Diagnostic evaluation of the patient with coronary artery disease

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■ **BACKGROUND** Evaluation of patients with possible coronary artery disease is a challenge to clinicians who face conflicting pressures in the current practice environment. Sensitivity, accuracy, cost, and access have become considerations in the appropriate selection of diagnostic studies.

■ **OBJECTIVE** To review and compare the strengths and shortcomings of commonly employed noninvasive techniques for diagnosing coronary artery disease.

■ **DISCUSSION** The patient's history is still key in establishing a diagnosis. Exercise electrocardiography (ECG) is not as sensitive or specific as exercise echocardiography or radionuclide studies, but it is relatively inexpensive and accessible. Further, new criteria for interpreting the results of exercise ECG may improve its diagnostic accuracy. The predictive value of any test increases in populations where the prevalence of disease is higher, as in patients with known risk factors for coronary artery disease. Patients who cannot exercise or who have concomitant conditions that obscure the results of exercise ECG are candidates for other diagnostic techniques.

■ **CONCLUSION** Rational diagnostic plans for evaluating patients who may have coronary disease can be developed on the basis of existing information and reported experience.

■ INDEX TERMS: CORONARY DISEASE; DIAGNOSIS; SENSITIVITY AND SPECIFICITY
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THE DIAGNOSTIC evaluation of patients with coronary artery disease (CAD) provides an opportunity for the thoughtful clinician to use a synergistic mix of traditional medical skills and cutting-edge technology.[1] The history remains a mainstay, particularly as cost-effectiveness increasingly becomes an issue.[2] A description of classic exertional angina still provides a diagnostic accuracy that is hard to exceed, even using sophisticated diagnostic technology.[3]

THE PATIENT'S HISTORY

Careful consideration of symptoms such as chest discomfort and of the factors that influence them is key in differentiating CAD from other diseases.[4] This appraisal of ischemic symptoms also serves as an important guide for selecting appropriate diagnostic tests.[5] An assessment of life-style helps identify behaviors associated with a higher risk of CAD.[6]

RESTING ELECTROCARDIOGRAPHY

Resting electrocardiography (ECG) is often neglected in the diagnosis of CAD. The presence of pathologic Q waves (defined as >

0.04 seconds in duration),[7] the absence of R waves, and the presence of ST-segment elevation may be characteristic and, in certain situations, diagnostic. However, resting ECG can be highly ambiguous, particularly in the presence of hypertrophy, conduction delay, and certain drugs, such as digitalis. Evidence currently does not support obtaining screening electrocardiograms in men without evidence of cardiac disease or cardiovascular risk factors.[8]

EXERCISE ELECTROCARDIOGRAPHY

Exercise ECG has been valuable for nearly 50 years. Despite the continuing development of newer technologies, its diversified applications continue to grow.[1] While not very sensitive when used alone to evaluate chest pain, the reliability and cost-effectiveness of exercise ECG in monitoring the progression of disease and determining therapeutic efficacy is not equaled by other diagnostic means.[9]

The indications for exercise ECG have been expanding.[9,10] Studies have shown that the response to exercise permits assessment of the severity of underlying coronary disease[11] and of the patient's prognosis.[12,13] Ribisl[11] noted significant differences in clinical, electrocardiographic, and hemodynamic measurements among patients according to the severity of their coronary disease. Exercise ECG, however, cannot reliably locate the arterial blockage.[14] McNeer and associates[12] found that patients at high risk have more than 1 mm of ST-segment depression at less than 7 metabolic equivalents (MET), while those at low risk do not have ST-segment depression and are able to exceed 13 MET or achieve a heart rate greater than 160.

Exercise ECG is a most accessible and cost-effective means of assessing cardiac function. Three features essentially determine the prognosis of coronary artery disease: the amount of myocardial ischemia, the severity of left ventricular dysfunction, and the arrhythmic potential of the myocardial substrate. Studies suggest that certain parameters measurable by exercise ECG reliably predict outcome after acute coronary events.[14–19] Because survival can be improved only in specific clinical subsets of patients, it is important to carefully select patients for catheterization and subsequent revascularization who may benefit in terms of quality of life and survival.[20,21] Exercise ECG facilitates identification of these patients and enables the physician to fully inform the patient about the prognosis.

EXERCISE ELECTROCARDIOGRAPHY AS A SCREENING TOOL IN CORONARY ARTERY DISEASE

In asymptomatic individuals with fewer than two risk factors, exercise ECG may be more misleading than previously thought because of its relatively high rate of false-positive results.[22] In men with high cholesterol levels, Ekelund and colleagues[23] demonstrated that abnormal results of exercise ECG were associated with a 5.7-fold increase in deaths from CAD among men receiving placebo and a 4.9-fold increase among men receiving cholestyramine to control their cholesterol. Bruce and associates[24] have reported the results of more than 5 years' follow-up in 2365 healthy men who underwent exercise ECG as part of the Seattle Heart Watch. Individual risk factors did not significantly increase the 5-year probability of primary CAD events with univariate analysis, but they did when summed. Froelicher et al[25] point out that these results, in a population with a major risk factor that increases the pretest prevalence of CAD, argue against the use of exercise ECG as a routine screening test.

Reasonable strategies for using exercise ECG to screen for CAD have been described.[22] Refinements in Bayesian methods may lead to improved diagnostic ability.[26] Interpretive methods that consider more variables are more sensitive for detecting CAD than are methods that use fewer variables.[27] Reports have suggested that exercise ECG screening may be justified in patients with one clinical risk factor or a ratio of total cholesterol to HDL cholesterol of 6:1 or greater.[28]

SENSITIVITY AND SPECIFICITY

Sensitivity and specificity define how effectively a test separates diseased from healthy individuals. Sensitivity is the percentage of people with a disease who have abnormal tests results. Specificity is the percentage of those without the disease who have normal test results.

Sensitivity and specificity are inversely related: the more sensitive a test, the less specific it tends to be, and vice versa. Any test has a range of inversely related sensitivities and specificities that can be chosen by specifying a certain discriminant or "cutpoint" value. However, some of the electrocardiographic responses to exercise do not have established values that best separate normal individuals from those with CAD.

TABLE 1
FACTORS AFFECTING ACCURACY OF EXERCISE ELECTROCARDIOGRAPHY TO DETECT CORONARY ARTERY DISEASE

Factors that lower sensitivity
Classification of equivocal tests as normal
Comparison to "better" test
Inclusion of patients taking digoxin
Use in populations with high prevalence of systemic vascular disease
Factors that lower specificity
Use in populations with low prevalence of coronary artery disease
Classification of upsloping ST-segment depression as abnormal
Exclusion of patients with previous myocardial infarction
Use in populations with high prevalence of vasospasm
Use in populations with high prevalence of mitral valve prolapse
Inclusion of patients with left bundle branch block
Hyperventilation before exercise

Once a discriminant value is chosen that determines a test's specificity and sensitivity, then the population tested must be considered. If the population is skewed towards patients with more severe disease, then the test will have a higher sensitivity. For instance, exercise ECG has a higher sensitivity in individuals with triple-vessel disease than in those with single-vessel disease. Also, a test can have a lower specificity if it is used in individuals more likely to have false-positive results; exercise ECG has a lower specificity in individuals with mitral valve prolapse and in women who have a higher prevalence of ST-segment changes with hyperventilation before testing and upward-sloping ST-depression during exercise (*Table 1*).

The sensitivity and specificity of exercise-induced ST-segment depression can be demonstrated by comparing the results of exercise ECG and coronary angiography. The cut-point of 0.1 mV horizontal or downward-sloping ST-segment depression has a specificity of approximately 84% for detecting angiographically significant CAD. The mean sensitivity of exercise ECG for detecting significant CAD is 66%; it is 40% sensitive for detecting single-vessel disease and 90% sensitive for detecting triple-vessel disease.

Bayes' theorem states that the probability of a hypothesis being true is variably modified as additional data are taken into account.[26,27] Thus, if the likelihood of CAD is very low in a given person on the basis of known risk factors, then an abnormal test result is likely to be falsely positive. An understanding of this is especially relevant to the use of exercise ECG to screen asymptomatic populations, where the low prevalence of CAD (around 5% in asymptomatic men) results in a very poor predictive value (about 23%) for a positive result, but an excellent predictive value (about 99%) for a negative result.[29] For practical purposes, this means that one must regard abnormal results of screening exercise ECG with skepticism, but one may find normal results reassuring.[30]

TABLE 2
CURRENT CRITERIA FOR ABNORMAL RESULTS OF EXERCISE ELECTROCARDIOGRAPHY

Horizontal or downsloping ST-segment depression ≥ 1 mm, persisting at least 1 minute after exercise
Upsloping ST-segment depression > 1.5 mm in both inferior and lateral leads
Typical pain, upsloping ST-segment depression > 1.0 mm
ST-segment elevation > 1.0 mm in any lead other than aVR
Any symptomatic drop in blood pressure
Arrhythmia or significant dysrhythmia, exercise-induced or sustained supraventricular or ventricular tachycardia

Bruce and associates[24] identified four variables on exercise ECG that predict subsequent primary coronary events in healthy men: inability to exercise for 6 minutes (ie, < 6 to 7 MET), ST-segment depression ≥ 0.1 mV during recovery, heart rate impairment > 10%, and chest pain during maximal exertion. When used by itself, lack of endurance is the strongest predictor, imparting a relative risk of 10. Men with one or more classic risks for CAD, such as hypercholesterolemia, and two or more abnormal findings on exercise ECG have a relative risk of 18.[24] The criteria for an abnormal study are summarized in *Table 2*.

Experience has clarified the significance of various findings and methods, such as logistic regression applied in interpreting the results of exercise ECG. For example, it appears that the ratio of maximal change in exercise-induced ST-segment depression to the corresponding change in heart rate (ST/HR index) is not substantially better than standard ST-segment criteria, and adds little to multivariate analyses of other available variables.[31]

TABLE 3
INTERPRETING THE RESULTS OF EXERCISE ELECTROCARDIOGRAPHY: NEW PRINCIPLES

Ischemic ST-depression normally occurs in the lateral leads (I, V4, V5)
Changes in both inferior and lateral leads suggest severe coronary artery disease
Isolated inferior or anterior changes are often false-positives
ST-segment depression does not localize ischemia to an area of myocardium
ST-segment depression without angina suggests milder coronary artery disease and lower risk
ST-segment depression is not interpretable with left bundle branch block, previous coronary artery bypass surgery, Q-wave myocardial infarction, left ventricular hypertrophy, digitalis, Wolff-Parkinson-White syndrome, or ventricular pacemaker
ST-segment elevation over Q wave indicates myocardial damage or aneurysm, over non-Q wave areas means local myocardial ischemia

Herbert[32] has demonstrated that beta blockers have little effect on the ST-segment response during exercise ECG, as assessed by either the classic ST-segment criteria or the ST/HR index.[32] Thus, it does not appear that these drugs need to be stopped before diagnostic testing. Other, newer principles of performing exercise ECG and interpreting its results are summarized in *Table 3*.

RADIONUCLIDE IMAGING

Radionuclide imaging in combination with exercise or other forms of stress is commonly applied to diagnose CAD.[33] Ischemic myocardium has normal perfusion at rest, but during exercise or other forms of stress the blood supply is unable to satisfy increased oxygen demands. Thallium 201 or other radionuclides injected during peak exercise are proportionally distributed within the myocardium in relation to regional myocardial blood flow and muscle viability. In normal myocardium following stress, the initial accumulation of the isotope reflects the integrity of the regional blood supply. In areas of decreased initial perfusion, peak isotopic concentrations are delayed and are associated with slower "washout." Following exercise, transient perfusion defects that "fill in" on the delayed images or at rest are consistent with exercise-induced myocardial ischemia. Scarred areas characteristically show no uptake, either initially or during the later redistribution scan. In addition to the uniformity of isotopic uptake, radionuclide imaging can show ventricular cavity size, myocardial wall thickness, and pulmonary accumulation.

New tests have been added regularly to our diagnostic inventory.[34] These include the quantification of radionuclide imaging data, radionuclide tomography, and more recently, single-photon-emission computed tomography.[35] Together, these provide enhanced sensitivity and specificity. Newer available radiopharmaceutical agents, including some that incorporate technetium 99m, provide potential diagnostic benefits on the basis of variable biologic attributes. Dipyridamole and, more recently, adenosine, both potent selective coronary vasodilators, have been used with thallium scanning and with positron-emission tomography using thallium 201 or other isotopes such as rubidium 82.[36] These techniques have proven efficacy and are especially useful in patients unable to either exercise or achieve appropriate heart rates by exercising. However, no test is clearly superior to all others in every clinical circumstance.[37] Moreover, none has been shown consistently to provide sensitivities and specificities greater than 90%.[33] Therefore, their use in populations with a low prevalence of disease is of only moderate value. However, they have great value when used in conjunction with exercise ECG to assess the functional significance of CAD or the prognosis of patients with ischemic heart disease.

EXERCISE ECHOCARDIOGRAPHY

Exercise echocardiography permits side-by-side digital display of images obtained at rest and after (or during) exercise electrocardiographic testing.[38] We recently have shown exercise echocardiography to have a sensitivity of 80%, compared with 42% for exercise ECG ($P < .0001$). The sensitivity of exercise echocardiography was superior even after we excluded negative echocardiographic studies in which the patients could not achieve maximal stress and all nondiagnostic electrocardiographic studies, (87% vs 63% for ECG, $P = .001$).[39] Similar results have been recently reported by Crouse et al[40]—a sensitivity of 97% for exercise echocardiography compared with 51% for exercise ECG ($P < .0001$) in a large population with a very high prevalence of CAD (77%) and in whom a high percentage of patients were presumably symptomatic.

Exercise echocardiography also has a higher specificity than exercise ECG, though this was attenuated in our series by the exclusion of nondiagnostic tests (93% specificity in "normals" or 82% after exclusion of nondiagnostic tests vs 77% for ECG). Crouse et al[40] reported that exercise echocardiography provided the same specificity as exercise ECG, ie, 62%.

Because exercise ECG is substantially less expensive than most other noninvasive tests for ischemia, such as stress thallium radionuclide imaging or positron-emission tomography, its use as a screening test has been questioned. I believe it will still prove to be too expensive to use in asymptomatic individuals with no risk factors. Cost-benefit analysis is needed to definitively answer this question.

SELECTING THE APPROPRIATE DIAGNOSTIC TEST

The judicious and appropriate use of tests when evaluating the patient for CAD requires significant clinical judgment. An algorithm for evaluating patients who have chest pain is shown in the *Figure*. Tests can be used to confirm the diagnosis, define the coronary and ventricular anatomy, assess the extent of coronary involvement or the amount of myocardial damage, and thus assess prognosis and the risk for future untoward events.

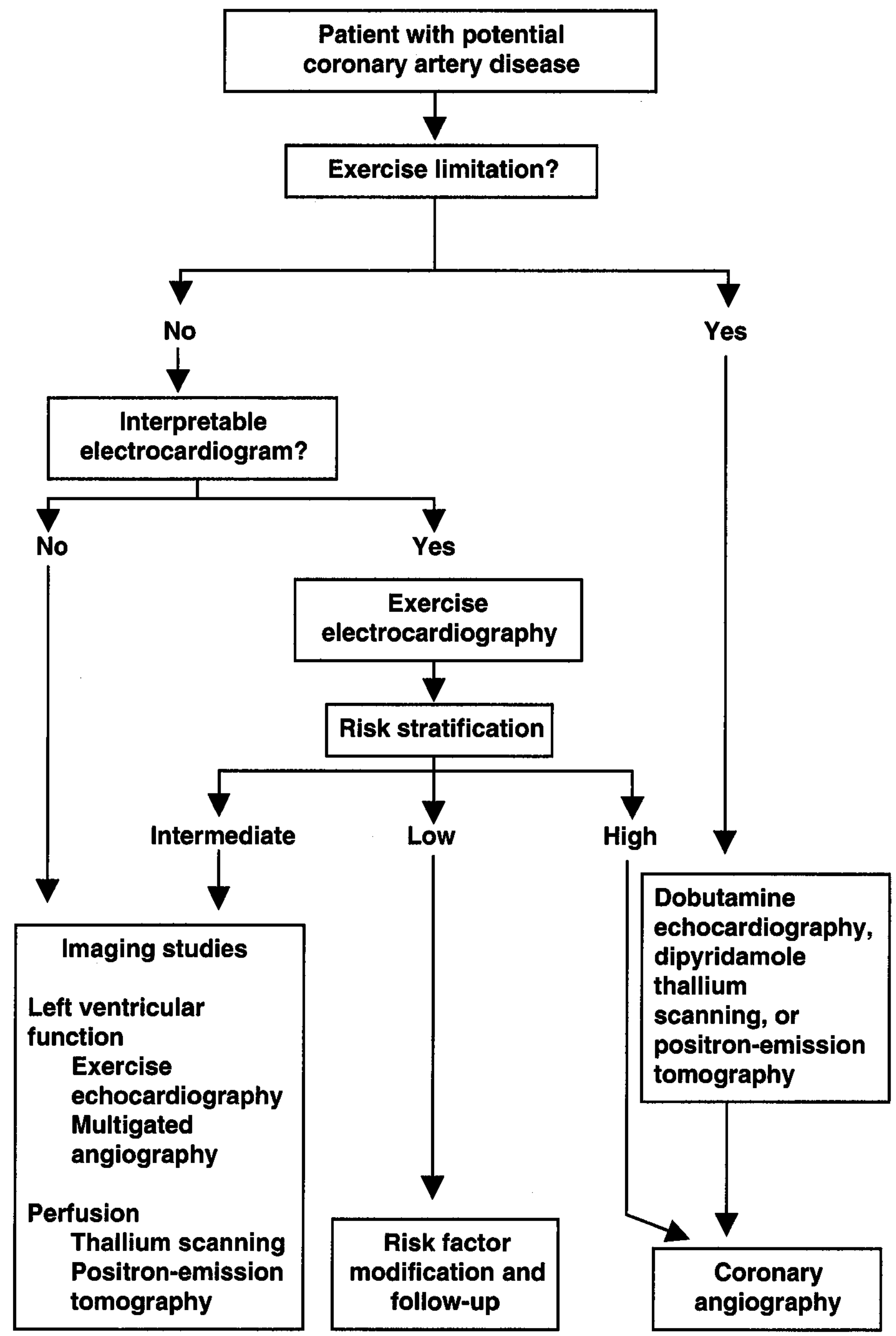

FIGURE. Algorithm for selecting studies to diagnose coronary artery disease.

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