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Cardiac Testing

Introduction

One of every 2.9 deaths in the United States is attributed to cardiovascular disease (CVD), which is more than cancer, lower respiratory tract disease, and accidents combined.[1] In 2010, CVD became the leading cause of death in developing countries.[2] Risk factors include hypertension, hyperlipidemia, diabetes, obesity, smoking, positive family history for CVD, increasing age, and male sex. Cardiac testing can be used to identify patients with coronary artery disease (CAD) who are in need of intensive intervention or treatment.

Sensitivity, Specificity, and Predictive Values

Sensitivity, specificity, and positive and negative predictive values are reported in the literature when assessing the accuracy of a diagnostic test. When evaluating these measurements, it is important to realize that the test is compared with the *gold standard* diagnostic test. It is important to understand the nature of the gold standard test to put the other diagnostic studies in perspective. For cardiac testing, the gold standard is angiography, with the most frequently cited measurement of >50% fixed coronary artery stenosis.

The sensitivity of a diagnostic test is inherent in the test itself. It is the test's ability to correctly identify people with a given disease or condition. Sensitivity is the probability that a patient with the disease has a positive test result. The specificity is the ability to correctly identify people who do not have a given disease or condition. Specificity is the probability that a patient without the disease will have a negative test result. For sensitivity and specificity, the closer the value is to 100%, the more accurate the test.

The classic 2 x 2 table is used to calculate sensitivity and specificity (*Figure 1*). Because diagnostic evaluations are imperfect tests, often as the sensitivity increases the specificity decreases, and vice versa.[3] A helpful mnemonic for sensitivity is **SNOut** – a highly **S**ensitive test with a **N**egative result is helpful for ruling **Out** the disease. A helpful mnemonic for specificity is **SPIn** – a highly **S**pecific test with a **P**ositive result is helpful for ruling **In** the disease.

Figure 1. Classic 2 x 2 table

	Disease (+)	**Disease (-)**
Test (+)	True Positive (TP)	False Positve (FP)
Test (-)	False Negative (FN)	True Negative (TN)

Negative predictive value = TN/(TN + FN); positive predictive value = TP/(TP + FP); sensitivity = TP/(TP + FN); specificity = TN/(TN + FP).

Positive and negative predictive values can also be calculated from the 2 x 2 table. The positive predictive value is the probability that a patient with a positive test result will have the disease. The negative predictive value is the probability that a patient with a negative test result will not have the disease. These values are not inherent to the diagnostic tests and change with the probability of the disease in each patient population.

The determination of disease probability in the population can be challenging. Each population might have a different risk for a given disease based on genetics, ethnicity, and lifestyle. Generalizations can and should be made given some basic data. For example, the pre-test probability for CAD can be estimated from the patient's age, sex, and chest pain symptoms (*Table 1*).

Table 1. Pretest Probability of Coronary Artery Disease By Age, Gender, and Symptoms*

Age	Gender	Typical/Deginite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30-39	Men	Interm	Interm	Low	Very low
	Women	Interm	Very low	Very low	Very low
40-49	Men	High	Interm	Interm	Low
	Women	Interm	Low	Very low	Very low
50-59	Men	High	Interm	Interm	Low
	Women	Interm	Interm	Low	Very low
60-69	Men	High	Interm	Interm	Low
	Women	High	Interm	Interm	Low

**No data exists for patients <30 or >69 years of age, but it can be assumed that the prevalence of coronary artery disease increases with age. In a few cases, patients with ages at the extremes of the decades listed may have probabilities slightly outside the high or low range. High indicates >90%; intermediate 10%-90%; low <10%; and very low <5%. Anginal chest pain is felt as pressure or crushing, occurs during exertion, is relieved by rest or nitroglycerine, and radiates to the shoulder, jaw, or inner arm. Atypical chest pain is defined as having some features of angina with some atypical features, for example, felt as a burning sensation or occurring at rest. Nonanginal chest pain is unrelated to activity, unrelieved by rest or nitroglycerine, and nonradiating.*

Reprinted from Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing), Circulation. *1997;96:345-354.*

Cardiac Tests

Cardiac testing is helpful for many conditions, but by far the most common is CAD. The remainder of this *CME Bulletin* will focus on the use of cardiac testing in the diagnosis, risk stratification, and management of patients with suspected CAD or who are at increased risk for CAD.

Electrocardiogram

The electrocardiogram (EKG) is often the first test administered to a patient with suspected myocardial infarction (MI) or CAD. EKG changes have been detected within 90 minutes of the onset of ischemia.[4] The reported sensitivity is 68% and the specificity is 97%. Consequently, the EKG is not adequate for ruling out CAD or MI. Up to 20% of patients will have a normal EKG result in the midst of an acute coronary syndrome.

The resting EKG result is normal in half of all patients with stable CAD. For an EKG performed during chest pain, ST segment elevation of at least 1 mm in 2 contiguous leads has been shown to be the most specific finding for ischemia.[5] Serial EKGs improve the sensitivity and specificity in the diagnosis of acute MI.

Exercise Stress Test

The 1997 and 2002 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for exercise testing recommend a graded exercise stress test (EST) for evaluation of potential CAD.[6] This test is well validated, inexpensive, readily available, and easy to perform. The overall diagnostic accuracy for the EST is 68% sensitivity and 77% specificity based on a 12,000-patient meta-analysis using coronary angiography as the gold standard.[7] An EST is best used in patients with a normal or minimally abnormal baseline EKG result (eg, ST depression <0.5 mm or right bundle branch block [RBBB]). The best results are obtained when using 1 mm of horizontal or downsloping ST segment depression as a positive finding.

Exercise stress testing is best applied in the patient with an intermediate pretest probability. Patients with a high pretest probability do not need the test for diagnosis; it adds little to the posttest probability, and the diagnosis is still likely even with a negative test result. Patients with a low pretest probability also do not need the test for diagnosis because it adds little to the posttest probability and still makes the diagnosis unlikely even with a positive test result (***see Figure 2***).[8] Screening of low-risk, asymptomatic patients for CAD using an EST is not recommended by the US Preventive Services Task Force (USPSTF) (grade D).[9]

Absolute contraindications to stress testing include acute MI within previous 48 hours; unstable angina; uncontrolled arrhythmias, severe valvular stenosis; decompensated congestive heart failure; aortic dissection; acute pulmonary embolism; and disorders affecting exercise, such as arthritis of the knees or hips, chronic obstructive pulmonary disease (COPD), or intermittent claudication.

Relative contraindications include preexcitation, ventricular pacing, complete left bundle branch block (LBBB), and 1 mm of ST segment depression at baseline, all of which make interpretation challenging. Patients with relative contraindications should undergo an alternate form of cardiac testing, such as stress myocardial perfusion imaging (MPI), to improve accuracy.[7]

The interpretation of the EST involves a number of factors. The following should be annotated:

- EKG changes such as ST segment depression and elevation and the amount of change, in millimeters
- The morphology of the ST segment depression: upsloping, horizontal, or downsloping
- Any changes in the baseline rhythm, as well as T wave changes such as inversion
- Blood pressure response; a hypotensive response is indicative of systolic dysfunction and possible multivessel disease
- Symptoms such as chest, jaw, and neck or arm pain, along with whether the symptoms are typical of angina
- Heart rate response, as well as the time to recovery
- Level of effort measured as metabolic equivalents, or METS; fewer than 7 METS (not due to musculoskeletal limitations) is concerning, and more than 10 METS is reassuring[7]

Exercise testing for CAD in women is especially problematic. Diagnostic accuracy is decreased for the EST because of a lower prevalence of CAD, atypical symptoms, fewer occurrences of obstructive CAD, and hormonal effects on the ST segments. Also, older age at symptom onset makes exercise more difficult.[10] The sensitivity for women is 31%-33% with a specificity of 52%-74%.[11] Women are more likely to have a false positive test result, which means more testing is needed. In addition, ST segment depression does not have as strong of a prognostic value as it does in men. Despite these concerns, exercise stress testing remains the recommended evaluation for women at intermediate risk for CAD. Although not recommended in the most recent ACC/AHA guidelines on exercise testing, myocardial perfusion imaging or stress echocardiography may be more accurate cardiac testing modalities in women.

Exercise capacity is important in all patients. Fewer than 7 METS may signify CAD or deconditioning, whereas achieving more than 10 METS is reassuring that a patient does not have significant CAD. Heart rate recovery is an independent predictor for CAD in women and men. Heart rate recovery is the peak heart rate minus the heart rate at 1 minute of recovery. A decrease of fewer than 12 beats per minute is abnormal.[12]

The Duke treadmill score was developed in 1987 in an attempt to improve the diagnostic accuracy of the EST and has been evaluated in men and women. The use of the Duke treadmill score is recommended in the 2002 ACC/AHA guidelines. In one study, the Duke treadmill score improved the sensitivity to 75%-78%. The formula is Duke treadmill score = exercise time – (5 x ST deviation) – (4 x angina score index), where the exercise time is in minutes, ST deviation is in millimeters, and the angina score is 0 for no angina, 1 for nonlimiting angina, and 2 for exercise-limiting angina. A low risk score is 5 or greater, moderate risk is -10 to 4, and high risk is less than -11.[13]

Myocardial Perfusion Imaging

Another option for the evaluation of CAD is the MPI study using single-photon emission computed tomography (SPECT). Other perfusion imaging options that are less well validated include cardiac positron emission tomography (PET) and cardiac magnetic resonance. Images can be obtained at rest or after stress induced by either exercise or pharmacologic agents, and involve measuring radioactive decay of injected isotopes such as thallium or technetium sestamibi. Technetium sestamibi is the preferred agent because of more rapid uptake in the myocardium and faster imaging.

Stress MPI is appropriate for the diagnosis and risk stratification of patients with chest pain with intermediate risk. Screening of low-risk, asymptomatic patients for CAD using MPI is not recommended by the USPSTF (grade D).[9] The sensitivity and specificity is reported at 90% and 70%, respectively. Exercise is the preferred method for stressing the myocardium because exercise tolerance and blood pressure response can be determined. However, if patients are unable to exercise, pharmacologic agents such as adenosine (eg, Adenoscan), dipyridamole, dobutamine, or regadenoson (Lexiscan) can be used. Adenosine is preferred because of a very short half-life, rapid reversal of side effects, and more predictable vasodilation. All of these agents can cause chest pain, dyspnea, and flushing.[14]

Stress Echocardiography

Echocardiography can be used in combination with exercise or pharmacologic agents to induce myocardial stress. The echocardiography technician or cardiology subspecialist searches for regional wall motion abnormalities associated with areas of myocardial ischemia. The sensitivity is reported at 76% with a specificity of 88%.[15] Although exercise is preferred, a pharmacologic agent such as dobutamine or dipyridamole can be used. This test is considered appropriate for patients with acute chest pain and an intermediate pretest probability for CAD with no EKG changes and negative biomarkers. It is especially helpful for patients with baseline EKG abnormalities where the EST cannot be interpreted.

The biggest challenge with stress echocardiography is that the images are subjectively interpreted with the accuracy dependent on the experience of the echocardiography technician or cardiology subspecialist.[16] Advantages include information on left ventricular mass and valvular function. Stress echocardiography has not been studied as well as EST, but it is faster, less expensive, and has no radiation exposure. Screening of low-risk, asymptomatic patients for CAD using stress echocardiography is not recommended by the USPSTF (grade D).[9]

Coronary Artery Calcium and Carotid Intima-Media Thickness

Calcium deposits in the coronary arteries are linked to atherosclerosis, and a direct correlation has been demonstrated between the amount of coronary artery calcium (CAC) noted on computed tomography (CT) scan and vessel luminal narrowing.[17] The sensitivity for the presence of >50% angiographic stenosis is 91% and the specificity is 46%. A CAC score of zero is associated with a very low risk of MI or death due to CAD. Increasing CAC scores are associated with an increased risk of MI or death.[18] CAC scores may add prognostic value to patients who are classified as intermediate risk by the Framingham risk calculator.[19]

Carotid intima-media thickness (CIMT) is measured with B-mode ultrasound. Increasing thickness is associated with an increased risk of MI, stroke, and death from cardiovascular disease. Carotid intima-media thickness seems to predict future stroke better than CAC scores.[20] This test is also best used to assess patients at intermediate risk to help further differentiate risk by determining whether atherosclerosis is present. No studies have shown that intensification of therapy in response to increased CIMT or CAC scores improves outcomes.[21,22] Screening of low-risk, asymptomatic patients for CAD using either the CAC score or CIMT is not recommended by the USPSTF (grade D).[9]

Coronary Computed Tomography Angiography

Coronary computed tomography angiography is a noninvasive method of studying the coronary arteries for stenosis. It is a fairly new test, and most studies are single-center with experienced observers involving small populations with fewer than 100 patients. The reported sensitivity is 94%-95% and the specificity is 82%, but these numbers will likely be lower with general use.[23] Disadvantages include a radiation dose that is twice that of a coronary angiogram, the need for intravenous contrast, high cost, and questions of quality because of the lack of experience in the general radiology community. Patients must be able to hold their breath for 5-10 seconds, have no severe coronary calcifications or metallic coronary stents, have a regular heart rhythm, have a BMI <40 kg/m^2, and have a heart rate less than 60-70 beats per minute. This last requirement often entails administration of beta blockers, to which patients might experience side effects.

A coronary CT angiogram may be appropriate for the patient with intermediate pretest probability of CAD with acute chest pain who has no known heart disease, especially if the patient is unable to exercise. Those patients who are able to exercise should have an EST, exercise MPI, or exercise stress echocardiogram to evaluate exercise capacity and blood pressure response. Coronary CT angiography is not indicated as a screening tool for CAD because of the radiation dose, the high cost, and the lack of studies showing improved outcomes for patients identified as high risk.[24]

Cardiovascular Magnetic Resonance Imaging and Positron Emission Tomography

Cardiovascular magnetic resonance is another new imaging technology that has promise in the diagnosis of CAD. Its advantages include lack of the following: radiation, iodine contrast, need for heart rate control, and issues with coronary calcium. In addition, it provides 3-dimensional images that may be helpful in planning surgical interventions. For CAD, the sensitivity is reported at 72% with a specificity of 87%.[25] A high degree of technician skill is required to perform this study, which can take up to 30 minutes to complete. Cardiovascular magnetic resonance imaging is not indicated for screening in asymptomatic patients because of the high cost and the lack of studies showing improved outcomes for patients identified as high risk.

Cardiac PET is still in the testing and experimental phase. Early reports indicate a sensitivity of 92% and specificity of 85%, similar to coronary CT angiography.[25]

Recommendations

When noninvasive testing is indicated (***see Figure 3***), exercise EKG with Duke treadmill score is recommended. For those patients who cannot exercise or who have other contraindications to an EST, reasonable options include pharmacologic MPI, stress echocardiogram, and coronary CT angiogram. Because these 3 tests have similar diagnostic accuracy and potential dangers, the selection will depend on local availability, cost, and expertise.

Routine screening of asymptomatic patients at low risk of CAD is not recommended by the USPSTF. There is insufficient evidence to recommend for or against screening asymptomatic patients at intermediate or high risk for CAD.

Take the Cardiac Testing quiz (Members only)