chapter 9

Chronic Coronary Heart Disease

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Myocardial Ischemia
Noninvasive Evaluation
Detection of Coronary Artery Disease
Imaging Techniques Used to Assess Prognosis of Patients with Chronic Coronary Artery Disease
Assessment of Myocardial Viability
Preoperative Cardiac Risk Evaluation for Noncardiac Surgery
Risk Assessment in Women

During myocardial ischemia, an imbalance occurs between myocardial oxygen supply and demand. Because the heart is an aerobic organ and relies almost exclusively on the oxidation of substrates for the generation of energy, it can develop only a small oxygen debt. The common clinical condition associated with anaerobic metabolism is an uncomfortable sensation in the chest, usually brought on by effort, called angina The underlying problem is usually disease of the coronary arteries or coronary atherosclerosis in which an abnormal narrowing of the coronary arteries decreases the blood supply to the myocardium to cause ischemia. Thus, the oxygen supply to the myocardial cells also falls, with anaerobic glycolysis and lactate production. Traditional objective methods used to determine the presence of ischemic heart disease include the measurement of metabolic products in the coronary venous drainage and contrast coronary angiography. Noncatheterization methods to detect ischemic heart disease depend on determinations of the consequences of altered regional coronary blood flow such as reduction in ventricular function or electrocardiographic changes from rest to stress (Figure 9-1). In addition to electrocardiograms acquired at rest and during stress, several cardiac imaging techniques are routinely used in clinical practice.

Because the objective demonstration of ischemia by electrocardiograms or cardiac imaging is associated with a significantly higher patient morbidity and mortality, the cellular basis of ischemia will be reviewed, and then the noninvasive techniques currently available for evaluating patients with possible ischemic heart disease will be outlined. The focus will be on the detection of ischemic heart disease and the determination of myocardial viability and prognosis.

MYOCARDIAL ISCHEMIA

In the heart, increased oxygen demands must be met almost entirely by increased coronary flow. The contractile function of myocardial cells becomes impaired during an ischemic insult lasting as little as 1 to 2 seconds, because anaerobic metabolism cannot adequately satisfy the metabolic demands of heart cells, and the heart cannot incur an oxygen debt. The detrimental effects of ischemia are usually reversible, but after periods of ischemia as short as 20 to 40 minutes, necrosis of myocardial tissue results. Most of the myocardial cell's energy use goes to maintain the contractile state. If energy is not constantly replenished by oxidative metabolism, energy stores will fall, metabolic by-products accumulate, and contractile activity declines. Although technically difficult, direct serial tissue measurements of myocardial energy stores (creatine phosphate and adenosine triphosphate) can provide a sensitive guide to the presence or absence of ischemia. Other less direct metabolic measures of ischemia include local Pco_2, lactate production, lactate/pyruvate ratio, potassium release, or phosphate release. However, most measurements that require myocardial sampling can only be used in experimental animals. Clinically, measurements of metabolites in coronary sinus blood require cardiac catheterization and can be altered by conditions other than ischemic heart disease, which makes direct evaluation of myocardial metabolism generally impractical in humans.

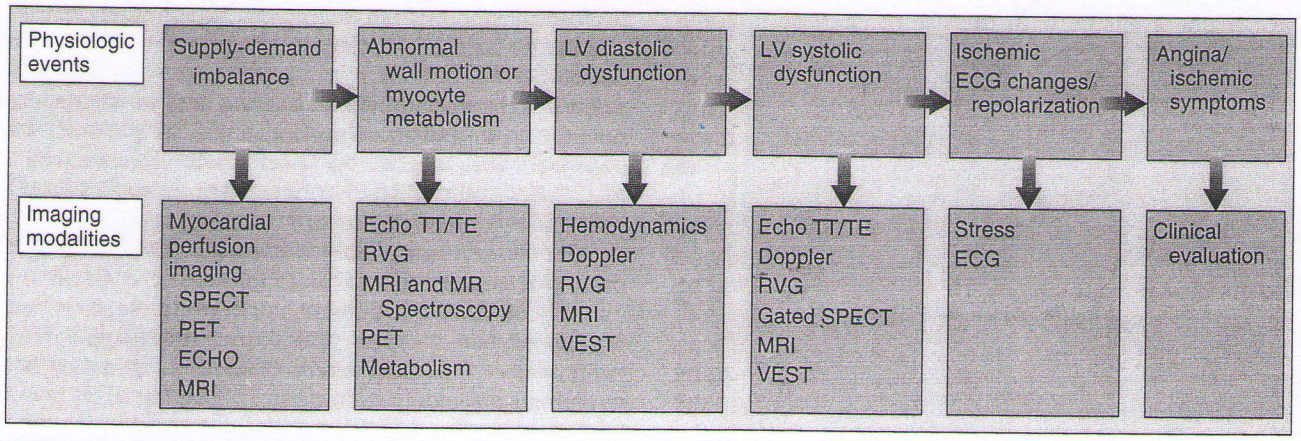

FIGURE 9-1. Schematic diagram of the cascade of physiological events during myocardial ischemia and the imaging correlates. Abn, abnormalities; ECG, electrocardiogram; LV, left ventricle; MRI: magnetic resonance imaging; RVG, radionuclide ventriculography; TT, transthoracic; TE, transesophageal; Vest, ambulatory radionuclide ejection fraction.

NONINVASIVE EVALUATION

Exercise Testing

Electrocardiogram

The pioneering work started by Master has led to an established role for the electrocardiogram-monitored exercise-stress test in the evaluation of ischemic heart disease. There are reports that question the usefulness of exercise testing, especially in populations in which ischemic heart disease would be expected to have a low prevalence. Nevertheless, dynamic exercise-stress testing supplies information useful for evaluating the predisposition to ischemia during normal daily activity. Most of the published reports in this field support the conclusion that ischemic heart disease is present when typical angina and reversible ST depression occur during a stress test.[1] In addition, a multifactor analysis of the entire stress test findings can improve the overall accuracy of an exercise evaluation and estimate prognosis.

The sensitivity of electrocardiographic testing for detecting coronary artery disease has in large part been based on the findings noted on coronary angiography. There are several potential problems with this analysis: (1) the presence of arterial stenoses does not necessarily imply that a region of myocardial tissue is ischemic, but rather that there is a potential for the attenuation of regional coronary reserve capacity; (2) electrochemical changes (ST depression) may not occur until the contractile state is already impaired, which suggests that a certain level of cellular ischemia must be reached before clinically apparent electrocardiographic changes; and (3) the effect of coronary collateral flow supply to the myocardium distal to a stenosis and the extent of small vessel disease is difficult to interpret. Therefore, one can conclude that in patients with angiographic coronary stenoses, the sensitivity of electrocardiographic evidence of ischemia ranges from 49% to 80%, and the specificity of this test is 41% to 95% (when 1 mm of ST depression was defined as a positive result).

Imaging

There are certain factors such as abnormal resting electrocardiogram, prior myocardial infarction, hyperventilation, neurasthenia changes, drug intake, and left ventricular hypertrophy that can make electrocardiographic interpretation difficult. It is in these more difficult cases and in patients with intermediate risk factors that noninvasive cardiac imaging can provide much greater diagnostic information.

The sequence of events occurring during the genesis of regional myocardial ischemia (Figure 9-1) emphasizes the concept that regional abnormalities in myocardial perfusion comprise a continuum from minor relative differences in flow without metabolic or regional functional consequences to the full expression of myocardial ischemia with systolic and diastolic dysfunction, electrocardiographic signs, and angina. Seminal studies of coronary blood flow in the early 1970s demonstrated that whereas a diameter stenosis of approximately 80% to 90% was necessary to induce a detectable regional coronary flow abnormality at rest, a stenosis on the order of approximately 50% diameter narrowing would result in regional flow disturbances during pharmacologically induced hyperemia. Radionuclide techniques evaluated myocardial perfusion and have been widely applied in the study of coronary blood flow in humans during stress. The concepts derived in animal models regarding the degree of stenosis required to induce a physiological flow abnormality during hyperemic stress were applied to radionuclide perfusion imaging studies, so that a 50% diameter stenosis on a coronary angiogram became the "gold standard" against which myocardial perfusion imaging was often tested. Other imaging modalities, including echocardiography and cardiac magnetic resonance imaging, are also being used to evaluate myocardial perfusion and with more widespread availability could reach the large population now being served with radionuclide techniques.

After perfusion imaging started, the ability to evaluate regional and global systolic ventricular myocardial func-

tion became available with the use of exercise radionuclide angiography, echocardiography, and, more recently, magnetic resonance imaging. These techniques were also applied to the study of patients with known or suspected coronary disease to find a noninvasive diagnostic modality that would also be more efficacious than an exercise electrocardiogram. This is accomplished by measuring a physiological parameter that occurs earlier in the sequence of events after a regional supply/ demand imbalance than the ischemic ST depression detected by electrocardiography or by symptoms of angina.

Conceptually, on the basis of the cascade of myocardial cellular dysfunction, myocardial perfusion imaging should be the most sensitive technique to detect the presence of an epicardial coronary stenosis, with the study of stress regional wall motion abnormalities the next most sensitive, and exercise electrocardiograms the least sensitive. To some degree, this is reflected in numerous studies evaluating the sensitivities for detecting coronary artery disease and particularly the findings in several studies that myocardial perfusion imaging detects coronary disease more efficiently at lower workloads than functional imaging or exercise electrocardiography. Furthermore, positron emission tomographic (PET) techniques are likely to be the most sensitive, because absolute values of regional coronary flow reserve can be quantitated, presumably detecting more modest heterogeneities in regional flow during a hyperemic stress.

DETECTION OF CORONARY ARTERY DISEASE

Identification of traditional and newer risk factors for coronary artery disease is the first step in the evaluation of an individual's risk for having coronary artery disease. Those include advanced age and male gender, hypertension, hypercholesterolemia, family history of coronary artery disease in first-degree relatives younger than the age of 60, diabetes mellitus, smoking, obesity, sedentary lifestyle, and elevated homocysteine. Various clinical prediction models can be subsequently applied to further stratify patients into low, intermediate, and high risk for future cardiac events, including cardiac death and nonfatal myocardial infraction on the basis of these risk factors. A modified version of the Framingham risk score has been incorporated into the Third Report of the National Cholesterol Education Program (NCEP Guidelines) to estimate the 10-year risk for coronary artery disease developing.[2]

Although it is well recognized that sensitivity and specificity define the quality of a diagnostic test, the result cannot be satisfactory interpreted without additional knowledge of the prevalence of disease in a given population. Defining the pretest likelihood of coronary artery disease in a certain individual and determining the posttest probability after a positive or negative result is a key feature and is based on the concepts included in Bayes' theorem of conditional probability, and it is now well appreciated that cardiac imaging is of particular importance in patients at intermediate risk (those with pretest probability between 20% and 80%), because a positive or a negative result influences further treatment decisions.

The decision to perform a stress test to obtain diagnostic and/or prognostic information in patients with chronic stable angina has been carefully reviewed in ACC/AHA guidelines.[3] There are also ACC/AHA Guidelines for exercise testing[1] and for the clinical use of radionuclide imaging[4] and prognostic risk indices developed for stress echocardiography.[5] There is also an expert consensus document concerning electron-beam computed tomography (EBCT) for the diagnosis and prognosis of coronary artery disease.[6] In general, these guidelines strongly recommend an imaging study as part of the evaluation in patients who are unable to exercise and in those with baseline electrocardiographic abnormalities (preexcitation, paced ventricular rhythm, >1 mm of resting ST-segment depression, complete left bundle branch block). The use of digoxin or the presence of left ventricular hypertrophy also decreases the specificity of exercise testing, whereas sensitivity may remain unaffected. Several other subsets of patients benefit incrementally with the use of cardiac imaging. Those groups involve patients with prior myocardial infarction, revascularization procedures (coronary artery bypass grafting [CABG] or percutaneous transluminal coronary angioplasty [PTCA]), known significant disease (for identification of the "culprit" lesion causing ischemia), diabetes, and patients with a previous positive imaging study (Box 9-1). At present, there are no specific guidelines for cardiovascular magnetic resonance (CMR) imaging, but information on this technique is included in this chapter for general information purposes and the expectation that this technique will play a more important role in routine clinical cardiology practice.

EBCT

The early detection of coronary atherosclerosis would seem desirable particularly among selected individuals

BOX 9-1 INDICATIONS FOR THE USE OF CARDIAC IMAGING RATHER THAN EXERCISE ELECTROCARDIOGRAPHY

- Complete left bundle-branch block
- Electronically paced ventricular rhythm
- Preexcitation (Wolff-Parkinson-White) syndrome or other, similar electrocardiographic abnormalities
- More than 1 mm of ST-segment depression at rest
- Inability to exercise to a level high enough to give meaningful results on routine stress electrocardiography*
- Angina and history of revascularization†

*Patients with this factor should be considered for pharmacological stress tests.

†In patients with angina and a history of revascularization, characterizing the ischemia, establishing the functional effect of lesions, and determining myocardial viability are important considerations.

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

who are either at increased risk for the development of overt coronary artery disease on the basis of established clinical risk factor algorithms or have a strong genetic predisposition for premature coronary artery disease. The theoretical purpose behind screening is to (1) identify early atherosclerosis and potentially prevent its progression through intensive risk factor modification and (2) identify asymptomatic individuals with advanced atherosclerosis and silent myocardial ischemia who might benefit from antiischemic medical therapy and/or coronary revascularization.

EBCT is a simple, rapid, reproducible, and highly specific technique for the detection of early coronary atherosclerosis based on the presence and extent of coronary artery calcification.[7] Unlike spiral CT scanners, where image acquisition speed is limited by the mechanical rotation of the X-ray tube, EBCT uses electron beam technology with a <50-ms image acquisition time. Such rapid imaging allows a "freeze-frame" image of the myocardium and coronary arteries in end-diastole and literally eliminates distortion or blur from cardiac motion. Contrast angiography has also been successfully performed with EBCT to visualize both coronary artery bypass grafts and native coronary arteries.[8]

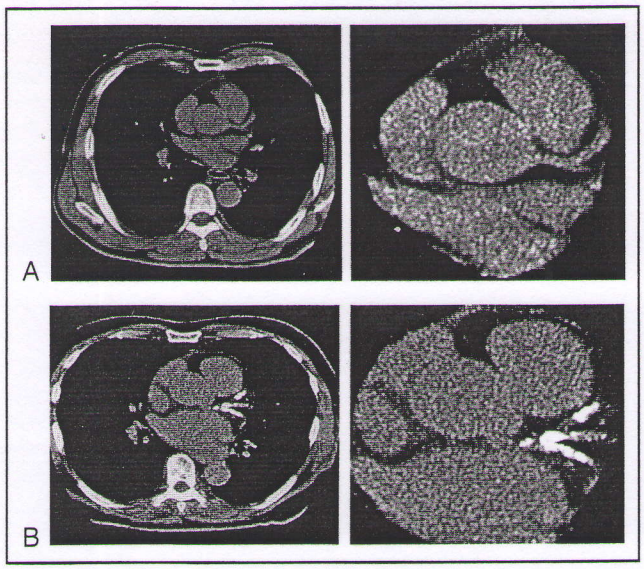

FIGURE 9-2. Single-level noncontrast EBCT scan of a normal subject *(top)* and an individual with severe coronary artery calcification *(bottom)*. Calcium is shown as intensely white areas within the coronary arteries.

Coronary Artery Calcification

The standard EBCT imaging protocol is to acquire 40 consecutive 3-mm-thick images at a rate of 100 ms/image from the base of the heart to just below the carina. Images are obtained at end-inspiration with electrocardiographic gating at end-diastole to accept beats within 80% of the predetermined RR interval. A calcified lesion is generally defined as either two or three adjacent pixels (0.68 to 1.02 mm^2 for a 512^2 reconstruction matrix and a camera field size of 30 cm) of >130 Hounsfield units (HU). The traditional Agatston scoring system multiplies each calcified lesion by a density factor as follows: 1 for lesions with a maximal density between 130 and 199 HU; 2 for lesions between 200 and 299 HU; 3 for lesions between 300 and 399 HU; and 4 for lesions >400 HU. The total coronary artery calcium score is calculated as the sum of each calcified lesion in the four main coronary arteries over all the consecutive tomographic slices (Figure 9-2).

The Agatston-derived coronary artery calcium score correlates extremely well with calcified areas found in individual coronary arteries as determined by histomorphometric measurements (Figure 9-3). Furthermore, excellent interobserver and intraobserver reproducibility is reported for recalculating the coronary artery calcium score on a single scan by use of the Agatston method. Temporal variability does exist when performing sequential imaging in the same patient, but this is primarily limited to patients with a very low initial coronary artery calcium score. Coronary artery calcium score variability has been demonstrated to be inversely related to the absolute value of the coronary artery calcium score and is greatest when the score is <10 (Figure 9-4).

A newer volumetric calcium scoring system calculates the volume of calcified plaque area rather than generating a coronary artery calcium score on the basis of an arbitrary plaque attenuation coefficient (i.e., Agatston method).[9] EBT shows promise in potentially tracking changes in calcified plaque.[10]

Calcium Score and Atherosclerotic Plaque Burden

The presence of coronary artery calcification indicates the presence of coronary atherosclerosis, and the coronary artery calcium score severity is directly related to the total atherosclerotic plaque burden present in the epicardial coronary arteries. Calcification is an active, organized, and regulated process occurring during atherosclerotic plaque development in which calcium phosphate in the form of hydroxyapatite precipitates in atherosclerotic coronary arteries in a similar fashion as observed in bone mineralization. Although lack of calcification does not categorically exclude the presence of atherosclerotic plaque, calcification occurs exclusively in atherosclerotic arteries and is not found in normal coronary arteries.

The presence and extent of histologically determined atherosclerotic plaque area has been compared with the total calcium area as assessed by EBCT in individual coronary arteries derived from autopsied hearts. A strong linear relation exists between the extent of total plaque area and coronary artery calcification in individual hearts and in individual coronary arteries. However, the total calcium area underestimates the total plaque area because of the presence of approximately five times as many noncalcified as calcified plaques. On the basis of current EBCT imaging protocols, small plaque areas of <5 mm^2 are generally not detected.

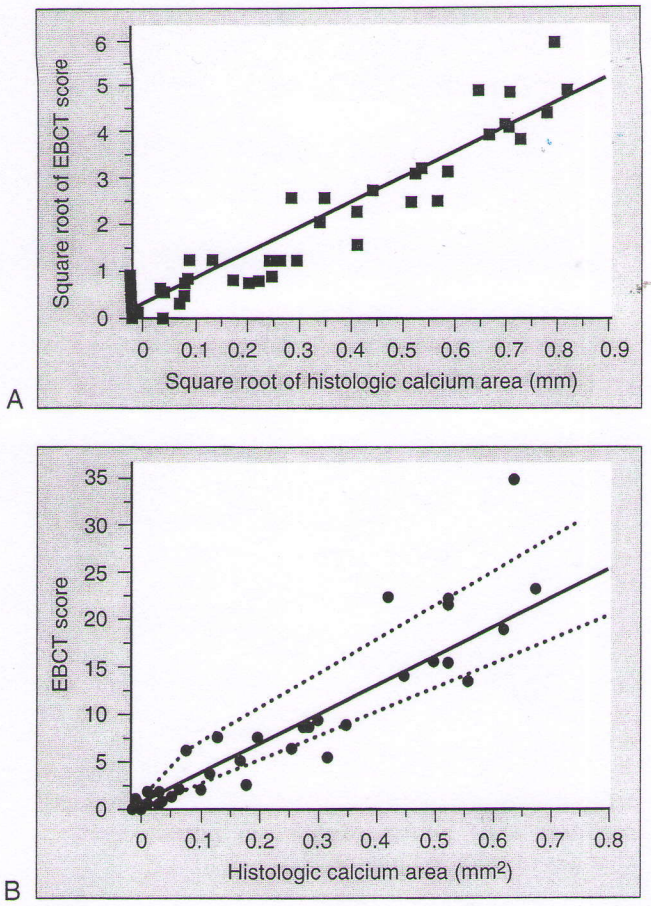

FIGURE 9-3. Linear regression comparing the EBCT coronary artery calcium score (square root transformation and actual data[2]) with the calcium area measured at histomorphometric examination. There is an apparent high-positive correlation between the EBCT calcium score and histomorphometric calcium area (r^2 = .92, r = .96; P < 0.0001). (From Mautner GC, Mautner SL, Froehlich J, Feuerstein IM, Proschan MA, Roberts WC, et al. Coronary artery calcification: assessment with electron beam CT and histomorphometric correlation. *Radiology* 1994; 192[3]:619.)

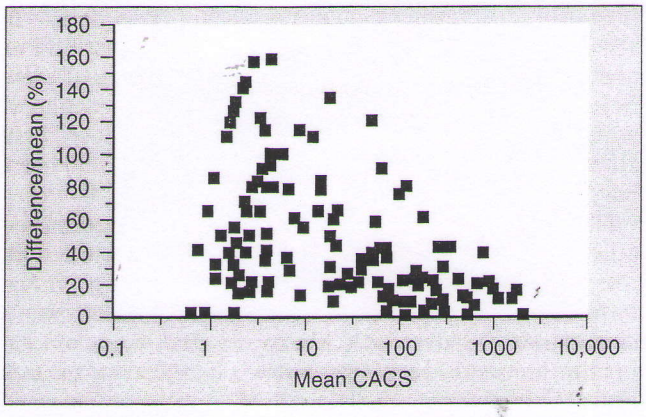

FIGURE 9-4. Graph depicts variability in sequential coronary artery calcium score results as a percentage of the mean coronary artery calcium score. Most variability in coronary artery calcium score is observed in subjects with an initial low score (<20). (From Bielak LF, Kaufmann RB, Moll PP, McCollough CH, Schwartz RS, Sheedy PF. Small lesions in the heart identified at electron beam CT: calcification or noise? *Radiology* 1994; 192[3]:631.)

Comparison of Coronary Artery Calcium Score and Angiography

Significant (>50%) coronary artery stenosis by angiography is almost universally associated with the presence of coronary artery calcium. However, stenosis severity is not directly related to the total coronary artery calcium score. A recent morphological study from autopsied hearts found a poor relationship between coronary stenosis severity and coronary artery calcium score, indicating the latter could not be used to estimate angiographic stenosis severity on a segment-by-segment basis. One explanation is that coronary artery diameter increases with increasing plaque burden, so as to maintain luminal patency. Although the extent of coronary calcification does not precisely predict stenosis severity, noncalcified plaques are almost universally associated with <50% diameter stenosis and typically <20% stenosis. Therefore, the lack of coronary calcification predicts a very low likelihood of obstructive coronary artery disease.

Clinical angiographic trials confirm the relationship between coronary artery calcium score severity and the presence of significant (≥50%) stenosis.[11] The likelihood of multivessel coronary artery disease increases with the calcium score in both men and women. A normal EBCT indicates a very low (<1%) risk of significant coronary artery disease. Although significant differences in coronary artery calcium score are noted among men and women, EBCT does predict significant coronary artery disease equally well in both genders on the basis of age-specific coronary artery calcium score thresholds (Figure 9-5). In the 15 largest studies evaluating EBCT and coronary angiography, the overall sensitivity and specificity for detecting obstructive (>50%) coronary artery disease were 97% and 39%, respectively (Table 9-1). The poor specificity of EBCT is not unexpected, because the presence of coronary calcification confirms the presence of atherosclerotic plaque that may not necessarily be obstructive in nature. Coronary artery calcium score severity may be a better barometer of obstructive coronary artery disease than the mere presence of calcium. Several reports in patients referred for coronary angiography have found that a coronary artery calcium score >100 best predicts obstructive coronary artery disease with an equally high sensitivity and specificity of 80%. There seems to be a threshold coronary artery calcium score above which most patients will have significant coronary artery stenosis. However, this may be gender-related and age-related (Figure 9-5). Despite the relationship between obstructive coronary artery disease and coronary artery calcium score severity, the latter is still too imprecise in itself to be used as a definitive criterion for proceeding directly to coronary angiography in asymptomatic persons.[12]

Coronary Artery Calcium Score and Stress Testing

Although patients with a normal EBCT are highly unlikely to have significant coronary artery disease and

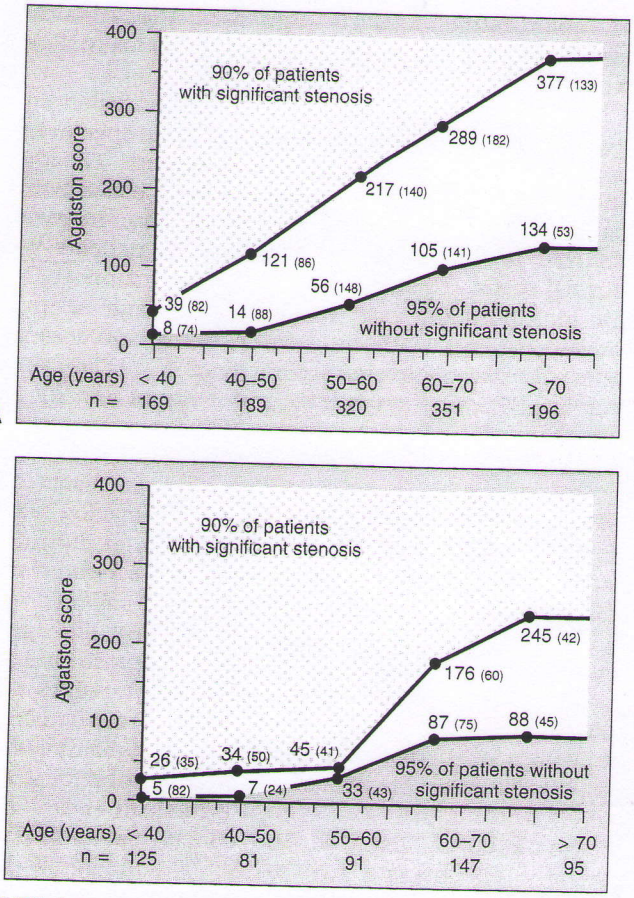

FIGURE 9-5. Diagnostic yield of calcium screening in symptomatic men **(A)** and women **(B)**. The lower scores define the calcium score thresholds for the 95% of patients without significant stenoses. The higher scores give the calcium score thresholds for the 90% of patients with significant stenoses. Within the central area, the diagnosis is uncertain. The numbers in parentheses give the number of patients within the area. For example, a man at the age of 50 years is probably free of coronary stenosis if his score is <56. At score values >217, he bears a high risk of stenosis. (From Haberl R, Becker A, Leber A, Knez A, Becker C, Lang C, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol* 2001; 37[2]:451. Reproduced with permission.)

require no further cardiac testing, an important clinical question is how best to proceed in patients with an abnormal EBCT who will have varying coronary artery calcium score severities. To proceed with invasive testing in this latter population is not warranted on the basis of the large degree of overlap between calcium scores and the presence of obstructive coronary artery disease. An alternative approach might be to perform noninvasive testing in selected patients at high risk for having myocardial ischemia on the basis of specific coronary artery calcium score thresholds. Stress myocardial perfusion imaging is one such well-established noninvasive technique for detecting the presence and determining the prognostic significance of coronary artery disease. Stress myocardial perfusion imaging can define high-risk and low-risk asymptomatic patients on the basis of the presence and extent of inducible myocardial ischemia. Although not recommended as a

TABLE 9-1 ACCURACY OF EBCT CORONARY ARTERY CALCIFICATION IN DETECTING SIGNIFICANT (>50%) CORONARY ARTERY STENOSIS AS DEFINED BY ANGIOGRAPHY

Study author/ year	*N*	Sensitivity (%)	Specificity (%)	Positive PA	Negative PA
Agatston 1990[a]	584	96	51	31	98
Breen 1992[b]	100	100	47	63	100
Bielak 1994[c]	160	96	45	57	93
Kaufman 1995[d]	160	93	67	81	86
Rumberger 1995[e]	139	98	39	59	97
Braun 1996[f]	102	93	73	93	73
Budoff 1996[g]	710	95	44	72	84
Detrano 1996[h]	491	95	31	51	89
Fallavollita 1996[i]	106	85	45	66	70
Baumgart 1997[j]	57	97	21	56	86
Kennedy 1998[k]	368	96	31	51	90
Schmermund 1997[l]	118	95	88	99	58
Haberl 2001[m]	1764	99	30	62	98
Bielak 2000[n]	213	99	39	64	98
Shavelle 2000[o]	97	96	47	80	82
Total	5169	97	39	61	92

PA, Predictive accuracy; [a]*J Am Coll Cardiol* 1990; 15:827; [b]*Radiology* 1992; 185:435; [c]*Radiology* 1994; 192:631; [d]*Mayo Clin Proc* 1995; 70:223; [e]*Circulation* 1996; 91:1363; [f]*Am J Kidney Dis* 1996; 27:394; [g]*Circulation* 1996; 93:898; [h]*J Am Coll Cardiol* 1996; 27:285; [i]*Circulation* 1994; 89:285; [j]*J Am Coll Cardiol* 1997;30:57; [k]*Am Heart J* 1998; 135:696; [l]*Circulation* 1997; 96:1461; [m]*J Am Coll Cardiol* 2001; 37:451; [n]*Circulation* 2000; 102:380; [o]*Am J Cardiol* 1995; 75:973.

screening test in asymptomatic patients because of the low prevalence of a positive test result (<5%), perfusion imaging might be used as a secondary test to identify myocardial ischemia once a certain threshold of atherosclerotic plaque burden had been identified by EBCT.

In a generally asymptomatic population who had risk factors for coronary artery disease development, the complimentary roles of EBCT and stress myocardial perfusion single photon emission computed tomography (SPECT) for identifying both preclinical coronary artery disease and silent myocardial ischemia were assessed.[13] The investigators attempted to identify patients with preclinical coronary artery disease who might benefit from aggressive risk factor modification and those at relatively higher short-term risk for cardiac events on the basis of the presence of silent myocardial ischemia. Among the 3895 subjects who had EBCT, 411 also underwent stress SPECT within a close temporal period (median, 17 days). Although only 22% of 374 subjects with an abnormal EBCT had an abnormal SPECT, the likelihood of an abnormal SPECT increased dramatically with the total coronary artery calcium score (Figure 9-6). Although only 1% of subjects with a total coronary artery calcium score <100 had an abnormal SPECT myocardial perfusion imaging (MPI), this was observed in 46% of those with scores ≥400. However, 10% of all 3895 subjects scanned with EBCT had a coronary artery calcium score ≥400. Large ischemic perfusion defects (i.e., ≥15% of the left ventricle) were virtually confined to subjects who had a coronary artery calcium score ≥400. Although a similar percentage of subjects had an abnormal SPECT (16%) or stress electrocardiogram (17%), only

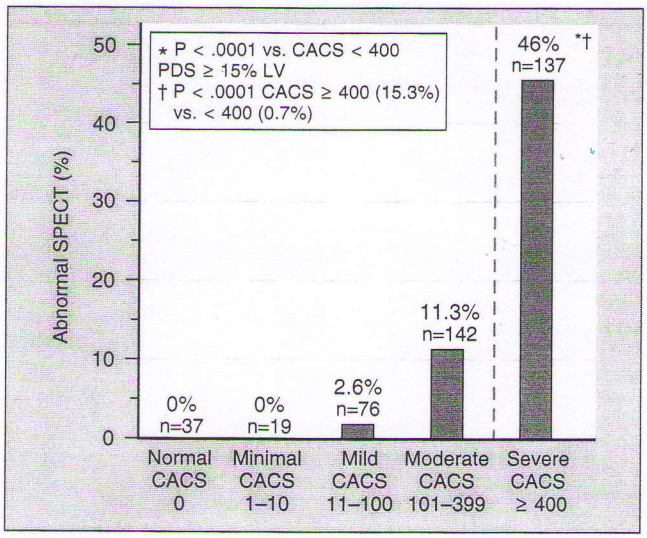

FIGURE 9-6. SPECT results based on total coronary artery calcium score (CACS). Few subjects with CACS <400 had abnormal SPECT (6.6%), and most (99.3%) had only small (<15%) perfusion defect size (PDS). LV indicates left ventricle. (From He ZX, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* 2000; 101[3]:244.)

the former was related to the total coronary artery calcium score, further illustrating the poor predictive accuracy of treadmill testing for detecting coronary artery disease in asymptomatic subjects.

The results of this study support the role of EBCT as an initial screening test for identifying subjects with varying degrees of coronary atherosclerosis. It also emphasizes the effectiveness of selectively combining SPECT with EBCT in the relatively small percentage of subjects who have a high (≥400) coronary artery calcium score to identify those with silent myocardial ischemia. This testing strategy may be optimal on the basis of the known prognostic value of SPECT and the apparent superior sensitivity of EBCT over SPECT for detecting preclinical coronary artery disease. Although the cost-effectiveness of the use of EBCT as a screening test demands further clinical investigation, it has been proposed that the coronary artery calcium score might be used to guide therapeutics and recommend the need for additional diagnostic testing.

Stress Myocardial Perfusion Imaging

Exercise Stress

Extensive data have demonstrated the high sensitivity of both ^{201}Tl planar and SPECT imaging for detecting coronary artery disease. With planar imaging incorporating visual assessment of myocardial scintigrams, sensitivity and specificity averaged 82% and 88%, respectively, in more than 4000 patients combined from multiple studies. Sensitivity varies with the extent of coronary artery disease. It approaches 79% for the detection of one-vessel disease (>50% stenosis), 88% for two-vessel disease, and 92% for three-vessel disease, with an average sensitivity of 86%. Application of quantitative analysis increases the sensitivity (approximately 90%) with equal or occasionally slightly worse specificity.

With tomographic SPECT myocardial perfusion imaging technology, sensitivity averages 90% and specificity is approximately 70% in large series of patients. The lower specificity may be attributed to a referral bias in which patients with abnormal scans were more frequently referred for coronary angiography than patients with normal scans. This explanation is further supported by the high normalcy rate (89%) seen in a large series. In similar patients without a prior history of coronary artery disease, the overall sensitivity of ^{201}Tl SPECT imaging was 85%, with an average sensitivity of 83% for the detection of single-vessel disease, 93% for two-vessel disease, and 95% for three-vessel disease (Table 9-2).

Only a few comparative studies between planar and SPECT ^{201}Tl imaging are available. SPECT imaging seems superior, given the fact that it can detect an individual stenosis on the basis of localization of stress-induced perfusion defects. Sensitivity is enhanced in patients with known or extensive coronary artery disease, high-grade coronary stenosis, proximal location of stenosis, and the presence of wall motion abnormalities. Variables that diminish sensitivity for coronary artery disease detection are single-vessel disease, left circumflex coronary stenosis, branch vessel or distal stenosis, mild degree of stenosis (<50% luminal narrowing), inadequate heart rate response during exercise, and concurrent antianginal therapy. The low specificity with ^{201}Tl scintigraphy generally may be caused by a failure to recognize attenuation artifacts in the inferoapical and anteroseptal regions. The introduction of ^{99m}Tc-gated SPECT imaging permits the assessment of systolic wall thickening of end-diastole to end systole on multiple SPECT tomograms. Normal systolic thickening in an area of hypoperfusion in both stress and rest images represents an attenuation artifact rather than a myocardial scar that will be associated with reduced systolic thickening. Taillefer at al[14] compared the diagnostic accuracy of ^{201}Tl and ^{99m}Tc-sestamibi SPECT in 115 women (85 patients and 30 controls) in a prospective design. Women in the study underwent both perfusion (^{201}Tl and ^{99m}Tc-sestamibi) and electrocardiographic gated ^{99m}Tc-sestamibi SPECT imaging, and most of them had coronary angiography. The overall sensitivities for detecting ≥50% and ≥70% stenosis were 75% and 84%, respectively, for ^{201}Tl, and 72% and 80%, respectively, for ^{99m}Tc-sestamibi perfusion studies (both P = 0.48). The specificity for lesions ≥50% was 71% for ^{201}Tl, 86% for ^{99m}Tc-sestamibi perfusion (P = 0.05), and 94% for ^{99m}Tc-sestamibi gated SPECT (P = 0.002). For lesions ≥70%, the specificity was 67% for ^{201}Tl, 84% for ^{99m}Tc-sestamibi perfusion (P = 0.02), and 92% for ^{99m}Tc-sestamibi gated SPECT (P = 0.0004). In summary, the authors concluded that both ^{201}Tl and ^{99m}Tc-sestamibi had a similar sensitivity for the detection of coronary artery disease; however, ^{99m}Tc-sestamibi SPECT perfusion imaging showed a significantly better specificity, which was further enhanced by the use of electrocardiographic gating. This strongly suggests that all nuclear perfusion imaging should be performed with simultaneous gated wall motion.

TABLE 9-2 SENSITIVITY AND SPECIFICITY OF EXERCISE THALLIUM-201 SPECT

		SENSITIVITY							
Study	**MI**	**Overall**	**MI**	**No MI**	**1VD**	**2VD**	**3VD**	**Specificity**	**Normalcy rate**
Tamaki[a]	39%	98%	100%	96%	—	—	—	91%	—
(N = 104)		80/82	32/32	48/50				20/22	
DePasquale[b]	26%	95%	100%	92%	91%	99%	100%	74%	—
(N = 210)		170/179	47/47	123/134	85/93	72/73	13/13	23/31	
Iskandrian[c]	18%	82%	98%	78%	64%	87%	91%	60%	94%
(N = 461)		224/272	49/50	174/222	45/70	93/107	86/95	35/58	123/131
Maddahi[d]	47%	95%	100%	90%	83%	97%	98%	56%	86%
(N = 138)		87/92	43/43	44/49	15/18	32/33	40/41	10/18	24/28
Mahmarian[e]	33%	87%	99%	79%	84%	91%	100%	87%	—
(N = 360)		192/221	73/74	68/86	119/142	60/66	13/13	65/75	
VanTrain[f]	40%	94%	100%	90%	88%	96%	100%	43%	82%
(N = 318)		185/196	78/78	106/118	56/64	69/72	60/60	15/35	62/76
Total	31%	90%	99%*	85%	83%	93%†	95%†	70%	89%
		938/1042	322/324	563/659	320/387	326/351	212/222	168/239	209/235

*P = 0.0001 vs. no MI.
†P = 0.0001 vs. SVD.
1VD, single-vessel disease; 2VD, double-vessel disease; 3VD, triple-vessel disease; SPECT, single photon emission computed tomography; MI, myocardial Infarction.
[a]*J Am Coll Cardiol* 1984; 4:1213; [b]*Circulation* 1988; 77:316; [c]*J Am Coll Cardiol* 1989; 14:1477; [e]*Am J Cardiol* 1991; 67:1d; *J Am Coll Cardiol* 1990; 15:318; [d]*J Am Coll Cardiol* 1989; 14:1689; [f]*J Nucl Med* 1990; 31:1168.
Adapted from Mahmarian et al. *Am J Cardiol* 1991; 67:2D and *J Am Coll Cardiol* 1990; 15:318.

Several studies have addressed the diagnostic accuracy of ^{99m}Tc-sestamibi in comparison with ^{201}Tl imaging in the setting of suspected coronary artery disease. An analysis of studies that used exercise SPECT imaging yielded a 90% sensitivity for ^{99m}Tc-sestamibi and 83% for ^{201}Tl for the detection of coronary artery disease. Specificity for ^{99m}Tc-sestamibi was 93% compared with 80% for ^{201}Tl imaging, and the normalcy rate was 100% for ^{99m}Tc-sestamibi imaging and 77% for ^{201}Tl SPECT. ^{99m}Tc-sestamibi SPECT MPI had an excellent sensitivity for the detection of single-vessel coronary artery disease (90%), which was almost 20% higher than planar imaging.

To overcome some of the difficulties in distinguishing reversible from irreversible defects, a dual-isotope (rest ^{201}Tl/stress ^{99m}Tc-sestamibi SPECT imaging) protocol has been validated in patients with suspected coronary disease and prior myocardial infarction.[15] In this protocol 3 mCi of ^{201}Tl is injected at rest, with images acquired 10 minutes later. Subsequently, an exercise test is performed with 25 to 30 mCi of ^{99m}Tc-sestamibi injected at peak stress. Dual-isotope SPECT demonstrated high sensitivity for detecting patients with ≥50% coronary artery stenosis (approximately 90%) and with ≥70% stenosis (approximately 95%). Although high values for specificity were recorded in the study (75% for <50% stenosis, and 82% for <70% stenosis), the significance was uncertain, given the small number of patients with normal coronary angiograms. However, the normalcy rate was 95%, which is higher than ^{201}Tl and similar to ^{99m}Tc-sestamibi SPECT studies. Segmental agreement for defect type between ^{201}Tl and ^{99m}Tc-sestamibi studies was 97% in zones without previous myocardial infarction. In myocardial infarct zones, segmental agreement for defect type was 98%. The agreement for defect reversibility pattern (normal, reversible or irreversible) between first and second readings was 95%, and for the exact segmental score (range, 0 to 4) it was 86%.

The incremental benefit of dual-isotope SPECT over combined clinical information and the results of treadmill electrocardiographic stress tests in predicting adverse outcomes in 2200 patients with no prior known coronary disease referred for stress testing has been demonstrated.[16] The risk of either death or myocardial infarction over the next 18 months was 0.3% in individuals with normal scans, 4.7% in those with mild perfusion abnormalities, and 10% in those with severe abnormalities. Mild and severe perfusion scan abnormalities were found in individuals with a predicted risk of 0.9% to 2.5% by use of the Duke Treadmill Risk Score (which takes into account exercise time, electrocardiographic ST deviation, and the presence or absence of angina), and it was calculated that the perfusion imaging scans resulted in a fivefold increase in prognostic information. Thus, in a patient population at an overall low risk of 2% for "hard" events (cardiac death and myocardial infarction), myocardial perfusion SPECT imaging added incremental prognostic information and added to risk stratification provided by clinical and treadmill exercise test information. The dual-isotope approach also allows the use of ^{201}Tl for the evaluation of defect reversibility and detection of myocardial viability (greater redistribution of ^{201}Tl into areas of ischemic and viable myocardium).

Pharmacological Stress

Pharmacological stress myocardial perfusion imaging has become an important alternative noninvasive tool in the detection of coronary artery disease in patients who are unable to exercise. It has been reported that submaximal stress SPECT myocardial perfusion imaging is significantly less sensitive than maximal exercise in detecting coronary disease and may incorrectly identify patients with multivessel disease. Agents commonly

used are dipyridamole, adenosine,[17] and dobutamine.[18] Both dipyridamole and adenosine induce a threefold to fivefold increase in myocardial blood flow with standard doses. Intravenous dobutamine is an alternative modality predominantly in patients with severe obstructive airway disease or high-grade atrioventricular block. Dobutamine infusion produces flow heterogeneity in the presence of significant coronary artery stenosis, because it increases myocardial oxygen demand by increasing heart rate, blood pressure, and contractility.

Multiple studies suggest a sensitivity of approximately 89% for dipyridamole, 90% for adenosine, and 82% for dobutamine myocardial perfusion imaging. Specificity is approximately 78%, 91%, and 73% for dipyridamole, adenosine, and dobutamine myocardial perfusion imaging, respectively. It seems that adenosine myocardial perfusion imaging has a slightly higher sensitivity and specificity compared with dipyridamole or dobutamine myocardial perfusion imaging, with a greater side effect profile. A recently published meta-analysis of 20 diagnostic studies that used dobutamine myocardial perfusion imaging for the detection of coronary artery disease confirmed a sensitivity of 88%, specificity of 74%, and diagnostic accuracy of 84%.[19] The combination of low-level exercise with intravenous adenosine infusions has been reported to be safe and reduces adverse reactions (especially related to bradycardia or first-degree atrioventricular block), improves image quality, and may provoke more episodes of myocardial ischemia.[20] This type of stress protocol may become a new preferred standard.

The diagnostic accuracy of myocardial perfusion studies in women is reduced by the high prevalence of single-vessel coronary disease, breast attenuation, and a smaller left ventricular chamber size than men.[21] With the use of gated SPECT the simultaneously derived information on perfusion and function helps differentiate attenuation artifact from myocardial infarction. Importantly, women are generally older when they are seen with coronary disease, and many are incapable of completing a symptom-limited exercise protocol and therefore those with an intermediate-to-high pretest likelihood of coronary artery disease should undergo pharmacological stress testing. There are insufficient data to firmly recommend a preference for a particular type of pharmacological stress test in women.[21] Finally, the ability of noninvasive tests to diagnose or localize coronary artery disease in patients with left bundle-branch block has been disappointing, although tomographic myocardial perfusion imaging with adenosine or dipyridamole stress provides important prognostic information in patients with left bundle-branch block.[22] Patients with left bundle-branch block and normal coronary arteries often have abnormal septal defects on exercise SPECT myocardial perfusion imaging. This false-positive rate of septal defects is significantly lower with dipyridamole or adenosine myocardial perfusion imaging. Current recommendations favor vasodilator stress imaging to determine the presence and prognostic significance of coronary artery disease in patients with left bundle-branch block.

PET

PET is increasingly being used for the noninvasive dete tion of coronary artery disease.[23] Most published lite ture and current clinical practice at PET centers rely relative rather that absolute quantitation of myocardi blood flow (MBF) for detection of coronary artery d ease, in a manner similar to the current practice wi interpretation of myocardial perfusion SPECT studi (Table 9-3). Overall, the available literature suggests th for diagnosis of coronary artery disease, relative quan tation of myocardial perfusion is sufficient for routi clinical application and that absolute quantitation MBF or coronary low reserve (CFR) by PET would not b required for this application.

Comparison Between PET and SPECT

PET has several theoretical advantages over SPECT ima ing for detecting coronary artery disease. PET has high spatial and contrast resolution. Furthermore, attenuatio correction is well developed and is applied routinely i PET imaging, which improves specificity by eliminatin attenuation artifacts. The pooled literature data for PE ^{201}Tl SPECT, and ^{99m}Tc-sestamibi SPECT suggest that th sensitivities of the three methods are similar (94%, 91% and 89%, respectively) for the detection of coronar artery disease. However, the specificity and normalc rates of PET (83% and 96%) are higher than those ^{201}Tl SPECT (70% and 89%) and ^{99m}Tc-sestamibi SPEC (36% and 81%). This is most likely related to a lowe false-positive rate of PET, which is attained by routin application of attenuation correction. The differenc between PET and SPECT, however, is likely to diminis with increasing application of gating and attenuatio correction to SPECT studies, which are expected t improve identification of attenuation artifacts Interestingly, no difference in patient management o cardiac event-free survival was demonstrated betwee management on the basis of ^{13}N-ammonia/^{18}-fluc prodeoxyglucose (FDG) PET and stress/rest ^{99m}Tc-ses tamibi SPECT imaging.[24]

TABLE 9-3 PET FOR DETECTION OF CORONARY ARTERY DISEASE

Lead author	Patients	Sensitivity	Specificity	Normalcy
Schelbert[a]	45	97%	—	100%
Tamaki[b]	25	95%	—	100%
Demer[c]	193	83%	95%	—
Tamaki[d]	51	98%	100%	—
Yonekura[e]	50	97%	100%	100%
Go[f]	202	93%	79%	—
Stewart[g]	81	84%	—	88%
Khanna[h]	35	98%	—	96%
Simone[i]	225	82%	91%	—
Williams[j]	287	87%	88%	—

[a]*Am J Cardiol* 1982; 49:1197; [b]*Eur J Nucl Med* 1985; 11:246; [c]*Circulation* 1989; 79: 825; [d]*J Nucl Med* 1988; 29: 1181; [e]*Am Heart J* 1987; 113: 645; [f]*J Nucl Med* 1990; 31:1899; [g]*Am J Cardiol* 1991; 67:1303; [h]*J Nucl Med* 1993; 33:825; [i]*Am J Physiol Imaging* 1992; 7:203; [j]*J Nucl Med* 1994; 35:1586.

Echocardiography

Echocardiography, whether obtained with or without stress, is commonly used in patients with documented coronary artery disease. Standard, nonstress (resting) echocardiography is used for a variety of reasons: to evaluate systolic function (e.g., ejection fraction), to investigate the presence of focal wall motion abnormalities, to rule out superimposed acute ischemia, to diagnose complications of myocardial infarction, and to quantitate associated mitral regurgitation. Increasingly, exercise and pharmacological stress echocardiography are also used in patients with chronic coronary artery disease to investigate chest pain syndromes and to detect and evaluate the presence of coronary artery disease.

Resting Studies

The evaluation of ventricular systolic function is the most common indication for echocardiography, not only in patients with coronary artery disease but in general cardiology practice. In most institutions, two-dimensional (2D) echocardiography is the principal noninvasive method used for quantitating left ventricular volumes and assessing global and regional systolic function, with transesophageal echo being reserved for those situations when standard transthoracic imaging yields suboptimal images. Two-dimensional echocardiography, because of its superior spatial resolution, is used to guide appropriate positioning of the M-mode beam and is used for direct measurements of ventricular dimensions and for calculation of left ventricular volumes and ejection fraction. Such spatial resolution is especially important in patients with coronary heart disease, because shape distortions caused by myocardial infarction are common. In clinical practice, visual estimation of ejection fraction from 2D echocardiography is perhaps the most common method used, and, when performed by experienced readers, ejection fraction by visual estimation corresponds closely to that obtained by angiography or gated blood pool scanning. The administration of an echocardiographic contrast agent improves the delineation of the endocardial/left ventricular cavity interface and improves the accuracy of 2D echocardiographic estimates of ejection fraction. The use of second harmonic imaging, even without the administration of contrast agents, also improves the endocardial interface, thus facilitating identification of abnormal wall motion.

Besides quantitation of systolic function, echocardiography can diagnose mitral regurgitation resulting from a variety of mechanisms. Recent studies using three-dimensional (3D) echocardiography suggest that altered mitral valve geometry, occasioned by apical papillary muscle displacement, contributes importantly to mitral regurgitation in this setting. Color flow Doppler is used to provide an estimate of the severity of mitral regurgitation, assisting the cardiologist and cardiac surgeon in planning for corrective surgery. In patients with heart failure or significant ventricular arrhythmias, the presence or absence of ventricular aneurysm can be established, which also may be useful in planning surgery.

Stress Studies

Stress echocardiography, an alternative to stress nuclear perfusion imaging, has proven to have excellent diagnostic accuracy for detecting inducible ischemia in patients with intermediate to high pretest probability of coronary artery disease.[25] An obvious virtue of stress echocardiography compared with electrocardiographic stress testing is the ability to localize inducible myocardial ischemia. As expected, the sensitivity of this technique is greater in patients with multivessel disease than in those with single-vessel disease, and in those with >70% stenosis compared with those with less severe lesions.

The weighted mean sensitivity of exercise stress echocardiography is 86%, specificity 81%, and overall accuracy 85% (Table 9-4). The corresponding values for dobutamine stress echocardiography are 82%, 84%, and 83% (Table 9-5). Some limitations of the methods bear emphasis. Treadmill stress echocardiography may have lowered sensitivity if there is a significant delay from the end of the exercise to the acquisition of postexercise images. Sensitivity can also be diminished if all myocardial segments are not adequately visualized, and the diagnostic accuracy of stress echo can be improved in this setting with the use of contrast agents and second harmonic imaging.

Pharmacological stress echocardiography is used in situations in which exercise is not feasible, with the most common agents used being dobutamine and dipyridamole. Dobutamine, the most commonly used of the adrenergic stimulants, increases oxygen demand by increasing contractility, blood pressure, and heart rate. Dobutamine is most commonly administered in graded doses to titrate myocardial workload in a manner akin to standard exercise testing. Vasodilator agents, in contrast, cause heterogeneous myocardial perfusion without actually altering workload (or wall motion) directly. Comparative studies suggest a somewhat lower sensitivity for stress echocardiography with vasodilators compared with dobutamine. However, pharmacological stress echocardiography using vasodilator agents does seem to be useful in detecting inducible myocardial ischemia and particularly valuable in determining prognosis. Dobutamine stress has been used in conjunction with transesophageal echocardiographic imaging in patients with poor transthoracic windows. In an asymptomatic patient with prior infarction, stress echocardiography may be helpful in assessing risk and determining the need for cardiac catheterization, but it can be challenging to detect residual ischemia within an akinetic zone.

Comparison of Stress Echocardiography and Myocardial Perfusion Imaging (MPI)

Literature analyses comparing the diagnostic accuracy of myocardial perfusion imaging and stress echocardiography in patients with suspected or known coronary artery disease suggest that exercise SPECT scintigraphy has a sensitivity of approximately 90% and a specificity of approximately 70%, and exercise echocardiography a sensitivity of approximately 80% and specificity of approximately 90%. It seems that exercise SPECT is more

TABLE 9-4 DIAGNOSTIC ACCURACY OF EXERCISE ECHOCARDIOGRAPHY IN DETECTING ANGIOGRAPHICALLY PROVED CAD, SERIES PUBLISHED SINCE 1990

Year	Author	N	Sens (%)	Sens 1-VD	Sens MVD	Spec (%)	PPV (%)	NPV (%)	Acc (%)
1990	Sheikh[a]	34	74	74	—	91	94	63	79
1991	Pozzoli[b]	75	71	61	94	96	97	64	80
1991	Crouse[c]	228	97	92	100	64	90	87	89
1991	Galanti*[d]	53	93	93	92	96	96	93	94
1992	Marwick[e]	150	84	79	96	86	95	63	85
1992	Quinones[f]	112	74	59	89	88	96	51	78
1992	Salustri[g]	44	87	87	—	85	93	75	86
1992	Amanullah[h]	27	82	—	—	80	95	50	81
1993	Hecht[i]	180	93	84	100	86	95	79	91
1993	Ryan[j]	309	91	86	95	78	90	81	87
1993	Mertes[k]	79	84	87	89	85	91	75	85
1993	Hoffmann*[l]	66	80	79	81	88	95	58	82
1993	Cohen*[m]	86	88	82	91	80	89	77	85
1994	Marwick[n]	86	88	82	91	80	89	77	85

*Coronary stenosis >70%.
Sens, Sensitivity; 1VD, single-vessel disease; MVD, multivessel disease; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy.
[a]*J Am Coll Cardiol* 1990; 15:1043; [b]*Am J Cardiol* 1991; 67:350; [c]*Am J Cardiol* 1991; 67:1213; [d]*Am Heart J* 1991; 122:1609; [e]*J Am Coll Cardiol* 1992; 19:74; [f]*Circulation* 1992; 85:1026; [g]*Am Heart J* 1992; 124:75; [h]*Clin Cardiol* 1992; 15:585; [i]*J Am Coll Cardiol* 1993; 21:950; [j]*J Am Soc Echocardiogr* 1993; 6:186; [k]*J Am Coll Cardiol* 1993; 21:1087; [l]*Am J Cardiol* 1993; 72:555; [m]*Am J Cardiol* 1993; 72:1226; [n]*Br Heart J* 1994; 72:31.

sensitive compared with exercise echocardiography, with a trend toward higher specificity for the latter. Adenosine, dipyridamole, and dobutamine myocardial perfusion imaging studies provide similar diagnostic accuracy (sensitivity 89%, 90%, and 91%; specificity 83%, 78%, and 86%, respectively), and all are more accurate than dobutamine echocardiography (sensitivity 81%, specificity 83%).[26] Clinical specificity is similarly high with adenosine SPECT, dipyridamole echocardiography, and exercise echocardiography and lower with exercise SPECT. Normalcy rate is high for exercise SPECT (89%) and similar to clinical specificity for exercise echocardiography (90%). When the two major pharmacological stress imaging modalities were compared, adenosine

TABLE 9-5 DIAGNOSTIC ACCURACY OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN DETECTING ANGIOGRAPHICALLY PROVEN CAD, SERIES PUBLISHED SINCE 1990

Author	Year	Protocol	N	Sens (%)	Sens 1-VD	Sens MVD	Spec (%)	PPV (%)	NPV (%)	Acc (%)
Sawada[a]	1991	DSE 2.5-30	55	89	81	100	85	91	81	74
Sawada[a]	1991	DSE 2.5-30	41	81	—	81	87	91	72	87
Previtali*[b]	1991	DSE 5-40	35	68	50	92	100	100	44	83
Cohen*[c]	1991	DSE 2.5-40	70	86	69	94	95	98	72	89
Martin[d]	1992	DSE 10-40	34	76	—	—	44	79	40	68
McNeill[e]	1992	DASE 10-40	28	71	—	—	—	—	-	71
Segar[f]	1992	DSE 5-30	88	95	—	—	82	94	86	92
Mazeika*[g]	1992	DSE5-20	50	78	50	92	93	97	62	82
Marcovitz[h]	1992	DSE 5-30	141	96	95	98	66	91	84	89
McNeill[e]	1992	DASE 10-40	80	70	—	—	88	89	67	78
Salustri[i]	1992	DSE 5-40	46	79	—	—	78	85	70	78
Marwick[j]	1993	DSE 5-4-	97	85	84	86	82	88	78	84
Forster[k]	1993	DASE 10-40	21	75	—	—	89	90	73	81
Günalp[l]	1993	DSE 5-30	27	83	78	89	89	94	73	85
Marwick[j]	1993	DSE 5-40	217	72	66	77	83	89	61	76
Hoffman*[m]	1993	DASE 5-40	64	79	78	81	81	93	57	80
Previtali[n]	1993	DSE 5-40	80	79	63	91	83	92	61	80
Takeuchi[o]	1993	DSE 5-30	120	85	73	97	93	95	80	88
Cohen*[p]	1993	DSE 2.5-40	52	86	75	95	87	94	72	87
Ostojic[q]	1994	DSE 5-40	150	75	74	81	79	96	31	75
Marwick[r]	1994	DSE 5-40	86	54	36	65	83	86	49	64
Beleslin[s]	1994	DSE 5-40	136	82	82	82	76	96	38	82

*Coronary stenosis >70%.
Sens, Sensitivity; 1VD, single-vessel disease; MVD, multivessel disease; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy.
[a]*Circulation* 1991; 83:1605; [b]*Circulation* 1991; 83:III27; [c]*Am J Cardiol* 1991; 67:1311; [d]*Ann Intern Med* 1992; 116:190; [e]*Am J Cardiol* 1992; 69:740; [f]*J Am Coll Cardiol* 1992; 19:1197; [g]*J Am Coll Cardiol* 1992; 19:1203; [h]*Am J Cardiol* 1992; 69:1269; [i]*Eur Heart J* 1992; 13:1356; [j]*Circulation* 1993; 87:345; [k]*J Am Coll Cardiol* 1993; 21:1591; [l]*J Nucl Med* 1993; 34:889; [m]*Am J Cardiol* 1993; 72:555; [n]*Am J Cardiol* 1993; 72:865; [o]*J Am Soc Echocardiogr* 1993; 6:593; [p]*Am J Cardiol* 1993; 72:1226; [q]*J Am Coll Cardiol* 1994; 23:1115; [r]*Br Heart J* 1994; 72:31; [s]*Circulation* 1994; 90:1168.

SPECT myocardial perfusion imaging had a significantly better sensitivity than dobutamine echocardiography (89% vs. 81%). Specificity for both modalities was 83%. In summary, both stress myocardial perfusion imaging and stress echocardiography have superior sensitivity and specificity compared with exercise electrocardiographic stress testing alone. Data from many studies confirm a higher sensitivity of SPECT myocardial perfusion imaging compared with stress echocardiography at the expense of specificity (Table 9-6). The addition of electrocardiographic-gated SPECT imaging with ^{99m}Tc-agents and the simultaneous evaluation of ventricular perfusion and function further improves the specificity and diagnostic accuracy of stress myocardial perfusion imaging.

TABLE 9-6 SENSITIVITY AND SPECIFICITY OF NONINVASIVE TESTS FOR THE DETECTION OF CORONARY ARTERY DISEASE

Diagnostic test	Sensitivity (range)	Specificity (range)	Number of studies	Number of patients
Exercise ECG	68%	77%	132	24,074
Planar scintigraphy	79% (70%-94%)	73% (43%-97%)	6	510
SPECT MPI	88% (73%-98%)	77% (53%-96%)	8	628
Stress echocardiography	76% (40%-100%)	88% (80%-95%)	10	1174

Data on the ranges of sensitivity and specificity are from *Ann Intern Med* 1999; 130:719. Data on the sensitivity and specificity of exercise electrocardiography are from *Circulation* 1989; 80:87.

CMR Imaging

CMR imaging is a new and rapidly evolving discipline. The clinical use of many CMR techniques is still being defined, and it is not yet in widespread clinical practice. The sequences and protocols described will probably change significantly in coming years, although the principles should remain constant. At this stage in its development, there is considerably more data on assessment of diagnosis in relatively limited populations rather than prognosis.

CMR Techniques for Assessing Regional Function

Cine CMR allows a qualitative assessment of regional cardiac function in the same way as echocardiography but with improved image quality and a lower loss of nonvisualized segments. CMR allows routine imaging in the true long and short axis of the heart, which assists in the comparison of regional wall motion between patients and as such does not suffer compromises that result from restricted angulation because of limited acoustic access.[27] Real-time CMR is now available, and comparisons with echo show superiority to echocardiography in patients with limited acoustic access.

In the assessment of resting ventricular function and mass, CMR has some fundamental advantages over other imaging techniques. CMR is both accurate and reproducible and does not require exposure to contrast agents or ionizing radiation. Early CMR techniques of assessing volumes and of the blood pool used the area-length method with long-axis views, assuming that the left ventricle was a prolate ellipsoid of rotation. This was performed because the more complicated 3D coverage of the heart was too time-consuming. However, with faster scanners, this is no longer the case, and the area-length method has largely been abandoned, because the problems of geometric assumptions are manifestly incorrect in remodeled hearts. The 3D CMR approach (volumetry) is now in widespread use and is robust and practical. CMR offers the best current reference standard for the assessment of cardiac function and mass (Table 9-7), being both accurate and reproducible in normal and abnormal ventricles. Although much early CMR validation work was done with conventional non-breath-hold cines, the results using current breath-hold sequences show that the reproducibility of old and new techniques is similar. The most important clinical measure is that of interstudy reproducibility, because this describes the fidelity of a technique to determine changes in clinical parameters over time. This applies to individuals in whom a therapeutic response is being looked for or for research in which small changes between groups need to be identified and the sample size requirement is directly linked to the interstudy reproducibility.

A number of methods have been used to quantify cine CMR assessment of wall motion and wall thickening, but myocardial dynamics are more complicated than simple

TABLE 9-7 NORMAL CMR VALUES IN ADULTS FOR VOLUMES AND MASS OF THE LEFT VENTRICLE (LV)

PARAMETER	MALES		FEMALES	
	Absolute	Normalized to BSA	Absolute	Normalized to BSA
LVEDV	136±30 (77-195) mL	69±11 (47-92) mL/m^2	96±23 (52-141) mL	61±10 (41-81) mL/m^2
LVESV	45±14 (19-72) mL	23±5 (13-3) mL/m^2	32±9 (13-51) mL	21±5 (11-31) mL/m^2
LVSV	92±21 (51-133) mL	47±8 (32-2) mL/m^2	65±16 (33-97) mL	41±8 (26-56) mL/m^2
LVEF	67±5 (56-78) %	—	67±5 (56-78) %	—
LVM	178±31 (118-238) g	91±11 (70-113) g/m^2	125±26 (75-75) g	79±8 (63-95) g/m^2

BSA, Body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; M, mass including papillary muscles. Values are quoted as mean ± 1 standard deviation, with the 95% confidence interval for the normal range in brackets.
Data adapted from Lorenz et al. *J Cardiovasc Magn Reson* 1999; 1:71.

thickening and 2D motion because of a complex interaction of contraction, expansion, twisting, and through-plane motion. This can now be approached using CMR tagging, which has been validated against animal studies and which can provide a 3D solution.[28] Tagging CMR has revealed a fairly consistent pattern of normal regional variation in heart wall motion. Normal ventricular contraction is characterized by base to apex shortening, with little apical motion. Free wall contraction exceeds that of the septum, and endocardial thickening exceeds that of the epicardium. Although there is a fairly large regional variation in normal displacement, the regional deformation is more uniform, with the greatest systolic lengthening being approximately radially directed. There is also a normal torsional motion of the ventricle about its long axis, with a wringing action, with the base and with an apical myocardial infarction rotating in opposite directions. When tagging is performed in myocardial infarction in humans, the region of altered contraction often extends beyond the region of the infarct itself. This finding, which is considered important in remodeling, has been shown to respond to angiotensin-converting enzyme inhibition therapy. Studies such as these suggest that tagging CMR may find significant clinical and research application in the future, particularly once acquisition protocols are established and analysis tools are simpler to operate within shorter time frames.

Myocardial Ischemia

Myocardial ischemia can be investigated by CMR through the use of stress with either wall motion or perfusion analysis. The use of dobutamine wall motion is better established with CMR at present, and there are some reasonable clinical studies available. Other stress techniques have also been used in coronary disease. Finally, perfusion CMR is currently still in development, although significant progress has been made, and some small clinical studies have been reported.

Wall Motion Studies with Exercise

Supine dynamic exercise in the magnet is uncomfortable and leads to motion artifact, and therefore the reports of the use of dynamic exercise with CMR are limited to proof of concept studies, and there are none for the diagnosis of coronary artery disease. However, nonferromagnetic exercise devices are now commercially available for fitting to the magnet, and their use with real-time CMR techniques may in due course prove useful for exercise imaging. MR spectroscopy has used prone exercise and handgrip for stress to examine changes in high-energy phosphates, both in normal individuals and those with cardiovascular disease. During myocardial ischemia, a fall in the ratio of phosphocreatine (PCr) to adenosine triphosphate (ATP) has been demonstrated, and this change is abolished by successful revascularization. This early study suggests that metabolic CMR studies may prove useful in the future in understanding ischemia at the metabolic level and possibly contribute to clinical assessment.

Dipyridamole Wall Motion Studies

CMR has been used to detect the induction of regional wall motion abnormalities in coronary artery disease using dipyridamole (Figure 9-7).[29] The sensitivity of this method has been limited, with an inability to detect small areas of ischemia. Because of the disappointing results of dipyridamole CMR, it is not being actively used.

Dobutamine Wall Motion Studies

Dobutamine CMR in doses of up to 20 μg/kg/min seems to be a more sensitive pharmacological method of detecting wall motion abnormalities than dipyridamole.[28] Concordance has been seen in segments affected by perfusion and wall motion abnormalities, and the sensitivity of dobutamine CMR and MIBI SPECT is similar for the detection of disease (approximately 85%). Dobutamine CMR is valuable in patients whose echocardiographic image quality is poor, even with second harmonic imaging, with good results (sensitivity and specificity approximately 83%). The event-free survival rate was also been shown to be excellent in patients with normal dobutamine CMR.[28]

Dobutamine Global Ventricular Function Studies

CMR velocity mapping can also be used to assess global left ventricular function through changes in aortic flow during dobutamine stress, but further work is needed to evaluate the full value of assessing global ventricular function with CMR.

In summary, there are now a number of reports of the value of dobutamine stress CMR in patients with coronary artery disease, and the results are excellent, with good patient tolerance. The duration of the study is similar to echocardiography with the use of breath-hold CMR, and real-time CMR may also assist in improving patient throughput. Comparison with thallium imaging and stress echocardiography shows excellent correlation with the former and significant improvement over the latter. For the future, it may be that a combination of perfusion and wall motion in the same dobutamine CMR study may prove useful, and the possible role of quantification of myocardial contraction with tagging would be a great advance in improving the objectivity of the technique. Consensus statements on the performance of dobutamine CMR have been published.[30]

Use of CMR Imaging to Measure Myocardial Perfusion

Techniques and Validation

Techniques used to assess perfusion by CMR in humans have used extracellular gadolinium contrast agents. These agents shorten T1 relaxation times and increase signal on T1-weighted images. At the current stage of development, the technique relies on first-pass imaging of a gadolinium bolus with analysis of the myocardial signal changes that occur to determine parameters of

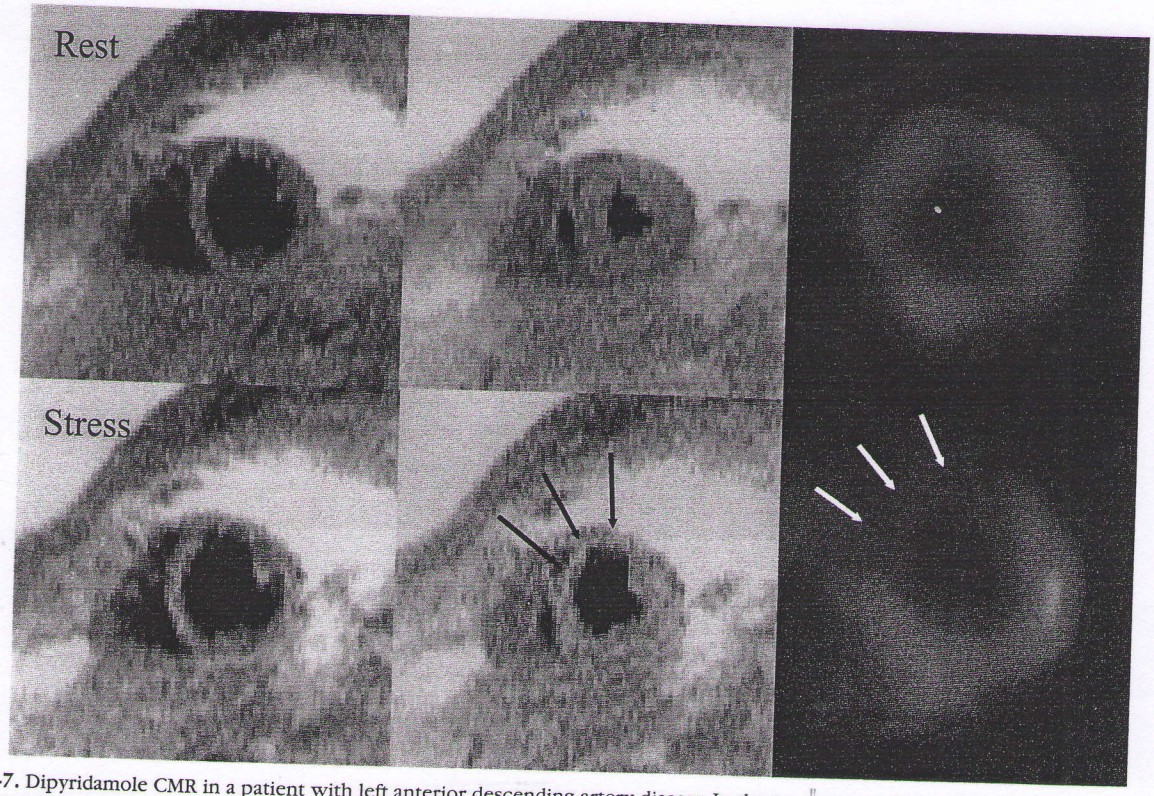

FIGURE 9-7. Dipyridamole CMR in a patient with left anterior descending artery disease. In the top row are short axis images before dipyridamole with postdipyridamole images in the lower row. End-diastole is in the left column, and end-systole is in the middle column. Left ventricular contraction is normal before vasodilatation but reduced in the anteroseptal region after dipyridamole *(black arrows)*. The stress-induced contraction abnormality is closely matched by the defect seen during dipyridamole thallium myocardial perfusion tomography *(white arrows on the color maps in the right column)*, which shows full reversibility. (Reproduced with permission from reference 29.) See also Color Insert.

perfusion. Ultrafast CMR techniques such as FLASH or hybrid echo-planar sequences provide the required temporal resolution to image the first pass through the myocardium with several short-axis-imaging planes per cardiac cycle, with good spatial resolution (2 to 3 mm). Pharmacological stress is used to provoke myocardial hyperemia, as is used with scintigraphic techniques, and has the advantage of limiting movement artifacts that would be created by exercise.

A good correlation has been demonstrated between inverse myocardial mean transit time and myocardial blood flow measured by microspheres. Different contrast enhancement has been shown in an occlusive rat model in perfused, and nonperfused, myocardium, and the technical feasibility of first-pass perfusion MR with gadolinium in humans has been demonstrated. Resting studies of patients with >90% coronary stenosis have found decreased peak signal intensity and a lower slope in distal perfused myocardium, and after revascularization the peak signal intensity returns to normal in most patients. The use of combined perfusion CMR with tagging reveals reduced regional deformation, and motion in myocardial areas with altered perfusion and a good correlation has been found between Doppler CFR and myocardial perfusion reserve in patients with nonsignificant coronary artery disease with multislice perfusion CMR.

Comparison of CMR with Thallium and MIBI SPECT Imaging

Gadolinium-enhanced snapshot MR imaging measuring first-pass signal intensity changes at several time points after bolus injection has generated circumferential profiles that were in close agreement with myocardial perfusion abnormalities detected by planar thallium scintigraphy in patients with coronary disease. A similar method has reported good correlations between CMR perfusion and results from planar or SPECT studies. In addition, Panting et al[31] reported the first clinical study of the use of a spin-echo, echo-planar MR technique at rest, and during adenosine stress, to assess perfusion in 26 patients with coronary disease and an abnormal thallium SPECT scan. For detecting abnormal coronary territories, this MR technique had a sensitivity and specificity compared with coronary angiography of 79% and 83%, which was similar to the results of thallium SPECT (Figure 9-8).

Comparison of CMR with PET and Coronary Angiography

Schwitter et al[32] reported the first comparison of multislice perfusion CMR with PET in 48 patients with coronary disease and 18 controls. A sensitivity and specificity of 87% and 85% vs. coronary angiography was

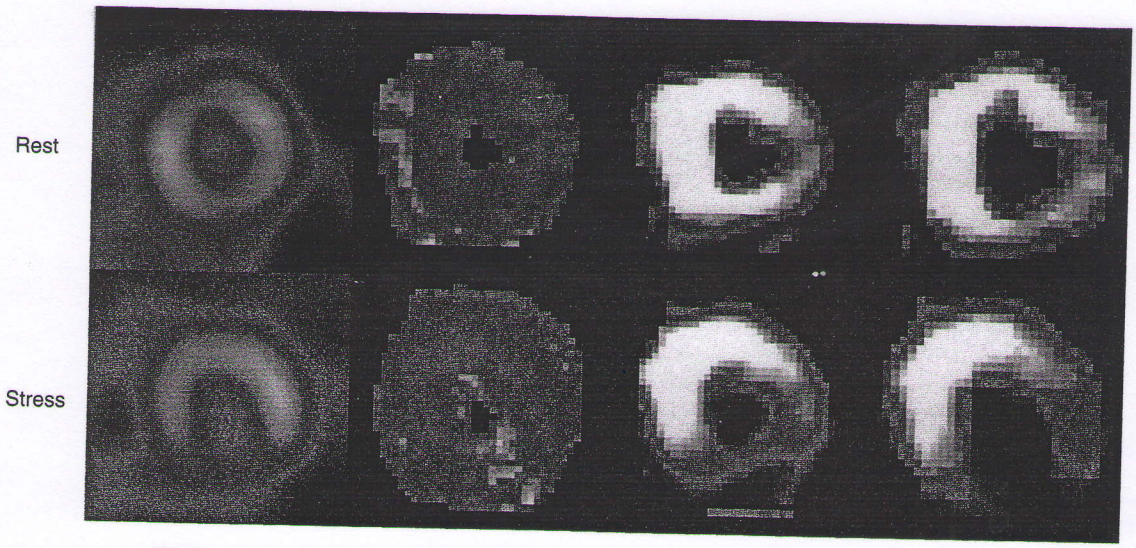

FIGURE 9-8. Parametric map analysis for representation of perfusion CMR in a patient with an inferolateral reversible defect, with the corresponding thallium images *(first column)*. Columns 2 through 4 show the time to peak CMR myocardial signal intensity, the peak signal intensity, and the peak slope of the signal intensity vs. Time curves. There is good correlation between the CMR maps and the thallium scan. (Reproduced with permission from reference 31.) See also Color Insert.

found, which increased to 91% and 94% when compared with the PET findings for significant perfusion abnormality.

Two-dimensional breath-hold coronary CMR has problems with relatively low signal/noise, misregistration of images between different breath-holds, a significant requirement for high operator experience, and patients' intolerance of multiple breath holds. However, with this technique for the diagnosis of significant coronary artery stenosis, a sensitivity and specificity of 90% and 92%, respectively, have been described, with better results for the left main stem and left anterior descending arteries and worse results for the right coronary and left circumflex arteries. Three-dimensional and non-breath-hold techniques have been developed so that a volume slab containing many thin slices is acquired by typically using a segmented gradient echo sequence. These sequences have usually been acquired with respiratory gating (navigators) but with the newer ultrafast scanners the 3D slab can be acquired in a single breath hold (Figure 9-9).

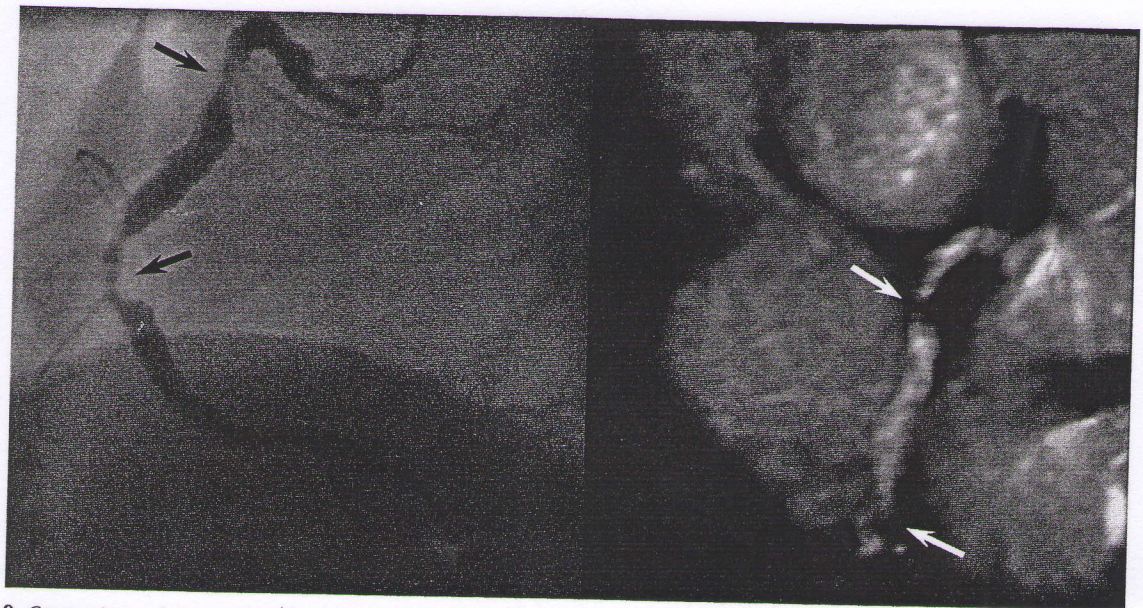

FIGURE 9-9. Comparison of x-ray invasive coronary angiography *(left)* in a patient with two tight stenoses of the right coronary artery *(black arrows)* with coronary CMR performed during a breath-hold showing similar appearances *(white arrows)*. (From van Geuns RJ, Wielopolski PA, de Bruin HG, Rensing BJ, Hulshoff M, van Ooijen PM, et al. MR coronary angiography with breath-hold targeted volumes: preliminary clinical results. *Radiology* 2000; 217[1]:270. Reproduced with permission.)

IMAGING TECHNIQUES USED TO ASSESS PROGNOSIS OF PATIENTS WITH CHRONIC CORONARY ARTERY DISEASE

Appropriate management of known coronary disease includes assessment of the individual risk of future cardiac events, including death and myocardial infarction. High-risk patients (e.g., those with left main disease and/or three-vessel disease with or without ventricular dysfunction) benefit from an aggressive approach with coronary angiography and revascularization. In contrast, most individuals with low annual risk for cardiac events can be managed conservatively.

Use of EBCT to Assess Coronary Artery Calcification

The likelihood of plaque rupture and the development of acute cardiovascular events are related to the total atherosclerotic plaque burden. Because there is a direct relationship between the coronary artery calcium score severity and the extent of atherosclerotic plaque, it would seem intuitive that the calcium score should predict risk for subsequent cardiovascular events among otherwise heterogeneous patient populations with cardiac risk factors.

Several recent trials have studied whether the extent of coronary artery calcification as assessed by EBCT can predict subsequent patient outcome. In an asymptomatic patient population referred for a screening EBCT and then followed for nearly 3 years, both the absolute coronary artery calcium score and the age-adjusted and gender-adjusted relative coronary artery calcium score percentiles predicted subsequent death and nonfatal myocardial infarction. Hard cardiac events occurred in only 0.3% of subjects with a normal EBCT, but this increased to 13% in those with a coronary artery calcium score ≥400.[33] In patients referred for coronary angiography, those with a coronary artery calcium score ≥100 had a 3.2-fold higher relative risk of death or myocardial infarction than those with a lower coronary artery calcium score during 7 years of follow-up.[34] A high coronary artery calcium score ≥1000 may portend a particularly high risk for death or myocardial infarction (i.e., 25%/year).[35]

The very low cardiac event rate in subjects with a coronary artery calcium score <100 is consistent with angiographic studies, indicating a comparably low likelihood of significant coronary artery disease and an extremely low incidence of stress-induced myocardial ischemia (1.5%) in such individuals. The increasing number of cardiac events with an ever-increasing coronary artery calcium score is also consistent with the dramatic increase in the incidence of stress-induced myocardial ischemia, particularly when scores are >400. All these data in asymptomatic patients indicate a potential novel role of EBCT in screening subjects for preclinical coronary artery disease on the basis of the presence and severity of coronary artery calcification.

Use of SPECT Imaging to Assess Prognosis

Combined myocardial perfusion and function results from stress MPI (^{201}Tl or ^{99m}Tc agents) have the ability to distinguish patients at high risk (greater than 3% annual mortality rate) from those at intermediate risk (1% to 3% annual mortality rate) or low risk (less than 1% annual mortality rate).[16,17,21,22,36] A normal ^{201}Tl or ^{99m}Tc-sestamibi scan is generally associated with low risk of future cardiac events. This low event rate approaches that of a normal age-matched population and also of patients with normal coronary angiograms. The same benign prognosis seems to persist even in patients with strongly positive electrocardiograms or angiographically significant disease. Studies demonstrating high-risk features (extensive ischemia of more than 20% of the left ventricle, defects in greater than one coronary vascular supply region, reversible ischemia in multiple segments, transient or persistent left ventricular cavity dilatation, increased ^{201}Tl lung uptake) predict an increase risk of cardiac events (Box 9-2; Figure 9-10).

Perhaps the most important feature of exercise or pharmacological stress perfusion imaging with ^{201}Tl or a ^{99m}Tc-labeled agent is its excellent negative predictive value for predicting low mortality and myocardial infarction rates (<1% per year) in patients with totally normal scans. The excellent prognostic value of ^{99m}Tc-sestamibi has been confirmed in a review of a large series of patients from 14 different prognostic studies.[37] A normal ^{99m}Tc-sestamibi image was associated with an average annual "hard" event rate of 0.6%, and patients with abnormal scans had a 12-fold higher event rate (7.4%).

The value of exercise MPI has been studied extensively in many large studies. The prognostic value of exercise testing with dual-isotope imaging (rest ^{201}Tl/stress ^{99m}Tc-sestamibi SPECT imaging) has been assessed on the basis of gender and race. In a large series of 4136 consecutive patients (2742 men and 1394 women), event rates for both men and women with normal results and increased clinical risk were similar (1.9% vs. 0.8%).[16] An abnormal study result, the presence of reversible perfusion defect, and summed scores reflecting the extent and severity of perfusion defects were associated with increased risk of cardiac death in both genders. However, the total mortality was greater in women with an abnormal study result than men (11% vs. 6%). On the basis of this finding, the investigators

BOX 9-2 PREDICTORS OF STRESS-INDUCED ISCHEMIC EXTENT AND SEVERITY WITH MYOCARDIAL PERFUSION SPECT

- Number and/or location of reversible defections
- Magnitude (severity and extent) of stress defects
- Post stress pulmonary ^{201}Tl uptake*
- Transient ischemic left ventricle cavity dilatation after exercise*
- Delayed redistribution

*Best assessed by obtaining a 5-minute poststress and 4-hour redistribution or rest anterior planar scintigram before the initiation of SPECT imaging.
Adapted from *Prog Cardiovasc Dis* 2001; 43:281.

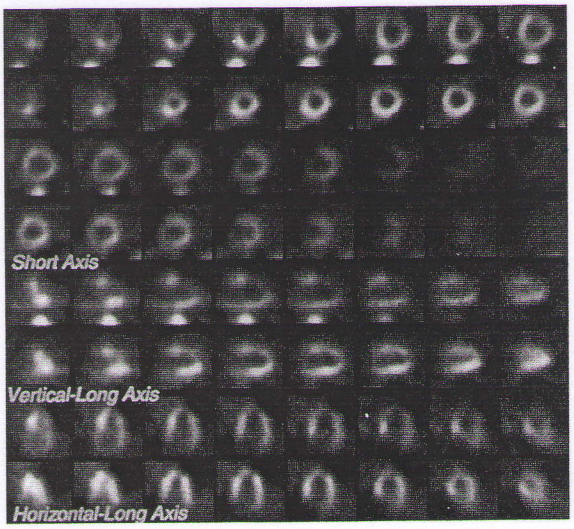

FIGURE 9-10. High-risk scan: Demonstration of exercise ^{99m}Tc-sestamibi myocardial perfusion imaging in multiple views (short-axis, vertical long-axis, horizontal long-axis; stress images on top of each row with test images on the bottom). Stress images demonstrate transient cavity dilation and extensive ischemia involving the anterior, anteroseptal, anterolateral, and anteroapical distribution. Rest images reveal normalization of the cavity size and elimination of the perfusion abnormalities. These findings predict a high risk for future cardiac events for the particular patient. See also Color Insert.

TABLE 9-8 RATES OF HARD EVENTS AND CARDIAC DEATH PER YEAR AND RATES OF REFERRAL TO EARLY CATHETERIZATION BY SCAN RESULT*

Summed stress score	Total	Normal (0-3)	Mildly abnormal (4-8)	Moderately abnormal (9-13)	Severely abnormal (>13)
Hard events (%/y)	4.9	1.6	3.5	5.7	10.6†¶
Cardiac death (%/y)	6.6	0.9	0.9	3.4	7.4†¶
Early catheterization (%)	14.1	3.8	9.7	23.1	27.2†¶

Hard events = cardiovascular death and myocardial infarction.
*The denominator for the hard event calculation is based on the censored population (n = 1079); the denominator for early catheterization is the entire population (N = 1159).
†Significantly different as a function of summed stress score.
Modified from Hachamovitch et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. *Am J Cardiol* 1997; 80:426.

concluded that dual-isotope SPECT MPI is able to risk stratify women more effectively than men. In other studies MPI has provided similar prognostic information, regardless of racial difference.

Pharmacological stress imaging can also be used to assess prognosis in patients with chronic coronary artery disease who are unable to exercise and especially in patients who are scheduled to undergo major vascular surgery.[18,37] In these studies, a normal MPI is associated with a low annual event rate (cardiac death or nonfatal myocardial infarction) of less than 2% for men and women. In multivariable models, an abnormal MPI and/or a reversible defect are the strongest predictors for subsequent occurrence of cardiac death or nonfatal myocardial infarction. A normal MPI is usually associated with low cardiac event rate (<2%) compared with a 7% to 17% event rate for an abnormal study, a reversible perfusion defect, or a fixed defect, depending on the patient population under study. Both Cox proportional hazards and Kaplan-Meier analyses reveal that nuclear tests add incremental value after adjusting for known clinical and historical variables (Table 9-8).

In summary, the prognostic value of exercise and pharmacological tests with ^{201}Tl, ^{99m}Tc-sestamibi, and dual-isotope SPECT MPI in patients with stable coronary artery disease is comparable and provides valuable information. A normal study is generally associated with a low annual event rate of ≤2% for nonfatal myocardial infarction or death. Conversely, abnormal studies, particularly those with a reversible defect, are associated with significantly increased risk, with annual event rates from 7% to 17% for nonfatal myocardial infarction and death. Extent and severity of reversible defects and the presence of left ventricular cavity dilation may provide additional prognostic information.

Prognostic Value of Stress Echocardiography

The presence or absence of inducible myocardial ischemia has prognostic value in both exercise and pharmacological stress echocardiography (Table 9-9). In general, a negative stress echocardiogram is associated with a low cardiovascular event rate. Specifically, in patients with an exercise electrocardiographic response suggestive of ischemia but no inducible wall motion abnormality detected by stress echo, there is a very low rate of adverse cardiovascular events during follow-up, but a higher rate than that seen in patients with no electrocardiographic evidence of ischemia. In patients with a positive wall motion abnormality provoked by stress echo, future cardiovascular events are more likely. Pooled results of studies involving approximately 6000 patients with chronic coronary artery disease indicate that the risk of future cardiac events can be stratified on the basis of the presence or absence of inducible ischemia on stress echocardiography testing.

ASSESSMENT OF MYOCARDIAL VIABILITY

Left ventricular function is a well-established powerful predictor of outcome after myocardial infarction. The occurrence of left ventricular dysfunction (LVEF <35%) after MI, especially if linked with symptoms of heart failure, is associated with poor survival. In selected patients with severe left ventricular dysfunction, revascularization seems to offer a long-term survival benefit. However, the selection of patients with low ejection fraction who would benefit the most from revascularization is critical because of the high operative mortality risk.

TABLE 9-9 PROGNOSTIC VALUE OF STRESS ECHOCARDIOGRAPHY IN VARIOUS PATIENT POPULATIONS

						% ANNUALIZED EVENT RATE		
Author	Year	Total Pts	Stress	Follow-up (mos)	Events	Ischemia	No Ischemia	Normal
Sawada[a]	1990	148	NL TSE	28	D, MI	—	—	0.6
Mazeika[b]	1993	51	DSE	51	D, MI, UA	16	3.8	—
Krivokapich[c]	1993	360	TSE	~12	D, MI	10.8	3.1	—
Afridi[d]	1994	77	DSE	10	D, MI	48	8.9	3
Poldermans[e]	1994	430	DSE	17	D, MI	6.6	3.4	—
Kamaran[f]	1995	210	DSE	8	D, MI	69	1	-
Williams[g]	1996	108	DSE	16	D, MI, Re	32.6	7.3	-
Anthopoulos[h]	1996	120	DSE*	14	D, MI	13.6	0	-
Marcovitz[i]	1996	291	DSE	15	D, MI	12.8	8.2	1.1
Heupler[j]	1997	508w	TSE	41	D, MI, Re	9.2	1.3	—
McCully[k]	1998	1325	NL TSE	23	D, MI	—	-	0.5
Chuah[l]	1998	860	DSE†	24	D, MI	6.9	6.3	1.9
Cortigiani[m]	1998	456w	DSE or DIP	32	D, MI	2.9	0.3	-
Davar[n]	1999	72w	NL DSE	13	D, MI	—	-	0

Prognostic value of inducible ischemia, detected with different forms of stress echocardiography.
*New wall motion abnormality considered "positive" for inducible ischemia.
†Any wall motion abnormality (at rest or with stress) considered "positive."
Adverse event rate = percentage of patients, per year, who had at least one adverse event develop during follow-up, depending on whether inducible ischemia was, or was not, demonstrated by stress echocardiography. The annualized event rate is also tabulated for those series describing patients who had normal resting and normal stress results (NL); CHF, development of severe congestive heart failure; D, death; DIP, dipyridamole stress echocardiography; DSE, dobutamine stress echocardiography; LD-DSE, low-dose dobutamine stress echocardiography; MI, nonfatal myocardial infarction, NL, series describing follow-up only in subjects with normal stress echo test results; Re, revascularization necessary; Stress, stress echocardiography protocol; TSE, treadmill stress echocardiography; Total pts, number of patients studied with stress echocardiography and subsequently followed for the development of adverse events (including death, nonfatal myocardial infarction, revascularization, or unstable angina; in posttransplant patients, development of severe congestive heart failure was also considered an adverse event); UA, unstable angina; w, patients in these series were all women.
[a]*Am Heart J* 1990; 120:49; [b]*Am J Cardiol* 1993; 71:33; [c]*Am J Cardiol* 1993; 71:646; [d]*Am Heart J* 1994; 127:1510; [e]*Am J Med* 1994; 97:119; [f]*Am J Cardiol* 1995; 76:887; [g]*J Am Coll Cardiol* 1996; 27:132; [h]*J Am Coll Cardiol* 1996; 28:52; [i]*Am J Cardiol* 1996; 78:404; [j]*J Am Coll Cardiol* 1997; 30:414; [k]*J Am Coll Cardiol* 1998; 31:144; [l]*Circulation* 1998; 97:1474; [m]*J Am Coll Cardiol* 1998; 32:1975; [n]*Am J Cardiol* 1999; 83:100-2,A8.

The assessment of myocardial viability by any imaging technique is extremely helpful in distinguishing hibernating from irreversibly injured myocardium in patients with ischemic cardiomyopathy who exhibit marked regional and/or global left ventricular dysfunction.[38] Thus, the accurate noninvasive determination of myocardial viability is critically important for clinical decision making with respect to revascularization. Although the assumption is that an improvement in left ventricular systolic function after revascularization may improve symptoms and prolong survival, this does not apply to all patients with low ejection fraction. It is also possible that additional benefits can be obtained from an improvement in blood flow to areas of stress-induced ischemia downstream from a severe coronary stenosis that are neither stunned nor hibernating. It is well documented that a revascularization strategy improves survival in patients with severe left ventricular dysfunction and anginal symptoms compared with medical therapy alone. However, this benefit has not been consistently associated with an improvement in resting left ventricular ejection fraction after revascularization. On the other hand, in patients with severe left ventricular dysfunction and predominant heart failure symptoms, revascularization of large areas of viable myocardium may lead to improved global left ventricular function, symptoms, and survival. In the same group of patients but with nonviable cardiac tissue, there is no difference in cardiac events after a medical treatment or revascularization strategy, and perioperative events at the time of revascularization are higher than in patients with viable myocardium. A meta-analysis of myocardial viability testing and the impact of revascularization in a total of 3088 patients (2228 men) with a mean left ventricular ejection fraction of 32% who were followed for 2 years has been reported.[39] In patients with myocardial viability, coronary revascularization was associated with a major reduction in annual mortality compared with medical treatment (16% vs. 3.2%). Patients without demonstrated myocardial viability had an intermediate mortality with revascularization vs. medical therapy (8% vs. 6%, P = NS) (Figure 9-11). Among patients with viable myocardium, there was a direct relationship between the severity of left ventricular dysfunction and the magnitude of benefit with revascularization. Therefore, viability assessment is less important in patients with low ejection fraction and severe angina with or without heart failure symptoms, because they seem to benefit from revascularization regardless of viability information. However, viability information is extremely helpful in most patients with left ventricular dysfunction, minimal or no anginal symptoms, and heart failure. Finally, in patients with recent myocardial infarction and jeopardized myocardium, in the infarct-related artery territory, the presence of residual viable myocardium that is not revascularized is an independent risk factor for future cardiac events.

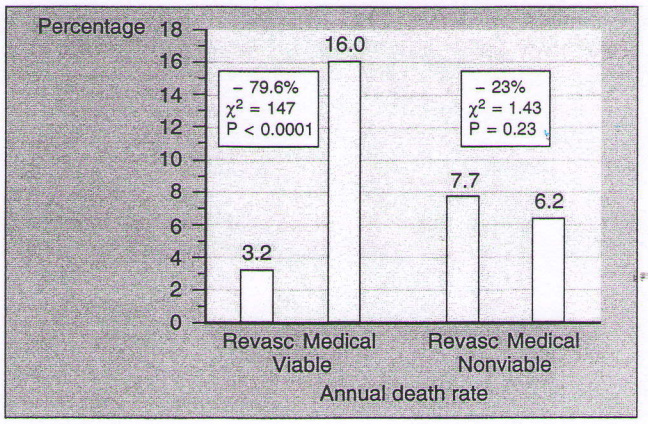

FIGURE 9-11. Death rates for patients with and without myocardial viability treated by revascularization or medical therapy. There is a 79.6% reduction in mortality for patients with viability treated by revascularization (16% vs. 3.2%, $\chi^2 = 147$, $P < 0.0001$). In patients without myocardial viability, there was no significant difference in mortality between the two strategies (7.7% vs. 6.2%, $\chi^2 = 1.43$, $P = 0.23$). (Reprinted and modified with permission from Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;39[7]:115.)

PET

PET imaging is considered by many to be the "gold standard" for noninvasive detection of viability with nuclear cardiology techniques.[24,32,40,41] Myocardial viability has been more extensively evaluated with the myocardial perfusion-FDG metabolism PET method than other protocols. With this protocol, regional myocardial perfusion is first evaluated with ^{13}N ammonia, ^{82}Rb, or ^{15}O water. Subsequently, FDG is used to assess regional myocardial glucose use. FDG is a glucose analog that crosses the capillary and sarcolemmal membrane at a rate proportionate to that of glucose. After myocardial uptake, FDG is phosphorylated to FDG-6-phosphate and is then trapped in the myocardium, because, unlike phosphorylated glucose, it is a poor substrate for glycogen synthesis, the fructose phosphate shunt, and glycolysis. Regional myocardial uptake of FDG, therefore, reflects relative distribution of regional rates of exogenous glucose use. In the fasting state, fatty acids are the preferred myocardial substrate for ATP production, and FDG is taken up minimally by the myocardium. In contrast, ischemic myocardial regions show substrate use shifts from fatty acid oxidation to glucose use. Hibernating myocardium, therefore, would demonstrate increased FDG uptake in the fasting state, unlike the surrounding normal myocardium. In the postprandial state, the normal myocardium shifts from fatty acid to glucose as the primary substrate for ATP production; thus hibernating and normal myocardium both would demonstrate FDG uptake. Therefore, preserved or even enhanced FDG uptake in dysfunctional myocardial regions represents presence of myocardial viability. Most clinical PET FDG studies are performed in the "postprandial" state to minimize heterogeneity in myocardial FDG uptake and to optimize image quality.

With the PET perfusion-metabolism protocol, when FDG is injected in the postprandial state, three different patterns of myocardial viability may be observed (Figure 9-12). Regional myocardial perfusion and FDG uptake may be concordantly reduced or absent, the so-called perfusion metabolism "match" pattern. On the basis of the severity of perfusion and FDG deficit, the "match" pattern may be categorized as transmural match (absent or markedly reduced perfusion and FDG uptake) or nontransmural match (mildly to moderately reduced perfusion and FDG uptake). These two terms were originally used to indicate that transmural match implies presence of transmural myocardial infarction, whereas nontransmural match suggests the presence of a mixture of viable and nonviable tissue in a given myocardial region and, thus, nontransmural myocardial necrosis. When regional myocardial FDG uptake is disproportionately enhanced compared with regional MBF, the pattern is termed perfusion-metabolism "mismatch." This PET pattern is thought to represent hibernating myocardium. Normal blood flow and normal, enhanced, or reduced glucose use may manifest regional dysfunction because of myocardial stunning.

Myocardial distribution of FDG may be evaluated by either coincidence imaging devices or by standard SPECT equipment and 511-keV collimators. To compare cardiac FDG uptake with perfusion, either ^{201}Tl or ^{99m}Tc-labeled tracers are used (Figure 9-13). The ^{99m}Tc-labeled tracers allow dual-isotope imaging, thereby avoiding misalignment between the FDG and the perfusion study. A number of studies have compared FDG PET with FDG

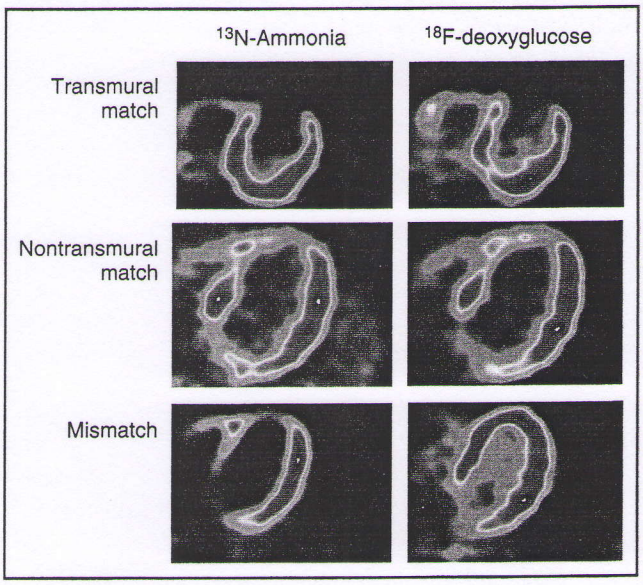

FIGURE 9-12. Regional myocardial perfusion (as evaluated by ^{13}N-ammonia) compared with ^{18}F-deoxyglucose (FDG) uptake in types of clinical situations. There may be concordant uptake of both tracers (the so-called perfusion metabolism "match" pattern), which may be categorized as transmural match (absent or markedly reduced perfusion and FDG uptake) or nontransmural match (mildly to moderately reduced perfusion and FDG uptake). The third pattern is "mismatch," which is typical for hibernating myocardium (reduced perfusion and uniform glucose uptake). See also Color Insert.

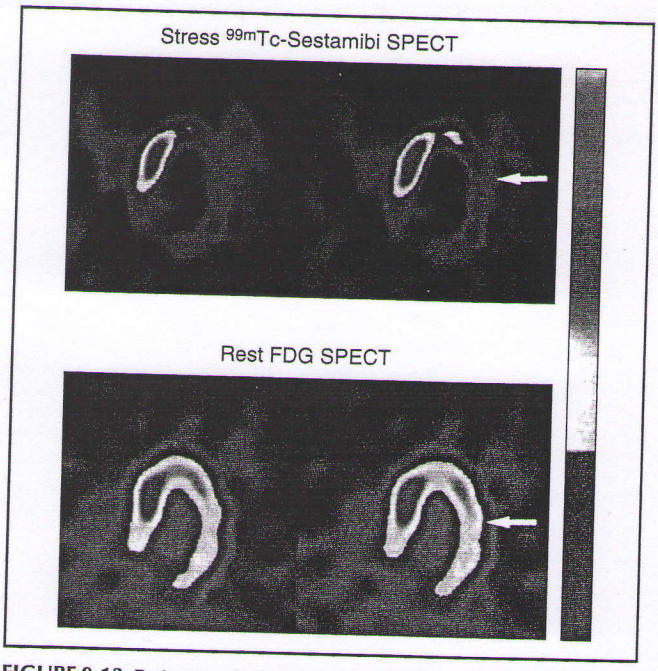

FIGURE 9-13. Patient study demonstrating "mismatch" of FDG (glucose metabolism) and sestamibi (perfusion) performed on a SPECT imaging camera (not a dedicated PET camera). There is decreased perfusion in the posterior lateral wall, but glucose uptake is preserved (viable myocardium). See also Color Insert.

SPECT, showing a good agreement between PET and SPECT in the assessment of viable myocardium, ranging from 76% to 100%. The main shortcoming of these comparative studies is the lack of outcome data after revascularization.

Prediction of Recovery of Regional Left Ventricular Dysfunction After Revascularization

The mean positive predictive value is 71%, and the negative predictive value is 86% when FDG PET is used to detect improvement in regional contractile function after revascularization (Table 9-10). The criteria for viability were a mismatch pattern in 15 studies, normal perfusion in 5 studies, and a cutoff level of regional myocardial glucose use/percentage FDG uptake in 7 studies. Combined perfusion-FDG imaging seems to be superior to FDG imaging alone in predicting improvement in myocardial function after revascularization.

Prediction of Improvement in Left Ventricular Ejection Fraction (LVEF) After Revascularization

Literature reports on the value of PET for predicting improvement in LVEF are predominantly presented as comparison between prerevascularization and postrevascularization LVEFs in patients with and those without significant perfusion-FDG metabolism mismatch (i.e., PET evidence of myocardial viability) (Table 9-11). Usually the average LVEF (%) significantly increases from prerevascularization to postrevascularization in patients who have the PET pattern of myocardial viability. In the absence of the PET pattern of viability, LVEF remains unchanged or decreased after revascularization.

TABLE 9-10 PET FOR PREDICTION OF RECOVERY OF REGIONAL LV DYSFUNCTION AFTER REVASCULARIZATION

Author/year	No. of patients	PPV (segments)	NPV (segments)
Tillisch, 1986[a]	17	85% (35/41)	92% (24/26)
Tamaki, 1989[b]	22	78% (18/23)	78% (18/23)
Tamaki, 1989[c]	11	80% (40/50)	38% (6/16)
Marwick, 1992[d]	16	68% (25/37)	79% (38/48)
Lucignani, 1992[e]	14	95% (37/39)	80% (12/15)
Carrel, 1992[f]	23	84% (16/19)	75% (3/4)
Gropler, 1993[g]	34	52% (38/73)	81% (35/43)
Paolini, 1994[h]	9	88% (23/26)	79% (11/14)
Vom Dahl, 1994[i]	37	48%-86% (NA)	84%-100% (NA)
Knuuti, 1994[j]	48	72% (23/32)	96% (50/52)
Tamaki, 1995[k]	43	76% (45/59)	92% (65/71)
Baer, 1996[l]	42	92% (24/26)	88% (14/16)
Gerber, 1996[m]	39	78% (18/23)	63% (10/16)
Vom Dahl, 1996[n]	52	68% (19/28)	93% (25/27)
Maes, 1997[o]	23	92% (10/11)	83% (10/12)
Wolpers, 1997[p]	30	90% (NA)	85% (NA)
Fath-Ordoubadi, 1998[q]	47	66% (190/286)	96% (48/50)
Pagano, 1998[r]	30	66% (190/286)	96% (48/50)
Kitsiou, 1999[s]	26	78% (NA)	82% (NA)
Weighted mean	563	71% (751/1059)	86% (417/483)

PPV, Positive predictive value; NPV, negative predictive value.
[a]*N Engl J Med* 1986; 314:884; [b]*Am J Cardiol* 1989; 64:860; [c]*Am J Cardiol* 1989; 64:86; [d]*Circulation* 1992; 85:1347; [e]*Eur J Nucl Med* 1992; 19:87; [f]*Eur J Cardiothorac Surg* 1992; 6:479; [g]*J Am Coll Cardiol* 1993; 22:1587; [h]*Eur J Cardiothorac Surg* 1994; 8:139; [i]*Circulation* 1994; 90:2356; [j]*Am Heart J* 1994; 127:785; [k]*Circulation* 1995; 91:1697; [l]*J Am Coll Cardiol* 1996; 28:60; [m]*Circulation* 1996; 94:651; [n]*J Am Coll Cardiol* 1996; 28:948; [o]*J Am Coll Cardiol* 1997; 29:62; [p]*Circulation* 1997; 95:1417; [q]*Am J Cardiol* 1998; 82:26; [r]*Heart* 1998; 79:281; [s]*J Am Coll Cardiol* 1999; 33:678.

Prediction of Improvement in Heart Failure Symptoms After Revascularization

Because most patients with poor left ventricular function have heart failure symptoms, an important goal in assessing myocardial viability is to predict improvement

TABLE 9-11 PET FOR PREDICTION OF IMPROVEMENTS IN LEFT VENTRICULAR EJECTION FRACTION (LVEF) AFTER REVASCULARIZATION

Author/year	No. of patients	Patients with mismatch LVEF (%)		Patients without mismatch LVEF (%)	
		Pre	*Post*	*Pre*	*Post*
Tillisch, 1986[a]	17	30 ± 11	45 ± 14	30 ± 11	31 ± 12
Lucignani, 1992[b]	14	38 ± 5	48 ± 4	—	—
Paolini, 1994[c]	17	28 ± 5	43 ± 8	—	—
Depre, 1995[d]	23	43 ± 18	52 ± 15	35 ± 9	24 ± 8

Pre and Post, Revascularization process.
[a]*N Engl J Med* 1986; 314:884; [b]*Eur J Nucl Med* 1992; 19:874; [c]*Eur J Cardiothorac Surg* 1994; 8:139; [d]*Am J Physiol* 1995; 268:H1265.

in heart failure symptoms after myocardial revascularization. This question has been addressed in three publications by use of myocardial perfusion-FDG metabolism PET imaging. Improvement in heart failure, by at least one class, seems to be related to the PET pattern (presence or absence of mismatch) and type of treatment (revascularization or medical therapy). More patients with the PET mismatch pattern who undergo revascularization have improvement in heart failure class than the other subgroups. Furthermore, the total extent of a PET mismatch before surgery seems to correlate linearly and significantly with a percent improvement in functional state after revascularization. Patients with large mismatches achieve a significantly higher functional state compared with those patients with minimal or no PET mismatch.

Thus, the PET pattern of myocardial viability predicts recovery of regional and global left ventricular dysfunction after myocardial revascularization and also identifies a subgroup of patients with poor left ventricular function and heart failure who are most likely to show relief of heart failure symptoms as a result of revascularization. Patients with large perfusion metabolism mismatches (i.e., greatest magnitude of ischemic viable myocardium by PET) exhibit the greatest clinical benefit after revascularization.

Prediction of Improved Survival After Revascularization

A major goal of noninvasive diagnostic procedures in the assessment of coronary artery disease is to evaluate prognosis and to assess the potential of survival benefit from a treatment plan. Because survival of patients with left ventricular dysfunction relates to the resting LVEF, it may be implied that perfusion-FDG metabolism PET imaging by predicting improvement in LVEF can also predict survival after myocardial revascularization. This hypothesis has been addressed in a few studies (Figure 9-14). The results indicate that in the subgroup of patients treated medically with viable myocardium as assessed by PET FDG imaging, the event rate (death or myocardial infarction) was approximately 50%. Importantly, in the patients with viable myocardium who underwent revascularization, the event rate was significantly lower at 13%. In patients without PET FDG evidence of myocardial viability, event rates were similar with medical therapy, and revascularization had similar event rates (15% vs. 13%, respectively). These data suggest that in patients with ischemic cardiomyopathy, revascularization should be recommended only in those with PET FDG evidence of myocardial viability.

Influence of PET FDG Metabolism Evaluation of Myocardial Viability on Clinical Decision Making and Patient Management

Cardiac transplantation has been the ultimate therapy for end-stage heart failure; however, because of the limited number of available donor hearts, the waiting period for a heart transplant by eligible recipients has been prolonged and ranges from 8 months to 2 years. By detecting the presence of a sufficient amount of viable (hibernating) myocardium, potential candidates for myocardial revascularization may be identified. Such an approach not only lowers the number of patients who are waiting for a transplant but also reduces the overall cost of patient care by offering CABG to patients who would otherwise undergo more costly cardiac transplantation. Candidates for cardiac transplantation with ischemic cardiomyopathy may undergo PET perfusion-FDG metabolism imaging for assessment of the presence and extent of myocardial viability. If these patients have evidence of mismatch in at least two regions of the myocardium and suitable coronary targets for revascularization, consideration should be given to treatment with CABG, which is a more cost-effective therapy than cardiac transplantation with similar perioperative and long-term survival.

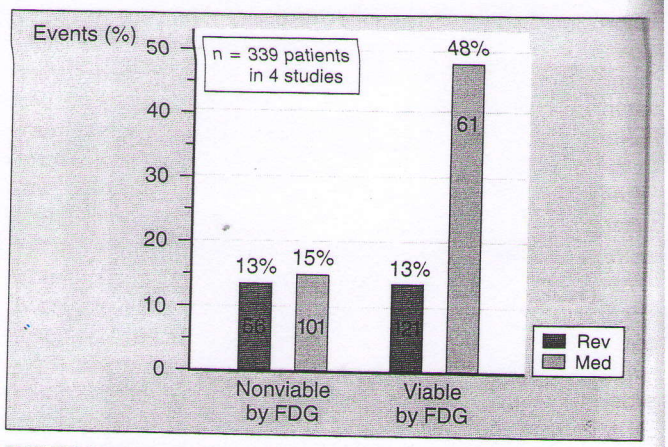

FIGURE 9-14. A summary diagram of four studies that have reported on cardiac events in patients after PET evaluations of myocardial viability. Patients are divided into two main groups (nonviable by FDG and viable by FDG) and then subdivided into those patients undergoing subsequent revascularization (Rev) or medical (Med) therapy. Events are highest in those patients who have viable myocardium and only get medical therapy.

Use of SPECT Imaging to Assess Myocardial Viability

A number of radionuclide techniques can be used to assess myocardial viability in patients with ischemic heart disease.[15,39] Thallium-201 SPECT MPI is the most widely used and validated modality and continues to be the cornerstone of single photon radionuclide assessment of tissue viability. A delayed uptake of ^{201}Tl on rest-redistribution imaging is related to the presence of viable cells with intact cellular membrane. Several different protocols have been used to assess myocardial viability with ^{201}Tl SPECT MPI: rest-redistribution (either 4 or 24 hours), stress-redistribution, and the addition of ^{201}Tl re-injection techniques. Criteria to identify viability with ^{201}Tl have traditionally included the demonstration of redistribution and the uptake of the tracer >50% of normal uptake in an adjacent region on 4-hour redistribution imaging. However, this perfusion criteria cutoff to distinguish between viable and nonviable myocardium is actually more of a continuum. Several studies have

shown an almost linear relationship between regional thallium activity and recovery of myocardium after revascularization. Myocardial segments with a low thallium uptake (<40%) are unlikely to improve after revascularization, and most myocardial segments with uptake greater than 80% will improve functionally after revascularization (Figure 9-15). The diagnostic accuracy of myocardial viability testing by use of ^{201}Tl rest-redistribution, ^{201}Tl stress-redistribution-reinjection, ^{99m}Tc-sestamibi MPI, ^{18}F-FDG PET, and low-dose dobutamine echocardiography in a pooled analysis suggests that the average sensitivity, specificity, and accuracy were 87%, 54%, and 70%, respectively, for ^{201}Tl techniques, but the specificity for both ^{201}Tl protocols was significantly lower than the other techniques. Although all techniques may accurately identify segments with improved contractile function after recovery, ^{201}Tl protocols may overestimate functional recovery. Low-dose dobutamine echocardiography appears to have a higher specificity and the highest predictive accuracy. However, because the differences in functional recovery generally involve small regions of myocardium, there is little or even no impact on late survival. This is supported by another prospective, randomized trial in which patients with ischemic cardiomyopathy were randomly assigned to clinical decisions for revascularization on the basis of ^{13}N-ammonia/^{18}F-FDG PET or ^{99m}Tc-sestamibi results.[24] There was no difference in patient management or cardiac event-free survival with either of the two techniques.

Although ^{99m}Tc-labeled agents (sestamibi, tetrofosmin) do not show significant redistribution over time, several studies have shown comparable accuracy for viability detection between these agents and ^{201}Tl. Analyses of the use of ^{99m}Tc agents to assess myocardial viability from multiple studies in patients with left ventricular dysfunction indicate an average sensitivity of 80%, a specificity of 60%, and diagnostic accuracy of 70%. The administration of nitrates (either sublingually or intravenously) before a resting injection of ^{201}Tl or ^{99m}Tc improves the sensitivity for the detection of viable myocardium.

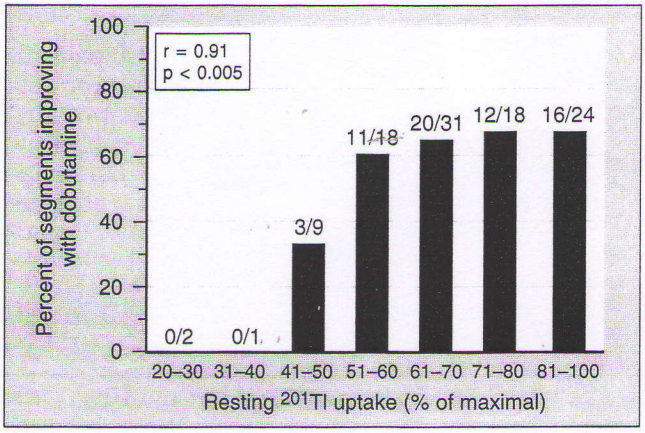

FIGURE 9-15. Demonstration of the linear relationship between the percentage of peak thallium activity on rest-redistribution imaging and the likelihood of segmental improvement after revascularization. Although various cutoff values have been proposed as thresholds, for viability, this figure indicates the continuous nature of this relation. (Reprinted with permission from Dilsizian V, Rocco TP, Freedman NM, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. *N Engl J Med* 1990; 323[3]:141.)

Use of Echocardiography to Assess Myocardial Viability

A common clinical question is to decide whether dysfunctional myocardium is irreversibly damaged or "hibernating" (i.e., myocardium with a chronic reduction in perfusion sufficient to impair normal contractile function but preserve viability).[38] In patients with multivessel coronary artery disease and depressed left ventricular function, improvement in regional left ventricular function during dobutamine stress echocardiography indicates contractile reserve and is predictive of improved ventricular function after revascularization (Figure 9-16, *A* and *B*). The lack of contractile reserve during low-dose dobutamine infusion denotes a low likelihood of improvement after bypass surgery, and the presence or absence of contractile reserve by low-dose dobutamine stress echocardiography has positive and negative predictive values of approximately 80% (Tables 9-12 and 9-13).

In patients with heart failure caused by ischemic left ventricular dysfunction, evaluation of myocardial viability by dobutamine stress echocardiography can help determine the potential benefit of revascularization. The demonstration of significant regions of hibernating myocardium, which would suggest a high likelihood of improved function after successful revascularization, can help in deciding whether patients need coronary revascularization rather than heart transplantation.

COMPARISON BETWEEN DOBUTAMINE STRESS ECHOCARDIOGRAPHY AND FDG SPECT

Low-dose dobutamine echocardiography demonstrates contractile reserve in approximately 70% of viable segments detected by FDG SPECT (i.e., there is underestimation of viability by dobutamine echocardiography compared with FDG SPECT). In contrast, more than 90% of segments classified as nonviable by FDG SPECT have absence of contractile reserve during dobutamine echocardiography. Segments with contractile reserve and metabolic activity are likely to recover function after revascularization, but the functional fate after revascularization of the segments with preserved metabolic activity without contractile reserve has not been studied extensively. PET allows a quantitative assessment of MBF and metabolism and thus a more direct investigation of the mechanisms underlying ischemic left ventricular dysfunction than stress echocardiography.[26,39] Both techniques can identify viable myocardium and its potential recovery after revascularization with similar accuracy. The greater availability and the lower cost of dobutamine echocardiography may favor the use of this method in

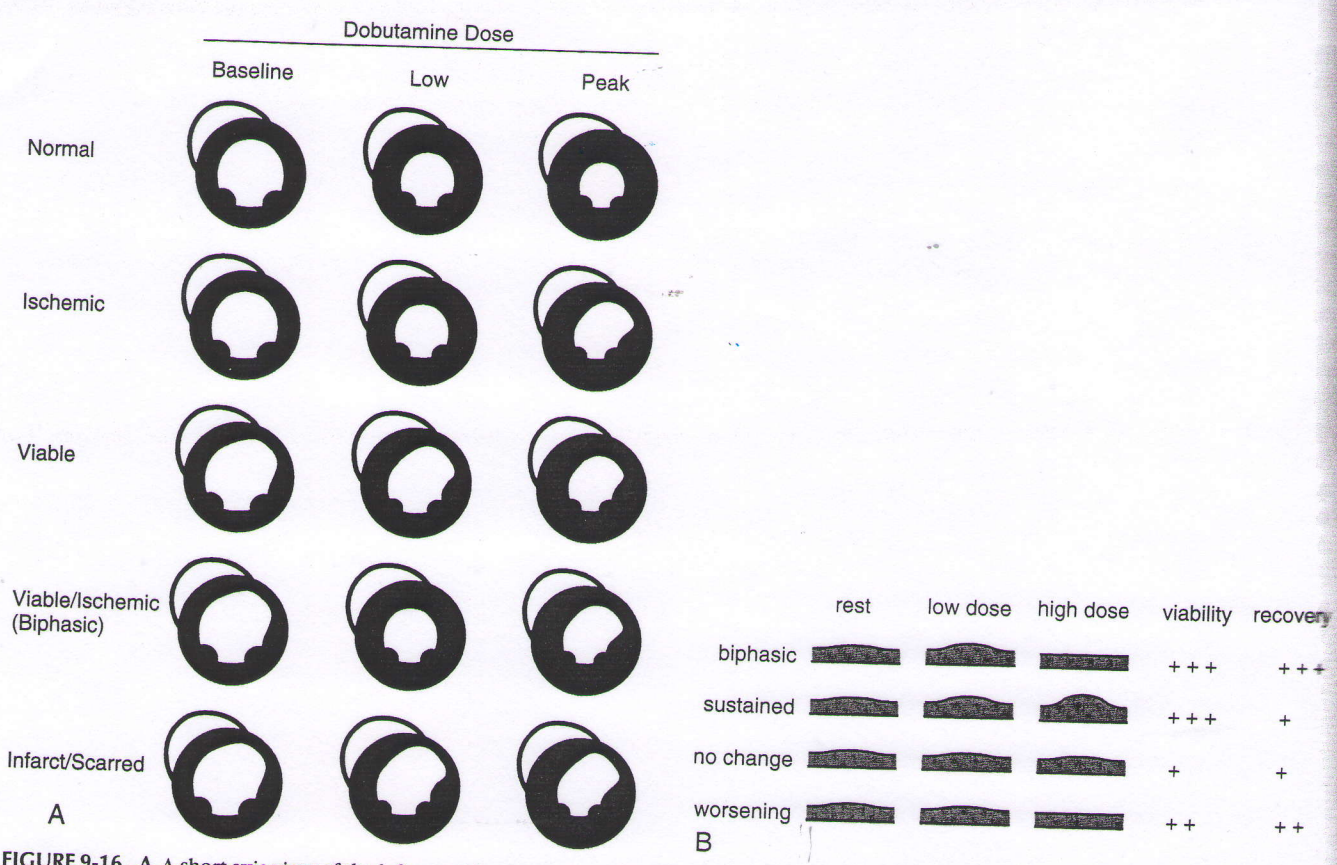

FIGURE 9-16. **A,** A short-axis view of the left ventricle at end-systole demonstrating various responses to a graded dobutamine infusion. The upper panel demonstrates a normal response. Subsequent panels show various abnormalities involving the anterolateral wall with a normal response in other ventricular segments. (From Orsinelli D, Daniels C. Pharmacologic stress echocardiography. *Cardiol Clin* 1999; 17:461. Reproduced with permission.) **B,** The different responses of dysfunctional myocardial segments to dobutamine at low dose and high dose and their relation to viability and recovery of contractile function after revascularization. (From Nagueh SF, Zoghbi WA. Stress echocardiography for the assessment of myocardial ischemia and viability. *Curr Prob Cardiol* 1996; 21:497. Reproduced with permission.)

TABLE 9-12 MYOCARDIAL VIABILITY: DETECTION OF STUNNED MYOCARDIUM BY DSE EARLY AFTER ACUTE MYOCARDIAL INFARCTION

Author	Year	Days after MI	Stress	N	Criteria	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
Pierard[a]	1990	7 d	LD-DSE	17	impWM*	100	70	70	100	82
Barilla[b]	1991	4 d	LD-DSE	21	impWM*	95	—	—	—	95
Smart[c]	1993	2-7 d	LD-DSE	51	impWM*	86	90	86	90	88
Previtali[d]	1993	8 d	LD-DSE	42	impWM†	79	68	50	89	71
Watada[e]	1994	3 d	LD-DSE	21	impWM†	83	86	89	80	84
Poli[f]	1996	<10 d	LD-DSE	51	impWM†	72	68	50	85	69
Bolognese[g]	1996	3 d	LD-DSE	30	impWM†	89	91	86	93	90
Minardi[h]	1997	3-5 d	LD-DSE	50	impWM†	86	100	100	94	96
Smart[i]	1997	2-7 d	LD-DSE	115	impWM†	86	83	80	88	84

Acc, Overall accuracy; Criteria, findings on DSE considered as a "positive" indicator of viability; impWM, improved segmental wall motion seen on follow-up echocardiogram; d, days; LD-DSE, low-dose dobutamine stress echocardiography; MI, myocardial infarction; NPV, negative predictive value (likelihood of lack of subsequent improvement in patients without viability); PV, positive predictive value (likelihood of subsequent improvement in patients with evidence of viability; Sens, sensitivity for detecting viable myocardium; Spec, specificity for detecting viable myocardium; Stress, DSE protocol used for pharmacological stress. Evaluation of myocardial viability with dobutamine stress echocardiography (DSE) early after acute myocardial infarction to detect stunned myocardium. The presence or absence of viability was established by follow-up resting transthoracic echocardiography.
N, Patients in this study were treated at admission with thrombolytic therapy.
*Wall motion analyzed by patient.
†Wall motion analyzed by segment.
[a]*J Am Coll Cardiol* 1990; 15:1021; [b]*Am Heart J* 1991; 122:1522; [c]*Circulation* 1993; 88:405; [d]*Am J Cardiol* 1993; 72:124G; [e]*J Am Coll Cardiol* 1994; 24:624; [f]*Heart* 1996; 75:240; [g]*J Am Coll Cardiol* 1996; 28:1677; [h]*Am J Cardiol* 1997; 80:847; [i]*Circulation* 1997; 95:1394.

TABLE 9-13 MYOCARDIAL VIABILITY: DETECTION OF HIBERNATING MYOCARDIUM BY DSE IN PATIENTS WITH CHRONIC CAD AND LV DYSFUNCTION

Author	Year	Stress	*N*	Criteria	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
Marzullo[a]	1993	LD-DSE	14	Improve WM*	82	92	95	73	85
Cigarroa[b]	1993	LD-DSE	25	Improve WM†	82	86	82	86	84
Alfieri[c]	1993	LD-DSE	14	Improve WM*	91	78	92	76	88
LaCanna[d]	1994	LD-DSE	33	Improve WM*	87	82	90	77	85
Charney[e]	1994	DSE	17	Improve WM*	71	93	92	74	81
Afridi[f]	1995	DSE	20	Improve WM†	80	90	89	82	85
Senior[g]	1995	LD-DSE	22	Improve WM*	87	82	92	73	86
Haque[h]	1995	LD-DSE	26	Improve WM*	94	80	94	80	91
Arnese[i]	1995	LD-DSE	38	Improve WM*	74	96	85	93	91
DeFilippi[j]	1995		23	Improve WM*	97	75	87	93	89
Iliceto[k]	1996	LD-DSE	16	Improve WM*	71	88	73	87	83
Varga[l]	1996	LD-DSE	19	Improve WM*	74	94	93	78	84
Baer[m]	1996	LD-DSE	42	Improve WM†•	92	88	92	88	90
Vanoverschelde[n]	1996	LD-DSE	73	Improve WM†	88	77	84	82	84
Gerber[o]	1996	LD-DSE	39	Improve WM*	71	87	89	65	77
Bax[p]	1996	LD-DSE	17	Improve WM*	85	63	49	91	70
Perrone-Filardi[q]	1996	LD-DSE	18	Improve WM*	79	83	92	65	81
Qureshi[r]	1997	LD-DSE	34	Improve WM*	86	68	51	92	73
Quresh[r]	1997	DSE	34	Biphasic resp*	74	89	72	89	85
Nagueh[s]	1997	LD-DSE	18	Improve WM*	91	66	61	93	75
Nagueh[s]	1997	DSE	18	Biphasic resp*	68	83	70	82	77
Furukawa[t]	1997	LD-DSE	53	Improve WM*	79	72	76	75	76
Cornel[u]	1997	LD-DSE	30	Improve WM	89	82	74	93	85

Evaluation of myocardial viability with dobutamine stress echocardiography (DSE) in patients with chronic coronary artery disease (CAD) and impaired systolic left ventricular (LV) function to detect hibernating myocardium. In these patients, percutaneous or surgical revascularization was carried out after DSE testing. Those patients demonstrating improved wall motion on follow-up resting transthoracic echocardiography were considered to have had impaired LV function caused by hibernating myocardium, whereas those demonstrating no improvement despite revascularization were considered to have had impaired LV function caused by necrotic myocardium.

Acc, Overall accuracy; biphasic resp, biphasic response, defined as improvement in wall motion during low-dose dobutamine stress followed by worsening at high doses; Criteria, findings on DSE considered a "positive" indicator of viability; DSE, dobutamine stress echocardiography (dobutamine infused at both low and high doses); improvWM, improved wall motion during dobutamine stress in a previously asynergic segment; LD-DSE, low-dose dobutamine stress echocardiography; NPV, negative predictive value (likelihood that absence of viability by DSE is indicative of lack of functional recovery after revascularization); PPV, positive predictive value (likelihood that presence of viability by DSE is indicative of subsequent functional recovery after revascularization); Sens, sensitivity; Spec, specificity; Stress, DSE protocol used for pharmacological stress; *N*, number of patients with chronic CAD and LV dysfunction in whom DSE studies were analyzed.

*Wall motion analyzed by segment.

†Wall motion analyzed by patient.

[a]*Am J Cardiol* 1993; 71:166; [b]*Circulation* 1993; 88:430; [c]*Eur J Cardiothorac Surg* 1993; 7:325; [d]*J Am Coll Cardiol* 1994; 23:617; [e]*Am Heart J* 1994; 128:864; [f]*Circulation* 1995; 91:663; [g]*Br Heart J* 1995; 74:358; [h]*Am Heart J* 1995; 130:553; [i]*Circulation* 1995; 91:2748; [j]*Circulation* 1995; 92:2863; [k]*Am J Cardiol* 1996; 77:441; [l]*Eur Heart J* 1996; 17:629; [m]*J Am Coll Cardiol* 1996; 28:60; [n]*J Am Coll Cardiol* 1996; 28:432; [o]*Circulation* 1996; 94:651; [p]*J Am Coll Cardiol* 1996; 28:558; [q]*Circulation* 1996; 94:2712; [r]*Circulation* 1997; 95:626; [s]*J Am Coll Cardiol* 1997; 29:985; [t]*Eur Heart J* 1997; 18:798; [u]*Eur Heart J* 1997; 18:941.

most clinical settings. Finally, myocardial contrast echocardiography, which is a developing technique, has been proposed to identify viable myocardium in patients with both acute and chronic ischemic left ventricular dysfunction.[42] The availability of contrast agents that can be injected into a peripheral vein to measure myocardial perfusion seems to be an attractive alternative to nuclear studies.

Use of CMR Imaging to Assess Myocardial Viability

Scar Formation and Left Ventricular Wall Thickness

After transmural myocardial infarction, severe wall thinning may be present within several months of the acute event. In recent transmural infarcts, thinning is less marked, because local infarct remodeling is incomplete. Nontransmural infarcts may develop some wall thinning in proportion to the degree of myocardial damage. Therefore, the finding of preserved diastolic myocardial wall thickness in the territory of a known chronic infarct is likely to represent nontransmural infarction with a substantial overlying rim of viable myocardium. CMR is well suited for defining regional wall thickness because of its resolution and ability to image in any plane without limitation. Using a cutoff of 5.5 mm for left ventricular wall thickness, which is similar to that defined in pathological studies of transmural MI, it has been shown that akinetic regions of myocardium that exhibit end-diastolic thinning have significantly reduced FDG uptake. In most patients, the viability assessments based on FDG-PET and CMR are identical.

Contractile Reserve of Viable Myocardium

The predictive value of preserved end-diastolic wall thickness in determining recovery of myocardial function after revascularization is low. However, if contractile reserve can be demonstrated in dyssynergic segments, recovery of function is common after revascularization, and CMR is capable of providing such images.

Low-dose dobutamine CMR has been used to determine viability compared with FDG-PET and has shown a sensitivity of approximately 80% with a specificity of 95%.[29] Dobutamine CMR has also been used to predict postrevascularization functional recovery (sensitivity and specificity approximately 90%), and the use of FDG PET for comparison seems more sensitive than transesophageal echocardiography in detecting viable myocardium (81% vs. 77%) with similar sensitivity.

Late Gadolinium Hyperenhancement in Myocardial Infarction

Gadolinium contrast agents are used in CMR to decrease T1, which leads to an increased signal with appropriate imaging sequences.[32] Commercially available gadolinium agents distribute in the extracellular space, which is limited in the heart, and therefore there is rather little myocardial enhancement. During acute myocardial infarction, myocyte rupture occurs, which expands the extracellular space and increases effective voxel concentration of gadolinium. In addition, infarct tissue kinetics for the passage of gadolinium are slow compared with normal myocardium. Both of these effects lead to significant signal enhancement within the infarct.[43] The recent implementation of inversion recovery sequences, which null signal from normal myocardium, has allowed dramatic increases in contrast between infarcted and normal myocardium. The optimal time for imaging infarction after injection of a gadolinium bolus is when blood pool activity is falling, and this occurs about 10 minutes after injection. Therefore, this technique is referred to as "late enhancement." The technique has now been extensively validated in animal experiments, with the area of late gadolinium contrast enhancement correlating closely with areas of infarction, and, for the first time in vivo, high-quality imaging of the transmural distribution of scar is possible (Figure 9-17). Late enhancement of infarction also occurs in chronic infarcts because of a continuing increase in partition coefficient for gadolinium and delayed contrast agent kinetics. The technique has obvious implications for the assessment of viability, and a significant relationship exists between the transmural extent of gadolinium hyperenhancement within a segment and its potential for postrevascularization functional recovery in both animals and humans. With transmural enhancement of 25% or less, recovery is usual, but with enhancement of greater than 50%, there is little likelihood for recovery. When borderline (25% to 50%) hyperenhancement is demonstrated, recovery of myocardial function with revascularization is unpredictable.

Clinical Applications for Quantitation of Absolute MBF and Flow Reserve

Quantitative PET has been used to study MBF in response to interventions and in a variety of cardiac diseases such as syndrome X, hypertrophy cardiomyopathy, and cardiac transplantation vasculopathy. In these conditions, MBF is affected fairly uniformly (i.e., no significant regional differences in MBF are detectable). Therefore, absolute quantitation of MBF and flow reserve rather than relative quantitation of MBF are helpful in evaluating these conditions.

Syndrome X

Patients with syndrome X typically exhibit subjective (chest pain) or objective (ST-segment depression) evidence of myocardial ischemia despite absence of angiographically detectable coronary artery disease. In syndrome X patients, compared with normal volunteers, no significant differences in resting and hyperemic MBF or CFR are noted. However, some syndrome X patients have a reduced flow reserve that may be a result of significantly higher resting blood flow and consequently lower relative hyperemic MBF. Others have demonstrated a more heterogeneous distribution of blood flow at rest and during pharmacological hyperemia in syndrome X patients. Overall, quantitative flow measurements with PET have not yet suggested a uniform coronary flow mechanism in patients with syndrome X.

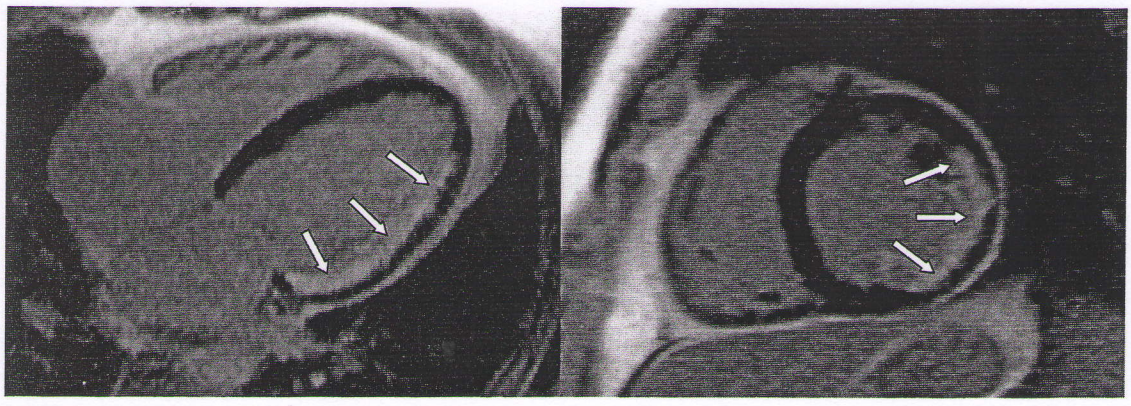

FIGURE 9-17. CMR using late gadolinium enhancement in a patient with an occluded left circumflex artery and lateral wall infarction *(arrows)*. *Left,* horizontal long axis; *right,* short axis. The infarction is nontransmural except for one small area seen on the short axis. Myocardial infarctions caused by ischemia invariably involve the subendocardium, but the transmural extent depends on the time to reperfusion and the presence of any collaterals.

Use of CMR Imaging to Evaluate Transmural Perfusion

The high spatial resolution of perfusion CMR facilitates the study of in vivo transmural variations in myocardial perfusion. Areas of myocardium perfused by a stenotic coronary artery have decreased subendocardial enhancement and lower enhancement in subendocardium compared with subepicardium.

Evaluation of Coronary Flaw Reserve (CFR)

In addition to homeostatic functions, the normal vascular endothelium may regulate vascular tone, and blood flow, by production of vasodilators (e.g., nitric oxide) and vasoconstrictors (e.g., endothelin-1), and because endothelium can be damaged by atherosclerosis, endothelial dysfunction may ensue. By use of CMR, acute cigarette smoking has been shown to be associated with an increased resting MBF and a reduced hyperemic myocardial flow. By use of dynamic ^{13}N-ammonia PET imaging in conjunction with intravenous adenosine, an abnormal vasodilatory response has been detected in male patients with a family history of coronary artery disease and high-risk lipid profiles, and CFR may also be decreased in anatomically normal coronary arteries of hypercholesterolemic patients. Improved cardiovascular conditioning alone, or in association with a low-fat diet, may improve coronary vasodilator capacity.

PREOPERATIVE CARDIAC RISK EVALUATION FOR NONCARDIAC SURGERY

Ischemic heart disease is a major cause of morbidity and mortality among patients undergoing elective noncardiac surgery and accounts for approximately one half of all perioperative deaths. Fortunately, most patients with known coronary artery disease can safely undergo major noncardiac surgery. The physiological importance of the coronary lesion(s) rather than the coronary anatomy per se has been established as the standard for evaluating cardiac risk in patients with coronary artery disease undergoing elective noncardiac surgery.

The major question is which subpopulations benefit from preoperative cardiac risk stratification. Recently, the ACC/AHA Task Force on Practice Guidelines has published an update on the recommendations for perioperative cardiovascular evaluation for noncardiac surgery.[44] These guidelines suggest that noninvasive cardiac testing should be used in patients with intermediate cardiac risk factors (mild angina, prior myocardial infarction, compensated or prior heart failure symptoms, or diabetes mellitus) who have either low functional capacity (<4 METs) or high-risk surgery (especially vascular). Patients with minor risk predictors do not need noninvasive risk stratification unless both their functional capacity is poor (<4 METs) and they are undergoing a high-risk surgical procedure. The results of noninvasive testing (typically exercise testing or stress MPI or echocardiography) can be used to determine further preoperative management, such as cardiac catheterization and/or coronary revascularization, intensive medical therapy, or delay and/or cancellation of an elective noncardiac operation.

It is well appreciated that clinical indices alone (such as the Goldman index) have insufficient sensitivity or specificity for predicting perioperative cardiac events in patients with known coronary artery disease. Reviews of pharmacological stress MPI or echocardiography have shown that both techniques are useful in the risk stratification of these types of patients. In addition, MPI studies have demonstrated significant prognostic value in the later follow-up period and the perioperative period. Reports on the use of dobutamine echocardiography also support its utility in cardiac risk assessment in the perioperative period.[45] A number of investigators that used dipyridamole perfusion imaging to risk stratify patients with transient perfusion defects have shown a cardiac event rate of 1% to 2% in patients with normal scans and a gradient of risk of events from 8% to 50% as more coronary vessel perfusion defects are noted. Echocardiography also reveals a prognostic gradient of wall motion abnormalities that can predict increasing vulnerability to adverse short-term outcomes.

Preoperative risk stratification allows the clinician to predict the short-term risk for a particular patient but also to estimate a late cardiac event. In patients having dipyridamole ^{201}Tl MPI before elective vascular surgery, the best predictor of late cardiac events was the presence of moderate to large-sized fixed defects reflecting abnormalities in systolic ventricular function.

Finally, although myocardial SPECT imaging can successfully identify patients at high risk for perioperative and long-term cardiac events, the validity of a strategy of routine coronary revascularization before noncardiac surgery remains unclear.

In summary, stress MPI and echocardiography in conjunction with clinical predictors of risk, functional capacity, and surgery specific risk can accurately assess the perioperative cardiac risk among selected patients (intermediate-risk group) undergoing noncardiac surgery. A normal study has a high negative predictive value, whereas a positive study predicts a higher event rate that seems to increase in proportion to the magnitude of jeopardized myocardium or ventricular dysfunction.

RISK ASSESSMENT IN WOMEN

The selection of the appropriate noninvasive prognostic test in women requires careful consideration. Several factors play an important role in this decision. First, the risk profile in women differs compared with men. Second, epidemiological data suggest that women tend to present with their first anginal symptoms 10 years later and sustain their first myocardial infarction 20 years later than their male counterparts. Nonrandomized trials and observational studies attribute this partially to the cardioprotective role of estrogen. Third, several studies

TABLE 9-14 DIAGNOSTIC ACCURACY OF STRESS ECHOCARDIOGRAPHY IN DETECTING ANGIOGRAPHICALLY PROVEN CAD IN WOMEN

Author	Year	Protocol	Signif CAD	Total Pts	Sens (%)	Sens 1VD	Sens MVD	Spec (%)	PPV (%)	NPV (%)	Acc (%)
Masini[a]	1988	DIP	≥70%	83	79	—	—	93	91	84	87
Sawada[b]	1989	TSE or UBE	≥50%	57	86	88	82	86	86	86	86
Severi[c]	1994	DIP	≥75%	122	68	—	—	96	90	86	87
Williams[d]	1994	UBE	≥50%	70	88	89	86	84	83	89	86
Marwick[e]	1995	TSE or UBE	≥50%	161	80	75	85	81	71	87	81
Takeuchi[f]	1996	DASE	≥50%	70	75	78	73	92	79	90	87
Roger[g]	1997	TSE or UBE	≥50%	96	79	—	—	37	66	54	63
Dionisopoulos[h]	1997	DASE	≥50%	101	90	79	94	79	90	79	86
Laurienzo[i]	1997	DS-TEE	≥70%	84	82	—	—	100	100	94	95
Elhendy[j]	1997	DASE	≥50%	96	76	64	92	94	96	68	82
Ho[k]	1998	DSE	≥50%	51	93	89	95	82	87	90	88

Diagnostic accuracy of stress echocardiography, using either exercise or pharmacological stress, in detecting angiographically proved coronary artery disease (CAD) in women. A new or worsening regional wall motion abnormality induced by stress generally was considered a "positive" result.
1 VD, test results positive in patients with single-vessel CAD; Acc, overall accuracy; CAD, coronary artery disease; DASE, dobutamine/atropine stress echocardiography; DIP, dipyridamole stress echocardiography; DSE, dobutamine stress echocardiography; DS-TEE, dobutamine stress transesophageal echocardiography; MVD, test results positive in patients with multivessel CAD; NPV, negative predictive value (likelihood of absence of angiographically significant CAD in patients without inducible wall motion abnormalities by stress echocardiography); PPV, positive predictive value (likelihood of angiographically significant CAD in patients with inducible wall motion abnormalities by stress echocardiography); Protocol, exercise or pharmacological protocol used in conjunction with transthoracic echo imaging; Pts, patients; Sens, sensitivity; Signif CAD, % coronary luminal diameter narrowing, documented by selective coronary angiography, considered to represent "significant" CAD; Spec, specificity; TSE, treadmill stress echocardiography; Total Pts, number of women in each series undergoing selective coronary angiography in whom stress echo studies were also carried out and wall motion analysis performed; UBE, upright bicycle stress echocardiography.
[a]*J Am Coll Cardiol* 1988; 12:682; [b]*J Am Coll Cardiol* 1989; 14:1440; [c]*Circulation* 1994; 89:1160; [d]*Am J Cardiol* 1994; 74:435; [e]*J Am Coll Cardiol* 1995; 26:335; [f]*Cor Art Dis* 1996; 7:831; [g]*Circulation* 1997; 95:405; [h]*J Am Soc Echocardiogr* 1997; 10:811; [i]*Am J Cardiol* 1997; 80:1402; [j]*Am J Cardiol* 1997; 80:1414; [k]*Am Heart J* 1998; 135:655.

have detailed the lack of diagnostic value of exercise testing in women. In those studies, sensitivity for the detection of significant coronary artery disease (≥50% or ≥70% angiographic stenosis) was similar in men and women (60% to 80% in women and 65% to 87% in men); however, specificity was significantly lower in women (63% to 68%) than men (74% to 89%).

Use of Stress MPI in Women

Stress MPI shows improved sensitivity and specificity in the detection of coronary artery disease in women.[14,16,21] Planar ^{201}Tl imaging has a sensitivity of 71% to 75% and a specificity of 91% to 97% in women with no prior history of coronary artery disease, and exercise SPECT MPI has been found to be more sensitive than planar imaging. Similar results can be obtained with pharmacological radionuclide imaging. By use of adenosine SPECT MPI with dual-isotope (rest ^{201}Tl/stress ^{99m}Tc-sestamibi for the detection of coronary stenosis of ≥70%) the sensitivity, specificity, and diagnostic accuracy was 95%, 66%, and 85%, respectively, with 93% normalcy rate. These results are similar for all women, regardless of the presenting symptoms, a history of myocardial infarction, or the pretest probability of coronary artery disease. The role of ^{99m}Tc agents and the addition of electrocardiographic-gated SPECT imaging further improve the specificity compared with ^{201}Tl imaging. In fact, stress MPI with either ^{99m}Tc or ^{201}Tl should be gated in all patients, not just women.

Thus, taking all data together, both exercise and pharmacological SPECT MPI provide significant independent and incremental prognostic information to clinical, physiological, and coronary angiographic data in women.

Use of Stress Echocardiography for Diagnosis of Coronary Artery Disease in Women

It has been established that the accuracy of exercise testing is lower in women than in men, owing in part to the higher prevalence of coronary disease in men. In studies of nearly 1000 women with suspected coronary artery disease where the presenting complaint was usually chest pain (Table 9-14), the diagnostic accuracy of stress echocardiography, with coronary arteriography as the reference standard, is good. The weighted mean sensitivity is 81% (89% in women with multivessel disease), specificity of 86%, and overall accuracy is 84%. Stress echocardiography clearly has a higher diagnostic accuracy than conventional treadmill exercise testing and may be a cost-effective diagnostic strategy in women with an intermediate pretest probability of coronary artery disease.

In summary, although a negative exercise stress test is extremely helpful in women with suspected coronary artery disease, a positive result may be misleading, especially in combination with atypical symptoms. Stress MPI improves the sensitivity and the specificity in the diagnosis of coronary artery disease and gives important prognostic information. The use of ^{99m}Tc agents with simultaneous assessment of perfusion and function further enhance the diagnostic accuracy of MPI in women.

REFERENCES

1. Gibbons RJ, Balady GJ, Timothy Bricker J, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol* 2002; 40:1531.
2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143.
3. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* 2003; 107:149.
4. Ritchie JL, Bateman TM, Bonow RO, et al. Guidelines for clinical use of cardiac radionuclide imaging: A report of the American College of Cardiology/American Heart Association Task Force on assessment of diagnostic and therapeutic cardiovascular procedures (Committee on Radionuclide Imaging)—developed in collaboration with the American Society of Nuclear Cardiology. *J Nucl Cardiol* 1995; 2:172.
5. Mazur W, Rivera JM, Khoury AF, et al. Prognostic value of exercise echocardiography: validation of a new risk index combining echocardiographic, treadmill, and exercise electrocardiographic parameters. *J Am Soc Echocardiogr* 2003; 16:318.
6. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *Circulation* 2000; 102:126.
7. SoRelle R. Incremental benefits seen for electron-beam tomography. *Circulation* 2003; 107:e9045.
8. Gerber TC, Kuzo RS, Karstaedt N, et al. Current results and new developments of coronary angiography with use of contrast-enhanced computed tomography of the heart. *Mayo Clin Proc* 2002; 77:55.
9. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology* 1998; 208:807.
10. Budoff MJ, Diamond GA, Raggi P, et al. Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography. *Circulation* 2002; 105:1791
11. Nallamothu BK, Saint S, Bielak LF, et al. Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis. *Arch Intern Med* 2001; 161:833
12. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. *Mayo Clin Proc* 1999; 74:243.
13. He ZX, Hedrick TD, Pratt CM, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* 2000; 101:244.
14. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of ^{201}Tl and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol* 1997; 29:69.
15. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. *J Am Coll Cardiol* 1993; 22:1455.
16. Hachamovitch R, Berman DS, Kiat H, et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. *J Am Coll Cardiol* 1996; 28:34.
17. Shaw LJ, Hendel R, Borges-Neto S, et al. Prognostic value of normal exercise and adenosine (99m)Tc-tetrofosmin SPECT imaging: results from the multicenter registry of 4,728 patients. *J Nucl Med* 2003; 44:134.
18. Navare SM, Kapetanopoulos A, Heller GV. Pharmacologic radionuclide myocardial perfusion imaging. *Curr Cardiol Rep* 2003; 5:16.
19. Geleijnse ML, Elhendy A, Fioretti PM, Roelandt JR. Dobutamine stress myocardial perfusion imaging. *J Am Coll Cardiol* 2000; 36:2017.
20. Samady H, Wackers FJ, Joska TM, Zaret BL, Jain D. Pharmacologic stress perfusion imaging with adenosine: role of simultaneous low-level treadmill exercise. *J Nucl Cardiol* 2002; 9:188.
21. American Society of Nuclear Cardiology consensus statement: Task Force on Women and Coronary Artery Disease. The role of myocardial perfusion imaging in the clinical evaluation of coronary artery disease in women. *J Nucl Cardiol* 2003; 10:218.
22. Wagdy HM, Hodge D, Christian TF, Miller TD, Gibbons RJ. Prognostic value of vasodilator myocardial perfusion imaging in patients with left bundle-branch block. *Circulation* 1998; 97:1563.
23. Simone GL, Mullani NA, Page DA, Anderson BA Sr. Utilization statistics and diagnostic accuracy of a nonhospital-based positron emission tomography center for the detection of coronary artery disease using rubidium-82. *Am J Physiol Imaging* 1992; 7:203.
24. Siebelink HM, Blanksma PK, Crijns HJ, et al. No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission computed tomography-guided patient management: a prospective, randomized comparison of patients with suspicion of jeopardized myocardium. *J Am Coll Cardiol* 2001; 37:81.
25. Marwick TH. Stress echocardiography. *Heart* 2003; 89:113.
26. O'Keefe JH Jr., Barnhart CS, Bateman TM. Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity. *Am J Cardiol* 1995; 75:25D.
27. Ichikawa Y, Sakuma H, Kitagawa K, et al. Evaluation of left ventricular volumes and ejection fraction using fast steady-state cine MR imaging: comparison with left ventricular angiography. *J Cardiovasc Magn Reson* 2003; 5:333.
28. Kuijpers D, Ho KY, van Dijkman PR, Vliegenthart R, Oudkerk M. Dobutamine cardiovascular magnetic resonance for the detection of myocardial ischemia with the use of myocardial tagging. *Circulation* 2003; 107:1592.
29. Baer FM, Crnac J, Schmidt M, et al. Magnetic resonance pharmacological stress for detecting coronary disease. Comparison with echocardiography. *Herz* 2000; 25:400.
30. Nagel E, Lorenz C, Baer F, et al. Stress cardiovascular magnetic resonance: consensus panel report. *J Cardiovasc Magn Reson* 2001; 3:267.
31. Panting JR, Gatehouse PD, Yang GZ, et al. Echo-planar magnetic resonance myocardial perfusion imaging: parametric map analysis and comparison with thallium SPECT. *J Magn Reson Imaging* 2001; 13:192.
32. Schwitter J, Nanz D, Kneifel S, et al. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. *Circulation* 2001; 103:2230.
33. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000; 101:850.
34. Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation* 2001; 104:412.
35. Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002; 39:225.
36. Elhendy A, Bax JJ, Poldermans D. Dobutamine stress myocardial perfusion imaging in coronary artery disease. *J Nucl Med* 2002; 43:1634.
37. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol* 1998; 32:57.
38. Kloner RA, Bolli R, Marban E, Reinlib L, Braunwald E. Medical and cellular implications of stunning, hibernation, and preconditioning: an NHLBI workshop. *Circulation* 1998; 97:1848.
39. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002; 39:1151.
40. Schelbert HR. PET contributions to understanding normal and abnormal cardiac perfusion and metabolism. *Ann Biomed Eng* 2000; 28:922.
41. Koskenvuo JW, Sakuma H, Niemi P, et al. Global myocardial blood flow and global flow reserve measurements by CMR and PET are comparable. *J Magn Reson Imaging* 2001; 13:361.

42. Senior R, Swinburn JM. Incremental value of myocardial contrast echocardiography for the prediction of recovery of function in dobutamine nonresponsive myocardium early after acute myocardial infarction. *Am J Cardiol* 2003; 91:397.
43. Messroghli DR, Niendorf T, Schulz-Menger J, Dietz R, Friedrich MG. T1 mapping in patients with acute myocardial infarction. *J Cardiovasc Magn Reson* 2003; 5:353.
44. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery—Executive Summary. A report of the American College Cardiology/ American Heart Association Task Force on Pract Guidelines (Committee to Update the 1996 Guidelines Perioperative Cardiovascular Evaluation for Noncardiac Surger *Anesth Analg* 2002; 94:1052.
45. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac eve after major vascular surgery: role of clinical characteristics, dobu mine echocardiography, and beta-blocker therapy. *JAMA* 20 285:1865.