Noninvasive Stress Testing for Coronary Artery Disease

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KEYWORDS

- Stress testing • Exercise treadmill testing (ETT)
- Single-photon emission computed tomography (SPECT) • Positron emission tomography (PET)
- Myocardial perfusion imaging (MPI) • Exercise echocardiography • Dobutamine echocardiography

KEY POINTS

- The most important use of stress testing is risk stratification.
- Most patients can be accurately classified as low or high risk from treadmill test scores.
- Standard exercise treadmill testing is the preferred initial testing strategy in patients without prior revascularization who can adequately exercise and have a normal or near-normal resting electrocardiogram.
- Selection between imaging modalities depends primarily on patient characteristics and local expertise.
- The usefulness of the ischemic burden identified by stress imaging for categorizing risk and serving as a guide for selection of optimal treatment of coronary artery disease remains uncertain.

INTRODUCTION

Stress testing remains the traditional noninvasive approach for assessing patients with possible or established coronary artery disease (CAD). The most commonly used modalities include standard exercise treadmill testing (ETT); nuclear myocardial perfusion imaging with single-photon emission computed tomography (SPECT) and, less commonly, positron emission tomography (PET); and stress echocardiography. The stress imaging procedures can be performed with exercise stress or pharmacologic stress. Exercise is the preferred approach whenever possible because it provides an opportunity to evaluate the reproducibility of a patient's symptoms and to measure important prognostic variables (especially exercise capacity) that are not available with pharmacologic stress. Although several exercise modalities including cycle ergometry and arm crank ergometry are available, in the United States the predominant type of exercise is graded treadmill walking. Pharmacologic stress testing can be performed in patients who cannot adequately exercise, generally defined as a workload less than 5 to 7 metabolic equivalents (METs), or in the presence of specific abnormalities on the resting electrocardiogram (ECG), such as left bundle branch block or paced ventricular rhythm. The most commonly used pharmacologic agents with nuclear imaging include the vasodilating agents regadenoson, adenosine, or dipyridamole, and with echocardiography the sympathomimetic agent dobutamine. Individuals who perform stress testing should be familiar with

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contraindications to exercise and to the use of these pharmacologic agents, which are described elsewhere.[1–4]

Stress Testing for Diagnostic Purposes

Stress testing has traditionally been performed as a diagnostic test. The variable for each modality that has been most commonly used to define an abnormal test includes standard ETT, greater than or equal to 1 mm horizontal or downsloping ST segment depression measured 0.06 to 0.08 seconds after the J point; SPECT or PET, a perfusion abnormality; and echocardiography, a regional wall motion abnormality (**Fig. 1**). Diagnostic test accuracy is expressed in terms of sensitivity (true-positives/true-positives + false-negatives) and specificity (true-negatives/true-negatives + false-positives). Average values for sensitivity are higher for the imaging procedures (SPECT, 87%; echocardiography, 86%) than ETT (68%); values for specificity are similar (SPECT, 73%; echocardiography 81%; ETT, 77%).[1,5,6]

Impact of Verification Bias on Diagnostic Accuracy

The gold standard for diagnosing CAD is the presence of a significant stenosis (defined as $\geq$50% or $\geq$70% diameter narrowing) in a major epicardial vessel by invasive coronary angiography. A stress test is not a definitive diagnostic study because the results of the test provide only the posttest probability that CAD is present or absent. The results of the stress test must be verified against the findings at coronary angiography. Nearly all studies that have been performed to address the diagnostic accuracy of stress testing have examined the minority subset of patients who are referred for coronary angiography following stress testing. Because coronary angiography is more likely to be performed in patients with positive versus negative stress test results, the angiographic subset is dominated by patients with positive test results. This concept, known as verification or posttest referral bias, drives sensitivity to 100% (many more true-positives than false-negatives) and specificity to 0% (many more false-positives than true-negatives).[7,8] The only pure approach to avoid the impact of verification bias on sensitivity and specificity is to design a study in which all patients who present for evaluation of CAD are referred for coronary angiography irrespective of the results of stress testing. The single study that applied this design using standard ETT reported test sensitivity of 45%, compared with mean sensitivity of 68% reported by meta-analysis.[9] Another approach to adjust for verification bias applies a mathematical correction based on statistical modeling to the derived values for sensitivity and specificity.[10–12] Studies performed at the Mayo Clinic using this approach reported substantially lower values for sensitivity after adjustment for referral bias (for men, SPECT 98% to 67% and echocardiography 78% to 39%) and for specificity higher values after adjustment (SPECT 9% to 64%, echocardiography 44% to 81%).[11,12] These findings show that the diagnostic accuracy of all stress testing modalities is only modest. In particular, true test sensitivity is lower than is commonly appreciated.

Stress Testing for Risk Stratification

The major role of stress testing has evolved from use as a diagnostic test to application as a prognostic tool. American College of Cardiology (ACC)/American Heart Association (AHA) guidelines define clinical risk from annual mortality: low (<1%), intermediate (1%–3%), or high (>3%).[13] The results of stress testing can be applied to categorize patients into these risk categories. General recommendations for patient management include referring most high-risk patients to coronary angiography versus proceeding with observation and, when indicated, medical therapy alone for most low-risk patients. Management of patients categorized as intermediate risk is less certain and commonly involves additional testing in an attempt to clarify risk with greater certainty as low or high. For diagnostic purposes the stress testing modalities focus on a single variable (ST segment depression, perfusion abnormality, regional wall motion abnormality) analyzed in a dichotomous manner (positive or negative). For risk stratification purposes the stress testing modalities analyze multiple variables in a continuous fashion. The more severely abnormal the test result, the greater likelihood that the patient has severe anatomic (left main and/or 3-vessel) CAD and worse clinical outcome. In contrast with diagnostic studies that include only the minority subset of patients who are referred for angiography, prognostic studies involve measuring clinical outcome in all patients, except those who undergo early revascularization. Early revascularization is defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) performed within the first 2 to 3 months following the stress test. The results of the stress test are major factors influencing the decision to proceed with early revascularization. By convention, these patients are excluded from analysis because they have received a treatment not administered to the