SECTION IX

Noninvasive Assessment

EDITOR

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CHAPTER 47

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Exercise Electrocardiographic Testing

I. INTRODUCTION

A. Exercise electrocardiographic testing is a field in flux. In the past decade, it has become clear that ST-segment changes during exercise have low sensitivity and specificity in the evaluation of coronary artery disease (CAD) and are poor predictors of risk. This may be partially due to the fact that stable obstructive plaques, which typically result in exercise-mediated ischemia, are less relevant to myocardial infarction (MI) and sudden cardiac death than unstable nonobstructive plaques. Although the bulk of obstructive CAD screening has now shifted towards various stress imaging modalities, many of the physiologic parameters measured during exercise have emerged as powerful prognostic indicators. As such, the main uses of exercise electrocardiographic testing should be *evaluation of prognosis* and as *a gateway to other imaging modalities.* Stand-alone testing for CAD diagnosis is reserved for patients with *intermediate risk for CAD* and should be ordered with a careful understanding of the limitations of the test for this purpose.

1. The **advantages** of exercise electrocardiographic testing are its ability to assess a variety of prognostic markers, most importantly **functional capacity**, which is a powerful predictor of mortality, widespread availability, safety, ease of administration, and relatively low cost. The assessment of functional capacity may be particularly advantageous in patients with valvular heart disease and congenital heart disease whereupon recognition of functional limitation is often difficult to ascertain by history alone.
2. **Disadvantages.** As a screening test for CAD in persons without symptoms, exercise electrocardiography is generally not helpful or indicated. It has a **low sensitivity and specificity,** which can be improved with careful selection of the patient population undergoing testing.

B. **Submaximal exercise electrocardiographic testing** (i.e., testing at submaximal heart rate, discussed later) is a useful assessment before hospital discharge for **patients who have had MI**. The advantages are as follows:

1. It assists in setting **safe levels** of exercise (exercise prescription) and reassuring patients and families.
2. It is beneficial in **optimization of medical therapy**, in triage for intensity of follow-up testing and care, and in recognition of exercise-induced ischemia and arrhythmias.
3. For patients with uncomplicated MI who have received reperfusion therapy, submaximal exercise testing may be safely **performed as early as 3 days after MI**, with maximal exercise testing 3 to 6 weeks later.

II. INDICATIONS.

The indications for exercise electrocardiographic testing are divided on the basis of the degree of likelihood of disease or severity of diagnosed disease, use in valvular heart disease, and use in congenital heart disease (Table 47.1).

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing

Exercise testing in the diagnosis of obstructive CAD

Class I[a]

- Adult patients (including those with complete right bundle branch block or < 1 mm of resting ST depression) with an intermediate pretest probability of CAD on the basis of sex, age, and symptoms

Class IIa

- Patients with vasospastic angina

Class IIb

- Patients with a high pretest probability of CAD on the basis of age, symptoms, and sex
- Patients with a low pretest probability of CAD on the basis of age, symptoms, and sex
- Patients with < 1 mm of baseline ST depression and taking digoxin
- Patients with electrocardiographic criteria of left ventricular hypertrophy and < 1 mm of baseline ST depression

Class III

- Patients with baseline electrocardiographic abnormalities
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - > 1 mm of resting ST depression
  - Complete left bundle branch block
- Patients with a documented myocardial infarction or prior coronary angiographic findings of disease and an established diagnosis of CAD (ischemia and risk can be determined with testing)

Risk assessment and prognosis among patients with symptoms or a history of CAD

Class I

- Patients undergoing initial evaluation with suspected or known CAD (exceptions in class 2b), including those with complete right bundle branch block or < 1 mm of resting ST depression
- Patients with suspected or known CAD previously evaluated, now presenting with marked change in clinical status
- Low-risk unstable angina patients 8–12 h after presentation who have been free of active ischemic or heart failure symptoms
- Intermediate-risk unstable angina patients 2–3 d after presentation who have been free of active ischemic or heart failure symptoms

Class IIa

- Intermediate-risk unstable angina patients with initial cardiac markers that are normal, a repeat electrocardiographic study without significant change, cardiac markers 6–12 h after symptom onset that are normal, and no other evidence of ischemia during observation

Class IIb

- Patients with baseline electrocardiographic abnormalities
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - 1 mm or more of resting ST depression

(Continued)

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing (*Continued*)

- Complete left bundle branch block or any interventricular conduction defect with QRS duration > 120 milliseconds
- Patients with a stable clinical course who undergo periodic monitoring to guide treatment

Class III

- Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization
- High-risk unstable angina patients

After acute myocardial infarction

Class I

- Before discharge for prognostic assessment, activity prescription, or evaluation of medical therapy (submaximal at about 4–6 d)
- Early after discharge for prognostic assessment and cardiac rehabilitation if the predischarge exercise test was not performed (symptom limited, about 14–21 d)
- Late after discharge for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the early exercise test was submaximal (symptom limited, about 3–6 wk)

Class IIa

- After discharge for activity counseling or exercise training as part of cardiac rehabilitation of patients who have undergone coronary revascularization

Class IIb

- Patients with electrocardiographic abnormalities
  - Complete left bundle branch block
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Left ventricular hypertrophy
  - Digoxin therapy
  - Electronically paced ventricular rhythm
  - > 1 mm of resting ST depression
- Periodic monitoring for patients who continue to participate in exercise training or cardiac rehabilitation

Class III

- Severe comorbidity likely to limit life expectancy or candidacy for revascularization
- Patients with acute myocardial infarction and uncompensated congestive heart failure, cardiac arrhythmia, or noncardiac conditions that severely limit exercise ability
- Before discharge, patients who have been selected for or have undergone cardiac catheterization (stress imaging tests are recommended)

Exercise testing for persons without symptoms or known CAD

Class I

- None

Class IIa

- Asymptomatic persons with diabetes mellitus to start vigorous exercise

Class IIb

- Persons with multiple risk factors

TABLE 47.1 *Continued*

Men older than 45 y and women older than 55 y without symptoms
- Who plan to start vigorous exercise (especially if sedentary)
- Who are involved in occupations in which impairment might affect public safety
- Who are at high risk for CAD because of other diseases

Class III
- Routine screening of men or women without symptoms

Exercise testing for persons with valvular heart disease

Class I
- None

Class IIa
- Patients with chronic AR and equivocal symptoms to assess functional capacity and symptomatic response

Class IIb
- Asymptomatic patients with AS may be considered to elicit exercise-induced symptoms and abnormal blood pressure responses
- In asymptomatic or symptomatic patients with chronic AR (with radionuclide angiography) for assessment of left ventricular function

Class III
- Exercise testing should not be performed in symptomatic patients with AS

Exercise testing for persons with congenital heart disease

Class I
- None

Class IIa
- Asymptomatic young adults < 30 y of age to determine exercise capability, symptoms, and blood pressure response
- Adolescent or young adult patient with AS who has a Doppler mean gradient > 30 mm Hg or a peak velocity > 50 mm Hg if the patient is interested in athletic participation or if the clinical findings and Doppler findings are disparate
- Asymptomatic young adult with a mean Doppler gradient > 40 mm Hg or a peak Doppler gradient > 64 mm Hg or when the patient anticipates athletic participation or pregnancy
- As part of the initial evaluation of adolescent and young adult patients with TR and serially every 1–3 y
- In patients with atrial septal defect with symptoms that are discrepant with clinical findings or to document changes in oxygen saturation in patients with mild or moderate PAH
- In patients with subvalvular AS testing to determine exercise capability, symptoms, ECG changes or arrhythmias, or increase in LVOT gradient is reasonable in the presence of otherwise equivocal indications for intervention
- In patients with supravalvular AS (along with other imaging modalities) testing can be useful to evaluate the adequacy of myocardial perfusion

Class IIb
- In patients with aortic coarctation, testing may be performed at intervals determined in consultation with the regional ACHD center

(Continued)

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing (*Continued*)

Class III

Patients with atrial septal defect or patent ductus arteriosus with severe PAH

Symptomatic patients with AS or those with repolarization abnormality on ECG or systolic dysfunction on echocardiography

[a]*Class 1,* conditions for which there is evidence or agreement that a given procedure or treatment is useful and effective; *Class 2,* conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment; *Class 2a,* weight of evidence or opinion is in favor of usefulness and efficacy; *Class 2b,* usefulness or efficacy is less well established on the basis of evidence and opinion; *Class 3,* conditions for which there is evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful. CAD, coronary artery disease; AR, aortic regurgitation; AS, aortic stenosis; TR, tricuspid regurgitation; PAH, pulmonary arterial hypertension; ECG, electrocardiogram; LVOT, left ventricular outflow tract; ACHD, adult congenital heart disease.

From Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol.* 2002;40:1531–1540, with permission. Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol.* 2008;52:e1–e142 and from Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). *J Am Coll Cardiol.* 2008;52:1890–1947.

III. CONTRAINDICATIONS. Contraindications to exercise testing are divided into absolute and relative categories (Table 47.2).

IV. LIMITATIONS OF EXERCISE ELECTROCARDIOGRAPHIC TESTING. Before ordering an exercise electrocardiography test, the physician should have an understanding of Bayes' theorem and the limitations of the test.

A. Bayes' theorem states that the probability of a positive test result is affected by the likelihood (i.e., conditional probability) of a positive test result among the population that has undergone the test (i.e., pretest probability). The higher the probability that a disease is present in a given individual before a test is ordered, the higher is the probability that a positive test result is a true-positive test result. Pretest probability is determined on the basis of symptoms, age, sex, and risk factors and can be divided into very low, low, intermediate, and high (Table 47.3).

B. Sensitivity and specificity. The likelihood that an abnormal electrocardiographic finding indicates CAD is much higher for an older person with multiple risk factors than for a young person with no risk factors. Sensitivity and specificity vary with the population being tested.

1. Exercise electrocardiographic testing is **best used** in the evaluation of a patient at intermediate risk with an atypical history or a patient at low risk with a typical history.
2. For the general population, the sensitivity is 68% and the specificity is 70%. Values are lower for persons at low risk.
3. Exercise electrocardiographic testing has a higher sensitivity and specificity for **persons at high risk**. For most of these patients, however, invasive testing is preferred for a more definitive diagnosis and possible intervention. Excluding patients with left ventricular hypertrophy or resting ST depression and those taking digoxin also improves sensitivity and specificity.

TABLE 47.2 Contraindications to Exercise Testing

Absolute contraindications
Acute myocardial infarction (within 2 d)
High-risk unstable angina
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
Symptomatic, severe aortic stenosis
Uncontrolled symptomatic heart failure
Acute pulmonary embolus or pulmonary infarction
Suspected or known dissecting aneurysm
Active or suspected myocarditis, pericarditis, or endocarditis
Acute noncardiac disorder that may affect exercise performance or be aggravated by exercise (e.g., infection, renal failure, or thyrotoxicosis)
Considerable emotional distress (psychosis)
Relative contraindications
Left main coronary stenosis or its equivalent
Moderate stenotic valvular heart disease
Resting diastolic blood pressure > 110 mm Hg or resting systolic blood pressure > 200 mm Hg
Electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia)
Fixed-rate pacemaker
High-degree atrioventricular block
Frequent or complex ventricular ectopy
Ventricular aneurysm
Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, and myxedema)
Chronic infectious disease (e.g., mononucleosis, hepatitis, and acquired immunodeficiency syndrome)
Neuromuscular, musculoskeletal, or rheumatoid disorders exacerbated by exercise
Advanced or complicated pregnancy
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Mental impairment leading to inability to cooperate

Adapted from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's Guidelines for Exercise Testing and Prescription.* Baltimore, MD: Williams & Wilkins, 1995; from Fletcher GF, Fletcher GF, Blair SN, et al. Statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation.* 1992;86:340–344; and from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol.* 2002;40:1531–1540.

C. Positive predictive value (PPV). After pretest probability and the sensitivity and specificity are known, PPV can be calculated. PPV is a measure of the likelihood that an abnormal test finding represents a true-positive result. It is highly dependent on pretest probability (i.e., prevalence of disease) in the population being tested. For example, in a population at low risk, the PPV of electrocardiographic exercise testing is only 21%, but in a population at high risk, PPV rises to 83%.

TABLE 47.3 Pretest Probability of Coronary Artery Disease according to Age, Sex, and Symptoms

Age (y)	Sex	Typical/ definite angina pectoris	Atypical/ probable angina pectoris	Nonanginal chest pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

Reproduced with permission from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 2002;40:1531–1540.

V. PATIENT PREPARATION

A. Instructions. Table 47.4 provides a typical list of instructions given to patients before testing.

B. Medications

1. Before diagnostic testing, **cardiovascular drugs are withheld** at the discretion of and under the guidance of the supervising physician. This greatly increases the sensitivity of the test.
   a. **β-Blockers** pose a special problem. Patients taking β-blockers often do not have an adequate increase in heart rate to achieve the level of stress needed for the test. Abrupt withdrawal of β-blockers is to be discouraged because of reflex tachycardia. The best possible solution is to withdraw the β-blocker over several days before an exercise test, if the test is for diagnostic purposes. This is not always possible, however, because of time constraints or the necessity of drug therapy. In these cases, the records should reflect β-blocker use at the time of testing.
   b. **Digoxin** may cause problems in test interpretation. To avoid a reading that cannot be used to confirm a diagnosis, digoxin should be withheld for 2 weeks before testing.
2. Patients undergoing diagnostic testing should take their **other usual medications** on the day of the test to reproduce more closely the conditions outside the exercise laboratory.

VI. EXERCISE PROTOCOLS.

There are advantages and disadvantages to each exercise protocol (Table 47.5). Selection depends on the patient characteristics, the equipment available, and the familiarity and comfort of the testing personnel with the protocol.

A. An **optimal protocol** achieves peak workload and maximizes the sensitivity and specificity of the test.

1. **Workload.** An optimal protocol incorporates a **gradual increase** in the level of work, so that the patient's true peak workload can be determined. If there are large increases in workload, maximum oxygen consumption (MVO_2 max) may

TABLE 47.4 Patient Preparation

Patients should refrain from ingesting food, alcohol, or caffeine or using tobacco products within 3 h of testing.
Patients should be rested for the assessment, avoiding significant exertion or exercise on the day of the assessment.
Patients should wear clothing that allows freedom of movement, including walking or running shoes, and a loose-fitting shirt with short sleeves that buttons down the front. They should not wear restrictive undergarments during the test.
Outpatients should be warned that the evaluation may be fatiguing and that they may wish to have someone available to drive them home afterward.
If the test is for diagnostic purposes, it may be helpful for patients to discontinue prescribed cardiovascular medication after discussion with their physician. Antianginal agents alter the hemodynamic response to exercise and significantly reduce the sensitivity of electrocardiographic changes for ischemia. Patients taking intermediate- or high-dose β-blockers should taper their medication over a 2–4-d period to minimize hyperadrenergic withdrawal responses.
If the test is for functional purposes, patients should continue their medication regimen on their usual schedule so that the exercise responses will be consistent with responses expected during exercise training.
Patients should bring a list of their medications with them to the assessment.

Reproduced with permission from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's guidelines for Exercise Testing and Prescription*. Baltimore, MD: Williams & Wilkins; 1995.

fall between two levels. The test is also more comfortable for the patient if the increases in workload are not large.

2. **Duration.** The optimal duration for an exercise test is **8 to 12 minutes**. Periods longer than this measure muscular endurance rather than cardiovascular fitness. Periods shorter than this do not allow adequate time for the patient to warm up and achieve maximum workloads.
3. **Stage length.** Steady-state oxygen consumption is reached after about 2 minutes of exercise at a given workload. The optimal protocol would have stage lengths of **2 to 3 minutes**.
4. **Exercise method.** Although **bicycle riding** is a better method for testing, **treadmill testing** is more commonly used in the United States.
   a. The primary physiologic **advantage of bicycle riding** is the ability to take **direct measurements** of workload in watts, which has direct linear relation to $M\dot{V}O_2$. With a **treadmill**, the examiner can only **estimate workload** because workload depends on the efficiency of walking, the weight of the patient, and the change in energy expenditure between walking and running. Other advantages of a bicycle are the stable platform that it provides for electrocardiographic and blood pressure recordings, the smaller amount of space it occupies, quieter use, and a lower initial cost of equipment.

B. Protocol options

1. **Bruce protocol**
   a. **Advantages.** The Bruce protocol has been widely used in the past and is often the basis of older studies; therefore, **comparisons are easier**. Because the Bruce protocol has a final stage that cannot be completed, it is a good protocol for a highly fit person.
   b. **Disadvantages**
      (1) The main disadvantage of the Bruce protocol is the **large increments of change in workload between stages**. These large increases mean that

TABLE 47.5 Common Exercise Protocols

			Treadmill protocol									
Functional class	O_2 cost mL/kg/min	MET	Bruce (3-min stages mph/grade)		Cornell (2-min stages mph/grade)		Balke (2-min stages mph/grade)		Naughton (2-min stages mph/grade)		Jogger (2-min stages mph/grade)	
World-class athlete	70.0	20	—	—	—	—	—	—	—	—	—	—
	66.5	19	6.0	22	—	—	—	—	—	—	—	—
	63.0	18	—	—	—	—	—	—	—	—	6.0	20.0
	59.5	17	5.5	20	—	—	—	—	—	—	6.0	17.5
Athlete	56.0	16	5.0	18	5.0	18	—	—	—	—	6.0	15.0
	52.5	15	—	—	—	—	4.0	20	—	—	6.0	12.5
	49.0	14	—	—	4.6	17	—	—	—	—	6.0	10.0
Fit	45.5	13	4.2	16	4.2	16	3.5	20	—	—	6.0	7.5
	42.0	12	—	—	—	—	—	—	—	—	6.0	5.0
	38.5	11	—	—	3.8	15	3.0	20.0	—	—	5.5	2.5
Normal and 1	35.0	10	3.4	14	3.4	14	3.0	17.5	—	—	5.0	2.5
	31.5	9	—	—	—	—	3.0	15.0	—	—	—	—
	28.0	8	—	—	3.0	13	3.0	12.5	2.0	21.0	—	—
	24.5	7	2.5	12	2.5	12	3.0	10.0	—	7.5	—	—
2	21.0	6	—	—	2.1	11	3.0	7.5	2.0	14.0	—	—
	17.5	5	1.7	10	1.7	10	3.0	5.0	2.0	10.5	—	—
	14.0	4	—	—	—	—	3.0	2.5	2.0	7.0	—	—
3	10.5	3	1.7	5	1.7	5	3.0	0	2.0	3.5	—	—
	7.0	2	1.7	0	1.7	0	—	—	2.0	0	—	—
4	3.5	1	—	—	—	—	—	—	1.0	0	—	—

MET, metabolic equivalent; mph, miles per hour.

peak workload falls somewhere between stages for many people. This is a problem in evaluating functional capacity and may result in a lower sensitivity for the test.

(2) The fourth stage of the Bruce protocol is an awkward stage that can be run or walked, resulting in divergent oxygen costs and workloads.

2. **Modified Bruce protocol.** Developed for less-fit persons, the modified Bruce protocol adds additional stages 0 and 1/2. These stages, at 1.7 mph (2.7 km/h) with 0% and 5% grades, respectively, provide a **lower workload for persons with poor cardiovascular fitness**. However, even these workloads may be too heavy for some debilitated patients and may result in premature fatigue.
3. **Other protocols.** Protocols superior to the Bruce protocol have been developed. These protocols have more gradual increases in workload and can be modified to suit the individual.
   a. The **Naughton protocol** is good for older or debilitated persons and allows a gradual increase in workload.
   b. The **Balke protocol** is good for younger, fit persons. It maintains a speed of 3, 3.5, or 4 mph (4.8, 5.6, or 6.4 km/h) and increases the grade every 2 minutes.
   c. The **Cornell protocol** is good for a wider range of fitness levels depending on starting grade. It allows for a gradual increase in grade and speed and may be started at 0%, 5%, or 10% grade, depending on fitness level.
   d. **Ramp protocols** are computer-driven protocols that continuously increase workload until maximum exertion is reached. This is the ultimate in continuous advancement, but steady state may not be reached at any given workload.

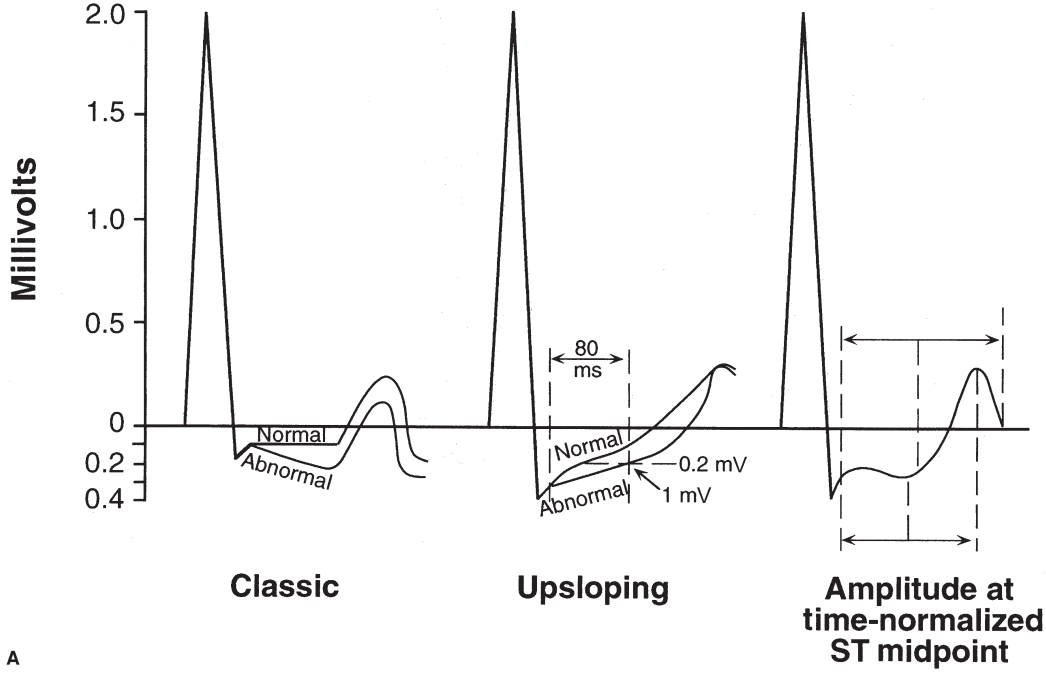
VII. DATA

A. Electrocardiographic data. Although not the only data that should be examined, electrocardiographic changes garner the most attention in test interpretation. The **portion of the electrocardiogram (ECG) most sensitive to ischemia** is the ST segment. The pathophysiologic mechanism of the ST change is net depression caused by a current of ischemia from the affected myocardial cells. The TP segment may be useful at rest and should be used when possible; however, it shortens or disappears with exercise. Baseline electrocardiographic abnormalities that can obscure the correct diagnosis of ST changes are listed in Table 47.6.

1. **ST-segment changes**
   a. **Measurement of the ST segment.** There is no clear consensus as to where to measure the ST segment. Traditionally, it is measured 80 milliseconds past the J point, but some investigators suggest measuring at the J point or at the midpoint of the ST segment (using the end of the T wave or the peak of the T wave to determine the end of the segment) (Fig. 47.1A).

TABLE 47.6 Baseline Abnormalities That May Obscure Electrocardiographic Changes during Exercise

Left bundle branch block
Left ventricular hypertrophy with repolarization abnormality
Digitalis therapy
Ventricular paced rhythm
Wolff-Parkinson-White syndrome
ST abnormality associated with supraventricular tachycardia or atrial fibrillation
ST abnormalities with mitral valve prolapse and severe anemia



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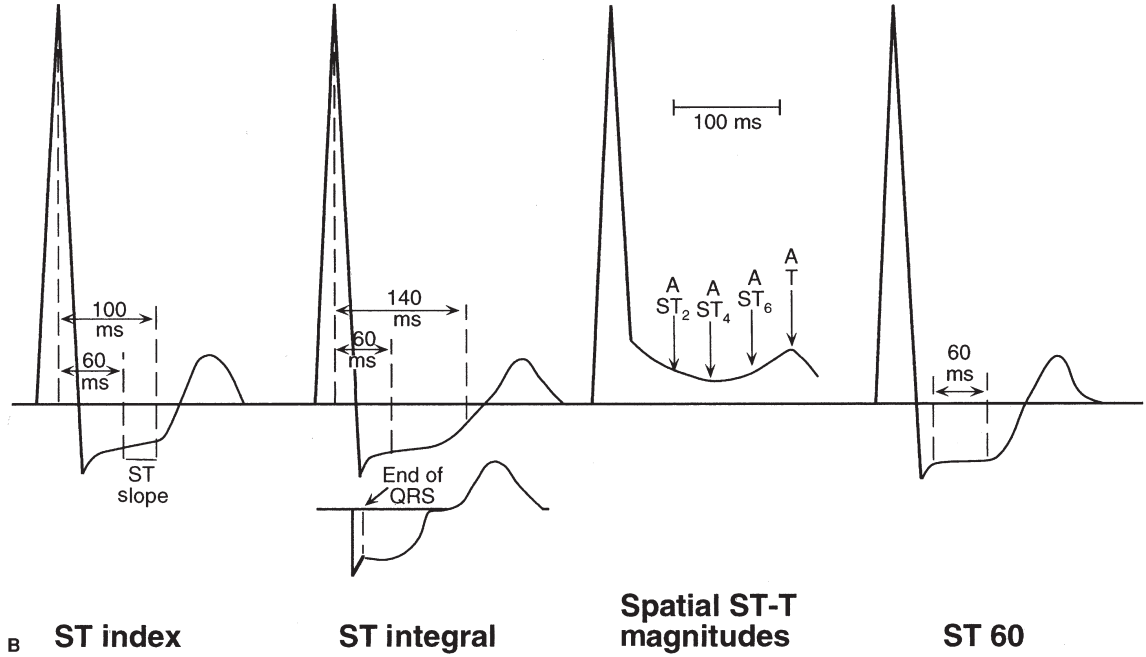

FIGURE 47.1 **(A)** Blomqvist recommended using the end of the T wave for measuring the midpoint of the ST segment, but Simons used the peak of the T wave. This change was made to have a more stable end point, because the end of the T wave is much more difficult to find than the peak of the T wave. **(B)** The ST integral, as defined by Sheffield, required that the end of the QRS complex, or J junction, be found and that the area measurement stop as soon as the ST segment crossed the isoelectric line or as the T wave began. The ST integral used by most commercial systems initiates the area at a fixed period after the R wave and then ends 80 milliseconds thereafter.

b. **ST-segment changes** are measured from the isoelectric baseline, which can be determined from the PR interval. If the ST segment is elevated at rest, any depression that occurs with exercise is still measured from the isoelectric line; early repolarization of the ST segment at rest is normal. If, however, the ST segment is depressed at rest, any further depression should be measured from the baseline ST segment (Fig. 47.1B).

c. **Normal response.** During exercise, there is depression of the J junction that is maximal at peak exercise and returns to baseline during recovery. This normal depression is upsloping and typically < 1 mm below the isoelectric line 80 milliseconds after the J point.

d. **ST depression** does not localize the area of ischemia.

(1) ST depression of at least 1 mm that is horizontal or downsloping is abnormal, as is upsloping ST depression of at least 2.0 mm.

(2) Baseline ST abnormalities are less likely to represent exercise-induced myocardial ischemia, and the baseline ST depression should be subtracted from the peak ST depression.

(3) **Criteria that increase the probability of ischemia** are the **number of leads** involved (i.e., more leads increase the probability of ischemia), the **workload** at which the ST depression occurs (i.e., lower workload increases probability), the **angle of the slope** (i.e., a downsloping angle has a higher probability than a horizontal one), **ST-segment adjustment relative to heart rate (ST/HR index)**, the **amount of time in recovery** before normalization of the ST segment (i.e., longer recovery increases the probability), and possibly the **magnitude of the depression**. Changes in the lateral leads, particularly V_5, are more specific than in any of the other leads. Changes in the inferior leads alone are likely to be a false-positive result.

e. The **meaning of ST elevation** depends on the presence or absence of Q waves of prior MI.

(1) ST-segment elevation **with Q waves of prior MI** is a common finding among patients who have had MI. It occurs among up to 50% of patients with anterior MI and 15% of patients with previous inferior MI, and it is not caused by ischemia. The mechanism is thought to be dyskinetic myocardium or ventricular aneurysms. There may even be reciprocal ST-segment depression. Patients with more extensive Q waves have more pronounced ST elevation. These patients typically have a lower ejection fraction than those without elevated ST segment with a Q wave. These changes do not imply ischemia (although they may imply viability) and should be interpreted as normal.

(2) ST-segment elevation **without Q waves of prior MI** represents marked transmural myocardial ischemia. ST elevation may also indicate the location of the ischemia. This finding should be interpreted as abnormal.

f. **ST normalization,** or the lack of ST changes during exercise, **may be a sign of ischemia.** This phenomenon occurs when ischemic ST depression and ST elevation cancel one another. This effect is rare, but it should be considered in tests of patients with no electrocardiographic changes but with a high likelihood of CAD.

2. **R waves may change in amplitude** during exercise. There is no diagnostic value in these changes.

3. **T-wave and U-wave changes**

a. The **T wave** normally decreases gradually in early exercise and begins to increase in amplitude at maximal exercise. One minute into recovery, the T wave should be back to baseline. T-wave **inversion is not a specific marker of ischemia** and may occur normally.

TABLE 47.7 Absolute and Relative Indications for Termination of an Exercise Test

Absolute indications
Acute myocardial infarction or suspicion of myocardial infarction
Onset of moderate to severe angina or increasing anginal pain
Drop in systolic blood pressure with increasing workload accompanied by signs or symptoms or drop below resting pressure
Serious arrhythmias (e.g., second- or third-degree atrioventricular block, sustained ventricular tachycardia or increasing premature ventricular contractions, and atrial fibrillation with fast ventricular response)
Signs of poor perfusion, including pallor, cyanosis, or cold and clammy skin
Unusual or severe shortness of breath
Central nervous system symptoms, including ataxia, vertigo, visual or gait problems, or confusion
Technical inability to monitor the electrocardiogram
Patient's request
Relative indications
Pronounced electrocardiographic changes from baseline > 2 mm of horizontal or downsloping ST-segment depression or > 2 mm of ST-segment elevation except in aVR
Any chest pain that is increasing
Physical or oral manifestations of severe fatigue or shortness of breath
Wheezing
Leg cramps or intermittent claudication (grade 3 on 4-point scale)
Hypertensive response (systolic blood pressure > 260 mm Hg and diastolic blood pressure > 115 mm Hg)
Less serious arrhythmias such as supraventricular tachycardia
Exercise-induced bundle branch block that cannot be differentiated from ventricular tachycardia
General appearance

Adapted from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's Guidelines for Exercise Testing and Prescription. 5th ed.* Baltimore, Md: Williams & Wilkins; 1995 and from Fletcher GF, Blair SN, et al. statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation. 1992;86:340–344

   b. If the U wave is upright at baseline, **U-wave inversion** may be associated with ischemia, left ventricular hypertrophy, and valvular disease.

4. **Arrhythmias.** Table 47.7 lists abnormal arrhythmias that may occur during exercise. Ectopic atrial and ventricular beats during exercise are not predictive of outcome, but ventricular ectopy during recovery may be associated with worse outcome. Sustained ventricular tachycardia and ventricular fibrillation are abnormal but occur rarely.
5. **Time to resolution of changes.** The longer into recovery that it takes for electrocardiographic changes to resolve, the higher is the probability that they are important. Rapid recovery (< 1 min) indicates less likelihood of disease and that disease if present is less severe.

6. Bundle branch block or conduction delay. Exercise-induced left bundle branch block is predictive of a worse outcome.

B. Age-predicted maximum heart rate (APMHR). Many formulas have been developed to predict maximum heart rate (MHR). These formulas are generated by measuring the MHR in a sample population and plotting a regression line against various factors that may affect heart rate. There is a great deal of scatter on either side of the regression line, and the fit of the line seldom reaches an r value > 0.9. Because MHR decreases with age, most equations incorporate age into the estimation. The two most common formulas are as follows:

$$\text{APMHR} = 220 - \text{age}$$

$$\text{APMHR} = 200 - \tfrac{1}{2}\,\text{age}$$

The APMHR may be much lower or much higher than a person's actual measured MHR. **Heart rate should not be used as an indicator of maximal exertion or in the decision to terminate testing, except in a submaximal test**. If MHR does not exceed 85% of APMHR during testing and there are no substantial electrocardiographic changes, the test is usually read as nondiagnostic. If there are substantial electrocardiographic changes, the test is read as abnormal, regardless of the heart rate achieved.

C. Rating of perceived exertion (RPE) is a better marker of maximal level of exertion.

1. A useful indicator of percentage of maximum workload achieved is the **RPE scale**. This is a subjective scale used to rate how much effort the subject feels he or she is expending during an exercise test. The subject should be advised to rate how he or she feels overall and not according to an individual element such as leg fatigue. Although subjective, the scale has been shown to be reproducible, and maximum ratings correspond well with maximum exertion.
   a. The **Borg scale** is used most often. The original scale ranges from 6 to 20, which is meant to correspond to a heart rate increase from 60 to 200 beats/min during exercise.
   b. The **modified Borg scale** ranges from 0 to 10. The scale includes word anchors, which are important for an accurate assessment of work level. The scales are not linear, and at higher workloads, the changes in RPE are closer together.
2. A maximal level of exertion is marked by a score > 18 (Borg scale) or 9 (modified Borg scale), respiratory quotient > 1.1 (if carbon dioxide exchange is monitored), and overall patient appearance.

D. In addition to electrocardiographic monitoring, **blood pressure monitoring** is an important aspect of the exercise test for safety and for the diagnosis of CAD. It should be checked in each walking stage. It may not be practical to check blood pressure while the subject is running.

1. **Systolic blood pressure** (SBP) normally rises during exercise. A **failure of SBP to rise** with increasing workload or a drop in SBP usually indicates the presence of CAD and is an indication to **terminate testing**.
2. **Diastolic blood pressure** decreases with exercise and may be audible down to 0 during vigorous activity. Unlike SBP, diastolic blood pressure is not useful in diagnosis or safety monitoring.

E. Symptoms. The presence or absence of symptoms and their change over time are included in the final report.

F. Functional capacity. Functional testing is a powerful marker for prognosis. Persons who achieve > 6 metabolic equivalents (METs) of workload have a significantly lower mortality rate than those who do not achieve this workload, regardless of electrocardiographic changes. On the basis of age and workload achieved, functional capacity can be divided into five classifications (Table 47.8). Among 3,400 patients with no history of diagnosed CAD undergoing exercise testing at the Cleveland Clinic, those with average or better classifications had a 2.5-year mortality of < 2% compared with 6%

TABLE 47.8 Functional Capacity Classifications by Age and Sex

Age (y)	Low[a]	Fair	Average	Good	High
Women					
20–29	< 7.5	8–10.3	10.3–12.5	12.5–16	> 16
30–39	< 7	7–9	9–11	11–15	> 15
40–49	< 6	6–8	8–10	10–14	> 14
50–59	< 5	5–7	7–9	9–13	> 13
60–69	< 4.5	4.5–6	6–8	8–11.5	> 11.5
Men					
20–29	< 8	8–11	11–14	14–17	> 17
30–39	< 7.5	7.5–10	10–12.5	12.5–16	> 16
40–49	< 7	7–8.5	8.5–11.5	11.5–15	> 15
50–59	< 6	6–8	8–11	11–14	> 14
60–69	< 5.5	5.5–7	7–9.5	9.5–13	> 13

[a]Functional capacities are given in metabolic equivalents.

and 14% for those who were in the fair and poor groups, respectively. The adjusted relative risk for fair or poor functional capacity in this population was almost 4.

VIII. TERMINATION OF EXERCISE TESTING. The American Heart Association (AHA) and American College of Sports Medicine (ACSM) have developed very similar indications for exercise termination (Table 47.7). The decision when to terminate a test ultimately relies on the expertise and judgment of those performing the test.

A. Absolute indications are all serious findings. A drop in SBP with increasing workload is a particularly ominous sign and usually, but not always, indicates the presence of severe CAD.

B. Relative indications for termination of testing are findings that should increase the level of concern and vigilance among those administering the test and possibly cause cessation of testing. Relative indications for termination rely heavily on the judgment of the personnel performing the test, and the decision to continue the test should not be made lightly (Table 47.7).

C. Indications for termination of submaximal exercise testing include any one of the following end points:

(1) Signs or symptoms of ischemia
(2) Achievement of a workload of 6 METs
(3) Eighty-five percent of the APMHR
(4) Heart rate of 110 beats/min for a patient taking β-blockers
(5) A score on the Borg RPE of 17 or modified Borg RPE of 7

D. Postexercise recovery

1. In **all routine exercise tests, a cool-down period** adds safety to the test. The length of the cool-down period may vary from 30 seconds to several minutes, depending on the person. A general rule is to allow enough time for the heart rate to drop to < 110 beats/min. A shorter cool-down period increases the sensitivity of exercise ECG because of increased venous return; resuming the supine position leads to increased wall stress. This same mechanism also increases the risk of testing.

2. The exception to observing a cool-down period may be made for exercise echocardiography, in which it is important to image the subject when he or she is as close as possible to MHR.

IX. INTERPRETATION OF DATA. An experienced clinician must interpret an exercise electrocardiographic test. Although the terms *positive* and *negative* are often used, these terms do not accurately describe the results of an exercise electrocardiographic test and should be avoided. The information to include in an exercise electrocardiographic report is listed in Table 47.9.

A. Exercise electrocardiographic test results can be normal, abnormal, normal except for, or nondiagnostic (Table 47.10). Nondiagnostic tests are those in which the subject does not achieve 85% of APMHR and has no abnormal electrocardiographic changes or in which baseline electrocardiographic changes are present that obscure ST changes (Table 47.6).

B. Prognosis

1. The **Duke nomogram** (Fig. 47.2) is a simple chart that factors in ST-segment deviation, amount of angina during exercise, and exercise capacity to give an estimate of a 5-year survival and average annual mortality. This nomogram was derived by means of regression analysis and can be a useful tool in determining prognosis and the degree of aggressiveness needed in treating a patient. The **Duke treadmill score (DTS)** is a numeric form of the nomogram and has been validated in several studies as an important predictor of mortality:

$$\text{DTS} = \text{duration of exercise (in minutes)} - (5 \times \text{maximal ST-segment deviation}) - (4 \times \text{angina score})$$

TABLE 47.9 Elements of Conclusion Section of a Modern Exercise Test Report

Exercise protocol used, duration of exercise, peak treadmill speed and grade, maximum heart rate and percentage of age-predicted maximum heart rate achieved, resting and peak blood pressure, and symptoms
Negative/positive/equivocal standard ST-segment response to exercise
"The ST/HR index of ≤ 1.6 μV/beats/min is consistent with the absence of obstructive coronary disease and makes anatomically, functionally, and prognostically important coronary disease unlikely"; "The ST/HR index > 1.6 μV/beats/min is consistent with the presence of obstructive coronary disease and predicts increased cardiovascular risk
The estimated functional capacity of (*x* METs) predicts (high/low) risk of all-cause mortality
The Duke treadmill score of (*x*) predicts a cardiac mortality of (*x*%) per year over the next 5 y. This implies a (low/intermediate/high) risk
The chronotropic response index of (0.*xx*) predicts an (increased/decreased) risk of death compared with the Duke treadmill score. For patients not on β-blockers, a value ≤ 0.80 raises concerns; for patients on β-blockers, a value ≤ 0.62 is abnormal
The heart rate recovery of (*x* beats/min) further predicts an (increased/decreased) risk of death
The presence/absence of frequent ventricular ectopy during recovery further increases/decreases predicted risk of death

Adapted from Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. *Circulation.* 2006;114;2070–2082.

TABLE 47.10 Guidelines for Interpretation of Results of Exercise Electrocardiography

Variable	Normal	Normal except for	Abnormal
Symptoms	Neuromuscular chest pain	Angina as an isolated finding	Syncope
	Fatigue, shortness of breath, and leg or joint pain	Atypical angina	Angina when associated with ST- or T-wave changes, including borderline
		Chest discomfort of questionable causation	Angina when associated with exercise hypotension
		Claudication	
		Dizziness and lightheadedness	
		Other noteworthy symptoms	
Blood pressure response (mm Hg)	SBP increases > 10 but is < 230 at peak	SBP ≥ 230 at peak exercise	Any drop in SBP as exercise intensity increases
	DBP increases ≤ 10 but is < 120 at peak	DBP ≥ 120 at peak exercise	
	DBP stays the same or decreases	DBP increases ≥ 12 from rest if peak is ≥ 100	
	DBP increases ≥ 12 from rest but peak is < 100		
Arrhythmias	Occasional PVCs	Paroxysmal SVT	Sustained SVTs, AF, atrial flutter, or junctional rhythm
	PACs	Increased frequency of PVCs or couplets during exercise	Nonsustained VT
	Frequent PACs or PVCs at rest that abate during exercise	Isolated run of nonsustained VT	Second- or third-degree AV block

(Continued)

TABLE 47.10 Guidelines for Interpretation of Results of Exercise Electrocardiography (*Continued*)

Variable	Normal	Normal except for	Abnormal
	Chronic AF, atrial flutter	Ventricular couplets	AV dissociation
		Paroxysmal escape rhythms	Exercise induced before excitation
			Idioventricular rhythm
			Very abnormal
			Sustained VT (≥30 s)
			VF/cardiac arrest
			Asystole
ST segments	< 1.0 mm ST depression or elevation	Borderline ST changes (0.5–0.9 mm ST depression)	≥1.0 mm H or D ST depression
		ST elevation in leads in area of prior MI	≥1.5 mm U ST depression
		T-wave inversion	≥1.0 mm U ST depression if associated with anginal symptoms
		Pseudonormalization of resting T-wave abnormalities	≥1.0 mm ST elevation in leads without Q waves or not over a prior MI
			Very abnormal
			≥2.0 mm H or D ST depression
			≥2.5 mm U ST depression
			≥2.0 mm ST elevation in leads without Q waves or not over a prior MI
Functional capacity	Normal or mildly impaired exercise tolerance	Low exercise tolerance	Inability to achieve 3 MET workload

AF, atrial fibrillation; AV, atrioventricular; D, downsloping; DBP, diastolic blood pressure; H, horizontal; MET, metabolic equivalent; MI, myocardial infarction; PAC, premature atrial contraction; PVC, premature ventricular contraction; SBP, systolic blood pressure; SVT, supraventricular tachycardia; U, upsloping; VF, ventricular fibrillation; VT, ventricular tachycardia.

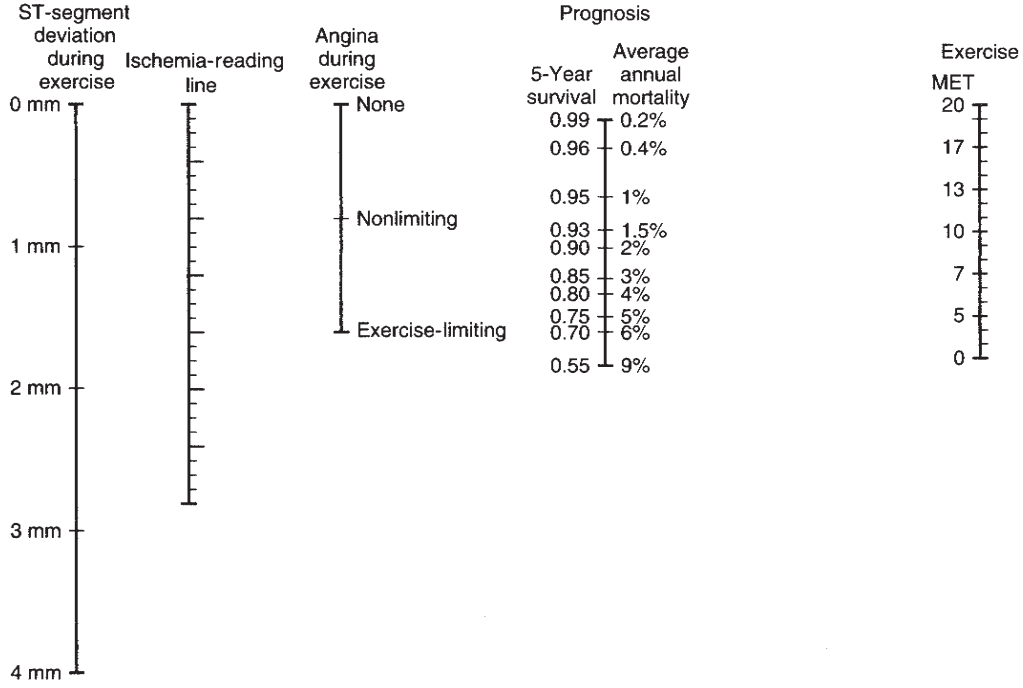

FIGURE 47.2 Duke nomogram for estimation of the prognosis. MET, metabolic equivalent.

In the previous equation, 0 = no angina, 1 = non–test-limiting angina, and 2 = exercise-limiting angina.

Low risk: DTS ≥ +5
Intermediate risk: DTS −10 to < +5
High risk: DTS < −10

2. The **heart rate recovery**, defined as the difference in heart rate at peak exercise and at 1 minute after cessation of exercise, has important prognostic significance. A heart rate recovery of 12 beats/min or less is considered abnormal during an upright cool-down period. For patients assuming an immediate supine position, such as during exercise echocardiography, a value of < 18 beats/min is considered abnormal.
3. The **chronotropic response index (CRI)** is a measure of MHR in relation to chronotropic reserve. A normal response is defined as a CRI of > 0.8 (0.62 for patients on β-blockers):

$$\text{CRI} = \frac{\text{peak HR} - \text{resting HR}}{\text{APMHR} - \text{resting HR}}$$

4. **Ventricular ectopy in recovery** from exercise, including frequent ventricular ectopics (> 7/min), couplets, bigeminy, trigeminy, ventricular tachycardia, and ventricular fibrillation, has been shown to be predictive of all-cause mortality. These findings in recovery are a better predictor of death than ventricular ectopy during exercise.
5. A published nomogram (1) for patients with suspected CAD and a normal ECG undergoing exercise treadmill testing demonstrates how a simple combination of clinical and stress-testing variables can be used to predict mortality.

X. POTENTIAL COMPLICATIONS. Complications of exercise electrocardiographic testing are rare, but they do occur (Table 47.11). Exercise testing of healthy persons without CAD rarely results in cardiac complications, which are most likely to occur among persons with underlying CAD. Several researchers have looked at large numbers of unselected persons involved in various activities to determine risk.

A. Cardiac arrest

1. For the **general population**, there is approximately 1 cardiac arrest per 565,000 person-hours of exercise.
2. Among **persons with known CAD**, there is an estimated 1 arrest per 59,000 person-hours of vigorous activity. Exercise testing may precipitate acute coronary symptoms. Acute MI has been reported in approximately 1.4 per 10,000 exercise tests.
3. Among **persons at low risk** for CAD, however, the risk for cardiac arrest during exercise testing is much lower. In one study, no complications occurred in 380,000 exercise tests of young persons with presumably no heart disease.

B. Arrhythmic complications are a potential hazard of exercise testing (Table 47.10). Arrhythmias are more likely among persons with a history of arrhythmia. In this population, they occur in 9% of tests compared with an overall incidence of 0.1%.

1. **Atrial fibrillation** is the most common arrhythmia that occurs during testing, occurring in 9.5 per 10,000 tests.
2. **Ventricular tachycardia** is less common, occurring in 5.8 per 10,000 tests.
3. **Ventricular fibrillation** is even less common, occurring 0.67 times per 10,000 tests.

C. Deaths during exercise testing are exceedingly rare among well-monitored patients, but may occur in 1 of 25,000 tests. If death occurs, it is usually caused by sudden cardiac death or MI.

TABLE 47.11 Potential Medical Complications of Exercise Electrocardiographic Testings

Cardiovascular complications

Cardiac arrest
Ischemia
- Angina
- Myocardial infarction

Arrhythmias
- Supraventricular tachycardia
- Atrial fibrillation
- Ventricular tachycardia
- Ventricular fibrillation

Bradyarrhythmias
- Bundle branch blocks
- Atrioventricular nodal blocks

Congestive heart failure
Hypertension
Hypotension
Aneurysm rupture

Underlying medical conditions predisposing to increased complications

Hypertrophic cardiomyopathy
Coronary artery anomalies
Idiopathic left ventricular hypertrophy
Marfan's syndrome
Aortic stenosis
Right ventricular dysplasia
Congenital heart defects
Myocarditis
Pericarditis
Amyloidosis
Sarcoidosis
Long QT syndrome
Sickle cell trait
Sudden death

Pulmonary complications

Exercise-induced asthma
Bronchospasm
Pneumothorax

(Continued)

TABLE 47.11 Potential Medical Complications of Exercise Electrocardiographic Testing (*Continued*)

Exercise-induced anaphylaxis
Exacerbation of underlying pulmonary disease
Gastrointestinal complications
Vomiting
Cramps
Diarrhea
Neurologic complications
Dizziness
Syncope (fainting)
Cerebrovascular accident (stroke)
Musculoskeletal complications
Mechanical injuries
Back injuries
Joint pain or injury
Muscle cramps or spasms
Exacerbation of musculoskeletal disease

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CHAPTER 48

Santosh S. Oommen

Nuclear Cardiac Imaging

I. INTRODUCTION. Nuclear cardiology has an integral role in the noninvasive detection of coronary artery disease (CAD), assessment of myocardial viability, and stratification of risk. It imparts improved sensitivity and specificity over standard exercise stress testing. For example, the average sensitivity and specificity of single-photon emission computed tomography (SPECT) with technetium 99m have been reported to be 90% and 74%, respectively—though the exact performance characteristics depend on the prevalence of the disease in the population being studied. Nuclear imaging can provide functional and prognostic information that is quantifiable, reproducible, and readily obtainable in diverse patient populations.

II. INDICATIONS (Table 48.1)

A. Diagnosis of CAD. Nuclear perfusion studies are performed to establish noninvasively the diagnosis of CAD in the following situations: history of **stable angina; chest pain of unclear causation; unstable angina** after stabilization; **abnormal exercise test result** without symptoms; **risk stratification** in the setting of multiple factors thought to confer a high likelihood of subclinical CAD; scheduled standard exercise testing in the setting of an **abnormal electrocardiogram** (ECG; due to left ventricular hypertrophy with associated repolarization changes, ST depression >1 mm, manifest pre-excitation pattern on ECG, digoxin use, left bundle branch block, or ventricular-paced rhythm); and previously **nondiagnostic graded exercise test**.

B. Assessment of the physiologic importance of known CAD. Perfusion imaging can assist in the determination of the functional significance of a coronary stenosis that is in the "moderate-to-severe" (50% to 70%) range on angiographic evaluation. It can therefore be useful to evaluate a specific coronary lesion before proceeding to percutaneous intervention. This remains an accepted indication for nuclear perfusion imaging, although its use for this purpose is being supplanted by other modalities that can assess the functional significance of coronary lesions at the time of angiography (e.g., fractional flow reserve).

C. Assessment after therapeutic intervention. In the past, perfusion imaging was often performed as a routine follow-up procedure after percutaneous intervention and coronary artery bypass grafting (CABG). More recent recommendations on appropriate use of this modality suggest that routine screening in *asymptomatic* patients who have been successfully revascularized by either method is not necessarily warranted, except in the evaluation of patients more than 5 years after CABG. On the other hand, radionuclide perfusion imaging is certainly appropriate in patients who have undergone prior revascularization and are presenting with recurrent symptoms consistent with coronary ischemia.

D. Risk stratification. With nuclear imaging, it is possible to stratify risk among patients with stable angina or unstable angina, those who have had myocardial infarction (MI), and those about to undergo noncardiac operations.

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging

Patient group	Condition	Imaging technique
ER patient with chest pain	For risk stratification in pt with *possible* ACS. Initial serum markers and enzymes. ECG is nondiagnostic.	Rest perfusion imaging (with ECG gating, if possible).
	For CAD diagnosis in pt with *possible* ACS and nondiagnostic ECG. Negative serum markers and enzymes or normal rest perfusion scan.	Same-day rest/stress (ECG-gated) myocardial perfusion imaging.
Acute MI/unstable angina	Assessment of LV function.	Rest myocardial perfusion imaging with ECG gating (rest gated radionuclide angiography is alternative option).
ST-elevation MI	Measurement of infarct size and residual viable myocardium, in an unrevascularized asymptomatic stable patient after completion of the infarct.	Rest myocardial perfusion imaging with ECG gating or with stress perfusion imaging with ECG gating.
	Thrombolysis without coronary angiogram, to identify inducible ischemia and myocardium at risk.	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible.
Non–ST-elevation MI/unstable angina	In an unrevascularized stable asymptomatic patient after completion of the infarct, to determine the extent and severity of inducible ischemia, either in the distribution of the "culprit" vessel or in remote myocardium.	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible.
	In individuals whose angina is stabilized on medical therapy or in whom the diagnosis is uncertain, to identify the extent and severity of inducible ischemia.	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible.
	To assess the functional significance of a coronary stenosis on angiography.	Rest and stress myocardial perfusion imaging.

(*Continued*)

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (*Continued*)

Patient group	Condition	Imaging technique
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* able to exercise to 85% MPHR or more	Those with pre-excitation, LVH, on digoxin, or >1 mm ST-segment depression on resting ECG.	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
	Individuals with left bundle branch block or ventricular-paced rhythm.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	Patients with an intermediate- or high-risk Duke treadmill score.	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
	In an individual with prior abnormal myocardial perfusion scan and new or worsening symptoms.	Repeat rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* not able to exercise	To identify the extent, severity, and location of inducible ischemia.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
Detection of CAD in patients with ventricular tachycardia	Patients without known CAD or ischemic equivalent.	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible.
Detection of CAD in patients with syncope.	Patients with intermediate and high risk for CHD and no ischemic equivalent.	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible.

(*Continued*)

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (*Continued*)

Patient group	Condition	Imaging technique
Prior to intermediate- and high-risk noncardiac surgery	Initial diagnosis of CAD in those with at least one clinical risk factor for adverse perioperative CV events, and poor (<4 METSs) or unknown functional capacity.	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible *or* In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	In individuals with established or suspected CAD and poor (<4 METS) or unknown functional capacity.	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible *or* In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	Diagnosis of CAD in patients with left bundle branch block or ventricular-paced rhythm and at least one risk factor for adverse perioperative CV events.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	In suspected or established CAD, prognostic assessment of those with left bundle branch block or ventricular-paced rhythm on rest ECG.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
Equivocal SPECT myocardial perfusion scan	Clinically indicated SPECT perfusion study is equivocal for CAD diagnosis or risk stratification purposes.	Rest and adenosine or dipyridamole stress PET myocardial perfusion study.

(*Continued*)

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (*Continued*)

Patient group	Condition	Imaging technique
CAD patient with systolic dysfunction and CHF, with little or no angina	Prediction of improvement in regional/global LV function following revascularization.	Stress/redistribution/reinjection thallium 201 SPECT perfusion imaging *or* Rest/redistribution SPECT perfusion imaging *or* Myocardial perfusion plus FDG PET metabolic imaging *or* Resting sestamibi SPECT perfusion imaging.
	Prediction of improvement in natural history following revascularization.	Stress/redistribution/reinjection thallium 201 SPECT perfusion imaging *or* Rest/redistribution thallium 201 SPECT perfusion imaging *or* Myocardial perfusion plus FDG PET metabolic imaging.

ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; ER, emergency room; FDG, [18F]fluoro-2-deoxyglucose; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; MPHR, maximal age-predicted heart rate; PET, positron emission tomography; pt, patient; SPECT, single-photon emission computed tomography.

E. Identification of prior MI among patients with angiographically normal coronary arteries is afforded by nuclear imaging.

F. Assessment of left ventricular (LV) function. Although nuclear imaging is used less often for this purpose than in the past—due to the desire to reduce patients' radiation exposure when possible—gated blood pool imaging remains an accurate method of determining the ejection fraction.

III. CONTRAINDICATIONS.

In addition to standard contraindications to exercise stress testing, specific considerations apply uniquely to nuclear imaging in general and the subgroup of dipyridamole stress perfusion studies.

A. General contraindications to nuclear studies. Nuclear imaging is contraindicated for patients who have had **iodine 131 therapy** within 12 weeks; **technetium 99m studies** within 48 hours, including bone, lung, multigated acquisition (MUGA), liver, tagged red blood cell (to evaluate gastrointestinal bleeding), and renal scans; **indium 111 scans** within 30 days; **gallium 67 scans** within 30 days; and **oral intake** within 4 hours (except for water).

B. Contraindications to dipyridamole, adenosine, or regadenoson administration include allergy to any of these agents, allergy to aminophylline, ongoing theophylline therapy (must be discontinued for 36 hours), history of uncontrolled asthma or reactive airway disease, significant atrioventricular nodal block, and caffeine consumption within 12 to 24 hours.

IV. EQUIPMENT.

The most basic tool in nuclear imaging is the **gamma or scintillation camera**, which is used to detect gamma rays (i.e., x-ray photons) produced by the chosen radionuclide. Three types of gamma camera exist.

A. A single-crystal camera consists of one large sodium iodide crystal. Other essential elements of this camera include the **collimator**, a lead device that screens out background or scattered photons, and the **photomultiplier**, an electronic processor that translates photon interactions with the crystal into electric energy.

1. Electric signals from the photomultiplier are processed by the **pulse height analyzer** before reaching a final form. Only signals in a specified energy range are incorporated into the interpreted images. The range recognized by the pulse height analyzer is adjustable and is established on the basis of the radiopharmaceutical used.
2. **Digitalization** of the single-crystal camera has greatly enhanced its performance.

B. A **multicrystal camera** works with an array of crystals with increased count detection capability. Because of the availability of an individual crystal to detect scintillation at any given time, this type of camera can be used to detect many more counts than can a single-crystal camera.

C. In the case of positron emission tomography (PET) scanning, a **positron camera** is a gamma camera used to detect the photon products of positron annihilation. Interaction between a positron and an electron causes annihilation, with the generation of two high-energy photons (511 keV) that travel in opposite directions.

1. An array of multiple concentric rings of crystals constitute a positron camera. Each crystal is linked optically to multiple photomultipliers. The crystals are oriented in diametric pairs in such a way that each pair of crystals must be struck simultaneously by annihilation photons to record activity. Background interference and stray photon energy are automatically accounted for, and artifact is limited.
2. Most positron cameras contain **bismuth germanate** for annihilation photon detection. The clinical utility and radiopharmaceuticals for PET are discussed in Section **X**.

V. MECHANICS AND TECHNIQUES

A. Image acquisition. Basic perfusion imaging can be performed by means of **planar** and **tomographic** techniques. The tomographic, or SPECT, method is the most commonly used today.

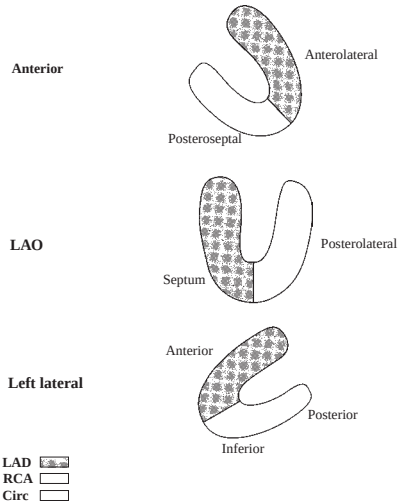

FIGURE 48.1 Standard planar views and vascular territories. Circ: circumflex artery; LAO, left anterior oblique; LAD: left anterior descending artery; RCA: right coronary artery.

1. **Planar images** are acquired in three views: **anterior, left anterior oblique (LAO)**, and **steep LAO** or **left lateral (LLAT) orientation** (Fig. 48.1). The patient is supine for anterior and LAO views but is placed in the lateral decubitus position for LLAT image acquisition. Although it allows examination of specific myocardial segments, planar imaging superimposes vascular distributions and therefore can compromise the ability to implicate a specific vascular supply when a defect is present. For example, normally perfused myocardial segments may overlap perfusion defects in a separate distribution.
2. Using **SPECT**, a series of planar images are usually obtained over a 180° arc to reconstruct a three-dimensional representation of the heart. The arc typically extends from the 45° right anterior oblique plane to the 45° left posterior oblique plane, with the patient in the supine position.
   a. Three orientations are analyzed in the final representation: **short axis, vertical long axis**, and **horizontal long axis**. A computer-generated display, the **polar map**, is also analyzed as a quantifiable representation of count density.
   b. Unlike planar imaging, **SPECT** can be used to **separate vascular territories** and improve image interpretation. SPECT, however, also **increases the time needed** for image acquisition and requires close attention to quality control issues.

B. Radiopharmaceuticals available for nuclear imaging include thallium 201, technetium 99m, and several positron imaging agents. Each possesses specific energy characteristics, kinetic profiles, and biodistribution (see below as well as Table 48.2 and Section **X** for further details).

1. **Thallium 201**
   a. **General characteristics.** Thallium 201 (i.e., thallous chloride) is a metallic element in group IIIA of the periodic table; it is produced in a cyclotron. Thallium emits gamma rays at an energy range of 69 to 83 keV and has a **half-life of 73 hours**. The biologic activity of this element is very similar to that of potassium; the ionic radii of the two elements are virtually identical. Thallium is actively transported into cells by the sodium–potassium adenosine triphosphatase (Na-K ATPase) pump.

TABLE 48.2 Characteristics of Common Perfusion Agents

Attribute	Thallium 201	Technetium 99m sestamibi	Technetium 99m tetrofosmin	Technetium 99m teboroxime
Energy (keV)	69–83	140	140	140
Dose (mCi)	2.5–3.5	20–30	20–30	20–30
Half-life (h)	74	6	6	6
Cyclotron required	Yes	No	No	No
Perfusion imaging	Yes	Yes	Yes	Yes
Viability evaluation	Yes	Yes	Yes?	No
Redistribution	Yes	Yes (minimal)	Yes (minimal)	Yes
Gating (electrocardiogram)	No	Yes	Yes	No

b. Kinetics. Approximately 5% of the administered dose of thallium 201 is distributed to the myocardium, proportionate to the blood flow delivered to the coronary circulation. Almost 85% of the thallium 201 is extracted by myocytes in the first pass.

(1) The **initial uptake** of thallium 201 by myocardium is directly related to regional blood flow. The myocardial extraction of thallium 201, however, increases at low flow rates (<10% of basal) and decreases at high flow rates (more than twice the basal rate).

(2) Washout. After initial uptake into myocytes, a state of continuous exchange across the cell membrane occurs. The distribution of this radiotracer changes after administration, and thallium 201 washes out from the myocytes, a process called **redistribution**. Thallium 201 washout generally approaches 30% at 2 to 2.5 hours after injection.

(3) Ischemic myocardium. Uptake of thallium 201 in ischemic myocardium is lower than uptake in nonischemic segments. Washout time from ischemic zones is slower than that from nonischemic zones.

(4) Over time, counts become equal in the ischemic and nonischemic regions (or thallium 201 concentration may increase in ischemic regions) so that thallium 201 concentrations in these disparate areas approach one another. This disparity is taken advantage of during thallium 201 viability imaging (described below).

2. Technetium 99m–labeled agents

a. General characteristics. Technetium 99m is a radiopharmaceutical that can be produced on-site in molybdenum 99–technetium 99m generators. It possesses several ideal imaging characteristics.

(1) Technetium 99m has a **half-life of 6 hours** and emits gamma rays with a single photopeak of 140 keV.

(2) Technetium 99m–labeled **perfusion agents** include ^{99m}**Tc-sestamibi**, ^{99m}**Tc-tetrofosmin**, and ^{99m}**Tc-teboroxime**. Although ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have similar properties, ^{99m}Tc-tetrofosmin may be less sensitive at detecting ischemic changes and its use for viability detection is less well validated.

b. Kinetics. After administration of ^{99m}Tc-sestamibi, approximately 40% to 60% of the agent is extracted by the myocardium. Initial uptake of the agent

is proportional to regional myocardial blood flow, and it is bound to the inner mitochondrial membrane. ^{99m}Tc-tetrofosmin has similar pharmacokinetics to ^{99m}Tc-sestamibi.

Myocardial washout of ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin is very slow, and little redistribution occurs. The absence of redistribution requires two separate injections of the agent, at **rest** and at **peak exercise** (or with pharmacologic stress). This can be performed with a same-day or 2-day protocol.

VI. IMAGING PROTOCOLS

A. Thallium 201

1. **General features.** Stress imaging with thallium 201 involves **injection at peak exercise** (or with pharmacologic stress) and **immediate imaging**, followed by **redistribution images** 3 to 4 hours after injection.
   - **a.** Because of the long half-life of thallium 201 (i.e., 73 hours), to reduce the total radiation exposure to the patient, limited amounts are administered. Although a single injection is typically used because of the redistribution phenomenon, a second injection may be given to enhance the filling of reversible defects.
   - **b.** The low energy range of thallium 201 is marginal for imaging with the gamma camera because of scatter and diminished spatial resolution.
2. **Variations from standard protocol.** Exact imaging techniques vary among institutions. Initial thallium 201 doses range from 2 to 3.5 mCi, acquisition times vary from 20 to 40 seconds per image, and the number of images varies from 32 to 64 depending on whether 180° or 360° image acquisition is used.
   - **a.** The use of **360° versus 180° imaging** has been the subject of debate. With 180° tomography, contrast is better, there is less artifact, and imaging times are shorter. Slight variations also exist depending on the use of exercise stress testing or pharmacologic stress protocols.
   - **b.** When **exercise thallium 201 scintigraphy** is performed, the radionuclide (2 to 3.5 mCi) is usually injected approximately 1 minute before peak exercise to allow time for distribution. Initial images are obtained within 5 to 10 minutes of injection. Redistribution images are obtained 2.5 to 4 hours after the initial images.
   - **c.** In some cases, persistent defects that would ordinarily be interpreted as myocardial scar represent viable myocardium.
     - **(1)** For this reason, some advocate **delayed (late redistribution) imaging** 18 to 24 hours after injection. Some studies indicate that up to 40% of persistent defects exhibit radiotracer uptake after revascularization. Delayed imaging has resulted in further redistribution in as many as 45% of patients.
     - **(2)** Alternative approaches in **differentiating viable tissue from scar** include **rest reinjection** of thallium 201, in effect to boost fill-in of perfusion defects. As many as 50% of persistent defects have been shown to exhibit improved thallium 201 uptake after rest injection of 1 mCi of thallium 201, suggesting viability.
   - **d.** Minor changes in imaging protocol may be observed with **pharmacologic stress testing** with adenosine, regadenoson, dipyridamole, or dobutamine.

B. Technetium 99m.

The relative lack of redistribution requires **two injections** of technetium 99m to obtain rest and stress images.

1. **Basic protocols**
   - **a. Same-day protocol.** At peak exercise, 25 to 30 mCi of technetium 99m is injected. Rest images are obtained first, and stress imaging follows to minimize residual scintigraphic activity caused by the higher dose stress injection.

(1) **Rest images** are obtained with injection of 7 to 10 mCi of technetium 99m and image acquisition up to 1 to 1.5 hours later. Imaging is delayed because of slower liver clearance with rest injection.

(2) **Stress images** are obtained approximately 45 to 60 minutes after injection. Hepatic uptake of technetium 99m occurs within 15 to 30 minutes of injection, and the tracer is excreted into the gastrointestinal tract through the biliary system. Appearance of the tracer in the gastrointestinal tract can interfere with imaging of the inferior wall of the left ventricle.

b. The **separate-day protocol** allows time for decay of activity. Larger doses of technetium 99m can be administered for rest and stress images, and there is minimal interference between the images.

(1) Between 22 and 30 mCi of technetium 99m is injected for stress and rest imaging, separated by 1 to 2 days.

(2) The higher doses possible with the 2-day protocol produce increased count density and better image quality at the cost of inconvenience.

2. Factors that affect image quality. Consumption of a **fatty meal** can enhance biliary excretion of technetium 99m and improve image quality. Because of possible interference from noncardiac uptake, image processing with technetium 99m relies on normalization to the brightest cardiac pixel.

C. Dual isotope imaging. Use of both thallium 201 and technetium 99m substantially reduces the time required to obtain stress and rest images.

1. The patient receives thallium 201 at rest (3.5 mCi) and, immediately after rest imaging, undergoes stress. At peak stress, the patient is given an injection of 25 mCi of technetium 99m. Stress images are obtained 15 minutes later.

2. This technique makes use of the dissimilar energy levels of the two radionuclides to shorten the protocol while still allowing acquisition of ECG-gated images (because of the use of technetium 99m).

3. The sensitivity (91%) and specificity (75%) of this combination protocol are comparable to the values for conventional technetium 99m SPECT.

VII. STRESS PROTOCOLS

A. Exercise stress testing. Standard exercise testing (see Chapter 49) is frequently complemented with nuclear imaging. The radioisotope is injected at peak exercise, and time is allowed for circulation of the agents (usually at least 1 minute before termination of exercise).

B. For patients who are unable to exercise, **pharmacologic testing** is used in concert with nuclear imaging. Adenosine, regadenoson, and dipyridamole are vasodilators that are useful in noninvasive testing because of differences in coronary flow reserve. In the presence of marked coronary stenosis, the distal vessel is maximally dilated and therefore possesses little flow reserve.

1. Adenosine acts at several different receptors (A_1, A_{2A}, A_{2B}, and A_3) and thus has several physiologic effects. Its desired effect for the purpose of pharmacologic stress is to substantially enhance coronary flow in normal beds (i.e., normal flow reserve), although much less so in distributions supplied by a stenotic artery. The resultant disproportionate flow is the basis for heterogeneous radiotracer uptake.

a. Administration. Adenosine is infused at 140 μg/kg/min for 6 minutes. The radiotracer is injected after 3 minutes of infusion.

b. Side effects commonly experienced include chest pain, headache, nausea, and flushing. Atrioventricular block and bronchoconstriction are the result of effects on the A_1 and A_3 receptors, respectively.

2. Dipyridamole is an adenosine reuptake inhibitor, leading to increased extracellular concentrations of adenosine, and thus has very similar effects. It has a longer distribution half-life than adenosine, however, of approximately 25 minutes.

a. **Administration.** Dipyridamole is infused over a 4-minute period (0.142 mg/kg/min). The maximum vasodilatory effect is achieved 4 minutes after completion of the infusion, and the radiotracer is injected at this point. A slight increase in heart rate (10 beats/min) and decrease in blood pressure (10 mm Hg) are frequently observed.

b. **Side effects.** Headache, nausea, chest pain, hypotension, dizziness, and flushing have been reported. Severe side effects may necessitate reversal of the dipyridamole effect with aminophylline, given as a 50- to 100-mg intravenous bolus.

3. **Regadenoson** is a selective A_{2A} receptor agonist that has been FDA approved for clinical use in myocardial perfusion imaging since 2008. Two randomized double-blind multicenter trials—ADVANCE-MPI 1 and 2—have demonstrated the safety of this agent in a total of 1,871 patients, as well as an efficacy similar to adenosine for the detection of reversible perfusion defects on SPECT imaging.

a. **Administration.** Regadenoson is given as a single 0.4 mg (in 5 mL) intravenous bolus and does not require adjustment for body mass index or renal or hepatic function. Its coronary hyperemic effects have an onset within 30 seconds and usually last for 2 to 5 minutes.

b. **Side effects** of chest pain, headache, nausea, and flushing do occur with regadenoson. However, atrioventricular block and bronchoconstriction are far less common than with adenosine or dipyridamole, due to the lack of agonism of the A_1 and A_3 receptors with this A_{2A}-selective agent. Aminophylline can be given intravenously to reverse intolerable or dangerous side effects if they occur.

4. **Dobutamine** is an agonist of the β_1 and β_2 receptors and thus increases both heart rate and contractility (with a mild reduction in systemic vascular resistance).

a. **Administration.** Infusion is begun at 5 μg/kg/min and increased every 3 minutes to a maximum dose of 40 μg/kg/min. The radiotracer is injected at maximum dose (or at 85% of age-predicted maximum heart rate), and the infusion is continued for 2 to 3 minutes.

b. **Side effects** associated with dobutamine include ectopy, headache, flushing, dyspnea, paresthesias, and hypotension.

VIII. IMAGE INTERPRETATION

A. **Standard view of normal anatomy.** The uptake of radiotracer is homogeneous in persons with normal myocardial perfusion. The tracer is predominantly distributed to the left ventricle; the right ventricle usually appears as a faint, thin structure. Understanding and interpreting these images, however, requires an understanding of standard planar and SPECT views of LV anatomic features.

1. **Planar images** are represented as LAO, anterior–posterior (AP), and LLAT views.
2. Standard **SPECT views** include the short axis, vertical long axis, and horizontal long axis. The short-axis view is further divided into apical, midventricular, and basal views.

a. As with planar views, SPECT images in various projections **correspond with specific myocardial segments** (Fig. 48.2).

b. In addition to the standard SPECT sections, short-axis sections can be compiled into a so-called **bull's eye display** (i.e., **polar map**). This computer-generated polar map (i.e., "bull's eye" image) arranges short-axis tomographic images such that the central portion represents apical slices and the periphery consists of the basal segments.

B. **Reviewing sequence.** Review of nuclear images follows an organized sequence.

1. **Examine unprocessed images** for artifact, extracardiac uptake, and evidence of increased lung uptake.
2. **Compare rest and stress images** for enlargement of the LV cavity.

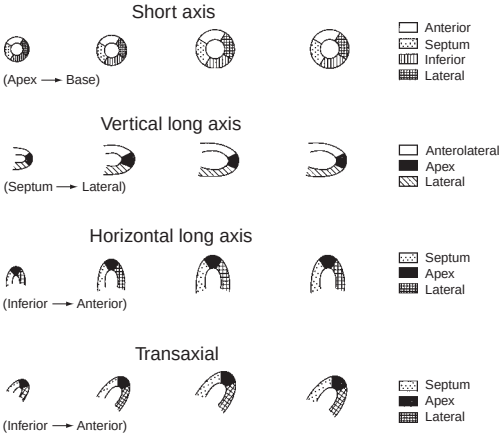

FIGURE 48.2 Standard tomographic projections and myocardial segments.

3. **Examine rest images.** Document fixed defects and the number of segments involved.
4. **Examine stress images.** Document defects and segments.
5. **Evaluate the polar map** in comparison with pooled normal images (derived from a database of patients with low probability of having CAD).
6. **Incorporate the gated SPECT images** to establish overall ventricular function and evaluate wall function in areas of questionable artifact. Segmental defects that demonstrate normal motion on gated SPECT images likely represent artifact.

C. **Characterization of defects.** Given that initial perfusion images represent regional myocardial blood flow, defects in these images represent an area of myocardium with relatively less uptake and diminished regional blood flow. Defects can be characterized as **fixed, reversible, or partially reversible** or as displaying **reverse redistribution**. (The term *redistribution* is not appropriately used in context with technetium 99m imaging.)

1. **Fixed defects.** Nonreversible or fixed defects are areas of absent tracer uptake that appear unchanged on both rest and stress images. Fixed defects can **represent scar or viable myocardium**. With thallium 201 imaging, nonreversibility suggests similar rates of clearance from the two regions.
   a. **Differentiating scar from viable myocardium** in the setting of a nonreversible defect can be accomplished through the use of **metabolic radiopharmaceuticals and PET, delayed imaging, or rest reinjection** with thallium 201. The level of tracer activity reflects viability. Severe deficits (<50% of normal counts) are less predictive of viability than are milder count deficits.
   b. Differentiating viable myocardium from scar is paramount because there is clinical and experimental evidence of improved LV function after revascularization of such hibernating regions (See Chapter 50). As methods of revascularization become increasingly applicable in an arena of increasingly complex patient problems, fully defining the so-called fixed defect through metabolic imaging assumes greater importance (see Sections **VIII.D.2** and **X.D**).
2. **Reversible defects** are present on initial stress images but resolve on rest or delayed images. This pattern is consistent with the presence of **ischemic myocardium** in the region of reversibility.

a. In the setting of **thallium 201 imaging**, resolution of the defect is a function of variable tracer concentrations in ischemic and nonischemic segments, which approach one another as redistribution occurs, along with continuous exchange of myocyte and blood pool thallium 201. **Fill-in** of reversible defects on thallium 201 images can be enhanced by means of delayed imaging or rest reinjection.

b. **Technetium 99m imaging**, which lacks redistribution, demonstrates reversibility on the basis of differential uptake during stress compared with rest.

3. **Partially reversible defects** are present on stress images and partially resolve on rest images but do not fill in completely. This type of defect is thought to reflect a **mixture of scar and ischemic myocardium**. Nonetheless, reversibility may be incomplete even in the absence of nonviable tissue and represent purely ischemic myocardium.

4. A pattern of **reverse redistribution** occurs when a defect appears larger on rest images or is absent on stress images but is present on rest images.

a. Such a pattern is seen in the presence of **acute MI** when the infarct artery has been rendered patent through thrombolysis, percutaneous coronary intervention, autolysis, or another form of revascularization.

b. The pattern is thought to reflect post-MI hyperemia with excess radiotracer uptake in a region of reperfused myocardium followed by accelerated myocardial washout of radiotracer in the defect region.

c. The regions in question may demonstrate viability on PET imaging and do not indicate ischemia.

5. **Artifacts.** Apparent perfusion defects can be attributed to soft tissue attenuation, a problem that occurs more often with thallium 201 imaging than when a higher-energy agent (technetium 99m) is used.

a. Common causes of the presence of artifacts include **breast attenuation** (affecting the anterolateral, septal, anteroseptal, and posterolateral walls of the ventricle) and **diaphragmatic attenuation** (predominantly altering the inferior and posterior walls).

b. Planar images with perfusion defects seen in only a single view are suspect, and the presence of artifact must be considered.

c. SPECT artifacts may be more elusive because of processing and reconstruction of tomographic images. However, with good technique, most are avoidable. When there is a suspicion for attenuation artifacts as above, **attenuation correction** processing techniques can be employed to account for these variables.

6. **High-risk perfusion scan.** Specific patterns of perfusion imaging that suggest high-risk coronary anatomic features include perfusion **defects in more than one vascular distribution, increased lung thallium uptake, and transient LV dilatation**.

D. **Quantitative analysis.** The principles of image analysis rely on visual inspection, which is fraught with observer variability.

1. **Computer-aided analysis** of planar data involves comparison of regional radionuclide activity on stress and rest images; count discordance coincides with reversibility. **SPECT** data are quantitatively analyzed by means of comparing count densities on short-axis images (displayed as a polar map) with normal count profiles. Although they improve sensitivity, these methods are **used in concert with visual analysis**.

2. **PET imaging**, although evaluated in large part in a visual manner, also possesses great clinical utility with the application of **quantitative analysis of myocardial perfusion and coronary flow reserve**. Moreover, significant advances have been made in the ability to quantify *absolute*—and not just relative—blood flow in different coronary vascular territories using PET imaging. On the basis of analysis of baseline blood flow and flow during vasodilator stress, this technique is

useful in revealing functionally important coronary lesions even in the presence of multivessel coronary disease.

The administration of adenosine, dipyridamole, or regadenoson should induce at least a twofold to threefold increase in coronary blood flow over baseline in a normal coronary vascular bed—but this "flow reserve" is not present in the setting of functionally significant epicardial coronary artery stenosis existing proximally to this bed (as discussed earlier in the chapter). Thus, relative differences in myocardial perfusion during hyperemia—which may not be appreciated on visual inspection—may be more precisely demonstrated with quantitative analysis of flow reserve. Furthermore, the ability to quantitate absolute myocardial blood flow regionally and globally may help surmount the difficulty in noninvasively diagnosing CAD in the setting of "balanced ischemia" from severe left-main or triple-vessel CAD.

IX. CLINICAL APPLICATIONS

A. Perfusion analysis

1. Detection of CAD

a. Sensitivity and specificity. Since the introduction of thallium 201 imaging in 1975, the utility of perfusion agents in the diagnosis of CAD has been well established. Quantitative planar imaging and SPECT demonstrate 90% or greater sensitivity.

(1) **Sensitivity** is affected by the number of vessels involved. Single-vessel disease is most likely to produce a false-negative finding. Multivessel CAD rarely produces a normal perfusion scan result. The **specificity** of planar imaging is 83% and that of SPECT is ~70%.

(2) In general, radionuclide imaging is best used to evaluate a population at intermediate risk for CAD. The choice of radionuclide agent seemingly has little effect on the accuracy of these techniques.

(3) The introduction of **PET**, however, has brought with it **advanced diagnostic accuracy**, with approximately 10% to 15% improvement over SPECT. The ability to detect CAD in a noninvasive manner offers numerous additional applications in risk stratification, prognosis, and imaging of acute infarction.

b. Causes of **false-positive** perfusion study results include attenuation defect, technical inadequacies, coronary vasospasm, anomalous coronary circulation, cardiomyopathy, conduction defects such as left bundle branch block, and recanalization of a thrombosed coronary artery.

c. Causes of **false-negative** perfusion study results include a submaximal exercise stress test, anti-ischemic medical therapy, collateral or overlap circulation, inaccurate interpretation of perfusion images or angiograms, acquisition of suboptimal images, presence of balanced coronary stenoses, and delay in stress imaging.

2. Risk stratification. In addition to indicators of higher risk taken from perfusion images, such as increased lung uptake, determinants in the assessment of risk are as follows.

a. Presence of reversible as opposed to fixed defects is associated with greater likelihood of cardiac events related to acute coronary syndrome at follow-up evaluation. This relation has clinical utility in a number of settings, including risk stratification after MI or in the preoperative setting. In one study involving patients who had had MI without complications, patients with single, fixed defects on thallium 201 images had a 6% cardiac event rate, compared with a rate of 51% for those with thallium 201 scans that indicated high risk of such an event.

b. Radionuclide **imaging abnormalities** have been identified as **independent predictors of subsequent infarction or death**. In general, the number of

abnormal segments identified on nuclear images can be seen as inversely proportional to survival rate. Normal findings on a nuclear perfusion study, however, suggest an excellent prognosis, with a yearly mortality rate <1% (in patients with a normal ejection fraction). The application of such prognostic information to the care of patients preparing for noncardiac operations reflects significantly on the patient's surgical risk and has an established role in preoperative evaluation and clearance. For this population, evidence of ischemia on perfusion images portends a higher risk of a perioperative cardiac event.

3. Myocardial perfusion imaging may aid in the diagnosis and risk stratification of patients with **acute coronary syndromes**.
   a. Patients with **chest pain of ill-defined origin** can be given an injection at rest of thallium 201 or technetium 99m. In the presence of true ischemia (i.e., without infarction), **reversible defects** are documented, and insight into **regional distribution of ischemia** and extent of myocardium involved is gained. The **absence of any perfusion defect with ongoing chest pain makes a diagnosis of angina less likely**.
   b. In the setting of **thrombolysis**, imaging with technetium 99m can provide important information about reperfusion or lack thereof. Injection of technetium 99m before initiation of thrombolysis captures a picture of hypoperfusion, which can, because of the extensive half-life, be imaged at a later time. Subsequent injections reveal the status of perfusion as the period after thrombolysis proceeds (i.e., persistent, large defect that represents failed reperfusion). Such applications in the setting of thrombolysis and in acute coronary syndromes have limited clinical utility because of the logistics of staffing and availability of radiopharmaceuticals.
   c. A further application that affects the arena of revascularization and management of ischemic syndromes involves **assessment of myocardial viability**.

B. **Assessment of ventricular function.** In addition to its use in perfusion analysis, radionuclide imaging can establish cardiac performance. Radionuclide-based assessment of ventricular function includes first-pass radionuclide angiocardiography and gated blood pool imaging.

1. **First-pass radionuclide angiocardiography** involves injection of a radionuclide and analysis as the agent passes through the central circulation.
   a. Technetium 99m–labeled agents are typically administered in bolus form, and scintigraphic data are recorded for 15 to 30 seconds after injection. Multicrystal cameras oriented in a straight anterior projection are used for detection of high count rates.
   b. This method of ventricular function analysis is more useful in evaluating **right ventricular function** than is gated blood imaging. In patients with **severe LV dysfunction**, the radiotracer may be dispersed, and proximal venous access and rapid administration may be necessary.
2. **Gated blood pool imaging**, also known as radionuclide angiography or MUGA, relies on ECG gating to correlate multiple individual images of the cardiac blood pool to specific phases of the cardiac cycle.
   a. The blood pool is labeled by means of removing a 2- to 3-mL sample of the patient's blood after the intravenous administration of stannous chloride. The sample is labeled with technetium 99m and reinjected into the patient intravenously. The stannous ions reduce the technetium, so they will not leak out of the tagged cells.
   b. A single-crystal gamma camera is used in the LAO, AP, LLAT, and sometimes left posterior oblique projections to obtain serial static images of the cardiac blood pool gated to the R-R interval.
   c. Because multiple cardiac cycles are averaged to obtain the final images, this technique is not optimal for evaluating regional wall motion. For many years, though, MUGA was considered a "gold standard" technique

for assessment of overall LV ejection fraction. Radionuclide angiography remains a well-validated and highly reproducible method of assessment of overall LV ejection fraction (and, importantly, retains this quality especially well at low ejection fractions). The use of this technique is diminishing in the current era of echocardiography and cardiac MRI.

3. **ECG-gated perfusion imaging.** Perfusion imaging with technetium 99m–labeled tracers produces sufficient count densities on individual images to allow ECG gating. The standard injection of 20 to 30 mCi of technetium 99m allows evaluation of **perfusion and function in a single study**. The *greatest* utility of ECG-gated perfusion imaging may be in elucidating perceived artifacts on perfusion images. For example, if a region has a perceived fixed perfusion defect, yet wall motion is normal in the same region, artifact becomes a more likely consideration as the cause of the filling defect.

   Comparison of this method with two-dimensional echocardiography in the evaluation of regional wall motion has shown good correlation between the two. This correlation is not applicable to stress echocardiography, however, because of the time lag from the period of stress to the acquisition of nuclear images.

X. POSITRON EMISSION TOMOGRAPHY.

PET has bolstered the evaluation of CAD by nuclear imaging techniques, both by improving blood flow imaging and by allowing evaluation of metabolic activity. Positron imaging agents can be divided into blood flow tracers and metabolic radiopharmaceuticals.

A. Blood flow tracers. A number of radiopharmaceuticals exist for the assessment of myocardial blood flow. They can be produced by a cyclotron or generator.

1. **Rubidium 82**, the most readily used blood flow tracer, can be generated on-site without the use of a cyclotron. Much like thallium 201, rubidium 82 is a potassium analogue that is actively transported into myocytes through the Na-K pump. **Uptake into myocardium** is proportionate to regional blood flow. Approximately 65% of the radiotracer is extracted at first pass. Because of a short half-life (76 seconds), rubidium 82–based imaging protocols can be used to assess myocardial blood flow rapidly (within 1 hour). However, the short half-life also precludes exercise stress PET imaging with this tracer.
2. Other perfusion agents include the cyclotron-produced **nitrogen 13 ammonia** (half-life 10 minutes) and **oxygen 15 water** (half-life 123 seconds). Image quality with **oxygen 15 water** is poor and requires extensive processing to subtract the blood pool. Rb 82 and ^{13}N-ammonia are the perfusion tracers that are used in clinical practice, with Rb 82 carrying the distinct advantage of requiring only a generator instead of a cyclotron. The image quality of ^{13}N-ammonia is excellent, although the impracticality of cyclotron production in most facilities is a limiting factor for this agent. For those facilities capable of ^{13}N-ammonia generation, however, it has the "upside" of a longer half-life than rubidium 82; thus, exercise stress cardiac PET imaging could be performed if desired.

B. Metabolic radiopharmaceuticals. Metabolic imaging with PET depends on the use of radiolabeled substrates of cardiac metabolism, largely in the form of [^{18}F] fluoro-2-deoxyglucose (FDG), carbon 11 palmitate, and carbon 11 acetate.

1. **FDG** is a glucose analogue used by ischemic myocardium because of a transition to alternative fuel sources in the hypoxic state. Ischemic myocardium diminishes the oxidation of long-chain fatty acids and increases the use of glucose as a secondary fuel source. FDG is phosphorylated to FDG-6-phosphate after transport across the cell membrane. FDG imaging therefore reflects myocardial use of exogenous glucose, and FDG is a widely used metabolic radiopharmaceutical. It has a half-life of 1.83 hours, which means it can be ordered on a daily basis by institutions that do not have an on-site cyclotron—making it the most commonly used metabolic PET imaging agent.

2. [^{11}C]Palmitate is taken up by myocytes, converted to acyl CoA, and relegated to triglyceride stores or β-oxidized to produce [^{11}C]carbon dioxide. The release of this product of β-oxidation is reflective of long-chain fatty acid oxidation in myocardium.
3. [^{11}C]Acetate is metabolized to [^{11}C]carbon dioxide after entering the tricarboxylic acid cycle. Measuring the production of [^{11}C]carbon dioxide in this setting correlates with myocardial oxygen consumption.

C. Protocols. Image acquisition with PET is similar to that with SPECT in that tomographic images are obtained in short-axis, horizontal long-axis (sagittal), and vertical long-axis (coronal) views. A positron camera consists of an array of crystals arranged in a circle. Unlike in SPECT, the camera remains stationary in PET.

1. The heart is localized with the patient's arms extended above the head. An **attenuation scan** is performed that allows the density of the surrounding thorax to be subtracted to leave only cardiac count activity. This performance of attenuation correction which makes **allowance for noncardiac interference** adds a great deal to the accuracy of PET.
2. After the attenuation scan, the **positron-emitting radiopharmaceutical is injected**, and **images are obtained** 2 to 5 minutes later. As mentioned earlier in the chapter, two photons are created by the annihilation of the emitted positron colliding with the nearest electron it meets in the tissue surrounding it. These two photons travel *exactly 180° apart* while the patient is lying in the circular scanner. This is an important concept because it means there is **no need for collimation**. The detector/analyzer merely has to "accept" the signal it receives only if a simultaneous signal strikes the detector directly across from it in the scanner. This *dramatically* improves the signal-to-noise ratio that can be achieved during imaging.
3. Metabolic imaging can be undertaken after flow imaging with the administration of 5 to 10 mCi of FDG. Tomographic images are typically obtained 30 to 50 minutes after FDG injection.

D. Patterns of perfusion and metabolic imaging. Specific patterns of perfusion and metabolic imaging are identifiable. For example, **normal flow–normal FDG (match)** indicates normal perfusion and normal metabolic activity. **Reduced flow with normal or increased FDG ("flow-metabolism mismatch")** demonstrates viability (i.e., hibernating myocardium). **Reduced flow–reduced FDG** identifies scar tissue.

E. Clinical applications

1. **Diagnosis of CAD.** Flow imaging with PET is highly sensitive and highly specific for the detection of coronary stenosis, approaching 93% for both.
   a. Higher-energy photons (511 keV), higher count densities, shorter half-life, and "built-in" attenuation correction place PET substantially ahead of SPECT in the accurate detection of CAD.
   b. As mentioned before, the ability to quantitate absolute blood flow regionally and globally may help improve the diagnosis of coronary ischemia in the setting of severe multivessel disease and balanced ischemia.
2. **Assessment of myocardial viability.** (see Chapter 50). The use of **PET with metabolic radiotracers is the standard for identifying viable myocardium**. The presence of a flow-metabolism mismatch, which indicates underperfusion in the presence of metabolically active myocytes, indicates hibernating myocardium. Revascularization of these zones as identified with PET has been shown to result in improvement in wall motion. This utility of nuclear imaging has found increasing application in the selection of patients for revascularization who have ischemic cardiomyopathy and heart failure with low ejection fraction.

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CHAPTER 49

Michael P. Brunner

Stress Echocardiography

I. INTRODUCTION. Stress echocardiography (SE) is an **effective method of evaluating for myocardial ischemia**, based on the detection of **stress-induced regional wall motion abnormalities** (WMAs). Stressors include exercise, pharmacologic agents, and pacing. SE is used to **screen for coronary artery disease** (CAD), and it can help **identify the coronary vessels involved**. The accuracy of SE in the detection of significant coronary artery stenosis is 80% to 90%, which is superior to that of exercise electrocardiographic testing and comparable to that of nuclear stress imaging. In patients with left ventricular (LV) dysfunction and documented CAD, SE can **differentiate viable myocardium from scarred myocardium**, which may help predict whether LV function will improve after revascularization. As a diagnostic test for CAD, **SE is safe and relatively inexpensive** and **can be rapidly performed by experienced hands**. However, interpretation of SE images remains primarily subjective and requires a considerable learning curve. SE can also be used to assess the severity of valvular disease, hypertrophic cardiomyopathy, and exercise-induced pulmonary hypertension. In addition, it provides important prognostic information after myocardial infarction (MI) and prior to noncardiac surgery.

II. PATHOPHYSIOLOGY

A. Exercise stress testing. Myocardial ischemia results from a mismatch between oxygen supply and demand. The ischemic cascade is illustrated in Figure 49.1. Echocardiography detects ischemia by identifying new or worsening WMAs earlier in the cascade than detected by the electrocardiogram (ECG) or the onset of symptoms, but usually after the onset of worsening diastolic function. Exercise can be performed with a treadmill or an upright or supine bicycle.

B. Pharmacologic stress testing. In patients who cannot exercise, pharmacologic stressors can be used. These drugs are sympathomimetic agents or vasodilators.

1. **Sympathomimetic agents.** Myocardial oxygen demand is determined by contractility (inotropy), heart rate (chronotropy), and wall stress (preload + afterload). Sympathomimetic agents produce stress by causing an **increase in myocardial oxygen demand through increased inotropy, chronotropy, and blood pressure (BP) (afterload)**. Although a number of agents have been evaluated in combination with echocardiography, **dobutamine** is most widely used. Low-dose dobutamine has positive inotropic effects mediated through cardiac α_1 and β_1 receptors. At higher doses, it has positive chronotropic effects mediated through β_2 receptors. The plasma half-life of dobutamine is 2 to 3 minutes. The normal response to dobutamine is an increase in heart rate and hyperdynamic wall motion, with only minimal effect on end-diastolic LV volume. It can be **combined with atropine** to achieve the usual target of at least 85% of age-predicted maximum heart rate (APMHR).
2. A **vasodilator stress test** is performed with **dipyridamole** or **adenosine** infusion. These agents result in perfusion abnormalities by causing blood to be preferentially shunted away from myocardial segments supplied by stenotic coronary arteries (i.e., coronary steal) and into more normal coronary vessels. This may lead to wall motion abnormality in the perfusion territory of the stenotic coronary artery that is seen on echocardiography. These agents are less commonly used for SE. Adenosine has fewer side effects than dipyridamole, owing to the former's shorter half-life. However, because of the shorter duration of action of adenosine, the echocardiographic findings tend to be less pronounced and of shorter duration, resulting in a lower sensitivity.

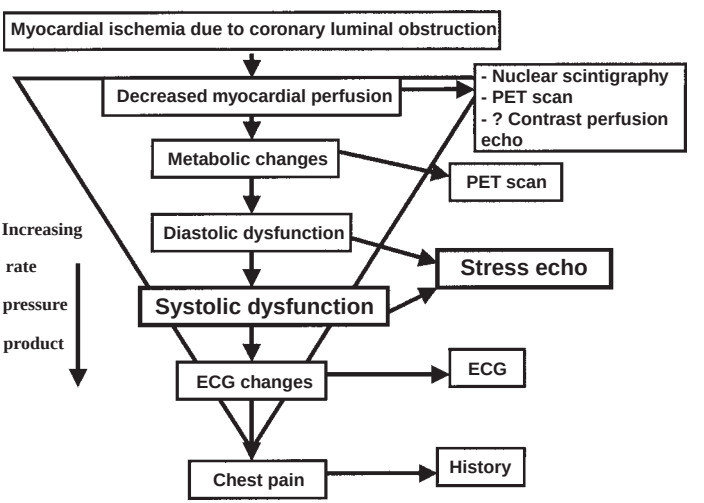

FIGURE 49.1 Ischemic cascade. PET, positron emission tomography; ECG, electrocardiogram.

3. **The 2007 American Society of Echocardiography (ASE) guidelines recommend dobutamine as the first-line agent for pharmacologic SE.** In addition, much of data for preoperative risk stratification and viability assessment using SE were derived from pharmacologic studies using dobutamine.

C. Atrial pacing. Tachycardia induced by atrial pacing is an alternative to pharmacologic testing in patients that cannot exercise. In patients with a permanent pacemaker, stress is achieved by increasing the pacing rate until the target heart rate is reached. Transvenous and transesophageal pacing are considerations in patients without a permanent pacemaker.

III. INDICATIONS AND CHOICE OF STRESSOR

A. The **indications and contraindications** for SE testing are similar to those used for exercise electrocardiographic stress testing (see Chapter 47). The addition of an imaging modality improves the sensitivity and specificity of exercise electrocardiographic stress testing. Table 49.1 lists factors that may limit the sensitivity of electrocardiographic stress testing to detect CAD; patients with these factors benefit from a stress test utilizing an imaging modality (i.e., echocardiography, nuclear scintigraphy, or positron emission tomography [PET]).

B. **Additional contraindications** to SE occur **with pharmacologic stress** and depend on the underlying pharmacologic stressor. Patients with severe bronchospastic obstructive lung disease or high-grade atrioventricular (AV) block should avoid dipyridamole and adenosine. Patients with unstable ventricular arrhythmias should avoid dobutamine infusion. **Relative contraindications to SE** include unstable angina, severe baseline hypertension, uncontrolled arrhythmias, mobile LV thrombus, critical aortic stenosis (AS), hypertrophic obstructive cardiomyopathy, and decompensated heart failure.

C. Exercise stress is preferred over nonexercise stress because it more closely reproduces daily activity and is more sensitive in the detection of ischemia, provided the patient is able to achieve an adequate level of stress. No single **exercise modality** has been shown to have superior sensitivity, although the **treadmill** is more widely accepted among patients and physicians. **Bicycle ergometry** can be performed in the upright and supine positions. Images with treadmill stress testing must be obtained after exercise, whereas images may be obtained at peak exercise with bicycle ergometry while the patient continues to exercise. The sensitivity of treadmill testing to detect ischemia is reduced if images are not rapidly obtained (< 90 seconds) after exercise. However, the treadmill usually results in a greater level of stress than is associated with bicycle ergometry, which is more dependent on patient effort.

TABLE 49.1 Factors Limiting the Sensitivity of Stress Electrocardiography to Detect Coronary Artery Disease

Left bundle branch block or other intraventricular conduction delay abnormalities
Paced rhythms
Abnormal ST segments at baseline:
Digitalis effect
Electrical left ventricular hypertrophy
Previous evidence of myocardial infarction
Nonspecific, abnormal ST-segment changes
Women (higher rate of false-positive ST-segment changes)
Left ventricular hypertrophy (even with normal-appearing electrocardiogram)

D. Up to **30% of patients referred for exercise echocardiography may not be able to achieve an adequate level of exercise stress** because of peripheral vascular disease, chronic obstructive pulmonary disease, or musculoskeletal problems. **Pharmacologic stress testing is usually indicated** in these patients.

IV. METHODOLOGY

A. Patient preparation

1. Patients should avoid heavy food intake for several hours before the test.
2. Rate-slowing agents (particularly β-blockers) blunt the normal heart rate response to exercise and may limit the ability of the patient to achieve at least 85% of the APMHR. This may reduce the sensitivity of the test results. If possible, these agents should be withheld before the stress test, unless the aim of the test is to evaluate their effectiveness in preventing exercise-induced ischemia.
3. The **standard connections for a 12-lead ECG** may be used with minor modifications to allow imaging in the parasternal and apical windows without affecting the accuracy of the exercise electrocardiographic testing results.

B. Equipment. All SE studies are conducted with **exercise electrocardiographic testing and standard hemodynamic monitoring equipment**. A SE software package on the echocardiographic machine is necessary to acquire digital images and to allow side-by-side comparison of pre-stress images with peak stress or post–peak stress images. Resuscitation equipment and a defibrillator should be readily available.

C. Performing the test

1. **Exercise SE.** Regardless of the exercise modality, a quick, complete **baseline** echocardiographic scan is obtained for all patients. Resting images are obtained in the parasternal long- and short-axis and apical two- and four-chamber views and stored digitally. An apical long-axis view may be substituted for a parasternal long-axis view if the parasternal images are suboptimal. If endocardial definition is suboptimal, intravenous ultrasound contrast should be given to optimize the images.
   a. **Treadmill exercise** is performed with standard protocols according to the functional status of the patient. Exercise is continued until at least 85% of the APMHR is reached, but it is preferably continued to the level of maximum exertion to maximize test sensitivity. APMHR equals 220 – age. **Post–peak stress images** are obtained as quickly as possible (in the left lateral decubitus position) after the patient transfers from the treadmill to the imaging table. Stress images in the same views as the baseline study are stored digitally and recorded on videotape. All post–peak stress images should be **obtained within 90 seconds of completing exercise** to maximize test sensitivity.
   b. During **upright bicycle echocardiography**, baseline images are obtained in the standard left lateral position and are repeated with the patient in the upright position on the cycle ergometer. Adequate parasternal images may be recorded by having the patient lean forward. These images are recorded and digitized to allow comparable windows for the rest and peak stress images. Cycle ergometry is started at a workload of 25 W and increased by 25 to 50 W every 2 to 3 minutes until the patient reaches his or her level of perceived maximal effort. During upright bicycle echocardiography, **images are obtained and digitized at rest, before peak, at peak, and after peak exercise**.
   c. With **supine bicycle exercise**, the entire study is performed while the patient is tilted 30° in the left lateral decubitus position, and images are obtained and digitized **at rest, before peak, at peak, and after exercise**. This exercise modality is not widely used.
   d. **Study end points** for exercise SE include **target heart rate** (85% APMHR), **severe electrocardiographic ischemia** (ST-segment depression > 5 mm), **intolerable symptoms** (chest pain and dyspnea), **severe hypertension**

(systolic BP > 220 mm Hg or diastolic BP > 110 mm Hg), **hypotension** (systolic BP < 90 mm Hg or a fall in systolic BP > 20 mm Hg from baseline), **ventricular tachycardia** or **sustained supraventricular tachycardia,** and the **development of new WMAs in at least two contiguous segments**.

2. **Pharmacologic SE**
   a. **Dobutamine SE**
      (1) **Dobutamine infusion** is started at 10 μg/kg/min and increased every 3 minutes to 20, 30, and 40 μg/kg/min. If the patient has not reached 85% of APMHR by the end of the 40 μg/kg/min dose, a 3-minute dosage of 50 μg/kg/min may be used. Infusion is begun at lower doses (5 μg/kg/min) if baseline LV function is abnormal and myocardial viability is being sought. Images are digitized at rest and at low dosage (5 to 10 μg/kg/min), pre–peak dosage (30 μg/kg/min), and peak dosage.
      (2) **Atropine** is used as needed to reach target heart rate > 85% of APMHR if dobutamine alone is not effective. Atropine (0.25 to 0.5 mg) is given intravenously every minute, starting at the 40 μg/kg/min dobutamine dose level and continuing until an end point is reached or a total dose of 2 mg is given. Atropine should be used with caution in patients that have glaucoma or benign prostatic hypertrophy. Isometric handgrip may be performed at the peak infusion rate to help achieve target heart rate.
      (3) **Study end points** for dobutamine SE are the same as those used for exercise SE. If 85% APMHR has been achieved without any other end points, it is preferable to complete the protocol to the end of the 40 μg/kg/min infusion to increase the sensitivity of the test.
      (4) **Side effects.** The most serious potential side effect of dobutamine is arrhythmia provocation. However, serious complications (e.g., arrhythmia, MI, and cardiac arrest) are rare, occurring in about 0.3% of studies in a large series of > 5,000 patients. Less serious side effects include tremor, nervousness, and marked hypertensive and hypotensive responses. The most common minor complication is hypotension, which usually responds to supportive therapy including intravenous fluids. A hypotensive response with dobutamine may be caused by ischemia and dynamic outflow tract obstruction or may result from the vasodilatory effect of dobutamine in combination with a small hyperdynamic LV and a low stroke volume.
      (5) **If angina or severe side effects develop**, the effects of dobutamine may be **reversed with intravenous β-blockade** (0.5 to 1 mg/kg esmolol given over 1 minute or 2 to 5 mg/kg metoprolol given every 2 to 5 minutes). Like dobutamine, esmolol has a very short half-life and, therefore, may be preferable.
   b. **Dipyridamole or adenosine SE**
      (1) Patients with hypotension, AV block, or a history of severe bronchospasm **should not undergo** testing with these agents.
      (2) Different protocols of **dipyridamole infusion** have been studied. The protocol recommended by the ASE is a low-dose two-stage infusion. The first stage begins at 0.56 mg/kg dipyridamole over 4 minutes; if no adverse effect or clinical end points are reached, an additional 0.28 mg/kg is infused over 2 minutes. **A high-dose** regimen of 0.84 mg/kg given over 10 minutes has been developed to improve the sensitivity of the test relative to low-dose protocols.
      (3) **Adenosine** is given as a continuous infusion because of its very short half-life. A typical protocol starts at a low dose of 80 μg/kg/min and is increased every 3 minutes by 30 μg/kg/min to a peak dose of 170 to 200 μg/kg/min.
      (4) **Regadenoson** is an adenosine receptor agonist with a 2 to 3-minute half-life, as compared with adenosine's 30-second half-life. Regadenoson is administered as one 0.4-mg dose over 10 seconds.

(5) **Study end points** for dipyridamole or adenosine SE are similar to those used for exercise SE. A notable exception is that patients are not stressed until the APMHR is achieved. Additional end points include third-degree AV block, severe hypotension, and intolerable side effects (e.g., bronchospasm). Symptoms usually start to resolve within 60 seconds after medication administration.

(6) **If hypotension, bradycardia, or bronchospasm occurs**, the effects of dipyridamole, adenosine, and regadenoson can be **reversed with intravenous aminophylline** 25 to 50 mg over 30 to 60 seconds.

D. Imaging techniques. Modern technology allows digital image acquisition of multiple cardiac cycles and side-by-side comparison in a split screen display, enabling easy comparison of regional wall motion at rest and peak stress or after stress. Detailed frame-by-frame evaluation of wall thickening or excursion is possible, which helps in the evaluation of regional myocardial function. Obesity and lung disease remain the primary reasons for poor quality images. **Harmonic imaging** has improved endocardial definition, which can be further optimized with **microbubble contrast agents**.

1. **Contrast echocardiography.** Microbubble contrast agents provide **improved echocardiographic resolution** and allow **real-time assessment of intracardiac blood flow**. These agents are helpful when baseline SE images are suboptimal.
   a. **Intravenous agitated saline** improves visualization of the right atrium and ventricle and enables visualization of intracardiac shunts. However, intravenous agitated saline is not able to cross the pulmonary circulation and opacify the left ventricle.
   b. **Second-generation microbubble contrast agents** such as **Optison** and **Definity** incorporate perfluoropropane gas encased in an albumin-based or phospholipid shell, are more durable, and are able to cross the pulmonary circulation and opacify the left ventricle.
   c. **These agents are well tolerated and have a low complication rate**. After initial concerns about safety, the FDA revised labeling requirements for second-generation contrast agents in 2008 and again in 2011. Patients with pulmonary hypertension or unstable cardiopulmonary conditions including acute coronary syndrome, worsening or unstable heart failure, serious ventricular arrhythmias, or respiratory failure no longer need to have their vital signs and oxygen saturation monitored for 30 minutes after injection. **Absolute contraindications to administration include previous hypersensitivity reaction and fixed right-to-left, bidirectional, or transient right-to-left cardiac shunts.** Intra-arterial injection is contraindicated.
2. **Real-time three-dimensional (3D) echocardiography.** Significant advances have been made in 3D data acquisition without the need for off-line reconstruction. Three-dimensional imaging may shorten the acquisition period of post-exercise images or peak exercise images, allowing improved sensitivity and minimizing the technical strains imposed on the technologist obtaining the images. However, 3D SE is not routine in clinical use and remains under investigation.

V. IMAGE INTERPRETATION

A. Qualitative versus quantitative approach

1. **Interpretation of SE findings is predominantly qualitative.** Visual assessment of LV wall thickening and motion remains the standard method of interpretation of SE but is **subject to interobserver and interinstitutional variability**. Suggestions to optimize interpretation of SE images are outlined in Table 49.2. Each myocardial segment is visually assessed for wall thickening, rather than just wall motion, which may be influenced by myocardial tethering and translation. LV wall motion normally becomes hyperdynamic with stress. Worsening of WMAs or the development of new ones is the hallmark of stress-induced myocardial ischemia. SE responses and interpretation are summarized in Table 49.3.

TABLE 49.2 Suggestions to Optimize Interpretation of Stress Echocardiographic Images

1. Ensure that pre-stress and post-stress images are comparable views
2. Ensure that the apex is not foreshortened, especially in two-chamber views
3. True two-chamber views should not show any of the right ventricle
4. Use ultrasound microbubble contrast agents when resting images are suboptimal
5. Check that digital images are timed to begin at systole. If digital clips include diastole, there is an increased likelihood of calling a false-positive wall motion abnormality
6. Check the heart rate for each post-stress image. If images are obtained after the heart rate has returned toward normal, the sensitivity of the test will be reduced
7. Compare the wall motion of individual segments from rest to stress in the four-screen display to define ischemia and infarction. Then compare segments in the post-stress images to identify differences in contraction and in the development of "hinge points"
8. Confirm any wall motion abnormality in a second view if possible
9. Avoid overcalling ischemia in the basal inferior or basal septal segments
10. Avoid calling a new wall motion abnormality if it is limited to only one myocardial segment; the abnormality should involve at least two contiguous segments

TABLE 49.3 Stress Echocardiographic Responses and Interpretation

Resting or baseline function	Response to low-dose pharmacologic stress	Peak and post-stress function	Interpretation
Normal	Normal	Hyperdynamic	Normal myocardium
Normal	Normal or new WMA	New WMA or lack of hyperdynamic response; LV dilation or decreased EF (with exercise only)	Ischemic myocardium
WMA	No change	No change	Infarcted myocardium
WMA	Improved	Decreased (biphasic response)	Viable (hibernating) myocardium
WMA	No change	Improved	Nonspecific

WMA, wall motion abnormality; LV, left ventricular; EF, ejection fraction.

2. **Quantitative methods** of analysis improve the reproducibility of interpretation and enhance the detection of CAD, particularly by less experienced physicians. However, at this time, **the ASE recommends further validation and simplification of quantitative analysis methods before they can be recommended for routine use**. Examples of quantitative analysis methods include Doppler assessment of global systolic and diastolic function; automated endocardial border detection using integrated backscatter; and tissue Doppler assessment of myocardial displacement, velocity, strain, and strain rate.
   a. **Tissue Doppler assessment** along the long axis using apical views allows quantification of regional longitudinal myocardial function. Tissue Doppler

is thought to be a potentially sensitive marker of subendocardial ischemia because abnormalities in regional contraction occur earlier in longitudinal than radial segments.

b. **Strain rate** is a measure of the speed or velocity of regional myocardial contraction (time from QRS to the onset of regional myocardial relaxation). During dobutamine SE, strain rate increases (interval of time from QRS to myocardial relaxation decreases) in normal hearts and is reduced in areas of myocardial ischemia. The optimal cutoff for strain rate that gives the best sensitivity and specificity has been reported to be an increment of < 0.6 per second. Strain rate imaging is a reliable predictor of coronary stenosis, is **more specific** than visually assessed wall motion scoring, and may allow readers to detect intermediate severity coronary stenosis that produces only subtle WMAs.

B. 17-Segment model. Regional wall motion is assessed using a 17-segment model (Fig. 49.2), with results geographically represented on a circumferential polar plot (Fig. 49.3). A **16-segment model** had previously been utilized for SE, whereas a 17-segment model was utilized for other cardiovascular imaging modalities including magnetic resonance imaging, nuclear scintigraphy, and PET. In 2002, the American Heart Association (AHA) proposed that all tomographic cardiovascular studies utilize the 17-segment model to allow for standardized segmentation and nomenclature. The ASE recommended the 17-segment model in their 2007 SE guidelines.

1. The individual **myocardial segments can be assigned to coronary artery territories**, as illustrated in Figure 49.4. Of note, this approach makes assumptions that are not always correct due to anatomic variability. For instance, the left anterior descending coronary artery does not always supply the entire apex and the posterior wall is not always supplied by the left circumflex coronary artery. The system may also be problematic if multivessel disease is present, in which case the territory with the most ischemia is identified and less severe lesions may not be apparent.
2. Wall motion is **subjectively graded** as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic and may be assigned a wall motion score of 1 to 4 (normal, hypokinetic, akinetic, dyskinetic, respectively). Each myocardial segment in the rest and stress images is graded in this manner.

C. Exercise SE

1. A **normal response** to exercise stress includes a global increase in contractility, the development of hyperdynamic wall motion, and a gradual rise in the heart rate. This is manifested by increased wall thickness and increased endocardial excursion with stress.
2. **Resting WMAs** usually indicate prior MI, although regional variability may be seen in diffuse myopathic processes. Resting WMAs may be defined as hypokinetic, akinetic, or dyskinetic. Akinesia and dyskinesia usually indicate transmural infarction, whereas hypokinetic segments may be partially infarcted or viable.
3. An **abnormal response to exercise is defined by the development or worsening of regional myocardial function**. Regional myocardial dysfunction, as **manifested by decreased endocardial excursion and wall thickening**, is **specific for myocardial ischemia**. Decreased excursion alone is less specific and can occur with conduction abnormalities and paced rhythms and in the normal basal inferior myocardial segments.
4. **Adjunctive diagnostic criteria** for a positive SE examination include **LV cavity dilation, a decrease in global systolic function diastolic dysfunction, and new or worsening MR**. However, these adjunctive diagnostic criteria are **more specific for detecting severe CAD and may not be sensitive** for detecting the presence of CAD.
5. **False-positive findings** may occur with left bundle branch block (septal WMA) and right ventricular pacing (apical WMA). A hypertensive response to exercise can cause LV dilation and systolic dysfunction.

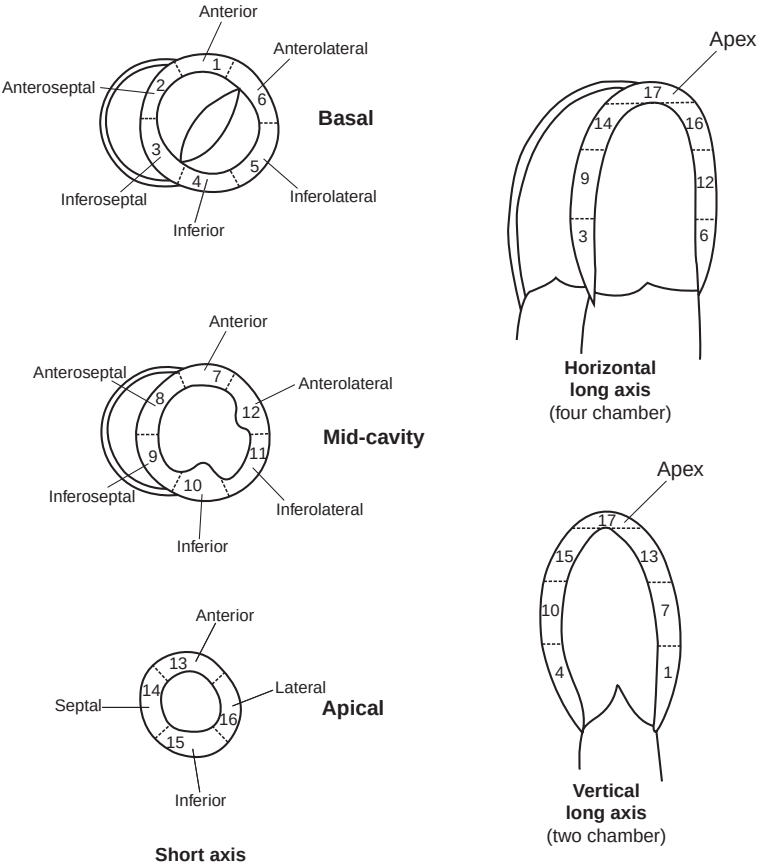

FIGURE 49.2 Diagram of vertical long-axis, horizontal long-axis, and short-axis planes showing the name, location, and anatomic landmarks for selection of the basal (tips of the mitral valve leaflets), mid-cavity (papillary muscles), and apical (beyond papillary muscles but before cavity ends) short-axis slices for the 17-segment system. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation.* 2002;105:539–542.

6. **False-negative findings** may occur with delay in capturing post-exercise images or low workload or heart rate response (i.e., inadequate stress). Additional causes of false-positive and false-negative findings are outlined in Table 49.4.

D. Pharmacologic SE. With only a few exceptions, the principles of interpretation of pharmacologic SE findings are similar to those used for exercise echocardiography.

1. The **typical ischemic response to dobutamine** is characterized by normal resting wall motion and an initial **hyperdynamic response at low doses followed by a decline in function at higher doses**. Ischemia may also be identified on the basis of deterioration of normal wall motion without any transient hyperdynamic response.

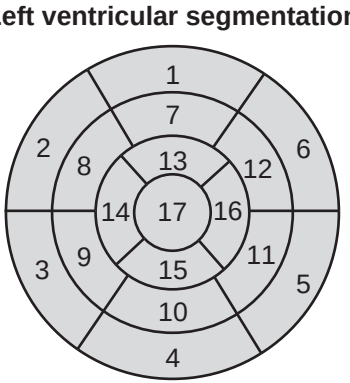

FIGURE 49.3 Display, on a circumferential polar plot, of the 17 myocardial segments and the recommended nomenclature for tomographic imaging of the heart. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

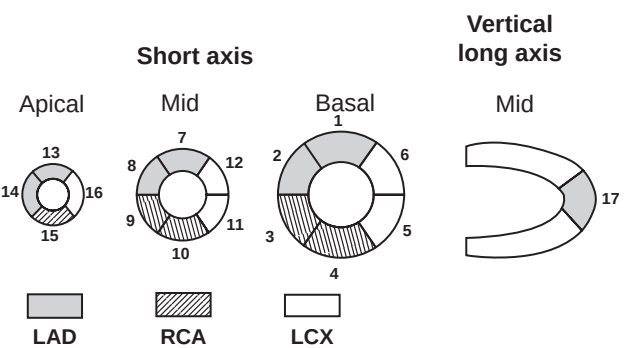

FIGURE 49.4 Assignment of the 17 myocardial segments to coronary artery territories. LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex coronary artery. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

TABLE 49.4 False-Positive and False-Negative Stress Echocardiographic Test Results

Causes of incorrect stress echocardiographic interpretation	Factors reducing specificity or sensitivity
False-positive results	
LBBB, prior cardiac surgery (e.g., myectomy)	Reduced or abnormal septal excursion with normal septal thickness
Right ventricular pacing	Apical WMA
Nonischemic cardiomyopathy	Regional WMAs (exact cause unknown)
Hypertensive response to exercise (SBP > 220 mm Hg, DBP > 110 mm Hg)	Nonischemic WMAs and/or LV dilation
Overinterpretation	Observer bias may result in a lower threshold for calling a positive study; it is important to be blinded
Basal inferior or septal WMA	Areas most likely to be overcalled because of reduced excursion due to annular tethering effects
Poor image quality	
False-negative results	
Single-vessel disease	More likely to have subtle, rapidly resolving WMA than multivessel disease
Inadequate level of stress (more likely with β-blockers)	Important to stress maximally; reach at least 85% of age-predicted maximum heart rate
LV cavity obliteration (more likely to occur with dobutamine)	Makes segmental wall motion analysis difficult
Left circumflex disease	Lateral wall dropout; more likely to miss ischemia
Delay in capturing images after maximal stress	
Poor image quality	

DBP, diastolic blood pressure; LBBB, left bundle branch block; LV, left ventricular; SBP, systolic blood pressure; WMA, wall motion abnormality.

2. **LV cavity dilation and a decrease in global systolic function are not considered adjunctive diagnostic criteria in dobutamine SE.** The LV cavity may not dilate, and global systolic function may improve with dobutamine despite new WMAs due to severe CAD.
3. Interpretation of results obtained from **dipyridamole or adenosine SE** requires detection of a new or worsening regional WMA during the infusion. There is only a mild increase in cardiac contractility during vasodilator stress.

E. Reproducibility. The person who interprets the images must be well trained to develop an acceptable level of accuracy and must interpret an adequate number of studies on a regular basis to maintain accuracy. Concordance within centers is generally good; however, concordance between different centers may be < 80%, particularly with technically difficult studies and studies of patients with mild CAD.

F. Limitations. The ability to interpret stress echocardiograms is mitigated by the image quality, the presence of arrhythmias, conduction abnormalities, respiratory

interference from hyperventilation, and difficulty in allowing for translational and rotational motion of the heart.

VI. DIAGNOSTIC ACCURACY. The **diagnostic accuracy of SE is superior to exercise electrocardiographic testing alone and similar to radionuclide perfusion techniques**. Reported sensitivities and specificities (using coronary arteriography as the gold standard) vary between studies, depending on the prevalence of disease in the study population, the angiographic definition of significant disease, and the criteria used for a positive test. Clinical factors such as age, cardiac risk factors, and symptoms that influence the pretest likelihood of CAD also influence sensitivity and specificity. For the overall detection of patients with CAD, **sensitivity ranges from 75% to 92%, depending on lesion severity**, and **specificity ranges from 64% to 100%**. As with other imaging methods, the sensitivity is less for the detection of single-vessel disease and greater for the detection of multivessel disease.

A. Exercise SE

1. **Comparison with exercise electrocardiographic testing.** Exercise electrocardiographic testing remains the first-line diagnostic test for CAD. However, **SE has greater diagnostic sensitivity and specificity**, which is predictable on the basis of the earlier occurrence of a systolic WMA before electrocardiographic changes or symptoms in the ischemic cascade (Fig. 49.1). Many factors limit the sensitivity of electrocardiographic testing alone to detect CAD (Table 49.1), and these subgroups should be considered for exercise electrocardiographic testing with an imaging modality.
2. **Comparison with myocardial perfusion scintigraphy**
   - **a.** Myocardial perfusion scintigraphy is based on the detection of a perfusion defect during maximal hyperemia, with reduced perfusion of areas subtended by significant coronary artery stenosis (> 50% stenosis). Perfusion abnormalities occur at an earlier stage in the ischemic cascade than do systolic WMAs, and nuclear scintigraphy should theoretically have a higher sensitivity than SE for CAD.
   - **b.** Studies using **single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy have demonstrated a sensitivity of > 90%, slightly higher than that for SE.** However, the **specificity of SE is superior to that of SPECT**, especially in cases with LV hypertrophy or left bundle branch block. The overall accuracy of SPECT and SE has been found to be similar in meta-analyses; the superior sensitivity of SPECT is balanced by the superior specificity of SE. The exception may be in women, where SE may be more accurate than SPECT, owing to less artifact from breast attenuation.
   - **c.** SE is **convenient** and **provides information on cardiac structure and function,** and **the results can be interpreted immediately**, with rapid feedback to the patient and referring physician. SE also **avoids exposure to radioactive tracers** and is substantially **less expensive than SPECT**.
   - **d.** SPECT allows for more objective interpretation, with quantification of perfusion abnormalities. It may also be slightly superior for patients on antianginal therapy when it is necessary to induce ischemia. SPECT appears to be more sensitive in the detection of single-vessel disease and may be superior in the detection of ischemia in the setting of resting WMAs, in which the recognition of worsening wall motion may be difficult. SPECT may also be superior in patients that have poor acoustic windows, for example, chronic obstructive pulmonary disease. **Local expertise, cost, exposure to radiation, and patient selection are all important factors in determining which imaging modality to use**.

B. Pharmacologic SE

1. **Dobutamine SE has a sensitivity ranging from 68% to 96% and a specificity of 80% to 85%**, similar to the values for exercise SE. **Vasodilator SE has a sensitivity of 52% to 92% and a specificity of 80% to 100%**. In general, the specificity of vasodilator SE is superior to that of other echocardiographic stress techniques. However, single-vessel disease is more difficult to detect with this technique.

2. **Myocardial perfusion scintigraphy.** Compared with dipyridamole SPECT, dipyridamole SE is believed to be less sensitive but more specific; however, few studies have compared the two tests in the same patients. As with exercise SE, dobutamine SE appears to be slightly less sensitive but more specific than SPECT.

VII. ASSESSMENT OF VIABILITY

A. Myocardial contractility ceases when 20% or more of the transmural thickness is ischemic or infarcted. Dobutamine SE can be used to detect **viable myocardium**, whether stunned or hibernating. **Myocardial stunning** after MI is common, and it is characterized by viable nonischemic noncontracting myocardium. Patients with **chronic ischemia** may experience **myocardial hibernation**. Hibernating myocardium is characterized by viable chronically ischemic noncontracting myocardium.

B. Dobutamine infusion may result in augmentation of regional myocardial function predictive of recovery of function after revascularization. This is important prognostically, as revascularization of hypoperfused but viable myocardium improves survival. A contractile response to dobutamine requires that at least 50% of the myocytes in a given segment are viable.

C. Demonstration of a **biphasic response** to low-dose (5 to 10 μg/kg/min) dobutamine strongly suggests viable myocardium. A biphasic response is present when a **resting WMA improves in response to low-dose dobutamine and decreases in function at peak stress or post-stress**. The initial improvement reflects recruitment of contractile reserve and hence viability. Higher doses lead to subendocardial ischemia and worsened WMA. A biphasic response predicts eventual functional recovery of the myocardium after revascularization. A uniphasic response is less predictive of recovery, and a classic ischemic response is not predictive of the recovery of resting function. Because the biphasic response is the most reliable finding, the preference is to induce ischemia whenever possible by proceeding to maximal stress (40 μg/kg/min).

D. **Myocardial wall thickness** is also an important marker of myocardial viability. When the wall thickness is **< 6 mm**, there is **a low likelihood of recovery of function**.

E. **The negative predictive value of dobutamine SE for determining viability is lower than that of thallium stress-redistribution-reinjection SPECT and Flourodeoxyglucose (FDG)-PET scanning**. However, **the positive predictive value is greater**. Concurrent use of β-blockers can reduce the number of viable segments detected and the sensitivity of testing.

F. **Assessment of myocardial perfusion with echocardiography.** Second-generation microbubble contrast agents are small in diameter and reliably traverse the myocardial microvasculature. The microbubbles are destroyed with ultrasound energy, and the rate of microbubble replenishment represents mean red blood cell velocity and myocardial perfusion. As contrast agents and detection algorithms improve, it is hoped that these techniques will allow real-time, noninvasive assessment of myocardial viability.

VIII. PROGNOSTIC ROLE OF STRESS ECHOCARDIOGRAPHY

A. **Suspected or known chronic CAD.** The **major determinants of prognosis** in patients with chronic CAD are **LV function and the anatomic extent and severity of myocardial ischemia**. SE is an excellent modality for the evaluation of both.

1. **Negative test result.** Perhaps the most important aspect of the prognostic literature is that **a negative test result portends an extremely low risk of subsequent cardiovascular events, as evidenced by an event rate of < 1%/y for the subsequent 4 to 5 years**. However, the risk is slightly higher in patients with diabetes or chronic kidney disease.
2. **Presence of ischemia.** Abnormal findings during SE indicate elevated risk for future cardiac events. Patients at intermediate risk for CAD who have abnormal SE findings have a 1-year cardiac event (i.e., MI, percutaneous coronary intervention, coronary

artery bypass grafting, or death) rate of 10% to 30%. However, this information needs to be integrated with other stress data (i.e., exercise capacity, hemodynamic responses to exercise, heart rate recovery, chronotropic index, Duke treadmill score, and the type and extent of WMA). Electrocardiographic changes and hypotension are relatively insensitive measures of ischemia during dobutamine SE. However, from the prognostic standpoint, the development of echocardiographic evidence of ischemia with dobutamine is analogous to its development during exercise.

3. **Presence of nonviable myocardium.** In patients with the same pretest probability of disease, those with evidence of nonviable myocardium during SE have higher rates of cardiac events than those with normal SE findings, but they have fewer events than those with evidence of ischemia during SE. Heart failure is a more common end point among the group of patients with nonviable myocardium.

B. Post–myocardial infarction. High-risk patients after acute MI are routinely identified by age, recurrent angina, LV failure, and shock. In addition, echocardiographic features predicting outcome after MI include LV ejection fraction, the extent of resting WMAs, inducible ischemia (detected as stress-induced WMA), and the amount of viable myocardium. All of these may be identified using SE, and several large studies (most with pharmacologic stressors) have gathered prognostic data using SE in patients post-MI.

C. Noncardiac surgery

1. Preoperative evaluation studies have been predominantly conducted with pharmacologic stress agents, primarily dobutamine. However, exercise SE should be considered if possible. A low ischemic threshold during stress (ischemia at heart rate < 70% APMHR) is the strongest predictor of perioperative cardiac events.
2. The predictive value of a positive test ranges from 7% to 25% for hard events (i.e., MI or death). The negative predictive value ranges from 93% to 100%. Only a few studies have compared SE and SPECT for the prediction of perioperative cardiac events. A meta-analysis concluded that the tests had comparable levels of accuracy, but the cost features weighted in favor of SE.

D. Cardiac transplantation. Transplant vasculopathy is a major cause of mortality after cardiac transplantation. Despite some promising data, SE appears to lack both sufficient sensitivity and specificity to be a viable alternative to routine angiography as a screening method.

E. Reading beyond wall motion. Important prognostic information can be obtained beyond traditional wall motion analysis. Ischemic heart disease may cause subclinical **diastolic dysfunction**. **Left atrial enlargement** correlates with the chronicity and severity of diastolic dysfunction. A normal resting left atrial volume index (< 28 mL/m^2) is strongly predictive of a normal stress echocardiogram. **Right ventricular dysfunction** is a significant predictor of events, independent of LV ischemia or ejection fraction.

IX. DIASTOLIC STRESS ECHOCARDIOGRAPHY

A. In many patients, "diastolic" heart failure is the dominant form of dysfunction, without any detectable systolic dysfunction at rest or during stress. The **transmitral peak early diastolic velocity (E)** and the **mitral annulus early diastolic velocity (e′)** are utilized to assess the diastolic dysfunction. In the presence of normal LV systolic function and volumes, an **E/e′ ratio > 15 suggests elevated LV filling pressure and diastolic dysfunction**, whereas a ratio < 8 excludes diastolic dysfunction. The primary utility of diastolic SE is to evaluate patients in whom diastolic dysfunction is suspected but the resting echocardiogram is indeterminate (i.e., E/e′ 8 to 15). Assessment for diastolic dysfunction should be completed during routine SE, as its presence and severity add to the negative prognostic value of resting or stress-induced systolic dysfunction.

B. Exercise or adrenergic stress normally results in improved myocardial lusitropy (relaxation) to allow for better filling in a shorter amount of time. The tachycardia associated with exercise results in an abbreviated diastolic filling period and an increase in the transmitral peak E velocity. In healthy patients, both the transmitral

peak E velocity and the mitral annulus early diastolic velocity increase with exercise, and the E/é ratio is not changed. However, **in patients with diastolic dysfunction, the mitral annulus early diastolic velocity is minimally affected by the change in preload caused by exercise and the E/é ratio increases**.

C. Assessment of diastolic dysfunction can be difficult at rest and is even more so with stress. Exercise SE is optimally performed using **supine bicycle ergometry**, as it allows for the acquisition of Doppler recordings during exercise. However, evaluation is routinely performed using treadmill exercise or dobutamine. Tachycardia may result in fusion of the transmitral E and A velocities at peak stress, making the tracings impossible to interpret. Therefore, Doppler assessment of the mitral inflow velocities should be assessed at rest, during exercise, and in recovery if possible.

X. STRESS ECHOCARDIOGRAPHY IN NONISCHEMIC CARDIAC DISEASE.

SE can be used to evaluate the functional significance of a variety of valvular lesions as well as hypertrophic cardiomyopathy. SE is especially helpful when there is a discrepancy between clinical symptoms and the assessment of valve severity at rest.

A. Aortic stenosis

1. Exercise testing is contraindicated (ACC/AHA class III recommendation) in patients with symptomatic AS. In asymptomatic patients, exercise testing may be considered (ACC/AHA class IIb recommendation) to elicit exercise-induced symptoms and abnormal BP responses.
2. Dobutamine SE is reasonable (ACC/AHA class IIa recommendation) in the diagnostic evaluation of patients with **low-flow/low-gradient AS**, defined as Doppler-derived aortic valve area < 1 cm^2 and mean gradients < 30 mm Hg. In these patients, **dobutamine is used to assess both the severity of AS and the presence of contractile reserve**.
3. In severe AS, low-dose (20 μg/kg/min) dobutamine infusion results in increased cardiac output with a parallel rise in the mean transvalvular gradient. Provided the calculated aortic valve area remains < 1 cm^2, **an increase in the mean transvalvular gradient to a value > 30 mm Hg or velocity > 3.5 m/s is consistent with severe AS**. If dobutamine infusion results in an increase in the valve area (typically to > 1 cm^2) with little change in the gradient, it is likely that LV dysfunction rather than AS is the critical problem, and aortic valve replacement is unlikely to be beneficial.
4. Dobutamine SE is also used to identify **contractile reserve** in patients with low-flow/low-gradient AS. Contractile reserve is defined as > 20% increase in stroke volume with dobutamine infusion. Lack of contractile reserve is associated with poorer prognosis with either medical or surgical therapy.

B. Mitral regurgitation. In asymptomatic patients with severe MR, exercise SE is reasonable (AHA/ACC class IIa recommendation) to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and severity of MR. SE can help predict latent LV dysfunction in patients with normal baseline LV systolic function, severe MR, and minimal or no symptoms. An increase in the LV cavity size or decrease in LV ejection fraction at peak stress suggests latent LV dysfunction and an increased risk of LV dysfunction after valve repair.

C. Mitral stenosis. Exercise SE should be performed (ACC/AHA class I recommendation) to assess the hemodynamic response of the mean gradient and pulmonary artery pressure in patients with mitral stenosis when there is a discrepancy among resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. An increase in the mean transmitral pressure gradient > 15 mm Hg and pulmonary artery systolic pressure > 60 mm Hg are indications to consider percutaneous valvotomy.

D. Hypertrophic cardiomyopathy. In patients with hypertrophic cardiomyopathy and high resting left ventricular outflow tract (LVOT) gradients, routine exercise testing is not performed owing to increased risks of arrhythmias and hypotension. Exercise SE provides valuable information, including exercise hemodynamics and the inducibility of LVOT, worsening of mitral regurgitation, and provocable

gradients in patients that are asymptomatic at rest. Although these patients may have only mild to moderately elevated resting LVOT gradients, using SE to identify elevated provocable gradients may help explain their exertional symptoms and quantify their exercise tolerance.

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CHAPTER 50

Arun Dahiya

Testing for Viable Myocardium

I. INTRODUCTION. Patients with left ventricular (LV) dysfunction secondary to coronary artery disease (CAD) have significant morbidity and mortality. Given the prognostic implications of poor ventricular function, it is imperative to identify any reversible myocardial dysfunction that may improve with revascularization.

II. DEFINITIONS

A. Viable myocardium is defined as myocardium that demonstrates abnormal function at rest and improves with revascularization.

1. From a pathophysiologic standpoint, chronically reduced perfusion leads to cellular changes that ultimately cause irreversible myocyte dysfunction.
2. Biopsies of myocardium reveal a spectrum of fibrosis and sarcomere loss that correlates with the likelihood of recovery of function. Several studies have found that once fibrosis is found in more than 35% of the myocardium, the likelihood of recovery of function is low.
3. **Stunning** refers to transient myocardial dysfunction, which is often caused by abrupt cessation of flow typical of an acute coronary occlusion.
4. Myocardial **scar** from cellular necrosis is irreversible and does not improve with revascularization.

B. Hibernation occurs when viable myocardium has altered its metabolism and thus reduced its contractile function as a mechanism to cope with chronically inadequate blood supply (chronic stable angina) or repetitive ischemic injury.

III. CLINICAL PRESENTATION. Ischemia, stunning, hibernation, scarring, and normal myocardium may coexist in the same patient. Unfortunately, clinical symptoms are unreliable in determining if a patient has viable myocardium, as often patients experience no symptoms in the face of considerable LV dysfunction and ischemia.

IV. TREATMENT OPTIONS. It has been demonstrated that revascularization of viable myocardium improves quality of life and survival. As medical and surgical technology improves in the field of cardiovascular medicine, it is important to accurately identify patients who will benefit from revascularization.

A. Thrombolytic therapy or emergency percutaneous revascularization is used in the setting of an acute thrombotic occlusion to restore normal blood flow and hopefully to minimize cellular damage.

B. Revascularization procedures, such as coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, may improve regional and global LV systolic function caused by significant CAD. The presence and extent of viable myocardium have been demonstrated as a marker for patients who will do significantly better with revascularization than with conventional medical care.

C. It is notable that patients with nonviable myocardium have similar outcomes with medical therapy as with revascularization.

D. Because not all patients benefit from revascularization procedures, the identification and referral of patients who will derive benefit are important to reduce costs and morbidity with the associated procedures. The goal, therefore, is to reliably identify patients who will benefit from revascularization and subsequently refer these patients for appropriate intervention.

V. TECHNIQUES TO ASSESS VIABILITY

(Fig. 50.1). Assessment of myocardial viability is indicated in patients with CAD and resting LV dysfunction who are eligible for revascularization. Coronary angiograms provide information about anatomy and feasibility of revascularization but do not predict recovery of function. Resting echocardiography provides information regarding overall LV function and segmental wall motion abnormalities but does not address recovery of function with revascularization techniques. Single photon nuclear imaging techniques (single photon emission computed tomography, SPECT), positron emission tomography (PET) with a metabolic agent, dobutamine echocardiography, contrast echocardiography, and, more recently, delayed-enhancement magnetic resonance imaging (MRI) have been identified as techniques that can distinguish viable myocardium from nonviable myocardium. Each technique exploits a separate property of dysfunctional myocardium to determine the potential for recovery of function after revascularization. The test that is used often depends on the strengths and preference of each medical center, although an approach based on the individual patient would be preferable.

A. Single photon emission computed tomography. SPECT is the most common technique used in the United States to identify viable myocardium. This technique has been successful because thallium 201 and technetium 99m radiopharmaceuticals act as perfusion agents that are only taken up by viable tissue. The long half-lives of these agents allow for regional distribution, which makes them feasible to use in medical centers without a generator or cyclotron. In addition, stress SPECT protocols (exercise or pharmacologic) are frequently used to assess for ischemia, which makes this technique cost-effective in a busy clinical center. Routine studies also include gated imaging analyses that provide further information regarding LV function and wall motion assessment, which are important in the evaluation of viability.

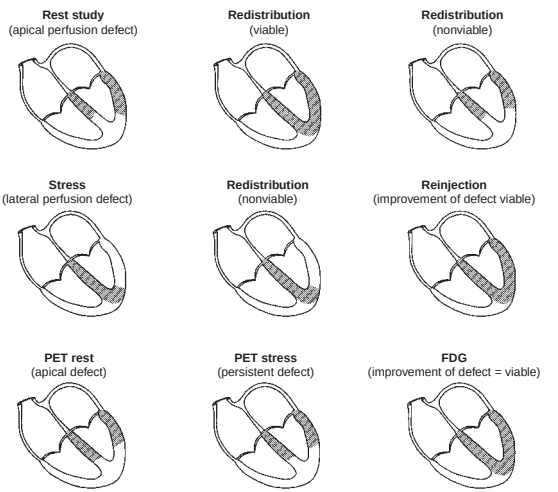

FIGURE 50.1 Viability testing.

FDG, 18F-fluorodeoxyglucose scanning

1. **Thallium 201** is a potassium analogue that utilizes the Na^+/K^+-ATPase active cellular transport system for concentration in cells and relies on intact cells. This characteristic of thallium makes it useful for the identification of viable cells as opposed to necrotic cells. Uptake of thallium is also dependent on regional myocardial perfusion.
   a. Thallium 201 has a relatively long half-life (73 hours), which means that a small dose (2 to 4 mCi) must be used. It emits x-rays from 68 to 80 keV (94% abundant) and γ-rays at 135 and 167 keV (10% abundant). There is a linear relationship between blood flow and uptake of thallium at rest, which is maintained with exercise making it as a reliable indicator of perfusion.
   b. **Redistribution** of thallium between the intracellular and intravascular spaces begins to occur after the first pass of thallium. It is recognized that with time, initial defects on thallium imaging improve. This is thought to be related to the accumulation of tracer in hypoperfused areas over time as well as rapid washout in normally perfused areas. On the basis of these principles, several protocols have been used to identify viable myocardium.
      (1) **Rest/redistribution thallium** imaging involves imaging 30 to 60 minutes after an initial injection followed by reimaging 4 hours later. Defects on the initial images that improve in 4 hours are considered to represent areas of viable myocardium. This protocol does not address ischemia and has been proven to be less sensitive for detecting viable myocardium than other protocols using thallium or PET with 18F-fluorodeoxyglucose (FDG).
      (2) **Stress/redistribution** imaging uses pharmacologic or exercise-induced stress with subsequent thallium injection and imaging, immediately followed by reimaging 4 hours later. Myocardium that is not perfused with stress or rest is considered to be scar. Myocardium that has a defect with stress but that improves on rest images is considered to be ischemic and viable. This protocol can identify ischemic viable myocardium, but it also shows lower sensitivity than other protocols, as many of the defects that do not improve at 4 hours may contain viable tissue. Imaging 24 hours after stress in a search for "late redistribution" improves sensitivity in the detection of viability but has low specificity and may be inconvenient. However, blood levels of thallium 201 may still be too low to be redistributed and picked up by viable myocardium. This led to the development of reinjection protocols mentioned later in this chapter.
      (3) **Stress/redistribution/reinjection** protocols involve the reinjection of 1 mCi of thallium with subsequent reimaging of the patient. This protocol is designed to increase the sensitivity by increasing the blood levels of thallium. It was shown that 50% to 70% of "scarred myocardium" after 4-hour redistribution imaging was actually viable, as demonstrated by this technique. Typically, reinjection of thallium and repeated imaging is performed immediately after the redistribution images or several hours after the initial stress images, followed by redistribution imaging 18 to 24 hours later. Sensitivity does not differ significantly between these two techniques. Scar is considered to be myocardium that has a defect on the stress images and does not improve upon reinjection and reimaging. Viable myocardium is indicated by uptake of tracer on reinjection in segments where no uptake occurred with stress.
2. **Technetium 99m–labeled radiopharmaceuticals** rely on mitochondrial function, sarcolemmal integrity, and intact energy production pathways for cellular accumulation.
   a. **Technetium characteristics.** Technetium 99m compounds have a shorter half-life (6 hours) than thallium, which allows for the administration of

larger doses (10 to 30 mCi), depending on the compound. Technetium 99m emits γ-rays at 140 keV. The commonly used agents include Tc 99m sestamibi, Tc 99m tetrofosmin, Tc 99m teboroxime, Tc 99m furifosmin, and Tc 99m NOET (bis(*N*-ethoxy, *N*-ethyl dithiocarbamato)nitrido).

b. Redistribution of technetium compounds is significantly less than that for thallium, making it relatively unhelpful as an aid in detecting viability.

3. Quantitation of SPECT imaging has been found to be a more accurate method to identify high- and low-risk populations than qualitative analysis. Quantification of perfusion has been proven to be an accurate predictor of recovery of function and superior to qualitative measurements at providing clinically useful information about future risk.

4. Diagnostic accuracy

a. Multiple studies have been performed comparing the various thallium protocols versus PET with FDG as the gold standard. Typically, sensitivity improves as one goes from redistribution to reinjection/redistribution and finally quantitative analysis of reinjection/redistribution. Semiquantitative analysis of stress/redistribution/reinjection has good concordance with PET.

b. In the prediction of functional improvement after revascularization, rest/redistribution thallium scans (sensitivity 90% and specificity 54%) and stress/redistribution/reinjection thallium scans (sensitivity 86% and specificity 47%) have been found to be less reliable. Regions that demonstrate < 60% regional thallium uptake on redistribution have a very low chance of recovery.

c. Unfortunately, attenuation and patient artifact frequently make SPECT thallium images difficult to interpret. In addition, methods for quantification have not been standardized across medical centers.

d. Quantification of sestamibi has compared favorably with that of thallium, with redistribution in the prediction of recovery of function after revascularization. Several other technetium compounds used for the assessment of viability have been tested (Tc 99m tetrofosmin, Tc 99m teboroxime, Tc 99m furifosmin, and Tc 99m NOET). None of these other agents has had significant use except for ^{99m}Tc-NOET, which has similar redistribution kinetics to that of thallium and may be a useful agent in the future. Sestamibi has a limited role in viability assessment owing to its cost.

B. PET in conjunction with a metabolic agent, usually FDG, has been considered the gold standard for assessment of myocardial viability. PET uses positron-emitting isotopes capable of releasing two high-energy (511 keV) photons at an angle of 180° from each other. The PET camera can detect these higher energy rays through coincidence counting. As a result, PET provides higher temporal and spatial resolution than SPECT, which translates into a higher quality image. Additional features of PET include quantification of the following:

1. Practical issues, including the cost of a PET camera and the short half-life of the several of the cyclotron-produced radiotracers, limit the use of PET to specialized medical centers.

2. Unlike SPECT, PET uses separate agents to measure perfusion and viability.

3. Perfusion agents commonly used in PET imaging include rubidium 82, nitrogen 13 ammonia, and oxygen 15 water.

a. Rubidium 82 is a generator-produced potassium analogue that relies on intact cellular functioning for its uptake and distribution. Hence, rubidium 82 is washed out of necrotic cells and trapped in viable cells.

b. Nitrogen 13 ammonia is cyclotron-produced radiotracer and also relies on intact cellular functioning for its uptake and distribution. This is the most commonly used perfusion agent in PET, and it can be used to quantify blood flow and assess for myocardial viability.

c. **Oxygen 15 water** is a freely diffusible agent that has been used to quantify blood flow. Blood flow < 0.25 mL/g/min within a region of myocardium is correlated with regions of scar. Unfortunately, intermediate blood flow ranges have not been reliable in predicting recovery of function, which makes this technology less useful for quantifying viability. Oxygen 15 water has also been used to create a perfusable tissue index that has been shown to improve the accuracy in the assessment of viable myocardium but has not been utilized by many centers.

4. **Metabolic agents** used in PET include FDG, carbon 11 acetate, and carbon 11 palmitate. **FDG** (cyclotron-produced) has the most clinical data to support its use. It has a long half-life, which makes its transportation to regional medical centers more practical. FDG is taken up by viable cells and then phosphorylated so that it cannot be metabolized further. This effectively traps FDG in the myocardium. In normal myocardium, free fatty acids are preferentially used. During periods of ischemia, metabolism is altered so that primarily glucose is utilized. The limitation of FDG has been in diabetics with impaired cellular uptake of glucose, where approximately 10% of studies are difficult to interpret owing to poor tracer uptake.
5. The combination of perfusion and metabolic tracers gives three possible interpretations:
   a. Normal perfusion is indicative of viability on its own and does not require specific assessment of metabolism.
   b. Reduced perfusion in myocardial segments with intact metabolic function as evidenced by the uptake of FDG is termed flow–metabolism mismatch and is indicative of hibernating, viable myocardium (Fig. 50.2).
   c. Impaired FDG uptake combined with reduced perfusion (flow–metabolism match) is indicative of myocardial scar (Fig. 50.2).
6. **Diagnostic accuracy.** PET-FDG and cardiac MRI are considered the most reliable tests of myocardial viability. Image quality with PET is better than that with SPECT, and myocardial metabolism may be assessed directly with FDG. The sensitivity and specificity of PET in predicting functional improvement in myocardial segments after revascularization are 71% to 100% and 38% to 91%,

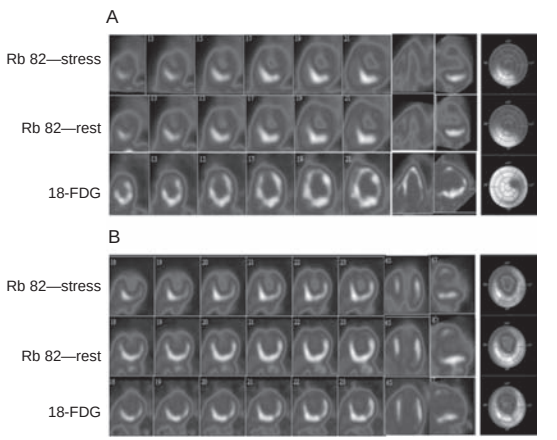

FIGURE 50.2 Rubidium PET followed by FDG PET: Patient **A** showing metabolism mismatch and is indicative of hibernating, viable myocardium. Patient **B** showing impaired FDG uptake combined with reduced perfusion (flow–metabolism match) is indicative of myocardial scar.

respectively. PET has been shown to predict low surgical risk in patients with LV dysfunction and viability, improvement in exercise capacity with revascularization, and benefit from revascularization over medical therapy.

C. Dobutamine echocardiography has proven to be a reliable predictor of recovery of function after myocardial revascularization.

1. **Protocol.** Viability studies with dobutamine echocardiography use low doses of dobutamine starting as low as 5 μg/kg/min and slowly increasing the dose at 3-minute intervals up to 40 μg/kg/min for the development of other end points, such as target heart rate and symptoms. Imaging is performed throughout the study at each level of dobutamine infusion. Accurate, consistent results are contingent on the acquisition of excellent images for interpretation and on an experienced reader to interpret the study.
2. **Pathophysiology.** Dobutamine echocardiography exploits the inotropic effect of dobutamine at low doses on viable myocardium. This improvement in function and wall thickening is referred to as contractile reserve. In viable myocardium, with increasing doses of dobutamine, myocardial oxygen consumption increases, and ischemia develops with worsening of wall motion abnormalities. Therefore, in viable myocardium a segment with reduction in wall thickening at rest demonstrates an improvement or even normalization of wall thickening upon infusion of low-dose dobutamine. At higher doses of dobutamine, wall thickening deteriorates and may revert to the baseline level or may be even more severely reduced than at baseline. This **biphasic response** during dobutamine echocardiography is thought to be the most specific sign of dobutamine echocardiography for predicting improvement in function in myocardial segments with revascularization and indicates segments with underperfused but viable tissue. Myocardial segments with impaired contraction at rest that do not improve upon infusion of dobutamine are considered to be scarred (nonviable). Those segments with impaired thickening at rest that show improvement in thickening upon dobutamine infusion but that do not show deterioration in thickening at higher doses of dobutamine infusion are considered to have a **uniphasic** response. A uniphasic response is seen in the setting of myocardial damage with subsequent reperfusion (i.e., an open artery without a flow-limiting stenosis) and is much less predictive of improvement after revascularization.
3. **Diagnostic accuracy.** Dobutamine echocardiography has good specificity for the detection of viability. Part of the high specificity is derived from the fact that echocardiography is the most common method of assessing postoperative improvement. In addition, improvement of hypocontractile myocardium in response to low-dose dobutamine is the defined end point that revascularization is trying to achieve, although it is less sensitive than cellular metabolic function as a marker of viability. Sensitivity and specificity for recovery of function are 84% and 81%, respectively.
4. **Limitations** of dobutamine echocardiography include difficulty in obtaining images in patients with poor ultrasound windows, interobserver variability, even among expert readers, provocation of ventricular arrhythmias with testing, and reduced sensitivity in comparison with nuclear imaging.

D. Cardiac MRI. Delayed-enhancement MRI using gadolinium-based agents given intravenously (0.2 mmol/kg) has been shown to reliably distinguish infarcted from viable myocardium. Unlike SPECT-based techniques, MRI poses no risk of ionizing radiation exposure.

1. **Pathophysiology.** Gadolinium-based contrast agents are extracellular compounds that, when injected intravenously, pass quickly through normal areas of myocardium. In scarred tissue, the interstitial space between collagen fibers is larger than in normal myocardium, causing a delayed "wash-in" of gadolinium contrast. The gadolinium then remains trapped in the scarred tissue, causing

a longer "washout" of gadolinium from the infarcted or fibrotic myocardium. Delayed-enhancement MRI takes advantage of this delayed wash-in and washout of gadolinium to detect fibrotic or scarred myocardium, which appear as hyperenhanced (bright) areas of myocardium on images taken 10 to 20 minutes after contrast injection.

2. In patients with ischemic heart disease, scarred or nonviable myocardium occurs in a coronary artery distribution. Scarring typically begins at the subendocardial surface and extends outward at a variable distance toward the epicardium. The **transmural extent of hyperenhancement** on delayed-enhancement images is then used to determine the viability of each myocardial segment. Segments with **0% to 25% transmural extent of hyperenhancement represent viable tissue** with mostly normal myocardium and minimal fibrosis. **Segments with 75% to 100% transmural extent of hyperenhancement represent scarred, nonviable myocardium**. Segments with 25% to 75% transmural extent are said to have intermediate viability, although in clinical practice the amount of viable tissue in adjacent myocardium is often taken into account when classifying these intermediate segments. Finally, the amount of hyperenhancement within a region can be correlated with segmental wall function and rest/stress perfusion to determine ischemia and viability.
3. The absence of significant hyperenhancement has been shown to correlate well with improvement in function, whereas hyperenhancement of more than 75% has been correlated with irreversible injury. Of interest to note, the mean transmural extent of hyperenhancement that predicted irreversibility was 41 ± 14% by MRI, which correlates with a biopsy series wherein 35% fibrosis predicted similar lack of improvement after revascularization (Fig. 50.3).
4. **Diagnostic accuracy.** Studies comparing different imaging modalities for viability have shown superior sensitivity and specificity for MRI compared with SPECT and similar sensitivity with slightly improved specificity compared with PET. The main advantage of MRI is its ability to delineate the transmural extent of infarction, owing to its better spatial and contrast resolution. The pattern of hyperenhancement on MRI can also be used to identify nonischemic causes of cardiomyopathy.
5. **Limitations.** MRI is generally contraindicated in patients with implanted ferromagnetic objects (e.g., pacemakers, implantable cardioverter–defibrillators [ICDs], and ferromagnetic cerebral aneurysm clips), although some centers will image selected patients with permanent pacemakers/ICDs under careful electrophysiologic evaluation. Gadolinium is contraindicated in patients with chronic kidney disease (glomerular filtration rate < 30 mL/min), particularly in those

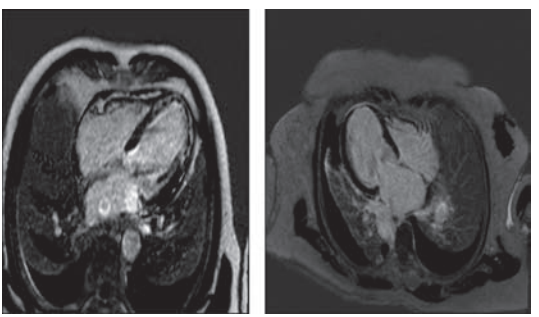

FIGURE 50.3 Late gadolinium-enhanced MRI: Both patients **A** and **B** have extensive akinesia in LAD territory; however, patient **A** has more extensive scar (> 50% in multiple segments) than patient **B** and is less likely to have LV function recovery post revascularization.

undergoing dialysis, owing to a small but important risk of nephrogenic systemic fibrosis (see Chapter 51). Finally, image quality may be compromised in patients unable to comply with breath-holding for the study (10 to 12 seconds each) and severe claustrophobia, as well as in patients with arrhythmias or frequent ectopy.

VI. CHOICE OF TECHNIQUE. Cost, clinical expertise, and access to radioisotopes are all issues that affect the appropriateness of each imaging technique. SPECT thallium and dobutamine echocardiography are significantly less expensive than PET and MRI, but they require significant clinical experience for appropriate data collection and interpretation. Both PET and cardiac MRI are robust techniques for the assessment of viability, but their use may be limited due to cost and availability, and, for MRI, the presence of patient's contraindications to MRI. The choice of technique is ultimately determined by local expertise and access to the appropriate technology. The recently published STICH (Surgical Treatment for Ischemic Heart Failure) viability trial failed to demonstrate a significant interaction between myocardial viability and medical versus surgical treatment with respect to mortality. These findings are most likely explained by improved modern-day medical therapy; however, there were several limitations of this trial which should be noted. Although the main STICH trial was a randomized controlled trial, the STICH viability substudy was not randomized. It was an observational study on almost half of all the main STICH trial patients who managed to get a viability study. Furthermore, viability testing in the trial was performed by using SPECT, thallium, and dobutamine only, and more robust techniques of cardiac MRI and FDG PET were not used.

VII. WHO SHOULD GET A VIABILITY TEST? Patients who are most likely to benefit from viability testing (preferably by cardiac MRI or FDG PET) are those with high operative risk, where presence or absence of viability may influence the management strategy. Viability can also be useful in choosing the optimal revascularization strategy (PCI vs. CABG) in patients with multivessel disease. Viability testing should not be performed in patients where it is unlikely to change management, such as in a young patient with angina, good distal target vessels, and minimal comorbidities.

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CHAPTER 51

João L. Cavalcante

Cardiovascular Magnetic Resonance Imaging

I. INTRODUCTION. Cardiovascular magnetic resonance imaging (CMRI) has undergone rapid developments over the last two decades and is now an important imaging technique of the heart and great vessels. Advantages of CMRI include its large field of view, high spatial and temporal resolution, and ability to do tissue characterization. In contrast to nuclear imaging and cardiac computed tomography (CT), magnetic resonance imaging (MRI) does not involve exposure to ionizing radiation. Applications of CMRI include acquisition of anatomic-quality still and cine images of the heart and great vessels in multiple planes, precise measurement of cardiac chamber volume and function, assessment of myocardial perfusion and fibrosis, quantification of blood velocity and flow, and noninvasive magnetic resonance angiography (MRA). As CMRI is not a "push-button" technique, clear communication between the ordering physician and the imaging staff is important, indicating the reason for the CMRI examination so that adequate pulse sequences and imaging planes are obtained aiming to answer the desired clinical question.

II. INDICATIONS. Common indications and components of the CMRI evaluation are listed in Table 51.1.

III. CONTRAINDICATIONS. Contraindications to CMRI are listed in Table 51.2.

IV. BASICS OF CARDIAC MRI

A. MRI Physics. Hydrogen is the most abundant atom in the body, and it is the excitation of hydrogen nuclei, often referred to as protons, that forms the basis for clinical MRI. Atoms behave like tiny bar magnets, aligning parallel to an external magnetic field while wobbling about the magnetic field at a certain frequency (precessional frequency) that creates the longitudinal magnetization. Application of a short radiofrequency (RF) pulse with the same precessional frequency as that of the atomic nucleus will cause excitation or resonance of the nucleus, temporarily changing its alignment within the magnetic field (transverse magnetization). However, this is an unstable state of higher energy. As the RF pulse is switched off, the spins quickly return to their resting state, i.e., aligned with the field, as this is energetically

TABLE 51.1 Cardiovascular Magnetic Resonance Imaging Indications and Applications

Indication(s)	Applications
Aortic disease	Aortic aneurysm morphology and size; acute aortic pathology (dissection, intramural hematoma, penetrating ulcer); coarctation of the aorta; branch vessel disease; evidence of vasculitis; postoperative graft stenosis, infection, or leak; assessment for aortic regurgitation or other associated pathologies
Ischemic heart disease	Ventricular volumes and function; myocardial scar and viability; quantification of mitral regurgitation; assessment for LV aneurysm, thrombus, VSD, and other complications
Nonischemic cardiomyopathies	Ventricular volumes and function; myocardial wall thickness; LV outflow tract obstruction in hypertrophic cardiomyopathy; presence and patterns of myocardial scar/fibrosis; assessment for myocardial iron deposition in suspected hemochromatosis; quantification of mitral regurgitation; evaluation for ARVD in patients with ventricular arrhythmias or syncope
Pericardial disease	Pericardial effusion; pericardial thickening with or without calcification; pericardial tethering; signs of constrictive physiology including conical/tubular deformity of the ventricles, diastolic septal bounce, early cessation of diastolic filling, and dilated IVC
Congenital heart disease	Anatomic definition; ventricular volume and function; valve morphology and function; shunt calculation; assessment for anomalous origin of the coronary arteries; anomalies of the aorta, pulmonary arteries, and systemic and pulmonary veins
Valvular heart disease	Valve morphology; regurgitation and/or stenosis etiology and severity; ventricular size and function
Cardiac masses	Size and extent of mass; tissue characterization
Pulmonary veins	Pulmonary vein anatomy and stenosis; cardiac anatomy and function

ARVD, arrhythmogenic right ventricular dysplasia; IVC, inferior vena cava; LV, left ventricular; VSD, ventricular septal defect.

TABLE 51.2 Contraindications to Cardiovascular Magnetic Resonance Imaging

Specific devices	Special issues
Cerebral aneurysm clips	Certain cerebral aneurysm clips pose a danger due to potential for displacement when exposed to a magnetic field. Aneurysm clips classified as "nonferromagnetic" or "weakly ferromagnetic" are safe.
Cardiac pacemakers and ICDs	The presence of a pacemaker/defibrillator is a strong relative contraindication to MRI owing to several potential problems, including (1) movement, (2) malfunction, (3) heating induced in the leads, and (4) current induced in the leads. In addition, artifact from the leads will often cause significant image degradation. FDA has recently approved the first MRI-safe pacing system (Revo MRI by Medtronic, Inc.) that allows patients to undergo, for example, brain and knee MRI scans. Currently it is not safe for the area of coverage to include the chest, although ongoing work is being done toward that goal.
Cardiovascular catheters	Catheters with conductive metallic components (e.g., pulmonary artery catheters) have the potential for excessive heating. Hence patients with such devices should not undergo MRI.
Cochlear implants and hearing aids	Most types of implants employ a strong magnet or are electronically activated. Consequently, MRI is contraindicated because of potential injury or damage to the function of these implants. External hearing aids can and should be removed before the MRI procedure.
Intravascular coils, stents, and filters	These devices typically become incorporated securely into the vessel wall within 6–8 wk after implantation; hence, most are considered MRI safe. However, specific information on the type of device should be obtained before MRI is planned (www.mrisafety.com). Intracoronary stents have been shown to be safe during MRI, even when performed on the day of implantation, although many stent manufacturers recommend waiting 6–8 wk.
ECG electrodes	MR-safe ECG electrodes are strongly recommended to ensure patient safety and proper ECG recording.
Foley catheters	Certain Foley catheters with temperature sensors have the potential for excessive heating. They are generally safe if positioned properly and disconnected from the temperature monitor during MRI.
Heart valve prostheses	All types of heart valve prostheses have been shown to be safe during MRI. However, prosthetic material may lead to image artifacts.
Metallic foreign bodies	All patients with a history of injury with metallic foreign bodies such as a bullet or shrapnel should be thoroughly evaluated, as serious injury may result from movement or dislodgement of the foreign body.
Metallic cardiac occluders (e.g., management of PDA, ASD, or VSD)	MRI is safe for nonferromagnetic devices immediately after implant. Weakly ferromagnetic devices are safe from approximately 6–8 wk after placement, unless there is concern about retention of the device.
Retained epicardial pacing wires	MRI in patients with retained epicardial pacing wires after cardiac surgery appears safe. Retained transvenous pacing wires are a contraindication to MRI.

ASD, atrial septal defect; ECG, electrocardiogram; ICD, implantable cardioverter–defibrillator; MR, magnetic resonance; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

the most favorable situation. The newly established transverse magnetization starts to disappear (a process called transversal relaxation), and the longitudinal magnetization grows back to its original size (a process called longitudinal relaxation). During this process, an RF signal is generated, which can be captured by the receiving coil and readily measured. This process constitutes the underlying principle of MRI.

The signal generated by an excited proton is dependent on its molecular environment, such that the magnetic resonance (MR) signal from a hydrogen atom in blood can be discriminated from the MR signal from a hydrogen atom in fat or other tissue types. An MRI machine, therefore, includes a strong magnet that creates a continuous magnetic field and RF coils for transmitting the excitation pulses and receiving the radio signals generated by the excited protons. Application of predictable variations or "gradients" in the magnetic field, using gradient coils within the magnetic bore, allows three-dimensional (3D) spatial localization of each signal. The raw data are initially mapped in "k-space" before a Fourier transformation to generate the final MRI image.

B. T1, T2, and image contrast. The rate of relaxation of an excited proton along the longitudinal axis (i.e., the direction of the external magnetic field) is described by its T1 time, whereas the transverse axis is described by its T2 time. T1 and T2 times depend on the molecular environment of the protons (intrinsic to the tissue characteristics) and the magnetic field strength. T1 and T2 relaxation times of different tissues are important determinants of image contrast and, although not measured directly, images can be either T1 or T2 "weighted" to facilitate tissue characterization.

C. Issues specific to CMRI. Cardiac and respiratory motion poses significant challenges to CMRI. In contrast to echocardiography, which is based on real-time imaging, CMRI sequences usually acquire a single image over several heart beats to optimize the spatial and temporal resolution. It is, therefore, necessary to gate images to the cardiac cycle with either an electrocardiographic or pulse signal. Electrocardiographic gating is usually retrospective, although prospective gating is sometimes useful, particularly in patients with arrhythmias. Respiratory motion is typically negated by performing breath-holds during the examination. In patients who are unable to maintain a breath-hold, averaging multiple MR signals may help to decrease the noise created by respiratory motion, at the expense of increasing the examination time by a factor of the *number of signals averaged*. Respiratory navigator sequences that coordinate imaging with a particular phase of diaphragmatic and hence respiratory motion are also effective, and they are typically used for pulse sequences that are too long for a single breath-hold, such as free-breathing whole-heart 3D coronary MRA sequences. Finally, real-time imaging using newer ultra-fast pulse sequences can be used in the absence of electrocardiographic or respiratory gating, at the expense of a significant decrease in temporal and spatial resolution.

D. CMRI pulse sequences and applications

1. **Spin echo.** Spin-echo sequences are characterized by a refocusing RF pulse after delivery of the initial excitation pulse. Rapidly flowing blood appears dark, hence they are also known as "black-blood" sequences. Spin-echo sequences provide still images, which are typically used for anatomic delineation of the heart and great vessels owing to their excellent tissue contrast and high signal-to-noise ratio (SNR). They are relatively insensitive to magnetic field inhomogeneities and artifacts related to ferromagnetic objects such as sternal wires and prosthetic heart valves. Turbo spin echo is a newer technique that provides faster acquisition times than standard spin echo does. The main disadvantage of spin-echo sequences is the relatively long time it takes to acquire an image, making them more susceptible to motion artifacts and unsuitable for cine imaging.
2. **Gradient echo.** Gradient echo sequences are characterized by the use of refocusing gradients after the delivery of the initial excitation pulse. Rapidly flowing blood appears bright, hence they are also known as "bright blood" sequences. Gradient echo is a fast imaging technique that is relatively insensitive to motion artifacts,

making it ideal for cine imaging. However, it has less tissue contrast and increased susceptibility to magnetic field inhomogeneities and ferromagnetic-related artifacts than spin-echo imaging but less than balanced steady-state free precession (B-SSFP). A variety of gradient echo sequences are widely used in CMRI for cine imaging, myocardial perfusion and scar assessment, coronary imaging, and MRA.

3. **Cine imaging.** The most widely used pulse sequence for cine imaging is a gradient echo sequence called balanced steady-state free precession (B-SSFP), which is characterized by high SNR, high image contrast between blood and myocardium, and low sensitivity to motion artifact. However, B-SSFP is relatively insensitive to blood flow and, therefore, can be suboptimal for imaging of valve dysfunction or intracardiac shunts, which can usually be better illustrated using other gradient echo pulse sequences, such as echo planar imaging or phase velocity mapping. In addition B-SSFP is also more susceptible to magnetic field inhomogeneities which can be problematic in patients with mechanical valves or other cardiac implants.
4. **Myocardial tagging.** RF pulses can be applied before the excitation pulse to generate dark saturation lines or grids on cine images, which are then tagged to the myocardium and further used to assess myocardial deformation. The tags can be used to help qualitatively assess myocardial motion and pericardial tethering or to quantitatively measure myocardial strain.
5. **Perfusion imaging.** Very fast gradient echo sequences are used for dynamic imaging of left ventricular (LV) myocardial perfusion during the first pass of a gadolinium contrast agent during rest and stress states. Fast gradient echo techniques are commonly used, such as fast low-angle shot or B-SSFP with a prepulse to null or darken the myocardium. Normally perfused myocardium shows an increase in signal intensity due to gadolinium contrast, whereas abnormally perfused areas remain dark or hypoperfused.
6. **Delayed imaging.** Delayed hyperenhancement imaging for myocardial scar or fibrosis is performed 10 to 30 minutes after injection of gadolinium contrast using gradient echo sequences with an inversion recovery prepulse to null signal from the myocardium. **Areas of myocardial scar or fibrosis have a larger extracellular space with a greater accumulation and slower washout of gadolinium and, therefore, appear bright compared with dark, normal myocardium on delayed imaging**.
7. **Phase-contrast velocity mapping.** The phase difference in the spin of protons in moving blood compared with nonmoving protons within a magnetic gradient is called the "spin phase shift" and is proportional to the velocity of the moving protons. A phase-encoded image is constructed, with the gray level of each pixel coded for velocity. Phase-contrast velocity mapping could be considered analogous to pulse wave Doppler echocardiography. It can be used to measure blood velocity and hence quantify cardiac output, shunts, and valve dysfunction. There are, however, limitations, given that the accuracy of this method is highly dependent on factors such as flow pattern, flow velocity, size, and tortuosity of the vessel. Flow-related signal loss can be a result of loss of phase coherence that can occur in cases of significant flow acceleration and even in higher orders of motion present in complex flow patterns.
8. **Magnetic resonance angiography.** MRA of the great vessels typically involves a 3D fast gradient–echo acquisition after injection of gadolinium contrast. The image resolution is typically $2 \times 2 \times 3$ mm, making MRA an excellent option for imaging of large to intermediate size arteries, but less optimal for imaging of smaller vessels.
9. **Parallel imaging.** A number of parallel imaging techniques make use of multiple receiving body coils to acquire extra data after each excitation pulse. This helps to decrease the imaging time and improve temporal resolution, but at the small relative cost of decrease in the SNR.

E. Contrast agents. A number of gadolinium chelates are used as contrast agents in clinical MRI. **Gadolinium significantly shortens the relaxation time of nearby**

protons, thereby increasing their signal intensity. These contrast agents are safe, with a low side-effect profile. Prevalence of adverse reactions is approximately 2% and includes transient headache, nausea, vomiting, local burning or cool sensation, and hives. Anaphylactoid reactions are extremely rare. Recently, gadolinium has been linked to a severe and rapidly progressive form of systemic sclerosis called **nephrogenic systemic fibrosis (NSF)**, which appears to be related to extracellular accumulation of gadolinium after its administration in patients with end-stage renal disease. The US Food and Drug Administration (FDA) has advised that **gadolinium contrast agents should not be administered to patients with a glomerular filtration rate of <15 mL/min. Caution should be exercised in patients with moderate or severe renal impairment**. Dialysis is only partly effective at filtering gadolinium and may not prevent development of NSF.

V. PRACTICAL CONSIDERATIONS

A. Safety

1. **Magnetic force.** Cardiac MRI scanners typically utilize powerful magnets of 1.5 to 3.0 T, several tens of thousands of times stronger than the earth's magnetic field (0.00005 T). Large or small ferromagnetic objects in the vicinity of the MRI magnet bore can become fast moving projectiles, which may cause severe injury to patients and/or damage the MRI scanner. A number of fatalities related to such events have been reported. Health-care professionals working in the vicinity of an MRI scanner require MRI safety training and should be vigilant to risk posed by patients and health-care professionals not familiar with the danger.
2. **Magnetic field gradients.** Switching of magnetic field gradients during a CMRI study produces high acoustic noise levels (up to 115 dB) and can also lead to peripheral nerve stimulation. The FDA has determined limits to the power of magnetic field gradients and noise exposure. Headphones and earplugs are recommended to prevent discomfort and hearing loss to patients and MRI staff in the vicinity of the scanner.
3. **Bioeffects of RF energy.** The majority of RF energy to the patient is dissipated as heat and is recorded as the specific absorption rate (SAR). One SAR equals 1 joule of RF energy per second per kilogram of body weight (i.e., watts per kilogram). The recommended SAR limit for the whole body is 4 W/kg.

B. Patient preparation

1. **Screening.** All patients should be screened for contraindications to MRI before the procedure (Table 51.2). Proper screening technique involves the use of a printed sheet and review of the completed form with the patient by an MR safety–trained health-care worker to verify the information.
2. **Patient size.** Although the maximum table load weight limit is fairly generous (~250 kg or 550 lbs), because of the fixed internal diameter of the magnet bore, very large patients may not fit within the MRI magnet. Typically, patients with a torso circumference of > 60 cm cannot be imaged. Discussion with the MRI technologist before scanning is recommended for specific recommendations related to your unit.
3. **Claustrophobia.** The enclosed space of the magnet poses problems for many patients, even those who do not have a history of claustrophobia. The study can usually be successfully completed with the help of clear communication with the patient before and during the procedure, presence of a friend or relative at the head of the MRI scanner, or light oral sedation (e.g., lorazepam 0.25 to 0.5 mg) 30 to 60 minutes before the procedure.

   Early versions of open MRI scanners had low magnetic field strength, gave poorer image quality than most closed systems, and required longer examination times. Newer open scanners include machines with higher magnetic field strengths and improved image quality and could become important alternatives in patients with claustrophobia.

4. **Attire.** Patients should wear a cotton hospital gown with no metal snaps. All metal items, jewelry, and nylon undergarments should be removed for reasons of safety and possible image degradation.
5. **Body coil.** Phased array body coils are placed on the patient's torso over the imaging area of interest. These use several smaller coils to acquire RF signals simultaneously and to facilitate parallel imaging. Some of these coils, for example, enable performance of 3D cardiac cine exams with full-ventricle coverage in a single breath-hold. The net result is not only better image quality but also reduced exam time for the patient.
6. **Electrocardiogram (ECG) monitoring.** A good electrocardiographic tracing is essential for CMRI. Although three or four MRI-safe, nonmetallic electrodes are placed on the patient's chest, and a single lead signal is used to trigger or gate the MRI images, the magnetic field affects the electrocardiographic tracing by inducing a voltage created by ions flowing within blood vessels (magnetohydrodynamic effect). This voltage artifact is commonly superimposed in the ST segment (during the ejection of blood in systole), which increases its amplitude causing false QRS detection in certain algorithms. Use of vector cardiogram allows the R-R interval to be registered as a 3D spatial vector that varies in magnitude and direction throughout the cardiac cycle. Furthermore, the use of fiber optic cables (instead of carbon leads) has also decreased the potential ECG interference of RF pulses and/or gradient field switches.
7. **Emergencies.** MRI is not appropriate in patients who are clinically unstable because of difficulties monitoring and treating patients within the magnet bore. Although MRI-safe equipment is available, it is safer to prescreen the patient's clinical status and determine the need of the MRI study before initiating the scanning.
8. **Pregnancy.** There is insufficient evidence regarding the safety of MRI in pregnant patients. Current guidelines state that MRI may be used in pregnant patients where other forms of nonionizing imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation.
9. **Children.** CMRI may be necessary in pediatric patients with congenital and acquired cardiovascular disease. Typically, children younger than 8 years will require general anesthesia.

VI. CLINICAL APPLICATIONS

A. Diseases of the aorta

1. **Aortic aneurysm.** MRI can clearly visualize both the aortic vessel wall and lumen. It is a reliable method for the identification, characterization, and follow-up of thoracic and abdominal aortic aneurysms, with accuracy comparable to that of CT. A combination of spin-echo sequences for characterization of the vessel wall, gradient echo cine sequences for dynamic imaging of the aorta and aortic valve, and contrast-enhanced magnetic resonance angiography (CE-MRA) for aortic and branch vessel luminography is characteristically used. The aorta may be highly tortuous and should be imaged in multiple planes, with double-oblique measurements performed from true short-axis cuts using reconstructed images.
2. **Aortic dissection.** MRI is a highly sensitive and specific technique for the detection of aortic dissection (sensitivity 98% to 100%, specificity 98% to 100%). Spin echo, B-SSFP, and CE-MRA are used to identify the intimal flap, true and false lumens, and involvement of aortic branch vessels, including the coronary arteries. Administration of contrast is not critical to the examination, so that MRI may be particularly helpful in patients in whom there is concern for significant renal impairment. In addition, potential complications of aortic dissection (e.g., pleural effusion, pericardial tamponade, and aortic regurgitation) are easily evaluated. However, the longer study acquisition time with MRI compared with CT and its unsuitability for imaging of unstable patients limit its application in

the acute setting. However, as a safe, noninvasive, relatively fast technique and without use of ionizing radiation, MRI is well suited for follow-up of both surgically and medically treated aortic dissections, in particular for young patients.

3. **Intramural hematoma and penetrating aortic ulcer.** Intramural hematoma can be considered as the *forme fruste* of aortic dissection with the spontaneous rupture of one of the vasa vasorum within the media of the aortic wall. It occurs in up to 30% of all acute aortic syndromes and appears as a smooth crescentic to circumferential area of thickened aortic wall without evidence of blood flow in the false channel on either B-SSFP or spin-echo sequences. Because of the short T1-relaxation time of fresh blood, differentiation from the adjacent mediastinal fat may be difficult. Intramural blood can be best detected on fat-saturated T1-weighted gradient echo or black-blood techniques. Furthermore, on spin-echo ("black-blood") imaging, the intramural hematoma may be isointense (acute) or hyperintense (subacute) relative to skeletal muscle. Penetrating aortic ulcers appear as deep ulcerations of an aortic atheroma that extend through the intima to disrupt the underlying media and cause bulging of the outer aortic contour. They commonly appear at the isthmus beyond the left subclavian artery and in the distal descending thoracic aorta near the diaphragm. If acute, there may be evidence of intramural bleeding in the rim adjacent to the ulcer.
4. **Atherosclerotic disease.** MRI can clearly show irregular thickening of the aorta in atherosclerotic disease. CE-MRA has good accuracy for detecting significant peripheral stenoses and occlusions. Recent research has focused on the ability of MRI to accurately identify and characterize atherosclerotic plaques in the aorta and carotid arteries, as well as the development of novel contrast agents that target atherosclerotic plaques.
5. **Trauma to the aorta.** MRI may detect chronic or missed aortic tears, usually related to a previous motor vehicle accident. Tears are usually found in the area of the ligamentum arteriosum and are characterized by a localized saccular aneurysm, with or without an associated periaortic hematoma.
6. **Aortitis.** In patients with inflammatory disorders affecting the aorta such as Takayasu's disease (which tends to also involve the arch branch vessels) or giant cell arteritis, MRI can accurately detect diffuse wall thickening of the thoracic and abdominal aorta (specially after gadolinium administration in T1-weighted images) as well as stenosis and occlusion of the aortic branch vessels (CE-MRA sequences). Special imaging sequences using T2-weighting and short-tau inversion recovery for fat suppression, one can also assess for (peri)vessel edema and wall thickening/inflammation, respectively.
7. **Aortic stents and stent grafts.** Aortic stents and stent grafts can be safely imaged using MRI; however, both cine sequences (gradient echo and B-SSFP) are prone to ferromagnetic artifacts. Spin-echo imaging can be used successfully to evaluate stent graft morphology. Artifacts may limit assessment for graft leaks using CE-MRA.

B. Assessment of ventricular function and coronary artery disease (CAD)

1. **Assessment of global ventricular function.** CMRI is now the gold standard for the assessment of ventricular mass, volumes, and systolic function. A significant advantage of CMR is its reproducibility and accuracy compared with 2D planar or projection techniques that depend on geometric assumptions in order to define mass and volume determinations. As a result, small changes in myocardial mass and/or volume can be detected over time or as a result of therapy. A typical approach is to perform a short-axis stack of B-SSFP cine sequences through the left and right ventricles. Manual or semi-automated tracing of the endocardial borders at end-diastole and end-systole is later performed off-line, and ventricular volumes and ejection fraction are calculated using Simpson's method of discs.
2. **Assessment of regional ventricular function.** As mentioned before, development of multichannel phase-array coils has enabled parallel imaging and significant

improvements in spatial and temporal resolution and scan times. This has led CMRI to become superior to echocardiography for precise assessment of regional wall motion. B-SSFP cine sequences provide excellent blood-myocardial contrast that permits clear definition of the endocardial border. Furthermore, myocardial tagging methods have also improved the assessment of regional myocardial function.

3. **Myocardial ischemia.** CMRI stress testing can detect myocardial ischemia with either wall motion or perfusion analysis. The use of dobutamine stress CMRI for wall motion analysis is more established than stress perfusion imaging with adenosine or dipyridamole. Studies of stress CMRI with dobutamine have revealed good sensitivity (83% to 92%) and specificity (86%) for the detection of significant CAD on a per-patient level. Furthermore, CMR tagging may further improve the accuracy of dobutamine CMR for ischemia detection. Stress perfusion imaging by CMRI appears to have slightly higher accuracy to that of thallium single-photon emission computed tomography (SPECT), with a sensitivity of 91% and specificity of 81% for the detection of significant CAD reported in a recent meta-analysis. The absence of ionizing radiation with MRI is an important consideration, particularly in younger patients. However, it is important to note that to accomplish these multicenter results, a facility capable of performing the stress testing with appropriate physician and staff training is required.
4. **Myocardial infarction (MI) and viability.** T2-weighted spin-echo sequences with fat suppression may show areas of increased signal intensity consistent with tissue edema in the acute or subacute phase of a MI. This field of myocardial edema has been gaining interest as a target for clinical trials in acute coronary syndrome. The concept is that the myocardium at risk would correspond to the edematous minus the scarred area (seen on delayed enhancement). However, this technique has potential imaging artifacts (cardiac/respiratory motion, low signal-to-noise ratio, slow flow, coil intensity profile, etc) which could hinder the reproducibility of results seen in single-center studies. The current state-of-the-art technique for myocardial scar detection remains delayed enhancement imaging with an inversion recovery gradient echo sequence 10 to 30 minutes after injection of a gadolinium contrast agent. This method shows areas of myocardial scarring as bright and normal myocardium as dark and has shown excellent correlation with the location and extent of scar on histopathologic analysis. The superior spatial resolution of CMRI makes it more sensitive for the detection of myocardial scar, and in particular subendocardial scar, than SPECT or positron emission tomography. In addition, detection of areas of microvascular obstruction, despite adequate epicardial vessel reperfusion, can also be identified with CMRI and appear to be associated with worsened outcomes. The transmural extent of scar is associated with myocardial viability. Transmural or near-transmural scar (> 50%) suggests nonviable myocardium, whereas the absence of myocardial scar suggests that functional recovery is very likely post revascularization.
5. **LV thrombus.** CMR is more sensitive than echocardiography for the detection of LV thrombus which is associated with a greater morbidity. Due to its high spatial resolution and tissue characterization capabilities, CMR can be quite advantageous in establishing or ruling out the diagnosis of intracardiac thrombus. The typical signal characteristics would include lack of contrast perfusion on 1st pass of Gadolinium and low-signal intensity on post-contrast delayed imaging with long inversion time (dark filling defect on the endocardial surface of the left ventricle).

C. Nonischemic cardiomyopathies There is increasing recognition of diffuse myocardial fibrosis occurring as a separate entity in a variety of conditions in the absence of ischemia, including hypertensive and diabetic heart disease, hypertrophic cardiomyopathy (HCM), and idiopathic dilated cardiomyopathy (DCM). In these situations, use of standard delayed enhancement CMR may become a problem: due to the often diffuse nature of the fibrotic process, no true normal, nonfibrotic myocardium can be used as a frame of reference.

To overcome this limitation, several new CMR techniques have been developed in trials for the detection of nonischemic myocardial fibrosis. Contrast-enhanced T_1 mapping using a modified Look-Locker inversion recovery sequence is the most promising technique that allows quantification of diffuse, nonischemic myocardial fibrosis with high temporal resolution within a single breath-hold. However, before it can be used for clinical applications, a more standardized histologically validated technique needs to be identified and assessed in clinical studies on various and larger groups of patients and in multicenter settings.

1. **Dilated cardiomyopathy.** CMRI is useful for precise assessment of cardiac morphology and function in patients with DCM. Delayed enhancement imaging typically shows focal or diffuse enhancement in a mid-myocardial distribution, with a predilection for involvement of the lateral LV wall. Delayed enhancement during the acute presentation of DCM has been shown to correlate with areas of active myocarditis. Thus, CMRI may help guide myocardial biopsy and improve its sensitivity. The extent of delayed enhancement tends to improve over time, but patchy areas often remain and may represent areas of ongoing inflammation or fibrosis.
2. **Hypertrophic cardiomyopathy.** MRI is accurate for the evaluation of the pattern and extent of hypertrophy, systolic anterior motion of the mitral valve, resting left ventricular outflow tract (LVOT) obstruction, and secondary mitral valve pathology and regurgitation. Because of the precise anatomic definition provided by CMRI, it is particularly helpful in planning for surgical myectomy or alcohol septal ablation. CMRI can also help identify abnormal chordal or papillary muscle attachments, which may contribute to LVOT obstruction and have been reported in up to 20% of patients with HCM. Delayed enhancement is frequently seen in patients with HCM and corresponds to areas of interstitial fibrosis. It is typically seen in areas of increased wall thickness as well as the right ventricular (RV) insertion points in the interventricular septum. The extent of delayed enhancement in patients with HCM is associated with the presence of risk factors for sudden cardiac death and associated with worse outcomes. However, further research is needed to prospectively validate and establish a role for myocardial fibrosis detection in risk prediction in patients with HCM.
3. **Restrictive cardiomyopathy (RCM).** Infiltration of the myocardium may lead to RCM, which is characterized by normal ventricular size and systolic function, severe diastolic dysfunction, and biatrial enlargement. LV and RV wall thickness may or may not be increased. CMRI can clearly visualize the typical findings of RCM and simultaneously distinguish it from constrictive pericarditis, the main differential diagnosis. In addition, specific causes of RCM may be diagnosed by CMRI. Amyloidosis is associated with thickening of the interatrial septum and atrial free walls, as well as increased LV and RV wall thickness. Furthermore, **delayed enhancement imaging can show a typical pattern of diffuse subendocardial enhancement in patients with cardiac amyloidosis**, albeit a particular characteristic, best seen in the contrast-enhanced T1-weighted scout (Look-Locker) sequence, is the "early" nulling of the infiltrated myocardium—almost concomitant with the blood pool. Several findings have been noted in patients with cardiac sarcoidosis, including areas of increased or decreased signal intensity on T2-weighted images and patchy areas of delayed hyperenhancement. **Hemochromatosis is characterized by extensive signal loss on T2-weighted images, resulting from iron deposition in the myocardium**. Measurement of the T2 relaxation time of the myocardium (T2* technique) allows more precise detection of iron overload. Furthermore, T2* technique is also prognostically important in patients with thalassemia major, identifying patients at high risk for heart failure and arrhythmia more so than serum ferritin and liver iron.
4. **Arrhythmogenic right ventricular dysplasia (ARVD). CMRI is the primary imaging test for patients with suspected ARVD**, although nonimaging criteria are also required to confirm the diagnosis. Although CMRI can identify typical features

of ARVD including RV wall thinning, fibrofatty replacement, and focal RV wall aneurysms, according to the recent revised Task Force criteria (Marcus et al, Circulation 2010) presence of RV dilation, global RV dysfunction, and/or regional hypokinesia are more important findings. Fibrofatty replacement of the RV myocardium on CMRI is no longer a diagnostic criterion requiring histopathology confirmation.

The CMRI examination for ARVD is different than that for other cardiomyopathies. Axial and short-axis stacks of high-resolution T1-weighted spin-echo images are acquired through the right ventricle for anatomic definition of the RV and LV myocardium. The spin-echo pulse sequences may be repeated with fat saturation prepulses to facilitate detection of fatty infiltration of the RV free wall. B-SSFP cines are performed in the same axial and short-axis imaging planes for identification of RV wall motion abnormalities. Finally, delayed enhancement imaging is performed for identification of myocardial fibrosis. ARVD must be differentiated from right ventricular outflow tract (RVOT) tachycardia, which is associated with less dramatic findings on CMRI, including focal wall thinning and regional hypokinesis above the level of the crista terminalis in the right ventricle and in the RVOT.

D. Diseases of the pericardium. Normal pericardium appears on MRI as a thin (≤2 mm) curvilinear line situated between the epicardial and pericardial fat. The normal pericardium is of low intensity on both T1- and T2-weighted imaging sequences.

1. **Pericardial effusions** are typically of low intensity on T1-weighted spin-echo images and of high intensity on gradient echo images. The exception is hemorrhagic effusion, which is of high intensity on T1-weighted spin-echo images and of low intensity on gradient echo images.
2. **Pericarditis and constriction.** MRI can readily define the presence and extent of pericardial thickening (≥ 4 mm), which may be present in acute pericarditis as well as constrictive pericarditis. In **inflammatory pericarditis**, the pericardium may have increased signal intensity on delayed enhancement imaging. CMRI is now the imaging technique of choice in the diagnosis and management of **constrictive pericarditis**. Typical features include **pericardial thickening and tethering associated with conical or tubular deformity of the ventricles**. Secondary changes include atrial enlargement, systemic and pulmonary vein dilation, hepatomegaly, ascites, and pleural effusions. Cine sequences can demonstrate features of constrictive physiology, including diastolic septal bounce and abrupt limitation of late diastolic filling of the ventricles, which is distinguishable from the more generally delayed diastolic filling patterns seen with restrictive cardiomyopathies. Furthermore, real-time cine sequences with free breathing are also important to demonstrate the interventricular dependence with exaggerated septal shift toward the left ventricle during inspiration. MRI is of limited value compared with CT in the evaluation of calcification of the pericardium because of its inability to reliably distinguish between fibrous tissue and calcification.
3. **Congenital absence of the pericardium**, which may be complete or partial and often left sided, can be demonstrated on CMRI and is typically associated with a leftward orientation and "teardrop" appearance of the heart. Insinuation of lung tissue between the aorta and pulmonary artery and between the inferior surface of the heart and left hemidiaphragm is also characteristically seen.
4. **Pericardial cysts.** These are benign developmental lesions formed when a portion of the pericardium is pinched off during embryogenesis. Pericardial cysts are classically seen at the right cardiophrenic angle. They typically contain fluid and are well marginated. Spin-echo images demonstrate round or ovoid lesions that are often contiguous with the normal pericardium. Simple cysts demonstrate low signal intensity on T1-weighted and high signal intensity on T2-weighted images. Hemorrhagic or proteinaceous filled cysts show high signal intensity on T1-weighted images.

E. Congenital heart disease. CMRI is now an essential tool in the management and follow-up of patients with congenital heart disease. Scans can be performed safely and

reliably from infancy through adulthood. CMRI provides excellent anatomic definition of simple and complex heart defects and precise, noninvasive quantification of cardiac function and shunts. Because of the complex morphology and physiology in a given patient, MRI examinations are tailored to the individual, with frequent adjustments made during the examination. Consequently, the supervising radiologist or cardiologist should have a thorough understanding of congenital heart disease and be ready to assist at the scanner during the test. Common applications of CMRI in adult congenital heart disease include noninvasive quantification of intracardiac shunts; evaluation of pulmonary regurgitation severity, ventricular volumes and function, and pulmonary artery branch vessel stenosis in patients post tetralogy of Fallot repair; identification of RVOT or branch pulmonary artery obstruction in patients who are post arterial switch for dextro transposition of the great arteries (D-TGA); evaluation of baffle stenosis or leak and RV dysfunction in patients post Mustard or Senning procedure for D-TGA; and assessment for dysfunction of the systemic ventricle in patients with congenitally corrected or levo transposition of the great arteries (L-TGA).

F. Valvular heart disease. Although echocardiography remains the primary imaging modality for the diagnosis and management of valvular heart disease, CMRI may provide additional important information in select cases. Particular strengths of CMRI in the evaluation of valve dysfunction include an often clearer visualization of valve morphology, valve planimetry, precise quantification of regurgitant volumes, accurate and reproducible measurement of ventricular volumes and function, and assessment of associated abnormalities (e.g., bicuspid aortic valve and ascending aortic dilation).

G. Cardiac masses. CMRI plays a major role in the evaluation of cardiac and paracardiac masses, because in addition to providing excellent anatomic detail, it also has the ability to perform tissue characterization. Thrombus is the most common intracardiac mass. Fresh thrombus has higher signal intensity than myocardium on T1-weighted images. Older thrombi may have increased signal intensity on T1-weighted and decreased signal intensity on T2-weighted images. Thrombi usually have low signal intensity on delayed enhancement imaging and do not demonstrate delayed enhancement even with long inversion time. Myxomas are the most common intracardiac tumor and in addition to a variegated and irregular appearance typically have higher signal intensity than myocardium on T2-weighted spin-echo imaging. Lipomas have a distinctive short T1 and, therefore, high signal intensity on T1-weighted images. Fat saturation sequences that null lipomatous tissue confirm the diagnosis. Fibromas are an uncommon cardiac tumor and are typically seen within the ventricular myocardium in pediatric or young adult patients. They have decreased signal intensity relative to myocardium on T2-weighted images and show rim enhancement on delayed hyperenhancement imaging.

Primary malignant tumors of the heart are rare. Imaging findings suggestive of a malignant cardiac tumor include a right atrial location, invasiveness without respect to the anatomical borders (ie: involvement of > 1 cardiac chamber, extension into the mediastinum or great vessels), associated hemorrhagic pericardial effusion and moderate or greater contrast perfusion/uptake and subsequent heterogenous delayed-enhancement of the cardiac mass. The most common is angiosarcoma followed by rhabdomyosarcoma. Angiosarcomas are most commonly seen in the right side of the heart and have a heterogenous appearance with hyperintense areas on T1-weighted images. Delayed hyperenhancement shows heterogenous enhancement, most marked in the periphery of the tumor. Metastatic disease of the heart is more common and typically involves the myocardium or pericardium. It is not always possible to differentiate benign from malignant cardiac tumors. Features of malignant tumors are local invasion, pericardial involvement, and increased signal intensity relative to myocardium after injection of gadolinium suggestive of increased vascularity. One limitation of CMRI is its reduced sensitivity for the detection of calcification in cardiac masses.

H. Pulmonary veins. With the growth of percutaneous RF ablation procedures for atrial fibrillation, imaging of the pulmonary veins is being increasingly performed.

CMRI with spin and gradient echo sequences complemented by CE-MRA is effective in assessing pulmonary vein anatomy and stenoses before and after the procedure.

VII. FUTURE APPLICATIONS

A. Coronary artery assessment. Coronary imaging with CMRI is usually performed with two-dimensional (2D) or 3D gradient echo sequences, with either fat saturation or T2 prepulses to enhance the signal difference between the coronary lumen and the surrounding myocardium, as well as decrease the venous signal. Three-dimensional acquisition with navigator-corrected (free-breathing) data set has higher signal-to-noise ratio when compared with 2D sequences and has now become the established approach to contrast-enhanced MR coronary angiography.

Although CMRI can be used reliably for the detection of coronary artery anomalies, it has not yet fulfilled its early promise for noninvasive imaging of coronary atherosclerotic disease, especially when applied to the broader patient population. The coronary arteries provide significant challenges to imaging by MRI because of cardiac and respiratory motion, their small size and tortuosity, normal cyclic variations in coronary flow, and competing signal from neighboring blood pools. Nevertheless, it can be valuable in patients with a low to intermediate pretest likelihood of CAD (< 20%) where the negative predictive value is similar to CT (> 95%), reliably ruling out CAD. These patients, who are often younger, predominantly female, and require more than one scan over their lifetime, would highly benefit from a radiation-free imaging study.

B. Molecular imaging. MRI shows significant promise for the selective imaging of target tissue or cells using novel molecular contrast agents. Magnetically labeled mesenchymal stem cells have been successfully tracked by MRI in a pig model of stem cell therapy for myocardial injury. Supermagnetic nanoparticles have also been used to detect atherosclerotic plaque in both animal and human studies. Similar to what has been seen in nuclear cardiology, this is a fast growing field with several lines of research.

C. Interventional CMRI. The use of MRI in interventional procedures is appealing because it does not entail exposure to ionizing radiation. MRI has been used successfully to guide a variety of interventional procedures including balloon angioplasty and interatrial septal puncture in animals. In addition, the first human MRI-guided stenting of the iliac arteries has been reported in a study of 13 patients.

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RECOMMENDED WEB SITES

http://www.mrisafety.com
http://www.scmr.org

CHAPTER 52

Parag R. Patel
Milind Desai

Cardiovascular Computed Tomography

I. INTRODUCTION. Cardiovascular computed tomography (CT) has continued to rapidly evolve over the past decade, gaining new and expanded indications for noninvasive assessment of the heart, great vessels, and peripheral vasculature. Technological improvements, including increasing numbers of detectors, improved temporal and spatial resolution, and advanced postprocessing, have broadened the clinical utility of this imaging modality. Advanced multidetector computed tomography (MDCT) scanners and new scanning protocols have significantly reduced radiation and contrast dosages. Numerous considerations are involved in the proper selection of cardiovascular CT protocols, and skilled operators are required to plan and interpret these examinations.

II. BASICS OF CARDIAC CT

A. CT physics. In CT, images are created by rotating an x-ray source emitting a fan-shaped beam of x-rays, which then pass through the body. Some x-rays are absorbed or scattered, but others are transmitted and subsequently sensed by detectors located directly across the x-ray source. In MDCT, the x-ray tube and detectors are mounted on a gantry that rotates rapidly around the patient as he or she passes through the scanner. As in traditional x-ray radiography, different structures **attenuate** the x-ray beam to differing extents depending on their atomic composition and density, as well as the energy of the incident photons. The data collected by the detectors then go through a complex set of mathematical reconstruction algorithms that create a set of axial images through the technique of **backprojection**. Each voxel in the resulting axial image is ascribed a specific attenuation value, which is expressed in **Hounsfield units (H.U.)**. Using a reference of 0 H.U. for water, –1000 H.U. for air, and +1000 H.U. for bony cortex, different points are assigned their respective attenuation values. This information is then converted into a grayscale image that can be manipulated by the interpreting physician.

B. Technical challenges for cardiac imaging

1. The fast cyclical motion of the heart requires high **temporal resolution** to avoid blurring or degradation of images due to cardiac motion artifact. In cardiac CT, image acquisition is referenced, or **gated**, to the cardiac cycle. Although data can be acquired throughout the cardiac cycle, most image data sets are reconstructed during periods of minimal cardiac motion, typically a brief 100- to 300-millisecond interval in late diastole (60% to 75% of the R-R interval).
2. High **spatial resolution** is required to image relatively small vessels such as the coronary arteries. Current MDCT scanners (64-slice) provide a spatial resolution of 0.4 mm compared with approximately 0.2 mm for invasive angiography, the gold standard.
3. Respiratory motion artifact can be minimized by having the patient hold his/her breath during image acquisition. Most clinically available scanners can cover the entire heart in 10 to 12 seconds, whereas the newest 256-slice MDCT scanners can cover this area in just one or two heartbeats.
4. Rapid improvements in CT technology and protocoling have outpaced research in the field. Many studies investigating the diagnostic and prognostic yield of information gained from cardiac CT are not based on the newest MDCT scanners—but rather on single-beam/detector systems. Further investigation involving randomized controlled studies has been limited by the ethical issue raised by radiation exposure, although this has also been significantly reduced by innovative scanning approaches.

C. Current CT hardware

1. **MDCT** involves using an x-ray tube mounted opposite multiple detector rows on a gantry, which is then rotated around the patient at a rapid rate (220 to 400 ms/rotation). The patient is moved at either a fixed or variable speed, or **pitch**, through the scanner. An increasing number of detectors allows for an increased *z*-axis (cranial–caudal) coverage, permitting faster scans with improved image quality due to less cardiac and respiratory motion artifact. Temporal resolution is improved by faster gantry rotation, the use of **two x-ray tubes** and detector arrays mounted at 90° angles to each other (dual-source MDCT), and special reconstruction techniques. Dual-source/dual-energy scanners provide substantial improvements by utilizing dual-source MDCT technology as well as dual-energy sources to improve temporal resolution and decrease scatter. The fastest scanners provide a temporal resolution of 83 to 105 milliseconds. Spatial resolution is largely determined by detector architecture (typically 0.4 mm isotropic resolution), although thicker slices (1 to 5 mm) can be acquired to reduce radiation dose according to the study indication. MDCT can be used for both

cardiac and noncardiac studies, and it is now the most widely used type of CT hardware for cardiac imaging.

2. **Electron beam computed tomography (EBCT)**, although rarely used today, was specifically developed for cardiac imaging. It involves the use of a rapidly oscillating electron beam reflected onto a stationary tungsten target. Because there is no mechanical motion within the gantry, EBCT is capable of very high temporal resolution (50 to 100 milliseconds). EBCT was used primarily for the quantitative detection of coronary artery calcification (CAC).

D. Image acquisition techniques

1. **Acquisition modes.** Most current MDCT scanners use spiral retrospectively gated acquisition techniques for cardiac imaging, as this mode provides the greatest flexibility in image selection during different phases of the cardiac cycle and the ability to edit the image data set for artifacts due to ectopic beats. Recently introduced software has made the older prospectively gated axial acquisition mode possible for cardiac imaging in selected patients, and this has resulted in a 60% to 70% reduction in radiation dose.
   a. **Sequential (axial, "step-and-shoot") mode.** Single transaxial slices are sequentially acquired while the patient table is incrementally advanced between successive rotations of the gantry.
   b. **Spiral (helical) mode.** Data are continuously acquired during constant rotation of the gantry with simultaneous, constant (*z*-axis) movement of the patient through the scanner. As the tube does not perform a complete rotation in any plane, x-ray data are interpolated from a series of sequential frames to create a single tomographic image.
2. **Electrocardiogram (ECG) gating**
   a. **Prospective triggering.** The trigger signal is derived from the patient's ECG based on a prospective estimation of the R-R interval. The scan is usually triggered to begin at a defined point after the R wave, usually allowing image acquisition to occur during diastole. Prospective ECG triggering is one of the most dose-efficient ways of cardiac scanning, as only the very minimum scan data needed for image reconstruction are acquired. Limitations of prospective triggering (or "**gating**") include the fact that the acquired data set will be of a limited portion (or phase) of the cardiac cycle only, limiting the opportunity for evaluating image data sets from other cardiac phases. In addition, prospective triggering depends greatly on the regularity of the patient's heart rate and can result in serious misregistration artifact in the setting of arrhythmia.
   b. **Retrospective gating.** Unlike prospective triggering, retrospective ECG gating collects data during the entire cardiac cycle. Once the scan is complete, data from specific periods of the cardiac cycle are used for image reconstruction by retrospective referencing to the ECG signal. This approach allows reconstructions to be made from multiple segments of the cardiac cycle and allows some assessment of cardiac function via four-dimensional reconstruction. However, retrospective gating requires higher radiation dose exposure, although this can be somewhat mitigated by **dose modulation** (see subsequent text).
3. **Other imaging considerations**
   a. **Segmented reconstruction** refers to image acquisition algorithms that use scan data from more than one cardiac cycle for image reconstruction. This can reduce the effective temporal resolution of the scan at the cost of a slight increase in radiation dose.
   b. **Dose (or tube current) modulation.** MDCT scanners may operate with fluctuating tube currents that increase radiation dose during portions of diastole (when diagnostic images are most likely to be obtained) and reduce it

during systole. Dose modulation typically reduces effective radiation dose by approximately 33%, and it is most effective at lower heart rates.

4. **Image reconstruction and interpretation.** Images are most frequently viewed from axial and double oblique planes, in which the three-dimensional data set is manipulated by the interpreting physician so that multiple planes can be viewed to assess cardiac morphology and coronary anatomy. Additional postprocessing techniques can be performed to provide further diagnostic information or, more frequently, to present to the referring physician.
   a. **Multiplanar reformation** involves creating straight or curved image planes by cutting orthogonally or obliquely through the three-dimensional acquisition. This aids in evaluating complex three-dimensional structures, such as the coronary arteries.
   b. **Maximal-intensity projections** are created by compressing a predetermined volume of image data into a two-dimensional projection of the brightest voxels. This is similar in principle to the two-dimensional images created by typical invasive angiography.
   c. **Three-dimensional or volume rendering** is an advanced image processing approach that uses semitransparent visualization of the outer contours of volumetric data, giving the appearance of a three-dimensional structure. Although often not as useful for assessing smaller structures, these reconstructions can be very helpful for understanding complex spatial relationships between major intrathoracic structures.
   d. **Four-dimensional or cine imaging** from spiral retrospectively gated images generates cine images of the CT data for evaluating cardiac and valvular function.

E. **Contrast-enhanced imaging.** Administration of iodinated contrast media increases the attenuation of the blood pool, improving vessel delineation and tissue characterization. When using contrast, image acquisition must be timed such that images are acquired when the blood pool saturation in the target structure is maximal. Various techniques exist to time the arrival of the contrast bolus in the arterial tree and initiate imaging. The specific risks of contrast media are discussed in Section **IV**.

III. INDICATIONS. The role of cardiac CT in evaluating patients with cardiovascular disease continues to evolve. Generally accepted indications for cardiac CT are listed in Table 52.1 and are discussed in the context of specific clinical situations in Section **VI**. The following is a brief listing of the more common indications for MDCT.

A. **Evaluation of chest pain** is performed in patients with low to intermediate pretest probability of disease and persistent chest pain after an equivocal stress test.
B. **Suspicion of coronary artery anomalies.** Due to high spatial resolution and the ability to create three-dimensional reconstructions of the vasculature, MDCT has very high sensitivity and specificity for coronary anomalies.
C. **Pulmonary vein evaluation** can be performed often before or after pulmonary vein isolation (PVI) for atrial fibrillation.
D. **Evaluation of cardiac masses** in conjunction with or when other modalities such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or magnetic resonance imaging (MRI) are unrevealing.
E. **Evaluation of pericardial disease** in conjunction with or when other modalities such as TTE, TEE, or MRI are unrevealing.
F. **Assessment of anatomy in complex congenital heart disease**.
G. **Presurgical evaluation, particularly before redo open heart surgery**. MDCT can aid in describing prior bypass graft location, identifying safe sites for surgical approach.
H. **Assessing graft patency after prior bypass surgery** is feasible in many cases, although it is sometimes limited by artifacts related to calcium and surgical clips.

TABLE 52.1 Appropriate Indications for Cardiac Computed Tomography

Category	Specific appropriate indications
Suspected CAD with symptoms	Intermediate pretest probability of CAD with uninterpretable ECG or unable to exercise
	Acute chest pain with intermediate pretest probability of CAD and no ECG changes and negative serial enzymes
	Evaluation of anomalous coronary artery anatomy
	Chest pain syndrome with uninterpretable or equivocal stress test (exercise, perfusion, or stress echo)
Evaluation of intra- and extra-cardiac structures	Evaluation of cardiac mass in patients with limited images from TTE, MRI, or TEE
Pericardial disease	Evaluation of pericardial conditions (pericardial mass, constrictive pericarditis, or complications of cardiac surgery) in patients with limited images from TTE, MRI, or TEE
Congenital heart disease	Assessment of complex congenital heart disease including anomalies of coronary circulation, great vessels, and cardiac chambers and valves
Pulmonary vein anatomy	Evaluation of pulmonary vein anatomy prior to invasive radiofrequency ablation for atrial fibrillation
Biventricular pacing	Noninvasive coronary vein mapping prior to placement of biventricular pacemaker
Aortic disease	Evaluation of suspected aortic dissection or thoracic aortic aneurysm
Pulmonary disease	Evaluation of suspected pulmonary embolism
Surgical planning	Noninvasive coronary arterial mapping, including internal mammary artery, prior to repeat cardiac surgical revascularization

CAD, coronary artery disease; ECG, electrocardiogram; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Adapted from the ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging. *J Am Coll Cardiol.* 2006;48:1475–1497.

I. **Evaluation of aortic disease.** MDCT is the test of choice for evaluating aortic aneurysm and suspected aortic dissection. It can be useful in the long-term follow-up of patients who have undergone prior aortic surgery or endovascular stenting.

J. **Evaluation of suspected pulmonary embolism (PE).**

IV. CONTRAINDICATIONS. Unlike with cardiac MRI, few absolute contraindications exist for cardiac CT. However, there are important risks associated with radiation and/or contrast exposure that must be weighed against the benefits of the scan. **Relative contraindications** to CT scanning are listed below.

A. **Renal insufficiency.** Given the potential for contrast-induced nephropathy, patients with significant renal insufficiency (i.e., Cr > 1.6 mg/dL) should not undergo contrast-enhanced CT unless the information from the scan is critical and the risks/benefits are thoroughly discussed with the patient.

B. Contrast (iodine) allergy. Patients with allergic reactions to contrast should be pretreated with diphenhydramine and steroids before contrast administration. A prior anaphylactic response to contrast is generally felt to be an absolute contraindication to intravenous iodinated contrast administration in many institutions.

C. Recent intravenous iodinated contrast administration. Patients who have received an intravenous dose of iodinated contrast should avoid contrast-enhanced CT scanning for 24 hours to reduce the risk of contrast-induced nephropathy. For younger patients with normal renal function without risk factors for contrast-induced nephropathy, contrast doses of up to 150 to 200 mL per 24 hours are generally well tolerated.

D. Hyperthyroidism. Iodinated contrast is contraindicated in the setting of uncontrolled hyperthyroidism due to possible precipitation of thyrotoxicosis.

E. Atrial fibrillation, or any irregular heart rhythm, is a contraindication to coronary CT angiography due to image degradation from suboptimal ECG gating.

F. Inability to breath-hold for at least 10 seconds. Image quality will be significantly reduced due to respiratory motion artifact, if the patient cannot comply with breath-hold instructions.

V. SAFETY

A. Radiation exposure is recognized as an important risk of various cardiac imaging modalities, including CT. Radiation doses of cardiac CT scans vary greatly depending on the scan parameter settings, scan range (cranial–caudal length of the scan), gender (women receive more radiation due to breast tissue), and patient's body habitus (obesity increases exposure).

1. **Estimates of radiation dose from MDCT** have varied widely in the literature. **Effective dose** is an estimate of the dose to patients during an ionizing radiation procedure and is expressed in **millisieverts (mSv)**. For reference, the estimated dose from a chest x-ray is 0.04 to 0.10 mSv, and the average annual background radiation in the United States is 3 to 3.6 mSv. Invasive diagnostic coronary angiography provides effective doses of 2.1 to 4 mSv. In comparison, coronary CT angiography studies have reported doses ranging from 3.6 mSv to as high as 18 mSv, depending on the scan parameters, with most estimates ranging from roughly 4 to 11 mSv. Table 52.2 lists radiation dose ranges for the most commonly used cardiac imaging modalities.
2. **Feasibility of low-dose coronary CT angiography.** With the use of prospective ECG triggering, axial imaging modes, dose reduction, and software adaptations, recent studies have reported the feasibility of coronary CT angiography with comparable image quality and substantially reduced radiation doses (i.e., 1.1 to 3.0 mSv). This remains an area of active investigation.

B. Contrast-Induced Nephropathy. Iodinated contrast media can cause renal ischemia by reducing renal blood flow or increasing oxygen demand and may also have a direct toxic effect on tubular epithelial cells. If a contrast-enhanced CT study is necessary in patients with significant renal insufficiency, prophylactic measures should be taken to reduce the risk of renal damage. Most cardiac CT studies require between 80 and 100 cc of contrast dye.

1. **Risk factors**
   - **(a)** Preexisting renal insufficiency
   - **(b)** Diabetes mellitus
   - **(c)** Volume of contrast media
2. **Prophylactic measures** include saline hydration, use of low-osmolar agents, and sodium bicarbonate infusion, although the data for each of these measures remain somewhat controversial. The use of *N*-acetylcysteine has been shown to have no effect in slowing the progression of contrast-induced nephropathy.

TABLE 52.2 Estimated Radiation Exposure from Cardiac Imaging Procedures

Diagnostic procedure	Typical effective dose (mSv)	Equivalent period of natural background radiation
Natural background radiation	3–4 (range 1.5–7.5)	1 y
Chest x-ray (PA and lateral)	0.04	6 d
Transatlantic flight	0.03	5 d
Lung ventilation (Kr 81m)	0.1	2–4 wk
Lung perfusion study (Tc 99m)	1	4–6 mo
Calcium scoring	0.8–2	3–6 mo
CT head	2	8 mo
Cardiac catheterization (diagnostic)	3–4	1 y
64-Slice MDCT (with dose modulation)	8–12	2–3 y
Myocardial perfusion (Tl 201)	15–18	4–5 y
CT abdomen/pelvis	10–20	3–6 y
Cardiac PET	14–20	4–6 y

PA, posterolateral; MDCT, multi-detector computed tomography; mSv, millisievert; CT, computed tomography; PET, positron emission tomography; R, Roentgen units.

VI. CLINICAL APPLICATIONS

A. Coronary calcium scoring uses the observation that coronary calcium is a surrogate marker for coronary atherosclerotic plaque. Studies have shown that the complete absence of coronary artery calcium makes the presence of significant coronary luminal obstruction highly unlikely and indicates a very low risk of future coronary events. Men tend to have higher calcium scores, and individuals of either gender with renal insufficiency or diabetes tend to have higher coronary calcium scores.

1. Either noncontrast EBCT or MDCT can be used (typically with 3.0 mm slice thickness). Contrast is not necessary because calcium is readily identified secondary to its very high x-ray attenuation coefficient (high H.U. score).
2. The **Agatston CAC volume score** is the most frequently used scoring system. It is derived by measuring the area of each calcified coronary lesion and multiplying it by a coefficient of 1 to 4, depending on the maximum CT attenuation within that lesion. It is important to realize the reproducibility of the Agatston score before applying the recommended guidelines for cut-off points. Importantly, the variability in the score has very little meaning at the very high and very low scores. Inter-reader variability can be as high as 3%.
   a. The **CAC score** can be classified into five groups: (1) zero, no coronary calcification; (2) 100, mild coronary calcification; (3) > 100 to 399, moderate calcification; (4) > 400 to 999, severe calcification; and (5) > 1000, extensive calcification.
   b. The CAC score is age specific and gender specific. Therefore, there has to be a comparison of the individual data with a "normal" cohort in order to produce meaningful data, usually presented as the percentile distribution. In

general, CAC develops 10 to 15 years later in life in women than in men. Similarly, CAC is generally five to seven times lower at any given age in women than in men.

c. In a typical cohort of coronary artery disease (CAD) patients, the median CAC score is 975 for men and 370 for women. In comparison with a CAC score of 0, the presence of any CAC is associated with a fourfold risk of coronary events over 3 to 5 years.

d. In patients at intermediate clinical risk for coronary events (e.g., by Framingham score), the CAC score can help reclassify patients to a higher or lower risk group. For instance, a CAC score of 0 confirms low risk of events. Conversely, a CAC score of > 400 is observed with a significant cardiac event rate (> 2% per year) in patients who appear to be of intermediate risk per Framingham score.

e. Because statins have no documented effect on CAC progression, there is no value in repeating CAC in persons with a score of > 100 or the 75th percentile.

3. However, not every atherosclerotic plaque is calcified, and even the detection of a large amount of calcium does not imply the presence of significant stenoses. Therefore, it adds only incrementally to traditional risk assessment and should not be used in isolation. The test is most useful in intermediate-risk populations, in which a high or low score may reclassify individuals to a higher or lower risk group, respectively. Unselected screening is not recommended.

B. Coronary CT angiography has been shown to be an accurate noninvasive modality for visualizing the coronary arteries, with high sensitivity (85% to 95%) and specificity (95% to 98%) compared with invasive angiography as the gold standard.

1. Coronary CT angiography for evaluating CAD is most useful in low- to intermediate-risk patients with angina or anginal equivalent. The **negative predictive value** of coronary CT angiography is uniformly high in studies, approaching 95% to 100%; in other words, coronary CT angiography is an excellent modality for ruling out coronary disease.
2. Patients who are generally poor candidates for coronary CT angiography include those who are likely to have heavily calcified coronary arteries (older than 75 years, end-stage renal disease, and Paget's disease), atrial fibrillation/flutter, frequent ventricular ectopic beats, or uncontrolled tachycardia. Quantification of stenosis severity is often impossible in densely calcified arteries, whereas image quality is significantly degraded in patients with arrhythmias or tachycardia. The negative predictive value dropped to 83% in one study, where patients with Agatston's CAC score of < 600 were included.
3. Known severe CAD is generally a contraindication to coronary CT angiography. However, cardiac CT has been shown to have high sensitivity and specificity for the assessment of bypass graft patency in patients with previous coronary artery bypass grafting (see subsequent text).
4. **Stent patency**. Patients with prior coronary artery stents are generally poor candidates for CAC and CT angiography, although selected patients with proximal left anterior descending or left main stents may be successfully imaged. Current CT technology does not allow for the accurate quantification of in-stent stenosis severity, due to blooming artifact from the metallic body of the stent.
5. When assessing the coronaries, **noncalcified plaque** appears as a low to intermediate attenuation irregularity in the vessel wall. **Calcified plaques** are bright, high-attenuation lesions in the vessel wall and may be associated with positive remodeling of the vessel. Densely calcified plaques are often associated with **calcium blooming artifact**, which can lead to overestimation of luminal stenosis severity.

6. The accuracy of coronary CT angiography is highest in the larger proximal to medium vessels, which are more likely to benefit from an invasive management strategy. Coronary stenoses are generally categorized as mild (< 50% diameter stenosis), moderate (50% to 70% diameter stenosis), or severe (> 70% diameter stenosis).

C. Bypass graft imaging

1. **Graft location.** MDCT can accurately characterize the origin, course, and touchdown of prior bypass grafts using intermediate slice thickness (e.g., 1.5 mm). This can be important for surgical planning (see details in subsequent text of this chapter).
2. **Graft patency.** Using a protocol similar to that used for coronary artery assessment (> 1 mm slice thickness), patency of both arterial and venous bypass grafts can be assessed. Studies have suggested that the sensitivity and specificity of MDCT for detecting stenosis or occlusion of bypass grafts, when compared with invasive angiography, are 97% and 97%, respectively. Occasionally, artifacts related to metallic clips can interfere with assessment of the distal anastomosis of an arterial graft (internal mammary or radial artery graft).

D. Coronary artery anomalies. Due to the three-dimensional data acquisition, MDCT is an excellent modality for assessing patients with known or suspected coronary artery anomalies. MDCT can accurately assess the origin and course of anomalous coronaries and can describe the relationship of the coronary artery to neighboring structures. Although MRI can also be used to assess anomalous coronaries without the need for radiation exposure, the spatial resolution, ease of data acquisition, and reliable image quality of MDCT make it a reasonable first choice. Intramyocardial **bridging** can also be detected with high sensitivity, although the clinical significance of this relatively common finding is uncertain.

E. Cardiac morphology/function. Contrast-enhanced MDCT can provide high-resolution morphologic images of the cardiac chambers as well as accurate assessment of right and left ventricular systolic function. However, other imaging modalities such as echocardiography or MRI, which do not require radiation exposure, are generally preferred initially for assessing cardiac morphology.

1. Patients with prior **myocardial infarction** can have fibrous replacement of myocardium with or without calcification, ventricular wall thinning, aneurysm formation, and cavitary thrombus. This is a rare indication for cardiac CT; rather, it is studied with delayed enhancement MRI.
2. **Ventricular dysplasia** is characterized by fibrous and/or fatty replacement of myocardium, ventricular wall thinning and/or focal aneurysm formation, and ventricular cavity dilation with regional or global wall motion abnormalities.
3. **Mass.** CT provides somewhat less information about tissue type than cardiac MRI, although the attenuation of a mass (in H.U.) can be helpful. For instance, lipomas have low CT numbers, cysts have water density (i.e., 0 to 10 H.U.), and thrombi have low to intermediate CT numbers. Atrial myxoma can be visualized easily in the left atrium, although right atrial masses may be difficult to visualize due to contrast mixing at the junction of the right atrium and inferior vena cava (IVC).

F. Pericardial diseases. The pericardium appears as a thin line (1 to 2 mm) surrounding the heart, usually visible with a small amount of adjacent pericardial fat. The pericardium normally enhances with contrast administration; hyperenhancement of the pericardium in the appropriate clinical setting is characteristic of pericarditis.

1. By CT, **congenital absence of the pericardium** is easily diagnosed.
2. Findings of pericardial **constriction** on CT include irregular pericardial thickening and calcification, conical or tubular compression of one or both ventricles,

enlargement of one or both atria, dilation of the IVC, and a characteristic diastolic bounce of the interventricular septum.

3. Pericardial effusions can be reliably detected by CT, and a small amount of fluid is normal even in healthy subjects. Pericardial tamponade is better evaluated by echocardiography, however, due to its ability to provide hemodynamic information.
4. A pericardial **cyst** will appear as a well-circumscribed paracardiac mass with characteristic water attenuation (H.U. = 0), usually in the right costophrenic angle.
5. Both primary **neoplasms** and, more commonly, metastatic neoplasms can be visualized in the pericardium.

G. Congenital heart disease. MDCT may be used in selected patients in whom echocardiography is nondiagnostic or inadequate and MRI is not available. The ability to evaluate cardiovascular anatomy in multiple planes is often helpful for delineating cardiac morphology in congenital heart disease, particularly with regard to the relationship of the great vessels, pulmonary veins, and coronary arteries. Specific situations in which MDCT is helpful include "hard-to-find" adult shunt detection (sinus venosus atrial septal defect and patent ductus arteriosus); visualization of pulmonary arteries in cyanotic congenital heart disease; precise definition of aortic anatomy in Marfan's syndrome or coarctation; and definition of partial or total anomalous pulmonary venous drainage. Additionally, CT can be useful for follow-up imaging in patients with congenital heart disease who have had prior pacemaker or ICD implantation, such as L-transposition of the great arteries.

H. Diseases of the aorta constitute a common and important indication for CT examinations. Contrast-enhanced MDCT is nearly 100% sensitive and specific for evaluating acute aortic syndromes. ECG gating is critically important for studies of the aortic root and ascending aorta, given the propensity for motion artifacts to appear similar to dissection flaps on nongated studies.

1. **Acute aortic dissection** (see Chapter 26) is characterized on CT by visualization of a dissection flap (i.e., separation of the intima from the media) that forms true and false lumens. The CT study can characterize the origin and extent of the dissection, classify it as type A or B, assess for concomitant aneurysmal aortic dilation, and identify branch vessel involvement.
2. **Aortic intramural hematomas** are believed to be caused by spontaneous hemorrhage of the vaso vasorum of the medial layer. They appear as crescent-shaped areas of increased attenuation with eccentric aortic wall thickening. Unlike dissections, hematomas do not spiral around the aorta.
3. **Aortic aneurysm** is a permanent dilation of 150% of the normal aortic caliber (usually > 5 cm in the thoracic aorta and > 3 cm in the abdominal aorta). Given the often tortuous course of a dilated aorta, it is important that these measurements be made in the true short axis of the aorta, as oblique cuts can result in erroneous overestimation of the aortic diameter. Quantitative measurements of an aortic aneurysm can be made for planning endovascular repair with a **stent graft**.
4. **Penetrating atherosclerotic ulcer.** These tend to be focal lesions of the descending thoracic aorta that appear as contrast-filled irregular outpouchings of the aortic wall.

I. Evaluation of pulmonary veins. In the context of electrophysiology interventions such as PVI, preprocedural MDCT can be used to define pulmonary venous anatomy and identify supernumerary veins, and postprocedural MDCT can be used to evaluate for pulmonary vein stenosis. Additionally, in the setting of congenital heart disease, CT can be used to identify anomalous pulmonary venous return.

J. Evaluation of PE. MDCT is highly accurate in detecting PE, which appears as a filling defect in the pulmonary arteries. This modality is most sensitive for proximal (main through segmental branches) thrombi, and small, distal emboli may be missed.

K. Valvular heart disease. Visualization of the valve leaflets, particularly the aortic valve, is feasible with newer generation scanners due to their improved temporal resolution. Nonenhanced MDCT is also useful for assessing mechanical valve leaflet motion in cases of suspected thrombosis or infection.

L. Surgical planning. The utility of MDCT in surgical planning before cardiothoracic surgery, particularly for reoperations, is increasingly recognized. Preoperative scans can evaluate the proximity of mediastinal structures to the sternum (i.e., aorta, right ventricle, and bypass grafts) and the degree of aortic calcification (i.e., to guide cannulation sites) and concomitantly provide information about cardiac morphology (e.g., presence of a ventricular aneurysm).

M. Peripheral arteries. MDCT can also be used to evaluate peripheral arteries, including the carotid, renal, visceral, and lower extremity vessels. Indeed, imaging these vessels is generally more straightforward than coronary imaging, due to their large caliber and minimal motion. CT can be used for planning and follow-up of vascular disease in these peripheral vascular beds. Given the larger caliber of these vessels, assessment of stent patency is often quite feasible.

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RELEVANT GUIDELINES AND APPROPRIATENESS CRITERIA

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