

## Clinical Practice

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

## NONINVASIVE TESTS IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

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A 58-year-old woman presents with chest discomfort while walking that is suggestive of coronary disease. She first noted the discomfort after beginning an exercise program three weeks earlier. The pain occurs within a few minutes after the beginning of exercise and resolves with rest. The physical examination and electrocardiogram are unremarkable. How should this patient be evaluated?

### THE CLINICAL PROBLEM

In patients with known or suspected coronary artery disease, diagnosis and risk stratification can be aided by noninvasive tests for myocardial ischemia. The most commonly used tests are exercise electrocardiography, myocardial perfusion imaging, and stress echocardiography. Guidelines for choosing among these approaches have been published (Table 1),<sup>1-4</sup> but physicians' use of these tests varies markedly.

Which of these tests is most appropriate for the initial assessment of a patient with known or suspected stable coronary artery disease? Exercise electrocardiography is of little diagnostic value in patients with particular electrocardiographic abnormalities at rest (Table 1); in such patients, and in patients who are unable to exercise, noninvasive testing with some form of imaging is indicated by default. In the case of other patients, however, selecting the most appropriate test requires consideration of the sensitivity and specificity, logistical requirements, and costs.

### STRATEGIES AND EVIDENCE

#### Exercise Electrocardiography

##### Characteristics

Exercise electrocardiography can safely be performed in outpatient settings by trained personnel

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**TABLE 1.** INDICATIONS FOR THE USE OF RADIONUCLIDE PERFUSION IMAGING RATHER THAN EXERCISE ELECTROCARDIOGRAPHY.\*

Complete left bundle-branch block  
Electronically paced ventricular rhythm  
Preexcitation (Wolff-Parkinson-White) syndrome or other, similar electrocardiographic conduction 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 a history of revascularization‡

\*The guidelines were developed by the American College of Cardiology, the American Heart Association, the American College of Physicians, and the American Society of Internal Medicine.<sup>3</sup>

†Patients with this factor should be considered for pharmacologic 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.

who are under the supervision of a physician. During this test, the physician should be nearby and available in case of emergency.<sup>1,5</sup> The rate of acute myocardial infarction or death is about 1 per 2500 tests.<sup>6</sup> Exercise electrocardiography is the least expensive noninvasive test for myocardial ischemia. The costs of stress echocardiography and stress single-photon-emission computed tomography (SPECT) are at least two and five times as high, respectively.<sup>3</sup>

Several drugs can influence the results of exercise electrocardiography, including digoxin, beta-adrenergic-blocking agents, vasodilators, and other antihypertensive agents that alter hemodynamic responses. Whenever possible, beta-blockers and other anti-ischemic drugs should be stopped four or five half-lives (usually about two days) before exercise testing is performed as part of the diagnostic workup and initial risk stratification for patients with suspected coronary disease.<sup>3</sup> Withdrawal of these medications is often not feasible. Nevertheless, even when medications are not withdrawn, the results of stress testing are usually abnormal in patients at highest risk for complications.<sup>3</sup>

#### Summary of Data

Pooled data from 132 studies indicate that exercise electrocardiography has a sensitivity for the detection of coronary artery disease of 68 percent and a specificity of 77 percent (Table 2).<sup>7,8</sup> However, results vary markedly among studies, reflecting the use of different criteria for abnormal results and various degrees of severity of coronary disease in the study

**TABLE 2. SENSITIVITY AND SPECIFICITY OF NONINVASIVE TESTS FOR THE DETECTION OF CORONARY ARTERY DISEASE.\***

DIAGNOSTIC TEST	SENSITIVITY (RANGE)	SPECIFICITY (RANGE)	NO. OF STUDIES ANALYZED	NO. OF PATIENTS
	percent			
Exercise electrocardiography	68	77	132	24,074
Planar scintigraphy	79	73	6	510
	(70–94)	(43–97)		
Single-photon-emission computed tomography	88	77	8	628
	(73–98)	(53–96)		
Stress echocardiography	76	88	10	1,174
	(40–100)	(80–95)		

\*Data on the ranges of sensitivity and specificity are from Garber and Solomon.<sup>7</sup> Data on the sensitivity and specificity of exercise electrocardiography are from Gianrossi et al.<sup>8</sup>

populations.<sup>8</sup> In patients without a high risk of extensive coronary disease, the sensitivity of exercise electrocardiography may be as low as 45 percent.<sup>9</sup> In women, exercise testing is less sensitive than in men, and some data suggest that it may also be less specific.<sup>3</sup>

The interpretation of the results of an exercise test as positive or negative on the basis of electrocardiographic changes alone is a simplification to be avoided. Other important information includes a patient's symptoms and exercise capacity and the hemodynamic changes (e.g., in blood pressure and heart rate) that occur in response to exercise. One approach to integrating data from exercise electrocardiography is through the use of the Duke treadmill score,<sup>10</sup> which is calculated as follows: duration of exercise in minutes – (5 × the maximal net ST-segment deviation during or after exercise, in millimeters) – (4 × the treadmill angina index). The angina index is assigned a value of 0 if angina is absent during exercise, 1 if typical angina occurs during exercise, and 2 if angina is the reason the patient stopped exercising. This score can improve the test's prognostic accuracy when it is considered in conjunction with data from the clinical evaluation, the results of coronary angiography, and the ejection fraction.

### Radionuclide Imaging

#### Characteristics

Most nuclear cardiology applications use SPECT to reconstruct anatomical slices of discrete thickness in standardized views. Positron-emission tomographic scanners include multiple rings of stationary detectors that detect emissions from tracers, which can be used to determine regional myocardial blood flow and metabolic processes. However, these scanners are more costly than SPECT scanners and are not widely available for routine use.

Tracers labeled with thallium Tl 201 and technetium Tc 99m are used to assess myocardial perfusion and viability (Fig. 1). The uptake of these agents by myocardial cells depends on both the perfusion and viability of that region of myocardium. Although both tracers can be used to assess myocardial perfusion, thallium remains the most widely used agent for testing viability.

Three technetium-99m-labeled tracers are available in the United States: sestamibi, teboroxime, and tetrofosmin. In contrast to thallium, which is actively transported into cells, sestamibi and the other technetium agents diffuse passively across cell membranes. Sestamibi is retained within functioning mitochondria and therefore reflects viability. The shorter half-life of the technetium agents (6 hours, as compared with 73 hours for thallium) makes possible the injection of larger doses, which also permits assessment of ventricular function.

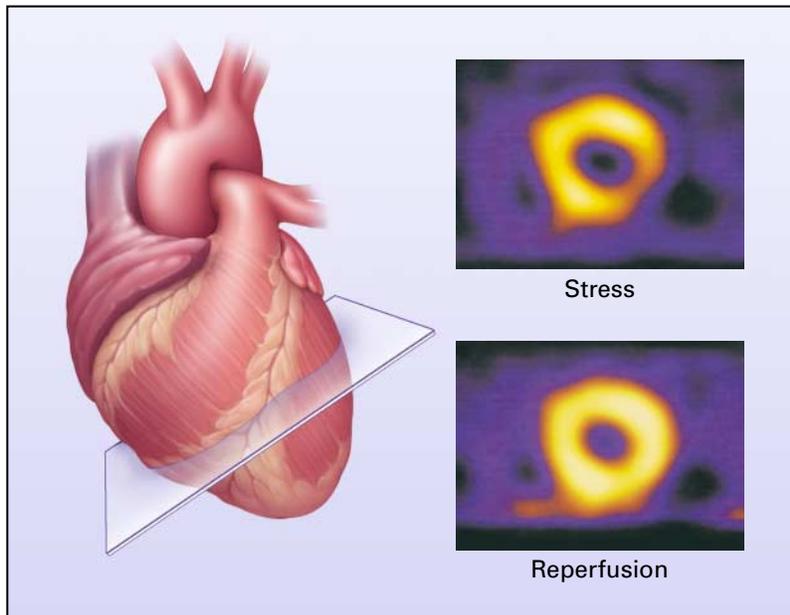
The initial distribution of these tracers is proportional to myocardial blood flow, whereas so-called redistribution images, which are obtained three to four hours later, reflect myocardial viability and are unrelated to flow. A myocardial defect on an initial scan that subsequently resolves is an indicator of myocardium that is viable. A defect that is apparent on both scans suggests a region of myocardium that has died, presumably as a result of a myocardial infarction. However, additional injections of thallium after redistribution imaging may reveal viable myocardium within such areas.<sup>11</sup>

Ischemia can be provoked with physical exercise or pharmacologic agents. Dobutamine is a positive inotropic agent that provokes ischemia by increasing myocardial work, whereas adenosine and dipyridamole are vasodilators that unmask coronary stenoses by causing relative increases in flow in coronary arteries that are not diseased. All three agents are useful in patients who are unable to perform physical exercise.

#### Summary of Data

The diagnostic performance of radionuclide imaging was initially studied in the 1970s and 1980s with an earlier scanning technique (planar scintigraphy); SPECT has higher sensitivity with similar specificity.<sup>7,12</sup> Either technique has a greater sensitivity for the detection of coronary artery disease and left main coronary artery disease than does exercise electrocardiography (Table 2).<sup>7</sup> The diagnostic performance of technetium-based agents is similar to that of thallium<sup>3</sup>; hence, the choice of tracers is not important for physicians ordering the test.

Published estimates of the performance of radionuclide perfusion imaging are highly variable (Table 2) and are complicated by differences in imaging techniques and standards for interpretation, even within a single laboratory. False positive results are an important problem, particularly with SPECT, given its



**Figure 1.** Use of Radionuclide Scintigraphy to Assess Myocardial Perfusion and Viability.

Radionuclide scintigraphy uses computer analysis of the distribution of a radionuclide tracer (e.g., thallium or technetium) to reconstruct slices of the heart at various levels and from various angles. The short-axis view shown here provides information on the presence of the tracer in a cross section of the left ventricle. The image obtained during stress shows little tracer in one segment of the left ventricle. With reperfusion, however, tracer is present throughout the slice. These images suggest the presence of a stress-induced, reversible perfusion defect, indicating viable myocardium.

use of computerized image enhancement. Apparent perfusion defects can be produced by attenuation artifacts (e.g., breast tissue and the diaphragm) situated between the heart and the imaging camera. Small differences of up to 25 percent between regions may represent the normal variation, and the extent of relative differences can be exaggerated on colored display scales or by the oversubtraction of adjacent background activity as part of contrast enhancement. Finally, false positive results may occur if inexperienced readers interpret regional tracer activity from computer-derived color images alone and do not study the original, unprocessed monochrome planar images used to generate the SPECT images.

Although the pharmacologic properties of dobutamine differ from those of adenosine and dipyridamole, the diagnostic yield of these agents with respect to radionuclide perfusion imaging is similar and is also similar to that obtained with exercise scintigraphy.<sup>2</sup> However, dobutamine has not been studied as extensively as the two vasodilators, and it does not cause as great an increase in coronary flow as the other agents; thus, it is recommended for use when there are contraindications to the use of adenosine or dipyridamole.<sup>3</sup> As is true with exercise electrocardiogra-

phy, concomitant use of beta-blockers and other anti-anginal medications may compromise the sensitivity of radionuclide imaging for the detection of coronary artery disease. When possible, such agents should be stopped four or five half-lives before testing.<sup>3</sup>

Radionuclide studies also provide prognostic information beyond that available from clinical evaluations and exercise electrocardiography in both men and women.<sup>13-15</sup> However, as is true of exercise electrocardiography, radionuclide perfusion imaging is less accurate in women than in men. Some data suggest that the better imaging properties of technetium-99m sestamibi may make it a superior agent for the evaluation of obese patients or women with large breasts or breast implants.<sup>16</sup>

#### **Stress Echocardiography**

##### *Characteristics*

Stress echocardiography can involve exercise or pharmacologic agents to provoke ischemia.<sup>17</sup> Echocardiographic images obtained while the patient is at rest and during or immediately after stress (e.g., one to two minutes after exercise) are compared side by side. A test is considered positive if wall-motion abnormalities develop with stress in previously normal

vascular territories or worsen in a segment that was abnormal at base line. As is true of radionuclide perfusion imaging, stress echocardiography provides information on the location and extent of jeopardized myocardium. In addition, this test provides insight into left ventricular and cardiac-valve function.

#### Summary of Data

The range of estimates for the diagnostic performance of stress echocardiography varies widely (Table 2), but summary data indicate that its sensitivity is in the same range as or slightly lower than that of radionuclide perfusion imaging.<sup>4,7</sup> As is true of other non-invasive tests for ischemia, the test has a higher sensitivity for multivessel disease (about 90 percent) than for single-vessel disease (56 percent).<sup>3,18</sup> Pooled data indicate that exercise echocardiography is more specific than exercise SPECT.<sup>19</sup> Dobutamine and dipyridamole stress echocardiography have similar diagnostic yields.<sup>20</sup>

Long-term data demonstrate the prognostic importance of information obtained from stress echocardiography. Among medically treated patients, the four-year rate of infarction-free survival was lower in patients with positive tests than in those with negative tests (87 percent vs. 94 percent).<sup>18</sup> These data suggest that patients with positive tests have a better prognosis if they are treated invasively.<sup>18</sup> A negative exercise echocardiogram is associated with rates of survival without cardiac events of 99.2 percent at one year and 97.4 percent at three years.<sup>21</sup>

#### Comparative Studies

Trials that compare outcomes for patients suspected of having stable coronary disease who are randomly assigned to these three testing strategies have not been performed, nor are they likely to be. Such a trial would require the enrollment and follow-up of large numbers of patients, because of the overall excellent prognosis of patients with chronic stable angina, and because variability in management strategies after initial testing would bias the results in favor of the null hypothesis. Thus, strategies for the use of these tests must be evaluated on the basis of observational data.

Published research consistently demonstrates that stress testing with radionuclide scintigraphy and echocardiography provides more information than exercise electrocardiography alone.<sup>7,13-15,22</sup> However, the fact that a test provides more information does not necessarily mean it is the most appropriate test. Other important issues are whether the additional information is sufficient to change patient care in ways that would be expected to improve outcomes, and whether those improvements in outcome can be achieved at a cost that is similar to that of other medical interventions.

Two recent analyses of cost effectiveness used observational data on outcomes to evaluate various diagnostic strategies for patients with chest pain.<sup>7,22</sup> Kuntz

et al. concluded that, for patients with typical angina, the use of exercise echocardiography instead of exercise electrocardiography improved survival at a cost of \$32,000 per quality-adjusted life-year; for patients with atypical angina, the cost per quality-adjusted life-year was \$41,900.<sup>22</sup> Exercise SPECT improved outcomes in these two populations of patients at costs of \$38,000 and \$54,900 per quality-adjusted life-year, respectively. These cost-effectiveness ratios are similar to those of other accepted medical interventions.

A second analysis yielded similar findings but concluded that stress echocardiography was a more cost-effective strategy than SPECT, with total costs equal to or lower than those of exercise electrocardiography.<sup>7</sup> This analysis assumed a higher specificity for stress echocardiography than the prior study<sup>22</sup> (88 percent vs. 77 percent). Some data support a targeted, staged approach in which exercise electrocardiography is used first, followed by SPECT for patients with an intermediate or high risk of complications on the basis of clinical and exercise-electrocardiographic data.<sup>15</sup>

#### AREAS OF UNCERTAINTY

Recommendations regarding the use of these tests are based on analyses of observational data, and these analyses by necessity include numerous assumptions about subsequent management, outcomes, and costs. Just as the overall superiority of any testing strategy in the general population has not been proved, the relative effect of these tests in key subgroups (e.g., women, the elderly, patients with diabetes, and patients who are taking antianginal medications) also has not been tested.

#### GUIDELINES

Guidelines from the American College of Cardiology and the American Heart Association consistently advocate exercise electrocardiography as the appropriate first test for patients with known or suspected chronic stable angina.<sup>1-3</sup> Table 1 summarizes the list of indications that, according to guidelines issued in 1999, define subgroups of patients who are good candidates for imaging as opposed to exercise electrocardiography.<sup>3</sup> These guidelines (which were developed in conjunction with the American College of Physicians and the American Society of Internal Medicine) acknowledge that there is uncertainty about the optimal testing strategies in women, but conclude that there are "currently insufficient data to justify replacing standard exercise testing with stress imaging when evaluating women" for coronary artery disease.<sup>3</sup>

#### CONCLUSIONS AND RECOMMENDATIONS

There are multiple tests and strategies for the evaluation of a patient with suspected or known stable coronary artery disease, and no single test or strategy

has been proven to be superior overall. Imaging is clearly appropriate for patients with uninterpretable electrocardiograms, and a pharmacologic agent is the most effective way to provoke ischemia in patients with poor functional status and in some patients who are unable to raise their heart rate as a result of medications (e.g., beta-blockers) or conduction-system disease. In other patients, however, the choice between exercise electrocardiography and an imaging test should be influenced by factors such as the diagnostic yield, costs, and convenience. Regardless of which test is used, a normal result should never be considered a guarantee that the patient does not have coronary disease or has no risk of cardiovascular events.

Our approach to the use of these tests is as follows. In a patient with newly diagnosed or suspected coronary artery disease, we recommend imaging as the first test if the electrocardiogram is uninterpretable or the patient cannot exercise sufficiently. We also recommend imaging in patients with poor myocardial function or a history of revascularization if the goal is to assess myocardial viability. If none of these factors are present, as in the patient described in the initial case vignette, then we recommend exercise electrocardiography as the first test for general diagnostic and prognostic assessment. The choice of imaging test (echocardiography vs. radionuclide imaging) should take into consideration the test that is most trusted and available at a given institution. These recommendations reflect variability in the performance of these tests at different laboratories, which leads to uncertainty about the relevance of published cost-effectiveness analyses of these tests<sup>7,22</sup> in all settings.

The results of imaging tests may also refine prognostic assessments based on initial clinical assessments, including exercise electrocardiography. Data from exercise electrocardiography can be used to classify patients according to the risk of complications with the use of tools such as the Duke treadmill score.<sup>10</sup> On the basis of these data, low-risk patients are those with a high heart rate and cardiovascular workload on exercise testing, no angina, and minimal ischemia or none at all. This group of patients has an excellent prognosis, and the results of imaging tests are unlikely to lead to changes in therapy. In contrast, high-risk patients are those with marked myocardial ischemia at low peak workloads, and aggressive treatment, including coronary revascularization, should be considered in these patients. The results of imaging tests are unlikely to influence the decision to recommend cardiac catheterization, although such tests may help pinpoint the ischemic zone in patients in whom angioplasty or stenting is contemplated for multiple coronary stenoses. The group at intermediate risk includes many patients with moderate exercise capacity, subtle evidence of ischemia, or atypical chest pain. In such patients, an imaging test may clarify the diagnosis and provide insight into the prognosis.

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