EDITORIAL

The detection of silent ischemia: cautions and precautions

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THERE IS NOW convincing evidence that myocardial ischemia may occur in the absence of symptoms.1 This phenomenon, which has acquired the label “silent ischemia,” is receiving considerable attention as a factor with potential prognostic significance in the management of coronary artery disease. Basic to an understanding of silent ischemia, its prevalence, precipitating factors, significance as a risk factor, and response to therapy, is knowledge of the effectiveness of the technologies used to detect it.

Twenty-five years of developments in the theory and practice of laboratory test interpretation have contributed to the rational use of noninvasive tests for the diagnosis of coronary artery disease. The principles governing test interpretation so arduously derived over this time should be, but perhaps are not being, applied to the detection of myocardial ischemia as an entity unto itself. Since the implications for management inherent in the diagnosis of ischemia may differ from those emanating from the diagnosis of coronary artery disease, tests designed to detect myocardial ischemia should be interpreted with the effectiveness of the test for that purpose in mind, and transfer of information relative to the effectiveness of the test for the diagnosis of coronary artery disease to ischemia should not be done without consideration of the appropriateness of such a transfer.

The tests that are used to evaluate patients with coronary artery disease can be divided into four categories (table 1): tests that assess the electrical consequences of coronary artery disease, such as stress and ambulatory electrocardiography; tests that assess myocardial perfusion; tests that assess contractile function; and tests that assess metabolic function. These tests can be used to define the probability of the presence of coronary artery disease and their ability to do so can be confirmed through correlation with results of coronary arteriography. There is at present no widely available gold standard to enable confirmation of the ability of these tests to define the probability of myocardial ischemia per se.

Determination of the effectiveness of a test is dependent on three elements: (1) test sensitivity, (2) test specificity, and (3) prevalence of the disease being tested for.2 If the prevalence of a disease in the population at hand is known, two other determinations can be made: the positive and negative predictive values of the test, as defined by Bayes’ theorem. Bayesian principles apply to any test for which sensitivity, specificity, and prevalence are known. Since the sensitivity and specificity of the noninvasive tests for ischemia, as opposed to coronary artery disease, are not known, nor is its prevalence throughout the wide spectrum of coronary artery disease, the issues involved in assessing the likelihood of silent ischemia from noninvasive testing can be discussed only in a conceptual format. For the purpose of this discussion, we will assume a linear relationship between the presence of coronary disease and myocardial ischemia. The almost certain inexactness of this assumption will not obscure our main aim, which is to illustrate how application of conventional Bayesian concepts can guide the appropriate use of tests for the evaluation of silent myocardial ischemia.

Exercise electrocardiography. The reported sensitivities and specificities of exercise electrocardiography are in the range of 60% to 85%, respectively. Figure 1, left, a characteristic Bayesian curve, illustrates the relationship between the pretest likelihood of disease (coronary artery disease or ischemia, assuming a linear relationship between the two), and the posttest likelihood of disease after exercise electrocardiography. The likelihood curves are plotted with normal test results (on the bottom) and abnormal test results (on the top). The curves are simply plots of Bayes’ theorem with the variables being disease prevalence (or pretest likelihood), sensitivity, and specificity. It may be de-
TABLE 1
Techniques for evaluation of coronary artery disease

<table>
<thead>
<tr>
<th>Techniques</th>
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<tr>
<td>Electrical alterations</td>
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<tr>
<td>Stress electrocardiography</td>
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<tr>
<td>Ambulatory electrocardiography</td>
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<tr>
<td>Perfusion scintigraphy</td>
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<tr>
<td>Thallium-201</td>
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<tr>
<td>Rubidium-82 (PET)</td>
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<td>Contractile function</td>
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<tr>
<td>Exercise radionuclide ventriculography</td>
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<tr>
<td>Exercise echocardiography</td>
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<td>Radionuclide “VEST”</td>
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<tr>
<td>Metabolic function</td>
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<tr>
<td>$^{18}$F-2-fluoro-deoxyglucose (PET)</td>
</tr>
<tr>
<td>$^{11}$C-Palmitate (PET)</td>
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<tr>
<td>Phosphorus-31 (magnetic resonance spectroscopy)</td>
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PET = positron-emission tomography.

rived from the plot that for an asymptomatic patient with a 5% likelihood of having angiographically significant coronary artery disease (the likelihood of disease in an asymptomatic 50-year-old man in the United States), if the test result is positive, the likelihood of having coronary artery disease is only 17%. Thus, in such an individual, there is an 83% likelihood that an abnormal ST segment response is not related to coronary artery disease. Even if patients with nonanginal chest pain, with an average 20% pretest likelihood of coronary artery disease, are included, the majority of patients with a positive exercise test will still not have coronary artery disease. Thus, patients with positive exercise electrocardiograms and no or highly atypical symptoms should not be labeled as having silent myocardial ischemia.

The high number of false-positive responses observed in low-prevalence populations results from a wide variety of conditions that can affect the electrocardiogram. Some of these conditions are technical: signal-averaging of the electrocardiogram (especially if arrhythmia is present), inadequate skin preparation that results in noise, or simply a wandering baseline. Patient-related factors that result in a false-positive test for coronary artery disease can be divided into those due to non ischemic factors and those that are due to ischemic but nonatheromatous processes. Nonischemic causes include drugs, electrolyte abnormalities, hyperventilation, neuroregulatory asthenia, intraventricular conduction defects, and Wolf-Parkinson-White syndrome. Left ventricular hypertrophy or hypertension itself (probably related to underlying left ventricular hypertrophy not manifested on the resting electrocardiogram), and mitral valve prolapse are also conditions associated with false-positive exercise electrocardiograms, although the underlying basis may be ischemia. In addition, there are some less common situations in which true ischemia might be present without atheromatous coronary artery disease, such as...
the patient with coronary vasospasm, abnormal coronary vasodilator reserve, and "syndrome X." Thus, a variety of technical and nonischemic conditions influencing the exercise electrocardiogram make it inappropriate to label patients without angina as having silent myocardial ischemia on the basis of a positive exercise electrocardiogram alone. In contrast, situations in which the prevalence of disease is high, the positive exercise electrocardiogram is much more likely to be indicative of coronary disease and, accordingly, may have greater predictive value for ischemia, even in the absence of pain on the exercise test.

**Ambulatory electrocardiography.** The ambulatory electrocardiogram is unlikely to be more specific for coronary artery disease than the exercise electrocardiogram; it may prove to be less specific. Ambulatory electrocardiographic monitoring systems were initially developed for the evaluation of arrhythmias. Due to the low frequency of ST segment signal compared with that of the QRS complex, the requirements for accurate ST segment analysis are very different from those for accurate detection of arrhythmia. The requirements include adequate high- and low-frequency cutoffs, ideally conforming to American Heart Association standards of 0.05 to 100 Hz, a flat amplitude versus frequency response within the pass band, minimal phase shift, and absence of baseline artifact. Recently, a variety of manufacturers have claimed to meet the American Heart Association specifications. However, it is important to realize that the specifications are frequently reported simply for the amplifier itself, whereas information is needed on the entire system, including the recorder, the playback system, and the printout of such devices. From a machine perspective, therefore, a variety of potential artifacts may contribute to false-positive or false-negative recordings of the ST segments on ambulatory electrocardiograms and these may be different than those that affect the exercise electrocardiogram. In addition, there are a variety of other conditions that may interfere with the ST segment during ambulatory monitoring that are not sources of false-positive studies in the more carefully controlled treadmill electrocardiographic examinations. Additional technical factors include poor amplitude versus frequency response of the systems (very common with systems used today), inadequate skin preparation, and positional changes. Skin preparation cannot be overemphasized: the skin-electrode interface determines the reliability of the signal. Furthermore, the ST segment may be affected by important physiologic factors not evaluated during conventional graded treadmill exercise. For instance, abnormal ST changes in normal individuals may result from sudden strenuous exercise not conforming to the kind of controlled exercise seen with graded treadmill exercise.

With an expectation that ambulatory monitoring will have a lower specificity than electrocardiographic stress testing for coronary artery disease, the lower specificity dictates, by Bayesian analysis, that for a low prevalence of disease, the likelihood that a positive test is a false-positive one will be even greater than that associated with a positive stress electrocardiogram. Stated more directly, in the asymptomatic patient with a positive ST response on ambulatory monitoring, the likelihood that this response is associated with coronary artery disease (and ischemia) will be even less than the 17% value calculated for the stress electrocardiogram.

A further caveat may be that the criteria for a positive ST segment response during exercise may not be transferable to the ambulatory electrocardiogram. There are no data with which to confirm that the criteria for significant ST segment depression on the ambulatory electrocardiogram (planar or downsloping ST segment depression of 1 mm or greater, measured at 0.08 sec) derived from exercise testing are translatable to the ambulatory state in which the conditions affecting repolarization may be quite different. Independent assessments of validity of the criteria are just beginning to become available through correlation with non-electrocardiographic indicators of ischemia, such as transiently diminished perfusion during myocardial scintigraphy or transient diminutions in left ventricular ejection fraction during ambulatory monitoring. These combined studies may eventually provide data on the sensitivity and specificity of ambulatory monitoring for silent ischemia and permit an assessment of the prevalence of silent ischemia throughout the spectrum of coronary artery disease, which is the information necessary to allow the predictive value of a positive or negative test to be known.

The sensitivity of ambulatory monitoring for myocardial ischemia also requires further evaluation for two reasons. First, as with all stress tests, conditions of maximal stress may not be imposed during the ambulatory monitoring period. Josephson et al. recently demonstrated that the ambulatory ST response was abnormal in only 11 of 46 patients (24%) with clinical, thallium, and/or exercise electrocardiographic evidence of ischemia. Second, compared with other measurements, it is increasingly evident that the surface electrocardiogram is a relatively poor reflector of ischemia. For instance, Friedman et al. demonstrated that among 14 patients undergoing angioplasty, 12 (86%)

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were found to manifest ischemia by epicardial electrode monitoring at the time of balloon occlusion, but only 6 (43%) manifested ST segment depression on appropriately placed surface leads.9

**Thallium scintigraphy.** The sensitivity of thallium testing for coronary artery disease is in the range of 80% to 90% and specificity is high, at approximately 90%, when both fixed and reversible defects are considered abnormal. Even with the high specificity of 90%, however, with a pretest likelihood of coronary disease at 5% (a low-prevalence population), a positive 201Tl test result is likely to be false-positive, with only 27% of patients having disease (figure 1, right). Thus, asymptomatic patients should not be labeled as having silent myocardial ischemia on the basis of a positive 201Tl scan alone.

Sources of false-positive thallium defects are most commonly technical, such as shifting breast artifact, inaccurate patient positioning between stress and redistribution studies, diaphragmatic attenuation of the inferior wall, and computer processing errors such as those resulting from over subtraction of portions of the myocardium.

Beyond these technical causes, false-positive findings may result from infiltrative or neoplastic myocardial disease, cardiomyopathy, mitral valve prolapse, and some noncoronary but potentially ischemic processes such as aortic stenosis and ischemia with normal coronary arteriograms or syndrome X. The causes of false-positive results, however, are not nearly as numerous or frequent for thallium studies as for exercise electrocardiography, so that this modality offers improved specificity for detecting myocardial ischemia.

In the patient with a high pretest likelihood of disease, 201Tl testing can be helpful in defining the presence of silent myocardial ischemia. We have recently demonstrated that patients with triple-vessel or left main coronary artery disease without angina often have extensive, reversible thallium defects on treadmill testing.10 The caveat in this case is the question of the relationship between decreased perfusion and the production of ischemia. Can all detectable perfusion deficits be equated with ischemia? Or, does perfusion need to be reduced to a certain level before ischemia can be said to exist?

**Exercise radionuclide ventriculography.** With the criteria for abnormality on an exercise radionuclide ventriculographic study being an exercise-induced wall motion abnormality and/or an abnormal ejection fraction response, in relatively broad populations the sensitivity of the test approximates 90% (probably higher than that for thallium scintigraphy), and the specificity approximates 80% (lower than that for thallium scintigraphy) for the detection of coronary artery disease. The reduction in specificity has a marked effect on the application of this test in the asymptomatic individual, the patient who begins with a 5% likelihood of having coronary artery disease. In this patient, a positive test indicates a 16% calculated likelihood of coronary disease.

Clearly, an abnormal exercise radionuclide ventriculographic study in a minimally symptomatic or asymptomatic patient cannot by itself be considered representative of silent ischemia. The reasons for the lack of specificity are, again, both technical and patient related. Technical factors are highly important and include computer processing errors, improper gating, sudden strenuous exercise, and inadequate exercise that might cause a flat left ventricular ejection fraction response to stress. In addition, even when the test is performed correctly, patient-related conditions may affect function without decreasing perfusion. These include drugs that might attenuate the ejection fraction response and a variety of noncoronary conditions that may alter this response.

Recently, a method for ambulatory monitoring of global left ventricular function has become available commercially through the “cardiac VEST” marketed by Capintec. This small device consists of a scintillation detector placed by direct visualization over the cardiac blood pool and a separate scintillation detector placed over a background region of interest. The approach has been validated, by direct comparison with scintillation camera measurements, for the measurement of left ventricular ejection fraction at rest and during exercise.11 The technique offers promise as a mechanism for corroborating the ischemic nature of ambulatory ST segment depression as detected on ambulatory electrocardiographic recordings.

**Sequential Bayesian analysis for myocardial ischemia.**

The imperfect nature of each of the commonly used tests for the diagnosis of coronary artery disease makes it difficult to identify the disease in patients with a low pretest likelihood of disease. Sequential Bayesian analysis of multiple test results may be used to improve accuracy in such patients. In sequential testing, the posttest likelihood of the first test becomes the pretest likelihood of the second and so forth, so the pretest likelihoods can be increased and higher posttest likelihoods can be achieved.

Sequential Bayesian analysis has been used for the diagnosis of coronary artery disease. The most commonly used test sequence is exercise electrocardiography followed by 201Tl testing. As stated above, in the
asymptomatic individual, the likelihood of coronary disease after a positive treadmill test is approximately 17%. When this posttest likelihood becomes the pre-test likelihood for thallium scintigraphy, the posttest likelihood of coronary artery disease (or myocardial ischemia) with a positive thallium scan becomes approximately 63%. Or, in the patient with nonanginal chest pain at age 50 with a pretest likelihood of coronary disease of 20%, if the exercise test is positive, the patient has only a 48% likelihood of having coronary disease (or myocardial ischemia). If thallium testing then follows, the likelihood of disease can increase to nearly 90% if the test is positive.

Some recent data support the sequential Bayesian approach in the asymptomatic patient or patient with nonanginal chest pain. Uhlig et al. studied 191 asymptomatic Air Force personnel with abnormal stress electrocardiograms. In these individuals, if the thallium scan was normal, the likelihood of disease was only 1.4%, but it was 74% if thallium scintigraphic results were abnormal. These findings illustrate that while a positive stress electrocardiogram alone cannot be used to signify the presence of coronary artery disease, the results of a second independent test can be used to sort out which findings do not represent coronary disease. The potential advantages of sequential testing for the identification of silent ischemia are obvious.

The use of sequential Bayesian analysis requires independence of the tests being performed. The available tests for coronary artery disease can be divided into the four categories mentioned in Table 1. Generally, sequential Bayesian analysis should not use tests from within the same category, such as evaluation by radionuclide ventriculography and subsequent exercise echocardiography, or, for example, and then ambulatory electrocardiography.

Conclusion. The predictive value, positive or negative, of cardiac testing depends on each test’s inherent sensitivity and specificity as well as the prevalence of the diseases or pathophysiologic processes in the population being evaluated. None of these data are available for the detection of ischemia per se. Assuming, however, that the tests used for the detection of coronary artery disease are direct reflectors of ischemia, the values for sensitivity and specificity of these tests are probably applicable in the case of ischemia as well. As for coronary artery disease, the positive predictive values of treadmill exercise testing, thallium perfusion scanning, and radionuclide ventriculography for myocardial ischemia are low for groups with a low prevalence of ischemia (e.g., asymptomatic patients) and high for patients with high prevalence of ischemia (e.g., those with typical angina). In situations in which the prevalence of disease is low, a single positive test indicates an intermediate likelihood of ischemia. Sequential use of a test that assesses an independent cardiac function results in a high likelihood of ischemia if positive and a low likelihood of ischemia if negative.

For tests such as ambulatory electrocardiography or others for which the sensitivity and specificity of the tests for coronary artery disease have not been derived and assessed as rigorously as is the case for exercise electrocardiography and other standard tests, the predictive values for silent ischemia may be quite uncertain. Caution is urged in accepting a diagnosis of silent ischemia on the basis of such tests alone. The critical relationships between the specificity of a test, prevalence of a disease or condition being tested for, and the test’s predictive value indicate that a low-prevalence disease state should be assessed by highly specific tests. In patients in whom the likelihood of disease is high, the sensitivity of a test becomes critical.

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