DETECTION AND EVALUATION OF CORONARY ARTERY DISEASE

Part of "53 - NUCLEAR IMAGING TECHNIQUES"

In the past decade, myocardial perfusion imaging with SPECT has evolved into the preeminent noninvasive technique for assessment of coronary artery disease (CAD). Although RNA during stress remains a useful technique in selected patients, it is most often used in the risk-stratification of patients who have experienced myocardial infarction (MI) or heart failure.

Myocardial Perfusion Imaging

The basic principle underlying the detection of CAD by perfusion imaging is a differential blood flow distribution through the left ventricular myocardium, with a normal flow (and normal tracer uptake) in the myocardium perfused by normal coronary arteries and *relatively* diminished flow (and diminished tracer uptake) in regions perfused by stenotic vessels. A perfusion abnormality may be present at rest in patients with previous MI or fibrosis, or in patients with high-grade (>85% of the luminal diameter) coronary stenoses. However, most functionally significant coronary stenoses, including severe ones, are associated with normal resting myocardial blood flow and, hence, normal resting perfusion images. Consequently, to demonstrate these stenoses, it is necessary to perform imaging of these patients during stress.

During maximal exercise or pharmacologic stress, blood flow increases through the normal coronary arteries but increases less or even fails to increase (occasionally, it decreases) in vessels with significant (>50% of the luminal diameter) stenoses. This diminished coronary flow reserve in stenotic vessels is not an all-or-none phenomenon; rather, the flow reserve decreases gradually as the severity of the coronary stenosis progresses. The most severe stenoses (>85%) typically have no flow reserve left.

[e in triangle] It is important to emphasize that the greater the flow differential between the normal arteries and the stenotic arteries, the greater the difference in tracer uptake and potentially the greater the likelihood that the stenosis will be detected. However, the relationship between myocardial blood flow and tracer uptake is only linear up to a flow of approximately 2.0- to 2.5-fold above the baseline values. Beyond these limits, the tracer uptake lags behind the flow (the so-called “roll-off” effect). This “roll-off” effect depends on two major factors: (a) the stress modality and (b) the flow tracer.

During exercise, the normal coronary flow increases approximately 2.5- to 3.0-fold over the baseline values. Although this is substantially less than the maximal normal coronary flow reserve in human beings, the relationship between flow and Tl-201 uptake remains approximately linear (12). During pharmacologic vasodilation induced by adenosine or dipyridamole, the coronary flow increases maximally or near-maximally (four- to sixfold above the baseline). However, when the flow is so high, tracer uptake diminishes considerably, so that the slope of the tracer uptake versus flow relationship becomes flattened. Tracers with high myocardial extraction, such as Tc-99m teboroxime and Tl-201, maintain a steeper slope, whereas tracers with lower myocardial extraction, such as Tc-99m sestamibi, Tc-99m tetrofosmin, and Tc-99m furofosmin, have a flatter slope. This nonlinear relation between flow and tracer uptake at high flow raises some theoretical concerns, especially about images acquired during pharmacologic stress. However, because the tracers with lower extraction fraction also have a longer residence time in the myocardium, it appears that the ability of pharmacologic stress to detect CAD is not compromised (24,32).

Exercise Myocardial Perfusion Imaging

[e in triangle] The most common indications for exercise perfusion imaging are listed in TABLE 53.1. Most studies are done to establish the diagnosis of CAD. The maximal diagnostic yield of SPECT imaging, according to Bayes 'theorem, is in patients with an intermediate likelihood (20% to 60%) of having CAD on the basis of their history. In patients with a very low pretest disease likelihood, a positive test is often false positive, whereas in patients with a very high pretest probability of CAD (e.g., middle-aged or older men with classical angina, in whom the pretest probability is ≥80%), a negative test is often false negative. On the basis of these considerations, some authorities have suggested that perfusion imaging should not be applied to patients with a very low or a very high pretest likelihood of CAD. This line of reasoning, however, fails to consider the prognostic value of perfusion scintigraphy; that is, patients who have a low pretest disease likelihood but a large perfusion defect, especially with a multivessel distribution, may still be at increased risk, whereas patients who have a high pretest likelihood but a negative scan have a very low risk for future cardiac events, and, arguably, their condition could be managed medically without need for cardiac catheterization (33,34).

TABLE 53.1 INDICATIONS FOR EXERCISE PERFUSION SCINTIGRAPHY

Recent reports have confirmed the diagnostic utility of perfusion imaging in patients with normal and with abnormal resting ECG results (35). The information provided by myocardial perfusion scintigraphy during stress transcends the mere categorization of the test results as normal or abnormal. On the basis of the location of the perfusion abnormality, one can infer which arteries are involved. It has been shown that stenoses involving the left anterior descending artery generally lead to a larger perfusion defect

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than stenoses in the right coronary or circumflex arteries (36,37) (eFig. 53.0.4). Patients with multivessel CAD have larger perfusion defects than patients with single-vessel disease (38). In addition to the extent of hypoperfusion, the reversibility of the defects needs to be assessed during the redistribution (in the case of Tl-201) or the rest images (in the case of the Tc-99m tracers). It is important to assess also the severity of tracer uptake reduction in the stress and rest or redistribution images. Transient cavity dilation during exercise or pharmacologic stress and increased Tl-201 lung uptake during stress are powerful predictors of poor prognosis (25,33).

***e*FIGURE 53.0.4** Mean left ventricular perfusion defect size (PDS) in patients with (*solid line*) and without (*broken line*) myocardial infarction (MI) for the left anterior descending coronary artery (LAD) **(A)**, the right coronary artery (RCA) **(B)**, and the left circumflex coronary artery (CX) **(C)**, with proximal (PROX), middle (MID), or distal stenosis. Although LAD PROX stenosis generally led to a larger perfusion defect size than did LAD MID stenosis, significant individual vessel heterogeneity was seen. For the RCA, the mean perfusion defect size was similar whether stenoses were PROX, MID, or distal in location, although the range was wide. Similar heterogeneity was seen for the proximal and obtuse marginal (OM) CX stenosis. LV, left ventricle. (From Mahmarian JJ, Pratt CM, Boyce TM, et al. The variable extent of jeopardized myocardium in patients with single vessel disease: quantification by thallium-201 single photon emission computed tomography. *J Am Coll Cardiol* 1991;17:355–362, with permission.)

The use of exercise perfusion scintigraphy to screen asymptomatic patients is controversial. It certainly cannot be recommended across the board, but it may be very useful in selected populations who are at increased risk for CAD despite being asymptomatic (Fig. 53.1). For example, the test is useful in patients with a conglomerate of risk factors and in adolescents or young adults who have familial hypercholesterolemia (39). Middle-aged siblings of patients who have had an MI also are at increased risk for cardiac events and are good candidates for a stress perfusion study (40).

FIGURE 53.1 Technetium-99m single-photon emission computed tomographic images during exercise and at rest in a 52-year-old diabetic male who was asymptomatic. The images during stress depict large defects involving the anterior wall, septum, apex, and inferior and posterolateral walls, with substantial improvement at rest. Subsequent coronary angiography showed severe proximal left anterior descending (90%) and left circumflex (75%) stenoses.

An extensive review of published studies that used exercise Tl-201 qualitative planar scintigraphy, which included 52 publications and 5,160 patients (41), shows an overall sensitivity and specificity of 83% and 88%, respectively. Several studies assessed the value of quantitative Tl-201 planar scintigraphy during exercise for the diagnosis of CAD (24). The mean sensitivity and specificity are 90% and 80%, respectively. With exercise Tl-201 SPECT, the average sensitivity and specificity are 89% and 76%, respectively, by qualitative analysis (24).

***e*FIGURE.** Pulsed wave Doppler of the mitral valve inflow in a patient with amyloidosis demonstrating a short deceleration time (134 ms) consistent with restrictive physiology.

***e*FIGURE.** Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*video*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient.

Video 53.1 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*video*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it* http://www.apple.com/quicktime/download/.

A comparison between qualitative and quantitative analyses of Tl-201 SPECT images has not shown a major difference in sensitivity or specificity between these two

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techniques (38,42,43,44 and 45). However, detection of the individual coronary arteries involved may be moderately improved by quantitative analysis. This is particularly true for detection of circumflex artery stenoses and coronary stenoses of moderate severity (between 50% and 75% of the luminal diameter) (45).

Use of Technetium-99m Perfusion Tracers in the Diagnosis of Coronary Angiography Disease

The newer Tc-99m flow tracers represent a substantial improvement in nuclear cardiac imaging. The more favorable physical characteristics of Tc-99m, such as an optimal emission energy for imaging with gamma cameras, and less physical scatter and shorter half-life (which allows administration of a much higher tracer dose) than Tl-201, are definite advantages of these agents. Interestingly, the few studies that have directly compared Tl-201 with Tc-99m sestamibi, teboroxime, or tetrofosmin have not shown an overall superiority for detection of CAD with any of these newer agents. The overall sensitivity of Tc-99m sestamibi using planar imaging is 87%, with a specificity of 62% and a normalcy rate of 92%. When SPECT imaging is used, the overall sensitivity and specificity are 90% and 74%, respectively (24). As mentioned, Tc-99m sestamibi imaging during stress has also been used in combination with Tl-201 resting imaging (dual isotope imaging). With this strategy, a sensitivity of 91% and specificity of 75% have been found by Berman and coworkers (29).

Because the Tc-99m–labeled agents undergo less attenuation than agents labeled with Tl-201, they may be particularly useful for patients who are prone to attenuation artifacts, such as women with large breasts or breast implants and obese individuals (46). Tc-99m teboroxime has been used with planar imaging and with SPECT imaging. Despite its high myocardial extraction rate and its good correlation with determination of myocardial flow using microspheres, it has a very short residence time in the myocardium, rendering SPECT imaging a challenging proposition. The initial favorable reports (which indicated an average sensitivity of 87% and specificity of 62% with either planar or SPECT imaging) (47,48) notwithstanding, this tracer is not currently used for clinical imaging. New research has focused on the idea of measuring absolute myocardial blood flow using dynamic imaging with teboroxime (49).

Tetrofosmin is another attractive Tc-99m–labeled perfusion agent. A high concordance rate has been found between this agent and Tl-201, both with planar and SPECT imaging (50,51). As is the case for sestamibi, the sensitivity and specificity of tetrofosmin imaging appear to be comparable, but not superior, to those of Tl-201 imaging. In the largest reported series, from a phase III multicenter trial, that used planar imaging and included 252 patients from ten centers in the United States and Europe, tetrofosmin and Tl-201 had similar sensitivity and specificity for CAD detection. Other studies have confirmed the diagnostic accuracy of tetrofosmin (52,53,54 and 55) and confirmed that it is comparable to sestamibi (56).

Furofosmin is another Tc-99m–labeled compound that has been tested in the United States but has not received FDA approval. In a large multicenter trial comparing Tc-99m furofosmin SPECT with Tl-201 SPECT during exercise, an overall agreement in the results of 86% was found (57).

The principal advantage of the Tc-99m tracers is that they can be administered in higher doses, and, hence, high-quality images are feasible even for large or obese individuals and women with large breasts. Another very attractive feature is the ability to gate the SPECT images, which allows an evaluation of the global and regional ventricular function by observation of the motion of the perfused ventricular walls. These agents also enable assessment of left and right ventricular function during the injection of the Tc-99m tracers by first-pass RNA.

Pharmacologic Perfusion Imaging

Approximately 20% to 30% of patients with suspected or documented CAD are unable to perform an exercise stress test and, thus, are good candidates for pharmacologic stress imaging. Other clinical conditions for which pharmacologic stress imaging is appropriate are listed in TABLE 53.2. Adenosine produces maximal or near-maximal coronary vasodilation through its agonistic effect on the adenosine A2 receptors located in the coronary arterial wall. Dipyridamole has an indirect vasodilator effect, through the inhibition of the cellular reuptake and metabolism of adenosine (24,30), leading to an increase in the interstitial and perimembrane levels of adenosine. The principal difference between these two agents, which have similar hemodynamic effects (24), is the much shorter half-life of adenosine. Both produce frequent side effects, but the reported experience in large numbers of patients has indicated that both are quite safe when properly used (58,59 and 60). Investigators in Japan have used intravenous adenosine triphosphate as yet another option for pharmacologic stressor (61,62).

TABLE 53.2 INDICATIONS FOR PHARMACOLOGIC PERFUSION IMAGING

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Studies comparing dipyridamole or adenosine Tl-201 scintigraphy with exercise Tl-201 scintigraphy have indicated excellent agreement between these stressors. The overall reported sensitivity with dipyridamole Tl-201 planar imaging is 82%, with a specificity of 75%. These values are slightly higher with SPECT imaging (89% and 78%, respectively). The average sensitivity of adenosine Tl-201 SPECT is 88%, with a specificity of 85% (24,30). Clinical studies have shown similar values when adenosine or dipyridamole is combined with Tc-99m sestamibi or tetrofosmin (63,64 and 65). Both adenosine and dipyridamole can be combined with a submaximal exercise test. The main advantage of such a combination is the decrease in splancnic uptake, which improves the quality of the images, especially with Tc-99m agents (66,67).

Adenosine and dipyridamole are contraindicated in patients who have active asthma or severe chronic obstructive pulmonary disease with wheezing. In these patients, dobutamine is a proven adequate stressor, with reported sensitivity ranging from 80% to 97% and specificity ranging from 74% to 89%, in combination with SPECT (24). Although a curious antagonism has been described between dobutamine and sestamibi in animal experiments (68), the reported sensitivity of this combination of agents in clinical patients is high thus far (69,70).

Causes of False-Negative Results of Myocardial Perfusion Scintigraphy

TABLE 53.3 lists several of the possible causes of false-negative myocardial perfusion images. Among these, the most frequent are an inadequate exercise stress test and concomitant administration of antiischemic medications. It must be emphasized that the gold standard for determination of diagnostic accuracy of perfusion imaging has traditionally been coronary angiography. The potential weaknesses of this gold standard have long been emphasized (71). It is not unusual for lesions that are considered “significant” by angiography to have a normal flow reserve. It is thus not surprising that some of them are also associated with normal myocardial perfusion images.

TABLE 53.3 CAUSES OF FALSE-NEGATIVE RESULTS OF SCANS

Causes of False-Positive Myocardial Perfusion Images

[e in triangle] TABLE 53.4 lists some of the causes that may be associated with false-positive results of imaging. Among them, the most important is photon attenuation, which may have a different impact on different myocardial walls. For example, anterior wall attenuation is common in women with breast implants or large breasts, whereas diaphragmatic attenuation is frequent in obese, stocky patients (eFig. 53.1.1). In individual patients, it may be extremely difficult to distinguish between attenuation artifacts and a true perfusion defect. The application of newly developed attenuation-correction techniques appears quite promising (72,73,74,75 and 76). Among the causes listed on TABLE 53.4, conduction defects are particular important, because they are potentially preventable. Patients who have a left bundle branch block often have perfusion defects involving the interventricular septum, which may be totally or partially reversible at rest, thus mimicking left anterior descending artery stenosis. These defects are much less frequently seen when dipyridamole or adenosine stress testing is used, and pharmacologic imaging with one of these agents is therefore preferable to exercise testing in patients with a left bundle branch block (22,24,30,77).

TABLE 53.4 CAUSES OF FALSE-POSITIVE RESULTS OF SCANS

***e*FIGURE 53.1.1** Single-photon emission computed tomographic (SPECT) images of an asymptomatic, short, middle-aged man who weighed 245 lb. The images taken during exercise show a postero-inferior defect (*first and fourth rows*) that disappears after photon attenuation correction (*second and fifth rows*) and after attenuation/scatter correction (*third and sixth rows*).