# Exercise myocardial perfusion imaging in the diagnosis and risk stratification of coronary heart disease

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**INTRODUCTION** — Coronary heart disease (CHD) is the most common cause of death in men and women in the United States [1]. As a result, identification of patients with CHD is an important goal, since risk factor modification and medical therapy can improve outcomes. (See "Risk factor reduction (secondary prevention) of cardiovascular disease and stroke").

Once the decision is made to perform a stress test to obtain diagnostic and/or prognostic information, the use of myocardial perfusion imaging (MPI) may be critical. The ACC/AHA guidelines for exercise testing [2,3] and for the clinical use of radionuclide imaging [4] strongly recommend an imaging study as part of the evaluation in the following groups of patients. (See "ACC/AHA guidelines for exercise testing: Special groups: Women, asymptomatic individuals and postrevascularization patients" and see "ACC/AHA guidelines for clinical use of cardiac radionuclide imaging: Clinical uses of radionuclide imaging").

- Those who are unable to exercise to a level high enough to produce meaningful results on exercise ECG testing.
- Those with baseline ECG abnormalities that interfere with the interpretation of the exercise ECG. These include preexcitation, paced ventricular rhythm, greater than 1 mm of resting ST segment depression, and complete left bundle branch block. The use of digoxin and the presence of left ventricular hypertrophy also reduce the specificity of exercise ECG testing, although the sensitivity may remain unaffected.

Several other subsets of patients benefit incrementally from the use of radionuclide imaging. This includes patients with prior myocardial infarction or coronary revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft), known significant disease (for identification of the "culprit" lesion causing ischemia), diabetes, or a previous positive nuclear study [5-8]. The clinical context for exercise stress testing and the role of MPI for patients with suspected ischemic heart disease is described in the 2002 update of the ACC/AHA guidelines for exercise testing (show algorithm 1) [2].

The following discussion will review the various modalities and indications for stress MPI in patients with suspected CAD. It will also describe the newer advances in the area of nuclear cardiology and how the information obtained from nuclear imaging helps in guiding therapy. Finally, we will examine the increasingly important role of MPI in women and in patients with diabetes mellitus.

The role of stress PCI in the predischarge risk stratification of patients with an acute coronary syndrome and after revascularization are discussed separately. (See "Myocardial perfusion imaging in predischarge risk stratification of medically treated patients with non-ST elevation acute coronary syndrome" and see "Use of myocardial perfusion imaging after coronary revascularization").

**ASSESSMENT OF INDIVIDUAL RISK** — Identification of traditional and newer risk factors for CHD is the first step in the evaluation of an individual's probability for having CHD. (See "Overview of the risk factors for cardiovascular disease").

The major risk factors include (show table 1) [9]:

- Increasing age over age 45
- Male gender

- Postmenopausal status in women
- Hypertension
- Hypercholesterolemia
- Family history of premature CHD before age 55 in male first-degree relatives and age 65 in female first-degree relatives
- Diabetes mellitus
- Smoking
- Obesity
- Sedentary life style

Various clinical prediction models can be applied to further stratify patients into low, intermediate, and high risk for future cardiac events, including cardiac death and nonfatal myocardial infarction based on these risk factors [10,11]. 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 developing CHD (show table 2A-2B) [12].

Although it is well recognized that sensitivity and specificity define the quality of a diagnostic test, the result cannot be satisfactorily interpreted without additional knowledge of the prevalence of disease in a given population [13]. Defining the pretest likelihood of CHD in a certain individual and determining the post-test probability after a positive or negative result are essential when considering MPI. Stress MPI is of particular importance in intermediate risk patients (those with pretest probability between 20 and 80 percent) since a positive or a negative result will have the greatest influence on treatment decisions [2-4,14]. (See "Determinants of accuracy of exercise ECG testing in the diagnosis of coronary heart disease", section on Probability theory in the interpretation of exercise test results).

**ADVANCES IN MPI** — For many years, planar imaging and SPECT (single photon emission computed tomography) with 201-thallium (Tl) constituted the only scintigraphic techniques available for detecting CHD and assessing prognosis. A major limitation of 201-Tl is the high false-positive rate attributed to image attenuation artifacts (eg, breast tissue in women and diaphragmatic attenuation in obese patients) and occasionally to variants of normal. Those limitations prompted the development of new radionuclides for cardiac imaging [15]. (See "Basic properties of myocardial perfusion agents").

**99m-technetium agents and gated SPECT** — At present, two 99m-Tc-labeled perfusion agents are primarily used for clinical purposes: 99m-Tc-sestamibi and 99m-Tc-tetrofosmin. These agents have improved imaging characteristics compared to 201-Tl due to higher photon energy and shorter half-life. Perhaps most important, they allow easy ECG gated acquisition (gated SPECT imaging), permitting the simultaneous evaluation of left ventricular systolic function and myocardial perfusion [16,17]. (See "Basic properties of myocardial perfusion agents").

The accuracy of wall motion assessment and the left ventricular ejection fraction (LVEF) calculated by gated SPECT imaging has compared favorably to angiography, echocardiography, radionuclide ventriculography, and cine-magnetic resonance imaging [18,19]. In one report, for example, there was an excellent segmental score agreement between stress gated SPECT 99m-Tc-sestamibi and echocardiography for wall motion (91 percent) and wall thickening (90 percent). There was also a very high correlation for global wall motion ($r = 0.98$), and global wall thickening ($r = 0.96$).

By also assessing left ventricular function, gated SPECT imaging can provide additional information related to diagnosis (eg, distinguishing ischemic from ischemic cardiomyopathy) [20] and prognosis (see "Exercise MPI for risk stratification" below).

Acquiring stress and rest-gated SPECT may also detect postexercise myocardial stunning. One report of 81 patients investigated whether the LVEF calculated from post-stress SPECT reflects the basal value or is reduced in some patients due to stress-induced ischemia [21]. Among the 61 patients with reversible perfusion defects, 36 percent had post-stress LVEF that was more than 5 percent lower than that at rest; in the remaining patients, the post-stress LVEF was either less than or equal to5 percent lower or greater than that at rest. Thus, if only a post-stress scan is obtained, the LVEF will be underestimated in a substantial number of patients. (See "Clinical syndromes of stunned or hibernating myocardium").

**Attenuation correction** — Despite the improvement in radionuclides and acquisition techniques, attenuation artifacts still decrease the specificity of SPECT imaging. Preliminary data suggested that application of attenuation correction could improve the accuracy of cardiac SPECT imaging for the detection and localization of CAD [22]. (See "Nonuniform photon attenuation in myocardial perfusion imaging").

The efficacy of correction for photon attenuation and scatter in SPECT MPI was directly addressed in a prospective multicenter clinical trial [23]. The normalcy rate was used as a surrogate for specificity; it is defined as the rate of normal perfusion scans in patients with <5 percent likelihood of CHD on the basis of

clinical and ECG stress data. The sensitivity for the detection of greater than or equal to50 percent stenosis was unaffected by the application of attenuation/scatter correction and resolution compensation (75 to 78 percent), although the detection of multivessel disease was reduced. On the other hand, these corrections improved the normalcy rate compared to uncorrected perfusion data using either the corrected images (96 percent versus 86 percent) or the corrected data and quantitative analysis (97 percent versus 86 percent).

A 2002 position statement from the American Society of Nuclear Cardiology (ASNC) describes pertinent information regarding the methods of attenuation correction, application, and quality control [24]. (See "Nonuniform photon attenuation in myocardial perfusion imaging").

## EXERCISE MPI FOR DIAGNOSIS

**Sensitivity and specificity** — As mentioned above, at any given sensitivity and specificity, the accuracy of a test varies with disease prevalence. Testing is of greatest value in intermediate risk patients (ie, those with a pretest probability between 20 and 80 percent) [2-4,14]. (See "Determinants of accuracy of exercise ECG testing in the diagnosis of coronary heart disease", section on Probability theory in the interpretation of exercise test results).

Both 201-Tl planar and SPECT imaging have excellent sensitivity for the detection of CAD. In a series of more than 4000 patients, planar imaging incorporating visual assessment of myocardial scintigrams had an average sensitivity of 82 percent (range 74 percent to 96 percent) and specificity of 88 percent (range 63 percent to 100 percent) [25]. The sensitivity varies with the extent of CHD, ranging in one report from 79 percent for the detection of single vessel disease (>50 percent stenosis) to 88 percent for two vessel disease to 92 percent for three vessel disease [26]. Application of computer-based quantitative analysis increases the sensitivity (91 percent in a series of 682 patients) [27] with equal (89 percent in the same series of patients) or occasionally slightly worse specificity [25].

The performance of exercise 201-Tl SPECT MPI was evaluated in a review of 1441 patients combined from six studies [28]:

- The sensitivity averaged 90 percent (range 82 percent to 98 percent) overall and 85 percent in patients without a prior history of CHD. As with planar imaging, the sensitivity varied with the extent of CHD, ranging from 83 percent for the detection of single vessel disease to 93 percent for two vessel disease to 95 percent for three vessel disease

- The specificity averaged 70 percent (range 43 percent to 91 percent). The lower specificity was thought to probably reflect referral bias, since patients with abnormal scans were more frequently referred for coronary angiography than patients with normal scans. This explanation was further supported by the high normalcy rate (89 percent), which is defined as the rate of normal perfusion scans in patients with <5 percent likelihood of CHD on the basis of clinical and ECG stress data.

Current consensus is that SPECT imaging has superior sensitivity partially due to its ability to detect an individual stenosis on the basis of localization of stress-induced perfusion defects [29]. Variables that increase sensitivity with MPI are [30]:

- Known or extensive CHD
- High grade coronary stenosis
- Proximal location of stenosis
- Presence of wall motion abnormalities

Variables that diminish the sensitivity for CHD detection are [30]:

- Single vessel disease
- Left circumflex coronary stenosis
- Branch vessel or distal stenosis
- Mild degree of stenosis (<50 percent luminal narrowing)
- Inadequate heart rate response during exercise
- Concurrent antianginal therapy

**Overcoming attenuation artifacts** — The low specificity with 201-Tl scintigraphy is generally considered to be caused by failure to recognize attenuation artifacts in the inferior and anterior regions. The introduction of 99m-Tc gated SPECT imaging permits the assessment of systolic wall thickening at end-diastole and end-systole on multiple SPECT tomograms [16]. Normal systolic thickening in an area of hypoperfusion in both stress and rest images represents an attenuation artifact rather than a myocardial scar, which is associated with reduced systolic thickening. In addition, application of attenuation correction

technology improves the diagnostic accuracy of MPI by reducing false positive results [22,24]. (See "Nonuniform photon attenuation in myocardial perfusion imaging").

**201-Tl versus 99m-Tc MPI** — A number of small studies have compared the diagnostic accuracy of 201-Tl and 99m-Tc MPI [31-34]. In one of these reports, the diagnostic accuracy of 201-Tl and 99m-Tc-sestamibi SPECT were prospectively compared in 115 women (85 with suspected CHD and 30 volunteers with a low pretest likelihood of CHD) [31]. All underwent both perfusion (201-Tl and 99m-Tc-sestamibi) and ECG gated 99m-Tc-sestamibi SPECT imaging, and the majority also underwent coronary angiography. The following findings were noted:

- The overall sensitivities of the 201-Tl and 99m-Tc-sestamibi perfusion studies were similar for detecting greater than or equal to50 percent stenoses (75 and 72 percent) and greater than or equal to70 percent stenoses (84 versus 80 percent).

- The specificity was significantly lower with 201-Tl imaging for detecting lesions greater than or equal to50 percent (71 versus 86 and 94 percent for 99m-Tc-sestamibi perfusion and 99m-Tc-sestamibi gated SPECT, respectively). A similar difference was noted for detecting greater than or equal to70 percent (67 versus 84 and 92 percent).

A pooled comparative analysis of studies using exercise SPECT imaging with 99m-Tc-sestamibi and 201-Tl found that 99m-Tc-sestamibi was associated with higher sensitivity (90 versus 82 percent), specificity (93 versus 80 percent), and normalcy (100 versus 77 percent) [35]. In addition, the sensitivity of 99m-Tc-sestamibi SPECT MPI for the detection of single vessel CAD (90 percent) was almost 20 percent higher than with planar imaging.

**Dual versus single isotope imaging** — The dual-isotope imaging approach, described in 1993, consists of rest 201-Tl/stress 99m-Tc-sestamibi SPECT imaging [36]. 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.

The dual-isotope separate acquisition approach was validated in patients with a previous myocardial infarction who underwent a rest 99m-Tc-sestamibi in addition to the dual isotope SPECT study as well as coronary angiography to determine sensitivity and specificity [36]. The following findings were noted:

- Dual-isotope SPECT was highly sensitive for detecting greater than or equal to50 percent coronary artery stenosis (91 percent) and greater than or equal to70 percent stenosis (96 percent).

- Although high values for specificity were recorded (75 percent for <50 percent stenosis, and 82 percent for <70 percent stenosis), the significance was uncertain given the small number of patients with normal coronary angiograms. However, the normalcy rate was 95 percent, which is higher than seen with 201-Tl (about 89 percent) [28] and similar to that seen with 99m-Tc-sestamibi SPECT studies [23].

- In patients assessed for defect reversibility, segmental agreement for defect type between rest 201-Tl in the dual isotope study and rest 99m-Tc-sestamibi was 97 percent in zones without previous infarction, 98 percent in infarct zones, 95 percent for defect reversibility pattern (normal, reversible, or nonreversible), and 86 percent and for the exact segmental score.

In addition to its use for diagnosis, dual-isotope imaging also has prognostic value that is additive to other parameters (see "Exercise MPI for risk stratification" below).

An alternative to dual-isotope imaging is single-isotope imaging using a technetium-based radiopharmaceutical. In many laboratories, throughput is addressed by stressing the patient immediately upon completion of the rest study if a rest/stress protocol is being used. This is accomplished if the patient is injected with three times the radiopharmaceutical at stress in relation to the resting dose offsetting residual radionuclide.

Single-isotope imaging has several advantages:

- Flexibility of performing rest/stress, one-day stress/rest or two-day stress/rest, and finally stress-only imaging with attenuation correction. Thus, the laboratory can choose the most appropriate protocol for an individual patient.

- Interpretation of images is easier in view of the fact that the same isotope is used for both rest and stress. This is particularly important for interpreting attenuation artifact when attenuation correction is not available with gated SPECT imaging. Furthermore, several algorithms for attenuation correction are validated only with technetium and not thallium.

- The presence or absence of transient ischemic cavity dilation, a specific marker for multivessel coronary artery disease and poor prognosis [37], can be determined much easier using single isotope protocols.

When technetium-based products were first released, the issue of myocardial viability assessment with rest redistribution thallium was an argument in favor of dual-isotope imaging. However, optimizing the dual-isotope protocol for viability requires that a separate rest thallium scan be obtained at least four hours after the initial injection. Furthermore, several studies have validated both 99m-Tc sestamibi and tetrofosmin as equivalent to rest redistribution 201-Tl for the assessment of myocardial viability [38,39].

Thus, the original concepts supporting the superiority of dual-isotope imaging are no longer valid, and the increased flexibility of single isotope imaging may be important in certain laboratories.

**EXERCISE MPI FOR RISK STRATIFICATION** — 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 5 percent annual mortality rate) from those at intermediate risk (3 to 5 percent annual mortality rate) or low risk (3 percent or less annual mortality rate) [40,41]. The following discussion will emphasize the predictive value in patients with known or suspected CHD; risk stratification with MPI in patients who have had an acute coronary syndrome is discussed separately. (See "Risk stratification for future cardiac events after myocardial infarction with myocardial perfusion imaging" and see "Myocardial perfusion imaging in predischarge risk stratification of medically treated patients with non-ST elevation acute coronary syndrome").

The following observations have been made in patients with known or suspected CHD:

- A normal 201-Tl or 99m-Tc-sestamibi scan is generally associated with low risk of future cardiac events [42,43]. This low event rate approaches that of a normal age-matched population and also of patients with normal coronary angiograms. The same benign prognosis appears to persist in patients with a strongly positive exercise ECG or angiographically significant disease [44,45]. Among patients with a normal scan, prognosis is poorer in those with known CHD, those with diabetes, males, and older patients; an 80 year old male with diabetes and known CHD has a significant increased incidence of cardiac death or MI at two years compared to a 50 year old female without diabetes and with no known CHD (4.9 versus 0.1 percent) [46].

- High-risk features predicting an increased risk of cardiac events include extensive ischemia involving more than 20 percent of the left ventricle, defects in more than one coronary vascular supply region, reversible ischemia in multiple segments, transient or persistent left ventricular cavity dilatation, and increased 201-Tl lung uptake, a marker of exercise-induced left ventricular dysfunction that is best assessed by obtaining a five minute post-stress and four hour redistribution or rest anterior planar scan before the initiation of SPECT imaging [37,40,41,47-49].

The predictive value of an abnormal test was demonstrated in an analysis of more than 5000 patients with prior CHD who underwent stress SPECT MPI [37]. At 1.8 years, there were 119 cardiac deaths. For patients with normal, mildly abnormal, moderately abnormal, or severely abnormal perfusion defects, the rates of cardiac death were 0.5, 2.7, 2.9, and 4.2 percent, respectively.

- The presence of post-stress left ventricular dysfunction has a significant impact on the predictive value of MPI. This was illustrated in a series of 1680 consecutive patients with known or suspected CHD [50]. Patients with an LVEF greater than or equal to45 percent had a mortality rate under 1 percent per year, even with severe perfusion abnormalities, while those with an LVEF <45 percent and mild to severe perfusion abnormalities had a mortality rate of 6.6 percent per year.

Dual-isotope testing, described above, also has prognostic value as illustrated in a report of 2200 consecutive patients with possible CHD [51]. In this population at overall low risk (1.8 percent at 1.5 years) for "hard" events (cardiac death and myocardial infarction), myocardial perfusion SPECT added incremental prognostic information to clinical data and to the Duke treadmill score on exercise ECG testing (show figure 1). (See "Exercise testing for the prognosis of patients with known or suspected coronary heart disease", section on Treadmill scores).

**MPI IN WOMEN** — A number of studies have documented the lack of diagnostic value of exercise testing in women [52-57]. In these reports, the sensitivity for the detection of significant coronary artery disease (greater than or equal to50 percent or greater than or equal to70 percent angiographic stenosis) was between 60 and 80 percent in women and between 65 and 87 percent for men. However, specificity was significantly lower in women (63 to 68 percent compared to 74 to 89 percent in men). The approach to the noninvasive diagnosis of CHD in women, including the role of MPI, is discussed in detail elsewhere. (See "Noninvasive diagnosis of coronary heart disease in women").

Summarized briefly, stress MPI can improve specificity without compromising sensitivity in the detection of CAD in women compared to exercise ECG testing alone. Exercise SPECT MPI is more sensitive than planar imaging and the introduction of 99m-Tc agents and the addition of ECG gated SPECT imaging further improves the specificity compared to 201-Tl imaging [31,58,59]. The following observations illustrate these findings:

- A prospective study evaluated 201 consecutive women who underwent adenosine SPECT MPI with dual isotope (rest 201-Tl/stress 99m-Tc-sestamibi). For detection of greater than or equal to70 percent stenosis, the sensitivity, specificity, and diagnostic accuracy were 95, 66, and 85 percent respectively, with a 93 percent normalcy rate. The results were similar for all women regardless of the presenting symptoms, history of myocardial infarction, or pretest probability of CAD.

- In a review of 115 women, the specificity for lesions greater than or equal to70 percent was 67 percent for 201-Tl SPECT perfusion, 84 percent for 99m-Tc-sestamibi SPECT perfusion, and 92 percent for 99m-Tc-sestamibi gated SPECT [31]. The sensitivities with Tl-201 and 99m-Tc-sestamibi SPECT perfusion were similar for lesions greater than or equal to50 percent (75 and 72 percent) and lesions greater than or equal to70 percent (84 and 80 percent).

A 2003 consensus statement describes a stratified approach in women at intermediate to high risk of CAD based upon exercise tolerance, the baseline ECG, and the presence of other comorbidities such as diabetes mellitus [60].

**MPI IN PATIENTS WITH DIABETES** — The prevalence, incidence and mortality from all forms of cardiovascular disease are two- to eight- fold higher in persons with diabetes [61]. The American Heart Association designates diabetes as "coronary risk equivalent" and indicates that patients with diabetes belong in the same risk category as patients with known CHD. Although early identification of subclinical CHD is desirable in patients with diabetes, there are no data to show a clinical benefit from early detection of CHD in the asymptomatic stage. (See "Epidemiology of and risk factors for coronary heart disease in diabetes mellitus").

There are several existing guidelines with respect to screening for CHD in asymptomatic diabetics [3,62]. The American Diabetes Association suggests that noninvasive cardiac testing should be performed in patients with diabetes and one of the following [62]:

- Typical or atypical cardiac symptoms
- Resting electrocardiographic changes
- Peripheral or carotid arterial disease
- Planning on beginning a vigorous exercise program if age is greater than or equal to35 years
- Presence of two or more cardiac risk factors in addition to diabetes including dyslipidemia, hypertension, smoking, a family history of premature CAD, and microalbuminuria or overt proteinuria.

The indications for stress MPI as opposed to exercise ECG testing in patients with diabetes are the same as those that apply to the general population. These include patients who are unable to exercise (in combination with pharmacologic agents), and those who are able to exercise but have baseline electrocardiographic abnormalities that could interfere with detection of exercise-induced ischemia. The diagnostic accuracy of stress MPI appears to be similar in diabetics and nondiabetics [63].

MPI is also an effective tool for risk stratification in patients with diabetes and CHD [63,64]. This was illustrated in a study of 4755 patients with symptoms of CHD, of whom 929 were diabetic [64]. At 2.5 years, diabetics had a significantly higher cardiac event rate than nondiabetics (8.6 versus 4.5 percent). Diabetics also had a higher incidence of abnormal perfusion scans (48 versus 42 percent). When adjusted for pretest clinical risk factors and the extent of perfusion abnormalities, the risk of cardiac death was not significantly different.

Another report included 1271 diabetics and 5862 diabetics with known or suspected CAD who underwent dual isotope SPECT imaging [63]. The diabetics had a significantly higher incidence of cardiac death or nonfatal myocardial infarction (4.3 versus 2.3 percent per year). Among the diabetics, the event rate was 1 to 2 percent per year in those with normal scans, 3 to 4 percent per year with mildly abnormal scans, and more than 7 percent per year in patients with moderate to severely abnormal scans.

**CONCLUSIONS** — Stress myocardial perfusion imaging has emerged as an important tool in the diagnosis of suspected CAD. As with all screening tests, it is of particular importance in intermediate risk patients (pretest probability between 15 percent and 80 percent). The main indications for stress MPI are those that limit exercise ECG testing: an inability to to exercise; and baseline electrocardiographic abnormalities that could interfere with detection of exercise-induced ischemia. However, as noted above, stress MPI can provide added value even in patients who an able to undergo exercise ECG testing.

The development of 99m-Tc-labeled agents with improved imaging characteristics and the ECG gated acquisition permits simultaneous assessment of myocardial perfusion and ventricular systolic function. This in turn translates into superior diagnostic accuracy and provides important prognostic information regarding cardiac events.

A normal stress MPI is associated with a low risk for future cardiac events (<1 percent annual mortality rate). In contrast, the presence of high-risk findings, such as extensive ischemia, reversible ischemia in multiple segments, transient or persistent cavity dilatation, or an LVEF <45 percent, predict an annual mortality rate above 3 percent. Those patients should undergo coronary revascularization, whenever feasible, since the cardiac event rate appears to increase in proportion to the magnitude of jeopardized myocardium.

Subpopulations that particularly benefit from MPI are women and patients with diabetes. In women, perfusion imaging has improved specificity without compromising sensitivity. Finally, in diabetics, MPI adds incremental information, which allows prediction of long term outcomes.



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