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Diagnosis of Coronary Artery Disease

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An estimated 16.7 million people die of cardiovascular diseases every year with 43% of these deaths being attributed to atheromatous coronary artery disease (CAD).[1] CAD represents the leading cause of death worldwide, with most cases occurring in developing nations. In recent years, there has been a decline in mortality rate associated with CAD in developed countries that has been attributed to a better identification of high-risk subjects, availability and rapid access to accurate diagnostic procedures, and also development of highly effective therapeutic interventions, all of which have contributed to a substantial increase of costs in health care. At times of economic constraints, it has become of paramount importance to ensure that medical care is delivered in the most cost-effective way around the world. A clear understanding of the disease and methods used for its identification

would provide the basis for a judicious management and a more efficient use of resources. In this regard, noninvasive diagnostic procedures have demonstrated to have a major role in the assessment of patients investigated for CAD.

Exercise electrocardiogram (ECG), myocardial perfusion scintigraphy (MPS), and stress echocardiography are the most frequently used techniques for this purpose. Exercise radionuclide ventriculography has been used in the past for the diagnosis of CAD but, currently, stress MPS is the preferred radionuclide technique for this purpose. Although still an evolving modality, cardiovascular magnetic resonance (CMR) has demonstrated to be highly effective in the detection of myocardial ischemia and, more recently, multislice computed tomography (MS-CT) has been introduced as a promising modality for assessment of coronary artery anomalies and also for identification of lesions and assessment of calcium in the coronaries. The clinical potential of the latter and also of electron beam computed tomography (EBCT) has been discussed in the previous chapter. Herein, after a short discussion on the initial approach to patients presenting with symptoms of CAD, we focus on the characteristics and role of the mainstream noninvasive imaging modalities and their relative strengths and limitations for diagnosing CAD.

1. Clinical Diagnosis of CAD

1.1 Medical History and Physical Examination

The medical history remains the first and most important diagnostic tool available to the physician, because a decision to investigate further relies on the initial clinical impression. Angina, the most specific symptom for myocardial ischemia secondary to obstructive CAD, is classically defined as a retrosternal, pressure-like discomfort or central chest tightness precipitated by exertion or emotional stress, accompanied by a sense of uneasiness, and relieved within minutes by rest or sublingual glyceryl trinitrate. However, not all patients with CAD present with typical angina, and thus it is a relatively insensitive marker of disease. In many patients, myocardial ischemia is associated with less typical features, including discomfort in one or both arms, shoulders, jaw, or epigastrium, as well as nonexertional symptoms. Moreover, comorbidities such as diabetes mellitus and ischemia-induced left ventricular dysfunction may affect the quality of anginal symptoms resulting in a wide constellation of manifestations, which are often referred to as angina equivalents. In the presence of typical symptoms of angina, the clinical diagnosis is straightforward and additional noninvasive testing might be indicated to assess the extent and severity of underlying myocardial ischemia. A complete medical history may therefore provide the correct diagnosis in some cases, and may also help identify cardiovascular risk factors, such as smoking and family history, which increase the probability of coronary disease and have important prognostic implications.[2,3]

Along with the clinical history, a complete physical examination may contribute to the diagnosis of CAD, although in the great majority of patients it will be normal. However, a careful examination may reveal signs associated with an increased risk of coronary disease, such as xanthelasma, corneal arcus, elevated blood pressure, and abnormal pulses suggestive of peripheral vascular disease. Moreover, it may help identify conditions that precipitate myocardial ischemia, such as thyroid disease, anemia, valvular heart disease, and hypertrophic cardiomyopathy, whereas signs of ventricular failure would suggest the presence of severe underlying CAD. Finally, it is important to consider conditions other than coronary disease that may compromise myocardial blood flow (MBF) and provoke ischemia, such as anomalous coronary arteries, vasculitis, Kawasaki's disease, and coronary embolization secondary to atrial tumor or thrombus (see also Chapter 14).

1.2 Resting Electrocardiography

The easy access to portable electrocardiographic equipment has made the ECG a readily available tool that alongside the clinical history and the physical examination aids in the diagnosis of CAD. When present, dynamic ST-segment and T-wave changes strongly suggest the presence of obstructive coronary disease. However, most patients with stable angina and angiographically proven coronary stenosis will have a normal ECG.[4] In the remainder, abnormal Q waves or repolarization changes suggestive of myocardial injury, and atrioventricular or intraventricular

conduction abnormalities [i.e., left bundle branch block (LBBB) and left anterior fascicular block] secondary to underlying ischemia can be observed. All these changes are nonspecific with an increased prevalence in the elderly as well as in hypertensive subjects and in those taking antiarrhythmic medication. Therefore, both the sensitivity and specificity of electrocardiographic findings are relatively low, adding little to the diagnosis of CAD.[5]

1.3 Chest X-ray

Normal in the majority of patients with chronic stable chest pain, a well-performed posteroanterior or frontal projection can provide additional information to the diagnosis of CAD. More importantly, it can be helpful in the differential diagnosis of chest pain (Table 8.1). An enlarged cardiac silhouette, opacification of lung fields with prominent upper lobe vessels, or interlobular septal lines or Kelley B lines, and pleural effusion can be observed in patients with significantly impaired left ventricular function secondary to severe ischemia. All these radiographic signs are, however, nonspecific because they can also be seen in patients with ventricular dysfunction of nonischemic cause.

Table 8.1. Common causes of chest pain

Cardiovascular
Ischemic
Coronary artery disease
Anomalous coronary artery
Muscle bridging
Aortic valve stenosis
Hypertrophic cardiomyopathy
Severe hypertension and LVH
Vasculitis
Coronary emboli
Nonischemic
Aortic dissection
Pericarditis
Mitral valve prolapse
Noncardiac
Respiratory
Pneumonia
Pulmonary embolism/infarction
Pleurisy
Pneumothorax
Gastrointestinal
Gastroesophageal reflux
Esophageal spasm/rupture
Esophagitis, gastritis
Peptic ulcer
Cholecystitis, pancreatitis
Neuromusculoskeletal
Costochondritis (Tietze's syndrome)
Cervical/thoracic spine disease
Thoracic outlet syndrome
Herpes zoster
Others
Severe anemia, hypoxemia
Psychosomatic disorders

LVH, left ventricular hypertrophy.

1.4 Assessment of Likelihood of CAD

To determine the need for further investigation, it is essential to estimate the pretest probability of angiographically significant coronary disease. In this regard, the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines on the management of chronic stable angina recommend the use of validated predictive nomograms.[5] The Diamond and Forrester predictive table integrates three clinical variables – quality of chest pain, gender, and age – to provide an estimate of the risk of significant coronary stenosis as defined by coronary angiography (Table 8.2).[6] This approach can be refined by incorporating other powerful predictors, such as serum cholesterol levels, systolic blood pressure, and diabetes.[7] Most predictive tables and nomograms clearly separate low- from high-risk subjects. However, most patients will have an intermediate pretest probability of CAD,[6] and thus will need further stratification.

1.5 Application of Bayes' Theorem

The Bayes' theorem is a basic principle to bear in mind when requesting, performing, and interpreting diagnostic tests. The application of the Bayesian analysis to the currently available techniques for the diagnosis of CAD indicates that the diagnostic power of any test that is not 100% accurate is highly dependent on the prevalence of disease in the population studied. According to this, a positive test in a population with a low prevalence of coronary disease (<10%) is likely to be false positive, and thus investigations will only increase costs while exposing subjects to unnecessary procedures and risk. Conversely, most patients with a high pretest likelihood of disease (>90%) can confidently be referred for coronary angiography with a view to intervening. Although noninvasive tests can be performed

Table 8.2. Pretest likelihood of angiographically significant coronary artery disease according to age, gender, and chest pain quality[9]

Age (yr)	Gender	Typical angina	Atypical angina	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

for other reasons (i.e., risk stratification and prognosis), it is important to bear in mind that a negative result in this group is likely to be false negative and thus disease cannot be ruled out. Additional diagnostic testing is therefore most valuable in patients with an intermediate probability of CAD, as further stratification is needed.

2. Exercise Electrocardiography

Since the introduction of the first standardized protocol in the late 1920s,[8] exercise ECG has remained the most frequently performed stress procedure for the assessment of patients with stable chest pain. Furthermore, current practice guidelines recommend exercise ECG as the initial diagnostic test in patients with an intermediate pretest likelihood of coronary disease and a normal resting ECG.[5,9] Its major advantages are its wide availability, relatively low cost, and ability to provide a dynamic assessment of the significance of coronary stenosis by reproducing the patient's symptoms and unveiling ischemia-induced electrocardiographic and hemodynamic changes.

2.1 Procedure

All currently available exercise protocols involve continuous exercise with incremental workloads between multiple stages, producing a progressive increase in myocardial oxygen demand up to the patient's maximal level. The choice of one protocol over the others depends on physical conditioning and familiarity to exercise (i.e., walking versus cycling). The treadmill Bruce protocol is the most popular test, with modified versions available for patients with limited exercise tolerance. Regardless of the protocol used, an optimal exercise test should last at least 6 minutes, ideally between 8–12 minutes, with patients achieving at least 85% of the age- and gender-adjusted maximum predicted heart rate (MPHR), unless limiting symptoms develop. The classical criterion of an electrocardiographically positive exercise ECG is the occurrence of ≥1 mm horizontal or down-sloping ST-segment depression calculated at 60–80 milliseconds after the J point in three or more consecutive beats on any ECG lead. Exercise-induced ST-segment depression is the result of diffuse subendocardial ischemia, and thus does not localize the site of coronary stenosis, nor does its magnitude correlate with the severity or extent of CAD.[10] In contrast, exercise-induced ST-segment elevation, which results from transmural involvement, does localize the vascular bed, but occurs rarely during diagnostic exercise testing.[11,12] Dynamic electrocardiographic changes therefore aid in the detection of myocardial ischemia but are limited in their ability to provide information on the magnitude of underlying disease. Because of the reduced value of electrocardiographic changes alone, other exercise variables including cardiac symptoms, exercise capacity, and hemodynamic response must be considered before reaching a conclusion.[9] An exercise ECG test is terminated when the patient achieves his/her MPHR, develops limiting symptoms, or produces an abnormal test. Exercise testing not only allows an objective assessment of patients' symptoms and their relation with electrocardiographic and hemodynamic changes, but also provides information on exercise capacity, an important independent prognostic marker of future cardiac events.[13]

Overall, exercise ECG performs relatively well for the detection of flow-limiting epicardial coronary stenosis, although its diagnostic accuracy

is not as high as that observed with imaging techniques. In the largest meta-analysis of 147 studies of 24 074 patients, 58 studies were considered free of bias, and they showed that the mean sensitivity of exercise ECG for diagnosis of CAD was 67%, with a specificity of 72%.[9] This varied according to the severity of underlying disease, with the highest sensitivity in patients with severe multivessel disease, and the lowest accuracy for single-vessel coronary stenosis. One approach to improving the diagnostic accuracy of the test is through the use of score systems that integrate several exercise parameters. The Duke treadmill score, a composite index that combines physical capacity measured in minutes of exercise, severity of angina, and magnitude of ST-segment changes to provide an estimate of risk of future cardiac events,[14] can also be used to stratify patients further according to their probability of having angiographically significant coronary stenosis.[15] This predictive tool provides both diagnostic and prognostic information that guide recommendations for optimal management according to risk categories (Figure 8.1).[16]

2.2 Limitations of Exercise ECG

From an electrocardiographic viewpoint, baseline abnormalities [e.g., LBBB, left ventricular hypertrophy (LVH) with repolarization changes, preexcitation syndromes, ST-segment depression of >1 mm] as well as digitalis therapy may complicate the interpretation of dynamic changes. Because the diagnostic performance of exercise testing is highly dependent on the patient's motivation and physical capacity to achieve an adequate workload, the value of the test is limited in populations with orthopedic, respiratory, or neurologic disorders (Table 8.3). Even after an optimal test is performed, conflicting findings such as borderline ST-segment or T-wave changes in the absence of symptoms are not uncommon and may lead to inconclusive results. Moreover, an inadequate hemodynamic response to exercise or the development of arrhythmias during the test, albeit nonspecific, warrants further evaluation, because these responses may be the result of significant CAD. In all these circumstances, the correct diagnosis of significant coronary disease

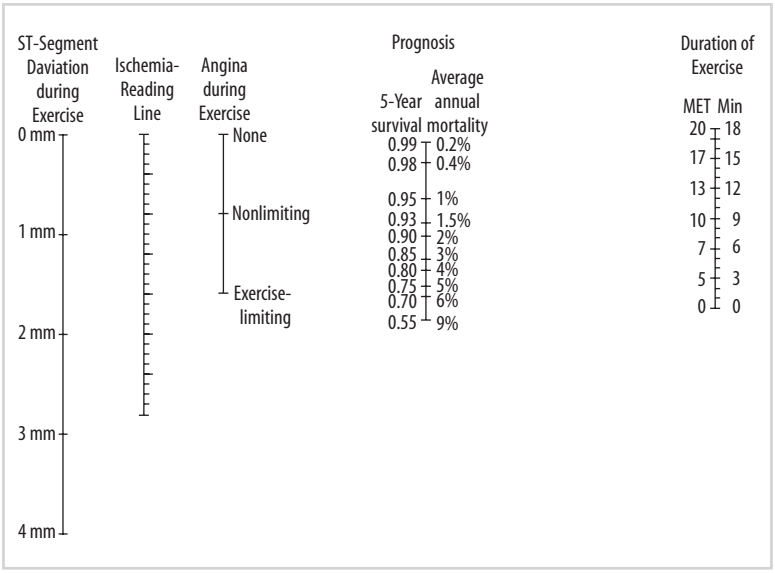

Figure 8.1. Nomogram of the Duke University prognostic treadmill score. Survival estimation is based on 1) the magnitude of exercise-induced ST-segment deviation from the isoelectric line expressed in millimeters; 2) development of chest pain, and 3) cardiac workload achieved measured in multiples of basal resting requirements (METS) or duration of exercise in minutes. The ST-segment deviation and the angina score points are connected with a straight line to determine the point on the ischemia reading line. A line is then drawn between this point and the maximal METS achieved or minutes of exercise performed to determine the point of intersection on the prognosis line. Information on prognosis is expressed as 5-year cardiovascular survival rate and average annual cardiovascular mortality. A patient who exercises for 6 minutes on the treadmill and develops 2-mm ST-segment depression associated with exercise-limiting angina has a 5-year survival rate in the region of 75% (average annual mortality rate, 5%) according to the nomogram.[16] (Reproduced with permission. Copyright © 1991 Massachusetts Medical Society. All rights reserved.)

Table 8.3. Contraindications to exercise testing

Absolute
Recent/unstable acute coronary syndrome
Known significant left main stem stenosis
Heart failure with resting symptoms
Acute inflammatory process of the heart
Myocarditis
Pericarditis
Endocarditis
Life-threatening arrhythmias
Severe fixed or dynamic left ventricular outflow tract obstruction
Aortic stenosis
Obstructive hypertrophic cardiomyopathy
Uncontrolled hypertension
Pulmonary embolism or infarction
Thrombophlebitis or deep vein thrombosis
Relative
Orthopedic, neurologic, or respiratory disorders that limit exercise capacity
Poor motivation to perform the test

could be jeopardized, and thus before embarking upon treatment strategies, an alternative diagnostic modality should be considered.

Exercise ECG has demonstrated to be less accurate in women than in men. In a meta-analysis of 19 studies in women undergoing exercise ECG for the diagnosis of coronary disease, the test had a weighted mean sensitivity of 61% and specificity of 70%.[17] This reduced diagnostic accuracy of exercise ECG in women has been attributed to the lower prevalence of disease, particularly among premenopausal patients,[18,19] the digitalis-like effect of estrogen responsible for repolarization changes, and the lower exercise tolerance of women compared with men.[20] Hormonal variations, higher prevalence of mitral valve prolapse, and abnormalities of microvascular function have also accounted for the suboptimal performance of exercise ECG in women.[20,21] However, higher accuracy can be achieved with the inclusion of additional parameters (e.g., functional capacity, treadmill scores) to the interpretation of the ST-segment response to exercise. Indeed, obstructive disease is more prevalent in women with high Duke treadmill score (see above) and they could benefit from referral to coronary angiography.

3. Stress Radionuclide MPS

Since its introduction 30 years ago, MPS has become an established technique for the detection of CAD, with important advantages over other diagnostic modalities. MPS is a robust technique that has demonstrated to be highly sensitive for the diagnosis of angiographically significant coronary stenosis by means of the detection of regional abnormalities of myocardial perfusion. Furthermore, myocardial perfusion imaging (MPI) overcomes the various diagnostic limitations of exercise ECG previously described. Myocardial perfusion can also be assessed accurately by positron emission tomography (PET) but, at present, its role in clinical practice is constrained by high cost and poor availability.

3.1 Procedure

In the ischemic cascade, impaired myocardial blood flow (MBF) reserve is one of the earliest events in the progression of disease from atherosclerotic changes to obstructive coronary lesions (Figure 8.2). MPS enables detection of such abnormality and provides accurate information on the state of myocardial perfusion that has both diagnostic and prognostic implications. MPS also assists in the identification of viable myocardium, which is facilitated by the simultaneous assessment of perfusion and function using ECG-gated imaging.

MPS relies on a camera that detects photons (usually gamma rays and/or X-rays), and the administration of a "perfusion tracer" (i.e., thallium-201, technetium-99m sestamibi, technetium-99m tetrofosmin) that is taken up by the myocytes in proportion to regional blood flow during stress as well as resting conditions (see also Chapter 4). In routine clinical practice,

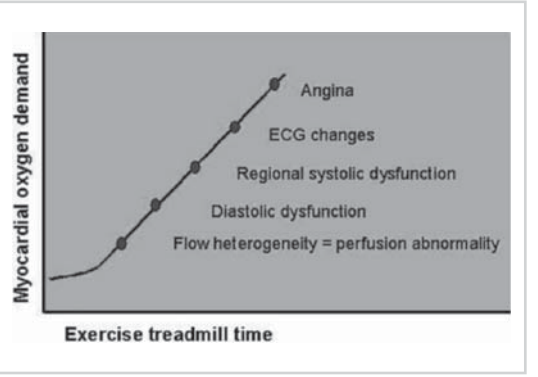

Figure 8.2. Ischemic cascade.

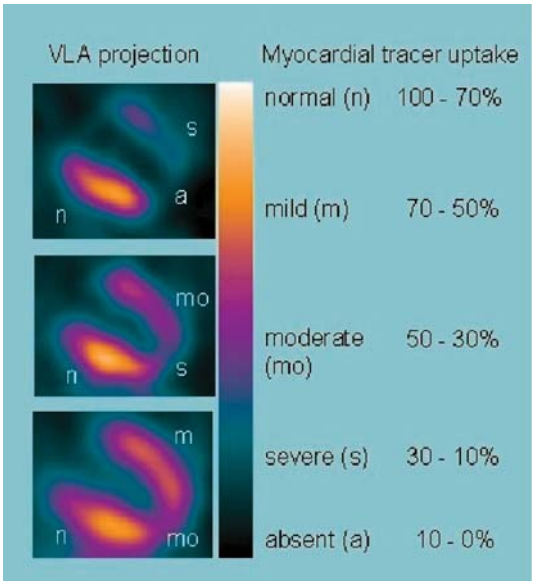

Figure 8.3. Tracer uptake within each myocardial wall or segment can be defined as normal, reduced, or absent. A segment of reduced tracer uptake can be further described as mildly, moderately, or severely reduced. These categories reflect the counts as a percentage of maximum in the whole set of tomographic projections. For instance, anything between 70%–100% of maximal myocardial tracer uptake is considered normal – this corresponds to the colors orange, yellow, and white on the Cool color scale. VLA: vertical long axis.

image interpretation relies on visual assessment of tracer uptake and its distribution into the myocardium (Figure 8.3; see color section). However, with advances in automated software algorithms and the availability of validated normal databases, quantitative analysis is becoming increasingly popular, and could be used to support visual interpretation (see Chapter 4).

3.1.1 Thallium MPS

Thallium-201 was the first perfusion tracer identified to image myocardial perfusion. Thallium-201 is a potassium analog that is rapidly transported into the myocytes through the Na-K adenosine triphosphatase pump, an active, energy-dependent mechanism. A small proportion enters the myocardial cell passively through an electropotential gradient and accumulates into the cytoplasm. After an injection of thallium-201 at peak stress, the tracer is rapidly extracted by the myocardium with a first-pass extraction fraction of 88%.[22] Thallium-201 uptake is proportional to blood flow until it reaches values >3 mL/min/g; at this point uptake levels off (roll-off phenomenon) despite further increments in blood flow.[23] Thallium-201 starts redistributing shortly after injection, and thus imaging 3–4 hours later allows assessment of resting perfusion and myocardial viability.[24] Comparison between the stress and redistribution images distinguishes between the reversible defect of inducible hypoperfusion and the fixed defect of myocardial necrosis, although, in some cases, redistribution may be incomplete at 4 hours. A second injection of thallium can then be given and reinjection images acquired for a more accurate assessment of myocardial viability.[25] In addition, administration of nitrates before a resting injection of thallium-201 (nitrate-enhanced thallium reinjection imaging) has been shown to improve the detection of viability.[26] Therefore, a resting injection of thallium increases the pool of circulating tracer whereas nitrates augment its delivery by increasing blood flow through collateral circulation.

Thallium-201 MPS is highly accurate for the diagnosis of CAD. Typical values of sensitivity and specificity are in the region of 85%–90% and 75%, respectively.[27] Thallium-201 imaging is used in many centers worldwide, although it is being largely superseded by the technetium tracers because of their superior imaging characteristics.

3.1.2 Technetium-99m MPS

Technetium-99m sestamibi and technetium-99m tetrofosmin are both well-validated perfusion tracers that can be used alone or in combination with thallium-201 imaging for the assessment of patients with suspected CAD. These agents are less vulnerable to attenuation and scatter, and therefore produce better-quality images, particularly in overweight and female patients with dense breast tissue. Because they exhibit minimal redistribution over time, imaging can be delayed for some time after the stress injection, and there is no need to inject close to the gamma camera. Injections can be given during treadmill exercise testing, in the catheter laboratory, or in the coronary care unit immediately before thrombolysis. In addition,

because of the higher doses that can be used with technetium-99m, ventricular function can be assessed either by first-pass imaging of the tracer as it passes through the central circulation or by ECG-gated acquisition of the myocardial perfusion images. In comparison with thallium-201, they are extracted less avidly from the circulation, with a first-pass extraction fraction in the region of 50%–55%,[28,29] and an early roll-off at blood flow velocities exceeding 2 mL/min/g myocardium.[23] In theory, these tracers will be less capable of tracking MBF at high flow velocities. Indeed, experimental models have demonstrated the nonlinear relation between myocardial tracer uptake and blood flow at high flow velocities for all available tracers, with the best uptake/flow relation for thallium-201, and the least favorable relation for technetium-99m sestamibi and technetium-99m tetrofosmin.[23] It has also been shown that technetium-99m MPS is less sensitive for the detection of mild coronary stenosis (≤70% luminal diameter reduction) than thallium-201 imaging.[28,30] However, such differences may not be important in clinical practice and indeed a large body of evidence indicates that the average diagnostic accuracy of technetium-99m MPS is similar to that observed with thallium-201 imaging.[27]

3.1.3 Exercise MPS

The addition of radionuclide imaging to conventional exercise stress testing not only enhances its diagnostic performance significantly but at the same time offers incremental prognostic information above that obtained by the exercise ECG data, thus allowing accurate stratification of patients into low- and high-risk groups of future coronary events.[31] Such classification is highly important for patients' management, because low-risk individuals are unlikely to benefit from further investigation and are best managed medically, whereas those with significant ischemia will usually be referred for coronary angiography.[32]

The diagnosis of flow-limiting coronary disease is based on the ability of exercise testing to decrease coronary arteriolar resistance as myocardial oxygen consumption increases. In the presence of a flow-limiting stenosis, a reduced vasodilator reserve will produce a heterogeneous distribution of tracer identifiable on the post-stress images. The diagnostic performance of MPS is therefore highly dependent on the adequacy of the exercise test, because failure to increase myocardial oxygen demand sufficiently would prevent the identification of vascular territories with an impaired vasodilator reserve.[33] As for exercise ECG testing, diagnostic exercise MPS should be conducted in patients physically able and sufficiently motivated to reach an adequate cardiovascular workload level.

The preparation for an exercise MPS study is similar to that of a conventional exercise ECG with the exception that patients should be advised to abstain from caffeine-containing products, because vasodilator stress may be undertaken if the patient fails to complete the exercise test satisfactorily (see below). Anti-ischemic drugs, especially beta-adrenergic blockers, increase the ischemic threshold, and should therefore be discontinued for a minimum of four half-lives before the test. Ideally, the exercise test should be symptom-limited, with patients achieving their maximal workload level or at least 85% MPHR unless cardiac symptoms and ECG changes suggestive of significant myocardial ischemia develop (>1 mm ST-segment elevation in non-Q waves leads or ≥2 mm horizontal or down-sloping ST-segment depression). The perfusion tracer is administered at peak stress, and the patient should continue exercising for 1–2 minutes to allow for adequate myocardial extraction of tracer.[34]

There is some variation in published data on the diagnostic accuracy of exercise MPS, partly because of differences in imaging protocols and standards of interpretation; however, well-designed studies have found high values of sensitivity and specificity (approximately 85% and 75%, respectively).[26] After exclusion of patients with documented previous myocardial infarction (MI), exercise MPS maintains its high sensitivity (87%) for the detection of disease.[26] Likewise, specificity for the identification of normal coronary arteries is good,[35–37] although most of the studies are influenced by referral bias, which leads to overestimation of sensitivity and underestimation of specificity, because most patients with a normal scan are spared from coronary angiography. To reduce the effect of referral bias on specificity, the performance of MPS in patients without disease is best assessed as normalcy. Based on estimation of the proportion of normal MPS studies in populations with

a low pretest likelihood of CAD (<10%), the normalcy rate of exercise MPS is in the region of 81%–95%.[33,38,39]

In addition to the traditional contraindications to exercise testing (see also Chapter 4), exercise should be avoided in patients with LBBB and electronically paced ventricular rhythm. Near half of patients with LBBB may develop perfusion defects in the interventricular septum and adjacent myocardial segments during exercise MPS in the absence of obstructive coronary disease (Figure 8.4; see color section).[40] The exact underlying mechanism remains unknown; however, there is evidence suggesting that, in LBBB, the temporal delay between left and right ventricular activation results in a prolonged systole and a reduced diastolic filling time for the septum. Because most coronary flow occurs in diastole, this has the effect of reducing septal myocardial perfusion, which would be exacerbated by increments in heart rate. Thus, any maneuver that increases heart rate (e.g., exercise, inotropic agents) should be avoided, because this increases the likelihood of perfusion defects arising from the conduction abnormality. Vasodilator stress has been found to increase the specificity of the technique by 40%, indicating that vasodilator MPS is the modality of choice in these patients (Figure 8.5; see color section).[40,41]

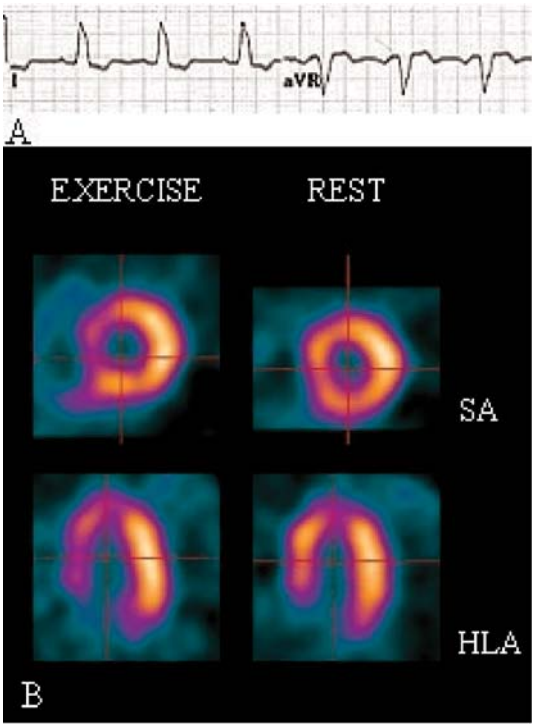

Figure 8.4. A 54-year-old man with atypical chest pain and no history of coronary artery disease underwent exercise thallium-201 myocardial perfusion scintigraphy. **A** ECG showing complete LBBB. **B** Short-axis and horizontal long-axis views showing exercise-induced septal hypoperfusion that normalizes at rest. Subsequent X-ray coronary angiography revealed normal coronary arteries.

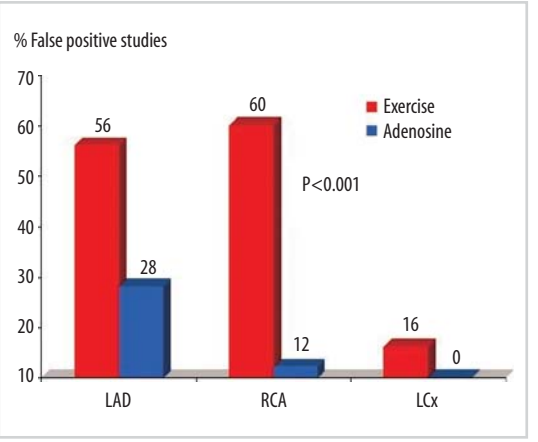

Figure 8.5. False-positive studies (%) in patients with LBBB undergoing exercise versus adenosine myocardial perfusion scintigraphy. LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex coronary artery.

3.1.4 Pharmacologic MPS

One of the major advantages of radionuclide imaging is its versatility among the different stress modalities currently available. MPS can be combined with a pharmacologic stress agent that mediates either direct (e.g., adenosine, dipyridamole, and selective $A2_A$ receptor agonists) or indirect (e.g., dobutamine) coronary vasodilation if exercise is contraindicated or discontinued.

3.1.4.1 Vasodilator MPS. Dipyridamole and adenosine are the two currently available vasodilators for the assessment of myocardial perfusion. Both drugs act via the activation of adenosine $A2_A$ receptors located on the membrane of the smooth muscle cells of the small resistance vessels, producing direct coronary arteriolar dilation and increasing MBF to a level

comparable to that achieved with intracoronary papaverine.[42] Dipyridamole and adenosine increase MBF up to 4 times its resting level, with absolute values in the region of 3.5–4 and 4–5 mL/min/g, respectively.[42,43] Contrary to exercise, vasodilators produce primary coronary arteriolar dilation and only rarely true myocardial ischemia through a mechanism known as coronary steal. During this, the driving pressure for collateral flow between normal and stenotic coronary territories decreases substantially as a result of the greater vasodilator response of the normal vascular bed to these agents (intercoronary steal).[44] This may lead to profound ischemia with the potential for myocyte injury.[45] Although this phenomenon seems to be uncommon, it is more prevalent in the elderly as well as in patients with long-standing CAD who have developed collateral circulation between obstructed and nonstenotic coronary vascular territories. Blood flow diversion from the subendocardial to subepicardial layer can also occur as the former is subjected to the highest wall stress (intracoronary steal).

Preparation for vasodilator stress testing requires the abstention from caffeine-containing beverages and food for a minimum of 12 hours, as well as discontinuation of aminophylline and theophylline for at least 48 hours. Methylxanthines, such as caffeine and theophylline, are nonselective competitive antagonists of adenosine receptors that have been found to reduce the sensitivity of vasodilator stress for the detection of coronary stenosis.[46] Dipyridamole should also be discontinued 24–48 hours before the test. The role of antianginal medications in vasodilator stress is not clear, although recent observations mainly from studies performed with dipyridamole indicate that they may reduce sensitivity and should be discontinued if the scan is performed for diagnostic purposes.[47] Data with adenosine are still sparse and further research is essential before final recommendations.

Adenosine is administered as an intravenous infusion at 140 μg/kg/min for 6 minutes with tracer injection after 3–4 minutes of infusion. Because of the rapid onset of action of adenosine on the coronary vasculature (84 ± 46 seconds),[42] several studies have evaluated the effectiveness of shorter protocols, observing a similar overall predictive accuracy for the detection of angiographic coronary stenosis with a 4–5- versus 6-minute infusion.[48] Shorter protocols (≤3-minute infusion) may adversely affect the diagnostic and prognostic value of the test by reducing the extent of perfusion abnormality and should therefore be avoided.[49,50] The potential for increasing patient throughput and reducing costs has encouraged the implementation of 4- and 5-minute adenosine protocols in nuclear cardiology laboratories worldwide. Despite this, the 6-minute adenosine infusion remains the standard clinical protocol. Dipyridamole is given intravenously at 140 μg/kg/min for 4 min (0.56 mg/kg), and the perfusion tracer administered 3–4 minutes after termination of the infusion.

Summarized data demonstrate that the diagnostic accuracy of vasodilator MPS is similar to that of exercise imaging. This has been confirmed in studies performed with either thallium-201 or technetium-99m sestamibi; however, data from studies with tetrofosmin are less consistent, with some studies reporting good accuracy with vasodilators and others showing it to be less sensitive than Tl-201 or sestamibi for detection of mild-to-moderate angiographic disease.[51,52]

Vasodilator stress is well tolerated and has an excellent safety profile (≤0.05% risk of nonfatal MI or major cardiac complications),[53,54] and a high success rate because little cooperation is needed to complete the test satisfactorily. The addition of dynamic exercise has demonstrated to reduce significantly the intensity and frequency of side effects resulting from peripheral vasodilation (e.g., headache, flushing, hypotension) as well as the incidence of atrioventricular conduction abnormalities.[55,56] Exercise also enhances image quality by provoking splanchnic vasoconstriction and thus reducing extracardiac accumulation of tracer and increasing heart-to-background activity ratio.[57] The addition of submaximal exercise to vasodilator stress has also been found to increase the sensitivity of the test,[55,58] and this seems to be independent of the effect of exercise on quality and image interpretation. A combined effect on the myocardial perfusion system has been postulated,[59] although the exact mechanism is not known. Adding exercise reduces but does not abolish vasodilator-induced side effects, and thus their impact on test compliance continues to be a matter of concern. As a result of this, selective agonists to the adenosine $A2_A$ receptors have been developed,[60] and preliminary data suggest that these new agents are associated with fewer side effects.[61] The effectiveness of $A2_A$ receptor agonists seems to be similar to that of adenosine.[62]

3.1.4.2 Dobutamine MPS. Dobutamine can also be used in combination with MPS to determine the presence of significant coronary artery stenosis in patients with clinically suspected CAD. Dobutamine has not been studied as extensively as the vasodilators, and published estimates of its diagnostic accuracy vary markedly.[27] This has been largely attributed to inadequate stress protocols, lack of standardized test endpoints, and other factors independent of the test such as the concomitant use of beta-adrenergic blockers. Dobutamine stress is therefore a less well-established protocol and should be limited to patients unable to exercise who have a contraindication to vasodilator stress. As for exercise testing, the sensitivity of dobutamine for the detection of CAD is highly dependent on the level of cardiac work achieved. Beta-blockers increase the threshold at which abnormalities of myocardial perfusion would become apparent; hence, these agents should be discontinued before the test. Overall, dobutamine MPS has a sensitivity for the detection of significant coronary stenosis in the region of 80%–90% and a specificity ranging between 64%–100%[27] with the higher values recorded more often with thallium-201 than with technetium-99m labeled tracers. This is probably because dobutamine produces an increase in calcium flux into the myocytes that may affect the ability of monovalent cations such as sestamibi to bind to the mitochondrial membrane, reducing its intracellular uptake.

Dobutamine is given as an intravenous infusion, starting at 5 μg/kg/min and increasing to 10, 20, 30, and 40 μg/kg/min at 3- to 5-minute intervals. The tracer is injected after 3–5 minutes on the maximal dose of 40 μg/kg/min unless the patient develops limiting symptoms or the age- and gender-adjusted MPHR is reached. Tracer injection at low dobutamine rates (<20 μg/kg/min) should be avoided whenever possible. Atropine is often given during dobutamine echocardiography if 85% of MPHR is not reached at peak dobutamine infusion. This practice may not be necessary for perfusion imaging as long as the patient is not taking beta-blockers because of the primary vasodilator effect of dobutamine.[63] Other protocols combining exercise with dobutamine or atropine have been investigated; however, their use in clinical practice is limited.

3.1.5 ECG-gated MPS

The diagnostic accuracy of MPS improves further by incorporating information on global and regional left ventricular function to myocardial perfusion with the use of ECG-gated MPS imaging. For this purpose, image acquisition is synchronized with the QRS complex of the ECG signal, and sets of 8–16 frames are acquired, each frame corresponding to a specific part of the cardiac cycle. Automated algorithms are applied to the acquired data to obtain an accurate estimation of ventricular volumes, left ventricular ejection fraction, mass and regional wall motion and thickening. Over the last decade, ECG-gated MPS has been validated in many studies, comparing favorably with other well-established imaging modalities, including radionuclide ventriculography, echocardiography, and magnetic resonance imaging.[64–67]

The addition of functional information derived from ECG-gated MPS to perfusion data not only improves substantially the specificity of MPS by differentiating myocardial scar from artifact but it may also increase the sensitivity of the technique for detecting CAD. Moreover, it provides incremental prognostic information above that obtained from perfusion assessment alone in patients with suspected or known CAD (see next chapter). Because of the minimal added cost, ECG-gated MPS has become a routine procedure in most nuclear cardiology departments (Figure 8.6; see color section).

3.1.6 Advantages of MPS

The increasing use of MPS for the diagnosis of clinically important CAD is the direct result of its strengths; MPS is a robust and highly validated technique, widely available, with a clear role in the assessment of patients investigated for CAD as stated by national and internationally published guidelines.[5,68,69] With very few exceptions, MPS can be performed to virtually all patients presenting with stable chest pain. Its versatility allows the technique to be adjusted to patients' needs and medical status, whether exercise or pharmacologic stress is being performed.

The diagnostic superiority of MPS over conventional exercise testing relies on the ability of

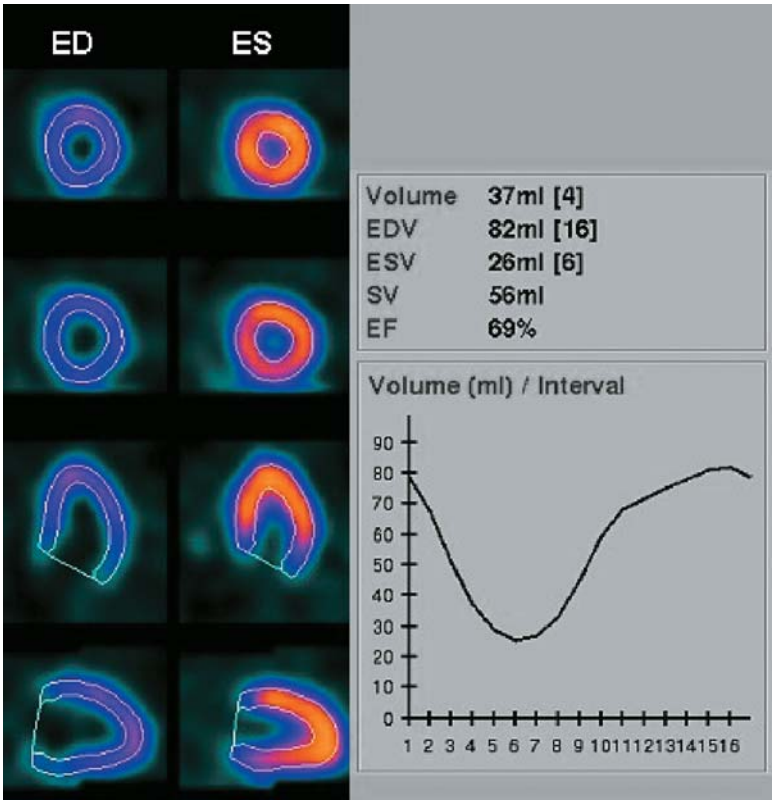

Figure 8.6. Quantitative gated SPECT (QGS) analysis of a 62-year-old woman with atypical chest pain of recent onset. The resting left ventricular ejection fraction (EF) is normal at 69% with normal left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV).

the technique to identify one of the earliest manifestations of CAD. MPS not only allows the detection of early abnormalities of myocardial perfusion but also defines the extent and magnitude of involvement of the vascular bed distal to the coronary stenosis and is the more sensitive test for detection of single-vessel coronary disease.

Radionuclide imaging has recently demonstrated to be more accurate than conventional exercise ECG for diagnosing CAD in women. In the past, MPS was highly vulnerable to soft tissue attenuation artifacts, producing a large proportion of false-positive tests in women. Modern camera technology and increasing use of high-energy tracers have both contributed to enhance the accuracy of MPS in women by reducing significantly the incidence of false-positive scans and increasing confidence in reporting.[70]

One of the most important advantages of MPS over other techniques is its high prognostic value. A normal MPS study not only suggests the absence of flow-limiting coronary disease, but it is also associated with a low likelihood of nonfatal MI or cardiac death (<1%/year). Conversely, an abnormal scan indicates the presence of significant CAD, and provides valuable incremental prognostic information that is based on the extent and severity of a perfusion abnormality, as well as the presence of other adverse prognostic signs, such as increased lung tracer uptake, transient left ventricular dilation, and global and regional left ventricular dysfunction (see next chapter). Reliable prognostication guides the selection of patients for further interventions, such as revascularization. This in turn allows more appropriate utilization of resources, with the potential for improved clinical outcomes and greater cost-effectiveness. Evidence from modeling and observational studies supports the enhanced cost-effectiveness associated with MPS use. In patients presenting with stable chest pain, strategies of investigation involving MPS are more cost-effective than those not using the technique (Figure 8.7; see color section).[71,72] MPS also has particular advantages over exercise ECG in the management of a number of patient

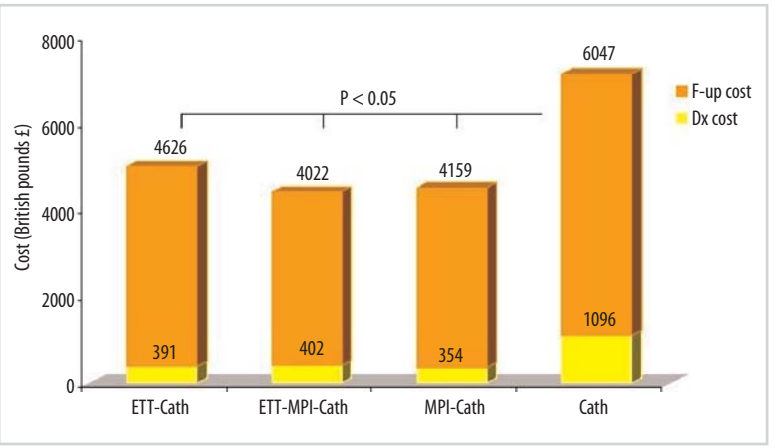

Figure 8.7. The Economics of Myocardial Perfusion Imaging (MPI) in Europe (EMPIRE) study explored the economic impact of four diagnostic strategies that combined exercise testing, MPI, and coronary angiography for the assessment of patients with chronic chest pain. The study, comprising 396 patients from eight hospitals in the United Kingdom, France, Italy, and Germany, showed significantly lower diagnostic and 2-year management costs when MPI was used as the gatekeeper to coronary angiography compared with direct referral to catheterization, with no effect on outcome. Dx, diagnostic; and F-up, follow-up costs of care estimated in British pounds (£).[71] (By permission of Oxford University Press on behalf of The European Society of Cardiology.)

subgroups, including the elderly[73] and those with diabetes,[74,75] and its use will have a favorable impact on cost-effectiveness in these groups. The high diagnostic and prognostic value of MPS in the setting of stable chest pain syndromes and chronic stable angina is widely recognized and MPS has become an integral part of the investigative strategies recommended by both European and American guidelines.

3.1.7 Disadvantages of MPS

Its vulnerability to artifacts has been largely recognized as the major limitation of radionuclide imaging. However, continuous improvement in imaging technology has had a tremendous impact on the diagnostic performance of the MPS, producing a significant reduction in the incidence of artifacts and thus improving the specificity of the technique. The increasing availability of automated software that allows quantitative analysis using normal databases has also contributed substantially to enhance the diagnostic profile of the technique over the last few years. ECG-gated MPS, motion, attenuation, and scatter-correction algorithms are available in most modern equipment. The correct use and application of these new tools may lead to a more accurate diagnosis of myocardial ischemia. Furthermore, dynamic cardiac single photon emission computed tomography (SPECT) based on the principle of tracer kinetics is another direction of current research that opens new horizons for the development of a potentially more sensitive tool for detecting myocardial ischemia.

The agreement between the magnitude of a perfusion abnormality and the severity of angiographically defined coronary stenosis is frequently referred to as moderate (60%–80%).[76] Initially considered as a potential disadvantage of MPS, it is now accepted that this is the result of the inability of conventional coronary angiography to fully assess the hemodynamic significance of coronary lesions.[77,78] Moreover, coronary angiography can underestimate the effect of diffusely distributed coronary atherosclerosis on distal perfusion, an observation that has been largely supported by numerous experimental studies showing the close relation between stress perfusion defects and coronary blood flow reserve.[76,79] Other potential causes of the discordance between MPI and coronary angiography are the presence of collateral blood flow, coronary vasospasm, and abnormalities of endothelial function and regulation of microcirculation.[80,81]

4. Cardiovascular Magnetic Resonance

In CMR, two main techniques are used in the assessment of CAD:

- Dobutamine stress CMR (DSCMR) – using the infusion of incremental doses of dobutamine to induce wall motion abnormalities as determined with high-resolution cine-CMR
- Adenosine perfusion CMR – using an infusion of adenosine as a coronary vasodilator to induce regional perfusion abnormalities, detected with the administration of a gadolinium contrast agent

CMR angiography is also feasible but, at present, is of limited value in the patients discussed here (see more in Chapters 3, 14, and 15).

Although CMR is a relatively new imaging modality compared with echocardiography and nuclear scintigraphy, both DSCMR and adenosine perfusion CMR are increasingly used in large cardiothoracic departments to diagnose coronary artery stenoses.

4.1 Dobutamine Stress CMR

Dobutamine has been extensively combined with echocardiography as a noninvasive diagnostic test for coronary artery stenoses, although diagnostic images may not be possible in obese patients or patients with bronchial asthma. Dobutamine increases myocardial contractility, heart rate, and systemic blood pressure, which increase myocardial oxygen consumption. In the presence of a significant coronary artery stenosis, this will produce myocardial ischemia leading to regional wall motion abnormalities, surface ECG changes, and the development of angina. "High-dose" dobutamine (30–40 µg/kg/min) is a safe agent to produce myocardial ischemia, but does have a small rate of serious complications in approximately 0.25% of patients, including MI (0.07%), ventricular fibrillation (0.07%), and sustained ventricular tachycardia (0.1%).[82,83]

DSCMR was used by Pennell et al.[84] in 1992 in the investigation of 25 patients with angina and an abnormal exercise tolerance test. Using a dobutamine infusion to a maximum of 20 µg/kg/min and non-breathhold gradient-echo cine imaging in two short-axis and two long-axis planes, they demonstrated inducible wall motion abnormalities in 20 of 21 patients with reversible ischemia on thallium tomography. Baer et al.,[85] using a similar technique in 28 patients with coronary artery stenoses, obtained sensitivity and specificity values for the detection of significant coronary artery stenoses of 87% and 100% for the left anterior descending, 62% and 93% for the left circumflex, and 78% and 88% for the right coronary artery, respectively. In a study of 45 patients, van Rugge[86] obtained an overall sensitivity for the detection of CAD of 81%, with a specificity of 100%. "High-dose" dobutamine (up to 40 µg/kg/min) with atropine (0.25 mg repeated up to 1.0 mg) to reach a target heart rate (>85% maximal predicted), was used by Nagel et al.,[87] in a large study (208 patients) that compared DSCMR with dobutamine stress echocardiography (DSE). The protocol was well tolerated with no significant adverse events. For the detection of significant coronary artery stenoses, the sensitivity of DSCMR was 86.2% compared with 74.3% for DSE, with a specificity of 85.7% for DSCMR and 69.8% for DSE (both $P < .05$). Of particular note was the improved image quality with DSCMR, with 69% of images rated as very good, compared with only 19.6% for DSE. In fact, 8.8% of DSE images were nondiagnostic, as compared with 1.6% for DSCMR. With the addition of myocardial tagging, Kuijpers et al.[88] were able to demonstrate an improved detection of CAD, and of 68 patients identified as having abnormal wall motion, 65 had significant ischemic heart disease with 62 needing revascularization. In the 112 patients with normal DSCMR, there was an event-free rate of 98.2% at a mean follow-up of 17.3 months.

4.1.1 Procedure

The patient is prepared for the scanner following standard procedures, including the checklist of contraindications to CMR. In addition, patients with specific contraindications to high-dose dobutamine (e.g., recent acute coronary syndrome, ventricular tachyarrhythmia) are excluded. Patients are asked to discontinue beta-blockers 48–72 hours before the examination. A 12-lead ECG and baseline observations (heart rate and blood pressure) are obtained. An intravenous cannula is inserted into a large peripheral vein and connected to a saline-flushed long-line. Continuous ECG monitoring and automated blood pressure recording are connected. The patient is then positioned in the magnet bore. Using rapid pilot scans for accurate positioning, multiple breathhold cardiac-gated cine images are acquired of the vertical long-axis, horizontal long-axis, and a stack of short-axis planes from the base to the apex of the left ventricle (Figure 8.8). The dobutamine infusion is then commenced at a rate of 5 µg/kg/min for 5–10 minutes. The dobutamine infusion rate is increased at 5 or 10 µg/kg/min doses until the heart rate increases by 10% over baseline. At this "low-dose" level, cine imaging is repeated in all planes to detect inotropic reserve in myocardial

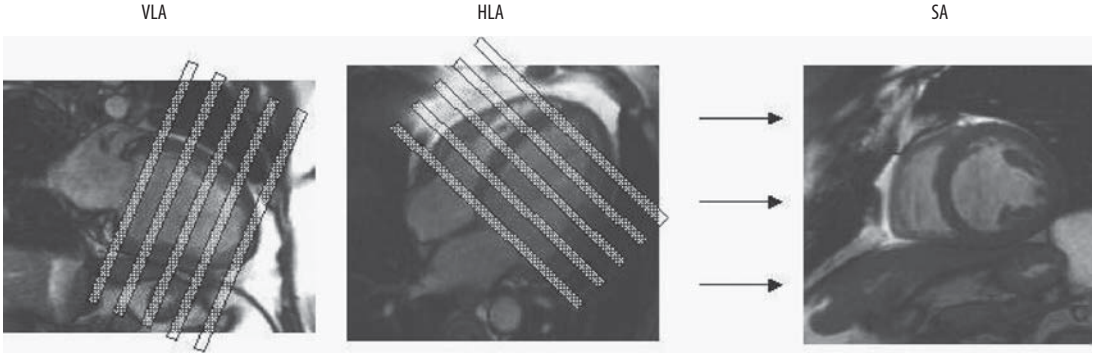

Figure 8.8. Rest and stress images are acquired in the vertical long axis (VLA) and horizontal long axis (HLA) of the left ventricle. These axes are used to pilot the short axis (SA) slices from the base to the apex of the left ventricle.

segments with resting abnormal wall motion. The dobutamine infusion rate is then increased at regular intervals until the target heart rate is obtained. After each incremental dose increase, it is important to perform a rapid visual analysis of the myocardial wall motion to avoid prolonging the study once wall motion abnormalities are induced. Blood pressure measurements and continuous ECG monitoring are performed. At this "high-dose" level, cine imaging is repeated in all planes. In some patients, atropine 0.5–3.0 mg may be necessary to allow the patient to reach the target heart rate. Once the study is complete, the patient can be removed from the magnet bore and allowed to recover. Analysis of the DSCMR is performed using a 17-segment model (6 basal-, 6 mid-, and 4-apical short-axis segments as well as the apical cap; Figure 8.9; see color section). At rest, each segment is scored as normal, hypokinetic, akinetic, dyskinetic. The scores are repeated for the "low-dose" – viability, and the "high-dose" – ischemia levels. A viable but ischemic segment (attributed to a critical coronary artery stenosis) may be scored hypokinetic at rest, normal at "low-dose," and hypokinetic at "high dose." In addition to the wall motion score, baseline and peak left ventricular ejection fraction can be calculated by summating the volume of each short-axis slice. Further quantitative information can be obtained including radial thickening, cardiac output, left ventricular volume-loops, and with the use of

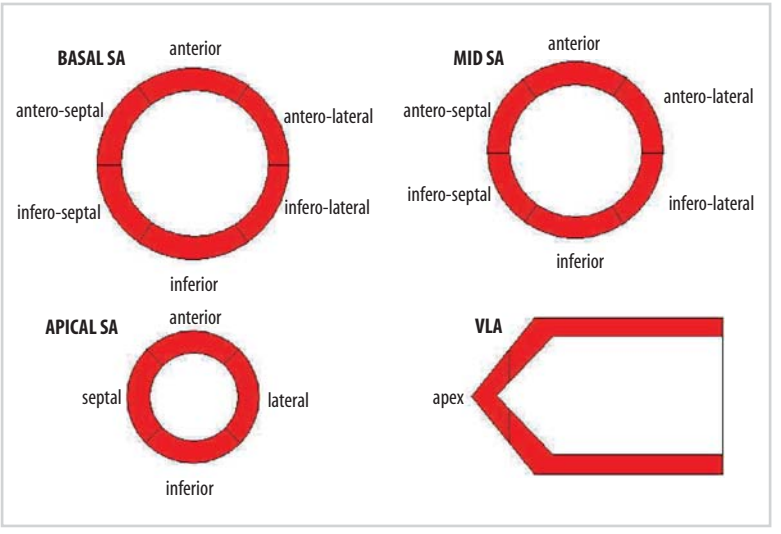

Figure 8.9. Analysis of dobutamine CMR is performed using a 17-segment model.

"tagging lines" complex three-dimensional data can be processed.

4.1.2 Advantages of DSCMR

DSCMR has certain advantages compared with DSE:

- DSCMR can produce high-quality images in almost all subjects. DSE can be limited by patients with poor echo windows because of obesity or chronic lung disease. In particular, the lateral wall can be problematic for DSE.
- Unlike DSE, which requires considerable operator skill in acquisition and interpretation, DSCMR is less operator dependent because the standard imaging planes can be acquired by most CMR technicians.

4.1.3 Disadvantages of DSCMR

The main disadvantages of performing dobutamine stress in a CMR environment result from the static and gradient magnetic fields:

- Monitoring equipment must be compatible with the static magnetic field and be remotely operated. In addition, the magnetic field distorts the surface ECG making ST-segment analysis difficult, although cardiac arrhythmias can be safely detected.
- Although dobutamine stress is a safe technique, there is a small risk of inducing a significant cardiac arrhythmia, e.g., ventricular tachycardia or ventricular fibrillation. Resuscitation must be performed outside the static magnetic field and so the patient needs to be rapidly extracted from the magnet bore. Regular simulated cardiac arrest training sessions are therefore essential.
- A small percentage of people experience claustrophobia inside the magnet bore. Performing a stress test on these patients (which can produce unpleasant symptoms) may not be possible.

4.2 Adenosine Perfusion CMR

MPI has been extensively performed with SPECT using exercise or vasodilator stress to produce regional differences in the uptake of radioactive tracers. Both adenosine and dipyridamole agents have more recently been used with CMR. The CMR sequences use a presaturation or inversion prepulse to null signal from the myocardium. An intravenous gadolinium-based contrast agent is then rapidly administered via a large peripheral vein. The gadolinium shortens the T1 of the blood pool and then the myocardium, which results in more signal being obtained and the images appear bright. In a normal subject, there will be homogenous myocardial enhancement with the gadolinium. A segment of myocardium supplied by a stenosed coronary artery will enhance slower than the surrounding myocardium and may reach a lower peak signal intensity. Infarcted myocardium with an occluded vessel and microvascular obstruction may remain black because no gadolinium can reach the tissue. These relative changes in signal intensity after gadolinium may be assessed qualitatively with a visual assessment by a trained observer, or semiquantitatively with the use of signal-intensity-time curves.

CMR-perfusion techniques were investigated in the early 1990s using single-slice inversion recovery (IR) gradient-echo sequences. The IR techniques were sensitive to heart rate variability and had limited spatial coverage. In 1990, Atkinson et al.[89] demonstrated the feasibility of CMR-perfusion in animal and human studies, using 0.1 mmol/kg gadolinium-DTPA, acquiring 32 ultrafast images in a transverse plane. In 1991, Manning et al.[90] studied 17 patients with chest pain, 12 of whom had significant coronary artery stenoses. They used 0.04 mmol/kg gadolinium-DTPA and were able to demonstrate that in myocardium supplied by a coronary stenosis, there was a lower peak signal intensity after gadolinium, and a lower up-slope. In 1992, Schaefer et al.[91] compared the results of thallium scintigraphy with dipyridamole CMR-perfusion in six patients with coronary artery stenoses and four normal volunteers. There were nine myocardial regions supplied by stenosed vessels, and CMR-perfusion matched the scintigraphy results in eight of them. In 1993 and 1995, Wilke et al.[92,93] performed quantitative studies in animal models. They used an IR Turbo-FLASH sequence combined with dipyridamole and a central injection of 0.05 mmol/kg gadolinium-DTPA in dogs. They found a linear relationship between the gadolinium concentration and the myocardial signal intensity at administered doses of between 0.2 and 1.2 mmol/L. Using an intravascular contrast agent (polylysine gadolinium-

DTPA), they produced good correlation with microspheres to accurately determine MBF and volume. In 1994, Eichenberger et al.[94] used gadolinium DOTA at 0.05 mmol/kg in 10 patients with >75% coronary artery stenosis, at rest and after dipyridamole administration. They were able to acquire three short-axis slices (one every heart beat), and obtained a sensitivity of 65%, specificity of 76%, and an accuracy of 74%, using thallium scintigraphy and coronary angiography as the gold standard. In 1995, Saeed et al.[95] performed rest-stress perfusion CMR in dogs with a critical circumflex artery stenosis. Measuring the peak signal intensity, they determined that at rest there was no difference between the myocardium with a normal blood supply compared with the myocardium subtended by the stenosed vessel. However, after dipyridamole, the normal territory increased signal intensity by a factor of three, compared with the stenosed region that increased signal intensity by a factor of two. In 1995, Walsh et al.[96] used a "key-hole" acquisition (only reacquiring the center of K-space every two heart beats and interpolating the data), with a small field-of-view, in 46 patients undergoing thallium scintigraphy. In 28 of 46 patients, there was 100% agreement (4 of 28 both normal, 24 of 28 both defects). In 8 of 46 patients, there were defects in both scans but not matched; in 5 of 46, the CMR was abnormal but SPECT was normal. In 5 of 46 patients, the CMR acquisition was not sufficient (one no gating, four not enough slices). A similar study was performed by Matheijssen et al.[97] in 1996, in which CMR-perfusion visually matched SPECT imaging in 90% of cases. Further analysis of the signal-intensity-time curves and a linear-fit approach, identified that the slope and the peak signal intensity increase were useful parameters. In 1997, Wilke et al.[98] used a central injection of gadolinium-DTPA to obtain a myocardial perfusion reserve index (MPRI) to differentiate between myocardium supplied by a normal coronary artery and that with a stenosed vessel. They produced a linear correlation between microspheres and MPRI in pigs, and between intracoronary Doppler flow and MPRI in humans. In 1999, Cullen et al.[99] studied the MPRI in 20 patients with ischemic heart disease and five normal volunteers. The MPRI in control patients was 4.21 ± 1.16 compared with 2.02 ± 0.7 for patients with ischemic heart disease. There also seemed to be a negative correlation between the MPRI and the diameter stenosis – >40% stenosis MPRI 2.8, >40% stenosis MPRI 1.93. In 2000, Al-Saadi et al.[100] performed a prospective study using single-slice CMP-perfusion and obtained sensitivity of 90% and specificity of 83% for detection of coronary stenoses >75%. In 2001, Schwitter et al.[101] studied 48 patients using a multislice hybrid echo planar imaging (EPI) sequence with 0.1 mmol/kg Omniscan (gadodiamide). Using parametric maps of the signal intensity up-slope, they obtained sensitivity of 91% and a specificity of 94% compared with PET. In 2003, Nagel et al.[102] performed rest-stress CMR-perfusion in 84 patients awaiting coronary angiography. Using Turbo-GRE/hybrid EPI sequence, they were able to obtain five slices per heart beat. The prevalence of CAD was 51%. They used an MPRI of 1.1 as a cut-off between normal and abnormal myocardium, and obtained sensitivity of 88%, specificity of 90%, and an accuracy of 89% for the detection of CAD. In patients with cardiac syndrome X, Panting et al.[103] identified subendocardial perfusion defects after adenosine vasodilatation, which could explain the angina symptoms and ECG abnormalities in these patients with normal epicardial coronary arteries.

4.2.1 Procedure

The patient is prepared for the scanner following standard procedures, including the checklist of contraindications to CMR. In addition, patients with specific contraindications to adenosine (e.g., bronchial asthma, patients taking dipyridamole) are excluded. Patients are asked to stop caffeine ingestion 24 hours before the examination, because caffeine reduces the vasodilator effects of adenosine. A 12-lead ECG is performed to exclude patients with second- and third-degree heart block. Baseline observations (heart rate and blood pressure) are obtained. Two intravenous cannulae are inserted into large peripheral veins, one connected to a saline-flushed long-line for the adenosine infusion, and the second to the gadolinium pump. Continuous ECG monitoring and automated blood pressure recording are connected. The patient is then positioned in the magnet bore. Using rapid pilot scans for accurate positioning, the perfusion slices are defined – this may include 2–5 short-axis slices, or a combination of short-axis and long-axis slices. A resting perfusion scan is then acquired using a saturation-

recovery or inversion-recovery sequence with ultrafast gradient-echo or EPI. The acquisition is obtained with the patient performing a breath-hold or very shallow breathing, to minimize respiratory artifacts. During the acquisition, gadolinium is injected at a dose of 0.01–0.05 mmol/kg and between 50–60 images are obtained for each slice. The sequential effects of gadolinium on the signal intensity of the blood pool and myocardium are demonstrated in Figure 8.10. After the rest acquisition, it is necessary to wait for 20–30 minutes to allow the gadolinium to disperse from the myocardium, before proceeding to the stress study. The adenosine infusion is then commenced at a rate of 140 µg/kg/min for 4–6 minutes, when the perfusion acquisition is repeated. Blood pressure measurements and continuous ECG monitoring is performed. Once the study is complete, the patient can be removed from the magnet bore and allowed to recover. Analysis of the adenosine perfusion CMR may be performed using a 17-segment model [six basal-, six mid-, and four-apical short-axis segments as well as the apical cap; Figure 8.9 (see color section)]. However, it is important that the images are analyzed with reference to coronary artery territory. The analysis can be performed qualitatively (by visually reviewing the images as a cine-movie; Figure 8.11) or semiquantitatively with the use of signal-intensity-time curves (Figure 8.12). For visual analysis, delayed signal intensity increase in a myocardial segment is consistent with a significant coronary artery stenosis or previous MI. A fixed defect (present on the rest and the stress images) may represent a previous full-thickness or subendocardial MI. This can be demonstrated with "delayed-enhancement" gadolinium imaging, and will exclude artifacts. An inducible perfusion defect (present only on the stress images) represents an area subtended by a critically stenosed coronary artery. Semi-quantitative assessment with signal-intensity-time curves and myocardial perfusion reserve indices can also be used for the detection of coronary artery stenoses.

4.2.2 Advantages of Adenosine Perfusion CMR

Adenosine stress CMR has certain advantages compared with MPS:

- There is no radiation exposure with CMR. This enables the safe study of women of child-bearing age, pregnant women, children, and for many follow-up and research studies that would otherwise represent a significant cumulative radiation dose.
- CMR has superior resolution that results in the ability to detect subendocardial perfusion defects.

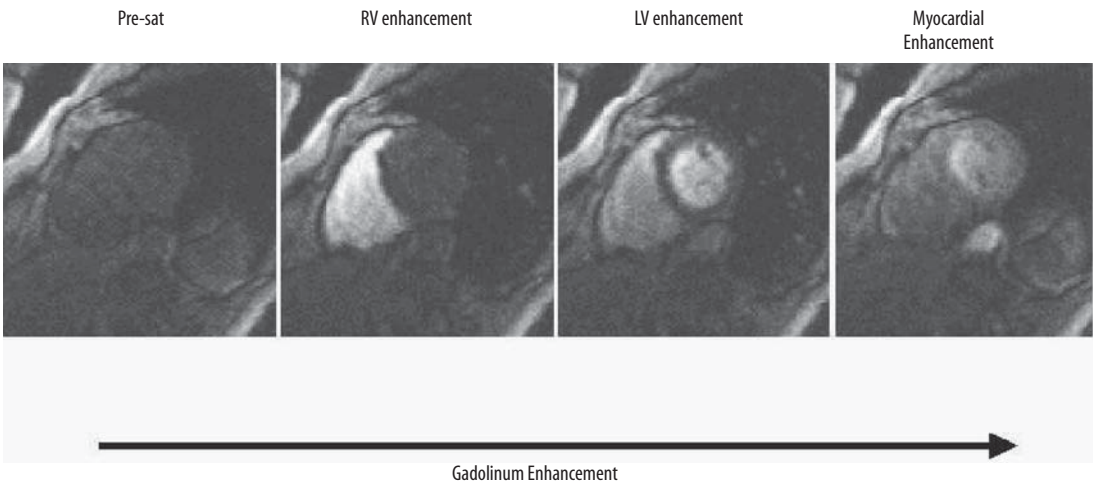

Figure 8.10. Before contrast administration, the saturation pulse nulls signal from the myocardium and blood pool. The gadolinium contrast enters the right ventricular (RV) blood pool producing "white-blood" images. The contrast rapidly transits the lungs and enters the left ventricle. The contrast then produces signal enhancement of the left ventricular (LV) myocardium. In a normal subject, there is uniform enhancement.

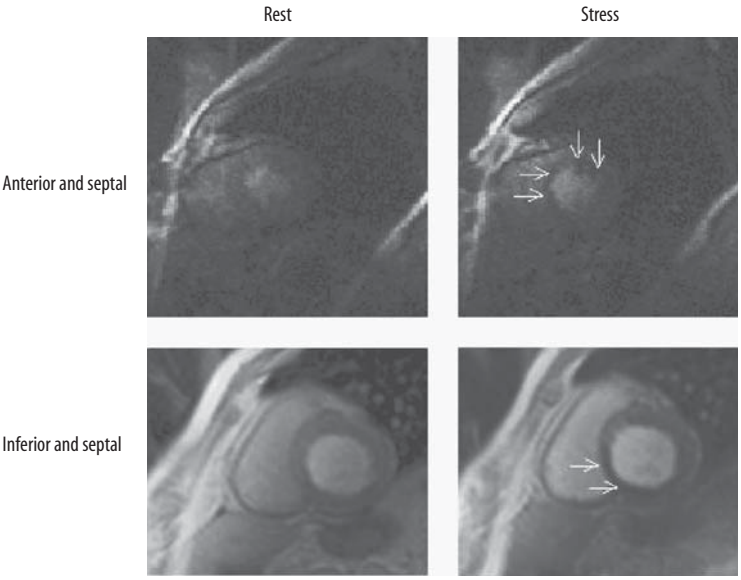

Figure 8.11. CMR perfusion images. The top panel demonstrates an inducible per-fusion defect in the anterior wall and anteroseptum consistent with significant disease in the left coronary artery. The lower panel demonstrates an inducible perfusion defect in the inferior wall and inferoseptum consistent with significant disease in the right coronary artery.

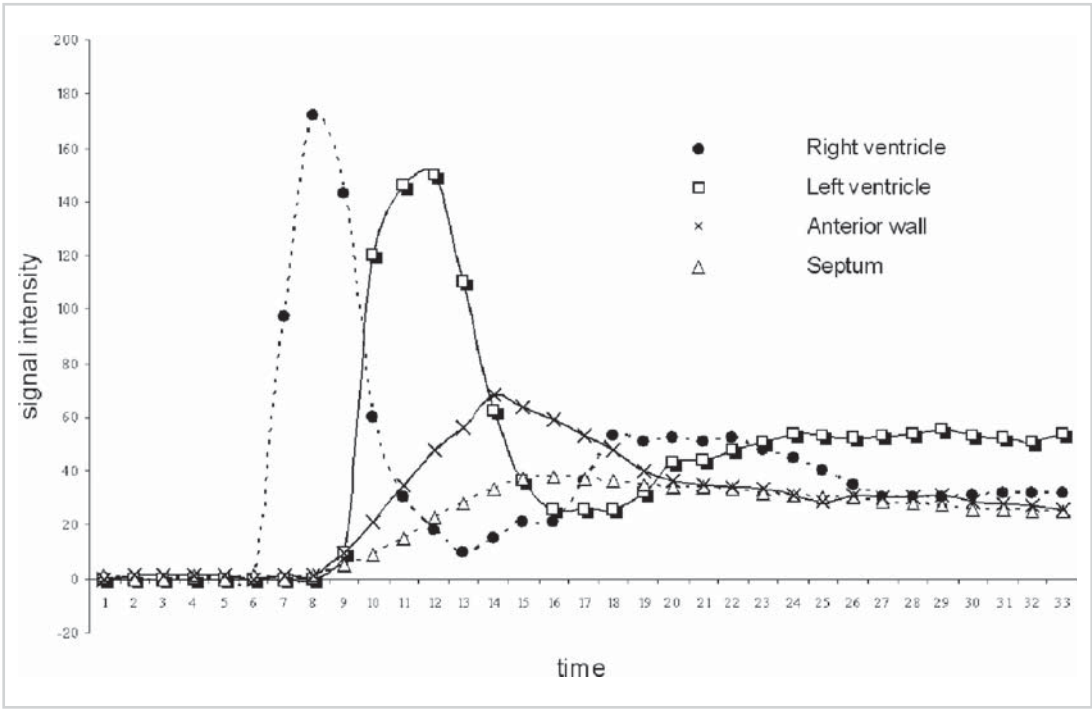

Figure 8.12. Signal-intensity-time curves. The left and right ventricular blood pools show a rapid up-slope and high peak signal intensity. The curve for the anterior wall is much steeper and reaches a higher peak compared with the septum (data plotted for the patient images in Figure 8.11 with an inferior and inferoseptal defect).

- CMR does not suffer from attenuation artifacts caused by breast or diaphragm that can reduce the accuracy of MPS.
- An adenosine perfusion CMR study can be performed in <60 minutes, which makes it more convenient for the patient than either the 1-day or 2-day MPS protocol.

4.2.3 Disadvantages of Adenosine Perfusion CMR

The main disadvantage of adenosine perfusion CMR compared with MPS or DSE is the novelty of the technique and its limited availability.

- SPECT and DSE are established techniques for the detection of CAD for male and female patients. In addition, both have prognostic data that can predict a future high or low likelihood of cardiovascular events.
- At present, there are limited data on detection of CAD in women and on cost-effectiveness.
- Because the administration of adenosine to a patient can produce unpleasant systemic side effects (flushing, abdominal pain, chest pain), patients with significant claustrophobia may not tolerate the scan.

5. Echocardiography

CAD can also be diagnosed with echocardiography by the presence of a regional wall motion abnormality that is seen at rest or during stress. Echocardiography, with its high spatial and temporal resolution, is an ideally suited noninvasive method of assessing such changes in wall motion. In the acute setting, the ability to detect these abnormalities can be very useful in the early detection of myocardial ischemia, even preceding changes on ECG. Equally, in patients presenting acutely with chest pain but inconclusive ECGs, normal regional wall motion may help exclude underlying ischemia. In nonacute situations, the presence of regional wall motion abnormalities and extent of left ventricular wall thinning can provide valuable information regarding the site and severity of damage together with the extent of remodeling. In patients with suspected CAD but no wall motion abnormality at rest, this may be induced by stress testing and detected by echocardiography. The improved image quality, particularly with harmonic imaging has allowed regional wall motion assessment to be much more reliable. Newer techniques that further improve endocardial definition, such as the use of contrast agents, now allow accurate assessment of wall motion in all vascular territories with improved reproducibility.

5.1 Regional Wall Motion Abnormality – How Does It Occur?

There is a well-established relationship between regional coronary blood flow and contractile function in the corresponding territory. In patients with normal coronary arteries, myocardial perfusion is maintained even when the oxygen demands of the tissue are increased. In patients with CAD, resting regional blood flow remains normal, despite severe stenosis of the supplying artery. This is achieved by compensatory vasodilation of the arterioles, which maintains resting MBF until the stenosis severity exceeds 80%–90% (although collaterals may maintain normal MBF even in this situation). As a result, resting wall motion may be entirely normal in patients with significant coronary disease. However, if the oxygen demand of the tissue is increased (e.g., during stress), because the vasodilator response is nearly exhausted, there is an inability to increase myocardial perfusion appropriately to that area. This leads to a reduction in the contractile function of that segment and, hence, to a regional wall motion abnormality. When the oxygen demands of that tissue are reduced and return to normal, there is resolution of the ischemia and wall motion returns to normal. However, severe CAD can give rise to prolonged persistence of wall motion abnormalities.

Acute coronary artery occlusion as seen in acute MI (AMI) leads to a rapid reduction in resting MBF and hence cessation of muscular contraction in the area supplied, leading to a reduction in ventricular function. Relief of the occlusion, either spontaneously or by treatment (such as thrombolysis) can lead to recovery of regional wall motion, but this depends on the duration of the occlusion and the extent of myocardial necrosis that has occurred as a result. The duration and severity of myocardial ischemia determines the degree of wall motion abnormality and indeed wall motion may not return to normal for several hours after the acute episode (“stunned myocardium”).

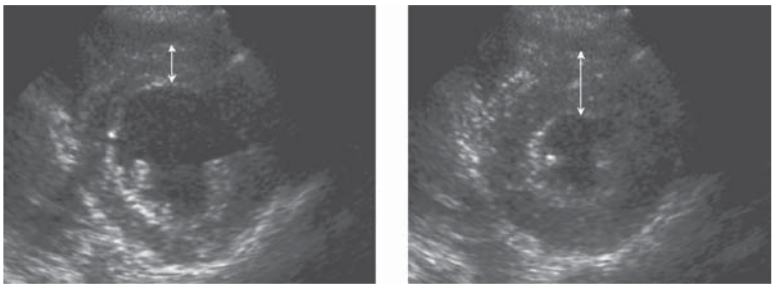

Figure 8.13. Parasternal short-axis views of the left ventricle during (**a**) diastole and (**b**) systole demonstrating normal systolic wall thickening.

In chronic CAD, progressive reduction in MBF caused by the progression of CAD may result in down-regulation of myocardial contractile function with preserved metabolic activity ("hibernating myocardium"). Diminished contractile function in chronic CAD may also occur as a result of myocardial stunning caused by repetitive episodes of ischemia followed by reperfusion. These episodes may either occur at rest (vasospasm) or during increased myocardial oxygen demand such as exercise. The detection of wall motion abnormalities during stress is the basis for diagnosis of CAD in patients without resting abnormalities. The wall motion abnormalities occur early in the "ischemic cascade," preceding ECG changes and symptoms (Figure 8.2).

5.2 Wall Motion Versus Systolic Wall Thickening for the Assessment of CAD

There are some limitations to using wall motion as the sole criterion for ischemia. The movement of any given segment of the ventricle is influenced by the adjacent muscle to which it is attached. For example, in a chamber with a dyskinetic ischemic segment, some of the adjacent normal tissue may appear hypokinetic because its motion is influenced by the attached dyskinetic muscle. The reverse phenomenon can also occur. If vigorously contracting normal muscle is next to an ischemic area, the hyperdynamic segment may pull the ischemic muscle toward the cavity, which may mask the abnormally perfused area. In general, wall motion abnormalities alone overestimate the degree of ischemia seen in the myocardium.

A more specific finding of ischemia is a deterioration of systolic wall thickening. Normal myocardial muscle increases in thickness during systole (Figure 8.13). During ischemia, there is a reduction or absence of systolic wall thickening. Indeed, there may also be systolic thinning during acute ischemia; i.e., wall thickening is greater in diastole compared with systole (Figure 8.14). It has been shown that the extent and severity of wall thickening abnormality

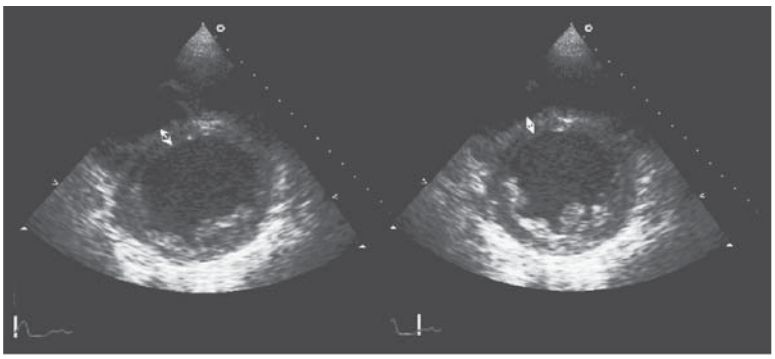

Figure 8.14. Parasternal short-axis views of (**a**) diastole and (**b**) systole of wall thickening in AMI.

is superior to that of wall motion abnormality evaluation for predicting outcome after AMI.[104]

Situations in which wall motion may be abnormal with preserved wall thickening include LBBB, Wolf-Parkinson-White syndrome, and when the patient has a paced rhythm. The presence of preserved systolic wall thickening in these conditions confirms that the wall motion abnormalities are not caused by underlying CAD.

5.3 Basic Anatomy and Echocardiographic Findings

The changes seen in regional wall motion correlate closely with the blood supply to that area of myocardium. Several methods have been used to portray the left ventricle in order that regional wall motion can be accurately described, although the basic principles remain the same. The ventricle is divided into three sections: base, mid-ventricular cavity, and the apex. Each section is then divided into segments that correspond to areas in the left ventricle wall. The most recent recommendations from the ACC and AHA[105] is to use a 17-segment model (Figure 8.15). This divides the base and mid-ventricular cavity into six segments each, with the apical section having four segments. A final segment is a very distal apical "cap" which is best assessed in the apical two- and four-chamber views. Often, a "bull's-eye" plot of all of these segments is used to note the individual segment scores, with the basal segments on the outside, followed by the mid-cavity and then the apex. This allows clear localization of any defect on a single form with an indication of vascular supply (Figure 8.16).

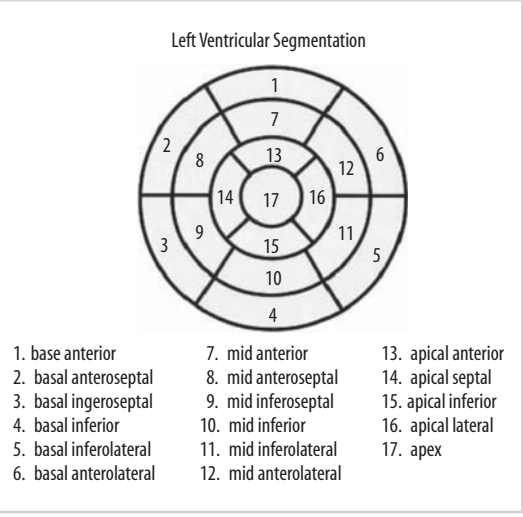

Figure 8.15. Diagram of the "bull's-eye" plot representing the 17 left ventricular segments in the recommended model.[105]

Once these changes have been established, wall motion can be scored according to a four-point semiquantitative scale:

1. Normal
2. Hypokinetic – normally directed motion, but reduced endocardial excursion and wall thickening

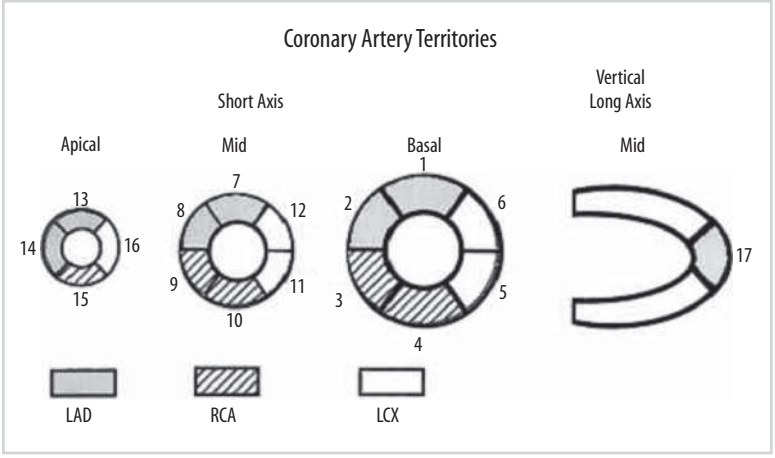

Figure 8.16. Assignment of the 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA), and left circumflex artery (LCx).[105]

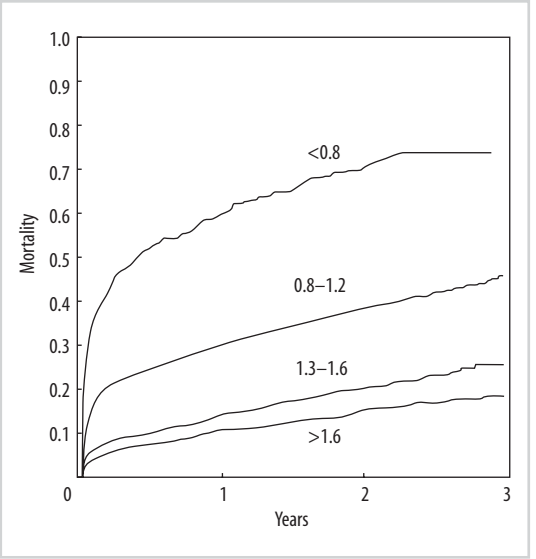

Figure 8.17. Graph demonstrating relationship between mortality and wall motion score index (WMSI).[106] (By permission of Oxford University Press on behalf of The European Society of Cardiology.)

3. Akinetic – absent wall motion/thickening
4. Dyskinetic – systolic bulging of the wall with no thickening

The sum of the individual segment scores gives a wall motion score (WMS), which can be used to give an indication of the severity of ischemia found; a WMS index (WMSI) can also be used (WMS divided by the number of segments assessed) and has been shown to be an important prognostic indicator in patients with CAD (Figure 8.17).[106,107]

5.4 Stress Echocardiography

5.4.1 Procedure and Interpretation

Stress echocardiography, which was first introduced in the early 1980s, has matured over the years as a reliable and cost-effective method for both the diagnosis and risk stratification of patients with suspected or known CAD (see also Chapters 2 and 9). It can be performed in conjunction with dynamic exercise (treadmill or bicycle). In patients who are unable to exercise, pharmacologic agents may be used, i.e., dobutamine or dipyridamole. With any form of stress testing, echocardiographic images are first acquired digitally during rest in parasternal and apical views. These views of the heart visualize all three vascular territories. Subsequently, stress images are acquired during low, intermediate, and peak stress, except for treadmill exercise in which images may be acquired immediately (60–90 seconds) after peak stress for optimal imaging. Stress and rest images are arranged digitally side by side in each view for analysis and archiving.

Rest and stress images are interpreted for global and regional left ventricular size, shape, and function. A normal response is when, during stress, the left ventricular size becomes smaller compared with rest while the shape is maintained and there is increased endocardial excursion and systolic wall thickening (Figure 8.18). Figure 8.19 is an example of a patient who had undergone exercise echocardiography, demonstrating a dilated left ventricular cavity with change in shape with marked reduction of systolic wall thickening of the septum, anterior and inferior wall suggestive of multivessel disease. Prolonged persistence of a systolic wall thickening abnormality may also identify severe CAD.[108]

Dobutamine echocardiography is particularly useful in patients with an existing resting wall thickening abnormality. Low-dose dobutamine increases myocardial perfusion, recruits potentially contractile myocardium, and hence increases myocardial contractility in dysfunctional myocardium if there is sufficient contractile reserve. At high dose, however, dobutamine increases myocardial O_2 demand and, in the presence of a flow-limiting stenosis, will result in demand/supply mismatch leading to myocardial ischemia and hence deterioration of regional function.[109] Thus, dobutamine at low doses depicts the presence of myocardial viability whereas at high dose, myocardial ischemia (biphasic response; Figure 8.20).

Dobutamine is also widely used as an alternative test in patients who are unable to exercise. Figure 8.21 describes the various myocardial responses to dobutamine in patients with and without resting wall thickening abnormality. Dipyridamole is used in some centers as a form of stress test but the study may be negative even in the presence of a significant flow-limiting coronary stenosis.[110]

5.4.2 Accuracy of Stress Echocardiography

The accuracy of stress echo, and other noninvasive imaging tests, for the detection of CAD is

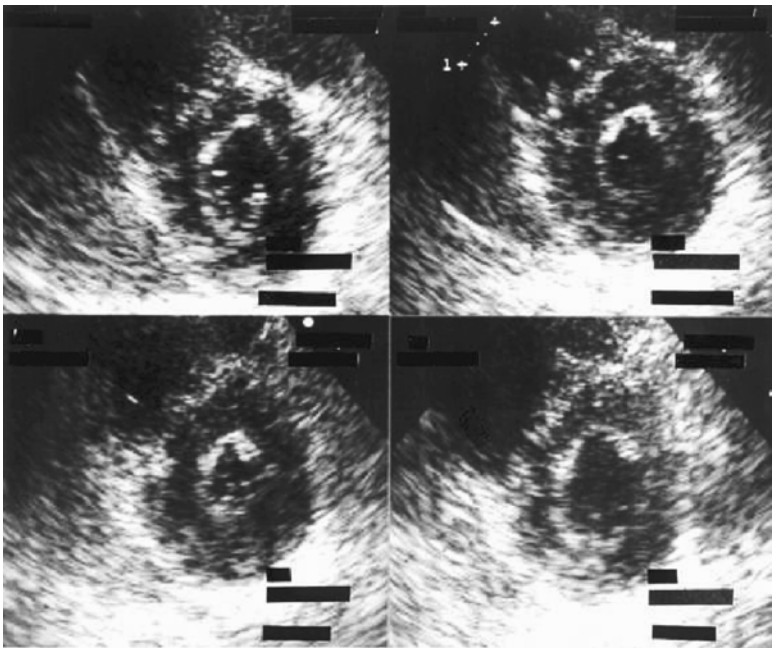

Figure 8.18. A normal left ventricular response during dobutamine stress in the short-axis view. Upper left (rest), upper right (low dose of dobutamine), lower left (high dose of dobutamine), and lower left post-stress.

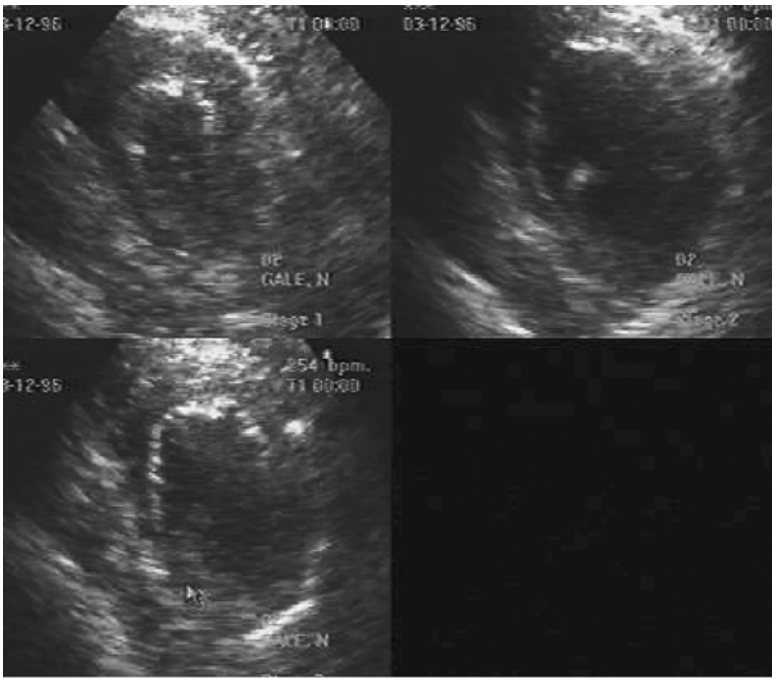

Figure 8.19. Abnormal left ventricular response during exercise. Left (rest); right (60 seconds after exercise). Left ventricle is dilated with severe systolic wall thickening abnormalities affecting septum, anterior and inferior wall, suggestive of multivessel disease.

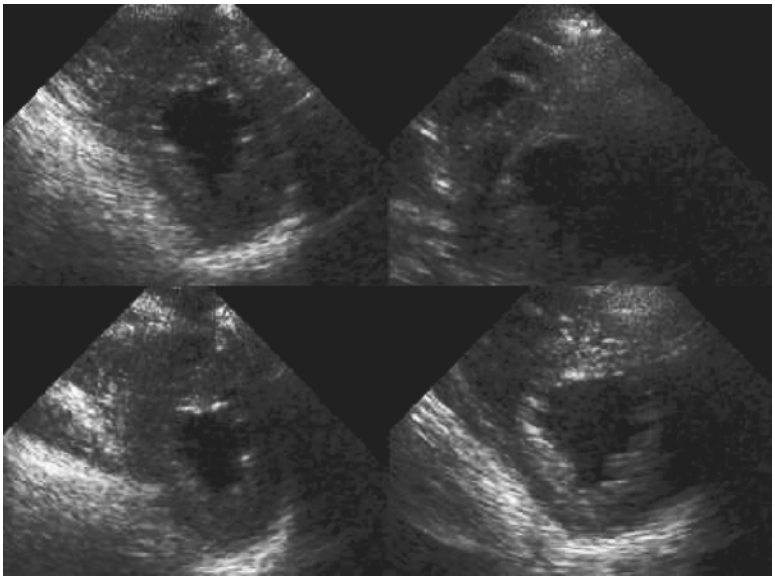

Figure 8.20. Biphasic response during dobutamine stress upper left (rest), upper right and lower left (low dose of dobutamine), and lower right (high dose of dobutamine). There was improvement of systolic wall thickness in a patient with left ventricular dysfunction with deterioration of wall thickness both anteriorly and inferiorly during high dose.

expressed as the sensitivity and specificity of the technique for the detection of angiographically demonstrated stenoses. Nonetheless, this approach has a number of limitations, which are mainly a reflection of the limitations of an angiographic cut-off for significant disease, including the variation of the physiologic effect of a stenosis based on site, length, and vessel size, as well as over- and underestimation of coronary lesion severity.[111] Therefore, it is probably more meaningful to correlate the findings of stress echo (and those of MPS and CMR) with functional and not anatomic parameters derived from coronary angiography (see above, MPS section).

Populations with a high prevalence of multivessel coronary disease and previous MI are more likely to develop ischemia in response to stress, and referral bias may also influence the recorded accuracy. Because stress echo is dependent on the induction of ischemia, the adequacy of stress has a pivotal influence on sensitivity. Finally, accuracy will be influenced by echocardiographic factors including image

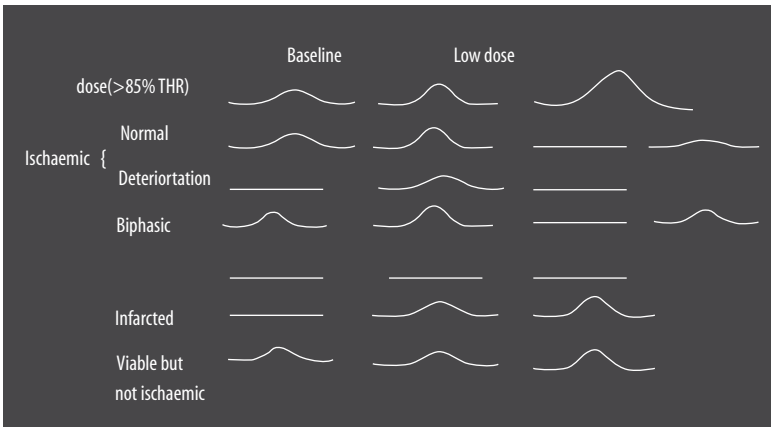

Figure 8.21. Different responses to dobutamine.

Table 8.4. Causes of false-negative and false-positive stress echocardiograms

False negatives	False positives
Inadequate stress	Over-interpretation, interpreter bias
Antianginal treatment (especially beta-blockers)	Localized basal inferior wall abnormalities
Mild stenoses	Abnormal septal motion (LBBB, post-CABG)
Left circumflex disease	Cardiomyopathies
Poor image quality	Hypertensive responses to stress
Delayed images post-stress	

LBBB, left bundle branch block; CABG, coronary artery bypass grafting.

quality and left ventricular morphology; the lateral wall is a frequent site of false negatives and the inferior wall for false positives. Causes of false-positive and -negative tests are listed in Table 8.4.

In studies of exercise echocardiography enrolling many patients (>100 patients), the sensitivity and specificity range from 74% to 97% and 64% to 86%, respectively (Figure 8.22; see color section).[112] Higher sensitivity may be obtained with bicycle exercise (because there is no loss of ischemia in the post-stress period), but this is at the cost of some impairment in specificity. Comparisons with quantitative angiography have shown stenosis diameters of 0.7–1.0 mm to be associated with ischemia.

With DSE, the sensitivity ranges from 61% to 95%, and the specificity from 51% to 95% (Figure 8.22; see color section). The increment in cardiac workload is less with dobutamine than exercise, and sensitivity can be compromised if workload is reduced by medical treatment or dose-limiting side effects. The addition of atropine augments sensitivity. Dobutamine echocardiography is a more sensitive marker of ischemia in lesions involving larger (>2.6-mm diameter) vessels than smaller vessels. The quantitative angiography parameters associated with ischemia are a lumen diameter of <1-mm diameter, percent diameter stenosis of 52%, and percent area stenosis of 75%, of which the minimal lumen diameter is most predictive of an abnormal dobutamine stress test.

The sensitivity and specificity of dipyridamole and adenosine stress echocardiography for the detection of CAD range from 61% to 81% and 90% to 94%, respectively (Figure 8.22; see color section). Some studies with these techniques have included populations with a high prevalence of extensive coronary disease or prior infarction – both of which are associated with a high sensitivity.

5.5 Comparison Between Stress Echocardiography and Radionuclide MPS

Stress echocardiography has been compared with both CMR (see above in the CMR section) and MPS in the setting of CAD. A recent meta-analysis by Geleijnse and Elhendy[113] of seven studies directly comparing exercise echocardiography and exercise MPS revealed comparable sensitivities (78% versus 83%, respectively) and specificities (91% versus 83%, respectively). In the same review, the authors also compared dobutamine echocardiography with dobutamine MPS; in eight studies, they found that dobuta-

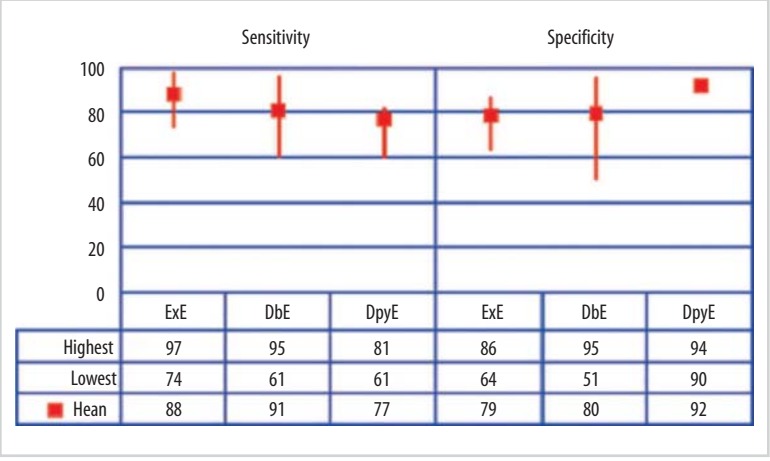

Figure 8.22. Summary of the mean, high, and low values for sensitivity and specificity in studies of >100 patients with exercise (ExE), dobutamine (DbE), and dipyridamole stress echo (DpyE).

mine echocardiography had a lower sensitivity than MPS (80% versus 86%, respectively, $P < .05$), but a higher specificity (86% versus 73%, respectively, $P < .005$).[113] The sensitivity of vasodilator echocardiography, however, was significantly lower than that of vasodilator MPS (66% versus 85%, $P < .0001$) in six studies.[113] This is not surprisingly because adenosine and dipyridamole cause blood flow heterogeneity, which is useful in MPS, but generally do not result in true myocardial ischemia, which is required for causing contractile abnormalities. Another meta-analysis by Schinkel et al.[114] examined 17 studies in which MPS was directly compared with stress echocardiography. Pooled data revealed that MPS was more sensitive than echocardiography (sensitivity 85% versus 80%, respectively, $P < .05$) but less specific (specificity 77% versus 86%, respectively, $P < .001$).

Few studies have directly compared MPS and stress echocardiography in women. One study has shown no significant difference between them,[115] whereas others have demonstrated a superior specificity of dobutamine echocardiography over dobutamine MPS in women.[116,117] It is, however, debatable whether such a comparison is appropriate and more studies are needed to assess fully the relative merits of each technique in this population. Based on the existing data (mainly from subpopulation analysis of mixed-gender studies), however, current European and American guidelines do not favor a superiority of one test over the other and accept that both stress echocardiography and gated SPECT MPS provide accurate diagnostic and prognostic information for women investigated for CAD.

Patients with generalized LVH is a group in which the specificity of MPS can be affected by perfusion defects that are caused by abnormalities in the microcirculation. Dobutamine echocardiography does not have these limitations and although some investigators have found it to be equally effective with MPS for detecting underlying CAD[118] others suggest that the former is probably the technique of choice in this clinical setting.[119]

5.5.1 Limitations in the Diagnostic Use of Stress Echocardiography

Although the presence of CAD is readily recognized in the setting of multivessel disease, and multivessel pathology is readily recognized in the presence of prior infarction ("ischemia at a distance"), the technique has a sensitivity of only 50% for the recognition of the multivessel disease pattern in normal ventricles. The development of global ventricular dysfunction (reduction of ejection fraction or left ventricular enlargement) should increase the interpreter's suspicion of multivessel disease. Clues to the presence of extensive disease despite apparently localized wall motion abnormalities include the early onset of ischemia, at a low heart rate and rate–pressure product, or at a low dose of pharmacologic stressor.

The detection of single-vessel stenoses may also be problematic, and the sensitivity of stress echo is less than that of MPS. This reflects the need for the ischemia to involve a significant area of the myocardium in order for the stress echocardiogram to be positive – which may not be fulfilled if the involved vessel is small or distal, or the stenosis is only mildly flow limiting.

Because of problems posed by identification of minor gradations of wall motion in the setting of abnormal function, the identification of ischemia within areas of resting wall motion abnormalities may be difficult. The problem is probably less significant during dobutamine stress because ischemic segments with abnormal resting function often show a biphasic response.

The last three issues reflect fundamental limitations of an ischemia-based technique,[120] which will require either a more sensitive tool for assessment of wall motion, or combination with a perfusion marker such as contrast echocardiography.

5.6 Stress Contrast Echocardiography

Myocardial contrast echocardiography is a newly developed technique that utilizes intravascular tracers, which are microbubbles (3–5 μ) that can be administered intravenously.[121] During infusion of contrast agent once steady state is reached, the contrast intensity represents microvascular blood volume.[122] During this steady state, microbubbles in the myocardium may be destroyed by a high-energy ultrasound pulse, after which microbubbles can be seen to replenish the myocardium. The rate at which the microbubbles replenish represents myocardial blood velocity.[123] The product of the myocardial blood velocity and

volume represents MBF.[123] It has been shown both experimentally and clinically that flow-limiting CAD can be detected during any form of stress which includes inotropic action, when contrast intensity diminishes because of capillary derecruitment and myocardial blood velocity is slower compared with the normal vascular bed.[124,125] There are several studies that clearly showed that addition of myocardial contrast echocardiography during stress improves the diagnostic value of stress echocardiography.[126–128]

6. Recommendations for Using Noninvasive Cardiac Imaging in Patients Investigated for CAD

Many centers use a staged approach with the exercise ECG being the initial stress test and noninvasive imaging next (usually in the form of stress MPS or stress ECHO) if the likelihood of disease is indeterminate after the exercise ECG, or if further information on myocardial perfusion or function is required to assist management decisions (Figure 8.23). The choice of which test to perform depends greatly on issues of local expertise and available facilities and also on the advantages and disadvantages of each technique discussed above. Noninvasive imaging should be the initial investigation in patients who are unlikely to exercise adequately and if the exercise ECG will be uninterpretable because of resting abnormalities such as LBBB, preexcitation, LVH, or drug effects.[5] For symptomatic female patients, there is a broad consensus on the use of either stress MPS or ECHO as a first-line investigation when the resting ECG is abnormal and, although more widespread use may be justified, there is some controversy on the strength of the existing evidence for supporting the primary use of these two tests in all female patients.[20b,68] At present, there is no strong evidence to justify the use of EBCT or MS-CT for the patients discussed here. It is conceivable, however, that as these techniques become more mature, they will find their place in the management algorithm. A suggested example of potential use is the group of individuals who on the basis of symptoms and risk-factor profile are judged to have a rather low pretest probability of coronary heart disease. Such patients are usually directed to an exercise ECG which does not possess an optimal specificity value that is essential in this clinical setting (see also previous chapter).

Of course, there will always be patients with symptoms but negative results on conventional imaging, on which occasion and, depending on clinical judgment, assessment of the endothelial function or microvascular circulation may

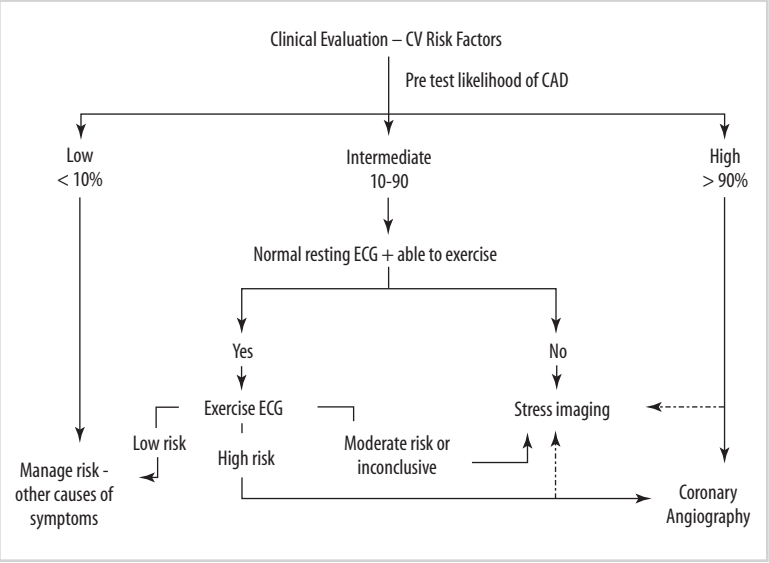

Figure 8.23. According to the ACC/AHA class I recommendations, patients should be classified into three categories based on clinical and cardiovascular risk-factors assessment: 1) low pretest likelihood of coronary artery disease (CAD) does not warrant further cardiac evaluation. Management of modifiable risk factors is recommended. 2) Patients with a high probability of CAD should be referred for coronary angiography. 3) Patients with an intermediate likelihood and a normal resting ECG who are able to exercise should undergo exercise ECG. Stress imaging is recommended in patients with an abnormal resting ECG, and in those unable to exercise adequately. Stress imaging is also indicated in patients with a moderate-risk treadmill score for further stratification, and for the assessment of the extent and severity of myocardial ischemia in patients referred for coronary angiography.

be appropriate. Brachial artery reactivity or coronary flow reserve testing (invasively by catheterization or noninvasively with special echocardiography, CMR, or PET techniques) are useful tools, and their role in this group of patients will be covered in Chapter 14.

7. Conclusions

Stress MPS, ECHO, and CMR are highly effective in diagnosing CAD. An inducible perfusion or contraction abnormality indicates impaired perfusion or contractile reserve, which in turn usually corresponds to epicardial coronary obstruction. The site and severity of the abnormality provide diagnostic and management information. Conversely, a normal result in a study that has been performed appropriately indicates the absence of coronary obstruction and hence of clinically significant disease. MPS is the most mature technique providing not only high diagnostic accuracy but also invaluable prognostic information stronger than any other technique for the management of patients investigated for CAD. Stress echocardiography has become an important counter player in this field because of its versatility and availability. In the hands of skillful operators, its diagnostic accuracy is comparable to that of MPS. CMR has been used less than the other two techniques in clinical practice, but with continuous improvements in the technology and skills of the operators and also increasing availability, it will have a more important role in the years to come. It is more versatile than MS-CT, allowing not only visualization of the coronary vessels but also assessment of perfusion, which is important for accurate assessment of the functional significance of a coronary lesion and hence for management decisions. However, combination of the latter with PET (PET/CT) offers a unique opportunity for a comprehensive imaging of cardiac morphology, perfusion, and function. It is difficult to predict the exact role of each technique in the years to come, and comparative data from good quality studies on clinical and cost effectiveness of the various imaging techniques in different subgroups of patients are still sparse. On the whole, however, it is expected that ongoing refinement of the existing techniques and introduction of new agents will allow a more accurate evaluation of different aspects of the wide spectrum of CAD and will pave the way toward molecular targeted cardiac imaging, thus increasing even further the diagnostic and prognostic value of noninvasive imaging.

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