EDITORIALS

Exercise Testing to Predict Outcome in Patients with Angina

Exercise testing, whether it is conventional exercise electrocardiography or exercise imaging with perfusion scintigraphy or echocardiography, has many purposes. Its best-known application is to diagnose coronary artery disease, and in this role it serves as a model for reasoning about diagnostic tests. Among the other uses of exercise testing, including measuring exercise capacity, evaluating the efficacy of therapy, establishing an exercise prescription, and reassuring the patient about the safety of exercise, assessing prognosis is one of the most important, but it has been overshadowed by the emphasis on diagnosis.

Exercise testing's value in establishing a patient's prognosis has been studied less often than its value in establishing the diagnosis of coronary artery disease. There are several methodologic reasons for this discrepancy. One reason is that the prognostic value of exercise testing is much harder to study than its diagnostic value. To assess the test's prognostic value, it is necessary to assemble a cohort of patients, follow them for several years, and document their outcome events. In contrast, one can assess the test's diagnostic value by performing a cross-sectional study and correlating the test's results with those of a "gold-standard" test. Therefore, the diagnostic value of exercise testing can be established quickly, but its prognostic value takes a long time to document, and waiting years for publishable data is not attractive to many investigators. Furthermore, the rate of positive test results, which is used to study the test's diagnostic value, is usually much higher than the rate of outcome events, which is used to study the test's prognostic value. For example, the prevalence of coronary artery disease in most test populations is 30% to 60%, but the yearly event rate for relevant outcomes is often less than 10%. The relatively low rate of outcome events means that studies of prognosis must enroll larger numbers of patients to achieve the same statistical power, which makes these studies more expensive and complex.

Apart from these practical barriers to conducting prognostic studies are several issues particular to analyzing data from prognostic studies. For example, patients being followed for cardiac death may die of noncardiac causes. Including noncardiac deaths in the analysis may blur the correlation between test result and outcome, yet excluding noncardiac deaths may introduce bias. Also, when a clinical finding indicates high risk, it can be difficult to measure prognostic value because patients may be treated differently because of the finding. This effect occurs when patients with a positive exercise test result are referred for coronary revascularization but patients with a negative test result are not. One solution might be to expand the definition of an adverse outcome to include "need for revascularization," but this solution introduces biases of its own, given the wide discretion physicians have in referring patients for revascularization. Finally, many prognostic studies are based on patients enrolled in randomized clinical trials. As valuable as these studies may be, patients in such trials are highly selected, so the picture of prognosis emerging from these trials may be incomplete.

Despite these problems, many studies have demonstrated the prognostic power of conventional exercise electrocardiography.[1–3] Several measurements from this test indicate higher risk, including shorter duration of exercise, ST-segment depression on the electrocardiogram, and the precipitation of angina or hypotension. Exercise duration is the most powerful of these prognostic markers—the longer the patient can exercise, the better the prognosis. (Indeed, in some studies,[4] the physician's judgment that a patient was unable to exercise at all was one of the most powerful negative prognostic factors!) Electrocardiographic evidence of ischemia is also a predictor of an adverse prognosis, and some studies suggest that the prognosis is worse when ST-segment depression is deeper, present in more leads, or longer lasting. The duration of exercise and the presence of ST-segment depression are independent indicators of prognosis, and evidence of ischemia at low levels of exercise is an ominous sign.[3]

Conventional exercise electrocardiography test results provide prognostic information for patients with established coronary artery disease. They also are useful for prognostic evaluation of patients with symptoms suggestive of coronary artery disease. These concepts have been expressed quantitatively in the Duke treadmill score,[3] which was developed with patients who had undergone coronary angiography and validated with outpatients being evaluated for coronary artery disease.[5] The score is a weighted sum of maximum ST-segment change, exercise time, and the presence of angina during the test.[3]

Exercise perfusion scintigraphy with thallium-201, or more recently with technetium-99m sestamibi, provides direct evidence of myocardial ischemia.[6,7] These agents are taken up by viable myocardium in proportion to coronary blood flow, and underperfused segments can be identified, localized, and measured. Perfusion scintigraphy is more accurate than conventional exercise electrocardiography as a diagnostic tool, but its higher cost has generally restricted its use to selected patients.[6,8,9]

Perfusion scintigraphy is also a powerful prognostic test in patients with known or suspected coronary artery disease.[6,7] Many studies have shown that the number and extent of perfusion defects are very good predictors of the outcome, and often the best predictors.[10] The real issue, however, is how much information about the prognosis perfusion scintigraphy *adds* to the information already available from simpler and cheaper methods. A standard clinical history and conventional exercise electrocardiography provide substantial information about patient outcomes,[3] and the information from the perfusion scintigram could be mostly redundant. This hypothesis can be tested by collecting all the relevant information on a cohort of patients and using the appropriate statistical tests to measure the incremental value of the information provided by exercise perfusion scintigraphy.

The study reported by Shaw and associates in this issue did just that.[11] Their study included only people who were able to exercise and had an interpretable exercise electrocardiogram, which was appropriate. The average follow-up period was 2.5 years, which was long enough to document 83 cardiac deaths, thus providing a sample of sufficient size to analyze the independent value of several prognostic factors. Noncardiac deaths were omitted from the analysis, which may have blurred the results. However, coronary revascularization was not counted as an adverse outcome, avoiding the bias introduced when physicians use test results to choose therapy. The value of adding data from perfusion scintigraphy to standard clinical data was tested appropriately using a series of stepwise, multivariate models. The results suggest that perfusion scintigraphy does add significant prognostic information to conventional exercise electrocardiography.[11] The added risk was proportional to the extent of ischemia or infarction measured by perfusion scintigraphy, which is plausible given the pathophysiology of coronary artery disease.

The application of exercise testing of any form to establishing the *diagnosis* of coronary artery disease has demonstrated that it is most informative for patients with an intermediate probability of disease. Patients with a very high or very low pretest probability of disease often do not have posttest probabilities of disease that are different enough to affect management decisions. Patients with an intermediate pretest probability of disease more often have test results that push the probability of disease across a diagnostic threshold and thus change management.

Exercise testing should be applied to predicting the *prognosis* of coronary disease in a similar, Bayesian manner. Patients with ominous findings after clinical examination and conventional exercise electrocardiography do not have that risk nullified by a normal or minimally abnormal exercise test with perfusion scintigraphy. Conversely, patients with otherwise benign findings after clinical examination and conventional exercise electrocardiography are unlikely to have a markedly abnormal exercise perfusion scan, and even if they do, it will not raise their risk as high as it would in other patients. These considerations argue that the incremental prognostic value of the exercise test with perfusion scintigraphy is greatest in the intermediate-risk group. This finding was amply demonstrated in the study of Shaw and associates.[11] An exercise perfusion scan indicating high risk was found in only 3% of the patients with a low-risk score on conventional exercise electrocardiography, and it raised them into only an "intermediate-risk" category (1.2% annual cardiac mortality). In patients with an intermediate-risk score on conventional exercise electrocardiography, however, a normal exercise perfusion scan dropped the risk to the very low level of 0.5% annual cardiac mortality, whereas a markedly abnormal exercise perfusion scan indicated the substantial risk of 2.5% annual cardiac mortality. These results suggest that perfusion scintigraphy will be most useful in patients who have an intermediate risk of adverse outcomes after conventional exercise electrocardiography.

A few unanswered questions remain. How low does a patient's risk need to be to avoid coronary angiography? How high does that risk need to be before angiography is indicated? One rough guide is that the mortality from coronary angioplasty is about 1%, so that patients with an annual cardiac risk of less than 1% would be hard pressed to gain a survival advantage from coronary revascularization. Consequently, a symptom-guided approach is reasonable in such patients. In higher-risk patients the situation is more complex. They have the potential to reduce their risk substantially after coronary revascularization, but the extent of benefit depends on many other factors.[12,13] Setting appropriate thresholds for angiography will require a careful weighing of the risks, benefits, and costs using a formal cost-effectiveness analysis.—**MARK A. HLATKY, MD,** *Department of Health Research and Policy and Department of Medicine, Stanford University School of Medicine, Stanford, Calif.*

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