

Applications of Stress Testing in Diagnosing Ischemic Heart Disease

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Cardiovascular disease is the most common cause of death in developed countries,¹ and treatment strategies for this disease are continually evolving. As these strategies become more sophisticated, physicians must ensure that they use appropriate diagnostic procedures to optimize patient care. For example, as progress in the development of effective methods of myocardial revascularization leads to more minimally invasive and noninvasive procedures, there is a greater need to estimate the probability of a patient having coronary artery disease (CAD) by means of noninvasive cardiac testing. Stress testing, a noninvasive diagnostic technique, plays an important role in this regard. This article reviews the use of stress testing in the evaluation of patients with suspected ischemic heart disease, including the use of risk factor analysis to assess a patient's candidacy for noninvasive testing. The basic methodology of performing a stress test is reviewed, as is the use of various imaging modalities during stress testing.

HISTORY AND RISK FACTOR ASSESSMENT

Chest pain typically associated with myocardial ischemia has the following characteristics: it is associated with exercise; it is retrosternal or left parasternal in location; it radiates to the left shoulder or arm; and it resolves with nitroglycerin or rest.

Taking a history from a patient who presents with chest pain is the first step in establishing a diagnosis. A thorough history that includes the assessment of coronary risk factors may allow a physician to stratify patients with chest pain into levels of low, intermediate, or high probability of having obstructive CAD.^{2,3} This information, in turn, can help the physician determine what type of diagnostic testing is appropriate in a particular patient.

Established major cardiac risk factors are as follows: smoking, hypertension, hyperlipidemia, diabetes mellitus, family history of premature CAD, and physical

inactivity. Male gender and postmenopausal status in women confer increased risk for developing atherosclerosis.^{2,3,4} Other more recently discovered factors (eg, high homocysteine levels, chlamydial infection) are not yet firmly established to be routinely evaluated.

The presence of chest pain characteristic of myocardial ischemia, together with 3 or more major cardiac risk factors, suggests a high probability of CAD in a patient. Characteristic pain with 1 or 2 risk factors decreases that probability to intermediate, and the absence of risk factors in a patient with characteristic chest pain decreases the probability of CAD to low. Presence of *atypical* chest pain—with or without risk factors—usually represents low to low-intermediate probability for the presence of significant CAD.

Noninvasive cardiac testing plays an important role in evaluating a patient for CAD and for referral for coronary angiography.^{5,6,7} However, the concept of pretest probability should be kept in mind when interpreting the results of noninvasive testing. It has been found that the most accurate results of noninvasive testing are obtained in patients with intermediate probability of having significant CAD based on history and risk-factor assessment. In patients with low pretest probability, the number of false-positive results on noninvasive testing tends to be higher. In patients with high pretest probability, the number of false-negative results may be higher. Patients with high pretest probability should therefore undergo coronary angiography even with a negative result on noninvasive testing. Patients with low pretest probability may not have to undergo cardiac stress testing unless symptoms become progressive.^{6,7,8}

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Table 1. Appropriate Indications and Clinical Settings for Exercise Stress Testing

Patient has chest pain and an intermediate pretest probability of CAD
Patient previously evaluated and has possible or known CAD, but has a change in clinical status
Patient has recurrent symptoms of ischemia after revascularization
Patient has known or suspected exercise-induced arrhythmias
For evaluation of medical therapy and assessment of prognosis in post-MI patients who do not have hypotension, CHF, or recurrent chest pain (symptom limited at 2–3 weeks or submax* at 4–7 days followed by symptom limited at 3–6 weeks)
For identification of appropriate settings in patients with rate adaptive pacemakers

CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction.

*Submax = 85% of maximal predicted heart rate.

EXERCISE STRESS TESTING

Exercise stress testing with electrocardiogram (ECG) monitoring is the original form of noninvasive cardiac testing. It is widely used and convenient for patients because it is often performed in the physician's office. Indications and appropriate clinical settings for this form of testing are listed in **Table 1**.

Exercise stress testing can be accomplished by either treadmill or cycle ergometry, though treadmills are predominantly used. There are several standard treadmill protocols that can be customized for patients to reach the endpoint of 85% to 100% maximum predicted heart rate. Among them, the Bruce protocol is the most popular. This protocol consists of a maximum of eight 3-minute stages with incremental increases in speed and incline.⁹

Maximum predicted heart rate is calculated by subtracting the patient's age from the number 220. Exercise capacity is then reported in minutes or, preferably, in estimated metabolic equivalents of oxygen consumption (METs). METs reflect the actual metabolic expense during exercise and can be compared among different patient populations. A test is considered adequate if at least 6 METs have been achieved. The patient is continuously monitored via ECG while heart rate and blood pressure are closely observed. Testing is stopped when the patient reaches

the target heart rate (a percentage of the predicted maximum heart rate).

Indications to stop testing (other than reaching the target heart rate) are as follows: decrease in blood pressure of more than 10 mm Hg from baseline, sustained ventricular tachycardia, ST elevation greater than or equal to 1 mm in leads without q waves, moderate to severe angina, or severe dizziness. Relative indications to conclude the test include ST depression greater than 2 mm, other arrhythmias, increasing chest pain, systolic blood pressure greater than 250 mm Hg or diastolic blood pressure greater than 115 mm Hg, claudication, shortness of breath, or the development of a bundle branch block that cannot be differentiated from the ventricular tachycardia.

Horizontal or downsloping ST depression greater than or equal to 1 mm for at least 60–80 ms is commonly considered a positive stress test. However, the capacity of a stress test to localize ischemia based on leads demonstrating ischemic changes is poor. An inappropriately slow heart rate or a decrease in blood pressure compared with baseline is also indicative of ischemia. Additional features pointing to coronary disease are exercise-induced ST elevation and sustained ventricular tachycardia.^{3,6,10}

Patients with positive results on stress testing are usually recommended to undergo coronary angiography to establish definite diagnosis. Patients with equivocal or nondiagnostic stress test results may be recommended for radionuclide or echocardiographic stress testing before a final decision regarding coronary angiography is made.

Baseline ECG abnormalities make interpretation of exercise ECG difficult, necessitating performance of radionuclide or echocardiographic stress testing. Also, it is better to perform exercise stress testing without certain medications, such as β -antagonists, calcium-channel blockers, or nitrates, in order to avoid false-negative results and allow the patient to reach the target heart rate. (However, a stress test may be performed while a patient is on medications in order to assess exercise capacity and adequacy of therapy in patients with previously diagnosed CAD.)

Overall, exercise stress testing is a safe procedure that is well tolerated. However, hypotension, arrhythmias, myocardial infarction, and even death can occur. The expected rate of serious complications is up to 1 per 2500 tests. For these reasons, a code cart and defibrillator should be available and a trained physician should supervise or be in close proximity. Contraindications are listed in **Table 2**. In a meta-analysis of 147 reports

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Table 2. Contraindications to Exercise Stress Testing

Acute MI less than 3 days prior to test
Unstable angina not controlled by medication
Uncontrolled arrhythmia
Uncontrolled congestive heart failure
Acute pulmonary embolism
Acute myocarditis or pericarditis
Uncontrolled hypertension (SBP > 200 mm Hg, DBP > 110 mm Hg)
Severe aortic stenosis
Known left main coronary artery stenosis
Aortic dissection
High-degree AV block
Hypertrophic cardiomyopathy
Mental or physical inability to exercise
Abnormal resting ECG secondary to LBBB, LVH, pre-excitation, > 1 mm ST elevation or depression, paced rhythms, or digoxin use

AV = atrioventricular; DBP = diastolic blood pressure; ECG = electrocardiogram; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; SBP = systolic blood pressure.

(24,074 patients undergoing exercise stress testing and coronary angiography) the mean sensitivity of exercise stress testing was 68%, with a mean specificity of 77%. Cost is \$200 to \$300 including interpretation fee.^{11,12} Stress testing is a cost-effective diagnostic procedure in the setting of the emergency department or chest pain unit.

Exercise stress testing also has a prognostic value in the evaluation of patients with known CAD and in patients who have undergone myocardial revascularization. In addition to the estimation of exercise tolerance and presence of exercise-induced myocardial ischemia, heart recovery rate can be measured. A decrease in heart rate of less than 12 beats/min 1 minute after stopping the exercise has significant negative prognostic value.^{6,7}

RADIONUCLIDE IMAGING

Radionuclide imaging may be added to regular ECG exercise stress testing on the treadmill. It can also be performed with pharmacological agents substituting for exercise. Indications and appropriate clinical settings for radionuclide cardiac imaging are given in **Table 3**. Two main isotopes are used: thallium Tl 201 and technetium Tc 99m.^{13,14} The advantages of technetium, which is given in combination with its carrier, sestamibi, are that the quality of imaging is better and the imaging itself

takes less time than with thallium.¹² When a full ECG exercise stress test is performed, these agents are injected at 1 minute prior to the end of exercise in order to allow tracer to circulate at maximal heart rate and be distributed within myocardium. Scintigraphic images of cardiac perfusion are then acquired.

The most popular method of imaging is the single-photon emission computed tomography (SPECT). A gamma camera collects data from multiple views, and its computer produces images for interpretation by the physician. Imaging is repeated, with isotope reinjection, after the patient has rested. Both immediate poststress and resting images are then compared. The presence of a perfusion defect on both stress and resting images indicates irreversible ischemia (ie, old myocardial infarction), whereas the presence of a perfusion defect on stress images but not on resting images suggests reversible ischemia (ie, coronary stenosis with viable myocardium).¹³⁻¹⁶

In patients who cannot exercise for various reasons, pharmacologic isotope imaging can be performed. The agent of choice is most commonly dipyridamole.¹⁷ This medication dilates nondiseased coronary arteries, creating myocardial perfusion shifts or so-called *coronary steal syndrome*. Blood flow is directed to the areas supplied by healthy coronary vessels and away from the areas supplied by stenotic arteries. As the isotope follows perfusion, it therefore concentrates in well-perfused areas. In order to distinguish between irreversible and reversible ischemia, another set of images is obtained 2 hours after dipyridamole injection. Areas not perfused on both sets of imaging represent old, irreversible ischemia. Reperfusion on the second set of pictures indicates reversible ischemia. Clinical symptoms as well as ECG are monitored during dipyridamole isotope studies. Presence of typical chest pain especially when associated with ischemic ST-T changes is highly indicative of myocardial ischemia. Adverse effects of dipyridamole are attributable to vasodilation and include headache, flushing, or feeling of fullness. Aminophylline can be used to quickly reverse effects of dipyridamole. Dobutamine may be used in place of dipyridamole, though dobutamine is more appropriate for stress echocardiography.

Average sensitivity of radionuclide myocardial imaging is approximately 90%, and specificity is 76%.¹³⁻¹⁶ Radiation dose is minimal, and there are practically no adverse effects from properly injected isotope. These studies are quite costly owing to the high equipment cost, isotope cost, personnel work, and physician-interpretation fees. In many hospitals the ECG part of the test is interpreted by a cardiologist or an internist, and the scintigraphic imaging portion

is read by a radiologist. In some laboratories, the cardiologist reads both parts. Total cost is in the \$900 to \$1400 range.^{11,12}

STRESS ECHOCARDIOGRAPHY

Stress echocardiography is the newest method of non-invasive testing to detect CAD. Indications for stress echocardiography are similar to those for radionuclide imaging.¹⁸ It is a valuable test in women, in whom a higher number of false-positive results of exercise stress testing are observed.¹⁹

The test is based on the principle that an ischemic myocardial wall becomes hypokinetic. Baseline echocardiography is performed first with assessment for any regional wall-motion abnormalities. Detection of such wall-motion abnormalities suggests previous infarction. Then, the patient exercises on the treadmill according to the regular exercise stress test protocol. Just after cessation of the exercise, another set of echocardiographic images is taken. Resting and poststress pictures are compared and evaluated for the presence of exercise-induced wall-motion abnormalities, which indicate reversible ischemia. The information obtained from this test also includes that obtained from regular ECG stress testing, because stress test on the treadmill is an integral part of the procedure.

In patients who cannot exercise, a pharmacologic agent—usually dobutamine—is used to simulate stress.^{20,21} By its positive inotropic and chronotropic effects, dobutamine may induce wall-motion abnormalities in segments of the myocardium supplied by diseased coronary artery, thereby simulating stress caused by the regular exercise. Echocardiographic imaging is applied in order to detect these abnormalities. Baseline and post-dobutamine sonograms are comparatively analyzed. Alternatively, dipyridamole may be used in pharmacologic stress echocardiography. It is less frequently used because the mechanism of action is based on perfusion changes rather than direct effects on myocardial contractility.

Stress echocardiography is available at most noninvasive cardiac laboratories and is relatively easy to perform. The cost is less than that of radionuclide imaging, as the equipment and materials are generally less expensive. The quality of echocardiographic imaging is the major limiting factor. In patients with chronic obstructive pulmonary disease or in obese patients, the acoustic window is limited. Therefore, precise assessment of regional wall-motion abnormalities may not be possible. Echocardiographic contrast materials may offer some help to overcome this barrier. The sensitivity of stress echocardiography in detecting coronary

Table 3. Appropriate Indications and Clinical Settings for Radionuclide Cardiac Imaging

Patient has chest pain with 1 or more of the following resting ECG changes: bundle branch blocks, left ventricular hypertrophy, early repolarization abnormalities, nonspecific ST-T changes, post MI, WPW
Patient has chest pain and cannot exercise (this is an indication for pharmacologic radionuclide imaging)
For evaluation after equivocal exercise stress test in patients with intermediate probability of CAD
For evaluation of the correlation between coronary stenosis and myocardial ischemia
To assess myocardial viability in patients after MI or revascularization
To assess existence of preoperative medical risk

ECG = electrocardiogram; MI = myocardial infarction; WPW = Wolff-Parkinson-White syndrome.

artery disease is approximately 90% with similar specificity.¹⁸⁻²¹ The total cost ranges from approximately \$600 to \$800.^{11,12}

SUMMARY

Stress testing is an important diagnostic tool in detecting CAD. Standard stress testing involves treadmill exercises to produce stress. Pharmacologic stress testing can be performed in patients unable to exercise. Stress testing is cost-effective for patients with intermediate or low-intermediate clinical probability of having CAD. Cardiac catheterization remains the gold standard of diagnosis. However, the noninvasiveness, cost-effectiveness, and prognostic value of stress testing are the major reasons why these tests are used in the initial evaluation of patients with suspected CAD. Also, newer imaging techniques like magnetic resonance imaging and electron beam computed tomography may play an important role in diagnosing CAD in the near future.^{22,23} **HP**

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