxaban (2.5 or 5 mg twice daily) or placebo in addition to standard post-ACS dual antiplatelet therapy. This well-powered trial found that the addition of rivaroxaban significantly reduced the risk of cardiovascular death, MI, or stroke, but at a cost of increased bleeding.[3] In 2017, GEMINI-ACS-14 reported the results of a phase 2 trial that randomized 3037 patients with recent ACS to rivaroxaban 2.5 mg twice daily plus single antiplatelet therapy (ticagrelor or clopidogrel) versus DAPT (aspirin plus ticagrelor or clopidogrel).[4] The trial was powered only for bleeding events and the rivaroxaban arm was found to be non-inferior to DAPT in this regard.

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ANSWER TO QUESTION 346

D (Braunwald, pp. 1241–1242; Fig. 61.14)

Venous graft occlusion occurs in 8% to 12% of patients before they leave the hospital, and by 1 year post-coronary artery bypass grafting 15% to 30% of vein grafts had become occluded.[1] Graft occlusion within the first year usually involves vessel thrombosis, with or without intimal hyperplasia. After the first year, atherosclerotic changes begin to accumulate in saphenous grafts. The histologic appearance of atherosclerosis in venous bypass grafts is indistinguishable from that seen in arterial vessels. The annual occlusion rate for vessels after the first year is 2%, although in grafts that are between 6 and 10 years old, an increased annual attrition rate of 4% is observed. The overall occlusion rate by 10 years is 40% to 50%. Internal mammary artery grafts have much longer durability than vein grafts, with patency rates of 95%, 88%, and 83% at 1, 5, and 10 years, respectively.[2] Aspirin (80 to 325 mg daily, started preoperatively and continued indefinitely) and lipid-lowering therapy have favorable impacts on the development of graft disease.

Historically, atherosclerotic progression in nongrafted arteries has occurred at a rate of 18% to 38% over the first decade, although this may potentially be lessened by aggressive lipid-lowering regimens. The risk of disease progression in the native circulation is three to six times higher in vessels to which a graft is placed, compared with ungrafted native arteries. This is the basis for the recommendation that arteries with minimal disease not receive a bypass graft.

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ANSWER TO QUESTION 347

A (Braunwald, pp. 1088–1092; Table 57.1; Figs. 57.25–57.28; eFigs. 57.7 and 57.8)

Myocardial stunning represents prolonged myocardial dysfunction that follows a brief episode of severe ischemia, with gradual return of contractile activity. Conversely, *Myocardial hibernation* is the term applied to myocardial dysfunction resulting from chronic hypoperfusion.[1]

Myocardial stunning affects both systolic and diastolic function and may occur in globally as well as regionally ischemic myocardium. Clinically, stunning is most frequently seen in patients recovering from ischemic arrest during cardiopulmonary bypass. It is also observed in ischemic regions adjacent to infarcted zones and in territories that are severely ischemic in patients with unstable angina. There are three likely mechanisms of myocardial stunning: (1) generation of oxygen-derived free radicals, (2) calcium overload, and (3) reduced sensitivity of myofilaments to calcium.[2,3]

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ANSWER TO QUESTION 348

D (Braunwald, pp. 1181–1182, 1189–1193; Table 60.5; Figs. 60.7–60.9)

Unstable angina/non-ST-segment elevation MI (UA/NSTEMI) is typically caused by atherosclerotic plaque rupture with formation of a platelet-rich intracoronary nonocclusive thrombus. Aspirin significantly reduces the risk of cardiovascular death and nonfatal myocardial infarction (MI) in this setting.[1] Clopidogrel is an irreversible inhibitor of the platelet $P2Y_{12}$ ADP receptor. The CURE trial demonstrated that the addition of clopidogrel to standard acute coronary syndrome (ACS) therapy resulted in a 20% reduction in death, MI, or stroke. Further analysis of this trial showed that the beneficial effects became apparent within 24 hours of treatment initiation and persisted for 12 months.[2]

The addition of an anticoagulant improves clinical outcomes of patients with UA/NSTEMI more than antiplatelet therapy alone.[1] Studies of patients with unstable angina in the era before the use of dual antiplatelet regimens showed that the addition of unfractionated heparin (UFH) to aspirin reduced adverse event rates.[1] Low-molecular-weight heparins (LMWHs) have been compared with UFH in the setting of UA/NSTEMI. In a large meta-analysis, new or recurrent MI occurred less often with the LMWH enoxaparin, with similar rates of bleeding.[3] Enoxaparin is the preferred LMWH for ACS on the basis of several clinical trials that demonstrate its efficacy, whereas the experience with other LMWHs has not been as convincing.

The factor Xa inhibitor fondaparinux was studied in patients with UA/NSTEMI in the OASIS-5 trial and was associated with a *lower* risk of major bleeding and of mortality at 30 days when compared with enoxaparin.[4]

Another anticoagulant option, bivalirudin, is a direct thrombin inhibitor. In the ACUITY trial of patients with non-ST-segment elevation MI (most of whom received aspirin plus clopidogrel) for whom an invasive strategy was planned, bivalirudin was compared with two other antithrombotic regimens: (1) bivalirudin plus a glycoprotein (GP) IIb/IIIa inhibitor, or (2) UFH or LMWH with a GP IIb/IIIa inhibitor. There were no differences in ischemic events between the treatment arms, but bivalirudin alone caused less bleeding than either regimen that included a GP IIb/IIIa inhibitor.[5] Thus, bivalirudin (with aspirin plus a $P2Y_{12}$ inhibitor, but without a GP IIb/IIIa inhibitor) is an alternative for an early invasive strategy in NSTEMI patients, particularly if there is an increased bleeding risk.

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ANSWER TO QUESTION 349

D (Braunwald, pp. 1087, 1106–1107)

Preexisting collateral vessels are small (20 to 200 μm) vascular channels that interconnect epicardial coronary arteries. They are normally closed and nonfunctional, because there is no pressure gradient between the arteries they connect. However, with an acute coronary occlusion, the distal pressure drops suddenly and any preexisting collateral vessels open quickly. The increased flow through these rudimentary collateral vessels triggers a maturation process that includes three stages. In the first 24 hours there is passive widening due to the increased flow. Over the next several weeks, increased flow and shear stress trigger endothelial cell activation, with subsequent inflammation and cellular proliferation with fragmentation of the basement membrane, dissolution of the extracellular matrix, and recruitment of leukocytes. Over several months, the collateral vessel wall thickens as a result of deposition of extracellular matrix. The resultant blood vessel is a three-layer structure that is nearly indistinguishable from a normal coronary artery, with a luminal diameter as large as 1 mm.[1]

Growth of the collateral circulation is triggered primarily by the severity of coronary obstruction. There is no clear evidence that exercise by itself triggers collateral formation. The reduction of myocardial ischemia in the setting of exercise training is more likely to be related to improved conditioning. Conditions that reduce endothelial production of nitric oxide, such as diabetes mellitus, may reduce the ability of collateral vessels to develop.

In angioplasty studies, collateral vessels typically provide <50% of normal coronary blood flow. Nonetheless, in the setting of an acute MI, they have been shown to decrease infarct size and contribute to improved survival. In patients with stable coronary disease, those with well-developed collateral circulations have a significantly lower rate of ischemic events.[2]

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ANSWER TO QUESTION 350

D (Braunwald, pp. 1237–1240; Figs. 61.11–61.13)

Several trials have compared pharmacologic therapy to percutaneous coronary intervention (PCI) for patients with chronic stable angina. In most of these, PCI has resulted in greater symptomatic relief as measured by severity of angina, the need for antianginal medications, and improved quality of life. However, with respect to major cardiac events (e.g., myocardial infarction [MI] or cardiac death), the two strategies appear equivalent. In the largest of the trials, COURAGE, 2287 patients with moderately severe chronic angina were randomized to PCI and optimal medical therapy (including aspirin, lipid lowering to a low-density lipoprotein goal of 60 to 85 mg/dL, antianginal drugs and angiotensin-converting enzyme inhibitors) or optimal medical therapy alone. Bare metal stents were used for PCI in the majority of patients in the PCI group. After 4.6 years of follow-up, there was no reduction in death and/or myocardial infarction in patients randomized to PCI compared with medical therapy.[1] Patients initially treated with PCI experienced less angina at 1 and 3 years, but by 5 years there was no difference compared with patients treated initially with optimal medical therapy alone.

The FAME 2 trial compared optimal medical therapy alone, to optimal medical therapy plus PCI, in patients with angina and at least one stenosis with a fractional flow reserve (FFR) ≤0.80 (rather than performing PCI simply for angiographic findings). The trial was terminated early after FFR-guided PCI was found to reduce the combined primary outcome of death, MI, or urgent revascularization. This benefit was entirely based on a highly significant reduction in the need for urgent revascularization in patients treated with PCI

plus medical therapy (1.6%) versus medical therapy alone (11.1%; hazard ratio 0.13, 95% confidence interval 0.06 to 0.30, $P < .001$). PCI did not confer a reduction in death or MI in this trial.[2]

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ANSWER TO QUESTION 351

D (Braunwald, pp. 1296–1299; eFig. 63.1; Figs. 63.3 and 63.4)

Although the average rate of expansion of abdominal aortic aneurysms (AAAs) is 0.4 cm per year, larger aneurysms tend to expand faster than smaller ones, as a consequence of Laplace's law (wall tension is proportional to the radius of the aneurysm). Once aneurysm rupture has occurred, mortality is extremely high: 60% of patients die before they reach the hospital, and 50% of those who are successfully hospitalized die perioperatively. Surveillance of asymptomatic aneurysms until the size is >5.5 cm is associated with a low rate of rupture (~1% per year). However, the 5-year risk of rupture is 30% to 40% for AAAs that are 5.5 to 6.0 cm in diameter. Thus for asymptomatic patients, current guidelines recommend repair of AAAs ≥5.0 to 5.5 cm.[1]

For AAAs >4.5 cm, computed tomography is preferred over ultrasound for imaging surveillance because of greater accuracy of measurement. The Society of Vascular Surgery recommends the following frequency of imaging: for AAAs 3.0 to 3.4 cm, every 3 years; 3.5 to 4.4 cm, every 12 months; and 4.5 to 5.4 cm, every 6 months.[2] Of note, women have a higher rate of rupture of AAAs than men and at a smaller aneurysm diameter. Rupture is also more common among current smokers and those with hypertension.

Clinical trials have examined the value of immediate repair of aneurysms 4.0 to 5.5 cm in diameter versus serial surveillance with ultrasound or computed tomographic scanning. These studies have found no mortality difference between the two strategies.[3] Important limitations of these trials were that they enrolled almost exclusively men and follow-up was much more intense than in general practice.

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ANSWER TO QUESTION 352

C (Braunwald, pp. 1307–1321; Tables 63.3 and 63.4; eTable 63.2; Figs. 63.11, 63.12, 63.18, 63.19, 63.21; eFigs. 63.20, 63.21, 63.24)

The figure displays a contrast-enhanced chest computed tomogram showing an intimal flap ("I") due to aortic dissection. Acute aortic dissection is a medical and surgical emergency. Mortality in untreated cases exceeds 25% in the first 24 hours and 50% in the first week after presentation. Immediate medical management should focus on reduction of blood pressure, reduction of arterial dP/dt (the force of left ventricular ejection), fluid resuscitation if necessary, and preparation of the patient for operative intervention if indicated. Beta blockers are the agents of choice for lowering blood pressure; labetalol is an appropriate initial choice of beta blocker because it combines blood pressure–lowering effects (alpha- and beta-blockade) with reduction of dP/dt (beta-blockade). IV sodium nitroprusside can be added for additional blood pressure control if needed.

Surgical therapy for type A (proximal) acute dissection improves survival compared with medical therapy alone.[1] This is because progression of proximal dissection can (1) compromise flow to major vessels, including the coronary arteries, (2) rupture into the pericardium, resulting in tamponade and death, or (3) lead to severe aortic valve regurgitation.[1] Uncomplicated type B (distal) dissections, however, can be managed with initial pharmacologic therapy alone, with a 30-day survival rate of 92%. For patients with complicated type B dissections (e.g., intractable pain or visceral ischemia), invasive intervention is necessary. Open surgical repair in such patients is associated with high mortality rates; endovascular repair is often appropriate instead.[2]

A small percentage of patients present with chronic aortic dissections. By surviving the acute stage, these patients represent a select subset of lower-risk patients who can be managed conservatively with medical therapy regardless of the location of the dissection, unless the dissection is complicated by aneurysm, rupture, vascular compromise, or aortic regurgitation.

When aortic regurgitation complicates acute dissection, decompression of the false lumen may be all that is required to correct the geometry of the aortic valve and restore valve competence. If abnormalities of the aortic valve leaflets prevent such repair, then aortic valve and root replacement are usually necessary.

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ANSWER TO QUESTION 353

D (Braunwald, pp. 1233–1234)

Ranolazine is an antianginal agent that may be used in combination with beta blockers, nitrates, and calcium channel blockers. Unlike beta blockers, nitrates, and calcium channel blockers, ranolazine exerts its anti-ischemic effect without significant effect on heart rate or blood pressure. Ranolazine inhibits the slowly inactivating component of the cardiac sodium current (late I_{NA}^{+}) and is therefore believed to reduce the deleterious effects of intracellular sodium and calcium

overload that accompany, and may promote, myocardial ischemia.[1]

Clinical trials have shown that ranolazine is effective as monotherapy, or in combination with traditional antianginal agents. In studies of patients with moderate angina, ranolazine decreased the frequency of angina and need for sublingual nitroglycerin.[2]

Ranolazine is generally well tolerated; its most common side effects are dizziness, headache, and constipation. Because ranolazine produces a concentration-dependent prolongation of repolarization and the QT interval, there has been concern that it may precipitate arrhythmias such as torsades de pointes. However, in the MERLIN-TIMI 36 study of 6560 patients with acute coronary syndromes, there was no difference in the rates of documented dysrhythmias or sudden cardiac death in patients receiving ranolazine compared with placebo.[1]

Ranolazine is metabolized in the liver (primarily by CYP3A), and its use is contraindicated in patients with significant hepatic impairment.

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ANSWER TO QUESTION 354

C (Braunwald, pp. 1296–1298; eFig. 63.1; Fig. 63.3)

The figure is an axial contrast-enhanced computed tomographic (CT) scan demonstrating a large abdominal aortic aneurysm (AAA). The majority of AAAs are asymptomatic. On physical examination, such an aneurysm may be appreciated as a pulsatile mass extending variably from the xiphoid process to the umbilicus. The size of an aneurysm tends to be overestimated by physical examination, owing to the difficulty in distinguishing the aorta from adjacent structures. AAAs may be sensitive to palpation, especially if they are rapidly expanding.[1]

Ultrasonography and CT are both helpful means to diagnose and quantitate the size of AAAs. However, ultrasonography is not sufficient for planning operative repair because it cannot define associated mesenteric and renal artery anatomy. Spiral CT with three-dimensional reconstruction provides a more comprehensive evaluation of the aortic tree. It also tends to measure aneurysms as slightly larger than by ultrasonography. Aortography, historically the gold standard for preoperative aneurysm evaluation, may actually underestimate the size of an AAA if nonopacified mural thrombus lines the wall. Magnetic resonance angiography is an alternative to angiography that is highly accurate in determining aneurysm size and, with three-dimensional reconstruction, can define the proximal extent of disease and iliofemoral involvement in more than 80% of cases.

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ANSWER TO QUESTION 355

D (Braunwald, p. 1192; Fig. 60.7)

The use of platelet glycoprotein (GP) IIb/IIIa inhibitors in the setting of percutaneous coronary intervention has been tested in multiple randomized trials, involving the full spectrum of coronary disease, from stable angina to ST-segment elevation myocardial infarction (MI). Excluding studies that used inadequate doses, the trials are consistent in demonstrating significant reductions in the composite endpoint of death, MI, and need for urgent revascularization over 30 days of follow-up.[1] Most of this benefit is realized by patients experiencing an acute coronary syndrome and relates to reductions in peri-procedural MI and the need for urgent revascularization. Several studies have concluded that patients who sustain a peri-procedural MI have a worse long-term prognosis. The disadvantage of GP IIb/IIIa inhibitors is an increased risk of bleeding complications.

The reduction in clinical events with GP IIb/IIIa inhibition is typically achieved in the first 48 hours, with little separation of the event rate curves after that time. They do not appear to have any long-term effects on rates of restenosis.[2]

For patients with acute non-ST-segment elevation MI who have received aspirin plus clopidogrel there is only a modest benefit of early "upstream" GP IIb/IIIa inhibitor administration, compared to provisional administration of the drug in the cardiac catheterization laboratory. In a meta-analysis of 12 studies involving more than 46,000 patients, there was a small reduction in the endpoint of death or MI at 30 days, but there was no reduction in mortality alone, and there was a 23% relative increase in major bleeding.[3] Thus, *routine* early administration of a GP IIb/IIIa inhibitor prior to transport to the cardiac catheterization laboratory is not recommended. For select high-risk patients on aspirin and a $P2Y_{12}$ inhibitor for whom an early invasive strategy is planned, and who have a low bleeding risk, early use of a GP IIb/IIIa inhibitor (specifically eptifibatide or tirofiban) can be considered (class IIb recommendation).[4]

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ANSWER TO QUESTION 356

D (Braunwald, pp. 962–966; Fig. 48.8)

Prinzmetal angina is caused by transient coronary artery vasospasm. Although the site of vasospasm may not appear to contain a significant plaque on angiography, intravascular ultrasound studies have shown that nearly all such sites have underlying atherosclerosis. Both nitrates and calcium channel blockers have been shown to be efficacious in treating and preventing attacks of Prinzmetal angina.[1] Provocative testing with ergonovine or acetylcholine is indicated only when Prinzmetal angina is suspected and ECG evidence of transient ST-segment elevation is lacking, because these agents can cause severe prolonged coronary spasm, resulting in myocardial infarction or arrhythmias. Coronary spasm has been observed after administration of ergot derivatives, 5-fluorouracil, cyclophosphamide, and serotonin reuptake inhibitors.[2] Patients with isolated Prinzmetal angina generally have an excellent prognosis, with very low rates of sudden cardiac death or myocardial infarction.

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ANSWER TO QUESTION 357

C (Braunwald, pp. 1344–1346; see also Answer to Question 325)

The figure shows atheroemboli to the left foot resulting in "blue toe syndrome." Showers of microemboli that arise from atherosclerotic plaques in the aortic or major arterial trunks lead to clinical and pathologic changes as the particulate material lodges in small arterial branches. Atheromatous embolism (also called "cholesterol embolism") occurs most often after surgery involving manipulation of an atherosclerotic aorta, such as major abdominal vascular procedures, especially resection of abdominal aortic aneurysms. Showers of atherosclerotic emboli may also be provoked by cardiac catheterization, cardiopulmonary bypass, and intra-arterial cannulations of any type and may occasionally occur spontaneously as well. Clinical findings in this disorder may include bilateral lower extremity and/or abdominal pain, livedo reticularis, purpuric and ecchymotic lesions in the lower extremities, and possibly visualization of cholesterol particles in the retinal arteries, when the proximal aorta is involved. Laboratory analysis may reveal eosinophilia, anemia, thrombocytopenia, and azotemia. While imaging studies (e.g., computed tomography, magnetic resonance angiogram, or transesophageal echocardiography) may document shaggy atheromatous sources of substrate, definitive diagnosis of atheroembolism rests upon identification of cholesterol crystals on skin or muscle biopsy specimens.

Two important recognized complications of cholesterol emboli after abdominal aortic surgery are pancreatitis and renal failure due to diffuse microinfarction of the affected organ. The resulting renal failure may be severe and irreversible. There is no specific therapy for cholesterol emboli; treatment of the resulting complications of the disorder is the cornerstone of management. The use of anticoagulants to prevent further episodes of embolization remains controversial. Antiplatelet and antilipid agents should be considered in affected patients because these therapies may prevent other cardiovascular events in this high-risk population.

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ANSWER TO QUESTION 358

D (Braunwald, pp. 1070–1075; eTable 57.1; Figs. 57.7 and 57.9)

Nitric oxide (NO) is formed in endothelial cells by the action of NO synthase on L-arginine. In this reaction, the terminal nitrogen from the guanidino group of L-arginine forms NO, and L-citrulline is produced as a by-product, which is recycled back to L-arginine. NO diffuses to neighboring smooth muscle cells, where it activates guanylate cyclase, causing an increase in cyclic *guanosine* monophosphate and smooth muscle relaxation.

Hypoxia, thrombin, and adenosine diphosphate all stimulate endothelial NO production. Acetylcholine (ACh) induces both endothelium-dependent (i.e., NO-mediated) vasodilatation and direct smooth muscle constriction. As a result, ACh induces vasodilatation in healthy vessels, but vasoconstriction predominates in atherosclerotic vessels in which there is dysfunctional endothelium. Some vasodilators (e.g., nitroglycerin, nitroprusside, and prostacyclin) act independently of endothelial NO production and continue to produce vascular smooth muscle relaxation even in the setting of a dysfunctional endothelium.

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ANSWER TO QUESTION 359

A (Braunwald, pp. 1321–1322; Fig. 63.24)

Intramural hematoma (IMH) is a condition closely related to aortic dissection. It consists of a hematoma contained within the medial layer of the aortic wall with no intimal flap or false lumen. Although the pathogenesis remains uncertain, rupture of the vasa vasorum has been postulated to be the initiating event. The hemorrhage occurs in the outer media and may extend into the adventitia. IMH is responsible for 10% to 20% of acute aortic syndromes. It localizes to the ascending aorta in 30%, to the aortic arch in 10%, and to the descending aorta in ~60% of affected patients.

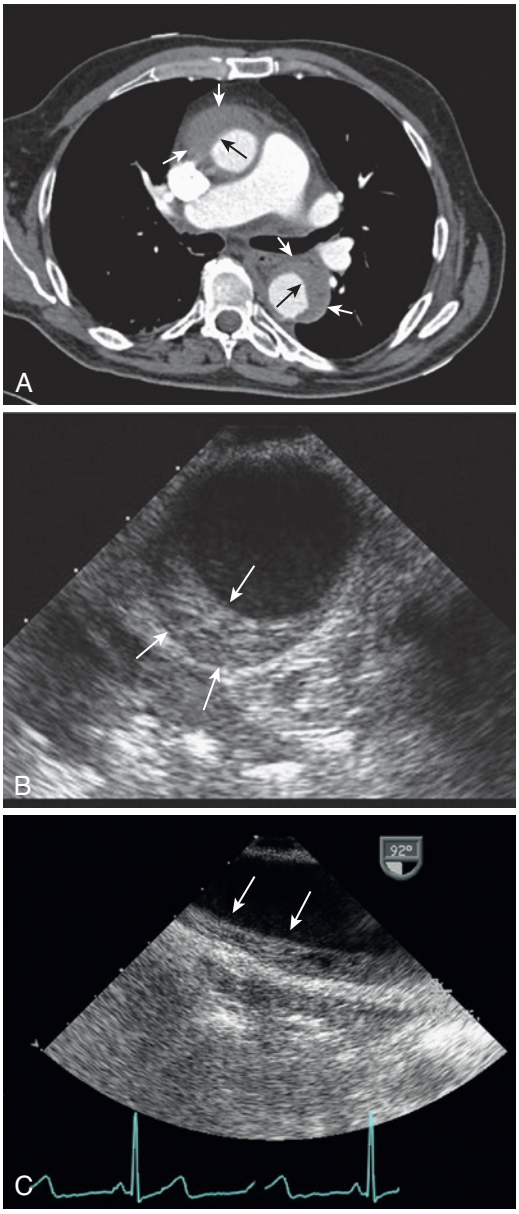

FIG. 3.13 *Intramural hematoma (IMH) of the aorta. (A) Contrast-enhanced computed tomography scan demonstrating type A IMH of the aorta. Note the circumferential hematoma involving the ascending aorta* (upper arrows) *and the crescentic hematoma involving the descending aorta* (lower arrows). *(B) Transesophageal echocardiogram short-axis view of the descending aorta demonstrating typical crescentic thickening of the aortic wall* (arrows) *in acute type B IMH. (C) Transesophageal echocardiogram longitudinal view of the aorta demonstrating IMH* (arrows).

Intramural hematoma can be identified by computed tomography (CT), transesophageal echocardiography (TEE), or magnetic resonance imaging (MRI). Non-contrast-enhanced CT demonstrates a crescentic, high-attenuation area along the aortic wall without an intimal tear. Contrast CT demonstrates failure of the intramural hematoma to enhance (Fig. 3.13A). TEE shows crescentic or circumferential aortic wall thickening, an eccentric aortic lumen, and echolucency within the aortic wall, with no intimal flap (see Fig. 3.13B and C). On MRI, an intramural hematoma is identified as a crescent-shaped area of high intensity along the aortic wall. Because there is lack of communication with the aorta, aortography actually has a low sensitivity for this diagnosis.

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ANSWER TO QUESTION 360

B (Braunwald, pp. 1135–1136)

Low-molecular-weight heparins (LMWHs) are derived from unfractionated heparin (UFH) through chemical or enzymatic depolymerization. The shorter molecules still contain the critical pentasaccharide sequence necessary for binding to and activating antithrombin (resulting in its anti-factor IIa effect), but the anti-Xa activity is much greater.[1] They do not cause a significant rise in the activated partial thromboplastin time, and that test is not useful for clinical monitoring. Although the anticoagulation effect of LMWHs can be determined by measuring anti-Xa activity, the stable pharmacokinetics of these drugs usually renders such measurement unnecessary.

Clearance of LMWH is reduced in patients with renal impairment, and dosage reduction is appropriate if used in such patients. Compared with UFH, treatment with LMWHs is less likely to result in type II heparin-induced thrombocytopenia (HIT). However, HIT antibodies can cross-react with LMWHs, and the latter should not be used when type II HIT has occurred.[1]

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ANSWER TO QUESTION 361

D (Braunwald, pp. 1182–1186; Figs. 60.4–60.6)

Unstable angina and non–ST-segment elevation myocardial infarction (MI) are heterogeneous conditions with a range of possible outcomes. Clinical trials have identified subgroups of patients who are at greatest risk and who are more likely to accrue benefit from therapeutic interventions.[1] High-risk individuals include those with acute rest pain or post-MI unstable angina, and those who are of advanced age or who have diabetes, cerebrovascular disease, or peripheral vascular disease.[2,3] In addition, patients who present with unstable angina despite having been on prior chronic aspirin therapy appear to be at particularly high risk.

The presence of ST-segment deviations of as little as 0.05 mV is associated with an adverse prognosis in unstable angina, and the greater the ST-segment deviation, the worse the outcome. Similarly, an elevated cardiac troponin level confers a higher risk of death.[4] Increased levels of C-reactive protein (CRP) have also been related to an augmented risk of MI and death. Although CRP, as a marker of inflammation, is often elevated in acute coronary syndromes, those patients with the highest levels have worse short- and long-term outcomes.[4]

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ANSWER TO QUESTION 362

C (Braunwald, pp. 1328–1329; Table 64.1; eFig. 64.1)

The prevalence of peripheral artery disease (PAD) varies depending on the population studied and the diagnostic methods used, but ranges from 6% in people 40 years and older to 20% in those 65 and older. The same risk factors that contribute to coronary artery disease are also associated with PAD, including cigarette smoking, diabetes mellitus,[1,2] hypercholesterolemia, hypertension, and hyperhomocystinemia. Of these, however, hypercholesterolemia is not one of the strongest predictors, conveying only a 1.7-fold increased risk. Rather, cigarette smoking and diabetes mellitus are more significantly associated, with relative risks of 4.5 and 2.7, respectively.

Evidence of PAD has been observed even in young individuals. Data from the Pathobiological Determinants of Atherosclerosis in Youth Study indicated that, in patients younger than 35 years, fatty streaks and atheroma form first in the dorsal portion of the abdominal aorta, later followed by similar lesions in the descending thoracic aorta.

The lack of symptoms is not a reliable way to exclude the presence of PAD, because only 10% to 30% of patients ≥50 years with PAD experience classic claudication.

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ANSWER TO QUESTION 363

C (Braunwald, pp. 1307–1311; Table 63.6)

Aortic dissection affects twice as many men as women and occurs most commonly in the sixth and seventh decades. Over 90% of patients presenting with aortic dissection complain of severe pain. The pain is usually sudden in onset, most intense at its inception, and may be described as "tearing" or "ripping" in quality. The discomfort tends to migrate in association with propagation along the aortic wall. On physical examination, patients may appear to be in shock, but the measured blood pressure is typically *elevated*, especially in patients with distal dissection. Characteristic physical findings associated with aortic dissection, such as pulse defects, are more common in proximal dissection. New aortic regurgitation may appear with proximal dissection that extends into the aortic valve apparatus.

Several conditions may mimic the pain of aortic dissection, including myocardial infarction, thoracic nondissecting aneurysm, mediastinal tumors, and pericarditis.

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ANSWER TO QUESTION 364

A (Braunwald, pp. 1331–1335; Fig. 64.4)

Intermittent claudication due to peripheral artery disease (PAD) is characterized by pain or a sense of fatigue during exercise that resolves with rest. In contrast, neurogenic pseudoclaudication (e.g., due to spinal stenosis) is associated with pain with both walking and standing. Classic physical findings in PAD include diminished or absent distal pulses, bruits over regions of stenosis, and coolness and signs of chronic low-grade ischemia such as hair loss, smooth shiny skin, and brittle nails of the affected extremity.

Among the simpler noninvasive diagnostic tests for PAD are systolic blood pressure measurements along select segments of each extremity. A pressure gradient of >20 mm Hg between successive segments in the lower extremities or >10 mm Hg in the upper extremities is evidence of significant stenosis. A sensitive office-based screening method for the diagnosis of PAD is the ankle/brachial index (ABI), the ratio between the ankle and brachial systolic blood pressures. An ABI value <1 is consistent with arterial insufficiency of the measured lower extremity and is 95% sensitive for that diagnosis. The ABI of patients with symptoms of leg claudication is typically 0.5 to 0.8, and in those with critical limb ischemia it is usually <0.5. Contrast angiography is the invasive gold standard for the identification of arterial stenoses. However, the resolution of gadolinium-enhanced magnetic resonance angiography (MRA) approaches that of conventional contrast-enhanced digital subtraction angiography. MRA is 95% sensitive and 96% specific for anatomic resolution of the aorta, iliac, femoral-popliteal, and tibial-peroneal arteries.

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ANSWER TO QUESTION 365

C (Braunwald, p. 1282)

Intravenous unfractionated heparin (UFH) has been the standard anticoagulant administered during percutaneous coronary interventions (PCIs) to prevent arterial thrombus formation on the percutaneous guidewires and catheters. Use of lower, weight-adjusted heparin dosing of 50 to 70 IU/kg has been shown to result in similar clinical outcomes. The routine use of intravenous heparin *after* the procedure is not recommended because that approach does not

reduce ischemic complications but does increase the risk of bleeding.[1]

In the ISAR-REACT 3 trial, which compared the intravenous direct thrombin inhibitor bivalirudin to UFH in patients pretreated with clopidogrel (600 mg), there were no differences in the rates of ischemic complications in patients undergoing PCI.[2] However, the incidence of major bleeding was lower in patients who received bivalirudin. The 2011 ACCF/AHA/SCAI guideline for PCI recommends bivalirudin as a useful anticoagulant in place of UFH for patients undergoing PCI, including patients with heparin-induced thrombocytopenia (class I recommendation, level of evidence: B). Of note, a later 2014 meta-analysis of 16 trials involving >33,000 patients with planned PCI confirmed a decreased rate of bleeding with bivalirudin compared with UFH, but an increased risk of myocardial infarction and stent thrombosis.[3]

In the EPILOG trial, in which glycoprotein (GP) IIb/IIIa inhibition was used, standard-dose UFH (10,000 unit bolus, with activated clotting time [ACT] goal >300 seconds) resulted in similar rates of ischemic events, but a greater number of hemorrhagic complications compared with weight-adjusted UFH (70 units/kg bolus, ACT goal >200 seconds). Therefore, when used in combination with a GP IIb/IIIa inhibitor, lower-dose weight-adjusted UFH is preferred.

The low-molecular-weight heparin enoxaparin is efficacious as an anticoagulant during PCI but cannot be monitored by the ACT test. However, the pharmacokinetics of this agent are so predictable that patients who received their last dose within 8 hours of the procedure do not require further anticoagulation. An intravenous bolus of 0.3 mg/kg is appropriate if the last dose was 8 to 12 hours before the procedure.[4] If the last dose was more than 12 hours earlier, then standard heparin anticoagulation during PCI is appropriate.

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ANSWER TO QUESTION 366

D (Braunwald, pp. 1231–1233; eFig. 61.3)

Nitrates are important agents in the treatment of ischemic heart disease. They directly relax vascular smooth muscle by activating intracellular guanylate cyclase, thus causing an increase in cyclic guanosine monophosphate, which triggers smooth muscle relaxation. Since nitrates act directly on smooth muscle, they do not require an intact endothelium to secrete nitric oxide (NO) as a secondary messenger. The vasodilating effect of nitrates is manifest in both arteries and veins but predominates in the venous circulation. The decrease in venous tone lessens venous return to the heart and thereby reduces preload and ventricular dimensions, which in turn diminishes wall tension. As well as decreasing wall tension and myocardial oxygen demand, nitrates may also increase oxygen supply by dilating coronary arteries. Such dilatation can be effected in vessels containing atherosclerosis, presumably because the pathologic atherosclerotic changes are eccentric and normal vascular smooth muscle, which can respond to nitrates, is present in a portion of the plaque.

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ANSWER TO QUESTION 367

A (Braunwald, pp. 1281–1282)

The glycoprotein (GP) IIb/IIIa inhibitors are a powerful class of antiplatelet agents. By impairing the final common pathway of platelet aggregation, they greatly limit thrombus formation. There are significant differences between the three agents of this class currently approved for use. Abciximab is a monoclonal antibody that has high affinity but relatively low specificity for the GP IIb/IIIa receptor. Although the original murine monoclonal antibody was chimerized with human immunoglobulin to minimize antibody formation, antichimeric antibodies develop in 5% to 6% of patients treated with abciximab. Although there has been no evidence of severe allergic reactions after the re-administration of abciximab to previously exposed patients, thrombocytopenia has been reported.

Eptifibatide and tirofiban are small-molecule GP IIb/IIIa inhibitors that have lower affinity but higher specificity for the GP IIb/IIIa receptor. Eptifibatide is a cyclic heptapeptide related to pygmy rattlesnake venom, whereas tirofiban is a nonpeptide molecule based on the structure of fibrinogen. Both have half-lives of about 2 hours. Current evidence suggests that the long-term benefits of GP IIb/IIIa inhibitors are greater when they are administered in conjunction with heparin.

The upstream administration of a GP IIb/IIIa inhibitor *before* transport to the catheterization laboratory in acute ST-segment elevation myocardial infarction has not been shown to benefit patients pretreated with dual antiplatelet therapy (aspirin plus clopidogrel 600 mg).[1,2] In a placebo-controlled trial of 9492 patients presenting with acute coronary syndrome without ST-segment elevation, early initiation of eptifibatide, at least 12 hours prior to angiography, did not lead to decreased ischemic events compared with eptifibatide started at the time of percutaneous coronary intervention (PCI).[3]

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ANSWER TO QUESTION 368

B (Braunwald, pp. 922–923; Fig. 46.6; Table 46.6)

Renovascular disease is common and can contribute to hypertension and progressive deterioration of kidney function. Renal artery stenosis (RAS) can be managed with percutaneous renal artery angioplasty and stenting, and the technical success rate of these procedures exceeds 95%. The use of stents has greatly improved the procedural outcome even for ostial lesions and reduces restenosis rates.[1] Clinical trial data of patients with unilateral RAS have demonstrated that surgical revascularization and percutaneous angioplasty lead to similar degrees of blood pressure improvement and stabilization of renal function.

Although successful percutaneous treatment of atherosclerotic RAS commonly improves blood pressure, at least modestly, complete resolution of hypertension is unusual because many affected patients have accompanying essential hypertension or intrinsic renal disease. As a result, only about two-thirds of patients who undergo successful intervention have a reduced requirement of antihypertensive medications.

Furthermore, recent data have not demonstrated superior benefit of percutaneous intervention compared with medical antihypertensive therapy alone. The ASTRAL trial prospectively randomized 806 patients with atherosclerotic renal artery disease to either percutaneous revascularization or medical therapy and the revascularization group did not experience superior clinical effect as measured by progression of renal dysfunction, blood pressure levels, or cardiovascular events. Among the patients assigned to percutaneous revascularization there were serious periprocedural complications, including cholesterol embolism leading to gangrene and toe or limb amputation.[2] In the CORAL trial,[3] 947 patients with atherosclerotic RAS and hypertension or chronic kidney disease were randomized to renal artery stenting or medical therapy. There was no benefit in terms of clinical outcomes with renal artery stenting. An important criticism of the ASTRAL and CORAL trials is that the patients enrolled had only modest RAS severity. Thus, the effectiveness of renal artery stenting in patients with severe RAS remains incompletely investigated.

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ANSWER TO QUESTION 369

D (Braunwald, p. 1199)

The syndrome of angina-like chest pain in the presence of a normal coronary arteriogram encompasses a heterogeneous population that includes patients with true heart disease as well as those with noncardiac chest pain. Although most studies have failed to reveal consistent biochemical evidence of ischemia, such as an elevation of myocardial lactate with exercise, evidence of decreased perfusion may be found in many of these patients by exercise testing or scintigraphy using single-photon emission computed tomography or positron emission tomography. The incidence of coronary calcification on multislice computed tomography is higher than that of normal subjects but lower than that of patients with obstructive coronary artery disease (CAD). Some patients with this syndrome have evidence of endothelial and microvascular dysfunction with inadequate vasodilator reserve and an exaggerated response to vasoconstrictor stimuli.[1] Increased sensitivity to pain has also been associated with this condition.

Largely because of the heterogeneous population, studies of potential treatments have given varying and often contradictory results.[2] Nitrates have been shown to both improve and reduce exercise tolerance. Calcium channel blockers and estrogen therapy in women are sometimes effective, perhaps by enhancing endothelial-dependent vasodilatation. In addition, some patients appear to benefit from antidepressant drugs. Overall, the cardiac prognosis of patients with this syndrome is very good and better than that of patients with obstructive CAD. Notably, however, in the Women's Ischemic Syndrome Evaluation study, women with angina and nonobstructive CAD who had persistent symptoms demonstrated more than a twofold increase in future cardiovascular events.[3]

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ANSWER TO QUESTION 370

E (Braunwald, p. 1299)

For patients with an abdominal aortic aneurysm (AAA) and suitable anatomy, endovascular aortic aneurysm repair (EVAR) is a less invasive approach than standard open surgery. The endograft is introduced percutaneously or via arterial cutdown into the femoral artery and maneuvered to the involved aortic segment. Anatomic constraints limit the use of EVAR, but reported primary success rates for aneurysm exclusion in carefully chosen patients have ranged from 78% to 99%. An endoleak (persistent flow into the aneurysmal sac external to the endograft after it has been deployed) is a serious complication of EVAR and leaves the patient at risk for aneurysm rupture.

Randomized trials have shown a lower 30-day mortality for endovascular repair of abdominal aortic aneurysm compared with an open surgical procedure.[1] Additional trials have begun to define the long-term outcomes of EVAR. In the United Kingdom Endovascular Aneurysm Repair 1 trial,[2] 1252 patients with a large AAA (≥5.5 cm) were randomized to endovascular or open operative repair. The 30-day mortality rate favored

endovascular repair, but there was no difference in mortality over the long-term (median follow-up of 6 years), and the endovascular procedure was associated with higher rates of complications (including fatal endograft rupture), need for re-intervention, and increased cost. Similarly, an analysis of 79,932 Medicare patients with abdominal aortic aneurysm showed that EVAR resulted in lower perioperative mortality and complications than open surgical repair, but at 8-year follow-up mortality rates were the same and EVAR-treated patients required more aneurysm-related reinterventions.[3]

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ANSWER TO QUESTION 371

B (Braunwald, pp. 1338–1340; Figs. 64.11 and 64.12; eFig. 64.5; Table 64.5)

Treatment of symptomatic peripheral arterial disease (PAD) is multidisciplinary. Currently available drug therapy is not as effective as agents used to treat chronic coronary artery disease (CAD). Pentoxifylline is a xanthine derivative, and its beneficial effects in PAD are believed to be mediated by its hemorheologic properties, including an increase in red blood cell flexibility, as well as by its anti-inflammatory and antiproliferative effects. Several studies have shown that pentoxifylline increases both the walking distance to initial claudication symptoms and the absolute distance able to be traveled. Cilostazol acts by inhibiting phosphodiesterase 3, thereby augmenting cyclic adenosine monophosphate (cAMP) levels, and it has been shown to enhance vasodilatation and inhibit platelet aggregation. Clinical trials have demonstrated that cilostazol improves walking distances and quality of life. It should not be prescribed to patients with heart failure, since other drugs with similar mechanisms of action decrease survival in that population.[1]

Supervised exercise rehabilitation significantly improves symptoms of claudication. Meta-analyses have found that walking programs increase maximum walking distances in patients with PAD by 50% to 200%.[2]

Revascularization options in patients with PAD include percutaneous transluminal angioplasty (PTA) and bypass surgery. PTA of the iliac artery results in patency rates of 60% to 80% at 4 years. This figure improves further with the use of stenting.[3] Aortobifemoral bypass surgery results in 10-year patency rates of nearly 90%.

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ANSWER TO QUESTION 372

C (Braunwald, pp. 1314–1318; Figs. 63.18 and 63.19; see also Answer to Question 352)

The immediate therapeutic goals in the management of aortic dissection are reduction of blood pressure and vascular wall stress and controlling pain. The 2010 thoracic aortic disease guideline recommends initiating an intravenous beta blocker (to reduce the rise in force of left ventricular contraction, dP/dt) such as labetalol. If systolic blood pressure remains >120 mm Hg, the addition of an intravenous vasodilator (e.g., sodium nitroprusside) is recommended to further lower arterial pressure. Such an approach allows for temporary stabilization in appropriate surgical candidates and is the treatment of choice for those patients in whom surgery is not indicated. The appearance of a life-threatening complication such as aortic rupture, acute aortic regurgitation, cardiac tamponade, or compromise of a vital organ mandates immediate surgical intervention.

As indicated in the Answer to Question 352, surgical repair is the standard of therapy for type A (proximal) acute dissection because it has been shown to improve survival. Conversely, patients with uncomplicated type B (distal) aortic dissection can typically be safely managed with initial pharmacologic therapy alone.

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ANSWER TO QUESTION 373

E (Braunwald, pp. 1007–1025; Table 51.1; Figs. 51.1–51.3, 51.7)

Diabetes is a major risk factor for atherosclerosis of the coronary, cerebral, and peripheral arteries, and the prevalence of this condition is increasing in both developed and developing countries.[1] According to the American Diabetes Association, diagnostic criteria for the presence of diabetes include a fasting plasma glucose concentration >126 mg/dL or a hemoglobin A1c level ≥6.5%.[2]

Aggressive and comprehensive risk factor modification reduces adverse cardiovascular outcomes in diabetic patients. In addition to glycemic control, key targets for intervention include hypertension, cigarette smoking, and modification of abnormal lipid levels. A strategy of antilipidemic therapy in diabetic patients without markedly increased cholesterol levels has been tested in several trials. In the CARDS study,[3] diabetic subjects without established coronary disease or high cholesterol levels were randomized to atorvastatin 10 mg daily or placebo. After 4 years, atorvastatin reduced major cardiovascular events by 37% and total mortality by 27%. Baseline lipid levels did not predict benefit from statin therapy: patients with lower than median LDL at entry received the

same advantage from statin therapy as did patients with higher cholesterol levels.

Patients with type 2 diabetes often display reduced serum high-density lipoprotein (HDL), increased triglycerides, and near-normal low-density lipoprotein cholesterol levels. Fibrate therapy (e.g., gemfibrozil or fenofibrate) is effective at reducing triglycerides and raising HDL cholesterol, but the impact of such therapy has not been shown to be beneficial on cardiovascular outcomes in diabetics. In the FIELD study, 9795 middle-aged type 2 diabetics were randomized to placebo or fenofibrate.[4] Over 5 years, fenofibrate did not significantly reduce the risk of the primary outcome of coronary events and there was a trend toward higher total mortality. Similarly, in the ACCORD trial, the addition of fenofibrate to statin therapy did not improve cardiovascular outcomes in type 2 diabetics over 4.7 years of follow-up.[5]

The rate of diabetes development can be reduced by interventions that target undesired lifestyles. In the Diabetes Prevention Program, 3234 nondiabetic persons with impaired glucose tolerance were randomized to an intense lifestyle-modification program (with goals of ≥7% weight loss and at least 150 minutes of physical activity per week), to standard lifestyles, or to metformin. After an average follow-up of 2.8 years, the incidence of diabetes was significantly reduced in both the intense lifestyle group and those taking metformin, but more so in the intense lifestyle group (reductions of 58% and 31%, respectively).[6]

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ANSWER TO QUESTION 374

C (Braunwald, pp. 1069–1082; Figs. 57.1–57.5)

Blood flow to the myocardium is determined by the perfusion pressure gradient and the vascular resistance of the myocardial bed. The latter is influenced by extrinsic forces (e.g., compression by the myocardium) and by intrinsic metabolic, neural, and humoral factors. Intramyocardial pressure is determined primarily by the ventricular pressure throughout the cardiac cycle. Because the ventricular pressure is so much higher in systole than it is in diastole, myocardial compressive forces acting on intramyocardial vessels are greater during this phase. Therefore, the subendocardium, which is subject to higher systolic pressures, receives less systolic flow than the subepicardium. However, *total* flow is greater in the subendocardium than the subepicardium because there is enhanced basal vasodilatation in the former as a result of higher metabolic demands.

Actions that reduce the perfusion pressure gradient during diastole, when the majority of subendocardial flow occurs, lower the ratio of subendocardial to subepicardial flow and may cause the subendocardium to become ischemic. Thus, an increase in ventricular end-diastolic pressure or a decrease in diastolic filling time (e.g., during tachycardia) can reduce subendocardial flow disproportionately. Because the subendocardium has lower basal vascular tone, the reserve for vasodilatation is less than in the subepicardium. Therefore, as perfusion is reduced, the deeper layers of the myocardium become ischemic sooner than the more superficial ones.

ANSWER TO QUESTION 375

C (Braunwald, pp. 1088–1092; Table 57.1; Figs. 57.24, 57.26–57.28; eFigs. 57.7 and 57.8)

As described in the Answer to Question 347, *myocardial stunning* is defined as myocardial dysfunction that persists after a period of severe ischemia, with gradual return of contractile activity. Molecular mechanisms include the generation of oxygen-derived free radicals, calcium overload, and reduced sensitivity of myofilaments to calcium.[1] Stunned myocardium does respond to inotropic therapy, hence the appropriateness of transient inotropic support in some patients after myocardial infarction until the adjacent stunned myocardium recovers contractile function.

In contrast, *hibernating* myocardium refers to myocardial dysfunction that results from chronically decreased coronary blood flow, a condition that can be reversed with revascularization.[2] Histopathologic studies reveal both myocyte dedifferentiation and apoptosis, suggesting that irreversible changes may occur if revascularization is not undertaken.

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ANSWER TO QUESTION 376

C (Braunwald, pp. 1181–1182; Fig. 60.1)

About 15% of patients who present with symptoms consistent with unstable angina are found to have no significant coronary artery disease on angiography. Approximately one-third of such patients present with impaired coronary flow, suggesting the presence of microvascular dysfunction. The short-term prognosis is excellent in this situation.

For patients with a clear culprit lesion, the responsible plaque is typically eccentric, with overhanging edges consistent with a disrupted atherosclerotic locus. Intravascular ultrasonography in patients with unstable angina often demonstrates more soft echolucent lesions (thin fibrous cap and lipid-rich core) and fewer calcified lesions compared with patients with chronic stable angina.

ANSWER TO QUESTION 377

B (Braunwald, pp. 1236–1249; Table 61.14; Fig. 61.16; eFigs. 61.6–61.8)

Comparison of outcomes of coronary artery bypass grafting (CABG) with those of percutaneous coronary intervention (PCI) is a "moving target" because new technologies for both strategies continue to improve outcomes and reduce complications. Nonetheless, randomized trials comparing the two approaches have yielded consistent results.[1] For the majority of patients, there is no difference in the rates of subsequent death or myocardial infarction. Such similar outcomes have been observed in patients with single-vessel coronary artery disease (including left anterior descending coronary artery disease) as well as in patients with multivessel disease. There is, however, consistent evidence that patients who undergo PCI are more likely to have recurrent angina or require additional subsequent interventional procedures.

The SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial, performed between 2005 and 2007, was a major randomized clinical study with long-term follow-up comparing CABG to drug-eluting stent (DES) implantation. It confirmed that CABG and PCI survival rates are similar in patients with relatively uncomplicated coronary disease, but for those with the most complex and widespread CAD, CABG appears to offer a survival advantage. In this trial, 1800 patients with multivessel disease were randomized to CABG or DES implantation. At 12 months, the rates of death or myocardial infarction were similar between the two groups, but the stroke rate was higher in the CABG patients. At 5 years of follow-up, all-cause mortality and stroke rates did not differ, but the occurrence of myocardial infarction or need for repeat revascularization was higher among the PCI patients.[2] Post hoc analysis revealed that at 3 and 5 years of follow-up, patients with the most severe and complex CAD had more adverse cardiac outcomes, including worsened survival, with PCI compared to CABG.

Among diabetic patients with multivessel disease, bypass surgery has also been shown to offer improved survival compared with PCI. For example, the Bypass Angioplasty Revascularization Investigation trial was a large comparison of the two treatment strategies among symptomatic patients with angina whose coronary anatomy was deemed suitable for revascularization by either technique (i.e., two- or three-vessel disease, but not left main stenosis). In this study, patients with diabetes and multivessel disease showed significantly improved survival with CABG compared with coronary angioplasty. These findings were confirmed in the Future REvascularization Evaluation in patients wtih Diabetes Mellitus study. This trial compared CABG and PCI with drug-eluting stents in 1900 diabetic patients with multivessel disease and found CABG reduced all-cause mortality and the incidence of myocardial infarction.[3]

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ANSWER TO QUESTION 378

C (Braunwald, pp. 971–974; Table 48.7)

Multiple studies have demonstrated the benefits of statin therapy in primary and secondary prevention of coronary disease. Most of the early studies compared a moderate dose of statin with placebo therapy. Subsequent trials examined the role of high-dose statins and more aggressive lipid lowering in patients with established coronary artery disease. For example, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial found that treatment with high-dose atorvastatin (80 mg/day) over 4 months reduced cardiac events by 16% compared with placebo.[1]

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial compared high-dose atorvastatin (80 mg/day) versus moderate-dose pravastatin (40 mg/day) begun within 10 days of an acute coronary syndrome (ACS) and found that the risk of death, nonfatal myocardial infarction, or revascularization was reduced by 25% by the more intense regimen, with a significant difference seen within 30 days of randomization.[2] The Reversal of Atherosclerosis with Aggressive Lipid Lowering study compared similar doses of pravastatin and high-dose atorvastatin and, using intravascular ultrasound, demonstrated reduction in atheroma size in the patients randomized to the high-dose atorvastatin over 18 months of therapy.[3]

Not all studies have demonstrated an advantage of high-dose statin therapy over less intense regimens. In the Aggrastat to Zocor (A to Z—TIMI 21) trial, patients with ACS were randomized to an initial therapy of moderate-dose simvastatin (40 mg/day) for 1 month followed by high-dose (80 mg/day) therapy versus placebo for 4 months, followed by low-dose simvastatin (20 mg/day). After 2 years of follow-up, there was no difference in the composite endpoint of cardiovascular events. However, myopathy (creatine kinase >10 times the upper limit of normal) occurred in nine patients receiving high-dose simvastatin versus one patient receiving the less intensive regimen (P = .02). Three patients developed rhabdomyolysis while taking the high-dose simvastatin regimen.[4] Furthermore, the SEARCH trial showed that the incidence of major vascular events was no lower in those randomized to simvastatin 80 mg daily compared with patients receiving 20 mg daily.[5]

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ANSWER TO QUESTION 379

B (Braunwald, p. 1281)

Antiplatelet agents act at a variety of sites to block platelet aggregation. Aspirin is an irreversible inhibitor of cyclooxygenase (COX) that impairs the formation of thromboxane A_2, a potent mediator of platelet aggregation and vasoconstriction. Because platelets are incapable of new COX synthesis, the effect is permanent for the 7- to 10-day lifetime of the affected platelet.[1] Other nonsteroidal anti-inflammatory drugs (NSAIDs) may prevent acetylation of COX by aspirin. For example, there is evidence that concomitant administration of some nonselective NSAIDs, such as ibuprofen, may inhibit the effects of aspirin on COX and *reduce* aspirin's antiplatelet efficacy.[2]

Clopidogrel and prasugrel are thienopyridine derivatives that block the adenosine diphosphate-dependent pathway of platelet activation. Both result in irreversible blockade of the $P2Y_{12}$ ADP receptor and therefore have long effective half-lives.[1] Prasugrel is a more potent inhibitor of the $P2Y_{12}$ receptor and has favorable pharmacokinetics with a more rapid onset of action than clopidogrel. In the TRITON-TIMI 38 trial of patients with moderate-to-high risk acute coronary syndromes with planned percutaneous coronary intervention, those who received prasugrel had a lower composite rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke compared with those who received clopidogrel, but at an increased risk of major bleeding.[3]

Cilostazol is a potent inhibitor of platelet phosphodiesterase-3 that has vasodilator properties. It has been shown to benefit individuals with intermittent claudication due to peripheral arterial disease (see Answer to Question 371).

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ANSWER TO QUESTION 380

B (Braunwald, pp. 1142–1143; see also Answer to Question 321)

The SAVE study was the first trial to demonstrate that angiotensin-converting enzyme (ACE) inhibitor therapy reduces mortality in patients with ST-segment elevation myocardial infarction. Many subsequent studies have demonstrated a similar and consistent benefit of these agents at reducing cardiovascular endpoints after myocardial infarction (MI). This has been shown with short-term use in all patients with MI and in long-term treatment of patients with depressed left ventricular systolic function after MI. Analysis of short-term trials indicates that one-third of the mortality benefit occurs within the first 2 days of ACE inhibitor therapy.[1]

Two studies, OPTIMAAL and VALIANT, evaluated the efficacy of the angiotensin receptor blockers (ARBs) losartan and valsartan, respectively, versus the ACE inhibitor captopril in MI patients. In OPTIMAAL, losartan was better tolerated but there was a nonsignificant trend toward improved survival with captopril. In the VALIANT trial, captopril and valsartan resulted in similar clinical outcomes. The combination of valsartan plus captopril did not offer any advantage of either drug used alone.[2] Thus, in patients intolerant of ACE inhibitors, an ARB is an adequate substitute, but there does not appear to be an advantage of combining the two together in post-MI patients.

The EPHESUS trial examined the role of the selective aldosterone inhibitor eplerenone in patients with MI complicated by left ventricular dysfunction. During 16 months of follow-up, this agent resulted in a 15% relative risk reduction in mortality compared with standard treatment. Such therapy must be prescribed with care, because significant hyperkalemia was more common among the patients treated with eplerenone.[3]

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ANSWER TO QUESTION 381

C (Braunwald, pp. 1341–1342; Fig. 64.14)

This history and angiogram are consistent with thromboangiitis obliterans (TAO), also known as Buerger disease. This disease of *small and medium* arteries of the arms and legs predominantly affects young individuals (onset usually <45 years) and is almost always associated with tobacco use.[1,2] TAO is more prevalent in Asia than in North America and Europe, and >75% of affected patients are men. The most common presentation includes resting pain of the feet, calves, hands, or forearms, and digital ulcerations are frequently observed. Raynaud phenomenon and superficial thrombophlebitis are common.

Angiography of affected limbs in patients with TAO demonstrates segmental occlusion of small and medium vessels, the absence of atherosclerosis, and corkscrew collateral vessels bypassing the occlusions.

Smoking cessation is the most important therapy for this condition. Patients who continue to smoke face a 40% to 45% risk of future amputation. There is no evidence that statin therapy is beneficial and there is usually no role for vascular surgery because of the diffuse nature of the disease and the generally poor distal vasculature.

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ANSWER TO QUESTION 382

D (Braunwald, pp. 950–952; Tables 47.14 and 47.15; Fig. 47.10)

The incidence of hypertensive emergencies is falling as a result of widespread treatment of chronic hypertension. In addition to a marked rise in blood pressure, a hypertensive crisis is associated with end-organ damage. Acute retinal effects include hemorrhages, exudates, or papilledema (termed *accelerated-malignant hypertension*). *Hypertensive encephalopathy* is manifest by headache, irritability, confusion, somnolence, stupor, focal neurologic deficits, seizures, and eventually coma. In previously normotensive individuals, encephalopathy may occur at a lower blood pressure than in those with a history of chronic hypertension. The pathogenesis of hypertensive encephalopathy is thought to involve failure of cerebral autoregulation, with *dilatation* of cerebral arterioles leading to excessive cerebral blood flow and damage to the arteriolar wall with *increased* vascular permeability.

Other clinical features of hypertensive crises include renal insufficiency *with* proteinuria, microangiopathic hemolytic anemia, congestive heart failure, and nausea and vomiting. Patients who have elevated blood pressure and any end-organ manifestations of hypertensive emergency require rapid therapeutic intervention, usually with parenteral drug therapy.

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ANSWER TO QUESTION 383

A (Braunwald, pp. 1307–1313; Table 63.5)

The transesophageal echocardiogram shows the proximal ascending aorta in long-axis view in a patient with proximal aortic dissection. The aortic valve, and true (T) and false (F) lumina are identified. The linear shadow (labeled "I") is an intimal flap. The major predisposing factor for aortic dissection is cystic medial degeneration. Of the conditions that promote cystic medial degeneration, age and hypertension are the two most common. Hereditary abnormalities of connective tissue—Marfan syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome—are all associated with cystic medial degeneration, as is bicuspid aortic valve.

Approximately half of all dissections in women younger than 40 years occur in association with pregnancy, most commonly in the third trimester or early postpartum period.[1] Cocaine, but not heroin use, has also been associated with aortic dissection.[2]

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ANSWER TO QUESTION 384

B (Braunwald, pp. 1148–1158)

Cardiogenic shock is defined as persistent hypotension with systolic arterial pressure <90 mm Hg and a reduction of the cardiac index (<2.2 L/min/m^2) with an elevated left ventricular (LV) filling pressure (pulmonary capillary wedge pressure >18 mm Hg). Mechanical complications of myocardial infarction, such as acute mitral regurgitation or ventricular septal rupture, should be excluded in order to attribute cardiogenic shock to LV dysfunction. The SHOCK trial randomized patients with cardiogenic shock due to LV failure to either medical therapy or urgent revascularization by percutaneous coronary intervention or bypass surgery. At 30 days there was no significant difference in cardiovascular outcomes between the medical and revascularization groups. However, after 1 year, survival rates were higher in the patients who had undergone revascularization therapies.[1]

From this evidence, urgent mechanical revascularization is recommended for patients with cardiogenic shock. Vasopressors, intra-aortic balloon counterpulsation, and percutaneous left ventricular assist devices all improve hemodynamics in cardiogenic shock and are often useful as temporizing measures. However, these interventions have not been shown to improve long-term survival in randomized trials.[2,3]

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ANSWER TO QUESTION 385

D (Braunwald, pp. 1153–1154; see also Answer to Question 334)

Right ventricular infarction (RVI) frequently accompanies inferior left ventricular infarction and may be recognized by a characteristic clinical and hemodynamic pattern. Hypotension or a marked hypotensive response to nitroglycerin or diuretics in patients with inferior infarction suggests the diagnosis of RVI. The hemodynamic picture of this condition is similar to that of pericardial disease and may include an elevated right ventricle (RV) filling pressure, a steep right atrial *y* descent, and a "square root sign" in the RV pressure tracing. The Kussmaul sign may also be present. The presence of unexplained systemic hypoxemia in the setting of RVI suggests the possibility of right-to-left shunting through a patent foramen ovale because of the elevated right-sided pressures. The placement of right-sided precordial ECG leads is helpful in establishing the diagnosis of RVI. ST-segment elevation in lead V_4R is specific and sensitive for this diagnosis.

Because left-sided filling pressures are dependent on the transport of blood from the right heart, RVI may reduce left ventricular preload and result in a marked reduction in LV stroke volume and systemic hypotension. Thus, initial therapy for hypotension in RVI should usually include volume expansion, and diuretics should generally be avoided.

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ANSWER TO QUESTION 386

B (Braunwald, p. 1333; Fig. 64.4)

Segmental pressure measurements and determination of the ankle/brachial index (ABI) are simple and very useful noninvasive methods to evaluate symptoms of peripheral arterial disease. To measure segmental pressures, pneumatic cuffs are placed over the upper and lower thigh, calf, and ankle and above the metatarsal area of the foot, then systolic pressures are measured using a Doppler probe. In the iliac and femoral arteries, a 70% to 90% decrease in the cross-sectional area of the artery must be present to create a pressure gradient. A gradient >20 mm Hg between successive levels of the cuffs is evidence of a significant stenosis.

Measurement of the ABI is an even simpler screening tool that represents the ratio of the systolic pressure at the ankle to that of the brachial artery, typically measured using a Doppler flow probe. A normal ABI is >1.0. An ABI of <0.9 is very sensitive for angiographic evidence of an arterial stenosis. Patients with critical limb ischemia typically have an ABI of <0.5. The sensitivity of the ABI is *decreased* in severely calcified arteries because such vessels do not compress and therefore have spuriously high systolic pressure readings.

The patient in this case has segmental pressure measurements consistent primarily with significant stenoses in the right iliac and common femoral arteries.

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ANSWER TO QUESTION 387

B (Braunwald, p. 1283)

Restenosis after percutaneous coronary intervention is due to the local proliferation of neointimal tissue. Factors that increase rates of restenosis include small vessels, long lesions, and the presence of diabetes. Original plain balloon angioplasty was associated with a high (30% to 40%) rate of restenosis. The introduction of bare metal stents reduced the rate of angiographic restenosis to 20% to 30%. The initial placement of a drug-eluting stent in appropriate lesions is the most effective means to suppress local neointimal proliferation and restenosis rates, as discussed in the answer to a subsequent question.

There is no evidence that treatment of in-stent restenosis with either direct coronary atherectomy or rotational atherectomy improves recurrences of in-stent restenosis compared with balloon angioplasty using a cutting balloon. Brachytherapy, using gamma radiation, prevents neointimal proliferation and reduces the rate of this complication; however, implantation of a drug-eluting stent is more effective for treating bare metal stent (BMS) restenosis.[1]

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ANSWER TO QUESTION 388

C (Braunwald, pp. 1278–1280; see also Answer to Question 324)

Drug-eluting stents (DES) release pharmaceutical agents that suppress neointimal proliferation, and are very effective at preventing restenosis after percutaneous coronary interventions. Currently available systems include those that slowly release sirolimus, paclitaxel, zotarolimus, or everolimus. *Sirolimus* is a cytostatic inhibitor of neointimal growth. In the RAVEL study, the first large study comparing a DES with a bare metal stent, there was no angiographic restenosis in the patients randomized to the sirolimus-eluting group.[1] The larger SIRIUS trial demonstrated a 4.1% restenosis rate compared with 16.6% in the bare-metal stent group.[2] *Paclitaxel* stabilizes microtubules and prevents cell division. The TAXUS-IV trial, a large randomized study of bare metal versus paclitaxel-eluting stents, found that the latter exhibited a marked reduction of subsequent in-stent stenosis. The target vessel revascularization at 9 months was reduced from 11.3% to 3%.[3] *Everolimus* and *zotarolimus* are rapamycin analogs with immunosuppressive and antiproliferative properties. Everolimus was compared with paclitaxel in the SPIRIT IV trial of patients with coronary artery disease undergoing percutaneous coronary intervention. Those who received the everolimus-eluting stent had *reduced* target lesion failure over 2 years of follow-up.[4] Zotarolimus-eluting stents were not shown to reduce target lesion revascularization (TLR) or late stent thrombosis more than sirolimus[5]; rates of TLR were similar when zotarolimus was compared to paclitaxel-eluting stents.[6]

Because a DES impairs endothelial regrowth after balloon expansion, extended use of aspirin plus an oral $P2Y_{12}$ platelet receptor antagonist (clopidogrel, prasugrel, or ticagrelor) is required after implantation to prevent thrombosis. Rare cases of life-threatening late stent thrombosis have been reported many months or years after DES implantation, particularly when dual antiplatelet therapy has been discontinued prematurely. A large randomized trial compared stent thrombosis at 3 years between zotarolimus and sirolimus DES and found no difference in the occurrence of late thrombosis.[7] Current guidelines recommend at least 12 months of dual antiplatelet therapy after DES implantation.[8]

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ANSWER TO QUESTION 389

A (Braunwald, pp. 897–899)

A program of regular exercise is associated with reduced cardiovascular risk presumably because of its beneficial effects on traditional risk factors such as hypertension, dyslipidemia, and diabetes. Regular exercise also appears to contribute to a less prothrombotic state by altering the activity of the fibrinolytic system: exercise reduces plasma fibrinogen and plasminogen activator inhibitor-1 levels and increases tissue plasminogen activator levels. In addition, although sudden exercise in chronically sedentary individuals may increase platelet activation, a program of regular exercise has the beneficial opposite effect.

Heart rate variability is a measure of autonomic function that is dependent on the relation between parasympathetic and sympathetic tone. Reduced heart rate variability is associated with an elevated risk of coronary artery disease and mortality. Regular exercise reduces parasympathetic tone and *increases* (i.e., improves) heart rate variability.

Exercise has been shown to improve the impaired endothelial-dependent vasodilatation typical of patients with coronary artery disease or coronary risk factors, likely because of increased expression of nitric oxide (NO) synthase and NO production. Exercise also tends to produce beneficial changes in the lipid profile, including higher levels of high-density lipoprotein and lower levels of low-density lipoprotein and triglycerides.

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ANSWER TO QUESTION 390

B (Braunwald, pp. 1069–1070; Figs. 57.1, 57.2)

The three major components of myocardial oxygen demand (MVO_2) are heart rate, the myocardial contractile state, and wall tension. In turn, wall tension during systole is proportional to the aortic pressure and intraventricular volume. An increase in any of these parameters results in augmented myocardial oxygen consumption.

Heart rate is generally the most important determinant of MVO_2 and the balance between myocardial oxygen supply and demand. For example, during tachycardia MVO_2 increases and, at the same time, coronary oxygen supply may suffer because the shortened diastolic filling period tends to reduce subendocardial coronary blood flow.

The circulating content of hemoglobin is an important determinant of myocardial oxygen supply, not MVO_2.

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ANSWER TO QUESTION 391

D (Braunwald, pp. 1012, 1023–1024)

Diabetes and hypertension frequently coexist and augment the risk of coronary events. Diabetics with even mild chronic renal disease are prone to hyperkalemia because of the associated syndrome of hyporeninemic hypoaldosteronism, combined with impaired insulin secretion, both of which increase the serum potassium concentration. Thus, supplemental potassium and potassium-sparing diuretics must be used with caution in such patients.

Although tomatoes and bananas are rich sources of potassium, it would be unusual for a normal diet to cause such a marked rise in potassium. Urinary tract infections may increase potassium in the setting of worsened renal function (which was not observed in this patient). Primary hyperaldosteronism and Cushing syndrome are more likely to cause hypokalemia than hyperkalemia.

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ANSWER TO QUESTION 392

C (Braunwald, p. 1281)

Prasugrel, like clopidogrel, is a thienopyridine derivative that impairs platelet aggregation through irreversible inhibition of the $P2Y_{12}$ receptor.[1] Active metabolites of prasugrel render it 10 times more potent an antiplatelet agent than clopidogrel. In the TRITON-TIMI 38 trial, 13 608 patients with acute coronary syndromes for whom PCI was planned were randomized to either prasugrel (60 mg loading dose, followed by 10 mg daily) or clopidogrel (300 mg loading dose, followed by 75 mg daily).[2] Over 15 months of follow-up, prasugrel reduced the outcomes of cardiovascular death, myocardial infarction, or stroke by 19%. In patients who received stents, prasugrel also reduced the risk of stent thrombosis by half. However, prasugrel was associated with an increased rate of fatal bleeding compared with clopidogrel (0.4 vs. 0.1%, $P = .002$). Bleeding complications were greatest in the elderly (≥75 years), patients with prior stroke or transient ischemic attack, and those who weigh <60 kg, so that prasugrel should be avoided in such patients.[3]

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ANSWERS TO QUESTIONS 393 TO 396

393–B, 394–C, 395–A, 396–D (Braunwald, pp. 859–869; Figs. 44.4, 44.5, 44.7)

Each of the cell types listed is involved in atherogenesis. *Endothelial cells*, which represent a large and extensive lining of the entire vascular tree, form a highly selective, permeable barrier to the bloodstream and maintain a non-thrombogenic surface. They also actively manufacture and secrete several important vasoactive substances. Endothelial cells have a surface coat of heparan sulfate, which reduces thrombogenicity, and produce prostaglandin derivatives, in particular prostacyclin. The latter is a vasodilator that inhibits platelet aggregation. In addition, endothelial cells secrete tissue plasminogen activator, which contributes to lysis of fibrin clots, and nitric oxide, which causes vasodilatation and inhibits platelet aggregation. Thus, endothelial cells regulate or provide protection against the development of inappropriate thrombus formation through several mechanisms.

Smooth muscle cells are primarily derived from the media of the vessel wall. Their principal physiologic role in the media is to maintain arterial wall tone via the capacity to alter contractile state in response to many substances. For example, prostacyclin induces relaxation and vasodilatation, whereas epinephrine and angiotensin cause smooth muscle contraction. During atheroma formation, smooth muscle cells migrate into the intima, likely attracted by platelet-derived growth factor and other chemoattractants. Extensive proliferation of smooth muscle cells in the intima contributes significantly to the development of mature atherosclerotic plaque.

Macrophages, derived from circulating blood monocytes, are capable of secreting a large number of biologically active substances that participate in inflammatory and immune responses. Macrophages become foam cells by extensive, non-low-density lipoprotein receptor-mediated, accumulation of cholesteryl ester and as such form the principal cells in the fatty streak. The macrophage foam cells provide a major source of proinflammatory mediators, which are thought to play a critical role in atherogenesis.

Platelets interact in an important manner with both the endothelium and developing atherosclerotic plaque. Although platelets are capable of little or no protein synthesis, they contain numerous substances in their granules that are released on platelet activation. These include contributors to the coagulation cascade as well as several potent growth factors or mitogens. Growth factors may play an important role in stimulating both vasoconstriction and subsequent proliferation in the injured vessel wall.

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ANSWERS TO QUESTIONS 397 TO 400

397–B, 398–A, 399–D, 400–C (Braunwald, p. 952)

Beta blockers inhibit the beta-adrenergic receptor, which is part of the adenylate cyclase system.[1] Inhibition results in lower levels of cyclic adenosine monophosphate and cytosolic calcium. Beta blockers can be divided into three general groups. First-generation agents are nonselective, inhibiting both $beta_1$- and $beta_2$-adrenergic receptors (e.g., propranolol); second-generation agents are relatively $beta_1$ selective, although this selectivity diminishes with higher doses (e.g., metoprolol or atenolol); and third-generation agents have additional vasodilatation properties (e.g., carvedilol, which has alpha- and beta-receptor blocking activities).

In addition to these pharmacodynamic properties, there are also important pharmacokinetic differences among beta blockers. For example, propranolol is very lipophilic, is readily absorbed from the gastrointestinal tract, is metabolized by the liver, and has a short half-life. In contrast, atenolol is very hydrophilic, is not as readily absorbed from the gastrointestinal tract, is metabolized by the kidney, and has a longer half-life so that it can be administered less frequently.

Some beta blockers (e.g., pindolol, acebutolol) have partial beta-agonist activity. These agents produce low-grade beta stimulation when sympathetic tone is low (e.g., at rest), but behave like more conventional beta blockers when sympathetic activity is high, such as during exercise.

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ANSWERS TO QUESTIONS 401 TO 405

401–A, 402–B, 403–B, 404–C, 405–B (Braunwald, pp. 1163–1164, 1155–1156; eFig. 59.8)

Both aneurysms and pseudoaneurysms can complicate acute myocardial infarction. A true aneurysm is a discrete dyskinetic region of the ventricular wall that results from expansion and dilatation of a segment of scarred, thinned myocardium. The wall always contains some myocardial elements. The base of a true aneurysm is wide and the risk of free wall rupture is low. Mural thrombus may form along the wall of the aneurysmal segment, and anticoagulation is usually appropriate, at least temporarily. Surgical repair is sometimes indicated, for example, if the aneurysm results in intractable heart failure or uncontrolled ventricular arrhythmias.

In contrast, pseudoaneurysms represent an incomplete rupture of the ventricular free wall that is sealed by organizing thrombus and pericardium. Pseudoaneurysms can become very large and communicate with the left ventricle through a narrow neck. Although the base is narrow, the risk of progressive rupture is high and surgical repair is indicated. The distinction between true aneurysms and pseudoaneurysms can usually be readily discerned by echocardiography.

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ANSWERS TO QUESTIONS 406 TO 409

406–C, 407–E, 408–D, 409–C (Braunwald, p. 1282)

Unfractionated heparin (UFH) is a glycosaminoglycan with a high binding affinity for antithrombin. When bound to heparin, antithrombin undergoes a conformational change that results in greater inactivation of factor IIa (thrombin) and factor Xa, thus interfering with clot formation.

Low-molecular-weight heparins (LMWHs) are derived from UFH via chemical or enzymatic depolymerization. The shorter molecules still activate antithrombin but have greater anti-factor Xa than anti-factor IIa activity. This feature causes LMWHs to inhibit thrombin generation more effectively, and the high bioavailability permits subcutaneous, rather than intravenous, administration. The reduced binding of LMWHs to plasma proteins allows a predictable drug effect such that routine monitoring of anticoagulant activity is not usually necessary. If the anticoagulant effect does need to be assessed (e.g., in obese individuals or patients with renal impairment), anti-Xa activity, not the activated partial thromboplastin time (aPTT), should be measured. LMWHs are less likely to trigger type II heparin-induced thrombocytopenia (HIT), but are still contraindicated in patients with this syndrome, because HIT antibodies can cross-react with LMWH.

Bivalirudin is a synthetic peptide that is an intravenous direct thrombin inhibitor—it binds directly to thrombin without requiring antithrombin. Because it is cleaved once bound to thrombin, bivalirudin has a very short half-life. It appears to be safe in patients with a history of HIT. Its anticoagulant effect can be followed by measuring the aPTT. The doses of both bivalirudin and LMWH require adjustment in the setting of advanced renal insufficiency.

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ANSWERS TO QUESTIONS 410 TO 414

410–B, 411–C, 412–D, 413–C, 414–A (Braunwald, pp. 859–869; Figs. 44.4, 44.5, 44.7; see also Answers to Questions 393–396)

The initial stages of atherogenesis include extracellular lipid accumulation and leukocyte recruitment.[1] The latter process is mediated by several groups of adhesion molecules. One group includes members of the immunoglobulin superfamily, including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. Another group includes selectins such as P-selectin and E-selectin. Expression of these adhesion molecules on the surface of endothelial cells regulates the adherence of monocytes and T cells to the arterial wall. Entry of leukocytes into the intima is then mediated by chemoattractant cytokines such as monocyte chemoattractant protein-1.

Once recruited into the arterial intima, monocytes imbibe lipid particles to become lipid-laden macrophages, termed foam cells. Although other cells in the body express surface low-density lipoprotein (LDL) receptors that regulate LDL uptake, this is not true of foam cells. In these cells, scavenger uptake receptors allow unregulated lipid accumulation. The precursor atherosclerotic lesion composed of foam cells is known as the fatty streak.

A subsequent step in formation of an atherosclerotic lesion involves smooth muscle cell migration and proliferation in the intima. Many of the smooth muscle cells in atherosclerotic lesions derive from the arterial medial layer.[2] The chemoattractants responsible for migration into the intima include platelet-derived growth factor, which is secreted by activated macrophages. With the addition of extracellular matrix consisting of collagen and proteoglycans secreted by the smooth muscle cells, the fibrous plaque is formed.

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ANSWERS TO QUESTIONS 415 TO 418

415–B, 416–D, 417–D, 418–A (Braunwald, pp. 1129–1132; Table 59.4; eFigs. 59.3 and 59.4)

Each of the available fibrinolytic drugs for use in acute ST-segment elevation myocardial infarction (MI) possesses unique characteristics. The first-generation fibrinolytic agent was *streptokinase* (SK), which is an indirect plasminogen activator and therefore relatively nonspecific for fibrin. In comparative trials, it had the lowest rate of intracranial hemorrhage. Produced by beta-hemolytic streptococci, SK is antigenic and allergic reactions occur in 5% to 6% of patients. *Alteplase* (tissue plasminogen activator [tPA]) is a second-generation, more fibrin-specific fibrinolytic. It has the shortest half-life (4 to 8 minutes) of all current fibrinolytics and therefore is administered as a bolus followed by continuous infusion over 90 minutes or longer.

Modifications to the basic structure of tPA have yielded a series of third-generation fibrinolytics with more prolonged plasma clearance rates, including *reteplase* (RPA) and *tenecteplase* (TNK-tPA). RPA is a deletion mutant of tPA with a longer half-life (15 minutes) but reduced fibrin specificity. It is administered as a double intravenous bolus, 30 minutes apart. TNK-tPA is a triple mutant with resultant increased fibrin specificity, a longer half-life, and reduced sensitivity to plasminogen activation inhibitor-1. It is administered as a single intravenous bolus.

The third-generation fibrinolytics result in 30-day post-MI mortality rates similar to tPA. However, they offer the convenience of bolus administration.

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ANSWERS TO QUESTIONS 419 TO 422

419–C, 420–C, 421–B, 422–A (Braunwald, pp. 1155–1158; Table 59.11; Figs. 59.27–59.30)

Rupture of the interventricular septum after acute myocardial infarction (MI) usually occurs in the setting of anterior wall infarction and in patients with poor collateral circulation.

In fibrinolytic trials, it developed in only 0.8% of patients, with an associated 30-day mortality of 74%. Septal defects in patients with anterior infarction tend to be apical in location, whereas inferior infarctions are associated with perforation of the basal septum (a more difficult area to surgically repair). Partial or total rupture of a papillary muscle (as shown in the figure) in the setting of acute MI is usually due to ischemic damage to the posteromedial papillary muscle in inferior wall infarction. Papillary muscle rupture occurs with relatively small infarctions in approximately half of the cases, in contrast to rupture of the ventricular septum, which almost always results from large infarcts.

Clinically, patients with both lesions develop a new holosystolic murmur. The murmur of interventricular septal rupture is often louder and accompanied by a systolic thrill. In both lesions, the murmur may decrease or disappear as arterial blood pressure (and therefore systemic afterload) falls. The distinction between acute ventricular septal rupture and mitral regurgitation can be made readily by echocardiography.

At heart catheterization, patients with either lesion may demonstrate tall *v* waves in the pulmonary capillary wedge tracing. Measurement of oxygen saturation via a pulmonary artery catheter can distinguish between the two: in ventricular septal rupture there is a "step-up" in oxygen saturation in the right ventricle (compared with the right atrium) as a result of oxygenated blood entering the right ventricle from the left ventricle.

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ANSWERS TO QUESTIONS 423 TO 427

423–C, 424–C, 425–A, 426–C, 427–A (Braunwald, pp. 971–977; Tables 8.8 and 48.9; Figs. 48.7 and 48.9)

The Scandinavian Simvastatin Survival Study (4S) was a secondary prevention trial that examined the effect of simvastatin over 5.4 years in 4444 individuals with known coronary disease and very high serum cholesterol. Treatment with simvastatin was associated with highly significant reductions in nonfatal myocardial infarction (MI) and cardiovascular death (34%) and overall mortality (30%).[1]

The HPS study compared the benefit of simvastatin (40 mg/day) with placebo in over 20,000 patients at risk for vascular events who would not have met criteria for lipid lowering at the time of enrollment. The study included patients with established atherosclerotic disease and those with multiple risk factors. Randomization to simvastatin was associated with a 24% reduction in major vascular events and 13% reduction in all-cause mortality. Subgroup analysis showed there was equal benefit for women, the elderly, and diabetic patients.[2]

The ASCOT-LLA investigators randomized 10,305 hypertensive patients with total cholesterol <250 mg/dL to either atorvastatin 10 mg daily or placebo. Patients with a history of myocardial infarction, cerebrovascular disease, or current angina were excluded. After 3.3 years, atorvastatin was associated with a 27% reduction in stroke and a 21% reduction in total cardiovascular events, but overall mortality was not significantly impacted.[3]

The JUPITER trial examined the effects of rosuvastatin 20 mg daily versus placebo over 1.9 years in 17,802 apparently healthy men and women who had low-density lipoprotein (LDL) cholesterol <130 mg/dL but high-sensitivity C-reactive protein >2.0 mg/L. Treatment with rosuvastatin was associated with a significant 44% reduction of the composite outcome of MI, stroke, revascularization, unstable angina, or cardiovascular death. The individual components of the primary outcome were also significantly reduced, as was overall mortality. There was a higher incidence of physician-reported diabetes in the rosuvastatin-treated group.[4]

The FOURIER trial randomized over 27,000 patients with atherosclerotic cardiovascular (CV) disease and LDL concentrations of ≥70 mg/dL on statin therapy to the PCSK9 inhibitor evolocumab or placebo.[5] Among these patients with LDL cholesterol levels not previously considered elevated, the addition of evolocumab resulted in a mean 59% further reduction in LDL concentration over a mean follow-up of 2.2 years. In the evolocumab group, there was a significant reduction in the primary composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, as well as the key secondary endpoint of CV death, MI, or stroke. MI and stroke were each individually reduced with evolocumab, though the reduction seen for CV death was not statistically significant.

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ANSWERS TO QUESTIONS 428 TO 431

428–D, 429–D, 430–B, 431–C (Braunwald, p. 971; Table 48.7)

Many medications affect serum lipid levels. Beta blockers (excluding those with intrinsic sympathomimetic activity and those with concurrent alpha-blocking properties) can lower serum high-density lipoprotein (HDL) cholesterol. Second-generation antipsychotic medications (e.g., clozapine, olanzapine) can contribute to weight gain, insulin resistance, and increased triglyceride and low-density lipoprotein cholesterol levels.[1] Corticosteroids raise triglyceride levels and lower serum HDL levels.

Examples of cardiovascular drugs that have no significant effect on plasma lipoproteins include calcium channel antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

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ANSWERS TO QUESTIONS 432 TO 435

432–A, 433–A, 434–C, 435–B (Braunwald, pp. 966–970; Tables 48.5 and 48.6)

Familial hypercholesterolemia (FH) is associated with specific dermatologic lesions. Heterozygotes may develop nodular swellings of the tendons around the knee, elbow, dorsum of the hand, and ankle, known as *tendon xanthomas*, as shown in part *B* of the figure. Microscopically, these consist of large deposits of cholesterol, both extracellularly and within scavenger macrophage cells.

Although deposition of cholesterol in the tissues of the eyelid and within the cornea, known respectively as *xanthelasma* (part *C* in the figure) and *arcus corneae*, may be observed in FH, they can also occur in adults with other lipid disorders and even in those with normal plasma lipid levels.

Patients with *homozygous* FH have dramatic elevations in plasma low-density lipoprotein from birth, with levels typically sixfold to eightfold higher than normal. In addition, they demonstrate a unique cutaneous finding, the *planar xanthoma*. The latter may be present at birth but always develops within the first 6 years of life. Planar xanthomas are yellow and occur at points of trauma over the knees, elbows, and buttocks. In addition, they may be found in the interdigital webs of the hands, especially between the thumb and index finger (part *A* in the figure). Tendon xanthomas, xanthelasma, and arcus corneae also occur in homozygotes.

Type III hyperlipoproteinemia, or familial dysbetalipoproteinemia, is a single-gene disorder that requires both the presence of a mutation in the gene for apolipoprotein E and contributory environmental or genetic factors. In this disorder, the plasma concentrations of both cholesterol and triglycerides are elevated because of the accumulation of remnant-like particles derived from the partial metabolism of both very-low-density lipoprotein and chylomicrons. Two specific dermatologic lesions are characteristic of type III hyperlipoproteinemia. Xanthoma striatum palmare appears as orange or yellow discolorations of the palmar and digital creases, as illustrated in part *D* in the figure. In addition, tuberoeruptive xanthomas are characteristically located over the elbows and knees in this disorder (not shown).

SECTION IV QUESTIONS

(CHAPTERS 67 TO 87)

Diseases of Heart Valves, Myocardium, Pericardium, and Pulmonary Vascular Bed

Fidencio Saldaña, Bradley A. Maron, David D. Berg, and Leonard S. Lilly

Directions:

For each question below, select the ONE BEST response.

QUESTION 436

A 62-year-old woman, previously healthy except for hypertension, presents to the hospital with severe substernal chest heaviness and dyspnea for the past 2 hours. The discomfort began minutes after being told that her son was seriously injured in an automobile accident. On examination she appears diaphoretic, the blood pressure is 152/84 mm Hg, heart rate 88 beats/min, O_2 saturation 96%, jugular venous pressure 8 cm, the chest is clear, cardiac examination shows no gallop or murmur, and there is no peripheral edema. The ECG shows new diffuse T-wave inversions, and the cardiac troponin T is 1.07 ng/mL (reference <0.01 ng/mL). She receives aspirin, clopidogrel, intravenous unfractionated heparin, metoprolol, and atorvastatin. The chest discomfort persists despite IV nitroglycerin, and coronary angiography is undertaken. No coronary stenoses are found. Left ventriculography is performed (Fig. 4.1). Which of the following statements is correct?

A. She should receive anticoagulation with warfarin for the next 4 months
B. An echocardiogram 2 months later will likely show apical akinesis
C. A recanalized coronary thrombus is the likely etiology
D. This syndrome occurs predominantly in postmenopausal women
E. Her expected in-hospital mortality is ~15%

QUESTION 437

A 55-year-old previously healthy man is brought to the emergency department because of left-sided chest pain over the past 3 hours. He denies shortness of breath or cough. The discomfort is less intense when he sits forward. The chest radiograph is unremarkable; the ECG is shown in Fig. 4.2. Which of the following statements regarding this patient's condition is TRUE?

A. Fibrinolytic therapy is indicated if cardiac catheterization is not immediately available
B. Nitrates will substantially relieve the chest pain
C. Nonsteroidal anti-inflammatory therapy is indicated
D. Glucocorticoid therapy should be initiated immediately
E. Measurement of serum cardiac troponin I would clearly differentiate the cause of his chest pain

QUESTION 438

Which of the following statements about coarctation of the aorta is TRUE?

A. After successful repair, systemic hypertension frequently persists
B. Coarctation is more common in females
C. Chest pain and palpitations are common symptoms in older children and adults
D. Atrial septal defect is the most common associated cardiac finding
E. A midsystolic murmur over the mid-anterior abdomen is common

QUESTION 439

An 80-year-old man presents with syncope. During evaluation a systolic murmur is auscultated and an echocardiogram is obtained. A continuous-wave Doppler recording through the aortic valve is shown in Fig. 4.3. Which of the following statements about this disorder is NOT correct?

A. A gradual decrease in exercise tolerance or dyspnea on exertion is the earliest manifestation
B. Up to 50% of patients with this condition who describe typical angina do not have significant coronary arterial obstruction
C. Syncope commonly occurs without significant change in systemic vascular tone
D. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema are late manifestations
E. Gastrointestinal bleeding has been associated with this disorder

QUESTION 440

A 28-year-old man presents to the emergency department because of severe chest pain and dyspnea after cocaine

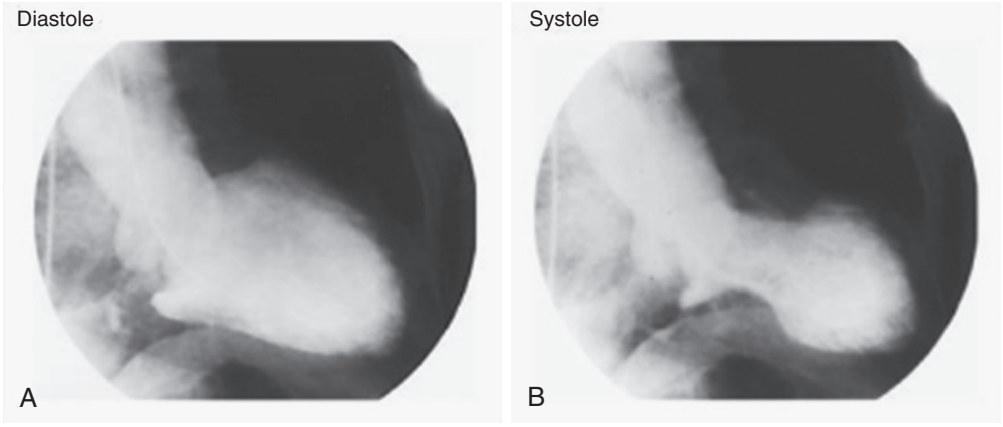

FIG. 4.1 *(A) Diastole; (B) systole.*

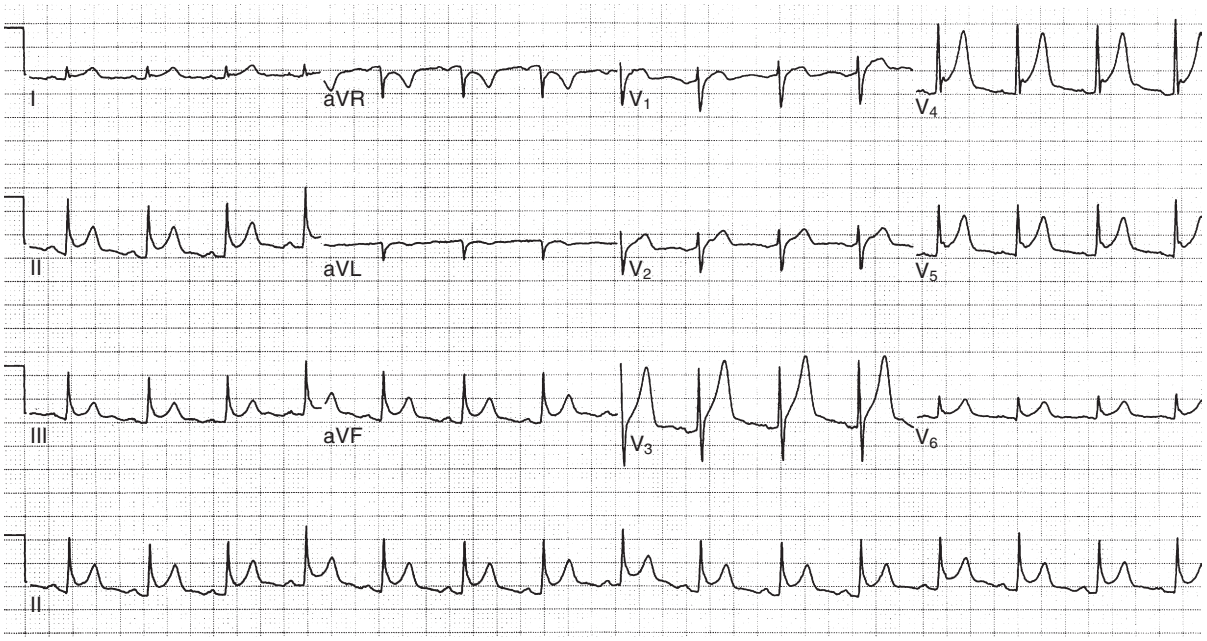

FIG. 4.2

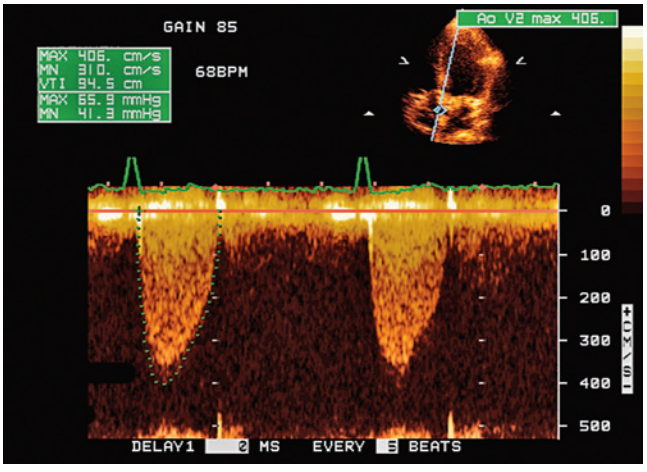

FIG. 4.3

use. His medical history is notable for several years of intermittent cocaine use, alcohol abuse, and cigarette smoking. He has no other known cardiac risk factors. Which of the following statements about cocaine use and the cardiovascular system is NOT true?

A. Cocaine use increases the risk of myocardial infarction (MI) 24-fold in individuals otherwise at low risk for MI
B. The risk of MI after cocaine is related to the amount ingested and the frequency of its use
C. Left ventricular systolic dysfunction can occur both acutely and after long-term cocaine use
D. Mechanisms of cocaine-related myocardial ischemia and infarction include coronary arterial vasoconstriction and enhanced platelet aggregation

QUESTION 441

Which of the following statements about atrial septal abnormalities is NOT correct?

A. The sinus venosus-type atrial septal defect (ASD) is almost always accompanied by anomalous pulmonary venous connections

B. A patent foramen ovale can be found in approximately 25% of healthy adults
C. The most common presenting symptoms of ASDs in adults are exercise intolerance and palpitations
D. Children with ASDs typically experience easy fatigability and exertional dyspnea
E. Atrial arrhythmias are uncommon in children with ASDs

QUESTION 442

True statements about the ECG in congenital heart disease include all of the following EXCEPT
A. First-degree atrioventricular (AV) block is often present in patients with AV septal defects, congenitally corrected transposition of the great arteries, or Ebstein anomaly
B. Atrial fibrillation is more common than atrial flutter in young patients with congenital heart disease
C. The presence of right ventricular hypertrophy suggests pulmonary hypertension or right ventricular outflow tract obstruction
D. In infants, the electrocardiographic pattern of myocardial infarction is associated with anomalous origin of a coronary artery
E. Deep Q waves in the left chest leads can be caused by left ventricular volume overload in a young person with aortic or mitral regurgitation

QUESTION 443

Which of the following statements regarding ventricular septal defects (VSDs) is NOT correct?
A. Muscular VSDs are bordered entirely by myocardium
B. Small VSDs pose a high risk of endocarditis
C. A restrictive VSD does not cause significant hemodynamic derangement and may close spontaneously during childhood
D. Infants with large, nonrestrictive VSDs come to medical attention at an earlier age than those with restrictive defects
E. The ECG after VSD repair usually demonstrates right bundle branch block

QUESTION 444

Which of the following statements regarding atrial septal defects (ASDs) is TRUE?
A. Percutaneous device closure of ASDs improves functional status in symptomatic patients and exercise capacity in both asymptomatic and symptomatic patients
B. Children who have undergone repair of an isolated secundum defect should receive lifelong endocarditis prophylaxis
C. Murmurs are not typically present in patients with uncomplicated ASDs
D. Left-axis deviation of the QRS complex on the ECG suggests the presence of a sinus venosus ASD
E. Surgical or device closure is not indicated in a patient with a pulmonary to systemic shunt ratio (Q_p/Q_s) <2.5

QUESTION 445

A 34-year-old woman presents with recurrent syncope. In recent months she has noted a 10-lb unintentional weight loss, malaise, and diffuse arthralgias. She denies dyspnea, palpitations, or chest pain. A two-dimensional echocardiogram (subcostal view) is shown in Fig. 4.4. Which of the following statements is TRUE about this patient's condition?

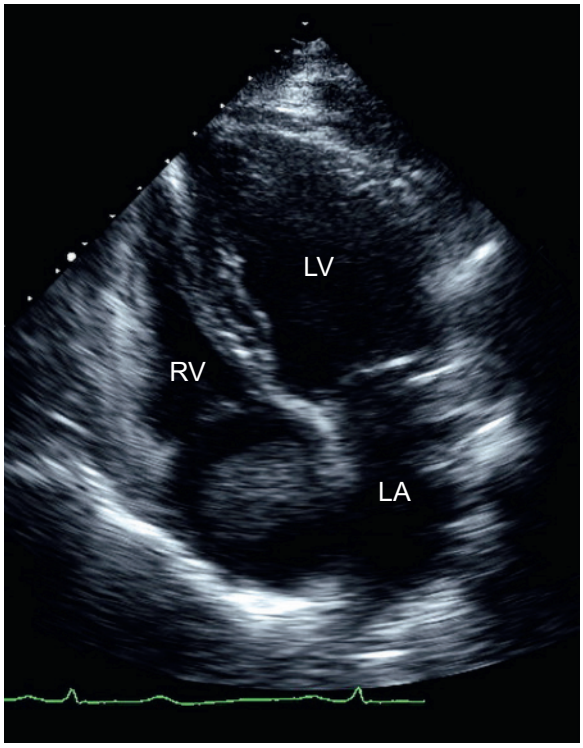

FIG. 4.4

A. The abnormality in the right atrium is most likely a thrombus
B. This lesion is more likely to develop in the right atrium than the left atrium
C. Embolism from this lesion is rare
D. The presence of fever would be indicative of active infection
E. Surgical resection is warranted

QUESTION 446

A 42-year-old woman underwent mitral valve replacement with a St. Jude mechanical prosthesis. She was maintained on warfarin therapy and was documented to have adequate anticoagulation. Two years after the operation she had recurrent transient ischemic attacks. Transthoracic echocardiography proved unrevealing. A transesophageal echocardiogram was performed (Fig. 4.5). Which of the following statements is NOT correct?
A. Large vegetations are seen on the left atrial surface of the St. Jude valve
B. *Streptococcus viridans* is the most likely organism to be cultured in this setting
C. The prosthetic mitral valve is seated in a normal position
D. Transesophageal echocardiography is consistently more sensitive than transthoracic studies for establishing this diagnosis

QUESTION 447

An 84-year-old woman comes for an office visit because of progressive exertional dyspnea. Evaluation, including

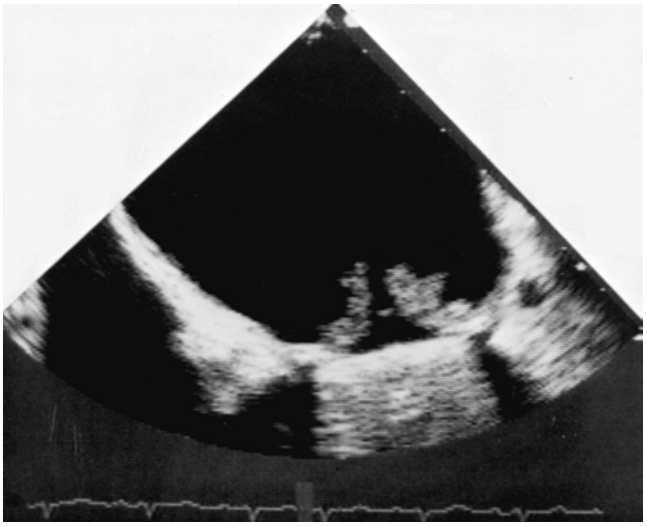

FIG. 4.5

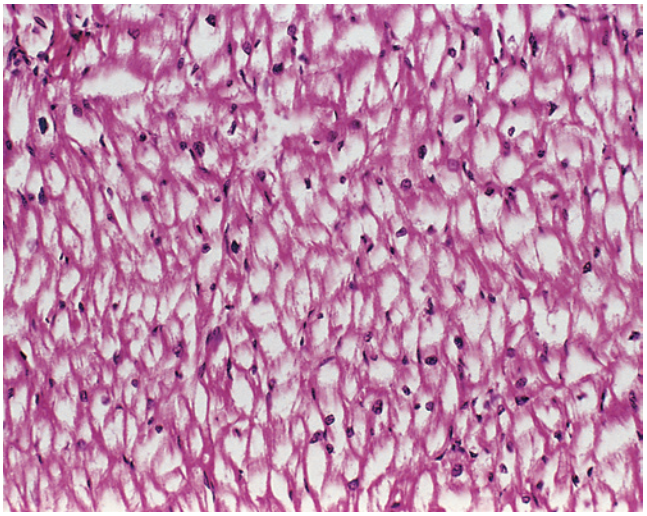

FIG. 4.6 *From Cotran RS, Kumar V, Collins T.* Robbins Pathologic Basis of Disease. *6th ed. Philadelphia: WB Saunders; 1999.*

echocardiography, reveals severe calcific aortic stenosis (peak transvalvular gradient 92 mm Hg, mean transvalvular gradient 45 mm Hg, calculated aortic valve area 0.6 cm^2), with normal left ventricular (LV) contractile function, moderate LV hypertrophy, and no significant mitral valve disease. Coronary angiography 2 years ago showed no coronary artery disease. Her review of systems is notable for chronic obstructive lung disease, hypertension, insulin-dependent diabetes, and moderate renal insufficiency. Her predicted cardiac surgical mortality determined by the Society of Thoracic Surgeons (STS) risk calculator is 18%. She is evaluated by a multidisciplinary heart team and is considered to be at high risk for surgical aortic valve replacement (AVR), but is not inoperable. Which of the following statements is correct?

A. Her predicted 2-year mortality is greater with surgical AVR than with transcatheter aortic valve replacement (TAVR)
B. The 30-day stroke risk is the same after surgical AVR compared to TAVR
C. The presence of more than trivial aortic insufficiency after TAVR is predictive of reduced late survival
D. Complete heart block requiring a permanent pacemaker occurs in <5% of patients who undergo TAVR

QUESTION 448

A 9-month-old infant is found to have a well-circumscribed mass in the left ventricle. There is a family history of tuberous sclerosis. Which of the following cardiac tumors is most likely?

A. Lipoma
B. Papillary fibroelastoma
C. Angiosarcoma
D. Atrial myxoma
E. Rhabdomyoma

QUESTION 449

A 3-month-old infant is referred for evaluation because of failure to thrive and cardiomegaly. Gestation and delivery were normal. The physical examination shows evidence of congestive heart failure and poor skeletal muscle tone. Chest radiography shows cardiomegaly and mild pulmonary edema. The ECG reveals tall, broad QRS complexes consistent with left ventricular hypertrophy and a PR interval of 0.08 second. An endomyocardial biopsy was obtained and the histopathology is shown in Fig. 4.6. The most likely diagnosis is

A. Endocardial fibroelastosis
B. Coarctation of the aorta
C. Shone syndrome
D. Type II glycogen storage disease (Pompe disease)
E. Friedreich ataxia

QUESTION 450

A 53-year-old woman with ischemic cardiomyopathy presents for percutaneous ablation of ventricular tachycardia. She tolerates the procedure well; however, a few hours after the procedure she develops hypotension and sinus tachycardia. An emergent echocardiogram reveals a large circumferential pericardial effusion with findings consistent with tamponade physiology. Each of the following statements about the pathophysiology of cardiac tamponade is correct EXCEPT

A. Cardiac tamponade occurs when the intrapericardial pressure rises to, or above, the mean right atrial and right ventricular diastolic pressures
B. In the presence of pulmonary hypertension, echocardiographic findings of right-sided chamber compression in cardiac tamponade are less notable
C. Equalization of intrapericardial and ventricular filling pressures leads to an inspiratory increase in left ventricular stroke volume
D. Sinus bradycardia may be a manifestation of severe cardiac tamponade

QUESTION 451

A 57-year-old woman comes to your office because of 6 months of fatigue, weight loss, and periods of tachycardia, flushing, and diarrhea. She also describes vague fullness in her neck. Examination discloses clear lungs, an irregular pulse, distended jugular veins with a prominent *v* wave, a holosystolic murmur at the lower left sternal border that intensifies with inspiration, and peripheral edema. She is afebrile. The likely cause of her illness is

A. Bacterial endocarditis
B. Carcinoid syndrome
C. Ebstein anomaly
D. Chronic pulmonary emboli
E. Pheochromocytoma

QUESTION 452

A 32-year-old woman with a history of IV drug abuse presents to the emergency department with fatigue and night sweats. Physical examination reveals a temperature of 38.4°C (101.1°F), scattered rhonchi and wheezes in the lung fields, tachycardia without heart murmurs, and needle tracks on her arms. The chest radiograph reveals several small infiltrates in the left lung field. A transthoracic echocardiogram is obtained and an apical four-chamber view highlighting the right-sided chambers is displayed in Fig. 4.7. Which of the following statements about this case is NOT true?

A. The vegetation displayed occupies the most common endocardial site of infection in IV drug abusers
B. The site of involvement displayed is associated with a higher mortality than other endocardial sites
C. The most likely associated organism is *Staphylococcus aureus*
D. Gram-negative bacilli are a prominent cause of such lesions
E. The majority of patients with this presentation are found to have pneumonia or multiple septic emboli on a chest radiograph

QUESTION 453

A 63-year-old man has a history of unrepaired patent ductus arteriosus and ventricular septal defect with long-standing cyanosis. He is admitted to the hospital because of urinary sepsis and intravenous ciprofloxacin is initiated. A urinary catheter is placed and oral tamsulosin is begun for prostatic obstruction. His fever resolves, but over the next day he develops hypotension and worsening cyanosis. Which of the following interventions would be most appropriate?

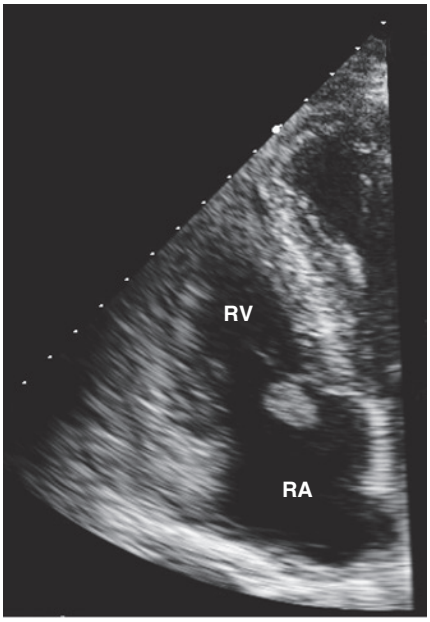

FIG. 4.7

A. Intravenous methylprednisolone and cefepime
B. Intravenous dobutamine and oral sildenafil
C. Intravenous phenylephrine and cessation of tamsulosin
D. Intravenous saline and magnesium

QUESTION 454

A 54-year-old man with a history of hypertension and previously unknown and untreated human immunodeficiency virus (HIV) infection presents with worsening shortness of breath. The chest radiograph shows diffuse bilateral infiltrates that is found to represent *Pneumocystis jiroveci* pneumonia. An echocardiogram is performed to assess left ventricular function, and the study is notable for a small posterior pericardial effusion without cardiac chamber compression. Which one of the following statements regarding pericardial effusion in patients with HIV infection is TRUE?

A. Progression to a symptomatic effusion and/or cardiac tamponade is likely
B. Direct HIV infection of the pericardium is almost exclusively the cause of such effusions
C. The presence of a pericardial effusion in HIV patients has no impact on prognosis
D. Most effusions of this type require glucocorticoid therapy for resolution
E. Pericardial effusion has become an extremely rare cardiac manifestation of HIV infection in patients treated with highly active antiretroviral therapy

QUESTION 455

Which of the following statements about the clinical findings in patients with atrial septal defect (ASD) is NOT correct?

A. A midsystolic ejection murmur and a diastolic rumbling murmur at the lower left sternal border are common features on cardiac examination
B. Patients with ostium primum defects usually show right ventricular hypertrophy, a small rSR′ pattern in the right precordial levels, and rightward axis on the ECG
C. Tall R or R′ waves in V_1 may signal the development of pulmonary hypertension
D. Echocardiographic features of ASD include right ventricular and pulmonary arterial dilatation and paradoxical intraventricular septal motion
E. Radiographic features include cardiomegaly, dilated central pulmonary arteries, and pulmonary plethora

QUESTION 456

A 54-year-old man presents with dyspnea on exertion. He had been routinely exercising four or five times a week, but over the past few months he has noted a decline in exertional capacity. His blood pressure has been consistently <130/85 mm Hg at his physician's office. An apical four-chamber view image from his echocardiogram is shown in Fig. 4.8. Which of the following statements regarding this condition is TRUE?

A. This variant represents <10% of hypertrophic cardiomyopathy in Japan
B. Tall peaked precordial T waves are typically present on the ECG
C. A subaortic dynamic pressure gradient is typically present
D. Magnetic resonance imaging would show a spade-like deformity of the ventricle

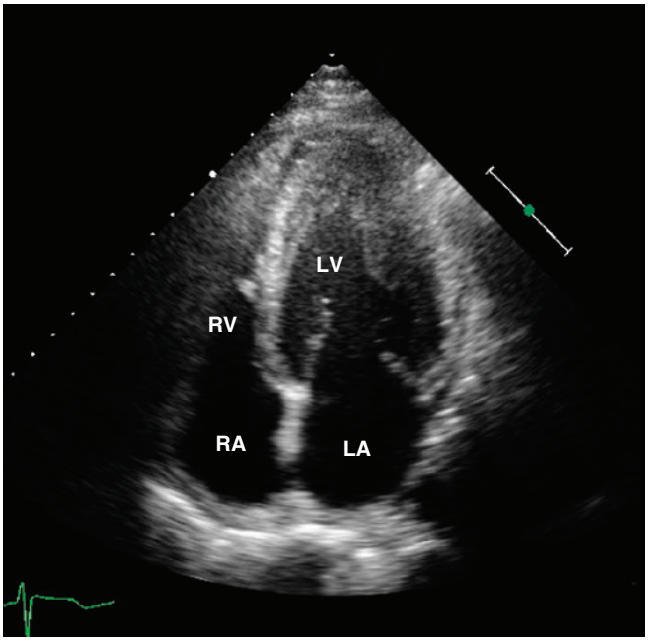

FIG. 4.8

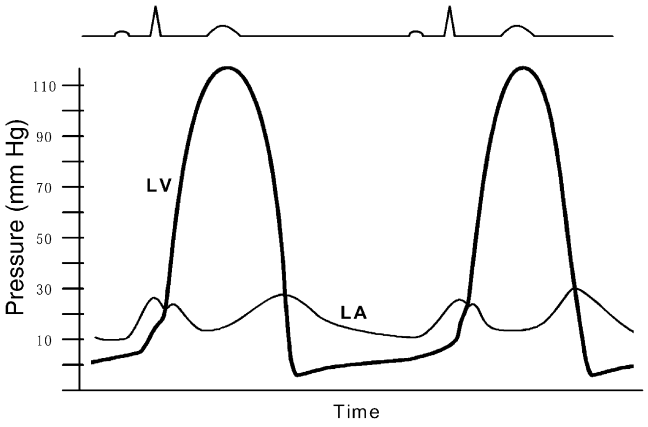

FIG. 4.9

QUESTION 457

A 36-year-old man from the Dominican Republic presents to the emergency department with shortness of breath. A grade III/VI systolic murmur is auscultated at the apex. The chest radiograph demonstrates pulmonary vascular congestion. Echocardiography in the emergency department confirms the presence of mitral regurgitation and vigorous left ventricular contractile function. Which of the following findings would suggest the *acute* onset of mitral regurgitation?

A. Presence of cardiomegaly on the chest radiograph
B. Left atrial and ventricular hypertrophy on the ECG
C. The systolic murmur is short and ends prior to S_2
D. Normal jugular venous pressure

QUESTION 458

The hemodynamic tracing in Fig. 4.9 is most consistent with

A. Constrictive pericarditis
B. Mitral stenosis
C. Mitral regurgitation
D. Restrictive cardiomyopathy
E. None of the above

QUESTION 459

A 45-year-old woman is evaluated by her physician because of the new onset of pleuritic, positional left anterior chest pain that radiates to the left trapezius ridge. Three weeks earlier she had been evaluated for a viral respiratory tract infection. Cardiac auscultation reveals evanescent coarse scratching sounds at the lower left sternal border with components in both systole and diastole. Which of the following statements about expected findings on this patient's electrocardiogram is correct?

A. ST-segment elevations with a convex upward configuration are likely
B. PR-segment depressions may be the only electrocardiographic manifestation
C. Reciprocal ST-segment depressions are typically present
D. Sinus bradycardia is common
E. T-wave inversions develop concurrently with ST-segment elevations

QUESTION 460

Which of the following statements regarding post-myocardial infarction (post-MI) pericarditis is correct?

A. Fibrinolytic therapy increases the incidence of early post-MI pericarditis
B. Post-MI pericarditis is more common after non–ST-segment elevation MI compared with ST-segment elevation MI
C. When present, clinical pericarditis does not arise until >48 hours after infarction
D. The use of heparin is associated with an increased risk of pericarditis
E. The incidence of early post-MI pericarditis is related to infarct size

QUESTION 461

The hemodynamic tracing in Fig. 4.10 is characteristic of which of the following disorders?

A. Aortic stenosis
B. Mitral regurgitation
C. Dilated cardiomyopathy
D. Hypertrophic cardiomyopathy
E. Infiltrative cardiomyopathy

QUESTION 462

A 24-year-old man presents for the evaluation of chest discomfort on exertion. A systolic murmur is auscultated and images from his echocardiogram (color Doppler and spectral Doppler images from parasternal short-axis views) are shown in Fig. 4.11. Which of the following statements is correct?

A. A likely physical finding is a midsystolic click at the second left intercostal space that increases with inspiration
B. Long-term survival of patients with this condition is reduced even if a corrective procedure is performed
C. Valve replacement with a mechanical prosthesis is indicated
D. Balloon valvotomy is typically a successful long-term strategy for this condition

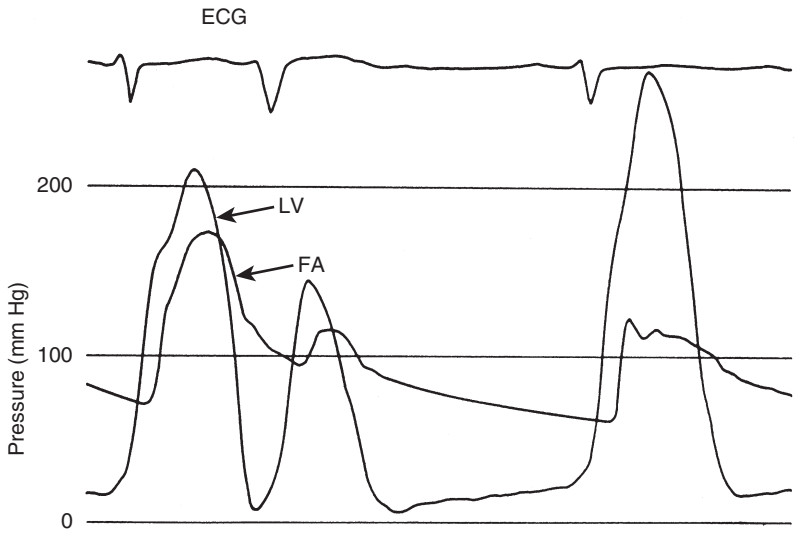

FIG. 4.10 LV, *Left ventricle;* FA, *femoral artery. From Baim D, Grossman W, eds.* Cardiac Catheterization, Angiography and Intervention. *Baltimore: Williams & Wilkins; 1996:794.*

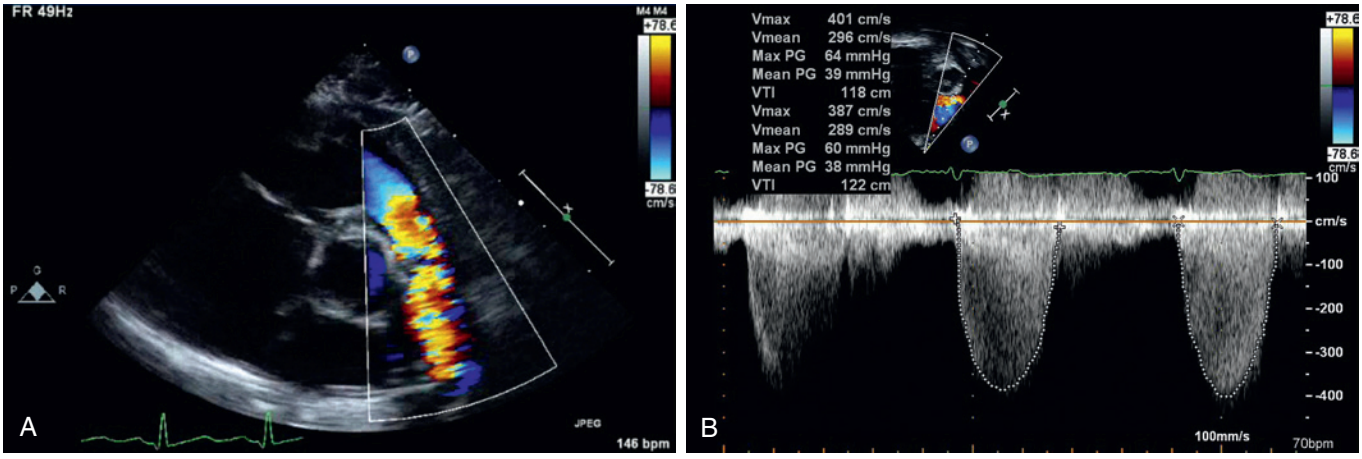

FIG. 4.11

QUESTION 463

Which statement about congenital heart disease in infancy and childhood is TRUE?

A. Extracardiac anomalies occur in ~75% of infants with significant congenital heart disease
B. Patent ductus arteriosus is found more commonly in males
C. Two-thirds of infants with both cardiac and extracardiac congenital anomalies have an established syndrome
D. Features of the rubella syndrome include patent ductus arteriosus or pulmonic valvular stenosis
E. Maternal systemic lupus erythematosus is associated with congenital cardiac malformations, including ventricular septal defect and pulmonic stenosis

QUESTION 464

According to the American Heart Association guidelines for the prevention of infective endocarditis, antibiotic prophylaxis is appropriate for each of the following cardiac conditions before invasive dental procedures EXCEPT

A. Presence of a prosthetic cardiac valve
B. Unrepaired cyanotic congenital heart disease
C. Cardiac transplantation recipients with cardiac valvulopathy
D. Mitral valve prolapse with audible murmur and severe mitral regurgitation
E. Previous episode of infective endocarditis

QUESTION 465

In patients with pulmonary arterial hypertension, which of the following is the most reliable predictor of mortality?

A. Elevated right atrial pressure
B. Elevated mean pulmonary artery pressure
C. Diastolic septal flattening on transthoracic echocardiography
D. Transpulmonary gradient ≤10 mm Hg

QUESTION 466

A 45-year-old man presents with fevers, chills, and shortness of breath. His chest radiograph shows pulmonary edema. Echocardiography reveals vigorous left ventricular contractile function. Vegetations are identified on the aortic valve and there is nonhomogeneous thickening within the aortic root concerning for abscess formation. Cardiac surgery is undertaken and an aortic valve homograft is selected as a means of

replacing the diseased structures. Which one of the following statements is TRUE regarding the use of aortic valve homografts in the surgical management of aortic valve disease?

A. Homografts have high thrombogenicity and require chronic anticoagulation therapy
B. The rate of structural degeneration of cryopreserved homografts is significantly less than that of porcine xenograft valves
C. Homografts are advantageous for patients with endocarditis of the aortic valve who require valve replacement and aortic reconstruction
D. Homografts offer a less favorable hemodynamic profile than mechanical valves
E. The operative mortality of aortic homograft placement is higher than that of mechanical valve replacement surgery

QUESTION 467

Which of the following statements concerning the auscultatory findings of the valvular abnormality depicted in Fig. 4.12 is correct?

A. In patients with leaflets that are flexible, S_1 is softened
B. In patients with heavily calcified leaflets, the intensity of S_1 is accentuated
C. As the severity of this condition increases, the A_2-opening sound (OS) interval (the interval between A_2 and the mitral opening sound) shortens
D. The intensity of the diastolic murmur is closely related to the severity of this condition
E. P_2 (the pulmonic valve closure sound) is commonly diminished

QUESTION 468

Which of the following statements regarding the physical examination in aortic regurgitation is TRUE?

A. The typical murmur is of low frequency and heard best with the bell of the stethoscope placed along the left sternal border
B. The severity of regurgitation correlates better with the intensity rather than the duration of the murmur
C. Dilatation of the ascending aorta should be suspected if the murmur is loudest at the right side of the sternum
D. The intensity of the murmur is decreased by isometric exercise (e.g., strenuous handgrip)

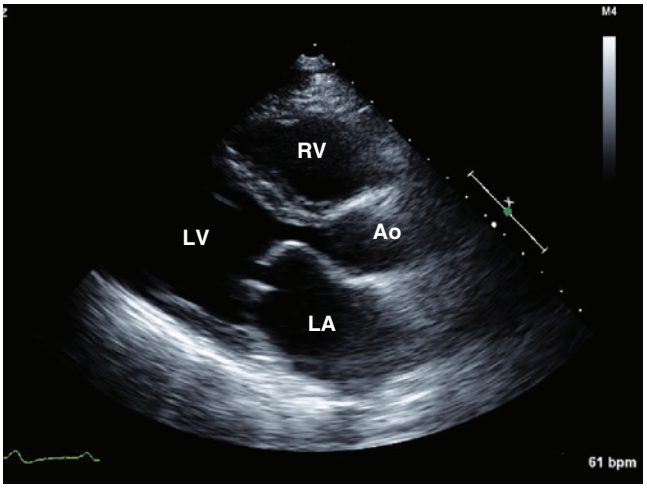

FIG. 4.12

QUESTION 469

A 75-year-old woman with chronic obstructive pulmonary disease and chronic renal insufficiency presents with fever, rigors, productive cough, and worsening shortness of breath. On physical examination she is overtly dyspneic, the temperature is 38.9°C (102.1°F), heart rate 120 beats/min, and blood pressure 82/50 mm Hg. The chest radiograph shows a dense left lower lobe infiltrate and symmetric enlargement of the cardiac silhouette. Echocardiography demonstrates a large circumferential pericardial effusion. She is admitted to the intensive care unit for suspected bacterial pericarditis. Which of the following statements is true?

A. Uremic pericarditis with a preexisting pericardial effusion predisposes to bacterial pericarditis
B. Direct extension into the pericardium of bacterial pneumonia accounts for only a minority of cases of purulent pericarditis
C. Bacterial pericarditis is most often a subacute illness
D. The modern survival rate of this condition is excellent
E. Antibiotics administered intravenously do not achieve high concentrations in the pericardial space

QUESTION 470

A 16-year-old asymptomatic teenager undergoes physical examination before competing in high school athletics. His mother states that a first cousin died suddenly while playing basketball and she recalls that there was something wrong with his heart. His vital signs are heart rate 64 beats/min, respirations 12 breaths/min, and blood pressure 120/75 mm Hg. His cardiac examination is remarkable for a grade 2/6 systolic ejection murmur along the left sternal border, which decreases with squatting and increases with sudden standing. The ECG shows left ventricular hypertrophy (LVH) with prominent septal forces and echocardiography confirms marked LVH. Your recommendations regarding participation in athletics are:

A. No competitive sports
B. Noncontact competitive sports are acceptable
C. Noncontact competitive sports with beta blocker therapy are acceptable
D. High-intensity competitive sports are acceptable with beta blocker therapy

QUESTION 471

Abnormalities of left ventricular (LV) function and hemodynamics in asymptomatic aortic stenosis typically include all of the following EXCEPT

A. Normal cardiac output at rest
B. Elevated LV end-diastolic pressure
C. Elevated LV end-diastolic volume
D. Increased *a* wave in the left atrial pressure curve
E. Normal LV stroke volume

QUESTION 472

A 76-year-old man presents to the emergency department with aphasia and dense right hemiplegia. His wife reports that he had experienced intermittent fevers and chills over the previous 2 weeks. Cardiac examination is notable for a

grade 2/6 systolic ejection murmur at the upper right sternal border and grade 1/4 early diastolic murmur at the upper left sternal border. Four sets of blood cultures grow *Staphylococcus aureus*. A transthoracic echocardiogram demonstrates normal left ventricular contractile function and mild aortic stenosis. No vegetations are seen. Computed tomography of the head shows an acute nonhemorrhagic stroke in the territory of the left middle cerebral artery. Which of the following statements is TRUE?

A. The presenting stroke is an indication for urgent valve replacement
B. Endocarditis caused by *S. aureus* is an absolute indication for surgery
C. Despite the aggressiveness of *S. aureus* native valve endocarditis, antibiotic therapy alone without surgical intervention is often curative
D. The presence of a vegetation >1.0 cm in diameter would be a class I indication for valve replacement
E. Even if intractable heart failure develops, corrective valve surgery should be postponed until after blood cultures have become sterile

QUESTION 473

Which of the following statements about tuberculous pericarditis is NOT correct?

A. Tuberculous pericarditis usually arises via retrograde spread from adjacent lymph nodes or by early hematogenous spread from the primary infection
B. Tuberculous pericardial effusions usually accumulate slowly
C. Measurement of adenosine deaminase in pericardial fluid is a highly sensitive and specific test for the diagnosis of tuberculous pericarditis
D. It is often difficult to isolate the organism from pericardial fluid
E. The addition of corticosteroids to a three-drug antibacterial regimen reduces mortality in patients with tuberculous pericarditis

QUESTION 474

A 42-year-old previously healthy salesman presents to his physician with a complaint of lower extremity edema. On further questioning, he says he has also experienced "flushing" episodes over the past several months, intermittent wheezing, and episodic diarrhea. On physical examination, there is jugular venous distention, a prominent holosystolic murmur at the lower left sternal border, a pulsatile liver, and peripheral edema. The urinary 5-hydroxyindoleacetic acid level is markedly elevated. Which of the following statements is TRUE?

A. The underlying disorder involves the liver
B. Echocardiography typically demonstrates thickened mitral and/or aortic valve leaflets with left ventricular dilatation
C. The symptoms are associated with low levels of circulating serotonin
D. The primary disease usually invades the myocardium

QUESTION 475

A 65-year-old woman, who is originally from Puerto Rico, presents for evaluation of known mitral stenosis. Over the past few months she has developed worsening exertional dyspnea, atrial fibrillation, and is found to have moderate pulmonary hypertension. Which of the following statements regarding percutaneous balloon mitral valvuloplasty for this condition is TRUE?

A. The risk of stroke during the procedure is 10%
B. Transthoracic echocardiography is the appropriate imaging study before the procedure to exclude the presence of left atrial thrombus
C. Balloon mitral valvuloplasty is the treatment of choice for patients with hemodynamically significant mitral stenosis, without left atrial thrombus and an echo score of ≤8
D. A small atrial septal defect is detected in 25% of patients after the procedure
E. Approximately 10% of patients develop severe mitral regurgitation as a result of the procedure

QUESTION 476

A 25-year-old man is an unrestrained driver in a head-on motor vehicle accident. He is brought into the emergency department trauma bay where he is unconscious and is noted to have multiple head lacerations, a large contusion on his anterior chest, and abdominal enlargement. Each of the following statements regarding the acute evaluation of a patient with blunt cardiac trauma is true EXCEPT

A. Chest radiography should be obtained urgently
B. Serum cardiac-specific troponin measurements correlate with the presence and prognosis of blunt myocardial injury
C. Common consequences of blunt cardiac trauma can be correctly identified by transesophageal echocardiography
D. Arrhythmias and conduction blocks frequently occur after blunt cardiac trauma
E. Traumatic ventricular septal defect formation is a recognized complication

QUESTION 477

Which of the following statements regarding patients with sarcoid heart disease is TRUE?

A. Fewer than 5% of patients with pulmonary sarcoidosis have cardiac sarcoid involvement
B. Granulomatous infiltration of the cardiac valves is found in most patients with sarcoid heart disease
C. Percutaneous endomyocardial biopsy (EMB) is a highly sensitive means to establish the diagnosis
D. Magnetic resonance imaging and positron emission tomography (PET) scanning are more sensitive than EMB in establishing the diagnosis of cardiac sarcoid

QUESTION 478

Which of the following statements about the natural history of untreated ventricular septal defect (VSD) in adults is NOT correct?

A. The natural history of VSD differs depending on the size of the defect and the magnitude of pulmonary vascular resistance
B. Regardless of size, the presence of a VSD confers an increased risk for endocarditis
C. Progressive pulmonary vascular disease with reversal of shunting (Eisenmenger complex) most often becomes manifest in the fifth or sixth decade
D. Women with VSDs and ratios of pulmonary to systemic flow <2:1 generally tolerate pregnancy well

QUESTION 479

Each of the following statements regarding endomyocardial fibrosis (EMF) is correct EXCEPT
A. This condition is characteristically found in tropical and subtropical Africa
B. It is predominantly a disease of children and young adults
C. Involvement of the mitral valve apparatus typically results in mitral stenosis
D. EMF involves the left ventricle, alone or in combination with the right ventricle, in 90% of patients
E. Echocardiographic features include increased endocardial reflectivity, fibrotic obliteration of the apex, atrial enlargement, and pericardial effusion

QUESTION 480

Which of the following is NOT an independent indication for placement of an implantable cardioverter-defibrillator in a patient with hypertrophic cardiomyopathy?
A. Recent unexplained syncope
B. Hypotensive blood pressure response to exercise
C. Left ventricular outflow tract gradient ≥30 mm Hg
D. Left ventricular wall thickness ≥30 mm
E. Family history of premature sudden death in a first-degree relative

QUESTION 481

An 8-month-old boy is evaluated because of cyanosis that was first noted at 2 months of age, which worsens with physical activity or crying. A systolic thrill is present at the left sternal border and there is a loud systolic murmur across the precordium. Echocardiography is diagnostic for tetralogy of Fallot. Which of the following statements about tetralogy of Fallot is correct?
A. Classic tetralogy of Fallot is composed of a large ventricular septal defect, infundibular or valvular pulmonic stenosis, right ventricular (RV) hypertrophy, and a cleft mitral valve
B. Downward displacement of the septal leaflet of the tricuspid valve commonly accompanies tetralogy of Fallot
C. A right aortic arch is present in ~25% of patients
D. Survival of patients with uncorrected tetralogy of Fallot into adult life is common regardless of the degree of RV outflow obstruction

QUESTION 482

A 54-year-old man with a bicuspid aortic valve presents with a 1-week history of fevers and chills. Initial blood cultures are negative, but echocardiography reveals a large vegetation on the aortic valve. On the fifth hospital day, blood cultures become positive for gram-negative bacteria. Which of the following is NOT a member of the fastidious, slow-growing group of HACEK organisms that may be the cause of this patient's endocarditis?
A. *Haemophilus parainfluenzae*
B. *Aggregatibacter actinomycetemcomitans*
C. *Cardiobacterium hominis*
D. *Escherichia coli*
E. *Kingella kingae*

QUESTION 483

Which of the following statements regarding endocardial fibroelastosis (EFE) is TRUE?
A. Symptoms of EFE first manifest in early adolescence
B. Myocardial involvement is characteristic
C. The clinical course is usually benign
D. Hypereosinophilia is typically present
E. There is an association with maternal mumps during pregnancy

QUESTION 484

Which of the following statements is TRUE regarding the Fontan procedure?
A. It involves creation of a transatrial shunt
B. It is a curative operation for the underlying congenital defect
C. Coronary-aorta fistula formation is a common complication
D. The most common cause of postoperative death is infection
E. Protein-losing enteropathy is a recognized complication

QUESTION 485

A 27-year-old woman presents with 2 days of shortness of breath. The plasma D-dimer level is elevated. A high-resolution chest computed tomographic scan reveals a segmental pulmonary embolism, and deep vein thrombosis is found in the right femoral vein. She denies any recent travel, immobility, or surgery. Which of the following primary hypercoagulable states is most frequent among patients who present with deep vein thrombosis?
A. Protein C deficiency
B. Activated protein C resistance
C. Antithrombin deficiency
D. Prothrombin gene 20210 mutation
E. Protein S deficiency

QUESTION 486

A 48-year-old man comes to the office because of episodic palpitations. His other symptoms include paroxysmal nocturnal dyspnea, nocturnal enuresis, and mild angina. His wife adds that he snores loudly. He has a history of several recent automobile accidents. On examination, his blood pressure is elevated at 190/100 mm Hg and he is moderately overweight. Laboratory evaluation reveals a hematocrit of 58%. The most likely cardiac finding would be
A. Mitral valve stenosis
B. Aortic valve stenosis
C. Right ventricular hypertrophy
D. Pulmonary valve stenosis
E. Atrial septal defect

QUESTION 487

A 78-year-old man describes exertional dyspnea 3 days after a 12-hour intercontinental flight. His blood pressure is 128/76 mm Hg, heart rate 92 beats/min and regular. His oxygen saturation is 96%. He weighs 78 kg. There is no jugular venous distension, the chest is clear to auscultation, and there is no peripheral edema or calf tenderness. The serum D-dimer is elevated and subsequent imaging demonstrates a segmental pulmonary embolism and thrombus within the

left femoral vein. There are no echocardiographic signs of right ventricular strain. Serum electrolyte measurements are normal, the serum creatinine is 1.0 mg/dL, and the estimated creatinine clearance is 62 mL/min. His current medications are atorvastatin 20 mg daily and lisinopril 10 mg daily. Of the following choices, which would be the best initial anticoagulation strategy?

A. Enoxaparin 1 mg/kg subcutaneous injection once, followed by oral warfarin daily to achieve an INR of 2.0-3.0
B. Dabigatran 150 mg orally twice daily
C. Rivaroxaban 20 mg orally once daily, with the evening meal
D. Apixaban 10 mg orally twice daily for 7 days, then 5 mg twice daily
E. Enoxaparin 1 mg/kg subcutaneously twice daily for 3 days, then oral edoxaban 30 mg once daily

QUESTION 488

A 20-year-old previously healthy woman is brought to the hospital because of fatigue and exertional dyspnea over the past month. Past medical history is unremarkable except for an upper respiratory tract infection 4 weeks earlier. She is not pregnant. There is no family history of cardiac illness. She does not consume alcoholic beverages or use illicit drugs. On examination in the emergency department, the patient's blood pressure is 90/60 mm Hg and the heart rate is 110 beats/min. The jugular veins are distended to 10 cm H_2O, the chest examination reveals bilateral rales, and on cardiac examination there is a prominent apical S_3 gallop. An echocardiogram demonstrates dilatation of both ventricles with diffuse hypokinesia; the left ventricular ejection fraction is 15%. Which one of the following statements regarding this patient's disorder is NOT correct?

A. The most likely etiology of this patient's disorder is viral
B. Myocardial biopsy would not likely reveal a specific etiology
C. Corticosteroids will likely slow progression of the illness
D. Cardiac magnetic resonance imaging would be a useful diagnostic modality
E. Serum cardiac troponin elevation may occur in the absence of coronary artery disease

QUESTION 489

A 28-year-old man is referred for evaluation after his brother was diagnosed with a cardiac condition that caused recurrent syncope. As part of his evaluation, he underwent echocardiography and cardiac magnetic resonance imaging. Representative images are shown in Figs. 4.13 and 4.14. Which of the following is correct in the management of this patient's condition?

A. Endocarditis prophylaxis is mandatory before dental procedures
B. Beta blockers are contraindicated
C. He should refrain from highly competitive sports
D. Digitalis glycosides are beneficial
E. Anemia is associated with a decrease in murmur intensity

QUESTION 490

A 32-year-old woman presents with progressive exertional dyspnea over the past year. Physical examination is notable for a blood pressure of 123/81 mm Hg, heart rate 91 beats/min, resting oxygen saturation 91%, clear lungs, a loud pulmonic component of S_2, and symmetric lower extremity edema. As part of her treatment, her physician prescribed a diuretic and warfarin. After 3 months there was no clinical improvement. Right heart catheterization is undertaken and demonstrates the following: right atrial pressure 14 mm Hg; pulmonary artery pressure (mean) 38 mm Hg; pulmonary vascular resistance 6.8 Wood units (544 dyn·sec·cm^{-5}); pulmonary capillary wedge pressure 8 mm Hg. A pulmonary angiogram is performed (Fig. 4.15). Which

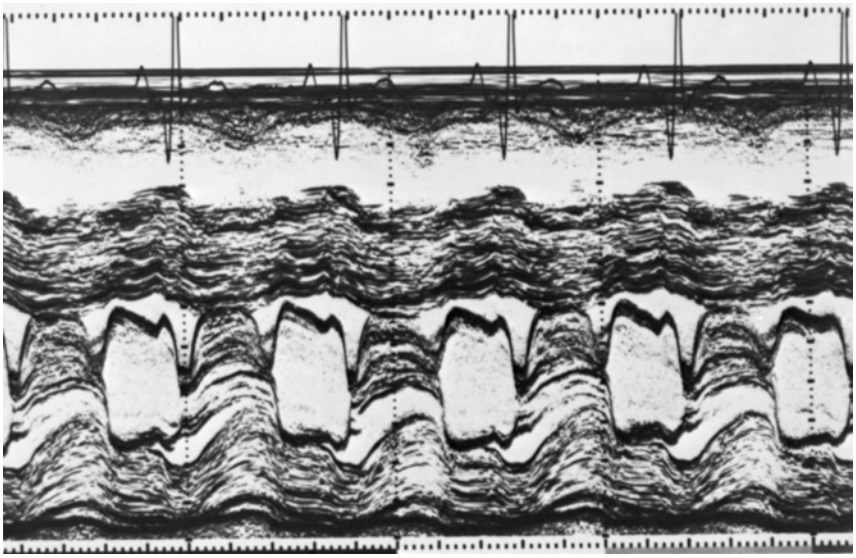

FIG. 4.13

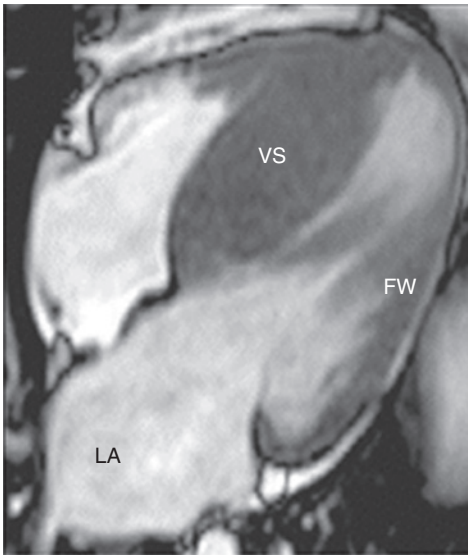

FIG. 4.14 *From Maron BJ, Maron MS.* Lancet. *2013;381:242.*

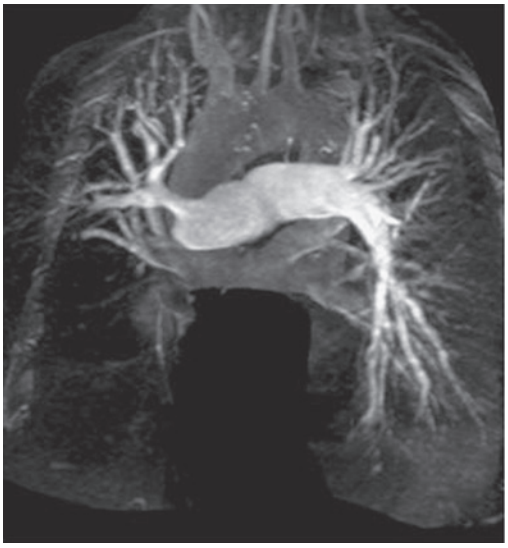

FIG. 4.15

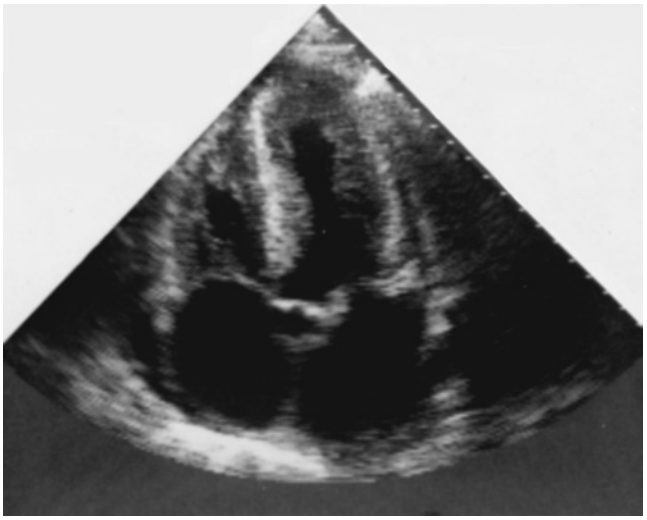

FIG. 4.16

of the following would be most appropriate in managing this patient?

A. Intravenous prostacyclin titrated to maximum tolerated dose
B. Oral sildenafil three times daily
C. Initiation of a nonselective endothelin receptor antagonist
D. Refer for cardiac surgical intervention

QUESTION 491

A 70-year-old man with multiple myeloma presents with new biventricular heart failure. An apical four-chamber view from a transthoracic echocardiographic study is shown in Fig. 4.16. Which of the following statements about this case is TRUE?

A. This disease is caused by sarcomeric gene mutation encoding for beta-myosin heavy chain
B. The ECG likely demonstrates criteria for left ventricular hypertrophy
C. The most common cardiac presentation of this disorder is restrictive cardiomyopathy
D. Recurrent blood transfusion is a risk factor for this disorder

QUESTION 492

The 2D and M-mode echocardiogram images in Fig. 4.17 were recorded from an asymptomatic 24-year-old woman. Valvular regurgitation is absent by Doppler interrogation. Which of the following statements is TRUE?

A. The patient should undergo repeat echocardiography every 6 months to follow this disorder
B. She should receive antibiotic prophylaxis to prevent infective endocarditis prior to invasive dental procedures
C. She is at increased risk of sudden cardiac death
D. She is at increased risk of thromboembolism and requires chronic oral anticoagulation therapy
E. Advanced age and male gender are risk factors for progression of this disorder and ultimate need for surgical intervention

QUESTION 493

A 75-year-old woman presented to her physician with severe fatigue and intermittent cyanosis. Initial evaluation revealed that cyanosis had been present for approximately 1 year and occurred chiefly during mild to moderate exertion. Transthoracic echocardiography (TTE) yielded images that were suboptimal; therefore, TEE was peformed. Part *A* in Fig. 4.18 shows a basal image from the TEE, and part *B* shows an image obtained after injection of agitated saline into the right antecubital vein. Which of the statements about this patient and the echocardiographic images displayed is NOT correct?

A. The saline contrast image demonstrates right-to-left interatrial flow
B. The images verify a secundum-type atrial septal defect
C. An anomalous pulmonary vein is demonstrated
D. In TTE, the subcostal position is most useful for studying the lesion displayed
E. When left atrial pressure exceeds right atrial pressure in this condition, echocardiography with IV saline contrast injection may demonstrate a negative contrast effect within the right atrium

QUESTION 494

A 29-year-old man is referred by his family practitioner for evaluation of a heart murmur that was first heard during childhood. He is asymptomatic. Part of his evaluation included an echocardiogram. An M-mode panel from that study is displayed in Fig. 4.19. Which of the statements about this case is NOT correct?

A. A vegetation is present on the anterior leaflet of the mitral valve
B. A bicuspid aortic valve is a cause of this finding
C. This disorder can be associated with ankylosing spondylitis
D. The M-mode finding may be present even in mild forms of this condition

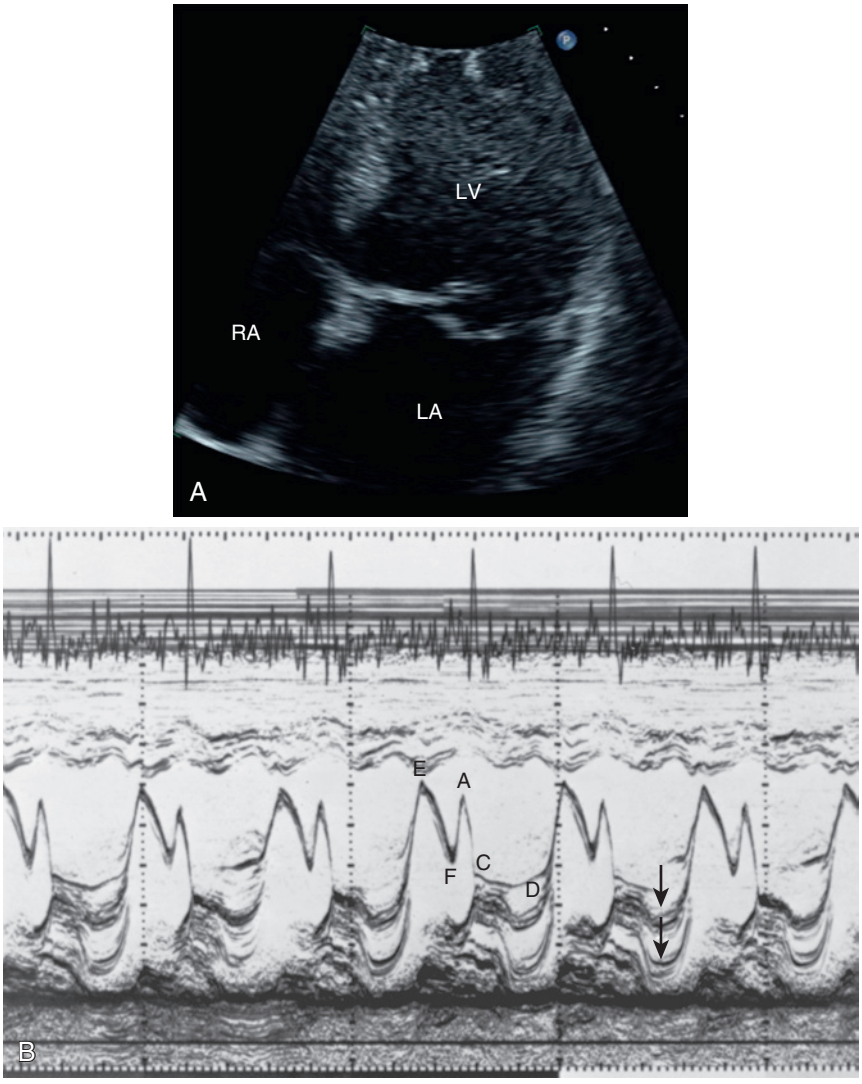

FIG. 4.17

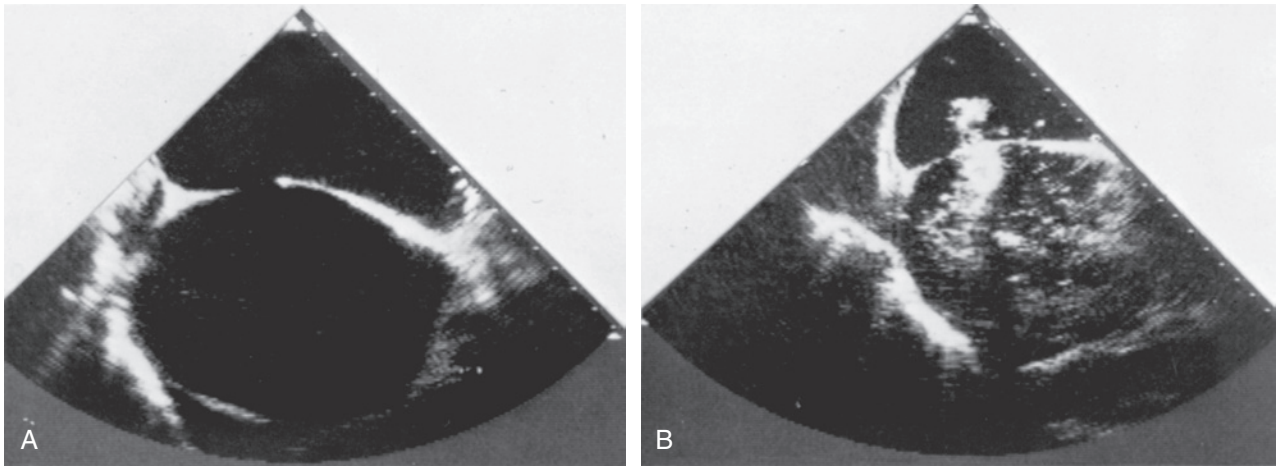

FIG. 4.18

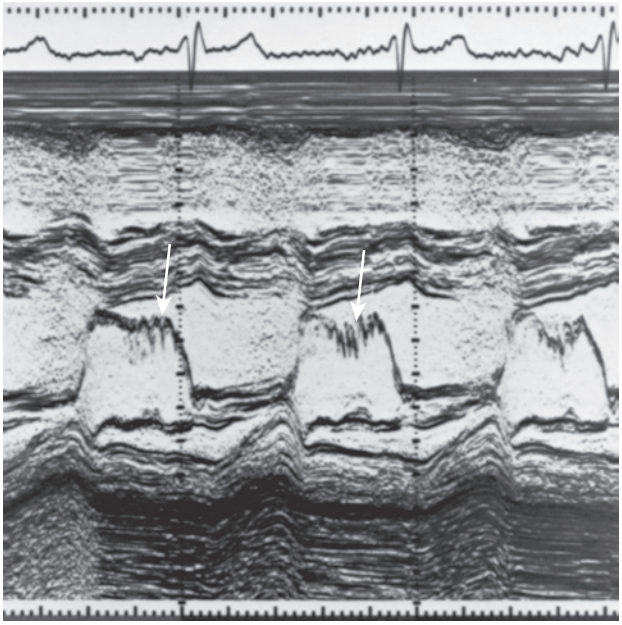

FIG. 4.19

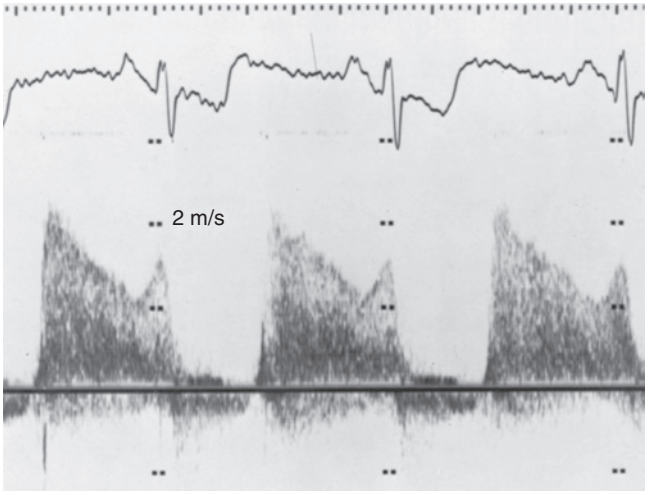

FIG. 4.20

QUESTION 495

A 34-year-old woman presents with dyspnea and is found to be in atrial fibrillation. Following conversion to normal sinus rhythm, an echocardiographic study is obtained. Fig. 4.20 displays a continuous-wave Doppler recording through the mitral valve. Which of the statements about this condition is NOT correct?

A. Two-dimensional echocardiography would demonstrate thickening of the valve leaflets and chordal apparatus
B. The peak velocity of transmitral flow in this case is decreased
C. In early diastole, the posterior leaflet of the mitral valve commonly moves in an anterior direction in patients with this condition
D. Mitral orifice size can be accurately determined by Doppler pressure half-time measurement
E. Elevation of the pulmonary artery systolic pressure, as estimated by the tricuspid regurgitant jet, would likely be present in this patient

QUESTION 496

A 34-year-old man with human immunodeficiency virus (HIV) infection presented with the recent onset of fever and dyspnea. Physical examination revealed fever, tachycardia, jugular venous distention, a pericardial friction rub, and hepatomegaly. The chest radiograph shown in part *A* of Fig. 4.21 was obtained. A diagnosis was ascertained by obtaining pericardial fluid and a pericardial biopsy specimen. The pericardial fluid was notable for an elevated level of adenosine deaminase. The chest radiograph in part *B* was obtained 3 weeks after the initiation of appropriate therapy. Which of these statements about this case is NOT correct?

A. In industrialized nations, the incidence of this disorder has decreased markedly in recent decades
B. This condition is the most common cause of pericardial disease in African HIV-infected patients
C. Clinical detection of this disorder usually occurs either in the effusive stage or after the development of constrictive pericarditis
D. The acute onset of characteristic severe pericardial pain is common
E. This disorder is most likely to be diagnosed if both pericardial fluid and a pericardial biopsy specimen are obtained

QUESTION 497

Which of the following statements about ostium primum atrial septal defects (ASDs) is NOT correct?

A. Ostium primum ASDs often displace and cause a "cleft" appearance of both the anterior and posterior leaflets of the mitral valve
B. The clinical features of ostium primum ASDs are similar to those of the ostium secundum type
C. Imaging usually reveals both right atrial and right ventricular enlargement
D. The presence of an ostium primum ASD accompanied by a ventricular septal defect comprises a complete atrioventricular canal malformation
E. Left ventriculography may demonstrate a "gooseneck" deformity

QUESTION 498

Which of the following warrants an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death in a patient with hypertrophic cardiomyopathy?

A. Sustained atrial fibrillation
B. Late gadolinium enhancement on contrast-enhanced cardiac MRI that comprises >15% of left ventricular mass.
C. Interventricular septal wall thickness of 25 mm
D. Loss of function mutation in the fibrillin-1 (*FBN1*) gene

QUESTION 499

A 53-year-old man has a grade III/VI apical holosystolic murmur. His echocardiographic apical three-chamber view with color Doppler imaging is shown in Fig. 4.22. Measurements included a left ventricular (LV) end-diastolic chamber diameter of 56 mm, end-systolic dimension of 38 mm, and LV ejection fraction of 60%. He is asymptomatic and has not experienced inordinate dyspnea on exertion, orthopnea, or lower extremity edema. For this patient, which of the

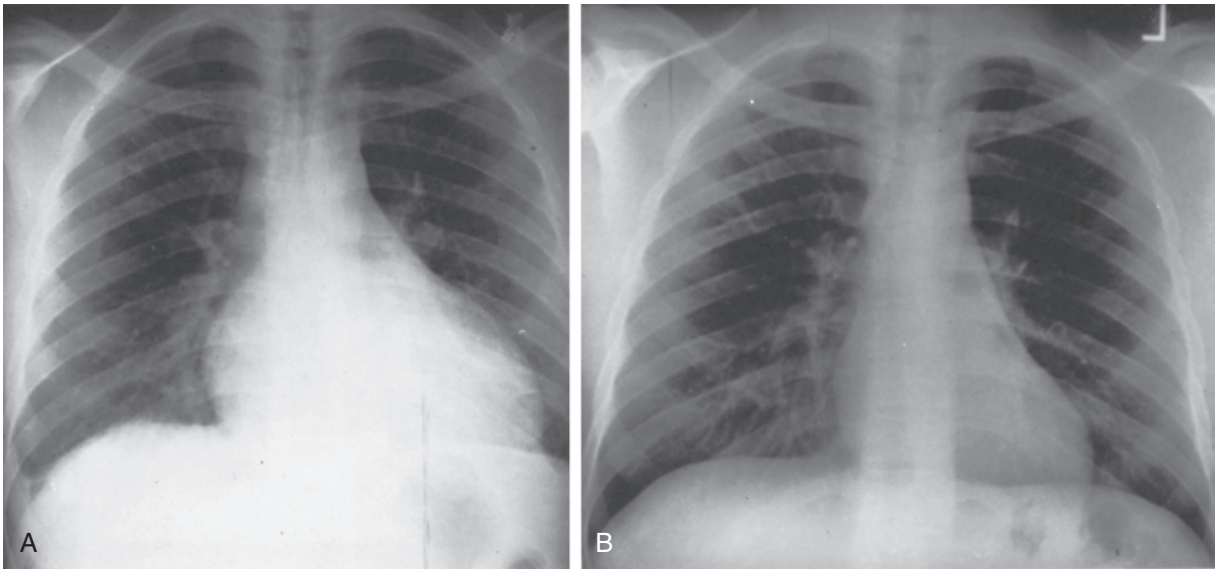

FIG. 4.21 *From Jay M.* Plain Film in Heart Disease. *Boston: Blackwell Scientific Publishing; 1992.*

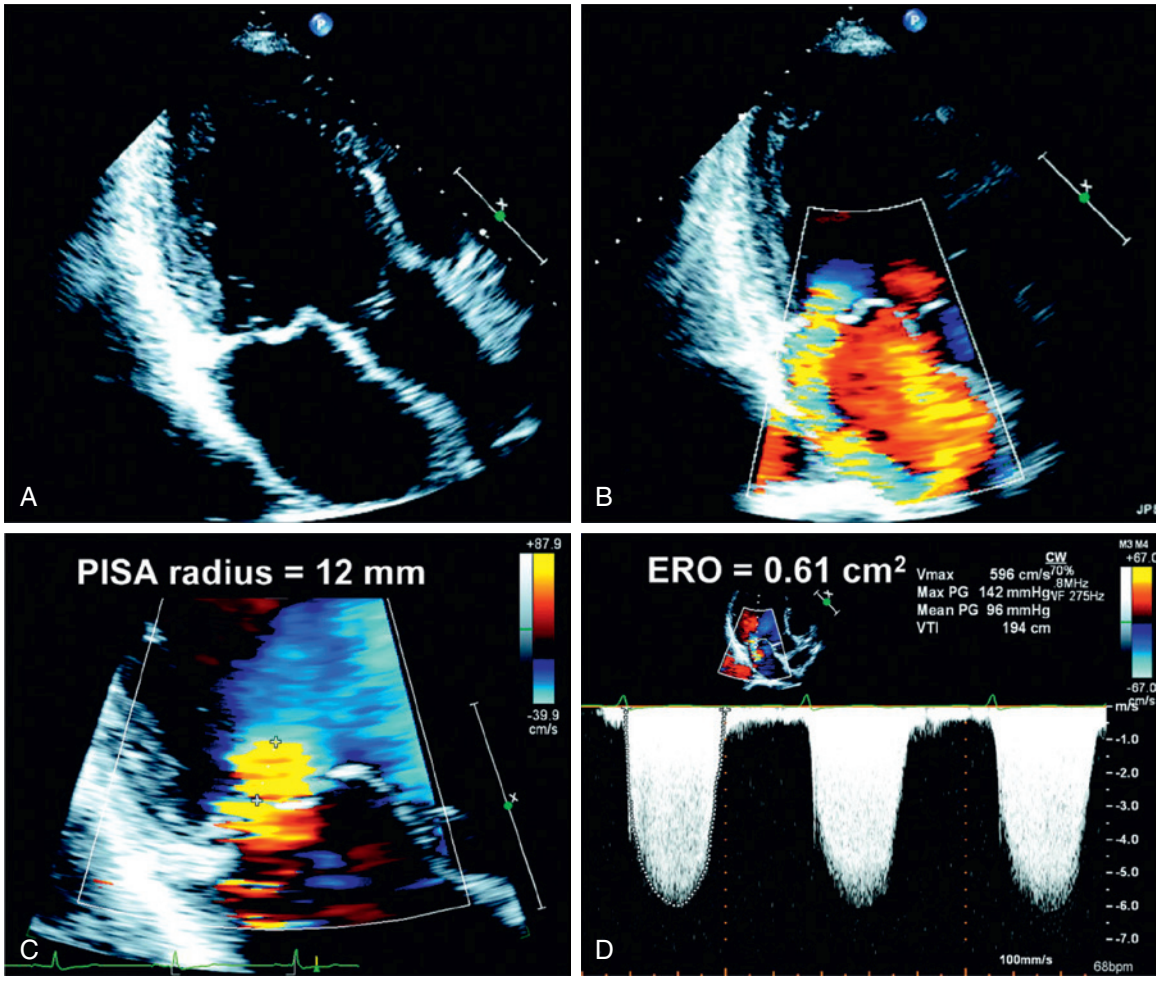

FIG. 4.22 *From Kang DH, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation.* Circulation. *2009;119:797.*

following statements is correct regarding the timing of mitral valve surgery?

A. Surgical correction should be undertaken as soon as possible
B. The risk of postoperative heart failure is low as long as the preoperative ejection fraction is >50%
C. His postoperative prognosis will not suffer if he undergoes valve surgery before the LV end-systolic diameter exceeds 55 mm
D. Chronic administration of an angiotensin-converting enzyme inhibitor would delay the need for surgery
E. A resting pulmonary artery systolic pressure of 55 mm Hg is a class IIa indication for mitral valve surgery

QUESTION 500

A 23-year-old women delivers a baby boy at 36 weeks' gestation. Soon after delivery, the neonate is noted to be cyanotic with a physical examination notable for a right ventricular impulse and a systolic thrill along the left sternal border. An echocardiogram reveals obstruction to right ventricular outflow, an outlet ventricular septal defect, overriding of the aorta, and right ventricular hypertrophy. With regard to the management of this condition, which one of the following statements is NOT correct?

A. Early definitive repair is indicated
B. Postoperative increases in pulmonary venous return often lead to right ventricular decompensation
C. The size of the pulmonary arteries is the single most important determinant in assessing candidacy for primary repair
D. If early corrective operation is not possible, a palliative procedure that leads to increased pulmonary blood flow is recommended
E. Bleeding complications are common in the postoperative period after repair

QUESTION 501

A 62-year-old man presents with the acute onset of shortness of breath 2 weeks after prostate surgery. A high-resolution contrast chest computed tomographic scan is shown in Fig. 4.23. Which of the following statements is correct?

A. Echocardiography would be useful for further risk stratification of this patient
B. Pulmonary angiography is required to make a definitive diagnosis
C. This technique is insensitive for detecting thrombi in subsegmental pulmonary arteries
D. The majority of patients with this disorder have evidence of deep vein thrombosis in the systemic venous system

QUESTION 502

Which one of the following conditions is NOT associated with elevated right ventricular diastolic pressures with the pattern shown in Fig. 4.24?

A. Cardiac tamponade
B. Acute right ventricular infarction
C. Massive pulmonary embolism
D. Constrictive pericarditis
E. Restrictive cardiomyopathy

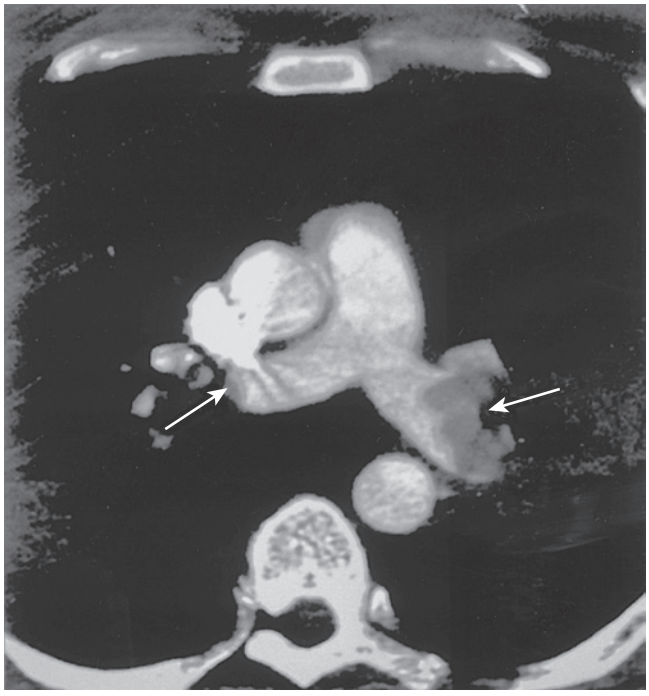

FIG. 4.23

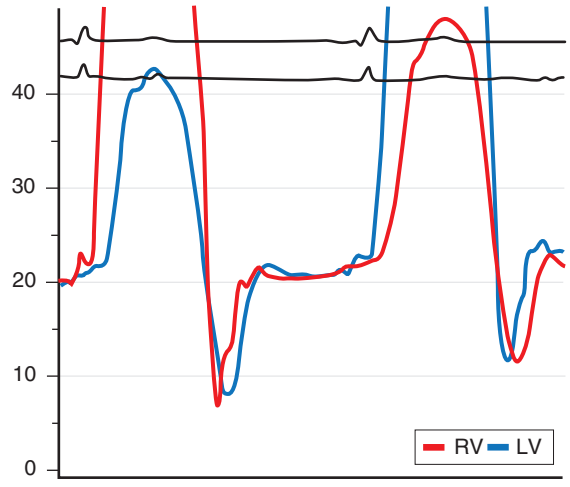

FIG. 4.24 *From Vaitkus PT, Cooper KA, Shuman WP, Hardin NJ. Images in cardiovascular medicine: constrictive pericarditis.* Circulation. *1996;93:834.*

QUESTION 503

A 54-year-old man presented with increasing dyspnea on exertion. He was initially treated for an upper respiratory tract infection; however, his symptoms persisted. A subsequent echocardiogram revealed an intracardiac mass suggestive of a malignant tumor. Regarding primary malignancies of the heart, which of the following statements is TRUE?

A. The right atrium is the most common site of involvement
B. The vast majority of patients already have metastases at the time of diagnosis
C. Malignant tumors account for half of primary cardiac tumors
D. Lymphomas are the most common primary malignancies of the heart

QUESTION 504

A 63-year-old man without known cardiac history presented with a 4-month history of dyspnea on exertion and lower extremity edema. Echocardiography revealed a normal LV ejection fraction with no significant valvular disease. A chest computed tomographic scan showed a dense rim of calcium around the heart. Coronary angiography showed no significant coronary disease. Hemodynamic evaluation demonstrated elevation and equalization of right and left ventricular diastolic pressures with a "dip and plateau" configuration. Which of the following statements about this condition is correct?

A. Evaluation for tuberculosis is appropriate
B. The mortality rate associated with pericardiectomy in the contemporary era is <1.0%
C. Nearly all patients develop a high-output syndrome immediately after pericardiectomy due to rapid expansion of the heart
D. Symptomatic improvement is reported in only 50% of surgical survivors
E. Pericardiectomy should be reserved only for patients with New York Heart Association functional class III or IV symptoms

QUESTION 505

A 25-year-old woman presents to her primary care doctor with fatigue and a rash. She recently returned from a New England vacation during which she hiked at least 6 miles daily. On physical examination she has a well-demarcated erythematous rash with central clearing on her chest. Lyme disease is suspected. Which of the following statements regarding cardiac involvement in Lyme disease is TRUE?

A. Cardiac manifestations of Lyme disease typically occur within days of the development of erythema chronicum migrans
B. Less than 10% of patients with Lyme disease develop cardiac manifestations in the current era
C. Supraventricular and ventricular tachyarrhythmias are the most common cardiac manifestations of Lyme disease
D. Cardiomegaly and congestive heart failure are common among patients who develop Lyme carditis

QUESTION 506

Which of the following statements regarding the natural history of idiopathic pulmonary arterial hypertension is TRUE?

A. The prevalence is equal in males and females
B. Chest pain related to right ventricular ischemia is the most common manifesting symptom
C. Sudden cardiac death is a potential complication, but only in patients with class IV symptoms
D. Increased intensity of S_1 is the most common physical finding
E. Electrocardiographic evidence of right ventricular hypertrophy is present in a minority of patients

QUESTION 507

Which of the following statements is TRUE about the heart valve abnormality shown in Fig. 4.25?

A. The abnormality is most likely congenital
B. Cardiac auscultation is almost certainly normal

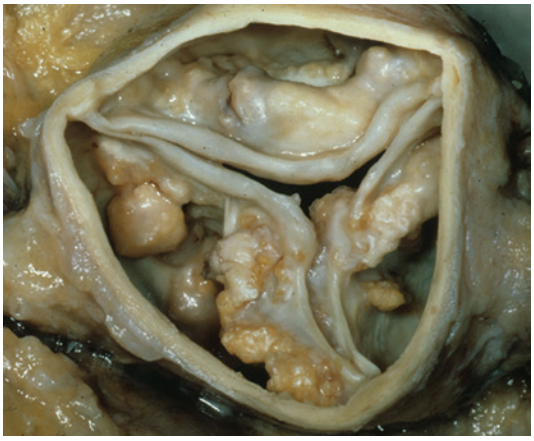

FIG. 4.25 *From Salem DN, Isner JM. Percutaneous aortic valvuloplasty.* Chest. *1987;92:326.*

C. Endocarditis frequently leads to this abnormality
D. Diabetes mellitus and hypercholesterolemia are risk factors for its development
E. A loud diastolic blowing murmur is likely

QUESTION 508

Which of the following statements about hemodynamic findings in constrictive pericarditis and restrictive cardiomyopathy is correct?

A. A diastolic "dip-and-plateau" pattern is present in the right ventricular (RV) waveform in constrictive pericarditis, but not restrictive cardiomyopathy
B. Concordance of left ventricular and RV systolic pressures during respiration is typical of constrictive pericarditis
C. In constrictive pericarditis, the ratio of RV systolic pressure to RV end-diastolic pressure is usually >3
D. An RV systolic pressure >50 mm Hg is more consistent with restrictive cardiomyopathy than with constrictive pericarditis

QUESTION 509

Riociguat is a recently approved medication that results in improved exercise tolerance in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. The mechanism of action of riociguat is

A. Nitric oxide donor
B. Soluble guanylyl cyclase stimulator
C. Heme oxygenase-1 inhibitor
D. Kv1.5 channel stabilizer

QUESTION 510

A 54-year-old man presents to his physician with a 1-week history of dyspnea on exertion, cough, and pleuritic chest pain. His examination is notable for an elevated jugular venous pressure, distant heart sounds, and mild bilateral lower extremity edema. The chest radiograph reveals an enlarged cardiac silhouette. Echocardiography demonstrates a large circumferential pericardial effusion. An echocardiographic-guided pericardiocentesis is performed, removing most of the fluid; cytologic evaluation reveals adenocarcinoma. Which one of the following statements is NOT correct?

A. The most likely primary malignancy in this patient is in the lung
B. The prognosis is poor despite aggressive surgery or chemotherapy
C. Pericardial sclerotherapy would not significantly improve the long-term prognosis
D. Total surgical pericardiectomy should be performed urgently
E. Echocardiography should be repeated within 72 hours

QUESTION 511

A 34-year-old man presents to the emergency department with pleuritic chest pain after a recent upper respiratory tract infection. The pain is positional, relieved by sitting up. Cardiac examination is notable for a three-component friction rub. The ECG demonstrates diffuse ST-segment elevation with PR-segment depression in several leads. Which of the following statements about the evolution of the ECG in this condition is correct?
A. PR-segment deviation occurs in fewer than 25% of patients with this condition
B. Initial ST-segment elevation is usually most prominent in lead aVR
C. The ratio of the height of ST-segment elevation to the height of the T wave in this condition is typically <0.25 in lead V_6
D. T-wave inversion is expected to occur within days, while the ST segment is still elevated
E. T-wave inversion may persist for months after the acute presentation

QUESTION 512

Which of the following statements regarding the natural history of untreated aortic stenosis (AS) is correct?
A. Average survival from the onset of syncopal symptoms is approximately 6 months
B. Average survival from the onset of congestive heart failure is approximately 2 years
C. Syncope due to AS usually occurs at rest
D. Sudden death in patients with AS usually occurs in previously asymptomatic individuals
E. Atrial fibrillation is typically well tolerated in patients with advanced AS

QUESTION 513

A 46-year-old postmenopausal woman with a history of systemic sclerosis is admitted to the coronary care unit because of progressive dyspnea and chest pain. Initial data include blood pressure 88/55 mm Hg, heart rate 104 beats/min, and oxygen saturation 95%. General examination is notable for cool extremities and symmetric edema of the lower extremities. The electrocardiogram demonstrates right ventricular hypertrophy with a strain pattern. The serum troponin T is 1.10 ng/mL (reference range <0.01 ng/mL), and contrast enhanced thoracic computed tomography demonstrates RV cavitary enlargement without pulmonary embolism. Coronary arteriography shows minimal coronary artery disease without coronary vasospasm. Right heart catheterization reveals the following: mean pulmonary artery pressure 61 mm Hg; mean pulmonary capillary wedge pressure 10 mm Hg; pulmonary vascular resistance 16.2 Wood units (1296 dyn·sec·cm^{-5}). Her body surface area is 1.6 m^2. Which of the following is the most appropriate initial treatment for this patient?
A. Oral macitentan 10 mg daily
B. Intravenous epoprostenol initiated at 2 ng/kg/min
C. Tissue plasminogen activator 100 mg, administered as a continuous IV infusion over 2 hours
D. Digoxin 0.125 mg daily

QUESTION 514

A 45-year-old man is transported to the emergency department, a victim of a stab wound to the chest that occurred during a robbery attempt at his convenience store. Which of the following statements about penetrating cardiac trauma is correct?
A. The left ventricle is the cardiac chamber most commonly injured by penetrating trauma
B. Penetrating injuries to the atria are associated with better survival than wounds to the ventricles
C. Rupture of the interventricular septum is a potential late complication
D. In penetrating cardiac injury with suspected tamponade, urgent pericardiocentesis is mandatory

QUESTION 515

Which of the following statements regarding persistent patent ductus arteriosus (PDA) in adults is NOT correct ?
A. Patients with small shunts and no audible murmur are at negligible risk of endovascular infection
B. Patients with moderate-sized PDA typically present with dyspnea or palpitations
C. Patients with moderate-sized PDA typically have a loud continuous “machinery” murmur and a narrow pulse pressure
D. Patients with large PDA may develop enlarged central pulmonary arteries with peripheral pruning on chest radiograph
E. Transcatheter devices result in successful closure rates of >95%

QUESTION 516

A 46-year-old man is admitted to the hospital because of worsening shortness of breath. His history is notable for hypertension, treated with an angiotensin-converting enzyme inhibitor. Social history reveals that he has consumed one-half pint of liquor daily for the past 10 years. Physical examination shows an elevated jugular venous pressure (14 cm), bibasilar rales on pulmonary examination, a laterally displaced cardiac apical impulse, a grade II/VI holosystolic murmur, an S_3 gallop at the apex, and pitting edema of both lower extremities. Echocardiography demonstrates a dilated left ventricle with an ejection fraction of 25% and moderate mitral regurgitation. Which of the following statements regarding the cardiac effects of alcohol is correct?
A. Chronic heavy alcohol consumption is associated with low systemic blood pressure
B. The likelihood of developing dilated cardiomyopathy correlates with the amount of alcohol consumed over a lifetime
C. Women are less susceptible than men to alcohol-associated cardiomyopathy

D. Moderate alcohol consumption is associated with an increased rate of sudden death
E. Dilated cardiomyopathy due to alcohol consumption is irreversible

QUESTION 517

Expected clinical manifestations of amyloidosis of the cardiovascular system include which of the following?
A. Constrictive pericarditis
B. High-output heart failure
C. Orthostatic hypotension
D. ECG voltage criteria for left ventricular hypertrophy
E. Electrical alternans

QUESTION 518

Which of the following statements regarding endocarditis caused by *Staphylococcus aureus* is correct?
A. Central nervous system complications are rare, occurring in fewer than 5% of patients
B. *Staphylococcus aureus* native valve endocarditis is an absolute indication for surgical debridement
C. The prognosis of right-sided *S. aureus* native valve endocarditis is similar to that of left-sided involvement
D. Empirical initial therapy with oxacillin or cefazolin is appropriate for suspected *S. aureus* endocarditis
E. Prosthetic valve endocarditis with *S. aureus* is associated with a 50% mortality rate in patients treated medically

QUESTION 519

Which of the following is NOT associated with Ebstein anomaly of the tricuspid valve?
A. Atrial septal defect
B. Paradoxical splitting of S_2
C. Ventricular preexcitation
D. A widely split S_1
E. Atrial flutter

QUESTION 520

A 42-year-old man from Uganda is diagnosed with Löffler endocarditis. Which of the following is NOT an expected finding?
A. Eosinophilia
B. Signs and symptoms of heart failure
C. Asthma and nasal polyposis
D. Right ventricular pressure tracing showing a "dip-and-plateau" pattern
E. Normal left ventricular ejection fraction

QUESTION 521

A 57-year-old man is referred for transthoracic echocardiography to investigate unexplained exertional dyspnea. The right ventricular outflow tract Doppler profile is shown in Fig. 4.26 and demonstrates midsystolic notching. This finding is most strongly associated with which of the following?
A. Decreased pulmonary artery pressure
B. Increased pulmonary vascular resistance
C. Pneumothorax
D. Left-sided heart failure

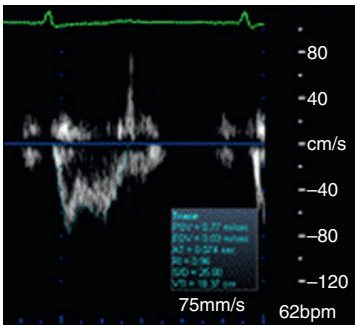

FIG. 4.26 *From Opotowsky AR, Clair M, Afilalo J, et al. A simple echocardiographic method to estimate pulmonary vascular resistance.* Am J Cardiol. *2013;112:873–882.*

QUESTION 522

A 55-year-old woman seeks medical attention because of progressive exertional dyspnea and rapid heart action. At age 12 she suffered from rheumatic fever, and a heart murmur has been subsequently noted. She has had intermittent episodes of atrial fibrillation over the past 2 years with good rate control on metoprolol succinate. Her vital signs include a heart rate of 80 beats/min, blood pressure 130/80 mm Hg, and respirations 16 breaths/min. She has inspiratory rales at the lung bases. Her cardiac impulse is displaced laterally. There is a loud S_1, a single S_2, an apical opening snap, a holodiastolic rumbling murmur at the apex, and a soft diastolic blowing murmur along the left sternal border. Isometric handgrip augments the diastolic murmurs. She has mild peripheral edema. Her ECG is shown in Fig. 4.27. The most likely valve lesions are
A. Mitral regurgitation and tricuspid stenosis
B. Mitral stenosis and mitral regurgitation
C. Mitral stenosis and aortic regurgitation
D. Mitral stenosis and pulmonic regurgitation
E. Tricuspid stenosis and pulmonic regurgitation

QUESTION 523

Which of the following statements regarding the medical management of mitral stenosis (MS) is NOT correct?
A. Antibiotic prophylaxis is not recommended for patients with MS undergoing dental surgery
B. Diuretic therapy is an appropriate measure for relieving symptoms of dyspnea
C. In pure MS with normal left ventricular function, digoxin is of benefit only if atrial fibrillation is present
D. The benefits of beta blocker therapy in MS include heart rate reduction and improved exercise tolerance
E. Anticoagulation is indicated to prevent thromboembolism in patients with MS regardless of the heart rhythm or history of previous thromboembolic events

QUESTION 524

Which of the following statements regarding infectious causes of pericarditis is correct?
A. Tuberculosis is the leading cause of constrictive pericarditis in developed nations
B. *Haemophilus influenzae* is the most common organism responsible for bacterial pericarditis
C. In the contemporary era, the prognosis of patients with bacterial pericarditis is comparable to that of viral pericarditis

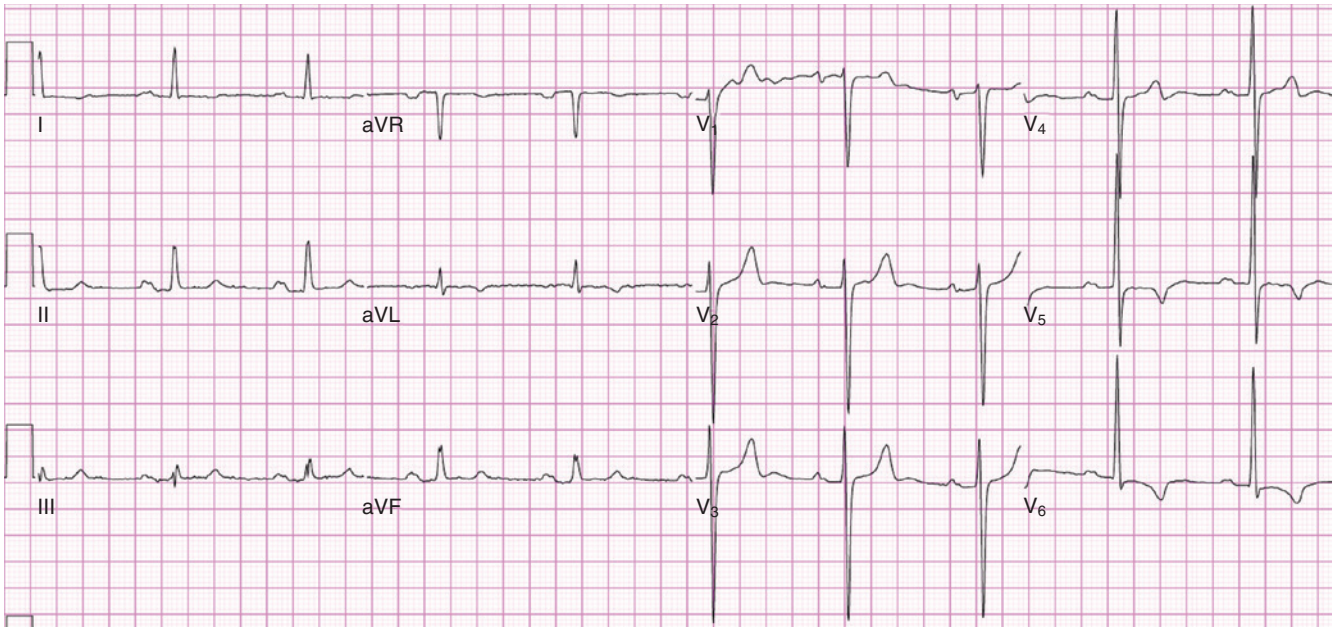

FIG. 4.27

D. Enteroviruses are among the most frequent causes of viral pericarditis
E. Prolonged antifungal therapy is required to manage isolated pericardial disease caused by *Histoplasma*

QUESTION 525

A 25-year-old graduate student presents to your office for physical examination. Several years ago, while growing up in Ecuador, he was diagnosed with Chagas disease when he had presented with fever, malaise, myalgias, and unilateral eyelid edema. Which of the following statements regarding Chagas disease is NOT correct?

A. The level of parasitemia does not correspond to the severity of chronic Chagas disease
B. The disease is transmitted to humans by the reduviid bug
C. An asymptomatic phase typically lasts for many years between initial infection and chronic manifestations of the disease
D. The most common ECG abnormality in chronic Chagas disease is left bundle branch block
E. The classic echocardiographic findings of chronic cardiac Chagas disease are those of a dilated cardiomyopathy with apical aneurysm formation

QUESTION 526

A 29-year-old woman was diagnosed with a congenital heart defect 6 years ago. At a routine office visit she describes occasional single palpitations during periods of emotional stress. An echocardiogram is obtained; the apical four-chamber view is shown in Fig. 4.28. Which of the following is demonstrated?

A. Bilateral atrial myxomas
B. Lipomatous hypertrophy of the interatrial septum
C. Normal position of an atrial septal closure device
D. Infiltrative disease, most likely amyloidosis
E. Normal echocardiogram

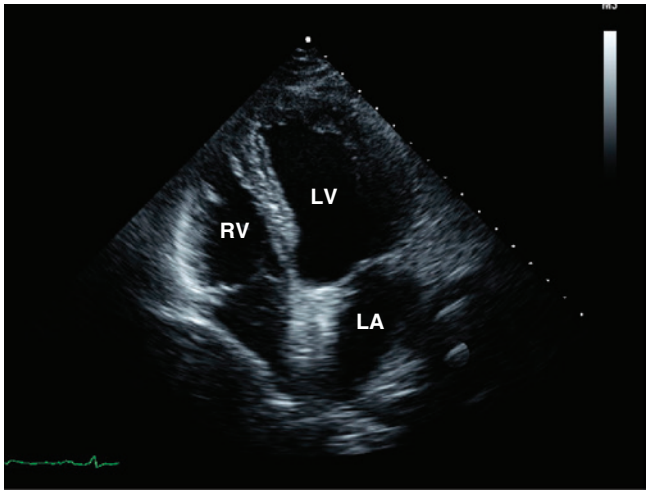

FIG. 4.28

QUESTION 527

A 42-year-old woman, originally from Thailand, presents for evaluation because of exertional dyspnea. As part of her evaluation, an echocardiographic study is performed; a parasternal long-axis view and a Doppler recording from the apical four-chamber view are displayed in Fig. 4.29. Which of the following statements is correct?

A. This abnormality results from myxomatous valvular degeneration
B. The Doppler profile in part *B* in the figure is essentially normal
C. The severity of this abnormality correlates with the likelihood of developing endocarditis
D. The risk of systemic embolism in this condition correlates with age
E. Chest pain accompanies this condition in the majority of patients

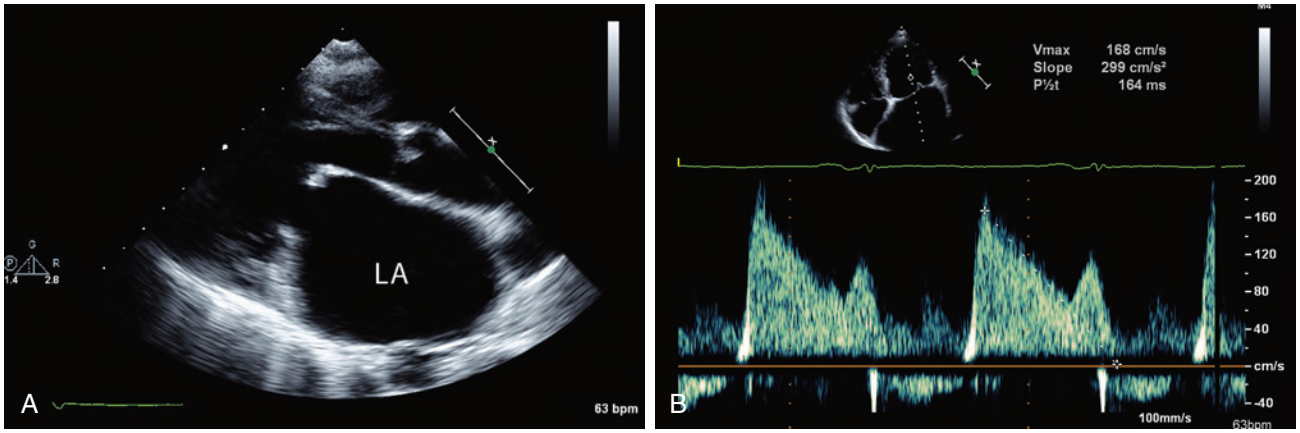

FIG. 4.29

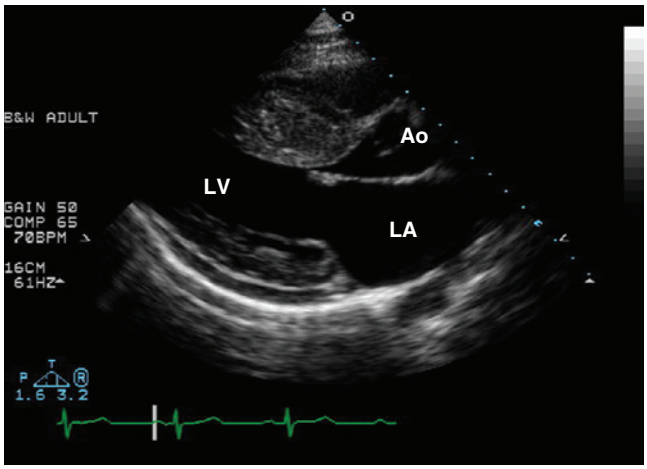

FIG. 4.30

QUESTION 528

A premature infant is found to have bounding peripheral pulses, a continuous murmur in the infraclavicular and interscapular regions, and precordial hyperactivity. An echocardiogram demonstrates a left-to-right shunt between the proximal descending aorta and the pulmonary artery. Which of the following statements about this condition is TRUE?

A. Most preterm infants with a birth weight <1500 g have this condition
B. Cardiopulmonary deterioration occurs in nearly all such infants
C. Chest radiography likely shows a decreased size of the cardiac silhouette
D. Surgical ligation is the only effective treatment
E. Noninvasive imaging typically shows right ventricular enlargement with normal left ventricular size

QUESTION 529

A 17-year-old boy has a syncopal event while playing soccer. He is noted to have a systolic ejection murmur on examination. An echocardiogram is obtained and a parasternal long-axis view is shown in Fig. 4.30. Which of the following statements about hemodynamic findings in patients with this condition is correct?

A. Diastolic function is usually impaired to a greater extent than systolic function
B. The majority of ventricular emptying is less rapid than usual
C. Left ventricular end-systolic volume is usually increased
D. Left ventricular ejection fraction is typically reduced

QUESTION 530

A 46-year-old man is admitted with fever, dyspnea, hypotension, and a new murmur of aortic regurgitation. Which of the following is typical of acute aortic regurgitation?

A. A widened systemic pulse pressure
B. A long, decrescendo diastolic murmur
C. Delayed closure of the mitral valve on echocardiography
D. Diastolic mitral regurgitation on echocardiography
E. An enlarged left ventricle

QUESTION 531

A 36-year-old woman with tetralogy of Fallot presents for routine outpatient evaluation. She had undergone surgical heart repair at age 5 months, including ventricular septal defect closure with a Dacron patch and relief of right ventricular outflow tract obstruction with a transannular patch. She denies shortness of breath or presyncope. Her electrocardiogram demonstrates normal sinus rhythm with intraventricular conducton delay (QRS duration = 190 msec). Cardiac magnetic resonance imaging reveals a low-normal left ventricular ejection fraction, severe pulmonary regurgitation, right ventricular dilatation with moderate right ventricular systolic dysfunction, and moderate tricuspid regurgitation. Cardiopulmonary exercise testing shows that her maximal oxygen consumption is 56% of the predicted value for her age and body surface area. Which of the following statements is correct?

A. She should be referred for pulmonary valve replacement
B. Her risk of sudden cardiac death is low
C. The presence of tricuspid regurgitation in this case does not influence the risk of developing atrial arrhythmias
D. She does not require antibiotic prophylaxis prior to dental procedures

QUESTION 532

A 68-year-old man presents for evaluation of progressive dyspnea. He has an extensive smoking history. Pulmonary

function testing is consistent with severe airway obstruction. An echocardiogram shows normal left ventricular systolic function, right ventricular hypertrophy and dilation, and an elevated calculated pulmonary artery systolic pressure. Which of the following therapies improves survival in patients with chronic obstructive lung disease with pulmonary hypertension?
A. Digoxin
B. Oxygen
C. Beta-adrenergic agonists
D. Theophylline
E. Bosentan

QUESTION 533

Which of the following statements regarding coarctation of the aorta is correct?
A. It is more common in females than males
B. Most infants and children with coarctation are asymptomatic
C. Ten percent of adults with coarctation also have a bicuspid aortic valve
D. Mean survival time in the presence of uncorrected coarctation is 60 years

QUESTION 534

A 30-year-old woman presented to the hospital after a recent transient neurologic event consistent with a small cerebral embolism. During her evaluation, a transthoracic echocardiogram was performed. An apical four-chamber view from the study is displayed in Fig. 4.31, with panels from both systole and diastole. Which of the following statements is TRUE?
A. The echocardiographic appearance is most consistent with an intracardiac thrombus
B. Systemic symptoms associated with this condition include fever, malaise, and an elevated erythrocyte sedimentation rate
C. Surgery is indicated only if there is hemodynamic compromise
D. The majority of such lesions are familial
E. Unlike this patient, this condition most commonly arises in the right atrium

QUESTION 535

A 54-year-old woman with chronic kidney disease presents to the emergency department because of sudden shortness of breath and right-sided pleuritic chest pain. She recently returned from vacation on a 12-hour flight. Physical examination demonstrates a tachypneic, normotensive, and tachycardic woman. The serum creatinine is chronically elevated, and precludes performing a chest computed tomographic angiogram. Which of the following results would be most useful in EXCLUDING the diagnosis of pulmonary embolism?
A. Normal PaO_2 by arterial blood gas determination
B. Normal cardiopulmonary examination
C. Intermediate probability (ventilation/perfusion) lung scan
D. Normal plasma level of D-dimer
E. Absence of right-sided heart strain or $S_1Q_3T_3$ pattern on ECG

QUESTION 536

Which of the following statements regarding primary tumors of the heart is NOT correct?
A. Benign tumors are more common than malignant tumors
B. The most common malignant cardiac tumors are angiosarcomas and rhabdomyosarcomas
C. The presence of a hemorrhagic pericardial effusion is more consistent with a malignant tumor
D. Malignant tumors are more likely to occur on the left side of the heart

QUESTION 537

A 67-year-old man with adenocarcinoma of the lung presents with dyspnea and weakness. Physical examination is notable for hypotension with pulsus paradoxus and jugular venous distention. An echocardiogram is ordered. Which of the following statements regarding echocardiography in cardiac tamponade is TRUE?
A. On inspiration, there is augmentation of transmitral flow velocities and reduction in transtricuspid flow velocities
B. The absence of right ventricular diastolic collapse ensures that the pericardial pressure is not elevated

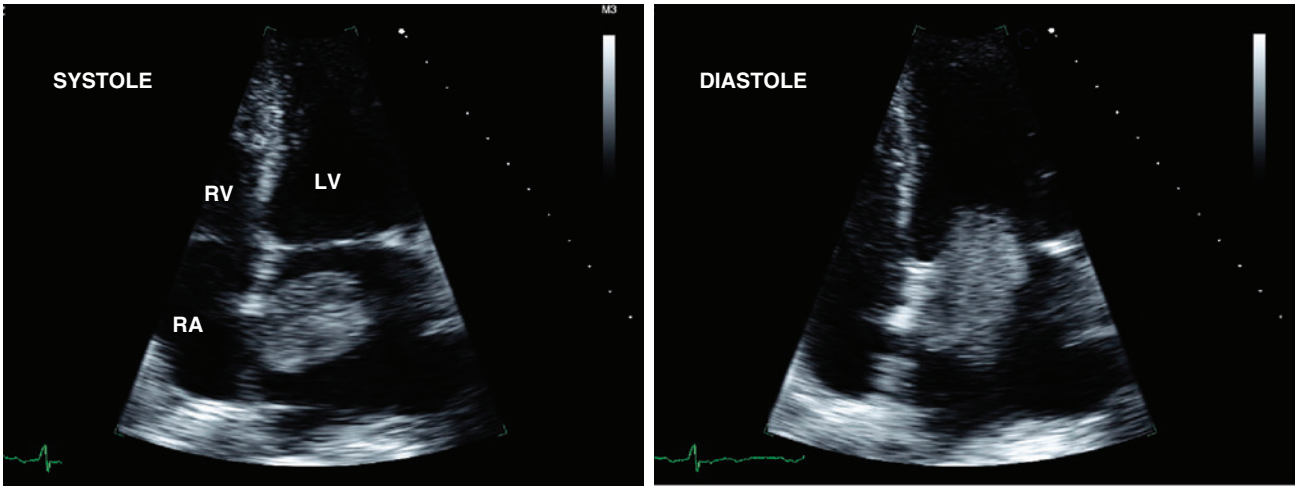

FIG. 4.31

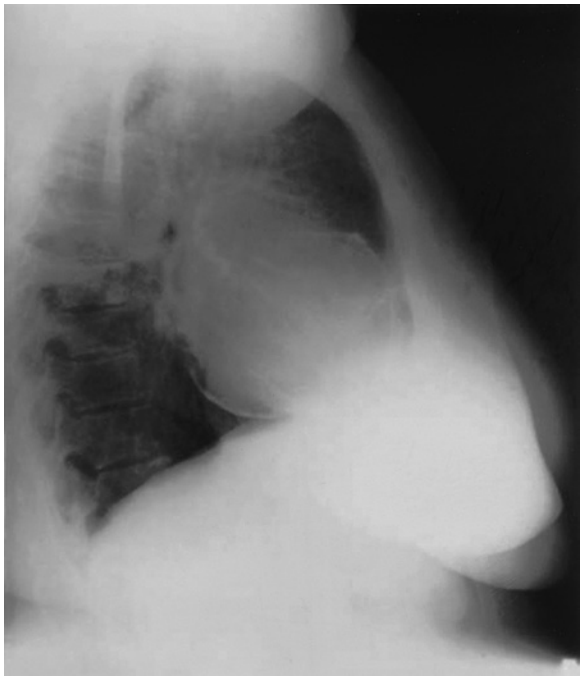

FIG. 4.32

C. Right ventricular diastolic collapse is more specific than right atrial collapse in the diagnosis of tamponade
D. Cardiac tamponade is associated with normal inferior vena cava collapse with inspiration
E. A small-volume pericardial effusion observed on echocardiography excludes the presence of tamponade

QUESTION 538

A 64-year-old woman with a remote history of chest irradiation presents with gradually progressive symptoms of fatigue, abdominal bloating, and lower extremity edema over the past 4 months. Her lateral chest radiograph is shown in Fig. 4.32. Which of the following findings would be inconsistent with the likely diagnosis?
A. Kussmaul sign
B. Hepatomegaly
C. Early diastolic pericardial knock
D. Right and left ventricular systolic pressure concordance during inspiration
E. Elevation and equalization of intracardiac diastolic pressures

QUESTION 539

Which of the following statements regarding the causes of aortic stenosis (AS) is TRUE?
A. A congenitally bicuspid valve accounts for 20% of patients requiring surgical treatment for AS in the United States
B. In patients younger than 70 years, rheumatic deformity is the most common cause of AS that leads to surgical valve replacement
C. There are no established risk factors for the development of calcific AS of a trileaflet valve other than age
D. Age-related calcification of a congenitally bicuspid, or normal trileaflet valve, is the most common cause of AS in adults in the United States
E. Isolated rheumatic deformity of the aortic valve, without mitral valve involvement, is more common than rheumatic involvement of both valves

QUESTION 540

A 68-year-old man with chronic aortic regurgitation presents for office evaluation. He describes reduced stamina, progressive symptoms of exertional dyspnea, and occasional orthopnea. His echocardiogram shows severe aortic regurgitation, a left ventricular (LV) end-systolic diameter of 48 mm, and an LV ejection fraction of 45%. Which of the following statements regarding valve replacement for chronic aortic regurgitation (AR) is NOT correct?
A. Asymptomatic patients with advanced AR who have normal LV function and end-systolic diameter <50 mm have an excellent prognosis such that surgery can be safely postponed
B. An LV end-systolic diameter >55 mm before surgical intervention portends a worse postoperative prognosis than does a smaller ventricular diameter
C. Angiotensin-converting enzyme inhibitors delay the need for aortic valve replacement in chronic AR
D. Patients with chronic AR who have symptoms of congestive heart failure accompanied by reduced LV ejection fraction should be referred for aortic valve replacement
E. A preoperative ejection fraction <50% increases the risk of postoperative death from LV dysfunction

QUESTION 541

A 44-year-old man with human immunodeficiency virus (HIV) infection and a history of non-adherence to prescribed antiretroviral therapy presents to your office for evaluation of shortness of breath. He reports 2 months of progressive fatigue and dyspnea on exertion. His CD4 count is 15 cells/mm^3 (normal = 500 to 1500 cells/mm^3). Transthoracic echocardiography reveals a dilated heart with a left ventricular (LV) ejection fraction of 15% and a small pericardial effusion. Which of the following statements is TRUE?
A. Fifty percent of HIV-infected individuals will ultimately develop symptomatic LV dysfunction
B. Large asymptomatic pericardial effusions are the most common cardiac manifestation of HIV infection, but the presence of effusion is not associated with increased mortality
C. In HIV-infected individuals, LV dysfunction has little bearing on 1-year mortality rates
D. Protease inhibitor therapy is associated with an increased risk of myocardial infarction

QUESTION 542

Which of the following statements regarding the cardiovascular consequences of Turner syndrome is NOT correct?
A. Cardiovascular defects are seen in fewer than 5% of patients
B. Coarctation of the aorta is the most commonly associated congenital cardiovascular abnormality
C. There is an increased risk of aortic dissection

D. Bicuspid aortic valve occurs at a higher frequency than in the general population
E. Partial anomalous venous drainage occurs more frequently than in the general population

QUESTION 543

A 20-year-old man with Duchenne muscular dystrophy presents for evaluation. Regarding cardiac involvement in this condition, which of the following statements is TRUE?
A. Fewer than 25% of patients with Duchenne muscular dystrophy >18 years develop a dilated cardiomyopathy
B. The ECG typically shows tall R waves with increased R/S amplitude in V_1 and deep narrow Q waves in the left precordial leads
C. There is a direct association between the presence of dilated cardiomyopathy and electrocardiographic abnormalities
D. The most common rhythm disturbance is ventricular tachycardia

QUESTION 544

A 34-year-old man is receiving doxorubicin chemotherapy for lymphoma. Which of the following statements regarding the risk of doxorubicin-induced cardiotoxicity is NOT correct?
A. Previous or concurrent mediastinal irradiation increases the risk of cardiotoxicity
B. The age groups most at risk are the very young and the very old
C. Cardiomyopathy does not develop unless the total cumulative dose exceeds 700 mg/m^2
D. Concurrent use of cyclophosphamide increases the risk of cardiotoxicity
E. A baseline left ventricular ejection fraction of 45% increases the risk of cardiotoxicity

QUESTION 545

A 63-year-old man with metastatic colon cancer is prescribed therapy targeting vascular endothelial growth factor (VEGF). Which of the following statements is correct about the use of the monoclonal antibody/VEGF antagonist bevacizumab?
A. The left ventricular ejection fraction tends to increase with use of this drug
B. Hypotension is a common side effect
C. The risk of arterial, but not venous, thromboembolic events is increased
D. Hemorrhagic pericardial effusion is associated with continuous use of this agent

QUESTION 546

A 2-year-old boy with Down syndrome and a heart murmur is brought to the pediatrician's office because of poor weight gain. The most likely finding on cardiac auscultation is
A. An early diastolic opening sound at the apex followed by a diastolic rumbling murmur
B. A midsystolic murmur at the upper left sternal border and wide, fixed splitting of S_2
C. A midsystolic click followed by a late systolic murmur at the apex
D. A blowing diastolic murmur at the right upper sternal border
E. A late-peaking systolic ejection murmur heard best at the upper right sternal border with a diminished S_2

QUESTION 547

A 35-year-old man presents with complaints of exertional dyspnea. His medical history is significant for chest radiation therapy as a teenager for treatment for a hematologic malignancy. Regarding cardiovascular effects of radiation therapy, which of the following statements is correct?
A. Most complications develop within 5 years of radiation exposure
B. Constrictive pericarditis is typically an acute reaction to radiation therapy
C. The conduction system is typically spared from adverse effects of radiation
D. Dilated cardiomyopathy is the most common manifestation of mediastinal radiation therapy
E. Cancer survivors who received head and neck radiation are at a heightened risk of stroke

QUESTION 548

Which of the following statements is correct regarding familial forms of dilated cardiomyopathy (DCM)?
A. Familial forms account for less than 3% of cases of DCM
B. Most inherited forms of dilated cardiomyopathy fit an autosomal recessive pattern
C. Familial DCM most commonly results from mutations in genes that encode sarcolemmal surface receptors
D. In symptomatic patients, histologic examination of the heart typically demonstrates extensive areas of interstitial and perivascular fibrosis
E. Familial cardiomyopathy can be readily identified as the cause of DCM by specific immunologic markers

QUESTION 549

A 65-year-old man with a history of chest radiation therapy for lymphoma presents with worsening exertional dyspnea. On physical examination the heart rate is 120 beats/min, blood pressure 90/55 mm Hg, with pulsus paradoxus of 15 mm Hg. The jugular venous pressure is 10 cm H_2O with a prominent *x* descent. He is found by echocardiography to have a large pericardial effusion, which is drained by pericardiocentesis in the cardiac catheterization laboratory. After the procedure, the intrapericardial pressure normalizes but the initially elevated right atrial pressure fails to decline and displays a prominent *y* descent. This scenario is most consistent with
A. Persistence of pericardial tamponade
B. Cor pulmonale
C. Effusive-constrictive pericarditis
D. Restrictive cardiomyopathy
E. Uremic pericarditis

Directions:

Each group of questions below consists of lettered headings followed by a set of numbered questions. For each question, select the ONE lettered heading with which it is most closely

associated. Each lettered heading may be used once, more than once, or not at all.

QUESTIONS 550 TO 553

For each statement below, match the appropriate lesion:
A. Osler nodes
B. Janeway lesions
C. Roth spots
D. Subungual hemorrhages
E. Bracht-Wächter bodies

550. Small (1- to 4-mm diameter), irregular, erythematous, nontender macules present on the thenar and hypothenar eminences of the hands
551. Small, raised red (or purple) tender lesions present in the pulp spaces of the terminal phalanges of the fingers
552. Collections of lymphocytes in the nerve layer of the retina
553. Linear or flame-shaped streaks

QUESTIONS 554 TO 558

For each cardiac condition, match the electrocardiographic finding that is most closely associated with it:
A. Low QRS voltage
B. Atrioventricular nodal block
C. Right bundle branch block
D. Global ST-segment elevation
E. Deeply inverted precordial T waves

554. Chronic Chagas disease
555. Sarcoidosis
556. Apical hypertrophic cardiomyopathy
557. Amyloidosis
558. Lyme carditis

QUESTIONS 559 TO 562

For each statement, match the appropriate prosthetic valve type:
A. Starr-Edwards caged-ball valve
B. Carpentier-Edwards Magna valve
C. St. Jude bileaflet valve
D. Medtronic-Hall valve

559. Single tilting disc valve
560. Lowest profile mechanical valve
561. Least thrombogenic mechanical prosthesis for the mitral position
562. Bovine pericardial valve

QUESTIONS 563 TO 566

For each description, match the related cardiac condition(s):
A. Constrictive pericarditis
B. Restrictive cardiomyopathy
C. Both
D. Neither

563. Atrial fibrillation, low QRS voltage
564. Right and left ventricular systolic pressure discordance with respiration during cardiac catheterization
565. Physical cause of abnormality often visualized by chest computed tomography
566. Reduced medial mitral annular E′ velocity by Doppler tissue imaging

QUESTIONS 567 TO 571

For each statement listed below, match the most appropriate condition:
A. Cardiac myxoma
B. Large papillary fibroelastoma
C. Both
D. Neither

567. Familial predilection
568. Risk of distal embolism
569. Surgical excision is management of choice
570. May undergo malignant transformation
571. Typically attaches to valves and subvalvular structures

QUESTIONS 572 TO 575

Match the description with the associated form of therapy for pulmonary embolism:
A. Unfractionated heparin or low-molecular-weight heparin
B. Fibrinolytic therapy
C. Both
D. Neither

572. May be effective in pulmonary embolism even 1 to 2 weeks after the onset of symptoms
573. Dissolution of recently formed thrombus is a major action
574. Should be administered along with an antiplatelet agent
575. May suppress aldosterone secretion

QUESTIONS 576 TO 580

Match each description with the associated condition:
A. Hemochromatosis
B. Amyloidosis
C. Both
D. Neither

576. May result in restrictive cardiomyopathy
577. Early-stage disease is reversible with chelating agents
578. Ventricular tachyarrhythmia is the most common initial presentation
579. Autosomal recessive inheritance may be responsible
580. Low-voltage QRS on ECG is typical

QUESTIONS 581 TO 585

Match each description with the associated condition:
A. Tricuspid stenosis
B. Pulmonic stenosis
C. Both
D. Neither

581. Usually rheumatic in origin
582. Typical of carcinoid heart disease
583. Most adults are asymptomatic
584. Ascites is common on physical examination
585. Balloon valvuloplasty is the treatment of choice

QUESTIONS 586 TO 589

Match each description with the associated drug therapy in patients with idiopathic (group 1) pulmonary arterial hypertension (PAH):
A. Calcium channel blockers
B. Epoprostenol (prostacyclin)

C. Both
D. Neither
586. Studies have shown a survival benefit in patients with PAH
587. Should be started empirically in all patients with group 1 PAH
588. Not approved for oral administration
589. Exert(s) an antithrombotic effect

QUESTIONS 590 TO 593

Match each hemodynamic scenario with the associated condition:
A. Chronic constrictive pericarditis
B. Cardiac amyloidosis
C. Both
D. Neither
590. Right ventricular (RV) pressure tracing shows a deep and rapid early decline at the onset of diastole, with a rapid rise to a plateau in early diastole ("dip and plateau" configuration)
591. Left ventricular end-diastolic pressure exceeds right ventricular end-diastolic pressure (RVEDP) by 10 mm Hg
592. Peak RV systolic pressure = 35 mm Hg, RVEDP = 18 mm Hg
593. Pulmonary artery systolic pressure = 68 mm Hg, RVEDP = 15 mm Hg

QUESTIONS 594 TO 597

Match the following descriptions with the appropriate symptom in aortic stenosis:
A. Palpitations
B. Angina
C. Syncope
D. Exertional dyspnea as a manifestation of heart failure
594. Most significant clinical marker for adverse outcome in aortic stenosis, predictive of a 1- to 2-year survival if the valve lesion is not surgically corrected
595. Associated with reduced survival in untreated aortic stenosis of 3 to 5 years
596. Associated with reduced survival in untreated aortic stenosis of 2 to 3 years
597. Not a marker of reduced survival in patients with aortic stenosis

QUESTIONS 598 TO 601

For each type of procedure below, match the appropriate prophylactic antibiotic regimen:
A. No antibiotic prophylaxis required
B. Amoxicillin, 2 g orally, taken 30 to 60 minutes before the procedure
C. Clindamycin 600 mg orally, taken 30 to 60 minutes before the procedure
D. Ampicillin, 2 g intramuscular (IM) or IV 30 to 60 minutes before the procedure
598. Elective colonoscopy in a patient with a mechanical mitral valve
599. Dental extraction in a patient with a bioprosthetic aortic valve
600. Dental extraction in penicillin-allergic patient with a mechanical aortic valve
601. Elective cholecystectomy in a patient with mitral stenosis

QUESTIONS 602 TO 606

Match the following descriptions with the appropriate condition:
A. Complete atrioventricular septal defect
B. Complete transposition (d-transposition) of the great arteries
C. Both
D. Neither
602. Presents with cyanosis
603. Right-axis deviation on the ECG
604. An interatrial communication is almost always present
605. On echocardiography, the AV valves appear abnormally aligned at the same level
606. A high-pitched, blowing, decrescendo diastolic murmur is common at the left sternal border

QUESTIONS 607 TO 611

Match the following descriptions with the appropriate condition:
A. Kartagener syndrome
B. Holt-Oram syndrome
C. LEOPARD syndrome
D. Noonan syndrome
607. Webbed neck, pulmonic stenosis, left anterior fascicular block
608. Deafness, pulmonic stenosis, complete heart block
609. Lentigines, pulmonic stenosis, PR prolongation
610. Sinusitis, dextrocardia, bronchiectasis
611. Abnormal scaphoid bone, atrial septal defect, right bundle branch block

QUESTIONS 612 TO 615

Match each photograph in Fig. 4.33 with the condition it represents:
A. Part A
B. Part B
C. Part C
D. Part D
612. Fabry disease
613. Infective endocarditis
614. Amyloidosis
615. Systemic sclerosis

QUESTIONS 616 TO 619

Match the following descriptions with the appropriate association:
A. Turner syndrome
B. Noonan syndrome
C. Both
D. Neither
616. Coarctation of the aorta
617. Normal karyotype

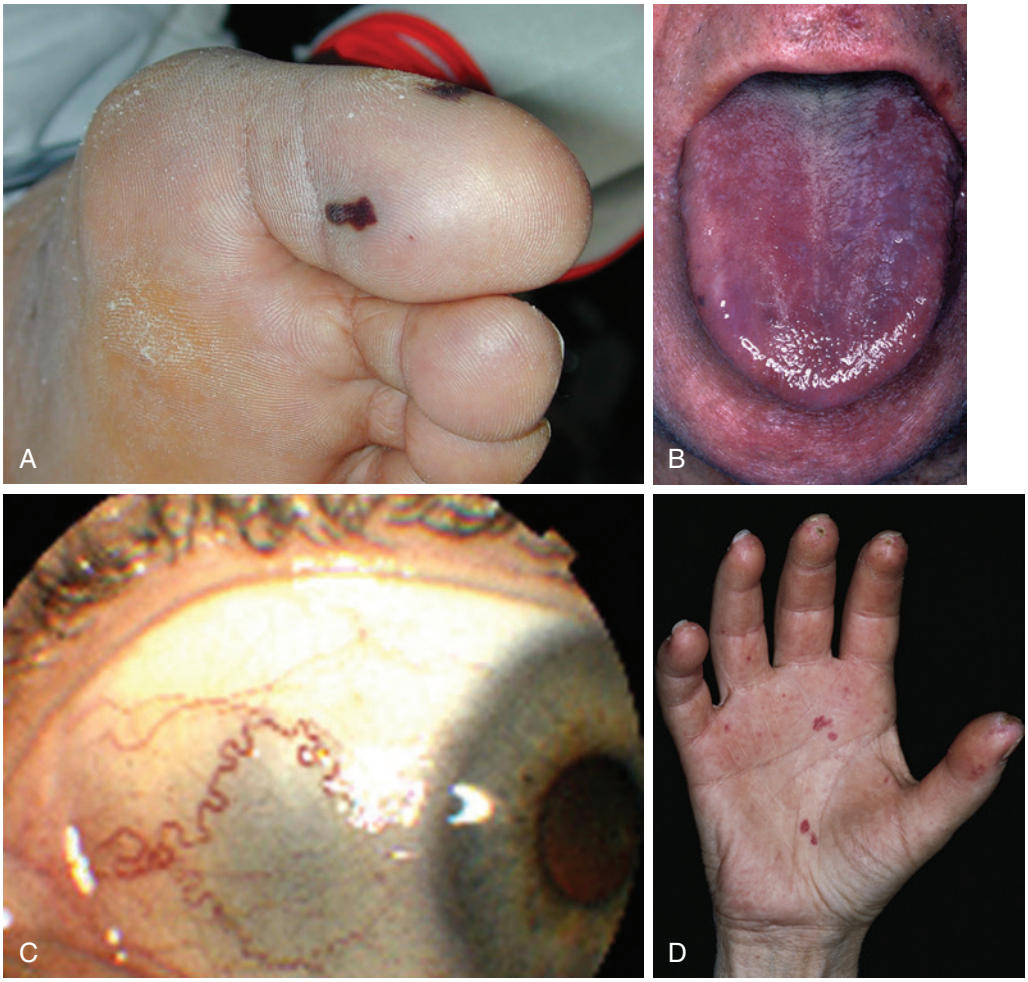

FIG. 4.33 *(A) Courtesy Alan J. Lesse, MD; (B) From duVivier A.* Atlas of Clinical Dermatology. *3rd ed. Philadelphia: Elsevier; 2002; (C) From Samiy N. Ocular features of Fabry disease: diagnosis of a treatable life-threatening disorder.* Surv Ophthalmol. *2008;53:416–423; (D) From Habif TP.* Clinical Dermatology. *5th ed. Philadelphia: Mosby Elsevier; 2009.*

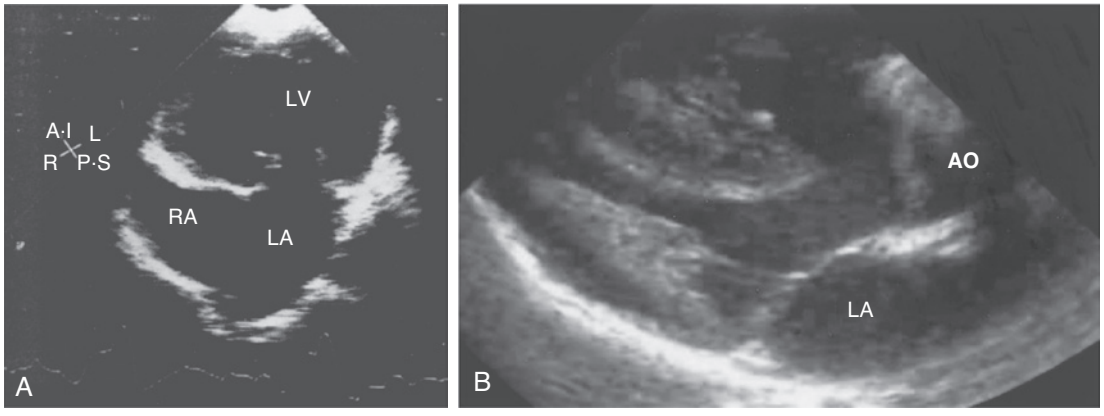

FIG. 4.34

618. Pulmonic stenosis
619. Short stature, webbing of the neck, skeletal anomalies, and renal anomalies

QUESTIONS 620 TO 624

Match the following descriptions with the appropriate part of Fig. 4.34:
A. Part A
B. Part B
C. Both
D. Neither

620. A ventricular septal defect typically accompanies this anomaly
621. d-Transposition of the great arteries is known to accompany this anomaly
622. Coronary variations in this disorder include abnormal origin of the anterior descending artery from the right coronary artery
623. Cyanosis and an electrocardiographic finding of left ventricular hypertrophy are typical
624. The Fontan procedure may be a useful intervention for this condition

QUESTIONS 625 TO 629

Match the following descriptions with the associated antineoplastic therapy:
A. Thoracic radiation therapy
B. Anthracycline therapy
C. Both
D. Neither

625. Pericarditis is the most common cardiac complication
626. Premature coronary atherosclerosis
627. Left ventricular systolic dysfunction
628. Ventricular arrhythmias
629. Aortic dissection

Section IV Answers

(CHAPTERS 67 TO 87)

Diseases of Heart Valves, Myocardium, Pericardium, and Pulmonary Vascular Bed

ANSWER TO QUESTION 436

D (Braunwald, p. 1590; Table 77.2; eFig. 77.6)

This woman presents with features of an acute coronary syndrome, but coronary angiography demonstrates no significant coronary disease. Rather, left ventricular (LV) angiography demonstrates a large region of apical akinesis and preserved contraction at the base. These features are consistent with takotsubo cardiomyopathy (also termed stress-induced cardiomyopathy or apical ballooning syndrome). This is a reversible condition that mimics acute myocardial infarction and occurs primarily in postmenopausal women, usually precipitated by a profound emotional or physical event. Regional contractile abnormalities are typical, usually causing apical akinesis with compensatory hypercontractility at the base. However, in some affected patients the akinetic or dyskinetic segment is located at the midventricle or base instead.

This syndrome is usually transient with rapid contractile recovery within days to weeks. However, early complications occur rarely, including malignant arrhythmias, thromboembolism, LV rupture, and cardiogenic shock, such that acute in-hospital mortality is 1.2%. The mechanism by which takotsubo cardiomyopathy arises is speculative; it may be a response to a catecholamine surge resulting in regional microvascular dysfunction in susceptible patients. Recurrences occur in <5% of patients. Anticoagulation is not routinely recommended, despite the frequently present apical wall motion abnormality (unless thrombus is visualized) because of the usually rapid resolution of the disorder.

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Pelliccia F, Kaski JC, Crea F, et al. Pathophysiology of takotsubo syndrome. *Circulation.* 2017;135:2426–2441.

ANSWER TO QUESTION 437

C (Braunwald, pp. 1663–1667)

The ECG demonstrates diffuse ST-segment elevations and PR-segment depressions that are most consistent with acute pericarditis.[1] ST-segment elevations in all leads except aVR develop in the majority of patients with acute pericarditis, and PR-segment depression is found in up to 80%.

Although chest pain is the most common symptom in acute pericarditis, its location and quality are variable. The pain is often positional in that it improves by sitting upright or leaning forward and is aggravated with coughing, deep inspiration, or lying supine. Fever is common, but the cardinal physical finding is a pericardial friction rub. The three components of the complete pericardial rub correspond to atrial systole, ventricular systole, and the early filling phase of ventricular diastole.

Cardiac serum biomarkers can be elevated in acute pericarditis because of inflammation of the adjacent myocardium. As a result, an initial determination of markers such as cardiac troponin I cannot reliably differentiate between acute pericarditis and myocardial infarction.[2]

Fibrinolytic therapy is of potential harm if administered to a patient with acute pericarditis, because hemorrhagic tamponade could follow. Initial therapy for patients with acute viral or idiopathic pericarditis should include aspirin or other nonsteroidal anti-inflammatory drugs. Randomized prospective clinical trials show that colchicine reduces the duration of acute symptomatology and recurrences of pericarditis.[3] For truly refractory symptoms, glucocorticoids may be beneficial, but should not be prescribed as initial therapy, as such use is associated with increased recurrence rates of pericarditis. Nitrates have no role in the management of pericardial symptoms.

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ANSWER TO QUESTION 438

A (Braunwald, pp. 1559–1561)

Localized coarctation of the aorta consists of a shelf in the posterolateral aortic wall opposite the ductus arteriosus. It is more common in males and there is a high degree of association with bicuspid aortic valve and Turner

syndrome. Other associated congenital cardiac malformations include patent ductus arteriosus, ventricular septal defect, and mitral valve abnormalities. Young patients with coarctation are usually asymptomatic. In older children or adults, symptoms may include headache, leg fatigue, and intermittent claudication. Patients may also come to medical attention because of symptoms associated with left ventricular failure, infective endarteritis, or aortic rupture or dissection.

Simultaneous palpation of the upper and lower extremities in patients with coarctation often reveals diminished and delayed femoral pulses compared with the radial pulse. Exercise typically accentuates this finding. A midsystolic murmur over the chest and back is often present. In addition, auscultation may demonstrate the ejection click and systolic murmur of a coexistent bicuspid aortic valve.

Persistent systemic hypertension after repair of the coarctation occurs in up to one-third of patients, even in the absence of recoarctation. Risk factors include older age at repair and higher blood pressure at the time of repair.[1,2]

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ANSWER TO QUESTION 439

C (Braunwald, pp. 1389–1399)

The Doppler recording displays a symmetric systolic profile with an elevated transaortic valve systolic velocity of 4 m/s, which corresponds to a peak instantaneous systolic gradient of 64 mm Hg (from the simplified Bernoulli equation: Pressure gradient = 4 × velocity^2). This patient thus presents with symptomatic aortic stenosis (AS). Angina pectoris, syncope, and heart failure are the cardinal symptoms of this condition.[1] The onset of symptoms in patients with AS is an ominous sign: natural history survival trends show that the time of death following symptom occurrence is approximately 5 years for patients with angina, 3 years for those with syncope, and 2 years for patients with heart failure. Angina is present in approximately two-thirds of patients with critical AS. It arises in the absence of significant coronary artery obstruction in up to half of patients, owing to both increased oxygen demand and impaired coronary vasodilatory reserve with microcirculatory dysfunction.[2] Whereas the most common early symptom in patients with AS is a decrease in exercise tolerance or dyspnea on exertion (due to left ventricular diastolic dysfunction or the limited ability to increase cardiac output with exercise), symptoms of advanced heart failure (orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema) occur late in the course.

Syncope in AS typically occurs with exertion and is due to systemic vasodilatation with reduced vascular tone in the setting of a fixed cardiac output.

An association between calcific aortic stenosis and gastrointestinal hemorrhage, particularly due to angiodysplasia, has been observed (termed the Heyde syndrome).[3] Associated bleeding is thought to arise because of shear stress-induced platelet aggregation by the stenotic valve with reduction of high-molecular-weight multimers of von Willebrand factor and an increased number of proteolytic fragments. This abnormality is correctable by aortic valve replacement.

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ANSWER TO QUESTION 440

B (Braunwald, pp. 1634–1636)

Cocaine is the most commonly used illicit drug among patients presenting to emergency departments, and associated cardiovascular consequences include ischemia and infarction, myocardial diastolic and/or systolic dysfunction, and arrhythmias.[1,2] The mechanisms of myocardial ischemia and infarction include (1) increased myocardial oxygen demand in the setting of limited oxygen supply, (2) intense coronary arterial vasoconstriction,[3] and/or (3) enhanced platelet aggregation and thrombogenicity. In addition, the vascular injury caused by cocaine may lead to increased endothelial permeability and accelerated atherogenesis. Cocaine use increases the risk of myocardial infarction (MI) 24-fold over the following 60 minutes in individuals otherwise at low risk for MI. Notably, the occurrence of myocardial infarction after cocaine is not associated with the amount ingested, route of administration, or frequency of use.

Mechanisms of myocardial dysfunction after long-term cocaine use include (1) myocardial ischemia or infarction, (2) cardiomyopathy due to repeated sympathetic stimulation, and (3) altered myocardial and endothelial cytokine production. Myocardial dysfunction can also occur acutely after cocaine use, likely reflecting drug-associated metabolic disturbances or direct toxic effects of the drug.

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ANSWER TO QUESTION 441

D (Braunwald, pp. 1535–1537)

The common anatomic types of atrial septal defect (ASD) include the sinus venosus or "high" ASD, the ostium secundum ASD, and the ostium primum ASD. The sinus venosus defect is often accompanied by anomalous pulmonary venous return. The ostium secundum type of ASD, which appears in the mid-interatrial septum, should be distinguished from patent foramen ovale, which occurs in up to 25% of adults.

Ostium primum ASDs are a type of atrioventricular septal defect, discussed in a subsequent question.

Patients with ASDs are usually asymptomatic in early life, and only rare children with this disorder experience exertional dyspnea and easy fatigability. Atrial arrhythmias are uncommon. Children with ASDs do tend to be underdeveloped physically and prone to respiratory tract infections. The diagnosis of ASD in the young is most often prompted by detection of a heart murmur on routine physical examination. In adults, the most common manifesting symptoms are exercise intolerance and palpitations.

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ANSWER TO QUESTION 442

B (Braunwald, p. 1528)

The ECG is helpful in the assessment of congenital heart disease. In particular, evaluation for right-axis deviation and right ventricular hypertrophy, and rhythm and conduction disturbances, is important. For example, right ventricular hypertrophy may be a sign of pulmonary hypertension or right ventricular outflow tract obstruction or other disorders causing right-sided pressure or volume overload, including septal defects.

Atrial arrhythmias commonly accompany congenital heart disease. Atrial flutter is much more frequent in young patients than atrial fibrillation. It often arises in patients with a history of surgical repair and can be challenging to treat. Pharmacologic agents are generally ineffective, and catheter ablation is usually necessary; recurrence is common. Conduction disturbances, such as first-degree atrioventricular (AV) block, are often evident in patients with AV septal defects, congenitally corrected transposition of the great arteries, and Ebstein anomaly.

The electrocardiographic findings of myocardial infarction in an infant suggest the presence of an anomalous origin of a coronary artery. Left ventricular volume overload due to aortic or mitral regurgitation can result in deep Q waves in the left precordial leads.

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ANSWER TO QUESTION 443

D (Braunwald, pp. 1541–1542)

Ventricular septal defects (VSDs) may be classified by their locations and margins. Muscular VSDs are bordered entirely by myocardium and may be found in the trabecular septum, inlet septum, or outlet septum. Membranous VSDs are bordered in part by fibrous continuity between an atrioventricular valve and an arterial valve. Doubly committed subarterial VSDs, which are more common in Asian and South American patients, are situated in the outlet septum and bordered by fibrous continuity of the aortic and pulmonary valves.

The size of a VSD relates to the consequent pathophysiology and potential complications. A restrictive VSD is small (Q_p/Q_s <1.4) and thus produces a significant pressure gradient between the left and right ventricles. It typically does not cause hemodynamic impairment and may eventually spontaneously close, but the turbulence of the high-pressure jet across the defect presents a high risk of endocarditis. Because of the high gradient, infants with a restrictive VSD demonstrate a loud murmur and often present at an early age. Conversely, infants with large nonrestrictive defects present at a later age because the equalization of pressures across the defect attenuates the systolic murmur. A large, nonrestrictive VSD (Q_p/Q_s >2.2) is accompanied by a substantial left-to-right shunt, with subsequent development of an elevated pulmonary artery systolic pressure. Such patients may eventually develop left ventricular volume overload, heart failure, and Eisenmenger syndrome (related to the progressive rise in pulmonary artery pressure). Closure of the defect, either surgically or by transcatheter device placement, is the treatment of choice for those with a significant VSD in the absence of contraindications (e.g., irreversible pulmonary hypertension). After repair, the ECG is usually notable for right bundle branch block.

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ANSWER TO QUESTION 444

A (Braunwald, pp. 1535–1537)

Although atrial septal defects (ASDs) are frequently asymptomatic, children may experience exertional dyspnea or frequent chest infections. Physical examination usually demonstrates wide fixed splitting of the second heart sound. Other common findings include a systolic murmur of increased flow across the pulmonic valve or a mid-diastolic rumble due to increased flow through the tricuspid valve. The ECG may be helpful in determining the type of ASD. Secundum ASD patients often exhibit right-axis deviation on the ECG, whereas those with primum ASD characteristically exhibit left-axis deviation. Patients with sinus venosus ASD exhibit left-axis deviation of the P wave.

ASD repair is advised for patients with a Q_p/Q_s ≥1.5, particularly if the anatomy is suitable for percutaneous transcatheter device closure. Repair improves New York Heart Association functional class in symptomatic patients. For adults who are asymptomatic or mildly symptomatic, device closure improves exercise capacity.[1–3] In patients who undergo successful repair of an isolated secundum defect (by surgery or by transcatheter device), lifelong endocarditis prophylaxis is not required. Prophylaxis *is* appropriate for the first 6 months after device closure, while the device endothelializes.

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ANSWER TO QUESTION 445

E (Braunwald, p. 1869)

The echocardiogram demonstrates a pedunculated mass in the right atrium that is most suggestive of an atrial myxoma. Features that suggest myxoma include (1) attachment of the mass to the interatrial septum (the most common site of attachment is in the region of the fossa ovalis) and (2) a mass that is pedunculated and heterogeneous in appearance. Other cardiac tumors, including lipomas and rhabdomyomas, would be within the differential diagnosis. However, these other tumors are rarely pedunculated and more often infiltrate into the myocardium itself. The echocardiographic appearance would also prompt consideration of an intracardiac thrombus. However, atrial thrombi tend to be located in the posterior portion of the atrium and have more of a layered appearance than the heterogeneous mottling apparent in this example.

Atrial myxoma is the most common primary tumor of the heart, and >80% of such tumors arise in the left atrium. The clinical presentation of a myxoma is related to intracardiac obstruction, embolization, and/or constitutional symptoms. Nearly 70% of patients with left atrial myxomas have cardiac symptoms, typically related to obstructive heart failure and syncope. Embolic events occur in approximately 30% of patients, with left atrial myxomas causing strokes and transient ischemic attacks and right atrial myxomas leading to pulmonary emboli. Myxomas may secrete interleukin-6, an inflammatory cytokine associated with systemic symptoms such as fever, malaise, and weight loss. Surgical resection of myxomas is warranted to relieve systemic or intracardiac obstructive symptoms and to prevent embolic complications.

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ANSWER TO QUESTION 446

B (Braunwald, pp. 1483–1502)

Prosthetic valve endocarditis (PVE) may occur "early," within the first 60 days after placement of the valve, or "late," in subsequent months or years. While this distinction is somewhat arbitrary, differences in both the clinical features and microbial patterns have been documented. Cases of early PVE usually are due to contamination in the immediate operative or perioperative setting. *Staphylococcus aureus* is the most common organism isolated in this group, occurring in ~35% of cases, of which one-quarter are methicillin resistant. Coagulase negative staphylococci account for ~28% of early PVE cases.

In late cases, as in this question, the source of infection is often difficult to identify but is presumed to be seeding of the valve by transient bacteremia. Staphylococci are also the most common organisms responsible for late PVE, but less so than for early PVE (~20% of late PVE results from coagulase negative staphylococci, and ~19% from *S. aureus*). Enterococci (~13%) and *Streptococcus viridans* (~11%) are less frequent causes of late PVE.

The transesophageal echocardiographic image displayed demonstrates that the mitral valve prosthesis is well seated in the appropriate position. The prominent vegetations seen on the atrial side of the valve are well delineated and provide an example of the increased sensitivity of this form of echocardiography compared with transthoracic studies (as described in a subsequent answer).

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ANSWER TO QUESTION 447

C (Braunwald, pp. 1398–1399, 1464–1466)

This patient with severe symptomatic aortic stenosis (AS) requires aortic valve replacement (AVR), but is at high risk for an open surgical procedure. Per American Heart Association/American College of Cardiology Valvular Guidelines, transcatheter aortic valve replacement (TAVR) is a class I indication for patients who warrant AVR, but who have a prohibitive risk for surgery and who otherwise have a predicted survival >12 months. TAVR also has a class I indication as an alternative to surgical AVR (sAVR) for patients at high surgical risk (e.g., Society of Thoracic Surgeons [STS] predicted risk of mortality ≥8%), as is this patient's circumstance.[1] Most recently, TAVR has been shown to be a reasonable alternative to sAVR (class IIa indication) for patients with symptomatic severe AS and an intermediate surgical risk (STS score 4% to 8%).[1] Approved transcatheter valves in the United States include balloon-expandable (e.g., Edwards SAPIEN) and self-expanding devices (e.g., Medtronic CoreValve).

The PARTNER randomized, prospective trial evaluated TAVR in patients with severe aortic stenosis who were either inoperable (Cohort B) or were at high risk for surgical AVR (Cohort A), using the first-generation transcatheter Edwards SAPIEN valve. In the patients who were considered inoperable, the outcome of TAVR was greatly superior to continued medical therapy, with absolute reductions in mortality of 20% at 1 year, 24% at 2 years, and 21.8% at 5 years.[2] Complications of TAVR in this cohort included an increased stroke rate at 30 days, and iliofemoral vascular complications associated with sheath placement and instrumentation. In patients who were candidates for surgical AVR but at high risk (Cohort A of the trial), TAVR was noninferior to surgical valve replacement, with similar mortality rates at 1, 2, and 5 years of follow-up.[3] Stroke and vascular complications were again more frequent with TAVR, but bleeding occurred more often with surgical AVR. As a result of the stroke risk with TAVR, cerebral protection devices have been devised to capture emboli during the procedure and continue to undergo study.[4]

Two randomized trials have compared TAVR (one trial with balloon-expandable valves, the other with self-expanding valves) with sAVR in patients at intermediate surgical risk.[5,6] Both trials showed noninferiority of TAVR compared to sAVR for the combined endpoint of death or stroke at 2 years.

Conduction abnormalities, including complete heart block requiring permanent pacemaker placement, may complicate TAVR because of device impingement on the LV outflow tract and underlying conduction tissue. The risk ranges from

10% to 30%, with recent studies showing a trend toward the lower end of this range.[7]

Paravalvular leaks may occur following TAVR because of poor sealing or alignment of the prosthesis. Even mild-to-moderate leaks are associated with reduced late survival.[8] Incremental design improvements in newer transcatheter valves have reduced this complication.

Since the long-term durability of TAVR prosthetic valves remains unknown, surgical AVR remains the procedure of choice for younger patients at low or intermediate risk for surgery.

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ANSWER TO QUESTION 448

E (Braunwald, pp. 1867–1874)

Primary tumors of the heart are rare—autopsy series indicate a prevalence of 0.001% to 0.03%. Metastatic tumors to the heart are far more common. Approximately three-fourths of primary cardiac tumors are benign. The most common benign primary cardiac tumor in children is rhabdomyoma, and 80% of such tumors appear before the age of 1 year. Rhabdomyomas typically arise in the left ventricle. The majority of such patients have a history (or family history) or tuberous sclerosis.

The most common malignant cardiac tumor in children is rhabdomyosarcoma. In adults, the most common benign primary cardiac tumor is the atrial myxoma. Lipomas and papillary fibroelastomas are the next most common benign primary tumors. The most frequent malignant primary tumor of the heart in adults is angiosarcoma, accounting for 30% to 37% of cases.

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ANSWER TO QUESTION 449

D (Braunwald, p. 1597)

The patient described has the clinical signs and findings of type II glycogen storage disease.[1] This disease is a consequence of the deficiency of alpha-1,4-glucosidase (acid maltase), a lysosomal enzyme that hydrolyzes glycogen into glucose. The condition commonly manifests in the neonatal period. Characteristic symptoms include failure to thrive, progressive hypotonia, lethargy, and a weak cry. Of all the glycogen storage diseases, type II (Pompe disease) is the most likely to cause cardiac symptoms. The ECG shows tall, broad QRS complexes with a short PR interval (commonly <0.09 second). The chest radiograph frequently shows cardiomegaly with pulmonary vascular redistribution. The diagnosis is confirmed by demonstrating the enzymatic deficiency in lymphocytes, skeletal muscle, or liver. The myocardial biopsy (Fig. 4.35B) shows prominent vacuoles within the myocardial

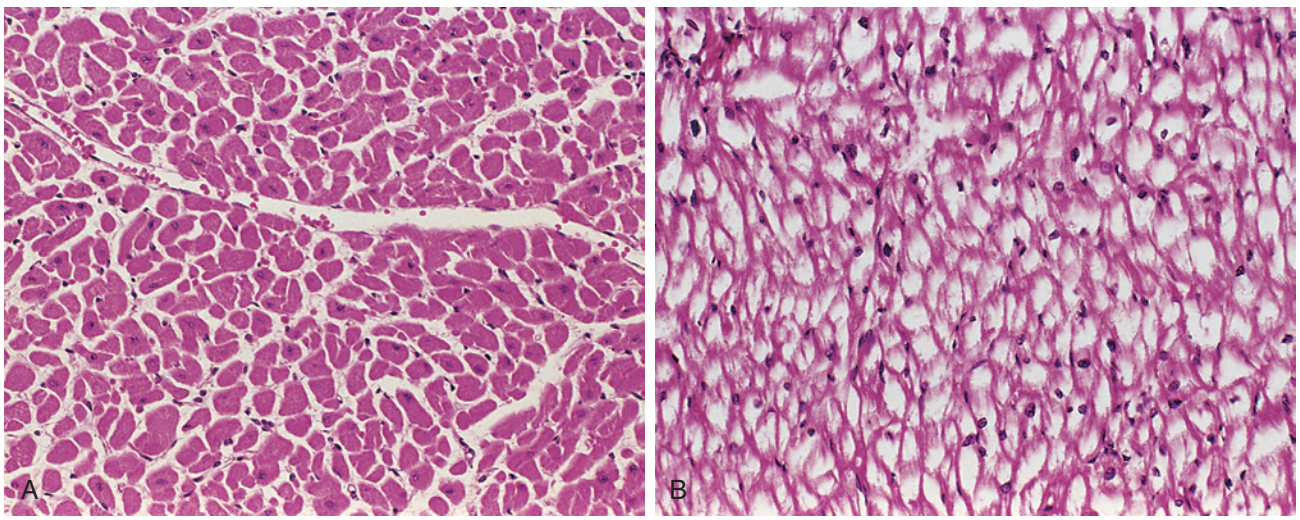

FIG. 4.35 *From Cotran RS, Kumar V, Collins T.* Robbins Pathologic Basis of Disease. *5th ed. Philadelphia: WB Saunders; 1999.*

fibers, which contain glycogen. Normal myocardial histology is shown in Fig. 4.35A for comparison.

Cardiac glycogenosis may be confused with other entities that cause cardiac failure, particularly in association with cardiomegaly in the early months of life. Endocardial fibroelastosis, a disease of unknown etiology, differs from Pompe disease in lacking the short PR interval and the fact that symptoms are limited to the cardiac system, whereas in Pompe disease skeletal muscle hypotonia is prominent. Furthermore, in endocardial fibroelastosis, mitral regurgitation and abnormalities of the cardiac valves, especially mitral and aortic, are frequent. Coarctation of the aorta, another cause of congestive heart failure in infants, can readily be distinguished by the presence of pulse and blood pressure discrepancies between the upper and lower extremities. Myocarditis, yet another cause of congestive heart failure, is usually of abrupt onset and is not associated with hypotonia. Anomalous pulmonary origin of the left coronary artery can cause cardiomegaly but usually has a distinctive electrocardiographic pattern of anterolateral myocardial infarction.

Shone syndrome is a developmental complex that consists of four obstructive anomalies: (1) a supravalvular ring of the left atrium; (2) a parachute mitral valve; (3) subaortic stenosis; and (4) coarctation of the aorta. It typically manifests with findings of mitral stenosis, because flow from the left atrium must pass through the abnormal intrachordal spaces of the mitral valve, which poses functional obstruction. Pulmonary venous hypertension is a common finding in this condition because of left ventricular inflow and outflow obstruction. Shone syndrome manifests more often in early childhood than in infancy and lacks the skeletal muscle changes of Pompe disease.

Friedreich ataxia is a hereditary autosomal recessive disease that manifests during late childhood with progressive ataxia. The limbs, in addition to being ataxic, generally show considerable weakness. About 50% of patients with Friedreich ataxia have cardiac involvement, typically hypertrophic cardiomyopathy.

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ANSWER TO QUESTION 450

C (Braunwald, pp. 1667–1672)

Cardiac tamponade occurs when the accumulation of pericardial fluid causes significant cardiac chamber compression. It is characterized by an increase in intrapericardial pressure and impedance to diastolic filling of the ventricles, with a consequent fall in cardiac output. Normal intrapericardial pressure is several millimeters of mercury lower than right ventricular (RV) and left ventricular (LV) diastolic pressures. As fluid accumulates in the pericardial space, intrapericardial pressure rises to, or exceeds, the level of right atrial (RA) and RV diastolic pressures and tamponade physiology ensues.

As intrapericardial and RV diastolic pressures rise toward the level of LV diastolic pressure, all three pressures equalize, leading to a marked decrease in transmural distending pressures, decreased filling, and to a fall in stroke volume. Cardiac output and blood pressure in this setting may initially be maintained by reflex tachycardia and increased vascular tone. However, as pericardial fluid further accumulates, compensatory mechanisms cannot maintain cardiac output and blood pressure falls. Whereas tachycardia is the usual response to falling stroke volume, bradycardia can be seen in severe tamponade. Both the cardiac depressor branches of the vagus nerve and sinoatrial node ischemia are believed to contribute to this phenomenon.

Normal inspiration causes increased right-sided cardiac filling and shifting of the interventricular septum toward the left, accompanied by reduced LV filling as a manifestation of ventricular interdependence. This effect is enhanced in tamponade since the ventricles are compressed and share a reduced total volume. Such proportionally greater *reductions* in LV filling and stroke volume with inspiration contribute to pulsus paradoxus.

Echocardiographic features of tamponade include RA inversion and RV diastolic collapse. In the presence of concurrent pulmonary hypertension, the elevated right-sided pressures blunt the effect of right-sided chamber compression.

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ANSWER TO QUESTION 451

B (Braunwald, pp. 1447–1450)

This woman presents with physical findings and symptoms of tricuspid regurgitation (TR). By history, the course of her illness is relatively rapid and includes systemic symptoms of fatigue, weight loss, and episodes of rapid heartbeat, flushing, and diarrhea. The most likely diagnosis is carcinoid syndrome. Carcinoid is a slowly growing neuroendocrine malignancy that leads to focal or diffuse deposits of fibrous tissue in the endocardium of the valvular cusps and cardiac chambers. The white fibrous carcinoid plaques are most extensive on the right side of the heart because vasoactive substances are released from hepatic metastases and drain through the inferior vena cava into the right atrium. This results in endocardial damage and fibrosis and causes the cusps of the tricuspid valve to adhere to the underlying right ventricle, producing TR (often accompanied by pulmonic valve disease on a similar basis, as described in a later question). Carcinoid syndrome is suggested by the coexistence of TR with flushing and diarrhea, which result from the release of vasoactive amines by the tumor cells.

Other causes of isolated TR may be divided into those involving an anatomically abnormal valve (*primary* TR) and those with an anatomically normal valve (*functional* TR). The latter, in which TR is due to dilatation of the right ventricle and tricuspid annulus, is more common. The most frequent cause of functional TR is right ventricular (RV) hypertension, especially as a result of mitral valve disease, congenital heart disease, pulmonary hypertension, or cor pulmonale. RV infarction may also cause functional TR.

Certain disease processes may affect the tricuspid valve directly, leading to primary TR. Among these are (1) congenital abnormalities of the tricuspid valve (e.g., Ebstein anomaly or an atrioventricular canal defect); (2) rheumatic tricuspid valve disease (which is much less common than rheumatic mitral or aortic disease); (3) connective tissue

disorders, including myxomatous redundancy of the leaflets; and (4) infective endocarditis. Other even less common causes include endomyocardial fibroelastosis, trauma, cardiac tumors (particularly right atrial myxomas), transvenous pacemaker leads, repeated endomyocardial biopsies in a transplanted heart, or exposure to certain drugs, such as methysergide or the appetite suppressant dexfenfluramine.

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ANSWER TO QUESTION 452

B (Braunwald, pp. 1483–1502)

This patient has right-sided endocarditis in the setting of illicit IV drug use. The echocardiographic image shows a large vegetation on the atrial surface of the septal leaflet of the tricuspid valve (*arrow* in Fig. 4.36). Injection drug users with endocarditis most frequently demonstrate right-sided valvular involvement (the tricuspid valve in 46% to 78%), with less common involvement of the left-sided valves (mitral valve involvement in 24% to 32% and aortic valve involvement in 8% to 19%); however, the latter group displays greater mortality. *Staphylococcus aureus* infections account for more than 50% of IV drug user endocarditis (and 60% to 70% of those with tricuspid valve involvement), with the remainder caused by streptococcal species, gram-negative bacilli, and fungi. Pulmonary findings are frequent in those with right-sided endocarditis, with 65% to 75% displaying evidence of septic pulmonary emboli on chest radiograph. Other pulmonary complications include pulmonary infarction, abscess formation, and empyema. Serious cardiac complications include destruction of the tricuspid valve apparatus, with consequent severe regurgitation and right-sided heart failure.

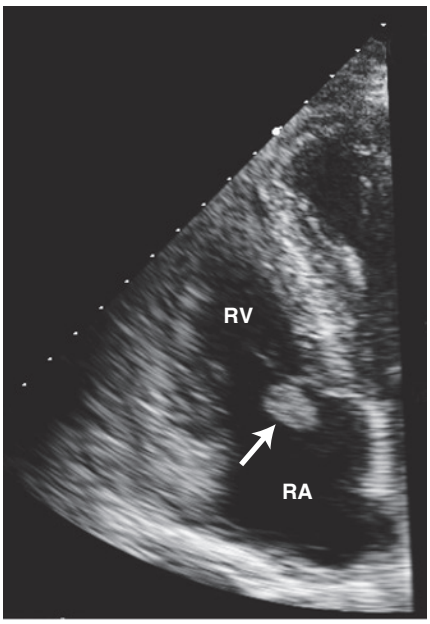

FIG. 4.36

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ANSWER TO QUESTION 453

C (Braunwald, pp. 1524–1526)

The patient has Eisenmenger syndrome, with currently exacerbated right-to-left shunting due to decreased systemic vascular resistance (SVR) after starting alpha-blocker (tamsulosin) therapy. Thus, initial treatment should include augmenting the SVR (e.g., using the alpha agonist phenylephrine) and discontinuing the alpha blocker.

Eisenmenger syndrome is characterized by irreversibly increased pulmonary vascular resistance with reversal of chronic left-to-right shunting to a bidirectional, or right-to-left, shunt direction, resulting in cyanosis. Shunts that may progress to Eisenmenger physiology include atrial septal defects, ventricular septal defects, patent ductus arteriosus, atrioventricular canal defects, and univentricular hearts. Such patients may survive into adulthood when the most common causes of mortality are sudden cardiac death, congestive heart failure, and pulmonary hemorrhage. The degree of right-to-left shunting in patients with Eisenmenger physiology is highly dependent on the SVR. For example, a decline in SVR (as a result of sepsis, hypovolemia, adrenal insufficiency, anesthesia, or vasodilators), as in this case, augments the right-to-left shunt and further reduces systemic oxygen saturation.

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ANSWER TO QUESTION 454

E (Braunwald, p. 1677)

The introduction of highly active antiretroviral therapy (HAART) greatly reduced the incidence of cardiac manifestations in patients with human immunodeficiency virus (HIV) infection. In a recent cohort trial of HIV patients, most of whom received HAART, pericardial effusion was present in <1%. Conversely, in the setting of untreated HIV infection, pericardial effusions are common. Such effusions tend to be small, rarely cause symptoms, and may spontaneously resolve without specific intervention. While cardiac tamponade rarely results, such effusions tend to occur in patients with lower CD4 counts and more advanced HIV disease and have been shown to be a marker for increased mortality.

The causes of pericardial effusions in HIV infection include opportunistic infections and malignancy (e.g., Kaposi sarcoma or lymphoma); however, a definite etiology is often not found. In some cases, the development of effusions (pericardial and pleural) may occur as a result of a capillary leak phenomenon induced by elevated cytokine levels in patients with advanced HIV disease. Tuberculosis

is the most common cause of pericardial effusion in African HIV patients.

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ANSWER TO QUESTION 455

B (Braunwald, pp. 1535–1537; see also Answer to Question 444)

Common findings on physical examination of patients with an atrial septal defect (ASD) include a prominent right ventricular (RV) impulse, palpable pulmonary artery pulsations, accentuation of the tricuspid valve closure sound, and a midsystolic ejection murmur due to increased flow across the pulmonic valve. If the shunt is large, a mid-diastolic rumbling murmur may be audible at the lower left sternal border. This murmur results from increased blood flow across the tricuspid valve.

The ECG may be helpful in the diagnostic evaluation of a patient with suspected ASD. In the common ostium secundum ASD, the tracing may show right-axis deviation and an rSR′ or rsR′ pattern in the right precordial leads with a normal QRS complex duration. The presence of negative P waves in the inferior leads (indicating a low atrial pacemaker) suggests the presence of a sinus venosus-type ASD. *Left*-axis deviation and superior orientation of the QRS complex in the frontal plane is consistent with an ostium primum defect. Tall R or R′ waves in V_1 may indicate the presence of pulmonary hypertension and concomitant RV hypertrophy.

The chest radiograph may reveal enlargement of the right atrium and right ventricle, pulmonary arterial dilatation, and increased pulmonary vascular markings. Echocardiographic evaluation of ASD may show pulmonary arterial and RV dilatation and paradoxical intraventricular septal motion if RV volume overload is present. The defect itself may be visualized by two-dimensional echocardiography, particularly on the subcostal view. Doppler interrogation reveals the presence and direction of the transatrial shunt and allows calculation of the Q_p/Q_s ratio.

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ANSWER TO QUESTION 456

D (Braunwald, p. 1603)

This patient displays the apical variant of hypertrophic cardiomyopathy (HCM), evidenced on this echocardiographic apical long-axis (four-chamber) view. This variant is marked by predominant hypertrophy of the left ventricular apex, which causes the chamber to display a "spade-like" deformity on cardiac imaging. This is even more clearly demonstrated on this patient's subsequent cardiac magnetic resonance imaging study (*arrows* in Fig. 4.37). Apical HCM is rare in other parts of the world, but in Japan it accounts for 25% of patients with HCM. The ECG in this condition is frequently striking for deep, *inverted* T waves in the apical precordial leads. Intraventricular pressure gradients are usually *absent*. Symptoms associated with the apical variant tend to be more mild and the risk of sudden death is lower than in the traditional septal form of HCM.

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ANSWER TO QUESTION 457

C (Braunwald, pp. 1429–1430, 1433, 1440)

Physical findings in mitral regurgitation (MR) are influenced by the compliance of the left atrium. In patients with severe, *acute* mitral regurgitation (e.g., due to rupture of chordae

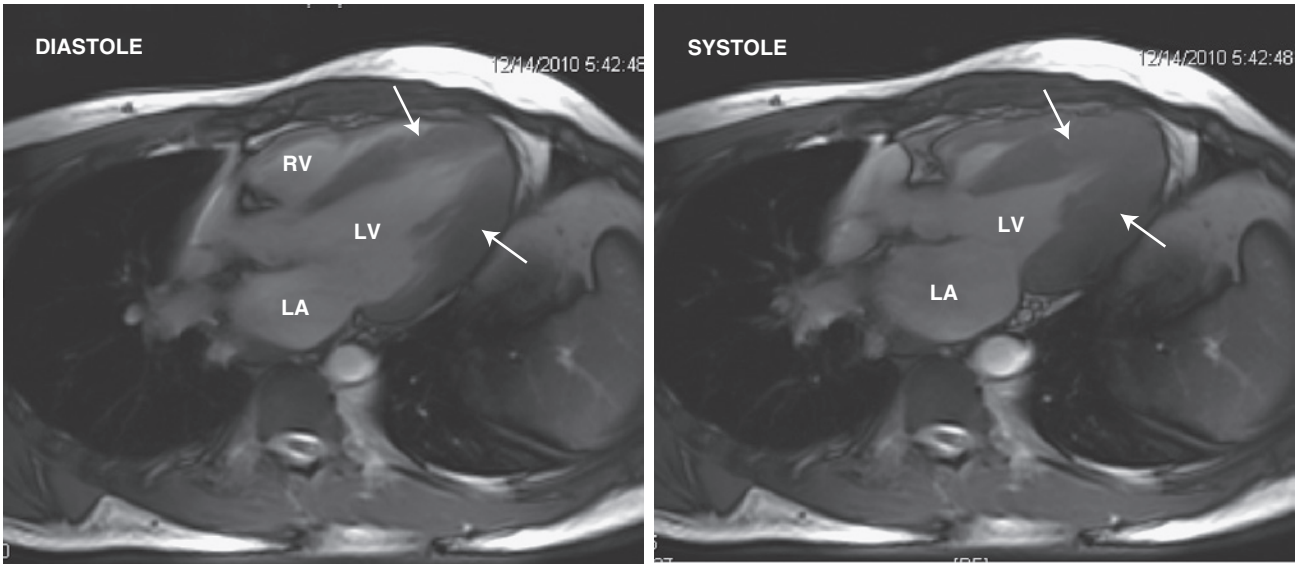

FIG. 4.37

tendineae), the regurgitant volume encounters an unprepared, relatively noncompliant left atrium. As a result, the left atrial pressure quickly rises, which serves to limit the pressure gradient between the left ventricle and left atrium late in systole, causing the systolic murmur to shorten and end before the second heart sound. However, the acutely elevated left atrial pressure also augments the pulmonary venous pressure and commonly results in acute pulmonary edema as well as findings of right-sided heart failure (e.g., jugular venous distention).

In contrast, the more gradual development of *chronic* MR allows the left atrium to gradually dilate and increase its compliance, such that the chamber is able to accommodate larger volumes without a substantial increase in pressure. As a result, in compensated chronic MR, substantial elevation in pulmonary venous and capillary pressures is avoided. However, the mitral regurgitant volume returns to the left ventricle during diastole, resulting in gradual left ventricular enlargement. Thus, in distinction to acute MR, patients with chronic MR commonly demonstrate left ventricular and left atrial enlargement on cardiac imaging.

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ANSWER TO QUESTION 458

B (Braunwald, pp. 1415–1417; Figs. 19.13 and 69.3)

The tracing shows the simultaneous recording of left atrial (LA) and left ventricular (LV) pressures and depicts the hemodynamic profile of mitral stenosis. The LA pressure is elevated (mean ~20 mm Hg) with a prominent atrial contraction *(a)* wave and an abnormally gradual pressure decline in diastole after mitral valve opening (*y* descent). There is a persistent gradient between LA and LV pressure throughout diastole, in contrast to the normal situation, in which there is rapid equilibration of LA and LV pressures in diastole.

Mitral regurgitation would be associated with prominent *v* waves on the LA pressure tracing, but not a persistent diastolic atrioventricular pressure gradient.

In constrictive pericarditis and restrictive cardiomyopathy, the atrial pressure decline in the earliest part of diastole is typically brisk (prominent *y* descent), the converse of this example.

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ANSWER TO QUESTION 459

B (Braunwald, p. 1664)

This patient has typical symptoms and signs of acute pericarditis. The majority of patients with pericarditis manifest electrocardiographic abnormalities. The most common early finding is global ST-segment elevation, particularly in the inferior, lateral, and apical leads. The ST-segment elevations are believed to represent a current of injury caused by superficial inflammation of the adjacent myocardium. In contrast to the acute ST-segment abnormalities of ST-elevation myocardial infarction (STEMI), the elevations in pericarditis tend to be oriented in a *concave* upward direction and reciprocal ST-segment depressions in the opposite leads are not present. In later stages of pericarditis (days or weeks after presentation), the ST segment returns to baseline, and thereafter the T waves may deeply invert.

The PR segment is found to be depressed (or elevated in lead aVR) in 75% to 80% of patients with acute pericarditis. This finding may be the result of abnormal atrial repolarization due to atrial inflammation and is not typical of other conditions such as acute STEMI. PR-segment depression may occur even in the absence of ST-segment elevation and can be the initial, or only, electrocardiographic manifestation of acute pericarditis. Sinus *tachycardia* is also a common finding in acute pericarditis, related to pericardial inflammation, pain, or fever.

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ANSWER TO QUESTION 460

E (Braunwald, p. 1677)

Two forms of pericarditis can follow acute myocardial infarction (MI): early and delayed. When present, early acute fibrinous pericarditis develops within the first few days after MI. The incidence and degree of such pericardial inflammation is associated with the size of the infarct. Acute percutaneous coronary intervention or fibrinolytic therapy for ST-elevation MI (STEMI), which limits infarct size, *reduces* the incidence of pericarditis. In addition, pericarditis is less common after non-ST-segment elevation infarction compared with STEMI. The use of heparin has not been associated with increased risk of pericarditis or tamponade. Clinical evidence of pericarditis can be found as early as 12 hours after MI, and the earliest sign may be a pericardial friction rub. In about 70% of patients, the rub may be accompanied by pleuritic chest pain.

The appearance of symptoms and signs of pericarditis more than 10 days after MI is consistent with the second type of post-MI pericarditis, termed *Dressler syndrome*. This delayed phenomenon is believed to be autoimmune in origin and has become rare in the era of acute reperfusion therapies.

Typical diagnostic electrocardiographic changes of pericarditis are uncommon in post-MI pericarditis or Dressler syndrome. Instead, atypical T-wave changes have been described, consisting of persistently upright T waves or premature reversal of initially inverted T waves after infarction.

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ANSWER TO QUESTION 461

D (Braunwald, pp. 1604–1606)

The tracing demonstrates simultaneous recordings of left ventricular (LV) and systemic pressure in a patient in

normal sinus rhythm. The second electrocardiographic complex is a ventricular premature beat (VPB). The beat following the VPB demonstrates a rise in LV pressure due to post-extrasystolic potentiation. However, the aortic systolic pressure and the pulse pressure decline in the post-VPB beat. This is an example of the Brockenbrough-Braunwald phenomenon that is typical of hypertrophic cardiomyopathy (HCM) and is a reliable sign of dynamic LV outflow tract obstruction.

In normal subjects, and even in those with valvular abnormalities such as aortic stenosis or mitral regurgitation, a post-VPB contraction is associated with *increased* systolic aortic pressure and pulse pressure. Conversely, in HCM, the premature contraction increases the force of contraction and the degree of outflow obstruction of the subsequent beat, causing a decline in the pulse pressure. While increased ventricular filling during the post-VPB compensatory pause would be expected to reduce the outflow gradient in HCM, that effect is outweighed by the increased contractility associated with post-extrasystolic potentiation. In addition to the narrowed pulse pressure, the peripheral arterial waveform may show a "spike-and-dome" configuration, reflecting the attenuation of LV output due to dynamic outflow obstruction (see Section I, Fig. 1.18).

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ANSWER TO QUESTION 462

D (Braunwald, pp. 1450, 1567–1569)

The color Doppler profile in part *A* of the figure demonstrates systolic turbulence due to valvular pulmonic stenosis. As quantitated by the continuous Doppler profile in part *B*, the peak velocity across the valve is ~4.0 m/s, corresponding to a peak transpulmonic valve systolic gradient of 64 mm Hg (calculated from the simplified Bernoulli equation, $P = 4v^2$). Thus, in light of his chest discomfort, this patient likely has symptomatic pulmonic stenosis (PS).

PS is most commonly due to congenital deformity of the valve; much less common causes are carcinoid plaques or rheumatic inflammation. Congenital PS is characterized by fused leaflets and doming of the valve in systole with a narrowed opening. Typical features on physical examination include a prominent jugular venous *a* wave (due to secondary right ventricular hypertrophy), a systolic ejection click, a crescendo-decrescendo ejection murmur at the upper left sternal border, and a widely split S_2. Unlike other right-sided valvular lesions, the systolic click *decreases* in intensity with inspiration (with inspiration, the augmented right-sided filling elevates the leaflets into the pulmonary artery prior to RV contraction, preempting the rapid tensing in early systole that is thought to produce the sound).

Mechanical treatment of PS is indicated for symptomatic patients with a mean transvalvular gradient ≥30 mm Hg or a peak systolic gradient ≥50 mm Hg. In asymptomatic patients, intervention is usually recommended for a mean gradient >50 mm Hg. The intervention of choice is transcatheter balloon valvuloplasty, which has shown excellent short- and medium-term results. For patients with prominently dysplastic valves, balloon valvotomy may not offer sufficient gradient relief, such that pulmonary valve replacement becomes necessary.

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ANSWER TO QUESTION 463

D (Braunwald, pp. 1519–1521)

Whereas the true incidence of congenital cardiovascular malformations is difficult to determine, it has been estimated that approximately 0.8% of live births are complicated by such a disorder. The most common significant malformation is ventricular septal defect, followed in frequency by atrial septal defect (ASD) and patent ductus arteriosus. These data do not include the common anomalies of a congenital, functionally normal bicuspid aortic valve and mitral valve prolapse.

Specific defects show a sex predilection. For example, patent ductus arteriosus and ASDs are more common in females, whereas valvular aortic stenosis, congenital aneurysms of the sinus of Valsalva, coarctation of the aorta, tetralogy of Fallot, and transposition of the great arteries are seen more frequently in males. Extracardiac anomalies occur in approximately 25% of infants born with significant cardiac disease and often are multiple.

Approximately one-third of infants with both cardiac and extracardiac anomalies have an established syndrome. For example, maternal rubella during pregnancy is associated with the rubella syndrome, which consists of cataracts, deafness, microcephaly, and some combination of patent ductus arteriosus, pulmonic valvular or arterial stenosis or both, and ASD. Maternal systemic lupus erythematosus during pregnancy has been linked to congenital complete heart block, but not to any specific anatomic abnormality.

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ANSWER TO QUESTION 464

D (Braunwald, pp. 1505–1508; Table 73G-1)

The American Heart Association guidelines for the prevention of infective endocarditis (IE) enumerate the type of patients for whom antibiotic prophylaxis is recommended. The statement recognizes that (1) IE is more likely to occur after random bacteremias (e.g., after daily tooth brushing) than from dental and/or genitourinary or gastrointestinal procedures; and (2) because prophylaxis may prevent only a small number of cases of IE, the risk of antibiotic use in many cases may outweigh the benefit.

According to current guidelines, prophylaxis is only recommended for those patients with cardiac conditions associated with the highest risk of complications from endocarditis, including the presence of (1) prosthetic cardiac valves or other prosthetic material for valve repair, (2) previous IE, (3) cardiac transplantation recipients with valvular lesions, and (4) specific types of congenital heart disease (unrepaired cyanotic lesions, repaired congenital lesions with residual

defects, or during the first 6 months after repair with prosthetic material or devices). Prophylaxis is not recommended for other valvular abnormalities such as mitral valve prolapse with murmur.

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ANSWER TO QUESTION 465

A (Braunwald, p. 1706; Table 85.4)

The prognostic importance of elevated right atrial pressure on mortality in pulmonary arterial hypertension has been demonstrated in large patient registries. Although increased mean pulmonary artery pressure (mPAP) is also associated with increased mortality, mPAP may decrease as right ventricular failure progresses. Therefore, a normal or low mPAP may be present despite the presence of end-stage pulmonary vascular disease. Diastolic flattening on echocardiography indicates right heart volume overload, but is not specific for pulmonary arterial hypertension. A low transpulmonary gradient (calculated as the difference between mean pulmonary capillary wedge pressure and mean pulmonary artery pressure) is indicative of an elevated left ventricular end-diastolic pressure relative to pulmonary artery pressure and excludes the diagnosis of pulmonary arterial hypertension.

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ANSWER TO QUESTION 466

C (Braunwald, p. 1456)

Homograft (also known as allograft) aortic valves are harvested from human cadavers usually within 24 hours of death, sterilized, cryopreserved, and then placed directly into the recipient's heart without the use of a prosthetic stent. Often the valve is implanted with a portion of attached donor aorta as a root replacement, with reimplantation of the coronaries into the graft. Aortic homografts provide potential advantages. The rate of thromboembolism is low, similar to that of animal-derived bioprosthetic valves, and therefore lifelong anticoagulation is not necessary. They provide a more physiologic hemodynamic profile than mechanical valves, and, because a prosthetic support stent is not used, they are also hemodynamically superior to stented porcine tissue valves. In addition, homografts have been considered to be more resistant to infection than other prostheses, so they are often chosen for patients with infective endocarditis of the aortic valve, particularly when complex root anatomy is present.

In experienced hands, the surgical mortality related to homograft placement is 1% to 2%, similar to that of other valve replacements. The rate of structural degeneration of cryopreserved homografts has been similar to that of porcine xenografts. In one recent retrospective review of 840 cryopreserved aortic allografts, durability exceeded 15 years in middle-aged and older patients. The estimated median time until structural deterioration in this study was 20 years.[1]

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ANSWER TO QUESTION 467

C (Braunwald, p. 1418; Fig. 69.3)

The echocardiographic image demonstrates diastolic doming of the mitral valve leaflets, typical of rheumatic mitral stenosis (MS). Patients with preserved flexibility of the leaflets in MS (i.e., fusion confined to the valve commissures) demonstrate an accentuated S_1. This is thought to occur because the persistent pressure gradient between the left atrium and left ventricle at the end of diastole keeps the flexible portion of the leaflets in a maximally separated position prior to ventricular contraction. Contraction then forces the leaflets together from a relatively wide position, causing the intensity of S_1 to be loud. If, however, the valve is markedly calcified, there is little movement of the leaflets during the cardiac cycle, such that S_1 becomes abnormally soft.

The opening snap occurs when the left ventricular diastolic pressure falls below that of the left atrium and the stenotic mitral leaflets open. The more severe the mitral stenosis, the higher the left atrial pressure becomes, such that mitral opening occurs earlier and therefore the interval between A_2 and the opening snap shortens. In patients with long-standing MS, pulmonary hypertension develops, in part because of the chronically elevated left atrial pressure. As a result, P_2 becomes accentuated. The intensity of the diastolic murmur is not a good guide to the severity of mitral stenosis. A more reliable sign is the duration of the murmur: increasing severity of stenosis causes greater persistence of the gradient between the left atrium and left ventricle, and therefore the murmur lasts longer in diastole.

ANSWER TO QUESTION 468

C (Braunwald, pp. 1403–1404)

The murmur of aortic regurgitation (AR) is of *high* frequency and begins immediately after A_2. It is best heard with the *diaphragm* of the stethoscope applied firmly while the patient is sitting up and leaning forward, with the breath held in expiration. The severity of regurgitation correlates better with the duration rather than severity of the murmur, and in cases of severe AR, a holodiastolic murmur with a "rough" quality may be heard. However, with the development of heart failure, equilibration of aortic and left ventricular diastolic pressures abolishes the late diastolic component and the murmur becomes shorter. When the murmur is musical ("cooing dove" murmur), it usually signifies eversion or perforation of a cusp. Regurgitation due to primary aortic valve disease is usually loudest at the left sternal border at the third and fourth intercostal spaces. When the murmur is loudest at the right side of the sternum, it usually indicates the presence of a dilated ascending aorta as the cause of valvular insufficiency. In general, maneuvers that increase afterload, such

as a strenuous handgrip, augment aortic regurgitation and the associated murmur.

ANSWER TO QUESTION 469

A (Braunwald, p. 1676)

Bacterial (purulent) pericarditis arises from one of several mechanisms, including hematogenous seeding during bacteremia, contiguous spread of infection after thoracic surgery, or via rupture of a perivalvular abscess in endocarditis. The majority of occurrences, however, are attributable to direct extension from an adjacent pulmonary infection. Several factors predispose to the development of purulent pericarditis, including a preexisting pericardial effusion in uremic pericarditis, or in immunosuppressed states such as hematologic malignancies or following severe burns. Bacterial pericarditis is usually an acute fulminant illness of rapid onset that is characterized by high spiking fevers, rigors, night sweats, and dyspnea. Typical symptoms of pericarditis may be absent, and the process may be heralded by new jugular venous distention and pulsus paradoxus as a result of cardiac tamponade.

Despite the lower incidence of purulent pericarditis in the antibiotic era, overall survival is poor, with a mortality of approximately 30% in most series. The poor prognosis is in large part due to delayed diagnosis, as well as disease severity and comorbidities. Early complete drainage (via pericardiocentesis and usually surgical drainage) and parenteral antibiotic therapy are critical. High concentrations of antibiotics are achieved in pericardial fluid with parenteral therapy; therefore, instillation of antibiotics directly into the pericardial space is not warranted.

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ANSWER TO QUESTION 470

A (Braunwald, pp. 1607–1609)

This 16-year-old youth has an examination and ECG consistent with hypertrophic cardiomyopathy, which should be confirmed by echocardiography. Current recommendations are that competitive sports not be allowed in this condition if high-risk clinical features are present, including marked ventricular hypertrophy, evidence of significant outflow gradient, supraventricular or ventricular arrhythmias, history of exertional syncope or hypotension, or history of sudden death in close relatives. Low-intensity sports may be allowed if none of these conditions is present. This teen has evidence of substantial left ventricular hypertrophy and a history of sudden death in a first cousin. Thus, competitive sports should be avoided.

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ANSWER TO QUESTION 471

C (Braunwald, pp. 1390–1391)

The left ventricle responds to *sudden* obstruction to outflow by dilatation and reduction of stroke volume. However, in most adults with aortic stenosis the obstruction develops slowly over a long period of time, resulting in significant compensatory measures. Fundamentally, left ventricular (LV) output is maintained by development of LV hypertrophy with generation of increased contractile force. This enables the LV to sustain a large pressure gradient across the aortic valve without reduction in cardiac output, chamber dilatation, or symptoms. The compensation is contributed to by coexisting left atrial (LA) hypertrophy; the more forceful atrial contraction helps to maintain LV filling, but also contributes to a large *a* wave in the LA pressure curve and an elevated LV end-diastolic pressure. The latter is also augmented by reduced LV diastolic compliance due to ventricular hypertrophy. However, it is only the patient with LV contractile dysfunction in whom dilatation and an increase in LV end-diastolic volume occur.

ANSWER TO QUESTION 472

C (Braunwald, pp. 1501–1502)

Although helpful, the observation of vegetations by echocardiography is not mandatory to establish the diagnosis of endocarditis. In addition, although the sensitivity of transesophageal echocardiography to detect vegetations in suspected endocarditis is 85% to 95%, the sensitivity of transthoracic echocardiography is substantially less. *Staphylococcus aureus* is an aggressive organism that results in rapid destruction of valves and perivalvular tissue. Nonetheless, antibiotic therapy alone is often curative for native valve endocarditis caused by this organism.

Vegetations >10 mm in diameter have a greater risk of thromboembolism than smaller vegetations, but it has not been definitively proved that early surgical intervention in patients with larger vegetations improves long-term outcome; early surgical intervention is an American Heart Association/American College of Cardiology class IIb indication for such patients. Although cerebral embolism can be a devastating complication of endocarditis, the rate of recurrence declines during the course of appropriate antibiotic treatment. Patients with endocarditis and intractable heart failure due to valve dysfunction have a 55% to 85% mortality rate when treated medically; the mortality falls to 10% to 30% with early surgical intervention.

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ANSWER TO QUESTION 473

E (Braunwald, p. 1676)

Although tuberculous pericarditis is now uncommon in industrialized countries, the disease continues to be an important problem in developing nations and in immunosuppressed patients, and is the most common cause of pericardial disease in

human immunodeficiency virus patients in Africa. Tuberculous pericarditis usually develops by retrograde spread from peritracheal, peribronchial, or mediastinal lymph nodes or by early hematogenous spread from the primary tuberculous infection. The process is usually chronic, with the gradual development of pericardial effusion. Symptoms may be systemic and nonspecific, and clinical detection of tuberculous pericarditis often does not occur until the effusive or late constrictive pericarditic stages are reached. The typical pericardial chest pain of acute viral or idiopathic pericarditis is uncommon in tuberculous pericarditis. In addition, typical signs and symptoms of cavitary pulmonary tuberculosis are usually absent.

Examination of patients with tuberculous pericarditis may reveal evidence of chronic cardiac compression, which can mimic heart failure. Common symptoms include cough, dyspnea, orthopnea, weight loss, and peripheral edema. Definitive diagnosis of tuberculous pericarditis is usually difficult because of the low yield of the bacillus in pericardial fluid, frequent failure to culture the organism, and/or the need to observe cultures for a minimum of 8 weeks. The probability of a definitive diagnosis is greatest if both pericardial fluid and a pericardial biopsy are obtained in the effusive stage of the disease. Polymerase chain reaction amplification of pericardial specimens offers the potential to obtain results more rapidly than standard cultures, but its sensitivity is low. Measurement of pericardial fluid adenosine deaminase *is* diagnostically useful, with reported sensitivity and specificity for tuberculous pericarditis of 88% and 83%, respectively.

Initial therapy for tuberculous pericarditis includes a three-drug regimen ordinarily consisting of isoniazid, rifampin, and streptomycin or ethambutol. The role of corticosteroids remains unclear. Studies have failed to show that the early use of corticosteroids affects mortality or progression to constriction, although such therapy may shorten the duration of symptoms.

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ANSWER TO QUESTION 474

A (Braunwald, p. 1598; see also Answer to Question 451)

This patient has findings of carcinoid syndrome, characterized by episodic flushing, diarrhea, and bronchoconstriction. The vast majority of carcinoid tumors originate in the appendix and other areas of the gastrointestinal tract, with the remainder arising in the respiratory tract. Carcinoid tumors secrete large amounts of vasoactive substances, including serotonin and bradykinin, which are usually inactivated by the liver, lungs, and brain. However, in the presence of large hepatic metastases, these vasoactive substances reach the systemic circulation and heart. Cardiovascular involvement occurs in up to two-thirds of patients with carcinoid syndrome and includes the formation of fibrous plaques in the right heart endocardium, which can lead to fixation and retraction of the tricuspid and pulmonic valves. This results in tricuspid and/or pulmonic valve dysfunction and eventual right-sided heart failure. Higher circulating serotonin levels are associated with greater severity and progression of cardiac disease. Left-sided heart involvement is not common (occurring in <10% of patients), presumably because of pulmonary inactivation of the vasoactive hormones.[1] Patients who do develop left-sided disease may have a right-to-left intracardiac shunt or a primary pulmonary carcinoid tumor. It is rare for a carcinoid tumor to actually metastasize to the heart.

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1. Patel C, Mathur M, Escarcega RO, et al. Carcinoid heart disease: current understanding and future directions. *Am Heart J.* 2014;167:789.

ANSWER TO QUESTION 475

C (Braunwald, pp. 1421, 1467–1468)

Percutaneous balloon mitral valvuloplasty (BMV) is the treatment of choice for patients with mitral stenosis who require mechanical intervention. Surgical valve repair or replacement is reserved for patients who are not candidates for the percutaneous procedure. In the most commonly practiced form of BMV, a catheter is maneuvered across the interatrial septum through a small septal puncture and a balloon device is advanced across the mitral valve. Balloon inflation separates and fractures the calcified valve commissures, improving the transmitral gradient, valve area, and cardiac output. Selection of patients for this approach is usually determined by echocardiographic features including (1) mitral valve rigidity, (2) leaflet thickening, (3) valve calcification, and (4) subvalvular apparatus thickening and calcification. In a commonly used scoring system, each of these factors is assigned a score from 0 to 4, with 0 representing the absence of each abnormality and 4 representing the most severe form. A total score ≤8 is associated with excellent results after balloon valvuloplasty. Transesophageal echocardiography is usually performed before the procedure to exclude the presence of left atrial thrombus, a potential source of embolism during catheter manipulation.

The major complications of BMV include death (1% to 2%), thromboembolism (1% to 2%), cardiac perforation (1%), and severe mitral regurgitation requiring surgical repair (approximately 2%). A small residual iatrogenic atrial septal defect persists in approximately 5% of patients and is rarely hemodynamically significant.

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ANSWER TO QUESTION 476

B (Braunwald, p. 1667)

The incidence of cardiac injury after blunt chest trauma varies by mode of injury and criteria for diagnosis, but ranges between 10% and 50%. Potential cardiac complications include septal rupture, free wall rupture, coronary artery thrombosis, rupture of chordae tendineae or papillary muscles, and dysrhythmias. Immediate evaluation should include assessment for cardiac tamponade (e.g., hypotension, pulsus paradoxus, distended jugular veins, and muffled heart sounds). Chest radiography is an important part of the evaluation that can identify pneumothorax, bony fractures, or an enlarged cardiac silhouette suggesting pericardial effusion. Echocardiography can confirm the presence of traumatic blood in the pericardial space, but a transthoracic study

has limited value in identifying other consequences of blunt trauma, as accompanying chest wall injuries typically render the study technically limited. Conversely, transesophageal echocardiography is sensitive in identifying the effects of blunt injury, including traumatic ventricular septal defects, rupture of chordae tendineae or portions of papillary muscle with valvular insufficiency, and wall motion abnormalities.

The most common electrocardiographic abnormalities in blunt cardiac trauma are sinus tachycardia and ventricular premature beats. Other ECG findings can include ST-segment abnormalities, atrioventricular blocks, right bundle branch block (with or without left anterior fascicular block), atrial fibrillation, and ventricular tachycardia. Although debate exists over the role of cardiac-specific biomarker elevations after chest trauma, studies have not shown a consistent correlation between cardiac troponin levels and the presence and prognosis of blunt cardiac injury.

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ANSWER TO QUESTION 477

D (Braunwald, pp. 1594–1595)

Cardiac sarcoidosis was previously thought to occur in ~5% of patients with pulmonary sarcoidosis based on clinical findings, but recent imaging studies have demonstrated cardiac involvement in >25% of patients with pulmonary sarcoid. The pathologic feature of cardiac sarcoidosis is the presence of noncaseating granulomas in the myocardium that result in ventricular dysfunction and eventually become fibrotic scars. The granulomas may involve any region of the heart, but the left ventricular (LV) free wall and interventricular septum are the most common sites. Infiltration of the conduction system may lead to atrioventricular (AV) block, and atrial and ventricular arrhythmias are also common. Sudden death is the most common cause of mortality in sarcoid heart disease, potentially resulting from paroxysmal ventricular arrhythmias or high-grade AV block. Involvement of cardiac valves is unusual. While the murmur of mitral regurgitation is often present, it typically results from LV dilatation or papillary muscle involvement rather than from sarcoid infiltration of the valve.

Percutaneous myocardial biopsy may be useful in establishing the diagnosis of sarcoid heart disease. However, cardiac involvement tends to be patchy such that biopsy is often low-yield and a negative biopsy does not exclude the diagnosis. Magnetic resonance imaging has emerged as a more sensitive modality for the diagnosis. Delayed gadolinium enhancement in this condition is usually nontransmural, typically appearing at the basal and/or midventricular septum. ^{18}Fluorodeoxyglucose (FDG) positron emission tomography (PET) is another useful imaging modality that reveals regions of inflammation in active sarcoid and can be used to monitor the response to anti-inflammatory therapies.

It is common to administer glucocorticoid therapy to patients with evidence of sarcoid heart disease, though the benefit of this approach has not been confirmed in randomized trials. In patients who do not respond, methotrexate is commonly used, based on experienced opinion. Management of arrhythmias may require permanent pacing and/or implantation of a cardiac defibrillator (ICD), including ICD implantation for primary prevention of sudden death in patients with markedly reduced LV ejection fraction, similar to other heart failure patients. Cardiac transplantation has been undertaken in patients with severe cardiac sarcoid after evaluating for noncardiac sarcoid involvement.

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ANSWER TO QUESTION 478

C (Braunwald, pp. 1541–1542)

The size of ventricular septal defects (VSDs) and the degree to which pulmonary vascular resistance is altered determine the clinical presentation. In general, adults with small defects are asymptomatic and are not at risk for the development of pulmonary vascular obstructive disease. However, all individuals with ventricular septal defects are at increased risk for infective endocarditis, which arises in up to 4% of patients with VSDs. The infection usually develops in the right ventricle at the site where shunted blood impacts the ventricular wall.

In an asymptomatic individual, a VSD with a normal pulmonary artery pressure and a pulmonary:systemic flow ratio <1.5:1 generally does not require surgical closure. Women with VSDs and pulmonary:systemic flow ratios <2:1 with only modest pulmonary hypertension generally tolerate pregnancy well. In women with larger left-to-right shunts, however, left ventricular failure may occur during pregnancy. In those who have Eisenmenger complex, pregnancy is poorly tolerated, with a maternal mortality between 40% and 45%.

The development of Eisenmenger complex due to progressive pulmonary vascular disease is one of the most serious complications of VSDs. This usually develops in early adulthood, in the second or third decade of life, and may be complicated by heart failure, hemoptysis, chest pain, cerebral abscess, thromboembolism, and sudden death.

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ANSWER TO QUESTION 479

C (Braunwald, p. 1599)

Endomyocardial fibrosis (EMF), a cause of restrictive cardiomyopathy, is found primarily in tropical and subtropical Africa, but has been increasingly recognized in tropical regions of South America, Asia, and the Middle East. It arises most commonly in children and young adults and only occasionally manifests in older individuals. It results in fibrous obliteration of the apex of the affected ventricle(s) and typically involves the papillary muscles and chordae tendineae. EMF affects both ventricles in approximately 50% of patients, purely the left ventricle in 40%, and solely the right ventricle in 10%. Its cause remains unknown.

Echocardiographic features include increased endocardial reflectivity, fibrotic obliteration of the affected ventricular apex, atrial enlargement, and pericardial effusion. Fibrotic lesions of the papillary muscles and chordae tendineae distort the valve apparatus and, in the case of the left ventricle, lead to mitral *regurgitation*.

Clinical features of EMF depend on which of the ventricles is involved: left-sided disease manifests as pulmonary congestion, and right-sided involvement may manifest as symptoms and signs similar to other restrictive cardiomyopathies or constrictive pericarditis. The clinical course of EMF tends to be progressive and complications include heart failure and thromboemboli, because the fibrotic tissue provides a site for thrombus formation. Up to 50% of patients with advanced disease die within 2 years.

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ANSWER TO QUESTION 480

C (Braunwald, pp. 1609–1611)

Among patients with hypertrophic cardiomyopathy (HCM), ICD implantation is appropriate for those at greatest risk of sudden death (SD). Those with prior cardiac arrest or sustained ventricular tachycardia warrant an ICD, while an ICD should be considered for primary prevention in HCM patients with any of the following high-risk predictors of SD: recent unexplained syncope (especially in a young patient), a family history of HCM-related sudden death, a hypotensive response to exercise testing, multiple nonsustained bursts of VT on ambulatory monitoring, or those with marked LV hypertrophy (wall thickness ≥30 mm). Patients with extensive late gadolinium enhancement on contrast-enhanced cardiac magnetic resonance imaging (involving ≥ 15% of the LV mass) are also at high risk of SD and prophylactic ICD implantation might be considered in such individuals.

Most studies have failed to establish an association between the left ventricular outflow tract (LVOT) gradient in HCM and risk of sudden death. Thus, an elevated LVOT gradient is not considered an indication for ICD placement in the absence of other risk factors.

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ANSWER TO QUESTION 481

C (Braunwald, pp. 1544–1545; Fig. 75.23)

Classic tetralogy of Fallot is marked by a large ventricular septal defect (VSD) in association with infundibular or valvular pulmonic stenosis or both, right ventricular (RV) hypertrophy, and an overriding aorta. In all cases, the VSD is located proximal to the level of the RV outflow tract obstruction and is therefore associated with elevated RV systolic pressure and right-to-left shunting. This is in contrast to the situation in patients who have a double-chambered right ventricle and a membranous VSD, in whom the septal defect communicates with the low-pressure distal portion of the right ventricle and leads to simple VSD physiology rather than the right-to-left shunting and cyanosis that mark tetralogy of Fallot.

Symptoms and clinical findings of tetralogy of Fallot depend on the severity of RV outflow tract obstruction. With only mild obstruction, a left-to-right shunt through the VSD is predominant and the patient may remain acyanotic. The condition in patients with RV obstruction severe enough to cause cyanosis usually is recognized during infancy or early childhood; such patients may then undergo palliative or total surgical repair. Patients with uncorrected tetralogy of Fallot who survive into adult life usually have at most moderate obstruction to RV outflow, in association with relatively well-preserved pulmonary blood flow.

Because the large VSD allows for decompression of the right ventricle in tetralogy of Fallot, the RV systolic pressure does not exceed that in the aorta, even in the presence of severe obstruction to RV outflow. Congestive heart failure is unusual in patients with tetralogy of Fallot. Instead, a decrease in cardiac reserve in adults with this condition is more typical, with symptoms of dyspnea and limited exercise tolerance.

Associated anomalies in patients with tetralogy of Fallot include a right aortic arch in ~25%, and coronary anomalies in ~5%.

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ANSWER TO QUESTION 482

D (Braunwald, p. 1485)

The HACEK group of organisms refers to a number of fastidious gram-negative bacilli that colonize the oropharynx and upper respiratory tract and are a cause of community-acquired subacute endocarditis. The E in HACEK stands for *Eikenella corrodens*, not *Escherichia coli*. Although they are fastidious and slow growing, HACEK organisms can usually be detected in blood cultures within 5 days. Native valve endocarditis with HACEK organisms have been associated with large vegetations and a high frequency of systemic emboli. All of these organisms share common antibiotic sensitivities.

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ANSWER TO QUESTION 483

E (Braunwald, p. 1598)

Endocardial fibroelastosis (EFE) is a rare disorder of infants in which there is thickening of the endocardium due to deposition of collagen and elastin. This entity is distinct from endomyocardial fibrosis (see Answer to Question 479), a tropical and subtropical condition in which there is prominent myocardial involvement and, commonly, eosinophilia. EFE does not appear to be a specific disease but rather a reaction in the first 1 to 2 years of life to stressors that include viral infections (including mumps exposure during fetal life), metabolic disorders, and congenital left-sided obstructive lesions. Recent reports also implicate mitochondrial disorders and placental insufficiency as causative. EFE predominantly involves the left ventricle and usually progresses to severe congestive heart failure and death.

The echocardiographic finding of a highly reflective endocardial surface of the ventricle suggests the presence of endocardial fibroelastosis.

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ANSWER TO QUESTION 484

E (Braunwald, pp. 1547, 1550)

The Fontan procedure, developed originally for tricuspid atresia, involves surgical diversion of systemic venous return directly to the pulmonary arteries without passing through a subpulmonary ventricle. It is a palliative, not curative, operation. The majority of patients (~90%) are in functional class I or II 5 years after the operation, but progressive deterioration over time is typical. The most common causes of death are congestive heart failure and arrhythmias.

Physical findings after the Fontan procedure include an elevated nonpulsatile jugular venous pulse and a single S_2 (the pulmonary artery is typically tied off).

Supraventricular arrhythmias are common (especially atrial fibrillation and flutter), observed in 15% to 20% of patients by 5 years after the operation, and the development of such arrhythmias can lead to hemodynamic deterioration and heart failure. Thromboemboli occur in 6% to 25% of patients, sources of which include atrial arrhythmias, right atrial dilatation with blood stasis, and the potentially thrombogenic material used to construct the circuit.

Protein-losing enteropathy (PLE) develops in 4% to 13% of patients, and 5-year survival in this subgroup is approximately 50%. This complication is diagnosed by the finding of low plasma $alpha_1$-antitrypsin levels and high $alpha_1$-antitrypsin stool clearance. Chronically elevated systemic venous pressure with resultant intestinal lymphangiectasia and protein leakage has been implicated in the pathogenesis of PLE.

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ANSWER TO QUESTION 485

B (Braunwald, p. 1686)

A primary hypercoagulable state (inherited thrombophilia) should be suspected when a patient presents with deep vein thrombosis (DVT) in the absence of a predisposing condition such as trauma, prolonged bed rest, or malignancy. Activated protein C (aPC) resistance is a form of thrombophilia in which aPC cannot appropriately cleave and inactivate coagulation factor V. This is caused by a single point mutation in the factor V gene, known as the factor V Leiden mutation, that abolishes a protein C cleavage site. Because factor V is critical in the conversion of prothrombin to thrombin and subsequent clot formation, the inability to inactivate it leads to a hypercoagulable state and triples the risk of DVT. This mutation has been found in nearly 20% of unselected patients with DVT.

The prothrombin gene 20210 mutation (a single G-to-A substitution at nucleotide position 20210) results in increased levels of prothrombin and doubles the risk of DVT. It has been identified in 5% to 8% of patients with venous thrombosis, whereas protein C deficiency has been found in 2% to 4%, protein S deficiency in 2% to 5%, and antithrombin deficiency in 1% to 3%.

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ANSWER TO QUESTION 486

C (Braunwald, p. 1726; Table 87.1)

This man has classic findings of sleep apnea, with daytime sleepiness, nighttime snoring with apnea, nocturnal awakenings, and automobile accidents due to falling asleep at the wheel. Specific findings include paroxysmal nocturnal dyspnea, morning headaches, cardiac arrhythmias, truncal obesity, pulmonary hypertension, nocturnal enuresis, peripheral edema, hypertension, and an elevated hematocrit on laboratory examination.

Three patterns of sleep apnea have been described: central apnea, obstructive apnea, and mixed apnea. In *central apnea*, there is impaired central nervous system control of respiratory effort. Conversely, in *obstructive apnea*, the upper airway becomes transiently obstructed, causing airflow to stop despite continuing efforts of the respiratory muscles. Affected patients experience apneic periods, which can occur between 40 and 100 times per hour. During prolonged periods of apnea, the Po_2 can fall to values as low as 20 to 25 mm Hg with oxygen saturation <50%. Sustained hypoxemia of this type leads to arrhythmias, including sinus bradycardia, sinus arrest, long asystoles, frequent atrial premature beats, and ventricular arrhythmias. Pulmonary hypertension may develop with secondary right ventricular hypertrophy.

An effective therapy for many patients with sleep apnea is continuous positive airway pressure (CPAP), applied during sleep via mask or nasal prongs. Patients treated with CPAP demonstrate improved neuropsychiatric function and reduced daytime somnolence. Nocturnal desaturation, pulmonary hypertension, and right-sided heart failure findings can all improve with this technique.

More severe forms of sleep apnea may require palatal corrective surgery or, in the most difficult cases, tracheostomy.

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ANSWER TO QUESTION 487

D (Braunwald, pp. 1691, 1823)

This patient with acute venous thromboembolism (VTE) after a prolonged airplane flight is hemodynamically stable without signs of right heart strain. Initial management should focus on anticoagulation therapy. In the absence of pregnancy, active cancer, or severely reduced renal function, effective anticoagulant approaches include: (1) subcutaneous

low-molecular-weight heparin (LMWH) followed by oral warfarin (which requires ~5 days of overlap to prevent the procoagulant effect of unopposed warfarin monotherapy) or (2) use of non-vitamin K antagonist oral anticoagulants (NOACs). The American College of Chest Physicians Guidelines recommend NOACs over the warfarin-based strategy, as NOACs are noninferior to warfarin in treatment of VTE and cause less serious bleeding. For patients with cancer-associated thrombosis, a continuous course of low-molecular-weight heparin is currently recommended over either warfarin or NOACs.

NOACs that are approved for treatment of VTE include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. Dabigatran and edoxaban require at least 5 days of pretreatment with a parenteral anticoagulant such as LMWH. Rivaroxaban and apixaban do not require preceding parenteral anticoagulation. Approved standard regimens for these agents are:

- Rivaroxaban 15 mg twice daily for 21 days, then 20 mg daily
- Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily
- Dabigatran 150 mg twice daily, after ≥5 days of a parenteral anticoagulant
- Edoxaban 60 mg daily (if creatinine clearance [Ccr] is 50 to 95 mL/min; 30 mg daily if Ccr ≤15 to 50 mL/min, or if weight ≤60 kg, or patient takes a potent P-glycoprotein inhibitor such as verapamil), after ≥5 days of a parenteral anticoagulant

Of the provided choices in the question, selection D would therefore be the most appropriate drug and dosage for this patient with normal renal function.

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ANSWER TO QUESTION 488

C (Braunwald, p. 1580; Table 77.1; Fig. 77.4)

This patient presents with symptoms of a dilated cardiomyopathy (DCM) of recent onset. In North America, the majority of new DCMs are not found to have a specific cause and the cause is often presumed to be related to viral myocarditis, which is relevant in this patient's case given her antecedent respiratory tract infection. The most common viruses that have been implicated are the enteroviruses (including coxsackie viruses) and adenovirus. There is also the possibility of a genetic form of cardiomyopathy, as familial forms are believed to be responsible for 20% to 30% of what were once classified as idiopathic DCM.

Endomyocardial biopsy (EMB) is rarely helpful in identifying the etiology of DCM because the findings are often nonspecific. Furthermore, a negative biopsy does not rule out active viral myocarditis, because the myocardial damage may be focal and not included in the biopsy specimen. EMB is more helpful in patients with fulminant new-onset heart failure, for example when giant cell myocarditis is suspected, to establish the diagnosis and direct therapy. In contrast to EMB, cardiac magnetic resonance imaging has high diagnostic accuracy for the presence of global or focal myocarditis and further can identify infiltrative or ischemic contributions to DCM.

When viral myocarditis is suspected, acute and convalescent serologic testing can be obtained to confirm a viral cause, but the findings are not available sufficiently rapidly to affect management. Myocardial damage in viral myocarditis is believed to be due to cell-mediated immunologic recognition of new antigens expressed on myocardial cells by the infecting virus, although direct invasion of the myocardium and production of a myocardial toxin may play a role. As a result of myocardial cell destruction, serum myocardial markers, including the cardiac troponins, can be elevated in active myocarditis even in the absence of coronary artery disease. Because of the immunologic nature of cell death, it stands to reason that corticosteroid therapy would be beneficial in the treatment of acute myocarditis. However, randomized trial data to date indicate that immunosuppressive therapy for acute viral myocarditis does not significantly affect left ventricular function or survival.

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ANSWER TO QUESTION 489

C (Braunwald, p. 1603; Fig. 78.2)

The M-mode and cardiac magnetic resonance images demonstrate marked asymmetric septal hypertrophy in this patient with hypertrophic cardiomyopathy. Furthermore, on the M-mode tracing, the motion of the mitral valve is abnormal: the anterior leaflet moves anteriorly during systole, toward the interventricular septum, consistent with dynamic outflow tract obstruction. The patient should be advised to refrain from competitive sports, because such activity may increase the likelihood of syncope and sudden death. Initial medical therapy for this disorder includes beta blocker therapy, to reduce myocardial oxygen consumption and lower the outflow gradient in patients with dynamic obstruction.

Diuretics should generally be avoided, or administered carefully, in patients with HCM to prevent intravascular volume depletion and intensification of the outflow gradient. Digoxin should be avoided in HCM in the absence of systolic dysfunction; the increased inotropic effect could exacerbate the LV outflow gradient. HCM is not an indication for routine antibiotic prophylaxis before dental procedures.

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ANSWER TO QUESTION 490

D (Braunwald, p. 1715)

This patient's clinical history and hemodynamic data are consistent with pulmonary vascular disease, with increased mean pulmonary artery pressure (normal <25 mm Hg) and pulmonary vascular resistance (normal <2.5 Wood units) but a normal pulmonary capillary wedge pressure. The pulmonary angiogram in the figure demonstrates abrupt

tapering and cutoff of vessels with decreased opacification of the medium and small pulmonary arterioles, consistent with chronic thromboembolic pulmonary hypertension (CTEPH). Unlike other forms of pulmonary hypertension, surgical pulmonary endarterectomy is the definitive treatment for CTEPH, typically resulting in improved symptoms and hemodynamics.

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ANSWER TO QUESTION 491

C (Braunwald, p. 1591; Figs. 77.9 and 77.10)

The provided apical four-chamber view demonstrates biventricular increased wall thickness, enlarged atria, and a small pericardial effusion, which are typical findings of cardiac amyloidosis. Systemic amyloidosis represents a collection of pathologic disorders that result in the extracellular deposition of insoluble fibrillar proteins in organs and tissues. The most common form is primary (AL) amyloidosis, which is associated with plasma cell dyscrasias such as multiple myeloma. Cardiac involvement occurs in approximately 50% of patients with AL amyloidosis, and the most common presentation is that of restrictive cardiomyopathy. In such cases, right-sided heart failure findings predominate on physical examination.

Another presentation of cardiac amyloidosis is congestive heart failure due to systolic dysfunction, generally a later finding. In approximately 10% of patients with amyloidosis, orthostatic hypotension occurs and is presumed to be a result of amyloid infiltration of the autonomic nervous system. A fourth, rare presentation of cardiac amyloidosis infiltration is impaired cardiac impulse formation and conduction. Such patients present with arrhythmias and conduction disturbances and sudden death may occur.

Although not obvious in this example, the echocardiographic findings in cardiac amyloidosis may include a distinctive granular, sparkling appearance of the thickened cardiac walls, representative of the infiltrative process. Despite the thickened ventricular walls, the ECG in cardiac amyloidosis typically demonstrates low limb lead voltage, often accompanied by ventricular conduction delay and pseudoinfarction patterns.

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ANSWER TO QUESTION 492

E (Braunwald, p. 1424)

The figure shows two-dimensional (apical four-chamber) and M-mode (mid-ventricular level) echocardiographic views demonstrating prominent late-systolic mitral valve prolapse (MVP). In part *B* of the figure, point C represents coaptation of the anterior and posterior mitral valve leaflets at the onset of systole. The posterior displacement (the U-shaped deformity) of the C-D segment represents prolapse of the leaflets into the left atrium in late systole.

By using standardized echocardiographic criteria, the prevalence of MVP in the population is 2.4%. MVP is twice as common in women as in men, and there appears to be a strong hereditary component. The majority of affected people are asymptomatic, and moderate or severe mitral regurgitation (MR) is found in only 10%. For asymptomatic patients who do not have significant MR, reassurance is appropriate, with follow-up every few years, including repeat echocardiographic evaluation if there is a clinical change. For patients with advanced MR, more frequent (e.g., yearly) clinical and echocardiographic evaluations are recommended. Patients with MVP do not routinely require predental antibiotic prophylaxis to prevent endocarditis (see Answer to Question 464).

The risk of sudden death in patients with MVP in the absence of significant MR is very low. Evaluation for arrhythmias is not warranted for asymptomatic patients, but should be pursued in those with a history of sustained palpitations, lightheadedness, or syncope. Cerebral embolic events have been reported to be more common in patients with MVP. However, a large case-controlled study showed no association between this disorder and ischemic neurologic events in patients <45 years. The most common serious complication of MVP is progressive MR. Those at the highest risk are men and individuals >50 years.

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ANSWER TO QUESTION 493

C (Braunwald, pp. 1591, 1533; Fig. 75.14)

These images reveal an ostium secundum atrial septal defect (ASD). Two-dimensional echocardiography, especially from the subcostal position, allows direct examination of the interatrial septum. Some types of ASDs, such as the sinus venosus defect, may be difficult to identify by transthoracic esophagography and can be more easily resolved by a transesophageal study. Both color flow Doppler and saline contrast echocardiography (part *B*) may be used to evaluate the direction of flow across an ASD. In the uncomplicated situation, in which flow is directed predominantly from the left to the right atrium, left atrial (noncontrast) blood passes through the ASD and produces a negative contrast effect within the right atrium. Conversely, when Eisenmenger syndrome has developed, as in the case described, the shunt reverses (i.e., right-to-left direction) and contrast medium passes from the right atrium into the left-sided chambers after a peripheral vein saline injection. Anomalous pulmonary venous return (not demonstrated in this case) is most commonly associated with the sinus venosus type of ASD and is best visualized by transesophageal esophagography.

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ANSWER TO QUESTION 494

A (Braunwald, pp. 1404, 1405, 1409)

This M-mode panel displays high-frequency vibration of the anterior leaflet of the mitral valve in diastole, which is characteristic of aortic regurgitation (AR). This sign is an echocardiographic correlate of the Austin Flint murmur, although, unlike the auscultatory finding, it may occur even in cases of mild AR.

AR develops due to abnormalities of the aortic valve itself and/or because of dilatation of the aortic root. In recent decades, primary aortic root pathology has become the most common cause of pure AR in the United States, reflecting the decline of rheumatic heart disease. AR due to dilatation of the ascending aorta is typically degenerative in origin (annuloaortic ectasia), and it may also be associated with specific disorders, including systemic hypertension, cystic medial necrosis of the aorta (isolated or in association with Marfan syndrome), giant cell arteritis, ankylosing spondylitis, rheumatoid arthritis, and syphilis. Causes of *valvular* AR include a bicuspid aortic valve, endocarditis, traumatic injury, and rheumatic aortic valve disease.

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ANSWER TO QUESTION 495

B (Braunwald, p. 1415; Figs. 69.1 and 69.2)

The transmitral Doppler pattern is typical of mitral stenosis (MS). Echocardiographic study in a patient with MS provides a wealth of information about the presence and severity of the lesion. Typical findings include leaflet thickening, decreased leaflet separation in diastole, and anterior movement of the posterior mitral valve leaflet during early diastole. The chordae are variably thickened, fused, and shortened.

Accurate determination of mitral orifice size can be obtained from two-dimensional and Doppler echocardiography (see Answer to Question 26). Planimetry of the mitral orifice in the parasternal short-axis view permits an accurate determination of the valve area. Doppler echocardiography is especially useful in quantifying the severity of MS. The peak velocity of transmitral flow is *increased* in MS, as in this case, and the rate of decline is reduced during early diastole. In the continuous-wave Doppler flow velocity signal illustrated, the peak velocity exceeds 2 m/s, yielding a peak transmitral gradient of >16 mm Hg (per the modified Bernoulli equation, $P = 4v^2$), consistent with advanced MS. In addition, the valve area may be estimated using the pressure half-time, which is based on the correlation between the size of the mitral orifice and the time required for peak pressure to reach half its initial level. Finally, Doppler interrogation of the tricuspid regurgitant jet can estimate the degree of elevated pulmonary artery pressure.

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ANSWER TO QUESTION 496

D (Braunwald, pp. 1663–1672; Table 83.1)

This case illustrates a patient infected with human immunodeficiency virus (HIV) presenting with tuberculous pericarditis during the effusive stage of the illness. Whereas the incidence of tuberculous pericarditis has decreased in industrialized nations in recent decades, the disorder remains an important problem in immunosuppressed patients, including those with HIV disease. It is also a major cause of pericarditis among populations in developing regions, especially in sub-Saharan Africa. Among Africans with HIV infection, tuberculosis is the most common cause of pericardial disease.

Tuberculous pericarditis usually manifests in the effusive stage, as in this case, or late in its course, following the development of constrictive pericarditis. The disease usually arises slowly and is marked by nonspecific systemic findings, including fever, night sweats, dyspnea, and fatigue. The acute onset of severe pericardial pain, which is seen frequently in viral or idiopathic pericarditis, is *uncommon* in tuberculous pericarditis. Abnormalities on physical examination may include fever, tachycardia, and a pericardial friction rub, as well as jugular venous distention, ascites, and hepatomegaly.

The chest radiograph in this case displays common features of effusive tuberculous pericarditis. These include an enlarged cardiac silhouette with accompanying mediastinal widening suggestive of a pericardial effusion, normal lung hila and apices, and a small pleural effusion. Patients may also present with chronic constrictive pericarditis with symptoms and signs consistent with severe systemic venous congestion. The diagnosis of tuberculous pericarditis requires a high index of suspicion and is best confirmed by obtaining both pericardial fluid and a pericardial biopsy specimen during the early effusive stage. The measurement of a high level of adenosine deaminase activity (>40 U/L) is also supportive of the diagnosis, with a sensitivity of 88% and a specificity of 83%. In addition, polymerase chain reaction to detect *Mycobacterium tuberculosis* from small amounts of fluid or pericardial tissue can sometimes accelerate the diagnosis. Without antituberculous therapy, the disease is fatal, with an early mortality >80%. The effectiveness of corticosteroids in tuberculous pericarditis remains unclear, but some trials suggest that the addition of steroid therapy to standard antituberculous agents may shorten the time to resolution of symptoms.

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ANSWER TO QUESTION 497

A (Braunwald, p. 1535; Fig. 75.18)

Atrioventricular (AV) septal defects include malformations characterized by varying degrees of incomplete

development of the atrial septum, the inflow portion of the ventricular septum, and the AV valves. These anomalies are also known as endocardial cushion defects or AV canal defects.

An ostium primum atrial septal defect (ASD), a type of AV septal defect, occurs immediately adjacent to the AV valves, either of which may be deformed or incompetent. Most commonly it is only the anterior leaflet of the mitral valve that is displaced and "cleft"; the posterior leaflet of the mitral valve and the tricuspid valve are generally not involved. Ostium primum ASDs lead to prominent left-to-right transatrial shunting and have clinical features that resemble those of ostium secundum defects. In addition to similar findings on physical examination, imaging typically reveals right atrial and right ventricular prominence and increased pulmonary vascular markings. Transthoracic echocardiography successfully displays the features of this condition. If cardiac catheterization is undertaken, left ventriculography may show a pathognomonic "gooseneck" deformity that results from a narrowed and elongated left ventricular outflow tract.

When a ventricular septal defect accompanies an ostium primum septal defect (and a common AV orifice is therefore present), the malformation is known as a *complete AV canal defect*. Approximately 35% of patients with common AV canal have accompanying cardiovascular abnormalities, including tetralogy of Fallot, double-outlet right ventricle, transposition of the great arteries, total anomalous pulmonary venous connections, left ventricular outflow tract obstruction, pulmonic stenosis, and persistent left superior vena cava. In addition, common AV canal is often present in patients with trisomy 21 (Down syndrome).

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ANSWER TO QUESTION 498

B (Braunwald, p. 1611; Fig. 78.12; Table 78.2)

As described in the Answer to Question 480, primary prevention risk markers in patients with hypertrophic cardiomyopathy (HCM) include family history of sudden death due to HCM, unexplained recent syncope, repetitive nonsustained VT on ambulatory monitoring, hypotensive or attenuated blood pressure response to exercise, left ventricular (LV) wall thickness ≥30 mm, and extensive or diffuse gadolinium enhancement on cardiac magnetic resonance imaging, defined as >15% of LV mass.

Mutations in the fibrillin-1 gene cause Marfan syndrome, not hypertrophic cardiomyopathy.

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ANSWER TO QUESTION 499

E (Braunwald, p. 1438; Fig. 69.22)

The figure demonstrates mitral valve prolapse with posteriorly directed severe mitral regurgitation by color Doppler (the blue/yellow jet, representing a high-velocity aliasing signal, extends to the posterior left atrium and pulmonary veins). The optimal timing of mitral valve repair or replacement in patients with chronic asymptomatic severe primary mitral regurgitation (MR) is often a difficult clinical decision. The goal is to operate, even in asymptomatic individuals, before irreversible left ventricular (LV) dilatation and dysfunction have developed. If congestive heart failure or ventricular dysfunction supervenes, surgery should be performed as soon as possible to prevent further dysfunction. Thus, serial evaluation of the LV ejection fraction can be helpful in deciding when to intervene. The ejection fraction should be supranormal in patients with advanced MR. Once it falls below 60%, early systolic dysfunction is likely and the risk of postoperative LV dysfunction increases. The LV end-systolic diameter (LVESD) is also helpful in timing surgical intervention. Patients should be referred for surgery before the LVESD exceeds 40 mm, to minimize the risk of postoperative LV dysfunction. Early pulmonary hypertension is considered a relative indication for mitral valve surgery, because patients with this complication, especially if it is accompanied by right ventricular dysfunction, have a worse prognosis. Although they may reduce the regurgitant fraction and improve forward cardiac output, neither angiotensin-converting enzyme inhibitors nor other vasodilators have been shown to delay the need for surgery or improve long-term outcomes in patients with chronic MR.

Per the updated 2017 AHA/ACC guidelines, class I indications for mitral valve surgery in chronic severe MR include symptomatic patients with left ventricular ejection fraction (LVEF) >30%, and asymptomatic patients with evidence of LV dysfunction (LVEF 30% to 60% and/or LV end-systolic diameter [LVESD] ≥40 mm). Class IIa indications include asymptomatic patients with preserved LV function in whom there is >95% likelihood of successful repair, patients with a high likelihood of repair and the development of either atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg), and patients with preserved LV function who demonstrate a progressive increase in LVESD or decrease in LVEF.

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ANSWER TO QUESTION 500

B (Braunwald, p. 1544; Fig. 75.23; see also Answer to Question 481)

This patient has tetralogy of Fallot, the components of which are (1) an outlet ventricular septal defect, (2) obstruction to right ventricular (RV) outflow, (3) overriding of the aorta, and (4) RV hypertrophy. In general, total correction of tetralogy of Fallot is advised for almost all patients, even in infancy.[1] Successful early correction appears to prevent the consequences of progressive infundibular obstruction and acquired pulmonary atresia, delayed growth and development, and the complications secondary to hypoxemia and polycythemia. The size of the pulmonary arteries is most important in determining candidacy for primary repair of tetralogy of Fallot, as opposed to the age or size of the infant or child. Marked hypoplasia of the pulmonary arteries is a relative contraindication to a total corrective operation. If this is present, a palliative procedure designed to increase pulmonary blood flow is generally recommended, such as balloon valvuloplasty of the right ventricular outflow tract and pulmonary arteries. Total correction of the tetralogy may then be carried out later in childhood or adolescence at lower risk.

The postoperative period after palliative or corrective surgery is susceptible to several common complications. A sudden increase in pulmonary venous return may lead to left ventricular decompensation, whereas varying degrees of pulmonic valvular regurgitation may increase right ventricular cavity size. In addition, bleeding difficulties may be seen, especially in older polycythemic patients. Complete right bundle branch block or left anterior hemiblock is often observed postoperatively.[2] The greatest cause of early and late mortality and poor surgical results is restriction of pulmonary arterial flow owing to persistent right-sided outflow tract obstruction.[3] Most often, surgical repair leads to relief of symptoms of hypoxemia and severe exercise intolerance that mark the preoperative period.

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ANSWER TO QUESTION 501

A (Braunwald, p. 1688; Figs. 84.8 and 84.9)

The high-resolution contrast-enhanced chest computed tomography (CT) shows large thromboemboli in the right and left main pulmonary arteries (*arrows* in figure). High-resolution chest CT is the primary imaging test in patients with suspected pulmonary embolism (PE), as it offers a number of advantages over other modalities, including direct visualization of thrombus within the pulmonary arteries, the ability to concurrently identify thrombi in the proximal veins in the legs, and imaging of the lung parenchyma to identify alternative diagnoses. Whereas early CT scanners could image the proximal pulmonary arteries, current generation multidetector devices allow high-resolution imaging of even subsegmental pulmonary arteries.[1] Although invasive pulmonary angiography was historically the gold standard for the diagnosis of PE, contrast CT has assumed that role.

Echocardiography is very helpful in risk stratification in patients with large PE. The presence of right ventricular dysfunction portends a higher risk of complications and may warrant consideration of more aggressive treatment such as fibrinolysis or catheter embolectomy.[2]

In patients with suspected PE, the identification of deep vein thrombosis (DVT) of the lower extremities by venous ultrasonography can provide circumstantial evidence of PE disease. The absence of DVT in such patients, however, does not exclude pulmonary embolism because the majority of patients with PE do not have imaging evidence of DVT elsewhere.[3]

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ANSWER TO QUESTION 502

A (Braunwald, p. 1673)

Each of the listed conditions results in elevated right-sided heart pressures. The diastolic "dip-and-plateau" pattern shown in the figure, also known as a "square root sign," is produced when early rapid diastolic inflow into the ventricle commences but is then abruptly halted by an opposing force. In the case of constrictive pericarditis, early diastolic inflow is terminated as ventricular filling reaches the volume limit imposed by the surrounding rigid pericardium. In restrictive cardiomyopathy, the myocardium is abnormally "stiff" and impaired relaxation accounts for a ventricular filling pattern that mimics pericardial constriction. Other conditions with similar right-sided hemodynamics as pericardial constriction include acute right ventricular infarction and massive pulmonary embolism. In these entities, filling of the acutely strained and dilated right ventricle is limited by an unprepared and relatively noncompliant pericardium.

In cardiac tamponade, the surrounding elevated pericardial pressure equalizes the diastolic pressures of the cardiac chambers. Because even early diastolic ventricular filling is impaired (manifest by blunting of the *y* descent on right atrial tracing), there is no dip-and-plateau configuration.

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ANSWER TO QUESTION 503

A (Braunwald, p. 1866)

Primary cardiac tumors are much less common than metastatic cardiac lesions. Approximately 25% of primary cardiac tumors display malignant characteristics, and up to 75% of these are sarcomas. Primary cardiac lymphomas are the next most common group. The sites of cardiac malignancies, in decreasing order of frequency, are the right atrium, the left atrium, the right ventricle, and the left ventricle.

Tumors limited to the myocardium without intracavitary involvement may be asymptomatic or cause arrhythmias or conduction disturbances. Other typical presentations of cardiac malignancies include precordial pain, heart failure, pericardial effusion, tamponade, conduction system disorders, and/or vena caval obstruction. Tumors that involve the right-sided heart chambers may predominantly cause right-sided heart failure. The prognosis of cardiac malignancies is poor, with common survival times of a few weeks to 2 years after diagnosis. Historically, 75% of patients with cardiac sarcoma had evidence of distant metastases at the time of death, but more recent series have shown that only 25% to 50% of patients have metastatic disease at the time of diagnosis, likely owing to earlier detection with improvements in noninvasive diagnostic capabilities.

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ANSWER TO QUESTION 504

A (Braunwald, p. 1675)

This patient has constrictive pericarditis, etiologies of which include prior idiopathic or post-cardiac surgical pericarditis, previous mediastinal radiation therapy, and tuberculosis. Because of the progressive nature of this condition, the majority of patients become symptomatic and come to medical attention because of weakness, peripheral edema, or ascites. The treatment of constrictive pericarditis is complete resection of the pericardium, including excision from the anterior and inferior surfaces of the right ventricle and the diaphragmatic and anterolateral surfaces of the left ventricle. This procedure has been performed more successfully via median sternotomy than by left thoracotomy because the former allows greater mobility of the heart. In recent series, the average operative mortality has ranged between 2.2% and 15%, with a correlation between the degree of the functional disability before the operation and survival after repair. Thus, it is generally recommended that patients undergo pericardiectomy soon after the development of symptoms. Between 14% and 28% of patients display a *low-output* syndrome in the immediate postoperative period, possibly related to rapid dilatation of the heart after release of the restraining pericardium.

Predictors of late survival include preoperative New York Heart Association class, age, renal function, pulmonary artery pressure, and history of radiotherapy exposure to the heart. Symptomatic improvement occurs in approximately 80% of survivors of pericardiectomy, although the time course for such recovery varies. Some patients experience an immediate decrease in symptoms, whereas others may have a delayed or partial response that requires weeks or months for resolution of elevated jugular venous pressure and abnormal filling pressures. The 5-year postoperative survival is approximately 75%. Outcomes are worst in patients with radiation-induced constriction.

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ANSWER TO QUESTION 505

B (Braunwald, p. 1621)

Lyme disease is a tickborne illness caused by the spirochete *Borrelia burgdorferi*. Patients who contract this condition typically develop a rash (erythema chronicum migrans) at the site of the tick bite. Weeks to months later, if the condition is untreated, patients may develop complications involving the joints, central nervous system, and cardiovascular system.[1] In early studies, up to 10% of untreated patients reportedly developed cardiac complications, but in the modern era with early use of antibiotics, Lyme carditis is rare (only 1.1% of patients with Lyme disease reported to the Centers for Disease Control and Prevention [CDC]).[2] The most frequent cardiac manifestation is transient atrioventricular (AV) nodal block, including complete heart block. Although some patients require temporary pacing, AV block usually improves spontaneously and a permanent pacemaker is rarely needed. Lyme disease can also result in myocarditis, which is usually mild and self-limited. Manifestations include nonspecific ST-segment and T-wave abnormalities on the ECG; only rarely do such patients develop symptoms of heart failure. The efficacy of antibiotics for Lyme carditis has not been established, although they are routinely prescribed.

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ANSWER TO QUESTION 506

C (Braunwald, p. 1701)

The natural history of idiopathic pulmonary artery hypertension was defined by a National Institutes of Health (NIH) Registry of patients studied in the 1980s. In this registry, 63% of the patients were female with a mean age of 36 years at the time of diagnosis. The most common initial symptoms were dyspnea (80%), fatigue (19%), syncope (13%), and Raynaud

phenomenon (10%). Patients may describe chest pain, but it is not a very common symptom. In the NIH Registry the most common physical finding was a loud pulmonic component of the second heart sound (P_2). Tricuspid regurgitation was found in 40% and peripheral edema in 32%. Eighty-seven percent of patients had electrocardiographic evidence of right ventricular hypertrophy.

The most common cause of death of patients in the NIH Registry was progressive right-sided heart failure (47%). Sudden cardiac death occurred in 26% and was limited to patients with severe (class IV) symptoms.

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ANSWER TO QUESTION 507

D (Braunwald, p. 1389)

The valve depicted is a calcified, stenotic aortic valve with three cusps. This is an acquired type of aortic stenosis (AS), and the thickened leaflets and nodular calcification are typical of the degenerative form seen in elderly patients. If the valve were bicuspid, it would reflect congenital AS. Historically, degenerative calcific AS was assumed to be due to long-standing mechanical stress on the valve, but more recent studies suggest that chronic inflammation with lipid accumulation is evident, a process that may be similar to the pathogenesis of coronary atherosclerosis. It is therefore salient that diabetes mellitus, hypercholesterolemia (elevated low-density lipoprotein), smoking, and hypertension increase the risk of aortic valve calcification.

The most likely murmur in this case would be crescendo-decrescendo during systole, loudest at the upper right sternal border and radiating toward the neck. Because apposition of the valve leaflets otherwise appears intact, it is unlikely that this individual has significant aortic regurgitation.

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ANSWER TO QUESTION 508

D (Braunwald, pp. 1673–1674; Table 83.7)

It is clinically important to differentiate constrictive pericarditis from restrictive cardiomyopathies, because the former is typically a treatable condition, whereas therapeutic options for the latter are very limited. Both conditions have similar hemodynamic findings during heart catheterization: all of the intracardiac diastolic pressures are elevated and the left and right ventricular pressure tracings usually demonstrate a "dip-and-plateau" configuration. There are, however, several hemodynamic features that can help differentiate these two entities. Because restrictive cardiomyopathy tends to cause some left ventricular (LV) systolic dysfunction as well as the diastolic abnormality, pulmonary hypertension and elevated right ventricular (RV) systolic pressure are frequently also present. Therefore, the ratio of RV systolic pressure to RV end-diastolic pressure (RVEDP) is usually >3 mm Hg, whereas in constrictive pericarditis it is typically <3 mm Hg. Similarly, an RV systolic pressure >50 mm Hg is more consistent with restrictive cardiomyopathy than with pericardial constriction.

Close inspection of simultaneous RV and LV pressure tracings can also help discern which of these conditions is present. The pathophysiology of ventricular interdependence imposed by constrictive pericarditis leads to a *discordance* of LV and RV systolic pressures during respiration. That is, in contrast to the normal situation or in patients with restrictive cardiomyopathy, simultaneous LV and RV pressure measurements during inspiration in constriction show that RV systolic pressure rises as LV pressure falls. Furthermore, in constriction, the LV end-diastolic pressure (LVEDP) and RVEDP are equal, whereas in restriction, disproportionate LV involvement often causes the LVEDP to be more than 5 mm Hg greater than the RVEDP. In restriction (but not constriction), an intravenous volume challenge in the cardiac catheterization laboratory can help accentuate this difference.

Other techniques are also used to distinguish constriction from restrictive cardiomyopathy. For example, chest computed tomography or magnetic resonance imaging most often (>80% of patients) demonstrate a thickened pericardium in constriction, but not in restrictive disease. Also, if performed, a transvenous endomyocardial biopsy is usually normal in constriction but abnormal in myocardial restrictive disease.

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ANSWER TO QUESTION 509

B (Braunwald, pp. 1709, 1715)

Riociguat is a first-in-class therapy approved to improve exercise capacity and functional class in patients with chronic thromboembolic pulmonary hypertension (CTEPH; World Health Organization [WHO] Group 4) who are inoperable, or who have persistent or recurrent symptoms after surgical treatment. It is also approved for use in patients with WHO Group 1 pulmonary arterial hypertension. Riociguat stimulates soluble guanylyl cyclase, which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The latter is a potent second messenger that results in vasorelaxation. Although nitric oxide is also a critical biological stimulator of soluble guanylyl cyclase, riociguat does not influence nitric oxide bioactivity.

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ANSWER TO QUESTION 510

D (Braunwald, p. 1678)

This patient has a malignant pericardial effusion. The most common tumors that invade the pericardium are, in order of decreasing frequency, lung, breast, and lymphoma.[1] Malignant pericardial effusions may result from direct extension of tumor into the pericardium or from hematogenous or lymphatic spread. In patients who develop malignant

pericardial effusions, the prognosis is poor; in a study of such patients, the mean survival was 15.1 weeks.[2] After initial drainage of a large malignant pericardial effusion, a repeat echocardiographic study should be obtained within 72 hours to assess the rate of reaccumulation and to ensure the absence of tamponade physiology. If the fluid reaccumulates at a rapid rate, repeat pericardiocentesis followed by more aggressive therapy is warranted. Intrapericardial instillation of a sclerosing agent, such as tetracycline, during catheter drainage has been advocated as a means of controlling recurrences, although complications such as fever, chest pain, and constriction may be troublesome and prognosis of the underlying condition is not significantly improved by this technique.[3] Surgical pericardiectomy is not usually advocated in this situation because of the high operative mortality and the poor prognosis related to the underlying condition. Rather, more limited subxiphoid pericardiostomy ("pericardial window") or video-assisted thoracoscopic pericardiectomy is appropriate for symptomatic palliation.

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ANSWER TO QUESTION 511

E (Braunwald, p. 1664; Fig. 83.2)

This patient has acute pericarditis, a condition with electrocardiographic alterations that are diagnostically useful. Four stages of abnormalities of the ST segments and T waves may be distinguished. *Stage I* includes ST-segment elevation, in which the segment is concave upward; this elevation typically occurs in all leads *except* aVR and V_1. The T waves during this stage are usually upright. PR-segment depression (or PR elevation in aVR) occurs in this stage in approximately 80% of patients. The return of ST segments to baseline, accompanied by T wave flattening, comprises *stage II* of this process. *Stage III*, which occurs in some but not all patients, is characterized by inversion of the T waves, such that the T wave vector is directed opposite to that of the ST segment. This should be contrasted to early inversion of the T wave in acute ST-segment elevation myocardial infarction (in the absence of successful early reperfusion), which occurs *before* the return of ST segments to baseline. In those who develop T wave inversions, *stage IV* represents reversion of the T wave to normal and may not occur for weeks to months after the acute event.

Whereas all four stages are detected in approximately half of patients with acute pericarditis, about 90% of patients will demonstrate *some* of these electrocardiographic abnormalities that allow characterization of an acute chest pain episode as pericarditis.

Stage I changes of pericarditis can be differentiated from the electrocardiographic presentation of early repolarization. An ST-segment/T wave ratio >0.25 in lead V_6 is more consistent with acute pericarditis, whereas a ratio <0.25 is more suggestive of early repolarization.

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ANSWER TO QUESTION 512

B (Braunwald, pp. 1393–1394)

The most serious symptoms of aortic stenosis (AS) in adults are angina pectoris, syncope, and heart failure. When symptoms become manifest, the prognosis for untreated AS is poor. Natural history survival studies show that the interval from the onset of symptoms to the time of death is approximately 5 years in patients with angina, 3 years in those with syncope, and 2 years in patients with heart failure (Fig. 4.38). Angina is present in approximately two-thirds of patients with critical AS, even in the absence of coronary artery disease, resulting from the combination of increased oxygen demand and the reduction of oxygen delivery.

Syncope in AS occurs most commonly *during or after exertion*. It is related to reduced cerebral perfusion caused by systemic vasodilatation during exercise in the presence of a fixed cardiac output. Sudden death occurs with increased frequency in patients with critical AS, but almost invariably in those who have had previous symptoms.

Symptoms of AS may become exacerbated by the development of atrial fibrillation. Because of the decreased diastolic compliance of the hypertrophied ventricle, patients with AS are highly dependent on atrial contraction to deliver preload and maintain cardiac output. Thus, when atrial fibrillation develops, significant hemodynamic deterioration may follow.

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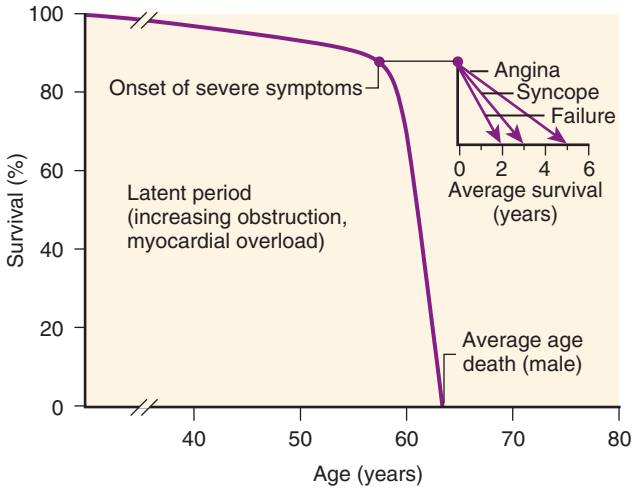

FIG. 4.38 *From Ross Jr J, Braunwald E. Aortic stenosis.* Circulation. *1968;38(suppl V):61.*

ANSWER TO QUESTION 513

B (Braunwald, p. 1708)

This patient has severe pulmonary hypertension with systemic hypotension. Using the provided data, the patient's cardiac output ([mean pulmonary artery pressure – mean pulmonary capillary wedge pressure] / pulmonary vascular resistance) is 3.1 L/min and the cardiac index (= cardiac output / body surface area) is reduced at 2.0 L/min/m^2, consistent with cardiogenic shock (see Answer to Question 384). Current guidelines recommend initiation of intravenous prostacyclin in patients with severe pulmonary hypertension and cardiogenic shock. Although macitentan, a nonselective endothelin receptor antagonist, is approved for the treatment of pulmonary arterial hypertension, no data are currently available for use of this therapy in patients with cardiogenic shock. The other two options (tPA and digoxin) would not be appropriate for this clinical scenario.

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ANSWER TO QUESTION 514

C (Braunwald, pp. 1667, 1671, 1677)

Penetrating cardiac trauma is most commonly due to stab wounds and gunshot injuries. The consequences of such injury depend on the nature of the penetrating object, the size of the wound, the entering location, and the structures that are impacted. The site of cardiac injury can be predicted by the location of entry on the chest wall. Because of its anterior location, the *right* ventricle is at greatest risk of penetrating chest trauma. Of note, survival is higher in patients who suffer penetrating injuries to the ventricles than the atria, because the former are thicker walled structures more likely to seal the laceration site.

Patients who suffer penetrating injuries to the chest wall are at high risk of cardiac tamponade because of bleeding into the pericardial sac. If this complication develops, patients usually have muffled heart sounds, jugular venous distention, and hypotension with a narrowed pulse pressure; pulsus paradoxus is often present. Many trauma surgeons discourage pericardiocentesis for suspected tamponade after acute trauma because clots form quickly and often cannot be drained successfully through a needle and a negative pericardiocentesis does not rule out tamponade. Furthermore, if there is continued bleeding from cardiac perforation, any beneficial effect of pericardiocentesis would be short-lived. Therefore, patients with penetrating chest injuries, significant bleeding, and a clinical picture that raises concern of tamponade should proceed directly to thoracotomy. Rupture of the interventricular septum has been described as a potential late complication in patients who have experienced penetrating chest trauma.

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ANSWER TO QUESTION 515

C (Braunwald, p. 1543)

The presentation of persistent PDA in adults depends on the degree of left-to-right shunting. Small *silent* shunts (i.e., those without murmurs) are almost always asymptomatic and are incidental findings during echocardiography. The risk of endarteritis is negligible in such patients. However, small *audible* shunts may occasionally present because of a superimposed endovascular infection.

Moderate shunts impose a volume load on the left ventricle and left atrium, resulting in left ventricular dysfunction and atrial fibrillation. Such patients typically present with either dyspnea or palpitations. On physical examination, a loud continuous "machinery" murmur is best appreciated in the first or second left intercostal space. The pulse pressure is usually *wide* owing to aortic diastolic runoff into the pulmonary trunk.

Large shunts initially cause left-sided volume overload, but subsequently lead to irreversible pulmonary hypertension and Eisenmenger physiology. Chest radiology at that stage reveals enlarged central pulmonary arteries with peripheral pruning. Closure of a clinically detectable PDA is recommended except when it is accompanied by irreversible pulmonary hypertension. A multicenter trial of the Amplatzer occluder device indicates that transcatheter closure can achieve a success rate of 99% for complete ductal closure at 1 year.

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ANSWER TO QUESTION 516

B (Braunwald, p. 1586)

Chronic heavy consumption of alcohol is associated with systolic and diastolic ventricular dysfunction, systemic hypertension, arrhythmias, and sudden death. Alcohol abuse is a leading cause of nonischemic dilated cardiomyopathy. The likelihood of developing alcohol-induced dilated cardiomyopathy correlates with the amount of alcohol consumed over a lifetime. Most men with this condition have consumed more than 90 g of ethanol daily for over 5 years. Women appear to be *more* susceptible to the development of dilated cardiomyopathy at the same level of alcohol consumption as men. With abstinence from alcohol, left ventricular systolic and diastolic function typically improve, often dramatically. Most of the improvement occurs in the first 6 months of abstinence, but systolic function may continue to normalize over a more prolonged time. The prognosis of patients who continue to drink heavily is poor.

Alcohol consumption at *moderate* levels in those without known coronary artery disease is associated with a reduction in cardiovascular mortality, including a *lower* incidence of sudden death.

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ANSWER TO QUESTION 517

C (Braunwald, pp. 1591–1592)

Amyloidosis can afflict the cardiovascular system in several ways. Restrictive cardiomyopathy with diastolic dysfunction is the most common presentation and is due to myocardial infiltration by amyloid protein. In this situation, right-sided heart failure symptoms often predominate, with peripheral edema, hepatic congestion, and elevated jugular venous pressure. A second common presentation is biventricular heart failure due to systolic dysfunction. In some patients, congestive symptoms may be exacerbated by amyloid deposition in the atria with loss of effective atrial transport, despite the presence of sinus rhythm. Orthostatic hypotension occurs in 10% of patients with amyloidosis and results from infiltration of the autonomic nervous system. Other cardiovascular presentations include rhythm disturbances (especially atrial fibrillation) and conduction system disease. The ECG typically demonstrates *low* limb lead voltage. Small pericardial effusions are often observed by echocardiography in cardiac amyloidosis; however, significant pericardial disease is rare and cardiac tamponade and pericardial constriction are not typical complications.

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ANSWER TO QUESTION 518

E (Braunwald, pp. 1484, 1498)

Staphylococcus aureus is one of the most aggressive organisms responsible for infective endocarditis, and infection with this bacterium results in rapid destruction of heart valves and surrounding tissues. *S. aureus* has a propensity to cause metastatic infections, including in the central nervous system, which is affected in 30% to 50% of patients.[1] Central nervous complications include cerebral embolism, meningitis, and cerebral and subarachnoid hemorrhage due to rupture of mycotic aneurysms. Patients with right-sided endocarditis (i.e., tricuspid valve involvement) due to *S. aureus* have a better prognosis than those with left-sided infections.

Because *S. aureus* endocarditis is so destructive, it requires prompt and aggressive therapy. Although some experts have advocated early surgical intervention for native valve endocarditis due to this organism, there is a risk of infecting the new prosthetic valve if surgery is performed before adequate sterilization of the blood. Therefore, initial aggressive antibiotic therapy should be undertaken, with surgery reserved for those who fail to respond or for those who develop complications such as intractable heart failure. In contrast, prosthetic valve endocarditis caused by *S. aureus* carries an extremely high mortality rate, approaching 50% in patients treated medically,[2] and early surgical therapy is generally recommended.

Methicillin-resistant *S. aureus* (MRSA) is a common cause of both nosocomial and community-acquired infections, such that empiric therapy for suspected *S. aureus* endocarditis should begin with an agent that is effective against MRSA, such as vancomycin.

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ANSWER TO QUESTION 519

B (Braunwald, p. 1565; Fig. 75.42)

In Ebstein abnormality, there is apical displacement of the septal leaflet of the tricuspid valve. Associated anomalies include atrial septal defects (or patent foramen ovale) in 50% of patients, accessory conduction pathways (usually right-sided) in 25%, and less commonly pulmonic stenosis or atresia, ventricular septal defects, aortic coarctation, and patent ductus arteriosus.

The usual clinical manifestations of Ebstein anomaly with severe tricuspid deformity in infancy are cyanosis, failure to thrive, and congestive heart failure. However, patients with less advanced disease may be asymptomatic until early adulthood, when symptoms include exertional dyspnea and fatigue, palpitations, and cyanosis due to right-to-left shunting. Cardiac examination typically shows wide splitting of S_1, a *widely* split S_2 (due to accompanying right bundle branch block [RBBB]), a right-sided S_3, and the murmur of tricuspid regurgitation.

The ECG may be normal, but common findings include right atrial enlargement, a prolonged PR interval, and RBBB. When an accessory conduction pathway is present, the ECG may show preexcitation with a shortened PR interval and delta wave.

The diagnosis of Ebstein anomaly can be confirmed by echocardiography, with the finding of apical displacement of the septal leaflet of the tricuspid valve, combined with an elongated anterior leaflet.

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ANSWER TO QUESTION 520

C (Braunwald, p. 1598)

Löffler endocarditis is a syndrome associated with eosinophilia that occurs in temperate climates. The typical patient with this condition is a male in his fourth decade with a persistent eosinophilia count >1500/mm^3 for at least 6 months, and evidence of organ involvement.[1] Cardiac manifestations are present in approximately 75% of patients. The eosinophilia may be reactive (e.g., associated with an allergic or parasitic disorder), associated with leukemia, or there may be no apparent cause. The combination of hypereosinophilia and cardiac involvement is also part of the Churg-Strauss syndrome, which can be differentiated from Löffler endocarditis by the coexisting presence of asthma, nasal polyposis, and necrotizing vasculitis.[2]

The pathology of Löffler endocarditis involves mural endocardial thickening of the inflow and apical portions

of both ventricles. Histologic findings include (1) an acute inflammatory eosinophilic myocarditis, (2) thrombosis and inflammation of intramural coronary vessels, (3) mural thrombosis, and (4) fibrotic thickening of the ventricular wall.

Clinically, patients present with weight loss, fever, cough, rash, and heart failure. Cardiomegaly is present early in the course and the murmur of mitral regurgitation is common. Systemic embolism occurs frequently and may lead to neurologic and renal dysfunction.

Laboratory findings include an elevated erythrocyte sedimentation rate and an increased eosinophil count. Imaging frequently demonstrates localized thickening of the posterobasal left ventricular wall with absent or reduced motion of the mitral posterior leaflet by echocardiography. The apex may contain thrombus. Systolic ventricular function is usually normal. The hemodynamic consequences of the dense endocardial scarring are those of a restrictive cardiomyopathy (RCM) with abnormal diastolic filling. Findings at cardiac catheterization are consistent with RCM, including elevated ventricular filling pressures with an early diastolic "dip-and-plateau" configuration.

Medical treatment of Löffler endocarditis is moderately effective. Administration of steroids and hydroxyurea can improve survival.

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ANSWER TO QUESTION 521

B (Braunwald, p. 1699)

The figure demonstrates a midsystolic notch in the right ventricular outflow tract Doppler velocity profile, which is indicative of elevated pulmonary vascular resistance. Notching occurs due to a reflective fluid wave from the pulmonary vascular bed toward the right ventricle and is a consequence of decreased pulmonary vascular compliance. It occurs more commonly in patients with pulmonary hypertension due to pulmonary vascular disease (e.g., group I pulmonary hypertension) than in patients with pulmonary hypertension on the basis of left heart failure.

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ANSWER TO QUESTION 522

C (Braunwald, p. 1418)

This woman has rheumatic heart disease. She has mitral stenosis (MS) based on the loud S_1 and apical opening snap. Many patients with advanced MS have an early blowing diastolic murmur along the left sternal border and a normal systemic pulse pressure. In the majority of such patients, the murmur is due to mild aortic regurgitation (AR) and it is usually of little clinical importance. However, approximately 10% of patients with MS have severe rheumatic AR. This can usually be recognized by peripheral signs of AR, such as a widened pulse pressure and signs of left ventricular (LV) enlargement by ECG and chest radiograph, with confirmation by echocardiography.

In patients with multivalvular disease, a proximal valve lesion may mask the presence of a more distal abnormality. Thus, significant AR may not be easily auscultated in patients with severe MS. The widened pulse pressure, in particular, may be absent in the presence of severe MS. Furthermore, the apical diastolic Austin Flint murmur associated with AR may be mistaken for the rumbling murmur of MS. These two murmurs may be distinguished during auscultation by means of bedside maneuvers. Isometric handgrip and squatting augment the diastolic murmur of AR (and the associated Austin Flint murmur), but have little effect on the murmur of MS. In this patient, the response to handgrip is consistent with the presence of an Austin Flint murmur.

The fact that the ECG of this patient shows LV hypertrophy in addition to left atrial enlargement is inconsistent with simple MS and suggests that the degree of superimposed AR is significant. There is no evidence on examination of tricuspid stenosis or mitral regurgitation. Pulmonic regurgitation due to pulmonary hypertension in patients with MS can also cause an early diastolic murmur along the left sternal border. However, such a murmur would be associated with a loud pulmonic component of S_2 and would not intensify with handgrip.

ANSWER TO QUESTION 523

E (Braunwald, pp. 1420–1421)

Diuretic therapy and negative chronotropic agents are the mainstays of medical therapy for patients with symptomatic mitral stenosis (MS). The high left atrial pressure in this condition elevates pulmonary venous pressure, resulting in dyspnea due to transudation of fluid into the alveolar spaces and stimulation of pulmonary J fibers. Diuretics reduce intravascular volume and left atrial pressure and therefore improve dyspnea. Maintaining a controlled, relatively slow heart rate prolongs diastole, maximizes the time for left atrial emptying, and reduces left atrial pressure. Thus, negative chronotropic agents such as beta blockers improve exercise capacity in MS patients, even in individuals in sinus rhythm.

Since left ventricular contractile function is normal in pure MS, digitalis glycosides have no beneficial hemodynamic effect and are useful only as agents for ventricular rate control if atrial fibrillation supervenes, though beta blockers are preferred for this purpose. There is insufficient evidence to support the routine use of anticoagulants to reduce the risk of thromboembolic events in patients with MS in the absence of atrial fibrillation, a history of thromboembolism, or extreme left atrial enlargement.

As reviewed in the Answer to Question 464, endocarditis prophylaxis before dental procedures is not recommended for native valve abnormalities such as MS.

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ANSWER TO QUESTION 524

D (Braunwald, pp. 1676–1677)

Most cases of infectious acute pericarditis are caused by a virus. The most commonly implicated viruses are the enteroviruses and adenovirus. In contrast, the incidence of nontuberculous bacterial pericarditis is low, approximately 5% of cases, and it develops most often as a complication of pneumonia, mediastinitis, or infective endocarditis. The most frequently involved bacterial organisms are streptococcal and staphylococcal species. The overall survival in bacterial pericarditis is poor, averaging 30%.

Tuberculosis was once the leading cause of constrictive pericarditis worldwide. However, with effective screening and treatment programs, the incidence of this condition is now rare in developed nations, and it is encountered mostly in immunocompromised hosts and in developing societies.

Pericarditis associated with fungal disease is most often caused by *Histoplasma*. It occurs in otherwise healthy young individuals and is thought to be a noninfectious inflammatory effusion secondary to fungal infection in nearby mediastinal lymph nodes. This process should be considered in patients with suspected pericarditis who live where the fungus is endemic—the Ohio and Mississippi rivers' valleys. It is generally a self-limited disease, and treatment typically consists of nonsteroidal anti-inflammatory agents without antifungal therapy. The latter is necessary only when there is evidence of disseminated histoplasmosis.

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ANSWER TO QUESTION 525

D (Braunwald, pp. 1621–1622)

Chagas disease is caused by the protozoan *Trypanosoma cruzi*. It is prevalent in Central and South America, where 8 to 10 million people are infected. The disease is characterized by three phases: acute, latent, and chronic. During the acute phase, the disease is transmitted to humans by the bite of a reduviid bug, commonly called the kissing bug. After inoculation, protozoa multiply and migrate widely through the body. Clinical manifestations during the acute phase may include fever, muscle pains, hepatosplenomegaly, myocarditis, and meningoencephalitis. The disease then enters an asymptomatic latent phase for many years. Typically, chronic cardiac manifestations become evident 5 to 15 years after the initial infection. Interestingly, only 30% of infected individuals develop symptoms of chronic Chagas disease, and many individuals with high parasite burdens do not. There is poor correlation between the level of parasitemia and the severity of disease later.

The major cardiovascular findings of the chronic phase of Chagas disease include myocardial fibrosis, conduction system abnormalities, ventricular dilation (dilated cardiomyopathy), and apical aneurysm formation. Associated clinical manifestations include progressive heart failure (predominantly right-sided), arrhythmias, conduction disturbances, and possible thromboembolism. There is usually severe cardiomegaly, with the most common electrocardiographic abnormalities being *right* bundle branch block and left anterior fascicular block; atrioventricular block occurs less frequently. Ventricular arrhythmias are common.

The diagnosis of Chagas disease is confirmed using a complement-fixation test (Machado-Guerreiro test). Antitrypanosomal therapy should be administered to patients with acute disease, those with positive serologies without symptoms of chronic disease, and those with early cardiac involvement. Such therapy is not effective in reversing pathologic changes and complications in those with advanced chronic Chagas cardiac disease; standard heart failure and antiarrhythmic treatments should be undertaken instead.

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ANSWER TO QUESTION 526

C (Braunwald, p. 1537)

The echocardiogram demonstrates prominent echogenicity along both surfaces of the interatrial septum (*arrow* in Fig. 4.39), consistent with normal deployment of a transcatheter atrial septal defect (ASD) closure device. Indications for this method are the same as for surgical closure of an ASD, but strict structural criteria must be met. Successful closure can be accomplished in the majority of patients, and complications, such as device embolization or atrial perforation, are rare.

Atrial myxomas are the most common primary heart tumor. When attached to the interatrial septum, echocardiography most commonly demonstrates a mobile mass attached to the limbus of the fossa ovalis by a stalk. Lipomatous hypertrophy of the interatrial septum occurs most

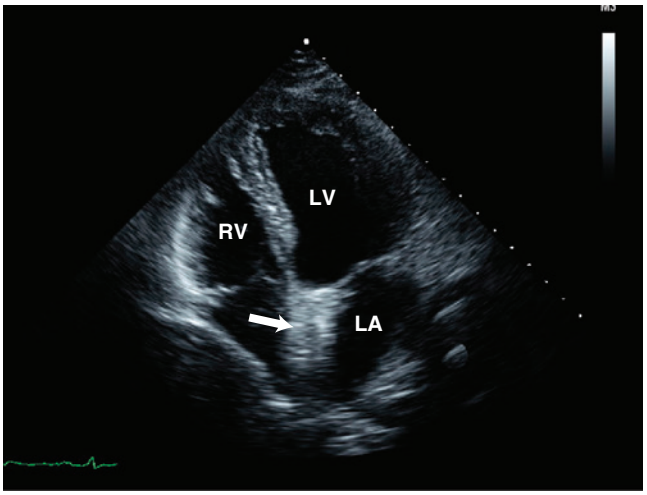

FIG. 4.39

often in obese, elderly female patients. It represents a prominent fatty deposition at the interatrial septum that spares the fossa ovalis, creating a thick "dumbbell" appearance on echocardiography. This condition is associated with a high incidence of atrial arrhythmias. In cardiac amyloidosis, infiltration causes increased thickness of all cardiac chamber walls, not just the interatrial septum.

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ANSWER TO QUESTION 527

D (Braunwald, pp. 1415–1420; Fig. 69.1; see also Answer to Question 467)

The parasternal long-axis view displays typical rheumatic deformity of the mitral valve with diastolic doming of the leaflets, with a "hockey-stick" appearance of the anterior leaflet (*arrow* in Fig. 4.40). There is accompanying left atrial enlargement. The transmitral spectral Doppler in part *B* in Fig. 4.29 shows an increased early diastolic velocity with a slowed diastolic descent, indicative of a diastolic pressure gradient across the valve due to mitral stenosis (MS).

Atrial fibrillation (AF) is common in patients with MS, and the prevalence increases with age. It tends to be poorly tolerated because of the lack of effective atrial contribution to left ventricular filling and the shortened diastolic filling time in patients with rapid ventricular rates. AF also predisposes to atrial thrombus formation and embolization. The risk of systemic embolism in MS correlates directly with patient age and left atrial size and inversely with cardiac output.

Infective endocarditis in MS tends to be more common in patients with milder forms of the disease, occurring less frequently on very thickened and calcified mitral valves.

Only about 15% of patients with isolated MS experience anginal-type chest discomfort. This symptom may arise from right ventricular hypertension, concomitant atherosclerosis, or coronary obstruction due to embolization of left atrial thrombus.

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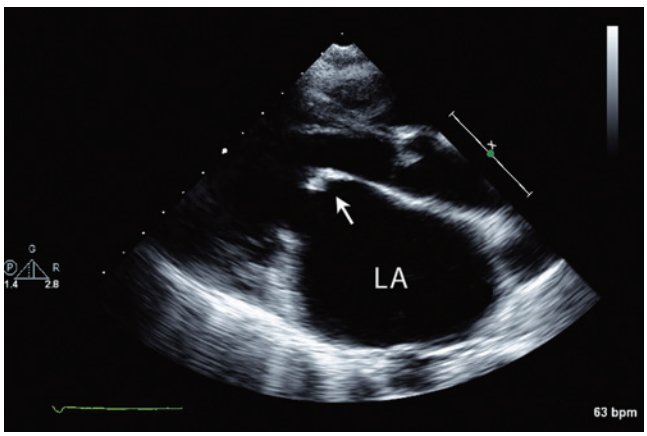

FIG. 4.40

Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline 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.* 2014;63:e57–e185.

ANSWER TO QUESTION 528

A (Braunwald, pp. 1542–1543)

These findings are consistent with patent ductus arteriosus (PDA). In the majority of preterm infants weighing <1500 g, a PDA persists for a prolonged period, and in approximately one-third of those infants, a large shunt leads to significant cardiopulmonary deterioration. Noninvasive evaluation may reveal evidence of significant shunting before the appearance of physical findings of ductal patency. Physical examination may reveal bounding peripheral pulses, an infraclavicular and interscapular systolic murmur (sometimes heard as a continuous murmur), a hyperactive precordium, hepatomegaly, and recurrent episodes of apnea and bradycardia. An increase in the cardiothoracic ratio is seen on sequential chest radiographs and may be accompanied by increased pulmonary arterial markings, perihilar edema, and ultimately generalized pulmonary edema. Echocardiography may demonstrate increased left ventricular end-diastolic and left atrial dimensions, and color Doppler confirms the presence of left-to-right shunting.

Management of the premature infant with a PDA depends on the clinical presentation of the disorder. In an asymptomatic infant, intervention is usually unnecessary, because the PDA will almost always undergo spontaneous closure and will not require surgical ligation and division. Infants with respiratory distress syndrome and signs of a significant ductal shunt usually are unresponsive to medical measures to control congestive heart failure and require closure of the PDA for survival. This is usually accomplished pharmacologically with indomethacin to inhibit prostaglandin synthesis and achieve constriction and closure. Approximately 10% of infants are unresponsive to indomethacin and require ligation.

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ANSWER TO QUESTION 529

A (Braunwald, pp. 1603–1609)

The echocardiogram demonstrates hypertrophic cardiomyopathy (HCM) with asymmetric septal hypertrophy. The most common physiologic abnormality in HCM is not systolic, but rather diastolic dysfunction. HCM is characterized by abnormal stiffness of the left ventricle, which results in impaired diastolic filling. The abnormal diastolic relaxation increases the left ventricular (LV) end-diastolic pressure with subsequent elevations of left atrial, pulmonary venous, and pulmonary capillary pressures.

Although the generation of a pressure gradient due to associated subaortic obstruction would imply that LV ejection

is slowed or impeded during systole, there is actually *rapid* ventricular emptying and a normal, or even augmented, ejection fraction in such patients. Hemodynamic studies have confirmed that the majority of LV output is unusually rapid in patients with HCM and is completed earlier in systole than normal, regardless of whether an outflow gradient is present. Thus, the common symptom of dyspnea in this condition is largely due to impaired diastolic relaxation rather than compromised systolic ejection. Although there is a strong temporal and quantitative relationship between mitral valve systolic anterior motion and the development of subaortic obstruction, symptoms do not necessarily correlate with the magnitude of the generated gradient. Furthermore, there can be significant variations on a daily basis in both the extent of the obstruction (and associated murmur) and symptomatology.

Exertional syncope and angina occur in some patients with HCM, and these symptoms are likely related, at least in part, to systolic obstruction.

The echolucent space posterior to the left ventricle in the echocardiogram represents a tiny pericardial effusion.

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ANSWER TO QUESTION 530

D (Braunwald, pp. 1409–1410)

Acute aortic regurgitation (AR) is most often caused by infective endocarditis, aortic dissection, or trauma. Many of the physical findings typical of chronic AR are not present in patients with acute AR. In acute AR, the left ventricle has not yet dilated and is relatively noncompliant, such that its early diastolic pressure rises rapidly. If the resulting left ventricular (LV) diastolic pressure exceeds the left atrial pressure, the mitral valve may close *prematurely* and can produce diastolic mitral regurgitation. Because the elevated LV diastolic pressure blunts runoff of blood from the aorta into the left ventricle, the aortic diastolic pressure does not decline as substantially as in chronic AR. Therefore, the pulse pressure does not widen significantly, and physical findings typical of an increased pulse pressure, such as Corrigan pulse (abrupt upstroke, then quick collapse of the arterial pulse), are absent. Similarly, the duration of the diastolic murmur is shorter than in chronic AR.

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ANSWER TO QUESTION 531

A (Braunwald, pp. 1544–1547, 1574–1575; see also Answer to Question 481)

Tetralogy of Fallot is the most common cyanotic congenital cardiac defect that presents after the newborn period. Most experts advocate surgical repair in the first 6 months of life to avoid chronic cyanosis and its complications. Although initial operative outcomes are excellent, provided that the ventricular septal defect is adequately closed and right ventricular outflow tract obstruction is relieved, many patients develop progressive pulmonary regurgitation, especially when a transannular patch is used to enlarge the right ventricular outflow tract. The optimal timing to correct this complication with pulmonary valve replacement (PVR) remains uncertain, but it is appreciated that PVR should be performed when there is severe pulmonary regurgitation with substantial right ventricular dilation or dysfunction, even in the absence of subjective dyspnea. In fact, adults with congenital heart disease tend to underestimate their exercise intolerance, underscoring the importance of objective measures of exercise capacity, such as cardiopulmonary exercise testing.

Patients with repaired tetralogy of Fallot are at increased risk of sudden death (SD). Although criteria for an implantable cardioverter-defibrillator for primary prevention remain controversial, a QRS width >180 ms and left ventricular dysfunction have been identified as risk factors for SD. Atrial arrhythmias are also common in patients with repaired tetralogy of Fallot; risk factors include left atrial dilation and tricuspid regurgitation.

The American Heart Association guideline for the prevention of endocarditis recommends predental antibiotic prophylaxis for patients with repaired congenital heart disease with residual defects at the site of, or adjacent to, prosthetic material (e.g., Dacron patch).

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ANSWER TO QUESTION 532

B (Braunwald, pp. 1713–1715)

The development of pulmonary hypertension in patients with chronic obstructive lung disease (COPD) arises from several factors including pulmonary vasoconstriction induced by alveolar hypoxemia, acidemia, the mechanical effects of high lung volumes on the pulmonary vessels, and small-vessel loss in regions of emphysema.[1] Right ventricular (RV) hypertrophy and dilatation may develop over time (Fig. 4.41).

The only effective treatment for patients with COPD and pulmonary hypertension is supplemental oxygen, with several studies showing an improvement in morbidity and mortality.[2] In a series of trials in the 1980s, continuous oxygen supplementation was more effective than nocturnal therapy alone. Thus, long-term oxygen therapy is recommended if the resting PaO_2 is <60 mm Hg.

Although digoxin may improve the RV ejection fraction in some patients with RV dilation and dysfunction, it can also contribute to adverse pulmonary vasoconstriction and has not been shown to have a beneficial effect on survival.

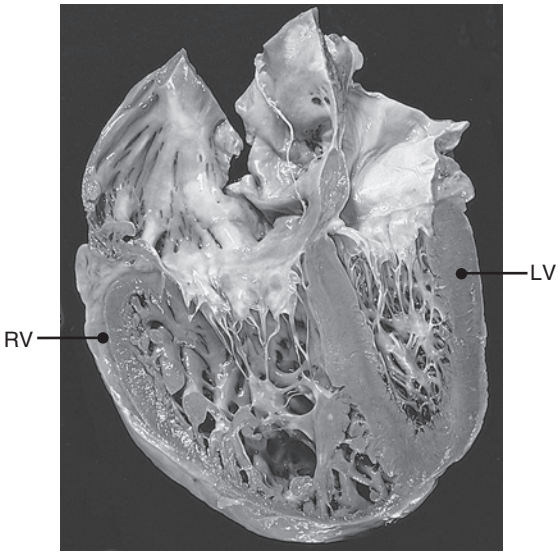

FIG. 4.41 *From Kumar V, Abbas AK, Fausto N, eds.* Robbins and Cotran Pathologic Basis of Disease. *7th ed. Philadelphia: Elsevier; 2005:588.*

Furthermore, digitalis toxicity may be precipitated by the hypoxemia and acidemia often associated with COPD. Theophylline, beta-agonists, hydralazine, and other pulmonary vasodilators (e.g., phosphodiesterase inhibitors, endothelin receptor antagonists such as bosentan) have not been shown to improve survival of patients with pulmonary hypertension due to COPD.[3–5]

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ANSWER TO QUESTION 533

B (Braunwald, pp. 1559–1561)

Coarctation of the aorta (Fig. 4.42) occurs two to five times more commonly in males.[1] Most infants and children with coarctation are asymptomatic. In contrast, neonates with severe coarctation often develop overt heart failure due to the sudden rise in left ventricular (LV) afterload when the ductus arteriosus closes at birth. Coarctations discovered in the adult are frequently associated with additional abnormalities, including bicuspid aortic valve (50% to 85%) and intracranial aneurysms.

Pathophysiologically, significant coarctation places a pressure load on the left ventricle, which leads to LV hypertrophy and ultimately heart failure. On physical examination, findings include a differential systolic blood pressure (brachial artery pressure greater than popliteal artery pressure by >10 mm Hg) and radial-femoral pulse delay. The mean survival time of patients with uncorrected coarctation is 35 years. Heart failure is the most common cause of death in adults, followed by bacterial endocarditis, intracranial hemorrhage, and aortic dissection. Surgical repair is associated with low mortality. Outcomes are most influenced by the presence of other congenital anomalies or more complex variants of aortic coarctation involving the aortic arch, rather than the type of surgery performed.

Recoarctation and true aneurysm formation at the site of repair can occur.[2] The reported incidence of these complications varies widely in the surgical literature, ranging from 6% to 60%. Prior hypertension resolves in up to 50% of patients but it may recur later in life.[2,3]

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ANSWER TO QUESTION 534

B (Braunwald, p. 1869)

The apical four-chamber views demonstrate a large mass attached to the interatrial septum, which in diastole prolapses across the orifice of the mitral valve and is most consistent with a left atrial myxoma. Echocardiography is helpful in differentiating between left atrial thrombus and myxoma. Thrombus usually produces a layered appearance and tends to localize to the more posterior segments of the atrium. In contrast, left atrial myxoma is often mottled in appearance and typically attaches along the limbus of the fossa ovalis of the interatrial septum. In some atrial myxomas, including the one demonstrated here, echolucent areas are seen within the tumor mass that correspond pathologically to regions of hemorrhage.

Eighty-three percent of cardiac myxomas appear in the left atrium and 12.7% in the right atrium; the remainder are biatrial or located in one of the ventricles. Signs and symptoms of left atrial myxoma may be similar to those of mitral valve disease owing to interference of the mass with normal mitral valvular function. Physical examination may demonstrate pulmonary congestion and an intensified S_1. It is believed that the loud S_1 occurs when there is late onset of mitral valve closure as a consequence of tumor prolapse through the valvular orifice. An early diastolic sound (tumor "plop") may be present, although this is often positional and may be confused with an S_3. Cardiac myxomas may also produce a variety of constitutional symptoms and extracardiac findings, including fever, weight loss, and arthralgias. These symptoms have been attributed to the tumor's production of interleukin-6. Several abnormal laboratory findings may be present, including an elevated erythrocyte sedimentation rate, polycythemia, leukocytosis, and anemia.

Approximately 10% of cardiac myxomas are familial. In such cases, patients typically present at a younger age

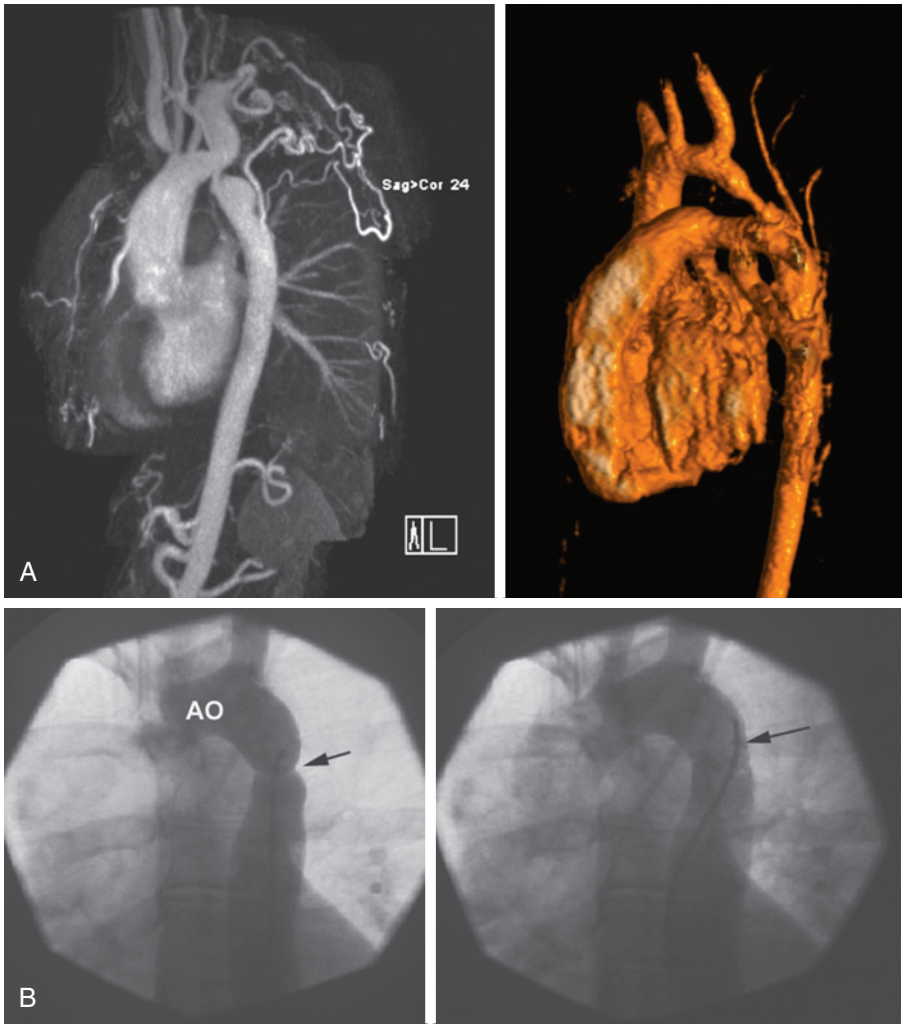

FIG. 4.42 *(A) Montage of coarctation of the aorta. The left image is a specimen that shows the site of the posterior shelf. The right image is from magnetic resonance imaging and shows the posterior shelf and some associated transverse arch hypoplasia. (B) Angiogram of coarctation of the aorta before and after stenting* (arrows). AO, *Aorta.*

and are more likely to have multiple additional myxomas in noncardiac locations. *Carney complex* is inherited as an autosomal dominant syndrome consisting of cardiac myxomas, along with dermatologic (hyperpigmented skin lesions) and endocrine abnormalities (adrenal, pituitary, testicular).

The treatment of symptomatic cardiac myxoma is prompt surgical resection of the tumor. Recurrences appear in approximately 3% of patients, with a higher incidence in those with familial myxomas.

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ANSWER TO QUESTION 535

D (Braunwald, pp. 1686–1689; Fig. 84.11)

The diagnostic approach for possible pulmonary embolism (PE) involves careful clinical assessment in conjunction with judicious diagnostic testing (Fig. 4.43). The most common symptoms of PE are dyspnea and pleuritic chest pain. Physical examination may be unremarkable, or findings may include tachycardia, tachypnea, and increased intensity of the pulmonic component of S_2.

Arterial blood gas determinations are generally not helpful in the diagnosis of PE. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, the PaO_2 did not differentiate between individuals with and without PE. Thus, normal values of the alveolar-arterial oxygen gradient do not exclude PE.

When PE is highly suspected, chest computed tomographic (CT) angiography is the superior imaging test.[1,2] This technique has the capability to visualize even subsegmental pulmonary emboli. When the clinical probability of PE is not high, a normal plasma D-dimer assay usually suffices to rule out this condition.[3,4] The D-dimer assay is highly sensitive for the presence of PE, but has low specificity because elevations also occur in sepsis, recent surgery or trauma, malignancies, and other systemic illnesses. A normal D-dimer assay therefore has excellent negative predictive value.

In patients with large PE, electrocardiographic signs of right-sided heart strain may be present (including ST-segment and T wave abnormalities in the right precordial leads (V1–V4), right-axis deviation, new right bundle branch block,

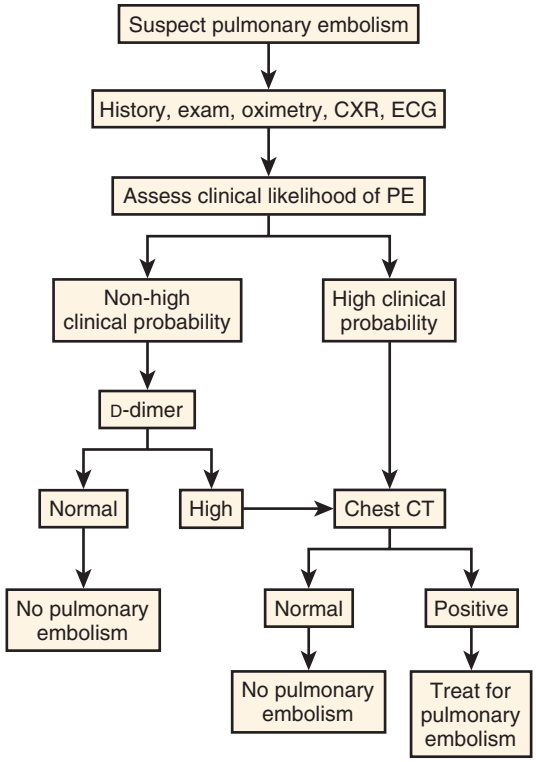

FIG. 4.43

and an $S_1Q_3T_3$ pattern), but such findings are generally absent when small PEs are present. The most common electrocardiographic abnormality in PE is simply sinus tachycardia, and a normal tracing does not exclude PE.

Ventilation-perfusion lung scanning results are often ambiguous. Although PE is very unlikely to be present with a completely normal scan, and very likely when the test is "high probability," scans frequently fall between these two extremes ("intermediate probability") and do not provide definitive results. This test is now useful for diagnosis of acute PE only in occasional circumstances (e.g., renal insufficiency, a history of anaphylaxis to IV contrast agents precluding a CT angiogram, or pregnancy).

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ANSWER TO QUESTION 536

D (Braunwald, pp. 1866–1973)

Primary tumors of the heart are rare (autopsy incidence 0.001% to 0.03%), with benign tumors representing >80%. The majority of benign cardiac tumors are myxomas, followed in frequency by lipomas, papillary fibroelastomas, rhabdomyomas, and fibromas. Among the malignant tumors, the most common are sarcomas, and of these, angiosarcoma and rhabdomyosarcoma are the most frequent forms.[1]

Although it can be difficult to differentiate benign from malignant tumors clinically, certain findings may be helpful. The presence of distant metastases, local mediastinal invasion, evidence of rapid growth in tumor size, hemorrhagic pericardial effusion, precordial pain, location of the tumor on the *right* as opposed to the left side of the heart, and extension into the pulmonary veins are all suggestive of a malignant rather than a benign tumor. Furthermore, infiltration of the myocardium is more indicative of a malignant process.[2] Benign tumors are more likely to occur on the left side of the interatrial septum and to grow slowly.

Cardiac symptoms caused by tumors are primarily determined by mechanical interferences. Myxomas that are located on the left side may produce mitral valve symptoms, whereas right-sided malignant tumors may produce signs of right-sided failure.[3]

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ANSWER TO QUESTION 537

C (Braunwald, pp. 1702–1704)

Echocardiography is the most useful noninvasive test to evaluate for cardiac tamponade.[1] Findings most suggestive of tamponade physiology include (1) a large pericardial effusion, (2) right atrial (RA) and right ventricular (RV) diastolic compression, (3) an exaggerated inspiratory *increase* in transtricuspid flow velocities with concurrent *decrease* in transmitral flow velocities, and (4) inferior vena caval dilatation with absence of normal inspiratory collapse.

RV diastolic collapse is the most predictive sign of tamponade. It is more specific than RA compression and more sensitive and specific than pulsus paradoxus in detecting increased pericardial pressure. However, diastolic RV collapse may not be evident in patients with elevated intrapericardial pressure who also have pulmonary hypertension, because RV pressures are higher than normal in that case.

A small pericardial effusion makes tamponade less likely, but does not exclude the diagnosis, especially if the pericardial fluid has accumulated rapidly. In addition, small pericardial effusions can be associated with "low-pressure" tamponade in patients with intravascular volume depletion. Small loculated effusions (e.g., after cardiac surgery) can also result in tamponade physiology because of localized chamber compression.

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ANSWER TO QUESTION 538

D (Braunwald, pp. 1672–1674)

The lateral chest radiograph shows calcification of the pericardium, suggestive of constrictive pericarditis. In this patient's case, prior radiation therapy is the likely cause of constriction.

The clinical presentation of patients with chronic constrictive pericarditis (CP) is predominantly that of right-sided heart failure. In early stages, signs include jugular venous distention (with a rapid *y* descent) and Kussmaul sign (inspiratory augmentation of the jugular venous pressure, instead of the normal decline), peripheral edema, and vague abdominal discomfort due to passive hepatic congestion. As the disease progresses, ascites, jaundice, and anasarca may ensue.

The most notable auscultatory finding observed in some patients with advanced CP is the pericardial knock, an early diastolic sound heard best at the left sternal border or apex that corresponds to the sudden cessation of ventricular filling imposed by the rigid, constricting pericardium. The pericardial knock occurs earlier and is of higher frequency than an S_3 gallop sound and may be confused with the opening snap of mitral stenosis (MS), but is not followed by the diastolic rumbling murmur of MS.

Heart catheterization in patients with CP is notable for elevation and equalization of the intracardiac diastolic pressures and a diastolic "dip-and-plateau" configuration of the ventricular pressure tracings. Intravascular volume depletion can mask these typical hemodynamic findings, but they can be uncovered with an intravenous fluid challenge. One important way to distinguish CP from restrictive cardiomyopathy (CMP) during catheterization is to observe the variation in simultaneously recorded right and left ventricular systolic pressures. In contrast to normal individuals or those with restrictive CMP, there is usually a striking *discordance* between these pressures during respiration in CP: with inspiration, the left ventricular systolic pressure falls while that of the right ventricle increases. This finding reflects the exaggerated ventricular interdependence that results from pericardial constraint.

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ANSWER TO QUESTION 539

D (Braunwald, pp. 1389–1390)

The three primary causes of valvular aortic stenosis (AS) are (1) a congenitally bicuspid valve that becomes calcified, (2) calcification of a structurally normal trileaflet valve, and (3) rheumatic disease (Fig. 4.44). Calcification of a congenitally bicuspid or of a normal trileaflet valve is the most common etiology of AS in adults.

Although calcific aortic valve disease was once considered to result from years of mechanical stress on the valve, it actually appears to represent proliferative and inflammatory changes, with lipid accumulation and infiltration of macrophages and T lymphocytes, in a manner similar to vascular calcification. As in atherosclerosis, cigarette smoking, hyperlipidemia, and diabetes are risk factors for the development of this valvular process.

Rheumatic valvular disease has declined in frequency in industrialized countries, but remains an important condition in developing nations. Rheumatic AS results from postinflammatory fusion and adhesion of the valve commissures and rarely develops in the absence of rheumatic mitral involvement.

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ANSWER TO QUESTION 540

C (Braunwald, pp. 1407–1409; Fig. 68.19)

Appropriate timing for surgical intervention in chronic aortic regurgitation (AR) depends on the patient's symptoms and state of left ventricular (LV) contractile function. Regardless of the severity of AR, patients who are symptomatic and have reduced LV systolic function should be referred for surgery, unless an absolute contraindication exists.[1] Asymptomatic patients with advanced AR who have normal LV systolic function without prominent ventricular dilatation (i.e., an end-systolic diameter <50 mm) have an excellent prognosis and typically can be observed clinically and by echocardiography to assess for changes in LV size and function.

In patients who do undergo aortic valve surgery, the end-systolic diameter is valuable in predicting the postoperative outcome. An end-systolic diameter <40 mm predicts a low likelihood of postoperative instability or heart failure. However, an end-systolic diameter >55 mm, or a preoperative ejection fraction <50%, increases the risk of postoperative death from LV dysfunction.[1]

Several vasodilators, including angiotensin-converting enzyme inhibitors, have been shown to provide beneficial hemodynamic effects in chronic AR. However, a randomized trial comparing nifedipine, enalapril, and placebo in patients with chronic AR did not demonstrate a benefit of either vasodilator regimen in reducing symptoms or LV dysfunction warranting valve replacement.[2]

Fig. 4.45 summarizes the current American Heart Association/American College of Cardiology Foundation management strategy for patients with chronic severe AR.[1]

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ANSWER TO QUESTION 541

D (Braunwald, pp. 1651, 1652, 1659)

Non-AIDS conditions (including cardiovascular disease) now account for the majority of deaths among human

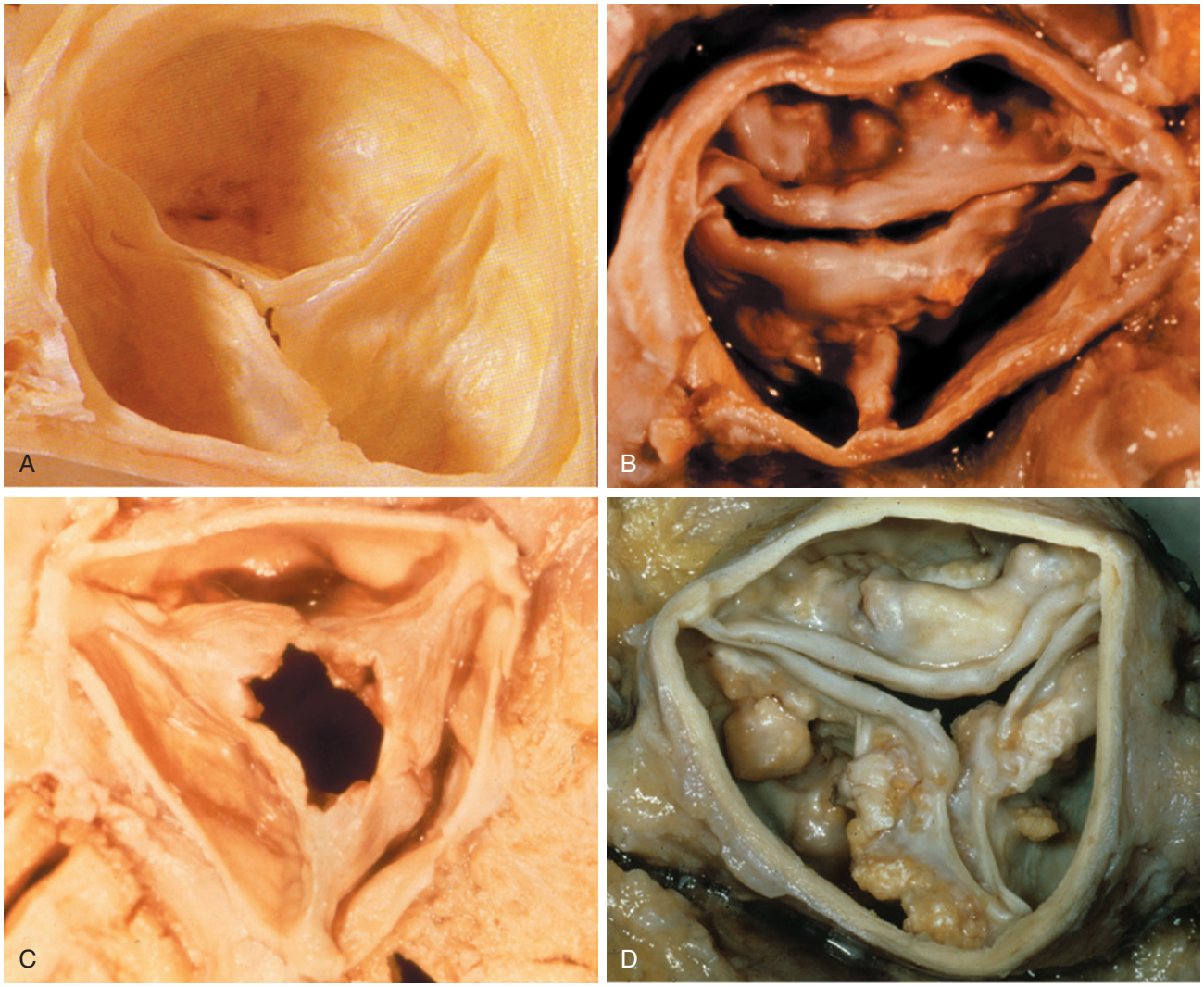

FIG. 4.44 *Major types of aortic valve stenosis. (A) Normal aortic valve. (B) Congenital bicuspid aortic stenosis. A false raphe is present at the 6 o'clock position. (C) Rheumatic aortic stenosis. The commissures are fused with a fixed central orifice. (D) Calcific degenerative aortic stenosis. (A) From Manabe H, Yutani C, eds.* Atlas of Valvular Heart Disease. *Singapore: Churchill Livingstone; 1998:6, 131; (B–D) Courtesy Dr. William C. Roberts, Baylor University Medical Center, Dallas, TX.*

immunodeficiency virus (HIV)-infected individuals taking antiretroviral therapy (ART).[1] Although most HIV-associated CV disease is related to atherosclerosis, HIV and ART can affect the myocardium and pericardium as well.[2] In the pre-ART era, HIV-associated cardiomyopathy was commonly seen in patients with advanced HIV disease and was associated with a poor prognosis. While the incidence of dilated cardiomyopathy has decreased dramatically in the current era, HIV patients who are not adherent to ART remain at risk.[3,4] In addition, more subtle LV dysfunction (both systolic and diastolic) may be detected on echocardiography in asymptomatic HIV patients taking ART.[5] Putative mechanisms for LV dysfunction include direct viral infection of cardiomyocytes, immune-mediated myocarditis, nutritional deficiencies, and direct toxicities of antiretroviral therapies.

Pericardial effusion was also common among HIV patients in the pre-ART era, but the incidence has declined significantly with current therapies.[6] Typically, such effusions are small and a large number resolve spontaneously. Most are of "idiopathic" origin, but can also be related to opportunistic infections, drug toxicities, uremia, or malignancy. The presence of a pericardial effusion increases the mortality risk in HIV-infected patients.

In the contemporary era, most cardiovascular complications in HIV-infected patients are the result of accelerated atherosclerotic disease. Potential contributory mechanisms may include direct HIV vasculopathy with endothelial dysfunction, chronic inflammation, or co-infection with other viruses. Moreover, ART drugs, especially earlier generation protease inhibitors, can contribute to dyslipidemia and insulin resistance, predisposing to increased risk of myocardial infarction.[7]

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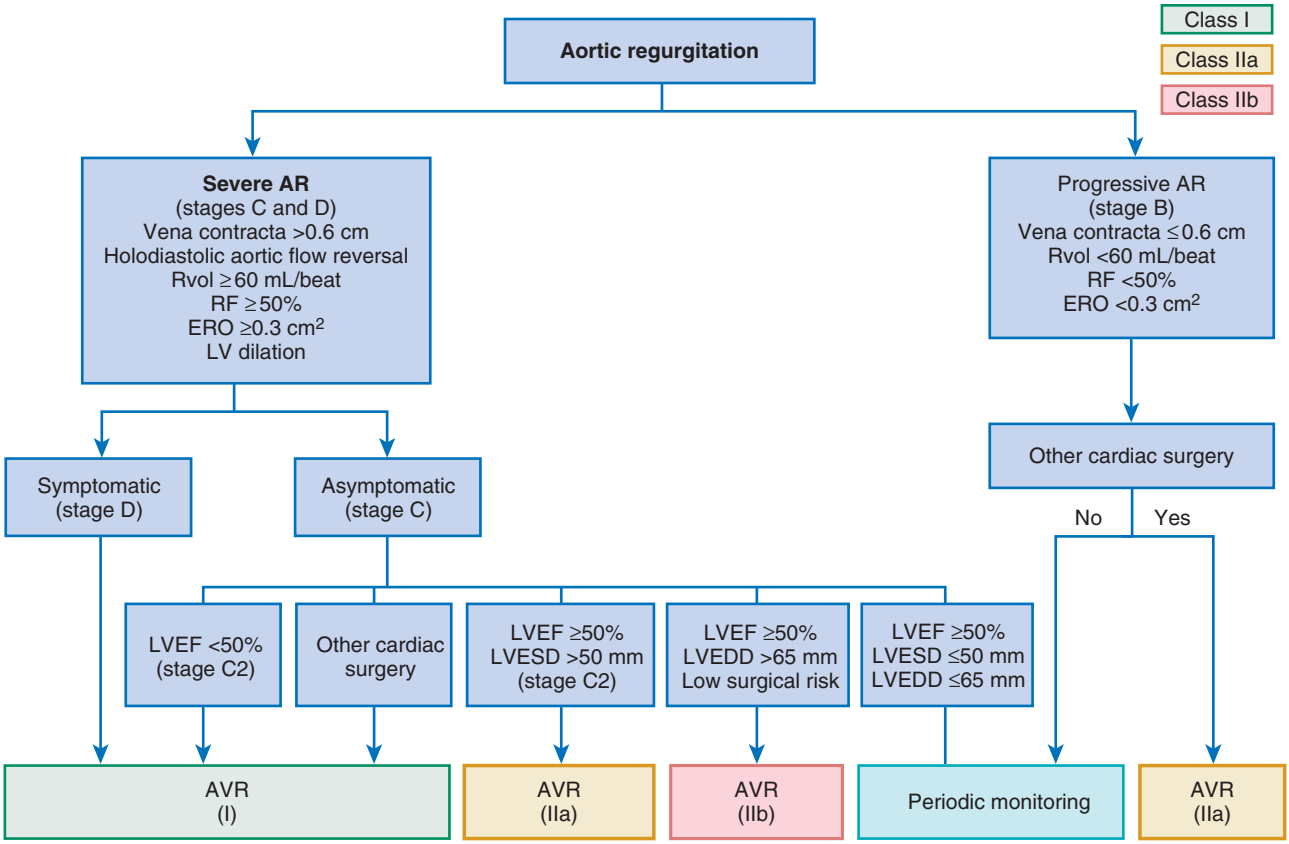

FIG. 4.45 AR, *Aortic regurgitation;* AVR, *aortic valve replacement;* ERO, *effective regurgitant orifice;* LVEDD, *LV end-diastolic diameter;* LVEF, *left ventricular (LV) ejection fraction;* LVESD, *LV end-systolic diameter;* RF, *regurgitant fraction;* Rvol, *regurgitant volume. From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63:e57.*

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ANSWER TO QUESTION 542

A (Braunwald, pp. 1527, 1560)

Turner syndrome, also termed *gonadal dysgenesis*, occurs in 1 of every 2500 females. Clinical features include primary amenorrhea, short stature, and immature genital and breast development. The condition arises from defects of the X chromosome, including the 45,XO karyotype in about 50% of cases. Cardiovascular abnormalities are common, occurring in 20% to 50% of patients.[1] The most frequent manifestation is coarctation of the aorta, found in 50% to 70% of patients with Turner syndrome who have cardiovascular defects. Coarctation can occur alone or in combination with other aortic abnormalities, including bicuspid aortic valve and a dilated aortic root.

Patients with Turner syndrome are also at increased risk for aortic dissection independent of other aortic abnormalities. Histopathologic studies have shown abnormalities of the elastic media similar to those in patients with diseases of collagen formation. Partial anomalous pulmonary venous drainage is also found frequently in patients with this condition.

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ANSWER TO QUESTION 543

B (Braunwald, pp. 1890–1893)

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that arises from mutations in the gene that encodes dystrophin.[1] Most patients with DMD develop dilated cardiomyopathy, and specific mutations in the dystrophin gene predict ventricular dysfunction.[2] Preclinical cardiac involvement is present in 25% of DMD patients by age 6. Up to 90% of patients with DMD who are 18 years of age or older will have developed echocardiographic evidence of dilated cardiomyopathy. There is a predilection for involvement of the inferobasal and lateral left ventricle, which likely accounts for the classic electrocardiographic abnormalities: tall R waves with increased R/S amplitude in V_1 and deep narrow Q waves in the left precordial leads (Fig. 4.46). There does not appear to be an association between the presence of dilated cardiomyopathy and electrocardiographic abnormalities.[3]

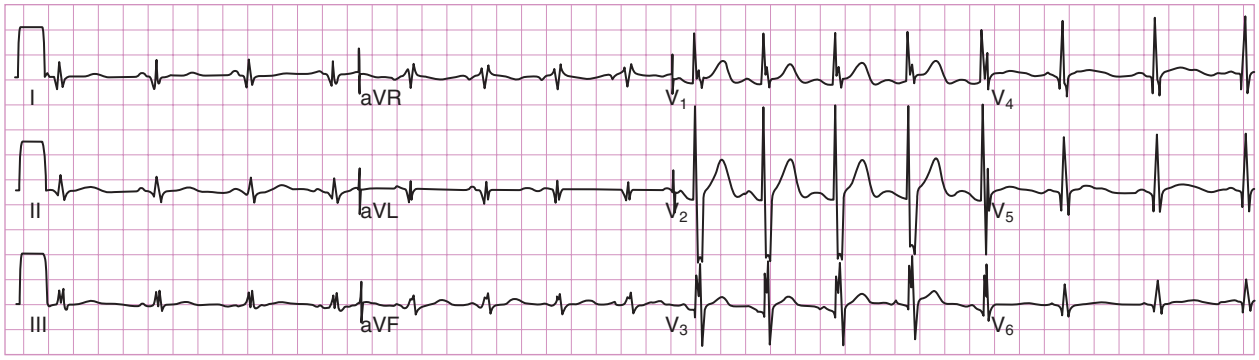

FIG. 4.46 *Dilated cardiomyopathy in a 19-year-old man with Duchenne muscular dystrophy. ECG shows a QRS complex that is typical of a Duchenne muscular dystrophy, with tall R waves in V1 and deep narrow Q waves in leads I and aVL.*

Persistent or labile sinus tachycardia is the most common arrhythmia in DMD. In advanced DMD cardiomyopathy, both atrial arrhythmias (including atrial fibrillation and atrial flutter) and ventricular arrhythmias occur, similar to other cardiomyopathies.[4]

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ANSWER TO QUESTION 544

C (Braunwald, pp. 1641–1643)

The anthracycline antineoplastic agents (doxorubicin, daunorubicin, and idarubicin) are widely recognized for their potential cardiac toxicity. Rarely, a single high dose of an anthracycline causes an acute cardiotoxic reaction manifested by atrial and ventricular arrhythmias and conduction disturbances. The more common complication is chronic cardiomyopathy after long-term exposure.[1] The major risk factor for this complication is the cumulative dose. Retrospective analyses have indicated that the incidence of heart failure is 1.7% at a cumulative dose of 300 mg/m^2, 4.7% at 400 mg/m^2, 15.7% at 500 mg/m^2, and 48% at 650 mg/m^2.[2] Thus, oncologists typically limit the total dose to no more than 400 to 450 mg/m^2. Age at the time of exposure is another important risk factor, because the very young and the very old are particularly susceptible.[1]

Additional risk factors for anthracycline cardiotoxicity include prior mediastinal radiation, the concurrent administration of other cardiotoxic agents (e.g., cyclophosphamide or trastuzumab), and a history of cardiac disease. For example, cardiotoxicity is more likely to arise when the baseline left ventricular ejection fraction is <50%.[3]

In randomized trials, the iron chelator dexrazoxane has demonstrated a protective effect against anthracycline cardiotoxicity. Because there has been concern that dexrazoxane may reduce anthracycline anti-neoplastic efficacy, its use is generally limited to patients who have received >300 mg/m^2 of doxorubicin or its equivalent.

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ANSWER TO QUESTION 545

C (Braunwald, p. 1645)

Vascular endothelial growth factor (VEGF) antagonists interfere with the vascular supply of tumors. The monoclonal antibody bevacizumab targets VEGF-A, and when combined with chemotherapy, improves survival in patients with metastatic colorectal cancer and metastatic nonsquamous non-small cell lung cancer. Several adverse reactions may occur with this agent. Hypertension (not hypotension) is a common side effect and can be severe in 8% to 20% of patients. Bevacizumab is also associated with heart failure, and although the risk of precipitating left ventricular dysfunction is low, it is more likely to develop in patients who have also received anthracyclines or irradiation. There is an approximately twofold increase in arterial (but not venous) thromboembolic events with bevacizumab.[1,2]

Hemorrhagic pericardial effusion is not a common side effect of bevacizumab therapy.

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ANSWER TO QUESTION 546

B (Braunwald, pp. 1527, 1538–1541)

Congenital heart lesions are the most common cause of morbidity and mortality in individuals with Down syndrome. The most frequent abnormalities are endocardial cushion defects, including partial or complete atrioventricular septal defects. The typical presentation includes a history of poor weight gain and frequent respiratory infections in the first year of life. Cardiac auscultation findings depend on the degree of atrial and ventricular septal communications and whether there is atrioventricular valve involvement. In patients with the more common partial endocardial cushion defect, the examination findings are similar to those of an ostium primum atrial septal defect. There is a prominent midsystolic flow murmur (because of increased flow across the pulmonic valve) followed by wide, fixed splitting of S_2. A middiastolic murmur is also common owing to increased flow through the tricuspid valve. When a cleft mitral valve is part of the partial endocardial cushion defect, a holosystolic murmur at the apex is present that frequently radiates toward the sternum, because the right atrium receives regurgitant flow in this condition. When interventricular communication exists as part of the defect, a holosystolic murmur is usually present at the mid- to lower left sternal border.

A midsystolic click followed by a late systolic murmur at the apex describes the auscultatory findings of mitral valve prolapse. Mitral valve prolapse occurs more frequently in patients with Down syndrome than in typical individuals, but it generally does not become evident until later in life. Choice A describes rheumatic mitral stenosis, choice D is the murmur of aortic regurgitation, and choice E represents aortic stenosis. These entities do not occur at an increased frequency in patients with Down syndrome.

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ANSWER TO QUESTION 547

E (Braunwald, pp. 1646–1647)

Radiation therapy is used to treat several types of malignancies. Historically, the heart and vasculature were subjected to high doses of radiation in patients with lymphoma and in those with cancers of the breast, lung, or esophagus. As a consequence, cardiovascular complications are leading causes of mortality among long-term cancer survivors treated with older radiation techniques. Modern approaches since the 1980s have limited and focused radiation delivery to minimize heart exposure, which has led to a decline in cardiovascular complications.

Radiation therapy may cause myocardial damage and fibrosis, endothelial dysfunction, and arterial intimal hyperplasia. The resulting clinical effects on the cardiovascular system usually do not manifest themselves until long after the irradiation has occurred, often arising 10 to 20 years (or longer) after exposure. Late cardiovascular complications include constrictive pericarditis, proximal coronary artery disease, conduction system disease, valvular disease (especially of the aortic valve), and heart failure due to myocardial fibrosis and restrictive cardiomyopathy. In addition, long-term cancer survivors who have received head and neck irradiation have a two- to threefold increased risk of stroke and transient ischemic attacks.

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ANSWER TO QUESTION 548

D (Braunwald, pp. 1580–1585)

Approximately 30% of patients with dilated cardiomyopathy (DCM) have an inherited form of the disease. Most familial examples of DCM fit an autosomal *dominant* pattern of inheritance, although some autosomal recessive and X-linked examples have been identified. Familial DCM appears to result primarily from mutations in genes that code for cytoskeletal, nuclear membrane, or contractile proteins; mitochondrial DNA mutations have also been reported.

Like other forms of DCM, cardiac histologic examination typically demonstrates extensive areas of interstitial and perivascular fibrosis, particularly in the left ventricular subendocardium. There are currently no specific immunologic, histochemical, or ultrastructural markers that can differentiate a genetic cause from other common forms of DCM.

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ANSWER TO QUESTION 549

C (Braunwald, p. 1676)

The clinical scenario is most consistent with effusive-constrictive pericarditis, which indicates the simultaneous presence of a hemodynamically significant pericardial effusion and visceral pericardial constriction. This pathophysiology leads to the hemodynamic hallmark of the condition, which is continued elevation of the right atrial pressure following aspiration of the pericardial fluid despite the return of intrapericardial pressure to normal. The causes of this entity are the same as those for chronic constrictive pericarditis. The most common include idiopathic or postviral pericarditis, neoplastic infiltration of the pericardium, mediastinal radiation therapy, and tuberculosis. The physical findings on initial presentation are most consistent with cardiac tamponade, including pulsus paradoxus and jugular venous distention with a prominent *x* descent.

The diagnosis of effusive-constrictive pericarditis is made at cardiac catheterization, with careful hemodynamic monitoring of intrapericardial and right atrial pressures before and after pericardiocentesis. Although intrapericardial pressure returns to baseline (i.e., ~0 mm Hg) after pericardiocentesis, intracardiac pressures do not normalize. Rather, hemodynamic findings convert to a form more consistent with constrictive pericarditis, with a prominent *y* descent in the right atrial pressure tracing and a "dip-and-plateau" pattern in the right ventricular pressure tracing. As might be expected from the pathophysiology, pericardiocentesis provides only partial and transient symptomatic relief; definitive therapy for this condition requires total pericardiectomy.

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ANSWERS TO QUESTIONS 550 TO 553

550–B, 551–A, 552–C, 553–D (Braunwald, pp. 1483–1487)

The classic peripheral manifestations of infective endocarditis (IE) are encountered only occasionally in the modern era. Janeway lesions are small, painless, nontender macular lesions on the thenar and hypothenar eminences of the palms and soles. They appear less often on the tips of the fingers or plantar surfaces of the toes. Lesions on the hands and feet blanch with pressure and with elevation of the extremities. In cases of acute valvular infections, the lesions tend to be purple and hemorrhagic.

In contrast, Osler nodes are small, raised, nodular, and tender lesions present most often in the pulp spaces of the terminal phalanges of the fingers. They may also be present on the backs of the toes, the soles, and the thenar and hypothenar eminences. The most characteristic feature of these lesions is their tenderness. Lesions may be fleeting in some cases, disappearing within a few hours after they have developed; however, they usually persist for 4 to 5 days. Although almost completely restricted to the subacute form of endocarditis, Osler nodes are occasionally present in acute valvular infection.

Subungual or splinter hemorrhages in IE are linear (or sometimes flame-shaped) dark red streaks in the proximal nailbed. Distal splinter hemorrhages at the nail tip are nondiagnostic and are frequently caused simply by trauma.

The ocular signs of endocarditis include retinal petechiae and Roth spots. The latter are located in the nerve layer of the retina and appear as hemorrhagic exudates. Histologically, they consist of aggregations of cytoid bodies (perivascular accumulation of lymphocytes with or without surrounding hemorrhage).

Bracht-Wächter bodies represent embolic events to the myocardium in IE that cause a localized inflammatory reaction consisting of collections of lymphocytes and mononuclear cells.

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ANSWERS TO QUESTIONS 554 TO 558

554–C, 555–B, 556–E, 557–A, 558–B (Braunwald, pp. 1593–1594, 1621)

The ECG is often nonspecific in cardiomyopathic disorders, but certain features are common in each of the listed conditions. In chronic Chagas disease, the most common electrocardiographic findings are right bundle branch block, left anterior fascicular block, atrial fibrillation, and premature ventricular complexes. Sarcoidosis has a propensity to infiltrate the atrioventricular (AV) node and bundle of His, producing heart block. Ventricular tachyarrhythmias are also common in this disorder. Apical hypertrophic cardiomyopathy is associated with deeply inverted T waves in the precordial leads. Amyloidosis results in low QRS voltage due to myocardial infiltration by amyloid proteins. Other electrocardiographic features in amyloidosis include rightward axis, first-degree AV block, and a pseudoinfarct pattern in II, III, aVF, and V1–V3. Lyme carditis results in variable degrees of AV block, often with transient diffuse ST-segment and T-wave abnormalities.

ANSWERS TO QUESTIONS 559 TO 562

559–D, 560–C, 561–C, 562–B (Braunwald, pp. 1455–1457)

Artificial cardiac valves consist of mechanical prostheses and bioprosthetic (tissue) valves (Fig. 4.47). Mechanical prostheses are divided into three structural groups: caged-ball, bileaflet, and tilting-disc valves. The Starr-Edwards caged-ball valve was one of the earliest prostheses used and has a long record of predictable performance. However, it has a bulky design, which makes it unsuitable for patients with a small left ventricular cavity or a narrow aortic annulus. Furthermore, the flow characteristics and action of the ball in the cage can generate low-level hemolysis. Tilting-disc valves have largely replaced the caged-ball prostheses, primarily because they are less bulky and have a lower profile. The Medtronic-Hall valve is a type of pivoting disc prosthesis. The bileaflet St. Jude valve has two semicircular discs that pivot between open and closed positions without need for supporting struts. It has a lower transvalvular gradient than either the caged-ball or tilting-disc types and has particularly favorable hemodynamic characteristics in the smaller sizes. Thrombogenicity of the bileaflet St. Jude prosthesis is the lowest of the mechanical valves listed, which makes it an excellent candidate for use in mitral valve replacement in adults.

All of the mechanical prosthetic valves are durable, but they are associated with a risk of thromboembolism, which is greatest in the first postoperative year. Without anticoagulation, the incidence of thromboembolism is three- to sixfold higher than in properly anticoagulated patients. Despite treatment with anticoagulants, the incidence of thromboembolic complications is still 1 to 2 nonfatal events per 100 patient-years. The incidence is significantly higher for prostheses in the mitral as compared to the aortic position. The thrombosis rate of mechanical prostheses in the tricuspid position is extremely high, and for this reason bioprostheses are preferred. Administration of warfarin also carries its own morbidity and mortality, estimated at 2.2 and 0.2 per 100 patient-years, respectively.

The high risk of thromboembolism inherent with the use of mechanical valves was the impetus for the development

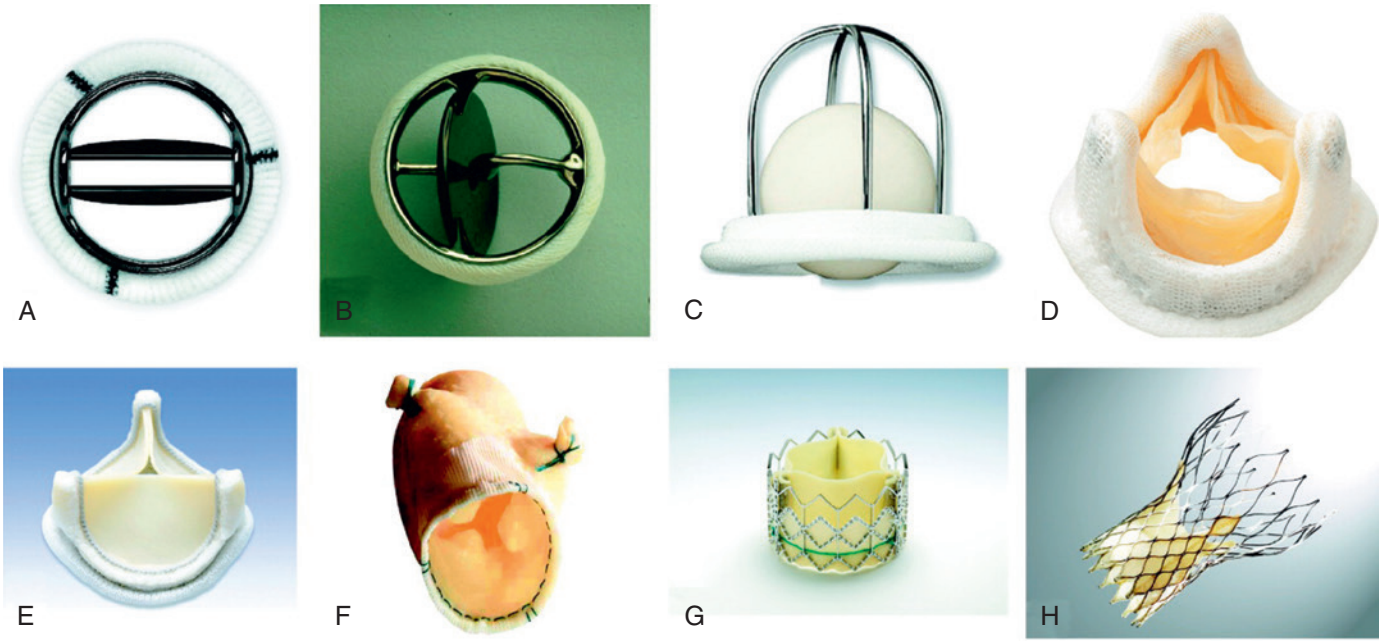

FIG. 4.47 *Types of prosthetic valves. (A) Bileaflet mechanical valve (St. Jude); (B) monoleaflet mechanical valve (Medtronic Hall); (C) caged ball valve (Starr-Edwards); (D) stented porcine bioprosthesis (Medtronic Mosaic); (E) stented pericardial bioprosthesis (Carpentier-Edwards Magna); (F) stentless porcine bioprosthesis (Medtronic Freestyle); (G) percutaneous bioprosthesis expanded over a balloon (Edwards Sapien); (H) self-expandable percutaneous bioprosthesis (CoreValve). From Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management.* Circulation. *2009;119:1034.*

of bioprosthetic prostheses. Among the tissue valves are the Hancock and Medtronic Mosaic porcine heterografts and Carpentier-Edwards Magna bovine pericardial valves. Anticoagulation for such valves is generally desirable for the first 3 months postoperatively (especially in the mitral position) while the sewing ring endothelializes. Thereafter, anticoagulants are generally not required. The main limitation of bioprosthetic valves is limited durability over time, and such deterioration occurs more frequently in the mitral than in the aortic position, and more rapidly in younger patients than in the elderly.

Selection of an artificial valve requires consideration of durability, hemodynamic properties, and thromboembolism risk. In general, tissue valves are preferred over mechanical prostheses for patients in whom anticoagulation is difficult or hazardous. Per the 2017 American Heart Association/American College of Cardiology valvular heart disease guideline update, an aortic or mitral mechanical prosthesis is reasonable for patients <50 years old without a contraindication to anticoagulation. A bioprosthesis is recommended for patients >70 years. For patients aged 50 to 70, either a mechanical valve or bioprosthesis is suitable, balancing the risk of bleeding (with a mechanical prosthesis on anticoagulation therapy) versus potential need for repeat intervention for valve deterioration (bioprosthetic valves).

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ANSWERS TO QUESTIONS 563 TO 566

563–C, 564–A, 565–A, 566–B (Braunwald, pp. 1674–1675; Table 83.7)

The clinical distinction between constrictive pericarditis (CP) and restrictive cardiomyopathy (RCM) may be difficult. Both RCM and CP may show electrocardiographic changes of left atrial abnormality, diffuse low voltage, and T wave flattening. The presence of atrioventricular block and conduction disturbances favors the diagnosis of RCM, especially infiltrative diseases such as amyloidosis.

In both conditions, right ventricular (RV) and left ventricular (LV) diastolic pressures are elevated, stroke volume and cardiac output are decreased, and LV end-diastolic volume is normal or decreased, with impaired diastolic filling. A diagnosis of RCM is more likely when marked RV systolic hypertension is present (pressure >60 mm Hg) and when LV and RV diastolic pressures at rest, or during exercise, differ by more than 5 mm Hg. Some patients with RCM may display hemodynamics that are indistinguishable from those seen with CP, including sustained and complete equilibration of RV and LV diastolic pressures, as well as the presence of a "dip-and-plateau" pattern in the ventricular waveform. However, simultaneous RV and LV systolic pressure measurements can aid in the differentiation of these conditions. Unlike normal individuals and those with RCM, patients with CP often demonstrate marked discordance of RV and LV systolic pressure during inspiration.[1,2] Specifically, with the onset of inspiration, LV systolic pressure declines with a reciprocal increase in RV systolic pressure (Fig. 4.48).

Echocardiography in restrictive cardiomyopathy may reveal abnormally thickened ventricular myocardium, often with a "sparkling" appearance if amyloidosis is present. Other useful differentiating features on echocardiography include

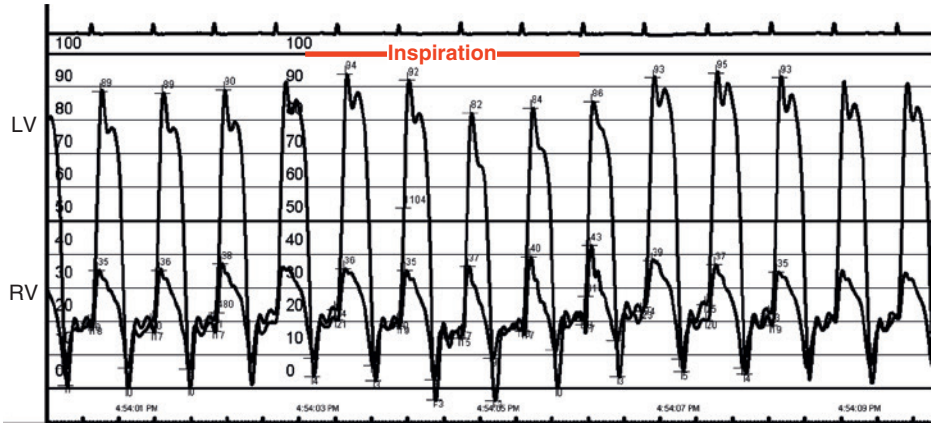

FIG. 4.48

a diastolic septal "bounce" and a normal or increased tissue Doppler medial mitral annular E′ velocity in constriction, in distinction to a blunted E′ value (<8 cm/s) in RCM.[3] Chest computed tomography and magnetic resonance imaging are also helpful in distinguishing these entities, demonstrating a thickened pericardium in >80% of patients with constrictive pericarditis, but not in patients with restrictive cardiomyopathy.[4]

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ANSWERS TO QUESTIONS 567 TO 571

567–A, 568–C, 569–C, 570–D, 571–B (Braunwald, pp. 1867–1869, 1871)

Cardiac myxomas and papillary fibroelastomas are two of the most common primary tumors of the heart. They are benign and do not undergo malignant transformation. Papillary fibroelastomas are the most common primary tumors found on cardiac valves. These lesions are usually small, frond-like structures that consist of a collagen core surrounded by elastic fibers and loose connective tissue. They are most often detected as an incidental finding on echocardiography or at postmortem examination. Papillary fibroelastomas are often clinically insignificant, but there is the potential for embolization or valve orifice obstruction if the tumor is large. Anticoagulation does not appear to protect against embolic risk. Surgical resection of these tumors is generally recommended, especially those in left-sided locations, to prevent thromboemboli. Resection can usually be performed with valve-sparing techniques. There is no known familial syndrome associated with papillary fibroelastomas.

Approximately 10% of myxomas are familial, transmitted in an autosomal dominant pattern. Sporadic myxomas most commonly attach to the interatrial septum; valvular origins for myxoma are rare. Myxomas have a high risk of distal embolization due to the friable nature of the tumor. Surgical resection is recommended to avoid new or recurrent complications, including progressive constitutional symptoms, embolism, and valvular obstruction.

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ANSWERS TO QUESTIONS 572 TO 575

572–C, 573–B, 574–D, 575–A (Braunwald, pp. 1835–1838, 1843–1845)

Unfractionated heparin (UFH) has been the historic acute therapy for pulmonary embolism. UFH is a porcine- or bovine-derived glycosaminoglycan that acts by binding to antithrombin with subsequent inhibition of the procoagulant factors thrombin (IIa), Xa, IXa, XIa, and XIIa. Heparin prevents additional thrombus formation and promotes endogenous fibrinolysis; however, it does not directly dissolve formed clots. For patients at average bleeding risk, a weight-based intravenous bolus of 80 units/kg is begun, followed by 18 units/kg/h by continuous infusion. The activated partial thromboplastin time should be maintained between 1.5 and 2.5 times the control value (typical therapeutic range is 60 to 80 seconds) for effective treatment. The major risk of heparin use is hemorrhage. Thrombocytopenia, osteopenia, and elevated liver enzymes can all complicate heparin therapy. Protamine may be used to reverse the anticoagulant effects of unfractionated heparin.

Low-molecular-weight heparin (LMWH) formulations are now the preferred parenteral therapy for acute management of PE in hemodynamically stable patients. LMWH has greater bioavailability than unfractionated heparin, has a more predictable dose response, and does not require serial measurements of the aPTT. Compared with UFH, LMWH results in reduced mortality, less bleeding, and fewer recurrent thromboemboli. If needed, the effectiveness of LMWH can be monitored by measuring the plasma heparin (anti-factor Xa) level. Both unfractionated heparin and LMWHs can inhibit the secretion of aldosterone, particularly with prolonged administration. This effect can result in hyperkalemia, especially in patients

with renal failure or diabetes. Alternatives to LMWH include subcutaneous fondaparinux, a factor Xa inhibitor with similar benefits and risks, and the oral factor Xa inhibitors rivaroxaban and apixaban. Dabigatan (an oral direct thrombin inhibitor) and edoxaban (another oral factor Xa inhibitor) are approved to treat acute venous thromboembolism following initial treatment with a parenteral anticoagulant.

Fibrinolytic therapy (alteplase) physically dissolves anatomically obstructing pulmonary arterial thrombus and improves pulmonary capillary blood flow, but is associated with a substantial risk of bleeding complications. High-risk subgroups who may benefit from fibrinolytic therapy include patients with massive pulmonary embolism who have moderate-to-severe right ventricular dysfunction and elevation of cardiac biomarkers. Unlike in acute ST-segment elevation myocardial infarction, fibrinolytic therapy for PE may be efficacious when used up to 2 weeks after the onset of symptoms.

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ANSWERS TO QUESTIONS 576 TO 580

576–C, 577–A, 578–D, 579–A, 580–B (Braunwald, pp. 1591–1594, 1597–1598)

Hemochromatosis and amyloidosis are both infiltrative diseases. Hemochromatosis results in deposition of excessive iron within the myocardium and other organs, including the liver, pancreas, and gonads. It most commonly arises on a hereditary basis (mutations in *HFE* gene, autosomal recessive transmission), from other causes of increased iron absorption (e.g., states of ineffective erythropoiesis), or as a result of multiple blood transfusions.

Cardiac amyloidosis refers to the deposition of misfolded products of various protein precursors in the heart. Light-chain (AL) amyloidosis results from production of a protein derived from immunoglobulin light chains by plasma cells, frequently in the setting of plasma cell dyscrasias such as multiple myeloma. A familial form of amyloidosis is inherited in an autosomal dominant fashion in which a mutant version of the hepatically expressed protein transthyretin represents the amyloid precursor protein. The previously termed "senile" form of amyloidosis is due to deposition of amyloid protein derived from normal (wild-type) transthyretin in older individuals. Secondary (AA) amyloidosis may arise in systemic inflammatory conditions, resulting in organ amyloid deposits derived from the inflammatory protein serum amyloid A, but this condition rarely involves the heart.

Because of the infiltrative nature of these conditions, each initially leads to a "stiffened" myocardium and usually presents as a restrictive cardiomyopathy. In later stages, however, dilatation of the ventricles may ensue. Although arrhythmias are common in both conditions, rhythm disorders are not usually prominent initial symptoms. The ECG in hemochromatosis usually shows diffuse ST-segment and T wave abnormalities as well as supraventricular arrhythmias. Abnormal rhythms, especially atrial fibrillation, are also common in amyloidosis, in addition to electrocardiographic findings of low-voltage QRS complexes and pseudoinfarction patterns.

If diagnosed early, the cardiomyopathy of hemochromatosis may be reversed with phlebotomy and chelating agents. Both computed tomography and cardiovascular magnetic resonance imaging have been used to detect early subclinical myocardial involvement at a time when therapy is most effective.[1] Cardiac amyloidosis generally carries a grim prognosis, but progress has been made at improving longer-term survival. For example, in AL amyloidosis, the proteasome inhibitor bortezomib has been successful at controlling the underlying plasma cell dyscrasia, with normalization of serum light chains and improvement in heart failure symptoms.[2] Cardiac transplantation has been performed for AL amyloidosis, however, outcomes tend to be poor due to progression of amyloidosis in other organs or recurrence in the transplanted heart. Some patients with mutant transthyretin amyloidosis may benefit from liver or combined liver-heart transplantation.

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ANSWERS TO QUESTIONS 581 TO 585

581–A, 582–B, 583–B, 584–A, 585–B (Braunwald, pp. 1445–1446, 1450)

Tricuspid stenosis (TS) is most commonly rheumatic in origin. It almost never occurs as an isolated lesion, but rather accompanies rheumatic mitral valve disease. Typical findings include fatigue, right-sided heart failure with hepatomegaly, abdominal swelling due to ascites, and anasarca. Auscultation usually reveals signs of mitral stenosis (MS), and these often overshadow those of TS. The diastolic murmur of TS is heard best along the lower left sternal border at the fourth intercostal space and is usually softer, higher pitched, and shorter in duration than the murmur of MS. The management of severe TS is surgical and requires valvulotomy or valve replacement when the orifice is less than ~2 cm^2. In general, tissue valves are used preferentially in the tricuspid position because of the high risk of thrombosis with mechanical prostheses.

The most common form of pulmonic stenosis (PS) is congenital. A rarer form results from carcinoid plaques. The latter cause constriction of the pulmonic valve ring, retraction and fusion of the cusps, and PS with or without pulmonic regurgitation. Carcinoid heart disease can also involve the tricuspid valve, but most commonly leads to tricuspid regurgitation.

Most adults with mild to moderate PS are asymptomatic, and it is only the more severe forms that result in dyspnea and fatigue. Patients with advanced PS may develop secondary tricuspid regurgitation and right ventricular failure.

In the majority of patients, valvular PS is a stable or slowly progressive disease. Physical examination is notable for a systolic thrill along the left upper sternal border, a prominent systolic ejection murmur heard at the location of the thrill, and often an associated ejection click. In contrast to the inspiratory increase in most right-sided cardiac sounds, the

intensity of the pulmonic click in PS decreases with inspiration. Echocardiography can define the lesion, and Doppler imaging allows accurate estimation of the gradient across the valve. In adults, percutaneous balloon valvuloplasty for advanced valvular PS is safe and effective and is the treatment of choice.

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ANSWERS TO QUESTIONS 586 TO 589

586–C, 587–D, 588–B, 589–B (Braunwald, pp. 1112–1114; Fig. 58.4)

Calcium channel blockers and prostacyclin are two forms of vasodilator therapy used in the chronic management of patients with idiopathic (group 1) pulmonary arterial hypertension (PAH). They are prescribed to carefully selected patients with hemodynamic guidance. Up to 20% of patients with idiopathic PAH show a vasoreactive response and demonstrate a dramatic drop in pulmonary artery pressure and resistance with high-dose calcium channel blockers.[1] Such patients have improved quality of life and survival compared with control subjects and with those who do not demonstrate a dramatic hemodynamic response. Potential adverse effects of calcium channel blockers in patients with PAH include a right ventricular negative inotropic effect and reflex sympathetic stimulation with tachycardia.

Chronic intravenous epoprostenol (prostacyclin) administration has been shown to improve symptoms, quality of life, and survival in patients with idiopathic PAH.[2] It also demonstrates antithrombotic effects that may be of benefit in the management of the thrombo-occlusive component of PAH and may help to restore the integrity of the pulmonary vascular endothelium. Epoprostenol therapy is, however, cumbersome because it requires a surgically implanted central venous catheter and an infusion pump system. The prostacyclin analogs iloprost (by inhalation) and treprostinil (subcutaneously or by inhalation) improve symptoms and are more easily administered, but evidence of survival benefit is lacking.[3]

Additional agents are available that improve the quality of life in patients with group 1 PAH. The phosphodiesterase type 5 inhibitors sildenafil, tadalafil, and vardenafil reduce pulmonary arterial pressure, improve exertional capacity, and are well tolerated. Additionally, a group of endothelin receptor blockers (bosentan, ambrisentan, macitentan) improve hemodynamics, symptoms, and stamina in this condition.[4] Side effects of this group include peripheral edema and hepatic toxicity. More recently, riociguat, a soluble guanylate cyclase stimulator, has been shown to improve exercise capacity and functional class in patients with PAH.[5]

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ANSWERS TO QUESTIONS 590 TO 593

590–C, 591–B, 592–A, 593–B (Braunwald, pp. 1674–1675; Table 83.7; see also Answers to Questions 563 to 566)

The clinical and hemodynamic features of restrictive heart disease such as those caused by cardiac amyloidosis may be very similar to those of chronic constrictive pericarditis. Endomyocardial biopsy, computed tomography, and magnetic resonance imaging may be useful in differentiating the two diseases. The typical hemodynamic feature present in both conditions is the deep and rapid early decline in ventricular pressure at the onset of diastole, followed by a rapid rise to a plateau in early diastole. Patients with restrictive cardiomyopathy may have left ventricular filling pressures that exceed RV filling pressures by >5 mm Hg (whereas there is <5 mm Hg difference between them in pericardial constriction), and this difference can be accentuated by exercise. Furthermore, the pulmonary artery systolic pressure may be >60 mm Hg in patients with restrictive cardiomyopathy, but is usually lower in constrictive pericarditis. As a result, the plateau of the RV diastolic pressure is usually greater than one-third of the peak RV systolic pressure in patients with constrictive pericarditis, while it is more commonly less than one-third in patients with restrictive cardiomyopathy.

In the atrial tracings, the dip-and-plateau sign manifests as a prominent *y* descent followed by a rapid rise in pressure. The *x* descent may also be prominent, and the combination results in the characteristic M-shaped waveform in the atrial pressure tracing.

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ANSWERS TO QUESTIONS 594 TO 597

594–D, 595–B, 596–C, 597–A (Braunwald, pp. 1393–1394)

The natural history of aortic stenosis (AS) has been described in a cohort of patients who did not undergo aortic valve surgery. Patients whose only symptom of AS was angina had an average survival of 3 to 5 years. Those with syncope had a shorter average survival of 2 to 3 years. Those with signs and symptoms of congestive heart failure had the worst prognosis—an average survival of only 1.5 to 2 years. Because of such reduced longevity, patients with AS and any of these symptoms should be referred for surgical correction,

especially if symptoms of heart failure are present. Palpitations are not a marker for adverse survival in patients with AS.

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ANSWERS TO QUESTIONS 598 TO 601

598–A, 599–B, 600–C, 601–A (Braunwald, p. 1507; Table 73G-1)

The American Heart Association (AHA) has published a set of consensus recommendations for antibiotic prophylaxis for the prevention of infective endocarditis (IE).[1] This statement simplified older guidelines and focused on prophylaxis for patients at the highest risk of complications from IE. High-risk patients are considered to be those with (1) prosthetic heart valves, (2) prior endocarditis, (3) specific types of congenital heart disease (unrepaired cyanotic lesions, repaired congenital lesions with residual defects, or during the first 6 months after repair with prosthetic material or device), and (4) cardiac transplant recipients with valvulopathy. Routine gastrointestinal or genitourinary tract procedures are not indications for antibiotic prophylaxis unless there is an active gastrointestinal or genitourinary tract infection in a patient with one of these high-risk cardiac conditions. These recommendations were incorporated in the 2014 American College of Cardiology/AHA valvular heart disease guidelines.[2]

The first patient in this question is at high risk owing to the prosthetic mitral valve, but prophylaxis is not recommended for routine gastrointestinal procedures such as colonoscopy. The second and third patients are at high risk owing to the prosthetic valves, and prophylaxis is recommended. The third patient is penicillin-allergic, so an alternative regimen such as clindamycin should be administered instead. The fourth patient is not at high risk, and prophylaxis for gastrointestinal procedures is not recommended unless there is active infection.

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ANSWERS TO QUESTIONS 602 TO 606

602–B, 603–B, 604–C, 605–A, 606–D (Braunwald, pp. 1538–1541, 1553–1555)

Complete atrioventricular canal defects (also known as endocardial cushion defects) comprise a group of abnormalities in which the common features are (1) absence of the membranous and muscular atrioventricular septum (causing the atrioventricular [AV] valves to appear at the same level on echocardiography), (2) inlet/outlet disproportion resulting in an elongated left ventricular outflow tract (producing a "gooseneck" deformity on angiography), (3) lateral rotation of the posteromedial papillary muscle, and (4) abnormal configuration of the AV valves (e.g., the left AV valve is trileaflet with a "cleft" appearance). Infants usually present in the first year of life with a history of poor weight gain and frequent respiratory infections, and heart failure is common. On physical examination, several murmurs may be present, including a holosystolic murmur along the lower left sternal border due to the VSD, a holosystolic murmur at the apex due to mitral regurgitation, and a right ventricular (RV) outflow tract systolic murmur. Because the direction of intracardiac shunting is left to right, cyanosis is not typical. Typical electrocardiographic findings include left-axis deviation due to left anterior fascicular block and incomplete right bundle branch block. Echocardiography is usually diagnostic for this condition.

In complete transposition (d-transposition) of the great arteries (d-TGA), the aorta arises from the morphologic right ventricle and the pulmonary artery arises from the morphologic left ventricle. This anatomic arrangement results in two separate and parallel circulations. Some communication between the pulmonary and systemic circulations must exist after birth to sustain life. Almost all patients have an interatrial communication, two-thirds have a patent ductus arteriosus (PDA), and one-third have an associated VSD. The typical clinical manifestations are dyspnea and cyanosis, progressive hypoxemia, and congestive heart failure. Cardiac murmurs are absent or insignificant in 30% to 50% of patients with d-TGA and an intact ventricular septum. In infants with d-TGA and a large PDA, fewer than half have the typical continuous murmur of the aortopulmonary connection. Electrocardiographic findings include right-axis deviation, right atrial enlargement, and RV hypertrophy. Echocardiography is usually diagnostic for identifying the abnormal great-vessel relationship and accompanying abnormalities. An arterial switch operation is the treatment of choice.

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ANSWERS TO QUESTIONS 607 TO 611

607–D, 608–C, 609–C, 610–A, 611–B (Braunwald, pp. 1521, 1527)

Noonan syndrome is a relatively common (1 per 1000) genetic disorder with autosomal dominant inheritance. About one-half of patients have mutations in the *PTPN11* gene on chromosome 12. This syndrome is characterized phenotypically by short stature, a unique facial appearance, mild mental retardation, webbing of the neck, cryptorchidism, and renal anomalies. Approximately half of all patients with Noonan syndrome have congenital heart disease, the most common lesion of which is valvular pulmonic stenosis. The ECG commonly displays left anterior fascicular block. Approximately 20% of patients with Noonan syndrome

have an accompanying atrial septal defect or hypertrophic cardiomyopathy.

The *LEOPARD* syndrome is a rare, single-gene complex of congenital malformations. The acronym LEOPARD symbolizes the main components of the syndrome: L, lentigines; E, electrocardiographic conduction defects; O, ocular hypertelorism; P, pulmonic valve stenosis; A, abnormalities of the genitals; R, retardation of growth; and D, deafness. Eighty percent of patients display lentigines, whereas deafness and abnormalities of the genitals occur in about 20%. The most common structural cardiac feature is pulmonic stenosis, which may exist as an isolated anomaly or in combination with aortic stenosis. The most common electrocardiographic conduction defects are PR-segment prolongation, QRS complex widening, left anterior fascicular block, and complete heart block. The most striking physical feature of the syndrome is the presence of small, dark lentigines, which are concentrated over the neck and upper extremities. LEOPARD syndrome is transmitted in an autosomal dominant fashion, with cardiovascular abnormalities in at least 95% of affected patients.

Kartagener syndrome is an autosomal recessive disorder, the primary defect of which has been elucidated by electron microscopic investigation of cilia from affected individuals' bronchial mucosa or sperm. Dynein arms, which are protein structures that normally form cross-bridges between adjacent microtubules in cilia and sperm tails, are abnormal in this disorder. Several mutations capable of producing the syndrome are recognized, and in each case, the mutant gene disrupts the synthesis either of the dynein protein itself or of a protein that binds dynein to the microtubules. Clinically, the syndrome consists of the triad of sinusitis, bronchiectasis, and situs inversus with dextrocardia. Cases of Kartagener syndrome usually come to attention in infancy due to recurrent upper respiratory infections or pneumonia, and development of classic sinusitis and chronic bronchiectasis occurs as childhood progresses. The majority of individuals with Kartagener syndrome have dextrocardia as the only cardiac manifestation, which leads to an abnormal 12-lead ECG, but no other clinical consequences. On rare occasions, associated cardiac anomalies may be present, including transposition of the great vessels.

Holt-Oram syndrome is a rare autosomal dominant disorder. The classic clinical manifestation is the simultaneous occurrence of congenital heart disease and an upper limb deformity. The most common cardiovascular abnormality is an atrial septal defect of the secundum type, with ventricular septal defect being the next most common. Electrocardiographic abnormalities are frequently present as well and may include first-degree atrioventricular block, right bundle branch block, and bradycardia. Deformities of the forearm and hand are the most apparent features of Holt-Oram syndrome (e.g., hypoplasia or triphalangeal abnormalities of the thumbs). The most specific upper extremity finding, an abnormal scaphoid bone or accessory carpal bones or both, may be detected by wrist radiography. One form of Holt-Oram syndrome has been linked to mutations in the *TBX5* gene located on chromosome 12. *TBX5* is a member of the T-box family of transcription factors that critically regulate morphogenesis in the developing embryo.

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ANSWERS TO QUESTIONS 612 TO 615

612–C, 613–A, 614–B, 615–D (Braunwald, pp. 1487, 1593, 1595–1596, 1856)

Extracardiac manifestations of systemic disorders that also have major cardiac involvement may provide important clues to the underlying diagnosis. One example is infective endocarditis, in which specific lesions may appear in the skin and the eyes. In the skin, these include petechiae, Osler nodes, Janeway lesions, Roth spots, subungual ("splinter") hemorrhages, and embolic infarcts of the digits, as may occur with *Staphylococcus aureus* infection of the left-sided valves; the last are illustrated in part *A* in the figure. Osler nodes are small, raised, nodular, and painful red to purple lesions that appear in the pulp spaces of the terminal phalanges of the fingers. Janeway lesions are small, irregular, flat, and nontender macules occurring most often on the thenar and hypothenar eminences of the hands and soles. Roth spots on the retina have the appearance on funduscopic examination of a "cotton wool" exudate and consist of aggregations of cytoid bodies. All of these peripheral stigmata of infective endocarditis have become uncommon in the modern era.[1]

Amyloidosis is a systemic illness in which unique protein-derived fibrils are deposited in a variety of organs. Cardiac involvement is common in primary (AL) amyloidosis (often a consequence of multiple myeloma) and in familial amyloidosis (an autosomal dominant condition that typically results from a mutated form of the protein transthyretin).[2] Cardiac sequelae include restrictive cardiomyopathy with diastolic dysfunction, conduction abnormalities, systolic dysfunction, and orthostatic hypotension. Dermatologic findings include small papules on the face, scalp, neck fold, or intertriginous folds. In addition, small, smooth, and yellowish papules may be seen in the area around the eyes and be mistaken for xanthomas. Amyloid infiltration can result in macroglossia, as shown in part *B*.

Fabry disease is a sex-linked disorder that is due to a deficiency of the enzyme alpha-galactosidase A. The disorder is characterized by the accumulation of glycosphingolipid within the myocardium, skin, and kidneys. Systemic hypertension, mitral valve prolapse, renovascular hypotension, and congestive heart failure are all common clinical manifestations. Fabry disease may also cause restrictive cardiomyopathy. Ocular signs in the disorder are common. Approximately 90% of patients have corneal opacities, whereas two-thirds of patients have conjunctival vessel tortuosity as illustrated in part *C* of the figure.[3] Hypertensive cardiovascular disease, renal failure, and cerebrovascular disease are the major causes of death in this disorder. Purified human alpha-galactosidase A is available as an intravenous therapeutic option, which reduces tissue storage of the offending glycosphingolipid.

Progressive systemic sclerosis, or scleroderma, presents as tightening and thickening of the skin, with Raynaud phenomenon occurring in almost all patients.[4] Cardiac involvement is common and is a frequent cause of death, second only to involvement of the kidneys as a factor shortening survival. Scleroderma heart disease is primarily a myocardial process, leading to vascular insufficiency and fibrosis in the small vessels of the heart, which produces cardiomyopathy with congestive heart failure, conduction system abnormalities, and/or ventricular dysrhythmias. Pericardial involvement with fibrinous pericarditis is common,

as is the development of pulmonary hypertension due to intrinsic pulmonary vascular disease or interstitial fibrosis. The CREST variant of this syndrome describes patients with calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Recurrent painful ulcerations of the fingertips, which may become infected, are a common problem in this disorder and are illustrated in part *D*.

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ANSWERS TO QUESTIONS 616 TO 619

616–A, 617–B, 618–B, 619–C (Braunwald, p. 1527; see also Answers to Questions 607 to 611)

The Turner and Noonan syndromes share several superficial features, including short stature, webbing of the neck, skeletal anomalies, renal abnormalities, and congenital heart disease. Because of these clinical similarities, Noonan syndrome is frequently referred to as male Turner syndrome or as Turner phenotype with normal chromosomes. However, there are several striking genetic and clinical differences that can readily distinguish these two disorders. Turner syndrome occurs exclusively in females. In about 50% of patients, the karyotype is 45,XO. The remaining patients are mosaics with various other X chromosome abnormalities. Most fetuses with the 45,XO form of Turner syndrome die in utero. Of those who survive, cardiovascular abnormalities occur in 35% to 50%. Coarctation of the aorta is the most common cardiovascular lesion. Other abnormalities include bicuspid aortic valve, hypertrophic cardiomyopathy, atrial septal defect, mitral valve prolapse, and dextrocardia. Stenosis of the pulmonic valve is rarely seen in Turner syndrome, in contrast to Noonan syndrome.

Noonan syndrome appears physically similar to Turner syndrome; however, as indicated in Answers to Questions 607 to 611, affected patients have a unique facial appearance, with hypertelorism, strabismus, small chin, and low-set ears. It is inherited as an autosomal dominant trait and, in contrast to Turner syndrome, both males and females are susceptible to this condition; the karyotype in both sexes is normal. In many families, the genetic abnormality maps to chromosome 12q24; about half have a mutation in the *PTPN11* gene in that region. Approximately 50% of patients with Noonan syndrome have congenital heart disease; the most common lesion is valvular pulmonary stenosis, occurring in about 60% of patients. Characteristically, the annulus of the pulmonary valve is normal, but the leaflets are thickened and immobile. Other findings include atrial septal defect and hypertrophic cardiomyopathy.

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ANSWERS TO QUESTIONS 620 TO 624

620–C, 621–A, 622–B, 623–A, 624–A (Braunwald, pp. 1544–1548)

The two-dimensional echocardiogram in part *A* of the figure displays an apical, four-chamber view of tricuspid atresia, demonstrating a dense band in the tricuspid annulus and an enlarged left ventricle. This anomaly is marked by the absence of the tricuspid orifice with an atrial septal defect, usually with hypoplasia of the right ventricle, and communication between the ventricles, typically via a ventricular septal defect. In 60% to 70% of patients with this condition, the great arteries have normal relationships; the remainder have d-transposition of these vessels. In addition, pulmonic stenosis or atresia may be present. Clinically, the marked diminution in pulmonary blood flow usually leads to severe cyanosis. In those infants in whom transposition coexists with a ventricular septal defect and an unobstructed pulmonary outflow tract, torrential pulmonary blood flow will occur, leading to heart failure rather than cyanosis as the predominant problem. The majority of infants with tricuspid atresia have pulmonary hypoperfusion and the clinical picture of cyanosis, with electrocardiographic findings of left ventricular hypertrophy, left-axis deviation, and right atrial enlargement.

Echocardiographic examination in this disorder is usually diagnostic. At cardiac catheterization, the right ventricle cannot be entered from the right atrium. When the great arteries are normally related, pulmonary blood flow is maintained via a ventricular septal defect or patent ductus arteriosus. However, in complete transposition, the pulmonary artery blood flow is derived directly from the left ventricle. Functional correction of tricuspid atresia has been accomplished by the Fontan procedure, which consists of construction of a prosthetic conduit between the right atrium and pulmonary artery and closure of the intra-atrial communication.

The two-dimensional echocardiogram in part *B* is a parasternal long-axis view of tetralogy of Fallot, which demonstrates (1) the aorta overriding the interventricular septum and (2) a ventricular septal defect. The two other components that comprise this malformation are (1) right ventricular (RV) outflow obstruction and (2) RV hypertrophy. The clinical presentation in tetralogy of Fallot is determined principally by the degree of obstruction to pulmonary blood flow. Infants with tetralogy of Fallot become symptomatic and cyanotic before the age of 1 year. There is a direct correlation between the time of onset of symptoms and the severity of pulmonary outflow tract obstruction. Intense cyanotic spells related to sudden increases in venoarterial shunting and simultaneous decreases in pulmonary blood flow occur between 2 and 9 months of age and may be life threatening.

Physical examination of infants with tetralogy of Fallot usually reveals varying degrees of underdevelopment and cyanosis, commonly with clubbing of the terminal digits within the first year of life. An RV impulse and systolic thrill

may often be appreciated along the left sternal border. A systolic flow murmur across the pulmonic valve is often present, and the intensity and duration of this murmur vary inversely with the severity of the pulmonic outflow tract obstruction. The ECG usually shows RV hypertrophy. On chest radiography, a normal-sized boot-shaped heart with prominence of the right ventricle and a concavity in the region of the underdeveloped RV outflow tract is typical. Echocardiographic findings are diagnostic. Cardiac catheterization is used to delineate the course of the pulmonary arteries and collateral channels when patients have pulmonary atresia as part of the syndrome and to document the coronary artery anatomy before surgical repair. Coronary variations in this disorder include the abnormal origin of the anterior descending artery from the right coronary artery or a single right or left coronary artery giving rise to the remaining coronary vessels.

The management of tetralogy of Fallot consists of total correction of the anomaly, with early definitive repair being advocated in most centers, often during the first 6 months. Pulmonary arterial size is the single most important determinant in evaluating a patient for primary repair. For those in whom marked hypoplasia of the pulmonary arteries is present, balloon dilatation may be used in a palliative manner to allow the infant to survive until an older age, at which time total correction may be carried out at lower risk.

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ANSWERS TO QUESTIONS 625 TO 629

625–A, 626–A, 627–B, 628–B, 629–D (Braunwald, pp. 1641–1643, 1646–1647)

Radiation therapy and chemotherapeutic agents both have potentially serious cardiac adverse effects. Cardiac exposure may occur as a result of therapeutic irradiation of lung, breast, or esophageal cancers or mediastinal radiation for lymphomas. All cardiac structures are susceptible to radiation damage, especially the pericardium, but also the myocardium, coronary arteries, conduction system, and valves. The effects of radiation on the pericardium may be acute (e.g., hemorrhagic effusions) or delayed for several years (fibrosis with constrictive pericarditis). Radiation therapy is also a cause of premature coronary artery disease (CAD). Retrospective studies have demonstrated that children treated with radiation therapy for Hodgkin disease have a significantly increased risk of developing symptomatic CAD at an early age. Radiation-induced myocardial fibrosis is common and may lead to restrictive cardiomyopathy. Radiation effects on the conduction system may cause sinus node disease and atrioventricular block. Radiation exposure of the aortic valve and papillary muscles has been implicated as a cause of regurgitation of the aortic and mitral valves.

As described in the Answer to Question 544, anthracycline chemotherapeutic agents can have an acute direct toxic effect on the myocardium, resulting in ventricular and supraventricular dysrhythmias as well as conduction system blocks. More commonly, cumulative exposure to anthracyclines results in a chronic cardiomyopathy, especially at a total cumulative dose >400 mg/m^2. Rare cases of acute myocarditis-pericarditis within 2 weeks of anthracycline therapy have been described.

Aortic dissection is not associated with these antineoplastic therapies.

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SECTION V QUESTIONS

(CHAPTERS 88 TO 99)

Cardiovascular Disease in Special Populations; Cardiovascular Disease and Disorders of Other Organs

David D. Berg and Leonard S. Lilly

Directions:

For each question below, select the ONE BEST response.

QUESTION 630

A 24-year-old man who is training for the Olympic decathlon team experiences a presyncopal event and is referred for evaluation. He has been training aggressively for the past 2 years and, aside from occasional single palpitations, has not noticed any prior lightheadedness, other cardiac symptoms, or physical limitations. He has no history of hypertension and his family history is free of premature coronary disease or sudden cardiac death (SCD). On physical examination his blood pressure and heart rate are normal. A grade II/VI rough crescendo-decrescendo systolic murmur is auscultated along the left sternal border, which becomes louder when the patient stands. The patient is anxious to return to his training regimen. Which of the following statements is TRUE?

A. Voltage criteria for left ventricular hypertrophy on this patient's electrocardiogram is sufficient to establish the diagnosis of hypertrophic cardiomyopathy (HCM) and should prohibit him from resuming competitive athletics
B. An echocardiographic end-diastolic septal wall thickness of 14 mm would be diagnostic of HCM
C. Persistent left ventricular hypertrophy by echocardiography 6 months after cessation of exercise is consistent with genetic HCM
D. A maximum oxygen uptake of 50 mL/kg/min on cardiopulmonary exercise testing is more consistent with HCM than "Athlete's Heart"
E. Anomalous origin of the left coronary artery is a more common cause of SCD in young athletes than HCM

QUESTION 631

A 66-year-old man with chronic kidney disease (CKD) is referred for office evaluation after a recent admission for an acute coronary syndrome (ACS). Which of the following statements is correct concerning CKD and cardiovascular disease?

A. Patients with CKD are at increased risk of bleeding but decreased risk of thrombotic events when compared with normal individuals
B. The outcomes of patients with CKD who present with ACSs are similar to those of patients with normal renal function
C. Patients with CKD who present to the hospital with chest pain comprise a relatively low-risk group of ACSs, with a cardiac event rate of <5% at 30 days
D. Renal dysfunction is the most significant independent predictor of mortality of patients in coronary care units
E. Uremia is associated with enhanced platelet aggregation

QUESTION 632

A 20-year-old female student presents to the emergency department with recent malaise, myalgias, fevers, sweats, and claudication of the right lower extremity and left arm. On physical examination the blood pressure is 160/90 mm Hg in the right arm and 120/85 mm Hg in the left arm. The left radial and right femoral pulses are diminished and a left-sided subclavian bruit is auscultated. The erythrocyte sedimentation rate is markedly elevated. Which of the following statements about this condition is TRUE?

A. Arterial biopsy would reveal a polymorphonuclear infiltrate
B. Aortic aneurysm formation is more common than arterial stenoses
C. This condition is 10 times more common in women than men
D. Claudication occurs more commonly in the lower extremities than the upper extremities
E. Coronary vasculitis is not typical in this syndrome

QUESTION 633

A 58-year-old woman complains of a new-onset severe headache, jaw pain with chewing, and temporal artery

tenderness. Laboratory examination shows an erythrocyte sedimentation rate (ESR) of 80 mm/h. Which of the following is TRUE regarding treatment of this condition?

A. Corticosteroids should not be administered until biopsy evidence confirms the diagnosis
B. Clinical improvement with appropriate treatment generally occurs over several weeks
C. Anti-tumor necrosis factor (TNF) therapies have been shown to be beneficial in this condition
D. In the absence of contraindications, low-dose aspirin should be prescribed
E. Normalization of the ESR is a reliable indicator of treatment response

QUESTION 634

A 35-year-old woman with hypertension is considering pregnancy. She is currently taking lisinopril 10 mg daily. Which of the following statements is correct?

A. She should remain on her current antihypertensive regimen before and during pregnancy
B. An angiotensin receptor blocker should be substituted
C. Labetalol should be avoided during pregnancy
D. Women with preexisting hypertension have a higher incidence of preeclampsia compared with those with new-onset hypertension during pregnancy
E. Antihypertensive therapy is effective in preventing preeclampsia during pregnancy

QUESTION 635

A 58-year-old woman in good health presents for evaluation. She is concerned about cardiovascular risk because her father sustained a myocardial infarction at age 70. Which of the following statements about heart disease in women is NOT correct?

A. Cardiovascular disease is the leading cause of death in women
B. In recent decades, age-adjusted cardiovascular mortality in the United States has increased in women while it has declined in men
C. Coronary heart disease presents approximately 10 years later in women than in men
D. Cardiovascular disease is twice as common in women with diabetes compared with nondiabetics
E. Hormone replacement therapy with estrogen does not reduce the risk of cardiac events in postmenopausal women

QUESTION 636

A 36-year-old woman with no prior history of cardiac disease develops exertional dyspnea and orthopnea 1 month after delivering a healthy full-term infant. Echocardiography demonstrates a dilated left ventricle with globally reduced contractile function. Which of the following statements regarding peripartum cardiomyopathy (PPCM) is TRUE?

A. Symptoms of PPCM always arise during the last month of pregnancy or within 1 week after delivery
B. Clinical and hemodynamic findings in PPCM are indistinguishable from those of other forms of dilated cardiomyopathy
C. The incidence of PPCM is greatest in first pregnancies
D. Approximately 10% of PPCM patients show recovery within the first 6 months after delivery
E. Younger maternal age is a risk factor for PPCM

QUESTION 637

A 67-year-old man with multivessel coronary disease is scheduled for coronary artery bypass graft surgery (CABG). Which of the following statements regarding CABG and perioperative complications is correct?

A. In-hospital mortality after isolated CABG has increased over the past 2 decades because of the increased complexity of patients who undergo the procedure
B. Early postoperative cognitive decline occurs in <10% of patients after CABG surgery
C. Atrial fibrillation appears in approximately 40% of patients after CABG surgery
D. Of patients who develop postoperative atrial fibrillation, only 20% will spontaneously revert to sinus rhythm within 24 hours
E. *N*-Acetylcysteine prevents renal dysfunction after CABG

QUESTION 638

The patient in Question 637 undergoes coronary artery bypass graft (CABG) surgery without complication. At his first postoperative office visit he reports resolution of his anginal symptoms and asks how long the benefit will last. Which of the following statements regarding CABG surgery is TRUE?

A. Fewer than 2% of saphenous vein grafts become occluded in the early perioperative period
B. Internal mammary artery grafts typically develop intimal hyperplasia over time
C. Saphenous vein grafts have a 10-year patency rate of >75%
D. Radial artery grafts are less likely to develop vasospasm than internal mammary grafts
E. Patients who receive internal mammary artery grafts suffer fewer late deaths and myocardial infarctions than those who receive only saphenous vein grafts

QUESTION 639

A previously healthy 17-year-old high school athlete collapses during a basketball game. He is noted to have brief seizure-like activity and has no initial pulse but is immediately resuscitated by a brisk precordial thump. Assuming that this event represents sudden cardiac death (SCD), which of the following statements is NOT correct?

A. Arrhythmogenic right ventricular cardiomyopathy is responsible for approximately 30% of SCD in young athletes
B. Anomalous origin of the left main coronary artery from the right coronary cusp is the most common of the congenital coronary abnormalities that result in SCD in young athletes
C. His normal pretraining history and physical examination do not exclude the possibility of hypertrophic cardiomyopathy (HCM)
D. Patients who experience SCD due to HCM often have no history of prior cardiac symptoms
E. Congenital aortic stenosis is a cause of SCD in young athletes

QUESTION 640

A 68-year-old woman with a history of hypertension presents to the emergency department with the new onset of dyspnea and nausea. The electrocardiogram shows anterolateral ST-segment depressions, and the initial serum measurement of cardiac troponin T is elevated. Which of the following statements is TRUE regarding women who present with acute coronary syndromes (ACS)?

A. Most women presenting with an acute myocardial infarction do not describe chest pain
B. Women presenting with myocardial infarction are less likely than men to have accompanying cardiovascular comorbidities
C. Women with ACS are more likely to present earlier in the course of symptoms than men
D. Women who present with chest discomfort are more likely than men to have nonatherosclerotic causes of ischemia, such as coronary vasospasm
E. Women are admitted to the hospital for the evaluation of chest pain less often than men

QUESTION 641

A 65-year-old man with end-stage renal disease, on stable hemodialysis, is diagnosed with atrial fibrillation. It is determined that he warrants anticoagulation for stroke prevention. Which of the following agents is labeled for use in patients on hemodialysis?

A. Rivaroxaban
B. Apixaban
C. Dabigatran
D. Edoxaban
E. None of the above

QUESTION 642

A 58-year-old postmenopausal woman presents for a routine office visit. She inquires about oral hormone replacement therapy recommended by her gynecologist. Which of the following statements is TRUE regarding the use of hormone replacement therapy and cardiovascular risk?

A. Current guidelines recommend hormone replacement therapy for postmenopausal women who do not have a history of coronary artery disease
B. The prospective Women's Health Initiative trial showed a reduced rate of coronary events in postmenopausal women randomized to estrogen-only treatment
C. The Women's Health Initiative showed no difference in the rate of stroke or pulmonary embolism in patients randomized to estrogen therapy
D. The American Heart Association guidelines assign a class III recommendation to starting or continuing estrogen plus progestin therapy for primary or secondary prevention of cardiovascular disease

QUESTION 643

A 55-year-old overweight man (body mass index = 31.0) with type 2 diabetes mellitus and atrial fibrillation is found to have three-vessel coronary disease at angiography and is scheduled for coronary artery bypass graft surgery in 1 week. Which of the following conditions is associated with increased perioperative mortality in this specific patient?

A. His age
B. Timing of surgery
C. Atrial fibrillation
D. Obesity

QUESTION 644

A 38-year-old woman presents at the 37th week of pregnancy because of severe substernal chest pain over the past 30 minutes. An electrocardiogram demonstrates 4-mm ST-segment elevations in leads V_1 to V_4. Which of the following statements is correct?

A. Coronary artery spasm is the most common cause of this finding during pregnancy
B. Coronary artery dissection is the most likely cause in the peripartum period
C. Pregnancy does not alter the risk of sustaining a myocardial infarction
D. Inferior wall myocardial infarction is more common than anterior wall myocardial infarction during pregnancy
E. Pregnancy is an absolute contraindication to angiography

QUESTION 645

An 83-year-old man with hypertension and diabetes underwent coronary artery bypass graft (CABG) surgery 14 hours ago on an emergency basis. Preoperative angiography revealed severe stenoses of the left main and right coronary arteries. During the operation, the left internal mammary artery was grafted to the native left anterior descending artery and saphenous vein grafts were anastomosed to the first obtuse marginal branch of the circumflex coronary artery and to the posterior descending artery. The surgeon consults you because he is concerned that the patient may have suffered a perioperative myocardial infarction (MI). Which of the following statements is NOT correct?

A. His age, the emergency nature of his procedure, and the presence of left main coronary artery disease put this patient at increased risk for perioperative MI
B. Chest pain is not a reliable sign of MI in the post-CABG patient
C. An elevation of cardiac-specific troponin T more than three times the 99% upper reference limit is diagnostic of MI in this setting
D. The finding of new Q waves on the electrocardiogram is a reliable sign of perioperative MI
E. Paradoxical motion of the interventricular septum on echocardiography is a common finding after cardiac surgical procedures and does not necessarily indicate MI

QUESTION 646

A 78-year-old man presents with chest pain and acute 2-mm ST-segment elevations in leads V_1 to V_3. Which of the following statements is true regarding the management of acute myocardial infarction (MI) in elderly patients?

A. Fibrin-specific fibrinolytic agents are not associated with heightened intracerebral bleeding rates in patients >75 years
B. Antiplatelet therapy with prasugrel leads to superior outcomes compared with clopidogrel in patients >75 years of age who undergo percutaneous intervention

C. Angiotensin-converting enzyme inhibitors have been shown to reduce fatal and nonfatal events after MI in elderly patients
D. Elderly patients are less likely than younger patients to benefit from beta blockade for secondary prevention

QUESTION 647

Which of the following preoperative clinical characteristics most strongly predicts an increased risk of perioperative cardiovascular complications in patients >40 years of age undergoing major noncardiac surgery?
A. Presence of an S_3 gallop
B. Active cigarette smoking
C. Serum creatinine = 1.5 mg/dL
D. Mitral stenosis with calculated valve area of 2.0 cm^2
E. Hypertension controlled on drug therapy

QUESTION 648

A 69-year-old woman presents for a routine office visit. She has a history of hypertension and her blood pressure today is 165/90 mm Hg. The only medication is metoprolol succinate 25 mg daily. Which of the following statements regarding hypertension in the elderly is TRUE?
A. Therapy for isolated systolic hypertension in the elderly does not reduce the incidence of future cardiac events
B. Clinical trials have shown that beta blockers offer less cardiovascular protection than diuretic therapy
C. The presence of left ventricular hypertrophy in hypertensive patients >65 years is not an independent risk factor for adverse cardiovascular outcomes
D. Hypertensive hypertrophic cardiomyopathy of the elderly is more common in men

QUESTION 649

Which of the following statements regarding hemodynamic changes during normal pregnancy is NOT correct?
A. Total blood volume increases
B. Cardiac output increases
C. Stroke volume increases
D. Systemic vascular resistance increases
E. Heart rate increases

QUESTION 650

Which of the following cancer therapies is NOT associated with the listed cardiotoxic side effect?
A. Trastuzumab: Systolic heart failure
B. Bevacizumab: Hypertension
C. Ipilimumab: Myocarditis
D. Anastrozole: Venous thromboembolism

QUESTION 651

A 60-year-old woman with a history of hypertension and diabetes mellitus is admitted to the hospital because of an acute severe headache, nausea, and vomiting. Physical examination demonstrates a blood pressure of 180/90 mm Hg, normal jugular venous pressure, bibasilar rales, no cardiac gallops or murmurs, and no focal neurologic signs. The troponin I is elevated at 0.62 ng/dL (normal: <0.10 ng/dL). Computed tomography of the brain demonstrates an acute subarachnoid hemorrhage. The patient's electrocardiogram is shown in Fig. 5.1. Which of the following statements is TRUE?
A. A ruptured coronary plaque with partially occlusive thrombus is likely present
B. QT interval prolongation is uncommon in this setting
C. All of the cardiac abnormalities can be attributed to autonomic dysfunction in the setting of acute brain injury
D. Beta blockers are not effective at controlling ventricular tachycardia and fibrillation in this situation
E. The magnitude of electrocardiographic abnormalities in such a patient correlates with a poor cardiovascular outcome

QUESTION 652

A 68-year-old man with a history of myocardial infarction is scheduled for elective hernia repair. Which of the following statements regarding perioperative medication use in coronary disease patients undergoing noncardiac surgery is TRUE?
A. Cardiac adverse event rates are reduced when high-dose beta blocker therapy is initiated immediately before surgery
B. Nitrates decrease intraoperative myocardial ischemia and reduce rates of adverse cardiac outcomes

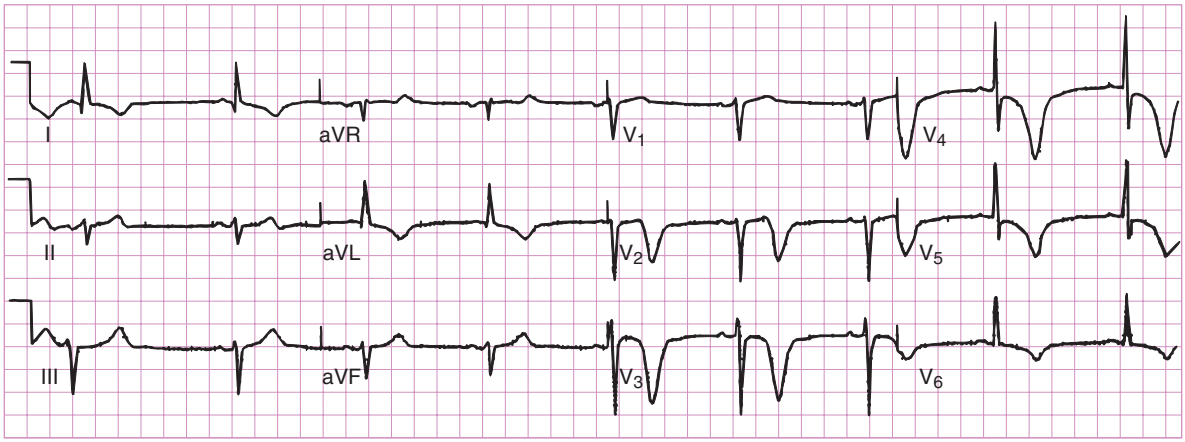

FIG. 5.1 *Courtesy Dr. Charles Fisch, Indiana University of Medicine, Indianapolis.*

C. Most cardiac medications should be discontinued 2 to 3 days before surgery and resumed as soon as the patient can tolerate oral intake
D. Statin therapy has been associated with reduced perioperative cardiovascular event rates in high-risk patients

QUESTION 653

Which of the following statements regarding alterations in cardiovascular function with aging is NOT correct?
A. Endothelial production of nitric oxide decreases with age
B. Left ventricular myocardial cells typically develop moderate hypertrophy
C. There is a fall in stroke volume due to a decrease in peak contractile force
D. Heart rate during exercise increases less in older, compared with younger, individuals
E. The resting ejection fraction tends to remain constant with age in the absence of cardiac disease

QUESTION 654

A 58-year-old diabetic man develops fever and tenderness at the sternal wound site 12 days after coronary artery bypass graft surgery. Which of the following has NOT been associated with the development of deep sternal wound infection after cardiac surgery?
A. Prolonged cardiopulmonary bypass time
B. Use of both internal mammary arteries as bypass vessels
C. Diabetes
D. History of cigarette smoking prior to surgery
E. Preoperative atrial fibrillation

QUESTION 655

A 27-year-old woman undergoes right-sided heart catheterization for the assessment of suspected pulmonary arterial hypertension. The mean pulmonary artery pressure (PAP) is 44 mm Hg, and the pulmonary capillary wedge pressure (PCWP) is 11 mm Hg. Infusion of epoprostenol reduces the mean PAP to 31 mm Hg with no significant change in systemic blood pressure or PCWP. Which of the following statements is NOT correct?
A. Both intravenous adenosine and inhaled nitric oxide are alternative useful agents to assess vasoreactivity
B. The observed drop in mean PAP is predictive of a favorable response to oral calcium channel blockers
C. The failure of the systemic blood pressure to decline suggests that the vasodilator challenge was ineffective
D. Very high doses of chronic calcium channel blocker therapy would likely be necessary to realize full clinical benefit
E. A rise in PCWP in response to vasodilator therapy would be of concern for impending left ventricular failure

QUESTION 656

Which of the following interventions has been shown to reduce the incidence of contrast-induced acute kidney injury after coronary angiography in patients with chronic renal insufficiency?
A. Infusion of 20% mannitol before angiography
B. Administration of atrial natriuretic peptide
C. Normal saline administration before and after angiography
D. Intravenous furosemide administration before angiography
E. Low-dose dopamine infusion

QUESTION 657

A 42-year-old woman presents to her primary care physician with recent fatigue and weight gain. Laboratory evaluation reveals a markedly elevated thyroid-stimulating hormone level. Which of the following is NOT a common cardiac finding in patients with hypothyroidism?
A. Hypotension
B. Decreased heart rate
C. Pericardial effusion
D. Decreased cardiac output
E. Prolonged QT interval on the electrocardiography

QUESTION 658

A 28-year-old woman with Marfan syndrome presents for an office visit. Her echocardiogram shows mitral valve prolapse, an aortic root diameter of 4.5 cm, and mild aortic regurgitation. Which of the following statements regarding cardiovascular disease in patients with Marfan syndrome is NOT correct?
A. Sixty percent to 80 percent of patients with Marfan syndrome have mitral valve prolapse on echocardiography
B. The development of aortic regurgitation correlates with the aortic root diameter
C. Patients with Marfan syndrome should be considered for elective aortic root replacement once the aortic root diameter exceeds 5.5 cm
D. Beta blockers should be administered to all patients with Marfan syndrome unless a contraindication exists
E. The risk of aortic dissection during pregnancy in patients with Marfan syndrome is increased if the diameter of the aortic root exceeds 4 cm

QUESTION 659

A 54-year-old man was admitted to the hospital because of acute pulmonary embolism. Intravenous administration of heparin was begun. On admission, the platelet count was 223,000/μL. Four days later it fell to 16,000/μL, although the patient remained asymptomatic, without overt bleeding. Which of the following statements regarding this patient's condition is TRUE?
A. Low-molecular-weight heparin can be safely substituted for intravenous unfractionated heparin
B. A direct thrombin inhibitor, such as lepirudin, should be substituted for heparin
C. Intravenous heparin should be continued, because the low platelet count represents a laboratory artifact without clinical significance
D. Antibodies directed against the platelet glycoprotein IIb/IIIa receptor participate in this disorder
E. This is a transient reaction to heparin and does not preclude future heparin treatment for this patient

QUESTION 660

A 51-year-old woman presents to discuss anticoagulation options for atrial fibrillation. Her history is notable for rheumatic mitral stenosis, which led to mitral valve replacement with a St. Jude mechanical prosthesis 6 years ago. She had

atrial fibrillation prior to cardiac surgery and it has persisted thereafter. She has been maintained successfully on warfarin anticoagulation, but she wishes to free herself of the required frequent testing of the prothrombin time and dose adjustments. She asks if one of the newer anticoagulants would be an option for her. She has normal renal function. Which of the agents below would be appropriate for this patient?
A. Rivaroxaban
B. Apixaban
C. Dabigatran
D. None of the above

QUESTION 661

Which of the following statements regarding metastatic disease involving the heart is TRUE?
A. Tumor metastases frequently involve the cardiac valves
B. A chylous pericardial effusion is characteristic of metastatic breast carcinoma
C. The most common cause of cardiac metastasis in men and women is lung cancer
D. A solitary cardiac mass is more likely to be malignant than benign

QUESTION 662

While volunteering at a medical clinic in rural India, you are asked to examine a 12-year-old girl who presents with fever, migratory polyarthritis, and an erythematous rash on her trunk that forms a snakelike ring with central clearing. Her cardiac examination is notable for a soft, high-pitched pansystolic murmur at the apex. She recalls a prolonged painful pharyngitis a few weeks ago. Two older family members are known to have mitral stenosis. In addition to the "major criteria" used for diagnosing this patient's likely condition, each of the following would offer supporting evidence EXCEPT
A. Prolonged QT interval
B. Fever
C. Elevated C-reactive protein
D. Arthralgia

QUESTION 663

A 42-year-old woman with rheumatoid arthritis (RA) presents with exertional dyspnea. Echocardiography demonstrates a small circumferential pericardial effusion without hemodynamic compromise. Which of the following statements regarding cardiovascular involvement in RA is TRUE?
A. Acute pericarditis related to RA occurs in 10% to 15% of patients
B. Patients with RA have a reduced incidence of clinical CAD compared to the general population
C. Conduction system disease in RA is most commonly due to inflammation of the conduction system.
D. Women with RA are twice as likely as age-matched controls to suffer myocardial infarction
E. At autopsy, epicardial coronary arteritis is found in >50% of patients with RA

QUESTION 664

A 76-year-old man with hypertension and diabetes is found to have atrial fibrillation for the first time at a routine office visit. He has no history of cardiac symptoms, and an echocardiogram shows normal left ventricular contractile function and no valvular disease or pericardial effusion. His physician initiates dabigatran etexilate for long-term anticoagulation. Which of the following statements is TRUE?
A. Anticoagulation for this patient is not warranted because his risk of thromboembolism is low
B. Dabigatran etexilate is an oral factor Xa inhibitor
C. The risk of stroke or systemic embolism with dabigatran 150 mg twice daily is lower than that with warfarin anticoagulation and a target international normalized ratio of 2.0 to 3.0
D. Dabigatran 150 mg twice daily is associated with a higher rate of hemorrhagic stroke than warfarin anticoagulation
E. Hepatotoxicity is the major gastrointestinal side effect of dabigatran

QUESTION 665

A 66-year-old man with a history of atrial fibrillation successfully suppressed by amiodarone presents with tremors and recent weight loss. His physician suspects amiodarone-induced thyroid dysfunction. Which of the following statements about amiodarone and thyroid function is NOT correct?
A. Amiodarone inhibits the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3)
B. During initial therapy, amiodarone decreases thyroid-stimulating hormone levels
C. Amiodarone contains 30% iodine by weight
D. Amiodarone's iodine content inhibits synthesis and release of T_4 from the thyroid gland
E. Glucocorticoid therapy is beneficial for patients with amiodarone-induced hyperthyroidism who have elevated circulating levels of interleukin-6

QUESTION 666

A 54-year-old man presents for evaluation of excessive daytime sleepiness. His wife has observed his prominent snoring and gasping at night. Which of the following statements regarding sleep-related breathing disorders and cardiovascular disease is NOT correct?
A. Individuals with obstructive sleep apnea exhibit persistently increased sympathetic activity, even during daytime wakefulness
B. Obstructive sleep apnea is associated with drug-resistant hypertension, automatic tachycardias, and nocturnal bradycardias
C. Positive airway pressure therapy in obstructive sleep apnea is associated with improved health-related quality-of-life, mood, and blood pressure
D. Unlike obstructive sleep apnea, central sleep apnea is not associated with cardiovascular disease
E. Positive airway pressure benefits both obstructive sleep apnea and central sleep apnea

QUESTION 667

A 38-year-old man with a recent history of unprovoked deep vein thrombosis presents to discuss long-term therapy for recurrent venous thromboembolism (VTE) prevention. He has just completed 6 months of warfarin anticoagulation without complication. Which of the following is NOT an evidenced-based regimen to reduce the risk of recurrent VTE?

A. Aspirin 100 mg daily
B. Warfarin 2 mg every other day
C. Apixaban 2.5 mg twice daily
D. Rivaroxaban 10 mg daily

QUESTION 668

Which of the following statements regarding perioperative cardiac risk assessment in patients undergoing noncardiac surgery is TRUE?
A. Preoperative serum creatinine concentration >1.5 mg/dL is an independent predictor of cardiac complications
B. Controlled insulin-dependent diabetes mellitus is a predictor of postoperative adverse cardiac outcomes
C. Transurethral prostate surgery is considered a high-risk procedure with respect to cardiac complications
D. In the current era, there is a 20% risk of reinfarction if surgery is performed 3 to 6 months after an acute MI
E. A history of exertional angina indicates high perioperative risk, even if the patient can carry a bag of groceries up one flight of stairs without stopping

QUESTION 669

A previously healthy 36-year-old woman presents to her primary care physician 3 weeks after the delivery of her second child because of new dyspnea, orthopnea, and peripheral edema. On examination, she appears fatigued. The blood pressure is 100/70 mm Hg and the heart rate is 120 beats/min. The jugular venous pressure is 12 cm H_2O. There are basilar rales, a prominent apical S_3 gallop, hepatomegaly, and bilateral lower extremity edema. An echocardiogram shows four-chamber cardiac enlargement and severe, global reduction of biventricular systolic function, compared with a normal study before pregnancy. Which of the following statements regarding this patient's condition is NOT correct?
A. The incidence of this disorder is greater with twin pregnancies
B. Approximately half of the patients with this disorder will completely recover normal cardiac function
C. Subsequent pregnancies are usually well tolerated
D. This condition becomes symptomatic in most patients during the last trimester of gestation or in the early postpartum period
E. The incidence of this disorder is higher among African American women than among whites

Directions:

Each group of questions below consists of lettered headings followed by a set of numbered questions. For each question, select the ONE lettered heading with which it is most closely associated. Each lettered heading may be used once, more than once, or not at all.

QUESTIONS 670 TO 674

For each description listed below, match the appropriate diagnosis:
A. Behçet syndrome
B. Systemic sclerosis
C. Ankylosing spondylitis
D. Reactive arthritis
E. Giant cell arteritis

670. Granuloma formation in the coronary arteries
671. Aortitis, uveitis, and urethritis
672. Myocardial fibrosis and contraction band necrosis
673. Histologically similar to syphilitic aortitis
674. Occlusion of the subclavian artery and aneurysms of the common carotid artery

QUESTIONS 675 TO 678

Match the cardiac medication with the potential adverse effect:
A. Heparin
B. Alpha-methyldopa
C. Procainamide
D. Ticagrelor

675. Erythematous rash, leukopenia
676. Coombs-positive hemolysis
677. Dyspnea
678. Thrombocytopenia

QUESTIONS 679 TO 683

Match the description with the associated disease:
A. Takayasu arteritis
B. Giant cell arteritis
C. Both
D. Neither

679. Occurrence is predominantly in women
680. Onset is typically during teenage years
681. Jaw muscle claudication suggests the diagnosis
682. Fever is almost always present
683. Steroid therapy is a cornerstone of management

QUESTIONS 684 TO 688

Match the chemotherapeutic agent with the likely cardiac complication:
A. Myocardial infarction
B. Acute myopericarditis
C. Capillary leak syndrome
D. Arrhythmias (acutely) and dilated cardiomyopathy (chronically)
E. Hypertension

684. Interleukin-2
685. 5-Fluorouracil
686. Cyclophosphamide
687. Doxorubicin
688. Sunitinib

QUESTIONS 689 TO 693

Match the cardiac finding with the most likely endocrine abnormality:
A. Hyperparathyroidism
B. Hypothyroidism
C. Hyperaldosteronism
D. Cushing syndrome
E. Hyperthyroidism

689. U waves on the electrocardiogram
690. Cardiac myxoma
691. Means-Lerman scratch
692. Shortened QT interval
693. Pericardial effusion

QUESTIONS 694 TO 697

Match the description to the associated fibrinolytic agent:
A. Streptokinase
B. Tissue-type plasminogen activator
C. Urokinase
D. Tenecteplase

694. Both single- and two-chain forms demonstrate proteolytic activity
695. Synthesized in renal tubular epithelial cells and endothelial cells
696. Prolonged half-life allows administration as a single bolus
697. Must form complex with plasminogen to exhibit enzymatic activity

QUESTIONS 698 TO 702

Match the finding to the associated anticoagulant:
A. Unfractionated heparin
B. Low-molecular-weight heparin
C. Both
D. Neither

698. Hyperkalemia
699. Bioavailability after subcutaneous injection is >90%
700. Inactivates clot-bound thrombin
701. Thrombocytopenia
702. Increases vascular permeability

QUESTIONS 703 TO 706

Match the following complications with the associated rheumatologic disorder:
A. Aortitis and headaches
B. Libman-Sacks endocarditis
C. Pulmonary hypertension
D. Aneurysmal dilatation of the subclavian and carotid arteries

703. Behçet syndrome
704. Systemic lupus erythematosus
705. Giant cell arteritis
706. Systemic sclerosis

Section V Answers

(CHAPTERS 88 TO 99)

Cardiovascular Disease in Special Populations; Cardiovascular Disease and Disorders of Other Organs

ANSWER TO QUESTION 630

C (Braunwald, pp. 1039–1040, 1042; Fig. 78.12; eTable 78.1)

In the United States, standard screening of young athletes typically consists only of history-taking and physical examination. This approach has a limited capability of detecting serious forms of cardiac disease that could lead to sudden cardiac death (SCD) during training, such as hypertrophic cardiomyopathy (HCM), anomalous origin of the coronary arteries, arrhythmogenic right ventricular cardiomyopathy, and inherited arrhythmia syndromes (e.g., long QT syndromes or Brugada syndrome). Patients with a family history of SCD or premature heart disease, and those with cardiac symptoms (including inordinate exertional dyspnea, chest pain, syncope, or near-syncope) or a heart murmur that augments with standing or Valsalva maneuver, warrant a more complete evaluation, usually including electrocardiography and echocardiography. This issue is particularly relevant since implantation of automatic defibrillators can prevent SCD in patients with predisposing conditions.

The most common cause of SCD in athletes in the United States is HCM. This diagnosis can be difficult to distinguish from the physiologic hypertrophy observed in individuals who participate in chronic endurance or isometric activities ("athlete's heart"), in whom left ventricular (LV) wall thicknesses of 13 to 15 mm can be observed (Fig. 5.2). Thus, voltage criteria for LV hypertrophy do not establish the diagnosis of hypertrophic or hypertensive cardiomyopathy in trained athletes. Echocardiographic findings more suggestive of *pathologic* hypertrophy include (1) LV wall thicknesses >15 mm, (2) prominent asymmetric LV hypertrophy, (3) LV end-diastolic cavity diameter <45 mm, (4) marked left atrial enlargement, (5) abnormal LV Doppler filling patterns, and (6) lack of regression of hypertrophy after a period of deconditioning. A distinguishing feature during cardiopulmonary exercise testing is that conditioned athletes with physiologic hypertrophy can achieve maximum oxygen uptakes >45 mL/kg/min (>110% predicted), whereas those with HCM typically cannot. Patients in whom cardiac assessment reveals HCM should be restricted from competitive athletics.

Anomalous origin of the coronary arteries is the second most common cause of SCD in athletes in the United States. Evaluation for this diagnosis includes coronary angiography or computed tomography angiography.

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ANSWER TO QUESTION 631

D (Braunwald, pp. 1910, 1917–1918)

Chronic kidney disease (CKD) identifies a patient population at high risk for cardiovascular events. Up to 40% of patients with CKD who present to the hospital with chest pain have a cardiac event within 30 days. Moreover, patients with end-stage renal disease have the highest mortality after acute myocardial infarction of any large population with chronic disease. Contributors to poor outcomes after acute coronary syndromes in patients with CKD include (1) high prevalence of comorbidities such as diabetes mellitus and heart failure, (2) reduced use of effective therapeutics due to fear of worsening renal dysfunction, (3) therapeutic toxicities, and (4) vascular dysfunction that is exacerbated by renal failure, including a procoagulable and proinflammatory state. Whereas the latter contributes to increased rates of coronary thrombosis, uremia is also associated with impaired platelet aggregation, so patients with CKD can display increased bleeding risk at the same time.

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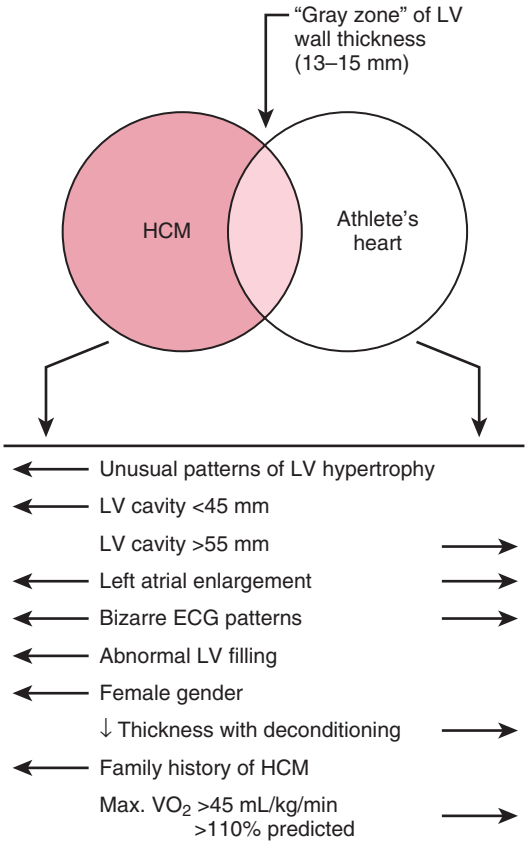

FIG. 5.2 *Modified from Maron BJ, Pelliccia A: The heart trained athletes: cardiac remodeling and the risks of sports including sudden death.* Circulation. *2006;114:1633.*

TABLE 5.1 "Red Flags" for Takayasu Arteritis

In patients younger than 40 years, the following may be indicative of TA:
Unexplained acute-phase response (raised ESR and/or CRP)
Carotidynia
Hypertension
Discrepant blood pressure between the arms (>10 mm Hg)
Absent/weak peripheral pulse or pulses
Limb claudication
Arterial bruit
Angina

CRP, C-reactive protein; *ESR,* erythrocyte sedimentation rate; *TA,* Takayasu arteritis.

TABLE 5.2 Clinical Profile of Giant Cell Arteritis

ABNORMALITY	FREQUENCY (%)
Atypical headache	60–90
Tender temporal artery	40–70
Systemic symptoms not attributable to other diseases	20–50
Fever	20–50
Polymyalgia rheumatica	30–50
Acute visual abnormalities	12–40
Transient ischemic attack or stroke	5–10
Claudication	
Jaw	30–70
Extremity	5–15
Aortic aneurysm	15–20
Dramatic response to corticosteroid therapy	~100
Positive temporal artery biopsy	~50–80

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ANSWER TO QUESTION 632

C (Braunwald, pp. 1850–1854, 1861; Table 94.3)

This patient has signs and symptoms of Takayasu arteritis (TA), an idiopathic large-vessel vasculitis that usually affects the aorta and its branches. TA is 10 times more likely to affect women than men, and the median age of onset is 25 years old. This disease occurs worldwide with a prevalence of 2.6 per million in the United States and 1.26 per million in northern Europe. Features that should prompt consideration of TA are listed in Table 5.1.

Clinically, arterial stenoses occur three to four times more often than aneurysms. Thus, claudication (more common in the upper than lower extremities) is the major symptom; on physical examination, bruits and asymmetric pulses are the most frequent findings. When aneurysms occur, the aortic root is the most common location, which can lead to aortic regurgitation. Hypertension is common and is often caused by renal artery stenosis. Coronary arterial vasculitis most often affects the ostia of the vessels, leading to myocardial ischemia. In addition, myocarditis occurs in about 18% of patients.

Treatment involves high-dose corticosteroids, but relapses are common. Patients with resistant or relapsing symptoms may respond to azathioprine, mycophenolate mofetil, methotrexate, leflunomide, or intravenous cyclophosphamide. More recently, anti-interleukin-6 therapy (i.e., tocilizumab) has been used successfully in some patients with TA that is refractory to conventional therapies. Anatomic bypass of clinically significant stenosis may be necessary. Involvement of the aortic root may necessitate aortic repair, with or without valve replacement.

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ANSWER TO QUESTION 633

D (Braunwald, pp. 1850, 1853–1854)

This patient has characteristic features of giant cell arteritis (GCA), which typically includes the new onset of headache, scalp and temporal artery tenderness, polymyalgia rheumatica, acute visual abnormalities, and claudication of the jaw (Table 5.2).[1] Such symptoms, in the presence of an

increased erythrocyte sedimentation rate (ESR), support the diagnosis of GCA and mandate treatment, even without proof of diagnosis from a temporal artery biopsy. Corticosteroid treatment is the most effective therapy for GCA, and dramatic clinical improvement typically follows within 24 to 72 hours. The ESR itself does not always normalize with effective therapy, and it should not be relied on as the main measure of disease activity.

Most cytotoxic and other immunosuppressive agents, including anti-TNF agents, have not proved effective in GCA in controlled trials. However, a recent trial of tocilizumab (anti-interleukin-6 therapy) used in combination with corticosteroids resulted in a higher rate of sustained remission from GCA at 1 year as compared to corticosteroids alone.[2] Two retrospective studies have demonstrated that the use of low-dose aspirin reduces cerebral ischemic events three- to fourfold compared with patients who had not received such therapy. Therefore, most patients with GCA should receive low-dose daily aspirin.[3]

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ANSWER TO QUESTION 634

D (Braunwald, p. 1791; Table 90.4)

Hypertension during pregnancy is associated with increased maternal mortality and morbidity and consists of four forms (Table 5.3): (1) chronic hypertension (hypertension that precedes pregnancy), (2) gestational hypertension (hypertension that develops after 20 weeks of gestation and resolves by the 12th postpartum week), (3) preeclampsia (de novo or superimposed on chronic hypertension), and (4) white coat hypertension. *Preeclampsia* is identified by the new onset of hypertension after the 20th week of gestation with proteinuria, maternal organ dysfunction, and/or uteroplacental insufficiency. It is more likely to occur in primigravid patients, in twin pregnancies, and in those with preexisting hypertension. Preeclampsia is an emergency and requires hospitalization for close maternal-fetal monitoring, control of hypertension, magnesium sulfate to prevent eclamptic seizures, and consideration of urgent delivery of the fetus, especially after 37 weeks' gestation, after which blood pressure usually normalizes rapidly. *Eclampsia* is present when findings of preeclampsia are accompanied by neurologic complications, including seizures.

Pharmacologic therapies that have been used successfully to lower blood pressure during pregnancy include methyldopa, beta blockers (particularly labetalol), calcium channel blockers, and hydralazine. Although these medications are effective in treating chronic hypertension that has worsened during pregnancy, they are not effective in preventing preeclampsia.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increase the risk of congenital malformations and neonatal renal failure and should *not* be used in pregnancy.

TABLE 5.3 Classification of Hypertension in Pregnancy

HYPERTENSION TYPE	DEFINITION/DESCRIPTION
Chronic hypertension	Hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) present before pregnancy or that is diagnosed before the 20th week of gestation
Gestational hypertension	• New hypertension with a blood pressure of 140/90 mm Hg on two separate occasions, without proteinuria, arising de novo after the 20th week of pregnancy • Blood pressure normalizes by 12 weeks postpartum
Preeclampsia superimposed on chronic hypertension	Increased blood pressure above the patient's baseline, a change in proteinuria, or evidence of end-organ dysfunction
Preeclampsia-eclampsia	• Proteinuria (protein excretion >0.3 g during 24 hours or grade ++ in two urine samples) in addition to new hypertension • Edema no longer included as diagnostic criterion because of poor specificity • In the absence of proteinuria, the disease should nevertheless be suspected when increased blood pressure is associated with headache, blurred vision, abdominal pain, low platelets, or abnormal liver enzymes

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ANSWER TO QUESTION 635

B (Braunwald, pp. 1767, 1770)

Cardiovascular disease is the number one cause of mortality for women in the United States, accounting for 1 in 4 deaths. Fortunately, age-adjusted heart disease mortality has *declined* in both men and women in recent decades, attributed to beneficial risk factor modifications and the influence of evidence-based therapies in the treatment of coronary artery disease, acute coronary syndromes, and heart failure.[1]

Coronary heart disease first presents approximately 10 years later in women than in men, most commonly after menopause. The INTERHEART study demonstrated that this pattern is widely consistent across the world. The age difference is likely contributed to by a protective effect of circulating estrogen before menopause. Nonetheless, pharmacologic replacement of estrogen after menopause does not prevent clinical cardiovascular events.[2,3]

As in men, hyperlipidemia, hypertension, tobacco use, diabetes mellitus, obesity, and a sedentary lifestyle are all important modifiable risk factors for the development of heart disease in women. In the United States, nearly 36% of women have a low-density lipoprotein cholesterol level ≥130 mg/dL and more than 45 million women are hypertensive, a prevalence that exceeds that of men after age 60. There are >15 million women with diabetes mellitus, a population in which the rate of fatal coronary heart disease is higher than that of diabetic men.

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ANSWER TO QUESTION 636

B (Braunwald, pp. 1589, 1790)

Peripartum cardiomyopathy (PPCM) is a form of dilated cardiomyopathy that occurs for the first time in the antepartum or postpartum period and is clinically indistinguishable from other types of dilated cardiomyopathy. PPCM is not a precisely defined entity, but general features include: (1) the development of heart failure (HF) in the last month of pregnancy or within 5 months of delivery, (2) reduced left ventricular ejection fraction (generally <45%), and (3) absence of previously known structural heart disease.[1,2] Recent studies have suggested significant overlap in the genetic predisposition to PPCM and other forms of idiopathic dilated cardiomyopathy.[3]

The incidence of PPCM varies by geographic region but is estimated to be between 1 in 1000 and 1 in 3200 live births. Risk factors for its occurrence include multiparity, African American race, older maternal age, and preeclampsia.

Approximately 50% of patients with PPCM show complete or near-complete left ventricular recovery on standard medical therapy. The other 50% demonstrate either continued deterioration or persistent left ventricular dysfunction and chronic HF symptomatology. Subsequent pregnancies in patients with PPCM with persistent cardiac dysfunction should be discouraged because of the high likelihood of relapse. Even patients who have recovered from an episode of PPCM have a 30% risk of experiencing relapse during subsequent pregnancies.[2]

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ANSWER TO QUESTION 637

C (Braunwald, pp. 1242–1243)

The frequency of perioperative complications in coronary artery bypass graft surgery (CABG) has increased because of the greater percentage of high-risk patients who undergo the operation.[1,2] However, the in-hospital *mortality* after isolated CABG has actually declined, from ~3% in 1997–1999 to ~2% in 2015. The reported incidence of perioperative myocardial infarction varies widely, with a median of 2.9%.

Cerebrovascular complications can occur after cardiac surgery by mechanisms that include atherosclerotic cerebral emboli from the aorta, emboli related to the cardiopulmonary bypass machine, and intraoperative hypotension. Prospective studies reveal a post-cardiac surgical incidence of stroke ranging from 1.5% to 5.0%.[3] Short-term cognitive decline has been identified in >50% of patients at the time of hospital discharge.

Atrial fibrillation (AF) is one of the most frequent complications of bypass surgery, developing in approximately 40% of patients within 3 days after surgery. It is associated with a two- to threefold increase in postoperative stroke. Up to 80% of patients spontaneously revert to sinus rhythm within 24 hours without treatment other than rate control agents. Prophylactic use of beta blockers or amiodarone reduces the occurrence of postoperative AF.[4]

The incidence of renal failure requiring dialysis after CABG is low (0.5% to 1.0%) but is associated with greater morbidity and mortality when it occurs. Predictors of postoperative renal dysfunction include advanced age, diabetes, preexisting renal dysfunction, and heart failure. In a randomized trial, *N*-acetylcysteine did not prevent renal dysfunction after CABG.[5]

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ANSWER TO QUESTION 638

E (Braunwald, pp. 1240–1241)

A variety of conduit options are available for coronary artery bypass graft surgery. Saphenous vein grafts are relatively easy to harvest, but they have several drawbacks. Approximately 8% to 12% of saphenous vein grafts become occluded during the early perioperative period. By 1 year, 15% to 30% of vein grafts occlude. Some of these occlusions may be due to endothelial denuding during surgical preparation, thereby predisposing the graft to early thrombosis. Intimal hyperplasia and accelerated atherosclerosis in vein grafts are common, and by 10 years after surgery, the patency rate of saphenous vein conduits is <50%.

In contrast, internal mammary artery (IMA) grafts, although more difficult to harvest, do not develop intimal hyperplasia and have 10-year patency rates of >80%. Several potential explanations for the superiority of IMA grafts have been suggested: (1) the medial layer of arterial grafts may derive additional nourishment from the vasa vasorum, (2) the endothelium of the IMA produces high levels of endogenous

vasodilators, and (3) the diameter of the IMA is closer to that of the recipient coronary artery than is the diameter of the saphenous vein. Compared to patients with saphenous vein grafts, patients who receive IMA conduits have a decreased risk of death, myocardial infarction, and reoperation. Other arterial conduits, such as the radial artery, are used less often. Although more likely to develop vasospasm than IMA grafts, radial artery grafts are also effective conduits with high long-term patency rates.

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ANSWER TO QUESTION 639

A (Braunwald, pp. 822, 1039–1040; see also Answer to Question 630)

Sudden cardiac death (SCD) in young athletes is a rare, tragic event. The most common cause of SCD in the United States is hypertrophic cardiomyopathy (HCM). It is common for SCD victims with HCM to have been asymptomatic throughout their lives, and even routine history and physical examination before undertaking competitive sports will miss many cases.

The second most common etiology of SCD in young athletes is anomalous origin of a coronary artery. The most frequent form is anomalous origin of the left main coronary artery from the right coronary cusp. The opposite configuration, anomalous origin of the right coronary artery from the left aortic sinus, has also been identified as a cause of SCD. Myocardial ischemia in individuals with anomalous coronaries may relate to a kinked takeoff of the artery or compression of the vessel between the aorta and pulmonary trunk during exercise. Like HCM, coronary anomalies are very difficult to identify by routine screening.

Much less common causes of SCD in young athletes include atherosclerotic coronary disease, myocarditis, aortic dissection, congenital valvular aortic stenosis, and arrhythmogenic right ventricular cardiomyopathy.

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ANSWER TO QUESTION 640

D (Braunwald, pp. 1770–1773)

Compared with men, women experiencing an acute coronary syndrome more frequently describe milder symptoms and are more likely to have "atypical" and often nonspecific symptoms, including dyspnea, pain or discomfort in other body locations, fatigue, indigestion, nausea, or generalized weakness. Despite sex differences in symptom perception of myocardial ischemia, however, the majority of women with acute myocardial infarctions report chest pain.[1] In addition, women presenting with myocardial infarctions typically have more comorbidities (e.g., hypertension) than men, and often present later in the course of symptoms and more frequently with high-risk clinical findings such as heart failure.[2]

Women are hospitalized more frequently than men each year for the evaluation of chest pain, but women who present with chest discomfort are more likely than men to have a nonatherosclerotic cause of ischemia, including coronary vasospasm, stress "takotsubo" cardiomyopathy, and spontaneous coronary artery dissection.

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ANSWER TO QUESTION 641

B (Braunwald, pp. 1841–1843; Table 93.10; see also Answer to Question 74)

The direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, are non–vitamin K antagonist oral anticoagulants (NOACs) approved by the US Food and Drug Administration (FDA) for the prevention of stroke in patients with nonvalvular atrial fibrillation (AF), and the treatment of deep venous thrombosis and pulmonary embolism. Each of these agents is in part cleared through renal excretion, and the doses of all four agents must be lowered in patients with reduced creatinine clearance (CCr). Additionally, rivaroxaban, edoxaban, and dabigatran should not be prescribed at all for patients with CCr <15 mL/min.[1]

Apixaban has the lowest proportion of renal excretion (25%) among the available NOACs. Its FDA-approved labeling recommends reduced dosage (2.5 mg twice daily, instead of 5 mg twice daily) for patients with AF and serum creatinine >1.5 mg/dL, *if* the patient also weighs ≤60 kg, or if age is ≥80 years. Apixaban is also approved for use in hemodialysis (5 mg twice daily, or 2.5 mg twice daily for age ≥80 years or body weight ≤60 kg) based on a small pharmacokinetic study.[2] In a retrospective review that compared apixaban with warfarin in patients with severe renal impairment, these anticoagulants resulted in similar bleeding and thrombotic complications.[3] Nonetheless, for patients with end-stage renal disease, and for those on dialysis, there is a long track record of acceptable safety with warfarin, which currently remains the anticoagulant of choice in these conditions.

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ANSWER TO QUESTION 642

D (Braunwald, p. 1770)

Past observational studies had suggested a benefit of postmenopausal hormone replacement therapy in primary and secondary prevention of coronary artery disease events. However, more recent large randomized prospective trials have shown that hormone replacement therapy fails to reduce coronary events. In the Women's Health Initiative estrogen-only trial, 10,739 postmenopausal women were randomized to placebo or 0.625 mg of oral conjugated equine estrogens daily. The trial was stopped early because there was no significant benefit of estrogen on the primary composite endpoint of death or nonfatal myocardial infarction, but the risk of stroke and pulmonary embolism *increased* in the estrogen arm of the study. Current American Heart Association guidelines assign a class III recommendation to the use of estrogen plus progestin for primary and secondary prevention (i.e., risk is greater than benefit and should not be used).

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ANSWER TO QUESTION 643

C (Braunwald, pp. 1242–1243)

Factors that significantly increase mortality with coronary artery bypass graft surgery (CABG) include increasing age, urgent or emergent surgery, prior cardiac surgery, serum creatinine >2 mg/dL, female gender, left ventricular dysfunction, peripheral arterial disease, severe neurologic disease, and chronic obstructive lung disease. Scoring systems including the Society of Thoracic Surgeons risk estimator and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) can be used to assess the risk of adverse outcomes in individual patients.[1,2] Obesity has not been shown to be an independent predictor of mortality or cerebrovascular accidents after CABG; however, it does predict risk of developing of postoperative mediastinitis. Although not included in the EuroSCORE, preoperative atrial fibrillation is also associated with increased perioperative mortality and morbidity in patients undergoing cardiac surgery.[3]

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ANSWER TO QUESTION 644

B (Braunwald, p. 1790)

Acute myocardial infarction (AMI) is rare in women of childbearing age, but pregnancy increases the risk three- to fourfold. AMI can occur during any stage of pregnancy and is more frequent in multigravida women. Most events occur in women >30 years and the majority of the time the location is the anterior wall. Although atherosclerotic disease is typically uncommon in young women, there is a relatively high incidence of traditional risk factors among those who experience AMI during pregnancy, including cigarette smoking, hyperlipidemia, hypertension, and diabetes. The most common findings at coronary angiography in pregnant women with AMI are atherosclerotic disease (with or without intracoronary thrombus) or coronary artery dissection, the latter being the most common cause of AMI in the peripartum period. Coronary spasm or embolism is much rarer. Even during pregnancy, acute management of ST-segment elevation AMI warrants urgent coronary angiography, with percutaneous coronary intervention and stenting if appropriate. The safety of drug-eluting stents and their required prolonged dual antiplatelet therapy is unknown in pregnancy, and most experience to date has been with bare metal stents.

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ANSWER TO QUESTION 645

C (Braunwald, p. 1243)

Perioperative myocardial infarction (MI) has a major adverse effect on early and late prognosis following coronary artery bypass grafting (CABG).[1] The reported incidence of this complication is variable (0% to >10%) because of heterogeneous diagnostic criteria, with a median of 2.9%. The diagnosis of MI immediately after CABG can be difficult because usual criteria are not often applicable. For example, symptoms are not reliable because most patients are sedated and may not sense ischemic pain. Conversely, any chest discomfort described by the patient may be difficult to distinguish from sternal or pericardial sensations. The electrocardiogram may not be diagnostic because ST-segment abnormalities are very common after CABG. If new ST-segment *elevations* are observed, however, there should be concern for acute graft failure or spasm, which must be differentiated from the common diffuse ST-segment elevations representative of postoperative pericardial inflammation. The most reliable electrocardiographic findings of a post-CABG MI are new and persistent Q waves. Echocardiography may aid in the diagnosis of postoperative MI, as new wall motion abnormalities support the diagnosis of myocardial injury. However, abnormal septal motion is not specific because most patients who undergo cardiac surgery have paradoxical septal movement for at least several months after cardiac surgery. Serum markers of myocardial necrosis are also difficult to interpret in the post-CABG setting. Total creatine kinase elevations are almost universally observed because of damage to skeletal muscle in the chest wall. Myocardial-specific creatine kinase-MB isoenzymes and cardiac troponins are frequently detected in the serum as a result of myocardial incisions made for cardiopulmonary bypass. As a result, the third Universal Definition of Myocardial Infarction defines MI after CABG as an elevation of cardiac biomarker values to more than 10 times the 99th percentile upper reference limit (in patients with normal baseline troponin values) in the presence of

other clinical findings supportive of myocardial infarction, including (1) new pathologic Q waves or new left bundle branch block, (2) angiographic evidence of new coronary or bypass graft occlusion, and/or (3) imaging evidence of new infarcted territory.[2]

Clinical risk factors for peri-CABG MI include older age, longer pump time, elevated left ventricular end-diastolic pressure, preoperative unstable angina, and significant left main coronary artery disease.

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ANSWER TO QUESTION 646

C (Braunwald, pp. 1745–1746)

Older patients (>65 years of age) comprise 60% of hospital admissions for acute myocardial infarction (MI). According to a review of Medicare beneficiaries, elderly patients who present with an acute MI are more likely to have comorbid illnesses and exhibit higher rates of congestive heart failure, ventricular rupture, and mortality compared with younger individuals. Like younger age groups, there is a significant survival benefit from reperfusion therapies (percutaneous coronary intervention [PCI] or fibrinolysis) in acute ST-segment elevation MI in older patients, although few individuals >75 years have been included in pertinent clinical trials. For individuals up to the age of 75 years, most trials show that fibrinolytic, antiplatelet, and anticoagulant therapies are associated with a survival advantage; however, bleeding and transfusion rates are higher in older patients. Even fibrin-specific fibrinolytic agents are associated with increased stroke risk due to intracerebral hemorrhage in those >75 years. In patients >75 years who undergo PCI, antiplatelet therapy with prasugrel is associated with an increased risk of fatal bleeding events compared with clopidogrel and should be avoided in that population.

Ventricular remodeling after infarction may differ in the elderly because of alterations in the inflammatory response, decreased ability of the myocardium to hypertrophy, and increased collagen content of cardiac tissue. However, elderly patients benefit as much as younger individuals from beta blocker therapy for secondary prevention. In addition, in patients >65 years of age who have sustained an MI with residual left ventricular ejection fraction <40%, angiotensin-converting enzyme inhibitors reduce fatal and nonfatal events just as they do for younger individuals.

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ANSWER TO QUESTION 647

A (Braunwald, pp. 102–103, 108)

Many patients >40 years old are likely to have coronary artery disease or other cardiac conditions that may influence the safety of noncardiac surgery. The Revised Cardiac Risk Index (RCRI) is one tool used to estimate the risk of perioperative cardiovascular complications. The RCRI includes the following six independent predictors of increased risk: high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure (e.g., the S_3 gallop described in the vignette), history of cerebrovascular disease, preoperative treatment with insulin, and a preoperative serum creatinine >2 mg/dL. The more variables present, the greater the risk of a perioperative cardiovascular complication.

Notably, statistically nonsignificant risk factors include smoking, hyperlipidemia, and mild to moderate hypertension. And while preoperative unstable symptoms of angina portend a complicated postoperative course, such is not the case for patients with stable class I to II angina or remote MI without active angina. A history of supraventricular arrhythmias such as atrial fibrillation should alert the clinician to the possible development of similar rhythm disturbances postoperatively. Nonsustained ventricular tachycardia has not been associated with poor postoperative outcomes.

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ANSWER TO QUESTION 648

B (Braunwald, pp. 1757–1758)

Data from several major randomized placebo-controlled trials indicate that therapy for systolic and/or diastolic hypertension in elderly patients reduces cardiovascular events. For example, in the landmark Hypertension in the Very Elderly trial, treatment of systolic hypertension reduced the incidence of both stroke and all-cause mortality. The 8th Joint National Committee on Prevention, Evaluation, and Treatment of Hypertension (JNC 8) had recommended a goal blood pressure of <150/90 in adults age 60 years or more.[1] More recently, however, the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults revised the target to a blood pressure <130/80 for all adults, with the caveat that clinical judgment, patient preference, and a team-based approach to assess risks and benefits be applied for older adults (≥65 years old).[2]

Several studies, including the ALLHAT trial, have demonstrated that thiazide diuretics are efficacious and

a preferred first-line antihypertensive agent in the elderly. In large clinical trials, beta blockers have resulted in less cardiovascular protection than diuretics as first-line therapy. Other first-line agents include calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Data from the Framingham Study have confirmed the importance of left ventricular hypertrophy as an independent risk factor for adverse cardiac outcomes in older, hypertensive subjects. Hypertensive hypertrophic cardiomyopathy in the elderly tends to be more common in women, and the presenting symptom is usually dyspnea.

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ANSWER TO QUESTION 649

D (Braunwald, p. 1780; Fig. 90.2)

Several hemodynamic alterations occur during normal pregnancy (Fig. 5.3). Blood volume increases substantially, beginning during the second month, then rising to an average volume expansion of 50% by late pregnancy. The increase in blood volume occurs more quickly than an increase in hemoglobin, so anemia is common. The increased blood volume augments ventricular preload and stroke volume. The heart rate also rises steadily, usually by 10 to 20 beats/min by the third trimester. The augmented heart rate and stroke volume lead to a rise in cardiac output throughout pregnancy. Systemic vascular resistance begins to fall during the first trimester, reaches its lowest level in mid-pregnancy, then returns to the pre-pregnancy level before delivery. The drop in systemic vascular resistance likely reflects a combination of circulating gestational hormones, vasodilating prostaglandins, atrial natriuretic peptides, and nitric oxide, as well as the low-resistance circulation of the gravid uterus.

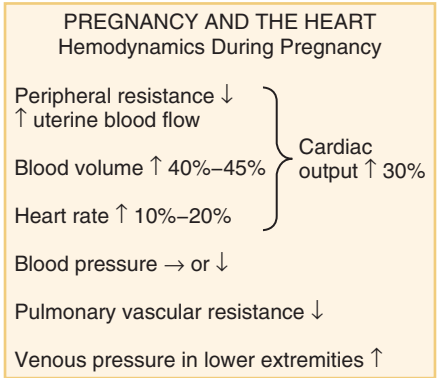

FIG. 5.3

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ANSWER TO QUESTION 650

D (Braunwald, pp. 1644–1646; Table 81.1)

Trastuzumab is a humanized monoclonal antibody that targets a subdomain of the human epidermal growth factor receptor 2 (HER2), termed ErbB2. It is predominantly used to treat HER2-positive metastatic breast cancer, but may also be effective in non-small cell lung cancer, gastric cancer, and esophageal cancer. The main potential cardiotoxicity of trastuzumab is cardiomyopathy, which may lead to severe clinical heart failure (HF). The risk of cardiomyopathy and HF is greatest in the setting of prior or concomitant anthracycline exposure. In many cases, the cardiomyopathy is partially or completely reversible with avoidance of trastuzumab and initiation of neurohormonal blockade.

Bevacizumab is a humanized recombinant monoclonal antibody that targets the vascular endothelial growth factor (VEGF) signaling pathway and has activity against a broad range of solid tumors. VEGF inhibitors may cause substantial systemic arterial hypertension through mechanisms that are incompletely understood. Less common cardiovascular complications of VEGF inhibitors include heart failure and arterial thromboembolic events.

Ipilimumab is an immune checkpoint inhibitor that targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Checkpoint proteins like CTLA-4 are important negative regulators of T-cell activation, and inhibiting their function results in antineoplastic activity by preventing tumors from evading the immune system. Because checkpoint inhibitors do not selectively enhance the anti-tumor immune response, they can also cause widespread adverse inflammatory reactions. Although the risk is low, these agents have been associated with clinically significant and in some cases lethal myocarditis.

Anastrozole is an aromatase inhibitor, which blocks the conversion of androgens to estrogen and is a highly effective therapy in the treatment of hormone-receptor positive breast cancer. In contrast to the selective estrogen receptor modulator tamoxifen, aromatase inhibitors are *not* associated with an increased risk of venous thromboembolism. They are, however, associated with increased total cholesterol and hypertension.

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ANSWER TO QUESTION 651

C (Braunwald, pp. 1906–1907)

This patient presents with an acute subarachnoid hemorrhage and a markedly abnormal electrocardiogram.

Electrocardiographic abnormalities are present in approximately 70% of patients with subarachnoid hemorrhage and can include ST-segment elevation or depression, deep symmetric T wave inversions as in this patient, and a prolonged QT interval that can lead to torsades de pointes. The mechanism of cardiac and electrocardiographic abnormalities in acute brain injury likely relates to autonomic nervous system dysfunction and excessive myocardial catecholamine release. In this setting, myocardial damage can occur with release of cardiac biomarkers, without primary acute coronary plaque rupture or thrombus formation. The magnitude of peak troponin elevation, but not the degree of electrocardiographic abnormality, is predictive of an adverse cardiac outcome. Beta blockers appear useful in minimizing myocardial damage and controlling arrhythmias in patients with subarachnoid hemorrhage.

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ANSWER TO QUESTION 652

D (Braunwald, p. 114)

It is generally safe and appropriate to continue most chronically administered cardiac medications up to the day of surgery and to resume them as soon as possible after the operation. This is true of beta blockers in patients with underlying coronary artery disease (or other indications for chronic beta blocker use) and continuing such therapy perioperatively is a class I American College of Cardiology/American Heart Association guideline recommendation.[1] However, there has been controversy about the role of *initiating* preoperative beta blocker therapy for the purpose of risk reduction.[2] Conclusions from randomized clinical trials have varied, in part related to methodologic differences in the studies. The evidence to date suggests that beta blockers reduce the perioperative risk of cardiovascular events (ischemia, atrial fibrillation, need for coronary interventions), but can be associated with bradycardia, hypotension, and stroke, particularly if high doses or long-acting preparations are initiated shortly before surgery.[3] If initiation of preoperative beta blocker therapy is planned, it should be started at least 2 to 7 days before surgery to assess tolerability and safety and to allow titration of the dosage if appropriate. Thus, current guidelines recommend against initiation of a beta blocker without dose titration immediately before surgery (especially high-dose or long-acting forms).[1]

Although nitrates reduce intraoperative ischemia, cardiac outcomes are not affected.

Statins have anti-inflammatory and plaque-stabilizing properties, and studies in patients undergoing vascular surgery have demonstrated reduced cardiac event rates in patients on statin therapy perioperatively.[4]

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ANSWER TO QUESTION 653

C (Braunwald, pp. 1735–1739)

Assessment of the heart's normal aging process is difficult because of the high prevalence of cardiovascular disease in older individuals. Studies in which coronary artery disease and other common cardiovascular conditions have been carefully excluded have revealed several pertinent findings. First, there is moderate hypertrophy of left ventricular myocardial cells, probably in response to increased arterial stiffness and loss of cardiac myocyte number with age. Although myocardial cells are unable to proliferate, they can increase in size as an adaptive response. Despite alterations in contractile proteins leading to reductions in the velocity of contraction and lengthening of contraction and relaxation times, peak contractile force production is maintained at normal levels, and there appear to be no changes in cardiac output, stroke volume, or ejection fraction at rest with normal aging. However, there are changes in beta-adrenoceptor-mediated inotropic and chronotropic cardiovascular responses with aging that result from generalized desensitization. Thus, the maximal heart rate during exercise and other cardiovascular responses to exercises are blunted.

Among the cellular and molecular changes that occur with aging, endothelial production of nitric oxide (NO) decreases, likely reflecting a combination of decreased endothelial cell mass (due to cell senescence and apoptosis) and increased NO utilization because of elevated vascular superoxide anion production in older subjects.

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ANSWER TO QUESTION 654

D (Braunwald, pp. 1242–1243)

Deep sternal wound infection is among the most serious complications of cardiac surgery. Patients with deep sternal wound infections present approximately 2 weeks after surgery with fever, leukocytosis, bacteremia, discharge, and erythema at the wound site. Risk factors for the development of

mediastinal infection include a prolonged cardiopulmonary bypass time, excessive bleeding necessitating reexploration for hemostatic control, the use of both internal mammary arteries, and older age. Atrial fibrillation is also a predictor of mediastinitis in patients undergoing coronary artery bypass grafting. Obesity is the most important risk factor for sternal dehiscence, whether or not infection is present.[1]

The incidence of postoperative deep sternal wound infection appears to be decreasing.[2] A significant contribution to this reduction is that the rate among diabetics has fallen from about 3.2% to about 1.0% over the past decade, possibly related to the introduction of perioperative intravenous insulin.

About half of deep sternal wound infections are caused by *Staphylococcus* species, and gram-negative organisms account for about 40%. Confirmation of a sternal wound infection often requires surgical exploration and removal of material for Gram stain and culture. Imaging techniques, including computed tomography or magnetic resonance imaging, are helpful. Intravenous antibiotics, with possible debridement and irrigation, may be required for prolonged periods. Early diagnosis and initiation of treatment enhance the prognosis. Mediastinal infections have not been shown to change patency rates of bypass grafts.

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ANSWER TO QUESTION 655

C (Braunwald, p. 1706)

Cardiac catheterization plays an important role in patients with suspected pulmonary arterial hypertension (PAH) to confirm the diagnosis, establish the severity of disease, and determine prognosis. Patients with PAH demonstrate a normal or low pulmonary capillary wedge pressure (PCWP), distinguishing PAH from pulmonary venous hypertension. A vasodilator challenge during catheterization allows assessment of pulmonary vasoreactivity and helps to guide therapy. Such a challenge can be accomplished with intravenous adenosine, intravenous epoprostenol, or inhaled nitric oxide. A favorable acute effect of these vasodilators (i.e., >10 mm Hg decrease in mean pulmonary artery pressure [PAP] to an absolute mean PAP lower than 40 mm Hg) without adverse effects (e.g., a decline in cardiac output or systemic blood pressure, or a rise in PCWP) is predictive of a favorable response to oral calcium channel blockers. An increase in PCWP during vasodilator testing would be consistent with pulmonary veno-occlusive disease or impending left ventricular failure.

When oral calcium channel blockers are used to treat PAH, high doses are required to achieve full clinical benefit.

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ANSWER TO QUESTION 656

C (Braunwald, pp. 1913–1914; Fig. 98.5)

Risk factors for contrast-induced acute kidney injury (CI-AKI) include chronic renal insufficiency, diabetic nephropathy, intravascular volume depletion, renal artery stenosis, and concurrent use of agents that alter renal hemodynamics (e.g., angiotensin-converting enzyme inhibitors). The smallest possible volume of contrast agent should be used in patients with renal insufficiency, because the risk of nephrotoxicity is related to the amount injected.

At present, the intervention that has been demonstrated to consistently reduce the incidence of this complication in patients at risk is intravenous (IV) normal saline hydration before and after the procedure. A randomized trial of IV isotonic sodium bicarbonate in elective coronary procedures showed no difference in post-procedure CI-AKI compared with IV saline, such that either could be used for hydration. Several other agents have been evaluated for prevention of CI-AKI, including mannitol, calcium channel antagonists, dopamine, and atrial natriuretic peptide; however, none has been shown to reduce the risk of renal complications.[1]

It has been hypothesized that lower ionic strength contrast agents should reduce the incidence of contrast nephropathy. Although that has not been demonstrated in patients with normal baseline renal function, the risk of contrast-induced nephropathy *is* reduced in patients with baseline renal insufficiency (with or without diabetes) if nonionic low-osmolar contrast medium is used.

Small studies had suggested that oral administration of *N*-acetylcysteine, an antioxidant, could reduce the risk of CI-AKI; however, several large randomized trials did not confirm this benefit.[2,3]

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ANSWER TO QUESTION 657

A (Braunwald, pp. 1817–1818)

The major cardiovascular changes that occur in hypothyroidism include a reduction in cardiac contractility, an increase in systemic vascular resistance, and a slowing of the heart rate. The decreased cardiac contractility and relative bradycardia result in a lower cardiac output. Thyroid hormone normally reduces smooth muscle tone, resulting in a decrease in peripheral vascular resistance. In the

relative absence of thyroid hormone, peripheral vascular tone increases and contributes to *hypertension*, which is common in hypothyroid patients. Thyroid hormone deficiency results in alterations in myocardial depolarization that can prolong the QT interval. Hypothyroidism is also associated with increased vascular permeability. Thus, pericardial effusions are common, developing in approximately one-third of patients, although progression to cardiac tamponade is rare.

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ANSWER TO QUESTION 658

C (Braunwald, pp. 1300, 1307; see also Answer to Question 67)

Marfan syndrome, caused by mutations in the fibrillin gene (*FBN1*), is associated with significant morbidity and mortality from cardiovascular causes. The most life-threatening complication is aortic dissection, to which patients with Marfan syndrome are predisposed because of aortic cystic medial degeneration. Such dissections usually commence just above the coronary ostia and may extend into the entire length of the aorta. Beta blockers limit aortic shear stress and are an important component of prevention. Prospective studies have confirmed a slowing of aortic dilatation and reduced risk of dissection in patients treated with beta-blockers. Limited data suggest that therapy with an angiotensin receptor blocker may also slow progression of aortic enlargement, presumably through effects on transforming growth factor beta signaling.

The dimension of the proximal aorta can be followed serially by transthoracic echocardiography, computed tomography, or magnetic resonance imaging. Prophylactic aortic root replacement is recommended in Marfan syndrome patients once the diameter approaches 5 cm to prevent dissection and progressive aortic regurgitation.[1,2] Some groups recommend replacement even earlier, when the diameter is in the 4.5- to 5.0-cm range.

Aortic dissection is an unfortunate potential complication of pregnancy in Marfan syndrome, occurring most commonly between the third trimester and the first month postpartum. The risk of dissection in this setting is related to the size of the aortic root and appears to be low in patients with root diameters of ≤4 cm.[3]

Progressive valvular impairments are also common in patients with Marfan syndrome. The risk of severe aortic regurgitation increases as the diameter of the aortic root enlarges. Mitral valve prolapse, associated with elongated and redundant leaflets, is detected in 60% to 80% of patients by echocardiography.[4] Progression to severe mitral regurgitation occurs in up to 25% of patients.

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ANSWER TO QUESTION 659

B (Braunwald, p. 1837; Tables 93.5 and 93.6)

This patient has heparin-induced thrombocytopenia (HIT), of which there are two forms. Type I HIT is the common, milder form that likely results from non–immune-mediated heparin-induced aggregation of platelets. Platelet counts usually drop within 2 days of therapy but rarely fall below 100,000/μL, and patients do not often develop bleeding complications. In the majority of such cases, heparin can be continued and the platelet count will improve.

Type II HIT, which has developed in the patient presented in this question, is the more dangerous form. It produces more severe thrombocytopenia, with levels often <50,000/μL. It develops when antibodies form against the heparin-platelet factor 4 (PF4) complex. These antibodies bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors, an action that stimulates platelet activation and thrombosis. The diagnosis can be confirmed by the measurement of anti-heparin/PF4 antibodies.

Type II HIT usually becomes manifest for the first time within 4 to 14 days of the initiation of heparin therapy. However, on subsequent exposure, it can present quickly after even small doses of heparin. Therefore, patients with a history of type II HIT should never receive any form of heparin.[1]

When type II HIT develops, heparin should be stopped immediately (Table 5.4). If further anticoagulation is needed, a parenteral direct thrombin inhibitor, such as lepirudin, argatroban, or bivalirudin, can be substituted.[2] Fondaparinux, a synthetic pentasaccharide with anti-factor Xa activity, is another anticoagulant that can be used safely in patients with HIT.[3]

TABLE 5.4 Management of Heparin-Induced Thrombocytopenia

Stop all heparin.
Give an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin, or fondaparinux.
Do not give platelet transfusions.
Do not give warfarin until the platelet count returns to baseline levels; if warfarin was administered, give vitamin K to restore the international normalized ratio to normal.
Evaluate for thrombosis, particularly deep vein thrombosis.

Low-molecular-weight heparins (LMWHs) are associated with a lower incidence of HIT than is intravenous unfractionated heparin (UFH). However, antibodies to UFH cross-react with LMWHs, so once a diagnosis of type II HIT is made, both types of heparin should be avoided.

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ANSWER TO QUESTION 660

D (Braunwald, pp. 1458, 1839–1843)

The non–vitamin K antagonist oral anticoagulants are approved for use in nonvalvular atrial fibrillation, among other indications. However, none of these agents is approved for use in patients with mechanical heart valves. Dabigatran was compared to warfarin in the randomized, prospective RE-ALIGN trial of patients with bileaflet mechanical heart valves. The trial was terminated early because dabigatran was associated with increased rates of thromboembolic and bleeding complications compared with warfarin.

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ANSWER TO QUESTION 661

C (Braunwald, pp. 1873–1874)

Metastatic tumors to the heart or pericardium are much more common than are primary cardiac malignancies. Metastases within cardiac structures are present at autopsy in approximately 9.1% of patients with malignant disease, whereas primary cardiac tumors are found in fewer than 0.1% of individuals postmortem. The most common malignancy that metastasizes to the heart is carcinoma of the lung (36% to 39% of metastases), followed in frequency by carcinoma of the breast and hematologic malignancies. Single metastases to the heart are rare, such that the finding of a solitary cardiac tumor is more likely indicative of a benign process.

Cardiac metastases typically involve the pericardium and myocardium, while the valves and endocardium are only rarely affected. Many cardiac metastases are clinically silent. For example, in malignant melanoma, 28% to 56% of patients have metastases to the myocardium or pericardium, yet cardiac symptoms are rare. The most common clinical manifestations of metastatic disease are due to pericardial effusion (i.e., tamponade), tachyarrhythmias, conduction blocks, and congestive heart failure.

A chylous pericardial effusion is characteristic of lymphoma.

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ANSWER TO QUESTION 662

A (Braunwald, pp. 1514–1515; Table 74.2)

This patient presents with acute rheumatic fever (ARF) after probable streptococcal pharyngitis. ARF typically manifests as a subset of five major manifestations (the "Jones criteria"): carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum. In addition, several other symptoms and laboratory findings are usually present in this condition and constitute minor criteria. These include nonspecific arthralgias, especially of large joints, fever, elevated acute-phase reactants (i.e., erythrocyte sedimentation rate and C-reactive protein), and electrocardiographic findings that include prolongation of the PR interval (not the QT interval). The diagnosis of ARF is made in the presence of preceding group A beta-hemolytic streptococcal infection when two major criteria, or one major and two minor criteria are present.

In 2015, the Jones criteria were revised to recognize that their clinical utility is determined by the background disease prevalence of acute rheumatic fever in a given population (i.e., the pretest probability). As such, different thresholds are required for meeting the major and minor criteria in low-risk versus moderate- and high-risk populations (Table 5.5).[1]

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TABLE 5.5 2015 Jones Criteria for the Diagnosis of Rheumatic Fever[a]

LOW-RISK POPULATIONS	MODERATE- AND HIGH-RISK POPULATIONS
Major Criteria	
Carditis (clinical or subclinical[b]) Arthritis (polyarthritis only) Chorea Erythema marginatum Subcutaneous nodules	Carditis (clinical or subclinical) Arthritis (including polyarthritis, monoarthritis, or polyarthralgia[c]) Chorea Erythema marginatum Subcutaneous nodules
Minor Criteria	
Polyarthralgia Fever (≥38.5°C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Monoarthralgia Fever (≥38°C) ESR ≥30 mm in the first hour and/or CRP ≥3.0 mg/dL[d] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

Joint manifestations are only considered in either the major or minor categories, but not both in the same patient.

[a]Annual ARF incidence of ≤2 per 100,000 school-aged children or all age RHD prevalence of ≤1 per 1000 people per year.

[b]Defined as echocardiographic.

[c]Polyarthralgia should only be considered as a major manifestation in moderate- and high-risk populations after exclusion of other causes.

[d]CRP value must be greater than the normal laboratory upper limit. In addition, as the ESR might evolve during the course of ARF, peak ESR values should be used.

ARF, Acute rheumatic fever; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *RHD,* rheumatic heart disease.

ANSWER TO QUESTION 663

D (Braunwald, pp. 1848, 1856, 1859; Table 94.1)

Rheumatoid arthritis (RA) is the most common systemic rheumatic disorder. Potential cardiac complications include pericardial, myocardial, coronary, or conduction system disease. The incidence of symptomatic pericarditis has declined (<2% of patients) with current aggressive management and increasing use of biologic therapies in RA, and asymptomatic pericardial effusions are more common than acute pericarditis. Very rarely, pericardial constriction develops.

Arrhythmias or conduction abnormalities (first-degree atrioventricular [AV] block, most commonly) are not unusual in RA, occurring in up to 50% of patients, but are rarely symptomatic. Conduction disease may result from impingement on the conduction fibers by rheumatoid nodules, or in the case of AV block, by rare rheumatic myocarditis or amyloid deposition.

Patients with RA have an increased incidence of atherosclerotic coronary artery disease (CAD), likely related to both traditional risk factors and disease-related inflammation. Symptoms of CAD may be masked in RA patients with limited physical mobility, but the risk for myocardial infarction is similar to that of diabetics. Women with RA are twice as likely as age-matched controls to suffer myocardial infarction. In the past, coronary arteritis had been reported in up to 20% of patients in autopsy series; however, in the current anti-inflammatory era, it is only rarely of clinical significance. The epicardial arteries are generally spared, because arteritis is usually confined to smaller intramyocardial vessels.

Autopsy studies have demonstrated rheumatoid involvement of the cardiac valves, but such lesions are only occasionally identified clinically. Valvular thickening may be evident echocardiographically, more commonly in patients with seropositive RA and prominent extra-articular nodular disease.

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ANSWER TO QUESTION 664

C (Braunwald, pp. 1841–1843)

A major goal of therapy in patients with atrial fibrillation (AF) is to prevent thromboembolic complications such as stroke. This patient is at increased risk for thromboembolism in the setting of AF because of his age, hypertension, and diabetes (CHA_2DS_2-VASc score = 4) and therefore warrants chronic anticoagulation therapy.

Dabigatran etexilate is an oral direct thrombin inhibitor that reduces the risk of stroke and systemic embolism in patients with nonvalvular AF. In the RE-LY trial, dabigatran (at doses of 110 and 150 mg twice daily) was compared prospectively with warfarin (dose adjusted to achieve an international normalized ratio between 2.0 and 3.0) for stroke and systemic embolism prevention in 18,113 patients with nonvalvular AF, followed for a median of 2 years. The annual rate of stroke or systemic embolism was 1.7% with warfarin, 1.5% with the lower-dose dabigatran regimen ($P < .001$), and 1.1% with the higher-dose regimen ($P < .001$). The lower-dose dabigatran regimen was noninferior to warfarin, whereas the higher dose regimen was actually superior for stroke and embolism prevention. The annual rates of major bleeding were 3.4% with warfarin compared with 2.7% and 3.1% with the lower-dose and higher-dose dabigatran regimens, respectively. That is, the lower-dose dabigatran regimen was associated with less major bleeding than warfarin, whereas the rates were similar in the higher-dose dabigatran and warfarin cohorts. Episodes of hemorrhagic stroke were significantly fewer with either dose of dabigatran compared with warfarin.

The most common gastrointestinal side effects of dabigatran are dyspepsia and gastritis; hepatotoxicity was not observed with dabigatran in the RE-LY trial.

The labeling for dabigatran recommends a dose adjustment to 75 mg twice daily for patients with a reduced creatinine clearance between 15 and 30 mL/min. There is insufficient experience to recommend a dose for a creatinine clearance <15 mL/min.

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ANSWER TO QUESTION 665

B (Braunwald, p. 1819; Fig. 92.7)

Amiodarone, a potent class III antiarrhythmic agent, has two primary effects on thyroid function. First, it inhibits the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3), causing a reduction of serum T_3 and a transient rise in thyroid-stimulating hormone (TSH). Within a short time, however, a compensatory increase in serum T_4 levels occurs and TSH returns to normal. Clinically, such patients are euthyroid, even though T_4 levels are elevated. Amiodarone's second effect relates to its large content of iodine (30% by weight), which inhibits synthesis and release of T_4 from the thyroid gland, causing a more sustained rise in TSH. In some patients, especially those with underlying thyroid disease, clinical hypothyroidism and a marked rise in TSH result.

Amiodarone-induced hyperthyroidism is less common and may arise from two distinct mechanisms. Type I develops primarily in individuals with underlying thyroid disease, typically in iodine-deficient environments. Such patients display evidence of thyroid autoimmunity, including antithyroid antibodies. In contrast, type II is a form of thyroiditis that develops in a previously normal gland, presumably mediated by proinflammatory cytokines, marked by an elevation of circulating interleukin-6. This condition is a thyroid-destructive process, and hyperthyroidism results from release of preformed thyroid hormone, a situation that can persist for months. Unlike type I, this form of hyperthyroidism tends to respond to glucocorticoid therapy.

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ANSWER TO QUESTION 666

D (Braunwald, pp. 1726–1727, 1729–1730, 1732; see also Answer to Question 486)

The two principal sleep disorders associated with cardiovascular disease are obstructive sleep apnea (OSA) and

central sleep apnea (CSA). OSA is characterized by transient upper airway occlusion that results in partial or complete cessation in airflow leading to hypoxia, sympathetic activation, repeated arousal and wakefulness, and sleep fragmentation. Individuals with OSA demonstrate persistently heightened sympathetic activity, even during daytime wakefulness. This in turn leads to peripheral vasoconstriction and hypertension, as well as automatic tachycardias driven by the augmented sympathetic tone. In addition, reflex parasympathetic activity can lead to profound nocturnal bradycardias.

Continuous positive airway pressure (CPAP) is the cornerstone of OSA management. This therapy effectively splints open the airway, thus preventing airway collapse, improving nocturnal hypoxia, and reducing sympathetic activity. Randomized controlled trials of CPAP in OSA have demonstrated decreased daytime sleepiness, improved health-related quality-of-life and mood, and lower blood pressure.[1] While observational trials have suggested decreased mortality with CPAP usage, randomized trials to date have not confirmed that.[2,3] Importantly, such trials have been limited by either inadequate power or modest CPAP adherence.

In contrast to OSA, CSA represents an instability of ventilatory control, resulting in oscillations in ventilation with periodic hyperpnea and apnea.[4] When manifest as Cheyne-Stokes respirations, it is associated with advanced heart failure. CPAP is effective in the management of CSA, is associated with decreased sympathetic drive, reduced ventricular afterload, and improvement in left ventricular ejection fraction. CPAP has been shown to improve nocturnal oxygen saturation and 6-minute walk distance in patients with class II to IV heart failure and CSA.

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ANSWER TO QUESTION 667

B (Braunwald, pp. 1692–1693; Table 84.7)

Approximately 20% of patients with unprovoked deep venous thrombosis experience a recurrence within 2 years of stopping anticoagulation therapy. Therefore, after the initial treatment period of at least 3 months, many experts recommend extended-duration anticoagulation. In a randomized trial of patients who had completed 6 to 12 months of anticoagulation for acute venous thromboembolism (VTE), both standard-dose apixaban (5 mg twice daily) and low-dose apixaban (2.5 mg twice daily) were shown to reduce the rate of recurrent VTE compared to placebo without increasing major bleeding.[1] Similarly, extended-duration treatment with rivaroxaban (20 mg daily) in patients who had completed 6 to 12 months of anticoagulation for VTE reduced the rate of recurrent VTE compared to placebo in the EINSTEIN DVT Continued Treatment trial.[2] More recently, in the EINSTEIN CHOICE trial, extended-duration treatment with either standard-dose rivaroxaban (20 mg daily) or low-dose rivaroxaban (10 mg daily) reduced the rate of recurrent VTE compared to aspirin.[3] Extended-duration anticoagulation with both standard-intensity warfarin (international normalized ratio [INR] target 2.0 to 3.0) or low-intensity warfarin (INR target 1.5 to 2.0) are also valid evidence-based options for extended-duration anticoagulation.[4] However, in contrast to the non-vitamin K antagonist oral anticoagulants, dosing of vitamin K antagonists requires close monitoring and dose adjustment rather than fixed dosing.

Two studies have tested low-dose aspirin (100 mg daily) versus placebo in patients with unprovoked VTE who had completed at least 6 months of standard anticoagulation.[5,6] In a meta-analysis, there was a 32% reduction in the rate of recurrence of VTE with aspirin during a median follow-up of >2 years, without an increase in major bleeding. Thus, while patients with unprovoked VTE derive the lowest recurrence rates with extended-duration standard anticoagulants, aspirin offers an evidence-based benefit for patients who do not wish to restrict their lifestyle or be subject to the bleeding risk of indefinite-duration standard anticoagulation.

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ANSWER TO QUESTION 668

B (Braunwald, pp. 102–103, 108)

When surgery is elective, it is appropriate to estimate cardiovascular risk using multifactorial indices. Independent predictors of complications with noncardiac surgery include (1) high-risk type of operation, (2) history of ischemic heart disease, (3) history of heart failure, (4) history of stroke, (5) diabetes with preoperative insulin use, and (6) preoperative serum creatinine >2 mg/dL. An example of a high-risk operation is abdominal aortic aneurysm surgery, whereas low-risk procedures include endoscopy, cataract surgery, superficial procedures and biopsies, and transurethral prostate surgery. Carotid endarterectomy poses an intermediate risk.

Ischemic heart disease is a major determinant of perioperative morbidity and mortality. However, if a patient is clinically stable, and can carry a grocery bag up one flight of stairs (the equivalent of >4 METS of activity) without stopping or experiencing anginal symptoms, most surgical procedures will be well tolerated and no additional preoperative cardiac testing is typically necessary. Conversely, a patient who develops shortness of breath or chest discomfort with only minor exertion is at high risk for postoperative cardiac events

and warrants additional cardiac testing, especially if more than a minor surgical procedure is planned.

Historically, the cardiac risk of noncardiac surgery in patients with prior myocardial infarction (MI) has related inversely to the length of time that has passed since the acute coronary event. Studies from the 1970s concluded that purely elective surgery should be delayed for 6 months after an MI to ensure that cardiovascular risk had returned to baseline. In those studies, the risk of reinfarction or death was approximately 30% when patients were operated on within 3 months of an MI, but only 5% when 6 months had elapsed before the operation. Later studies, in the era of careful perioperative monitoring, demonstrated much lower cardiac complication rates: approximately 6% risk of reinfarction for operations performed within 3 months of an MI and 2% risk for operations performed within 3 to 6 months. These historic risks are less relevant today in the era of early revascularization (mechanical or fibrinolytic) and aggressive postevent pharmacologic therapy for acute coronary syndromes (ACS). Current guidelines suggest that the highest risk of elective surgery for such patients is limited to the first 30 days after an ACS while the disrupted coronary plaque and myocardium are healing.

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ANSWER TO QUESTION 669

C (Braunwald, pp. 1589, 1790; see also Answer to Question 636)

The presentation of this patient is most consistent with peripartum cardiomyopathy (PPCM). This disorder is a form of dilated cardiomyopathy that manifests in the last trimester of pregnancy or in the early postpartum period. The incidence is higher in women >30 years of age, women with twin pregnancies, multiparous women, and African American women. Recent studies have suggested significant overlap in the genetic predisposition to PPCM and other forms of idiopathic dilated cardiomyopathy.

The prognosis of this disorder is favorable compared with other forms of dilated cardiomyopathy, with approximately 50% of patients showing marked improvement or complete recovery within 6 months postpartum. The remainder either stabilizes with reduced cardiac function or declines progressively, eventually requiring cardiac transplantation. The predictors for a poor outcome include older age, higher parity, severe left ventricular dilatation, and onset of symptoms later after delivery. There is a high risk of relapse of PPCM in subsequent pregnancies, and that risk appears to be greatest in women who have persistently impaired cardiac function.

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ANSWERS TO QUESTIONS 670 TO 674

670–E, 671–D, 672–B, 673–C, 674–A (Braunwald, pp. 1850, 1857–1859, 1862)

The spondyloarthropathies, including ankylosing spondylitis, reactive arthritis, and psoriatic arthritis, have a predilection for arthritis of the sacroiliac and lumbosacral joints. These diseases are associated with the histocompatibility antigen HLA-B27 and occur predominantly in men. *Ankylosing spondylitis* is the most common of these syndromes to involve the heart and classically causes dilatation of the aortic valve ring with fibrous thickening and inflammation.[1] The aorta in ankylosing spondylitis is histologically similar to that in syphilitic aortitis, including adventitial scarring, intimal proliferation, and narrowing of the vasa vasorum. Aortic regurgitation results from thickening of the valvular cusps and dilatation of the aortic root. Conduction system disorders, due to fibrous infiltration in the atrioventricular node and the bundle of His, may be seen in ankylosing spondylitis as well.

Reactive arthritis is a form of nonpurulent arthritis that may follow enteric or urogenital infections. It may be accompanied by uveitis/conjunctivitis and nongonococcal urethritis (formerly termed Reiter syndrome). The cardiac complications of reactive arthritis are similar to those of ankylosing spondylitis.[2]

Cardiac abnormalities in patients with *systemic sclerosis/scleroderma* often relate to systemic or pulmonary hypertension, but may also include myocardial fibrosis and contraction band necrosis, causing diastolic and/or systolic ventricular dysfunction. Symptomatic pericarditis occurs in 7% to 20% of patients. Conduction defects and thickening of the mitral and aortic valves may also occur.[3]

Giant cell arteritis predominantly causes inflammation of the aorta, its major branches, and coronary arteries. Weakening of the vessels may lead to dilatation, aneurysm formation, and valvular insufficiency. The vascular pathology often reveals granuloma formation.[4]

Behçet syndrome is a multisystem disorder characterized by recurrent oral and genital ulcers and uveitis. The ulcers are often painful and necrotic, and eye involvement occasionally progresses to blindness. The etiology of the disease is unclear, but appears to involve endothelial activation as a mediator of vascular inflammation. Venous and arterial thrombosis may occur, as well as aneurysm formation of the large vessels. Diffuse aortitis in Behçet syndrome can lead to aortic root dilatation and valvular insufficiency.[5]

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ANSWERS TO QUESTIONS 675 TO 678

675–C, 676–B, 677–D, 678–A (Braunwald, pp. 677, 1831, 1833, 1837)

Numerous cardiac medications can cause adverse effects. For example, heparin can result in thrombocytopenia by two main mechanisms as described in the Answer to Question 659.

A positive direct Coombs test is seen in up to 10% of patients who receive alpha-methyldopa, an antihypertensive that is sometimes used in pregnancy. In these patients, IgG antibody is directed against the Rh complex of red cells. Hemolysis may be severe but improves within several weeks after cessation of the medication.

The most common side effects of ticagrelor, a platelet $P2Y_{12}$ receptor inhibitor, are bleeding, dyspnea (~15% of patients in the PLATO trial),[1] and ventricular pauses, which are typically asymptomatic. Dyspnea, when present, usually occurs soon after initiating therapy and is self-limited. The mechanism is unknown.

Procainamide may cause a syndrome resembling systemic lupus erythematosus (SLE). Symptoms consist of polyarthralgias, pleuritis, and photosensitive rashes. Unlike conventional SLE, nephritis and central nervous system complications are very rare. Patients with drug-induced lupus are antinuclear antibody (ANA) positive with antibodies to histones but rarely display hypocomplementemia or antibodies to DNA. Discontinuation of procainamide typically results in improvement of symptoms within a few days to weeks. However, ANA levels may remain elevated for years.

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ANSWERS TO QUESTIONS 679 TO 683

679–C, 680–A, 681–B, 682–B, 683–C (Braunwald, pp. 1850–1852; see also Answers to Question 632 and Question 633)

Takayasu arteritis (TA), also termed *pulseless disease*, is of unknown etiology and is characterized by marked fibrous and degenerative scarring of the elastic fibers of the vascular media.[1] It most commonly involves the aorta and carotid arteries. The disease is 10 times more common in women than in men, and in most patients onset occurs during the teen years. Patients typically present initially with malaise, weight loss, night sweats, arthralgias, pleuritic pain, anorexia, and fatigue. Regardless of whether a patient goes through this initial phase, symptoms and signs referable to the obliterative and inflammatory changes in affected blood vessels begin to appear following a latent period. These include diminished or absent pulses with claudication (upper extremities > lower extremities), hypertension (related to renal artery stenosis or increased vessel rigidity), and aortic root aneurysms with aortic regurgitation. Common laboratory abnormalities include elevated sedimentation rate, low-grade leukocytosis, and normocytic anemia. Treatment includes glucocorticoid therapy. Patients with refractory symptoms may respond to azathioprine, mycophenolate mofetil, methotrexate, leflunomide, intravenous cyclophosphamide, tumor necrosis factor antagonists, or tocilizumab (an interleukin-6 receptor antagonist).

Giant cell arteritis (GCA; also termed temporal arteritis) is a disease of unknown etiology characterized by granulomatous inflammation of large- to medium-caliber arteries with a special predilection for the vessels of the head and neck.[2] It arises primarily in elderly people with a female predominance. Clinically, the triad of severe headache, fever, and marked malaise characterizes the illness. The headaches are often severe and are typically localized over involved temporal arteries. Claudication of the jaw muscles during chewing is present in up to two-thirds of patients. Involvement of the ophthalmic artery leads to visual symptoms and may result in irreversible blindness. The syndrome of polymyalgia rheumatica, consisting of diffuse muscular aching and stiffness, occurs in about 40% of patients with GCA. In a minority of cases, involvement of the aorta or its major branches may lead to symptoms and signs similar to those of TA, although renal artery involvement is rare in GCA.

Patients with GCA appear ill and are almost always febrile. Affected vessels feel abnormal to palpation and are tender, allowing experienced examiners to make the diagnosis of temporal arteritis at the bedside by identifying an indurated, beaded, tender temporal artery. Laboratory tests often reveal a very high erythrocyte sedimentation rate, normochromic, normocytic anemia, and elevated acute-phase reactants. Biopsy of an involved temporal artery confirms the diagnosis.

Management of GCA includes early intervention with high-dose steroid therapy followed by a gradual taper to a maintenance dose, which is typically continued for 1 to 2 years. Early administration of steroid therapy is crucial to prevent involvement of the ophthalmic arteries and possible blindness. Recent evidence suggests that combining tocilizumab with steroid therapy may lead to higher rates of sustained remission in GCA.[3]

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ANSWERS TO QUESTIONS 684 TO 688

684–C, 685–A, 686–B, 687–D, 688–E (Braunwald, pp. 1641–1645; Table 81.1)

Many chemotherapeutic agents have potential cardiovascular toxicities. The anthracyclines (e.g., doxorubicin, daunorubicin, and idarubicin) may cause acute cardiac effects (including atrial and ventricular arrhythmias and pericardial effusion) or more chronic impairment (dilated cardiomyopathy with heart failure). As described in the Answer to Question 544, heart failure due to anthracycline therapy is dose related and develops more frequently when concurrent risk factors are present, including prior heart disease, radiation therapy exposure to the heart, and use of other cardiotoxic chemotherapeutic agents (e.g., trastuzumab, paclitaxel).

Patients receiving 5-fluorouracil may experience acute chest pain and myocardial infarction during or immediately after infusion. The mechanism of this adverse effect is

unknown. Cyclophosphamide and ifosfamide are alkylating agents that can cause an acute hemorrhagic myopericarditis. Interleukins, which are potent modulators of the immune system, are associated with capillary leak syndrome, hypotension, noncardiogenic pulmonary edema, and nephrotoxicity.

Sunitinib is a tyrosine kinase inhibitor that targets vascular endothelial cell growth factor receptors and is used to inhibit progression of renal cell carcinoma and gastrointestinal stromal tumors. Hypertension is a common side effect, with marked elevation in blood pressure in 8% to 20% of patients.

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ANSWERS TO QUESTIONS 689 TO 693

689–C, 690–D, 691–E, 692–A, 693–B (Braunwald, pp. 1809–1810, 1812, 1815–1818)

Endocrine disorders often exhibit cardiovascular manifestations. Excess thyroid hormone levels result in tachycardia, palpitations, and hypertension, often with a widened pulse pressure.[1] Cardiac examination reveals a hyperdynamic impulse with an accentuated S_1. Systolic murmurs are common, and a *Means-Lerman scratch,* a grating systolic sound at the upper left sternal border, may be auscultated during expiration.

The cardiovascular manifestations of hypothyroidism include bradycardia, diastolic hypertension with a narrowed pulse pressure, cardiomegaly with a reduced ejection fraction, and pericardial effusion, which only rarely results in tamponade physiology.[1]

Cushing syndrome, a state of augmented glucocorticoid exposure, is associated with accelerated atherosclerosis, likely related to hypertension and hyperglycemia in this condition. *Carney complex* is a genetic syndrome that includes cardiac myxomas, pigmented dermal lesions, and endocrine overactivity that can include Cushing syndrome. This autosomal-dominant condition arises from mutations in the *PRKAR1A* gene, which encodes a regulatory subunit of protein kinase A.[2]

Hyperaldosteronism is associated with excess aldosterone production from an adrenal or extra-adrenal source. Hypertension, hypokalemia, and metabolic alkalosis are common findings.[3] Many of the cardiac findings are nonspecific and are a consequence of the metabolic and electrolyte abnormalities. For example, U waves and ventricular arrhythmias result from associated hypokalemia.

Parathyroid hormone has direct inotropic and chronotropic effects on the heart, likely due to increased myocyte calcium entry. Hypercalcemia associated with hyperparathyroidism may result in excess calcium deposition in the heart, hypertension, and shortening of the QT interval.[4]

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ANSWERS TO QUESTIONS 694 TO 697

694–B, 695–C, 696–D, 697–A (Braunwald, pp. 1843–1844)

Tissue-type plasminogen activator (tPA), the major physiologic activator of plasminogen, is both synthesized naturally by endothelial cells and produced commercially by recombinant DNA technology for the purpose of therapeutic fibrinolysis. The protein is synthesized in a single-chain form, which is subsequently converted to a two-chain form by proteolytic cleavage of a single plasmin-sensitive site. Both the single-chain and the two-chain forms have endogenous proteolytic activity. The alpha chain of tPA is derived from the amino-terminal portion of single-chain tPA and contains a pair of finger-like structures referred to as "kringle" domains. Lysine binding sites located on these domains confer binding specifically for fibrin. As a result, tPA is a relatively fibrin-specific activator that converts plasminogen to plasmin two or three times more efficiently in the presence of fibrin. The protease domain of tPA contains a proteolytic site responsible for this conversion. This portion is homologous with other serine proteases, such as urokinase and trypsin.

Urokinase is a two-chain serine protease that is synthesized in both renal tubular epithelial cells and endothelial cells. While urokinase converts plasminogen to plasmin by hydrolyzing the same bond as that acted on by tPA, the proteolytic activity of urokinase is not enhanced by the presence of fibrin. Therefore, urokinase may activate circulating plasminogen as effectively as plasminogen absorbed onto fibrin thrombi.

Streptokinase is a single polypeptide chain of 414 amino acids that is produced by a strain of hemolytic streptococci. Streptokinase does not cause thrombolysis by intrinsic enzymatic activity. Instead, it activates the fibrinolytic system by combining with plasminogen to form a plasminogen activator complex that is then capable of converting plasminogen to plasmin. Plasmin then degrades fibrin and other procoagulant proteins. Many individuals have circulating antibodies to streptokinase as a result of previous streptococcal infections. Therefore, a large dose of streptokinase is administered to neutralize these antibodies. Antistreptococcal antibodies may remain high for up to 6 months after administration.

Tenecteplase is a genetically engineered mutant form of tPA that displays a prolonged half-life and increased fibrin specificity. Unlike tPA, which requires a continuous infusion, tenecteplase is injected as a single intravenous bolus, which facilitates administration.

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TABLE 5.6 Advantages of Low-Molecular-Weight Heparin Over Unfractionated Heparin

ADVANTAGE	CONSEQUENCE
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Monitoring of coagulation is unnecessary in most patients
Lower risk for HIT	Safer than heparin for short- or long-term administration
Lower risk for osteoporosis	Safer than heparin for long-term administration

HIT, Heparin-induced thrombocytopenia.

ANSWERS TO QUESTIONS 698 TO 702

698–A, 699–B, 700–D, 701–C, 702–A (Braunwald, pp. 1835–1838)

Unfractionated heparin (UFH) is a naturally occurring compound that acts in vivo by combining with antithrombin (an inhibitor of thrombin and factors X, IX, and XI). The conformational change that occurs in antithrombin allows for an accelerated interaction with the activated clotting factors, limiting thrombin generation and fibrin formation. Commercial heparin is extracted from porcine intestinal mucosa and bovine lung and does not inactivate clot-bound thrombin or factor VII. Heparin is not absorbed by the gastrointestinal tract and is therefore administered in intravenous or subcutaneous forms. The bioavailability of subcutaneous injections of UFH is only 30%.

The activated partial thromboplastin time (aPTT) test is used to determine the inhibitory effect of UFH. For acute thrombosis or embolism, intravenous heparin is administered with a goal aPTT of 1.5 to 2 times the control value. Subcutaneous UFH is often used for patients who require a lower level of anticoagulation. Heparin therapy's major complication is bleeding. There is up to a 30% incidence of heparin-induced thrombocytopenia (HIT) that may be associated with thromboembolic events and often resolves with discontinuation of the drug (see Answer to Question 659). In addition, heparin may cause osteoporosis, elevated liver enzymes, increased vascular permeability, alopecia, and hypoaldosteronism (and associated hyperkalemia).

Low-molecular-weight heparin (LMWH) also produces an anticoagulant effect by binding to antithrombin. However, in distinction to UFH, LMWH preferentially inhibits factor Xa more than thrombin. LMWH formulations bind less with platelet factor 4, plasma proteins, and endothelial cells, and therefore have >90% bioavailability when administered by subcutaneous injection. Other advantages of LMWH include a prolonged half-life and predictable anticoagulant responses (Table 5.6).

Patients receiving LMWH do not require serial laboratory monitoring of the anticoagulant effect, except in the presence of renal failure, extreme obesity, or pregnancy. HIT can occur with LMWH but is less common than with UFH.

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ANSWERS TO QUESTIONS 703 TO 706

703–D, 704–B, 705–A, 706–C (Braunwald, pp. 1850, 1858–1860, 1862; see also Answers to Question 670 to Question 674)

Rheumatologic disorders often involve the cardiovascular system and can result in pericardial, myocardial, valvular, or arterial abnormalities. Aortic involvement is estimated to occur in 15% of patients with giant cell arteritis. Inflammation often involves the proximal aorta and aortic valve cusps, resulting in dilatation of the vessel and aortic regurgitation.[1] Other rheumatologic diseases that prominently involve the aorta include ankylosing spondylitis and psoriatic arthritis.

Valvular abnormalities are found by transesophageal echocardiography in 50% of patients with systemic lupus erythematosus. The most common involvement, termed *Libman-Sacks endocarditis,* represents noninfectious valve thickening, usually on the atrial side of the mitral valve and the arterial side of the aortic valve. Over time, fibrosis may result in valvular insufficiency. Much less commonly, the vegetations may occlude the valve orifice, causing stenosis. Clinical manifestations of Libman-Sacks lesions, such as infective endocarditis or peripheral embolism, are rare.[2]

Although pulmonary hypertension can develop in many rheumatologic disorders, it is a particularly prominent feature of systemic sclerosis and is one of the leading causes of morbidity and mortality in that condition.[3] Behçet disease typically results in inflammation of the thoracic aorta and branch vessels, leading to stenoses and aneurysmal dilatation of the subclavian and carotid arteries.[4] Thoracic and abdominal aortic aneurysms may also result.

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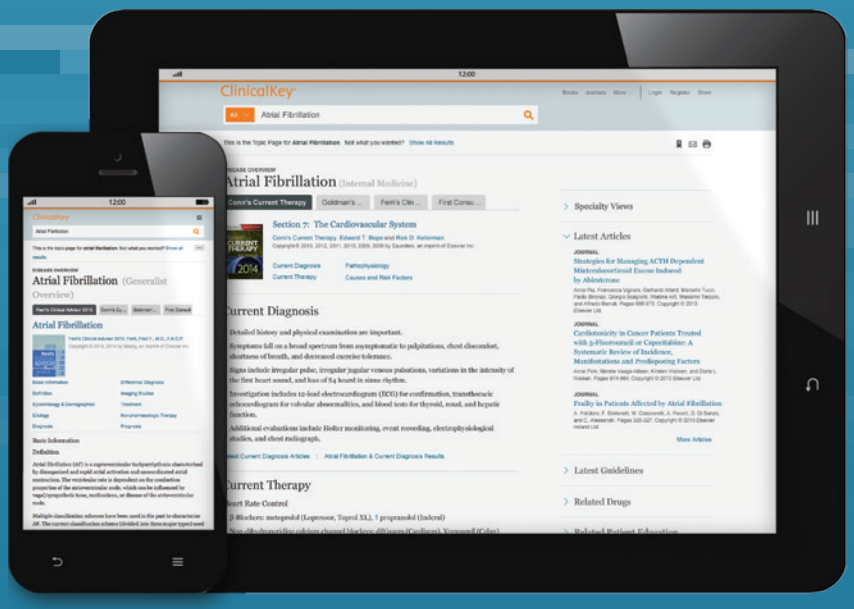

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