EDITORIAL COMMENT
Risk Stratification Using Stress Myocardial Perfusion Imaging: Don’t Neglect the Value of Clinical Variables*

George A. Beller, MD, MACC,
Denny D. Watson, PhD

A large amount of data has accumulated during the past 20 years demonstrating the value of exercise or pharmacologic stress planar and single-photon emission–computed tomographic (SPECT) perfusion imaging for risk stratification and prognostication in patients with suspected or known coronary artery disease (CAD) (1–14). The major goal of such noninvasive risk assessment is the identification of subsets of patients at high risk for subsequent cardiac death or nonfatal infarction who may benefit from prompt referral for cardiac catheterization with a view toward invasive strategies for revascularization (15). Conversely, patients deemed at low risk for subsequent cardiac events based on stress test and nuclear scan variables are treated medically and spared the premature or unnecessary referral for invasive evaluation, which also increases unduly the cost of diagnostic cardiology.

Another specific objective of the addition of perfusion imaging to conventional stress testing is to minimize the number of patients who are still classified as intermediate risk after the completion of testing (14,16). A significant limitation of symptom–limited treadmill testing, even when the Duke treadmill score (DTS) is used for risk separation, is that a substantial number of patients are still deemed at intermediate risk for subsequent cardiac death and nonfatal ischemic events. When they are further risk-stratified by exercise SPECT, those with normal scans have excellent outcomes (14–17).

Perhaps the most valuable contribution of exercise or pharmacologic myocardial perfusion imaging (MPI) is its excellent negative predictive value for predicting a low combined cardiac death and nonfatal myocardial infarction (MI) rate in patients with a totally normal scan (1,12,18,19). In a pooled analysis of 20,963 patients from 16 published studies in the literature with a follow-up of slightly more than two years, the hard event rate was 0.7%/year (1). This compares to a hard event rate in the range of 7% in patients with abnormal scans (3). Numerous studies have shown the incremental value of stress MPI variables over clinical and electrocardiographic (ECG) stress test variables for assessing prognosis (1,2). The event rate increases in proportion to either the extent of stress-induced hypoperfusion or the extent of defect reversibility indicative of an ischemic response. Other high-risk findings contributing to the prediction of an increased cardiac event rate are transient ischemic cavity dilation from stress–to–rest images (20), extent of regional wall thickening or wall motion abnormalities on gated SPECT, the ejection fraction and end–systolic and end-diastolic volumes measured on gated SPECT, and the extent of post-stress reversible regional dysfunction reflective of myocardial stunning (21–26). Patients at highest risk for subsequent events are those with a low resting left ventricular ejection fraction (LVEF) with associated moderate or severe stress-induced reversible perfusion abnormalities (26). Similarly, patients exhibiting poor exercise tolerance have a worse prognosis than patients with good exercise tolerance (27,28). Patients at the lowest risk for subsequent cardiac events are those who demonstrate good exercise tolerance by being able to achieve >85% of maximum predicted heart rate for age with a normal perfusion pattern on SPECT images (29).

The American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for evaluating patients with stable chest pain indicate that exercise stress ECG should be the initial test performed in patients with a normal ECG who are deemed able to adequately exercise (30). Patients with a high pretest likelihood of CAD are often referred directly to cardiac catheterization for diagnostic coronary angiography even if stable and no acute coronary syndrome is identified.

In this issue of the Journal, two reports are published that address the issue of whether MPI is a useful addition to the workup of certain subsets of patients (31,32). Poornima et al. (31) propose a rule-based strategy using a clinical score to decide which patients at low risk after exercise ECG stress testing (i.e., low DTS) would be most likely to benefit from the addition of MPI for further risk stratification. Hachamovitch et al. (32) examined whether it is of value and cost-effective to use MPI for risk stratification of patients with a >85% pretest likelihood of having CAD.

Diagnostic testing in patients having a low likelihood of CAD is problematic for a number reasons. The low yield of CAD detection results in poor cost-effectiveness. Aside from cost issues, there are other negatives to consider. If the probability of CAD is less than the false-positive rate of the test, then most positive tests will be false positives. Such false-positive tests have negative psychologic and negative medical impact. Also, the significance of a true positive test might be discounted when it is an unexpected result in a setting where positive results are usually false positive. Unfortunately, no single test for CAD is currently available that provides optimal screening for patients with a low

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Cardiovascular Division and Nuclear Cardiology Laboratory, University of Virginia Health System, Charlottesville, Virginia.
probability of CAD. Individuals with very low statistical probability of CAD are rarely tested for CAD. However, the population is very large, so even the rarely encountered need to rule out CAD in individuals from this population will result in a substantial number of referrals. Poornima et al. (31) recognize that, although ACC/AHA guidelines call for exercise stress testing as the initial diagnostic test for patients with normal resting ECGs, a normal stress ECG may not always provide adequate reassurance of the absence of CAD.

Poornima et al. (31) examined 1,461 patients with a low DTS and applied a clinical score developed by Hubbard et al. (33). This clinical score was developed retrospectively in a patient cohort undergoing evaluation for CAD as a predictor of three-vessel or left main disease. The variables included in this clinical score are male gender, history of MI, diabetes, typical angina, and age. The score is weighted for patients with advanced age and insulin-dependent diabetes. Poornima et al. (31) found that in their group of patients with low DTSs, a low clinical score was associated with an excellent seven-year survival regardless of the extent of perfusion abnormalities on MPI expressed as a global stress score. For example, the seven-year survival was 99% in patients with normal scans, 99% in patients with mildly abnormal scans, and 99% in patients with severely abnormal scans with this combination. In contrast, patients with a high clinical score in this group of patients with a low pretest likelihood of CAD had a survival rate of 94% for patients with normal scans, 94% for patients with mildly abnormal scans, and 84% for patients with severely abnormal scans. They concluded that in patients with low-risk DTSs and a high clinical score, with an annual cardiac mortality of >1%, MPI had independent prognostic value. In patients with low-risk DTS and a low clinical risk score, MPI was of limited prognostic value.

One possible limitation of the strategy proposed by Poornima et al. (31) is the observation that only 3% of their patient population had ≥1.0 mm of exercise-induced ST-segment depression. Yet, 28% had moderately abnormal or severely abnormal scans. Also, of the entire group of 1,461 patients, 1,158 (79%) had a low clinical score and would not have been referred for subsequent testing with MPI. The prevalence of exercise-induced ST-segment depression of ≥1.0 mm was 3% in this low clinical score patients, whereas the prevalence of an abnormal scan was 24%. If one assumes that half of the patients with low clinical scores and ST-segment depression had true-positive ECG responses for ischemia and thus would most likely be referred for catheterization, this would leave 255 patients with moderately or severely abnormal scans without ST-segment depression who might have the diagnosis of CAD missed. This highlights the difference between performing a test for diagnostic indications and performing the test for assessing prognosis. In patients with low DTSs and low clinical scores, prognosis is excellent. Nevertheless, >20% would not have their CAD detected.

The report by Hachamovitch et al. (32) in this issue of the Journal examines a group of patients with a high probability of CAD before any diagnostic testing. These are patients without previous MI or revascularization who are judged to have >85% pretest likelihood of CAD based on age, gender, character of the chest pain syndrome, and CAD risk factors. Myocardial perfusion imaging in this patient population may be superfluous for CAD detection because the assumption is that they have CAD and even a normal perfusion scan would not have sufficient statistical weight to adequately rule out CAD in patients with such a high pretest likelihood. Myocardial perfusion imaging can, however, be used to risk stratify these patients. Previous studies have suggested that even patients with angiographic CAD and normal or low-risk MPIs are at low risk of subsequent cardiac events with medical management (34). In an earlier study, Hachamovitch et al. (14) showed that patients with high DTSs and normal scans had a 1.4% hard event rate per year compared with a 9% event rate in patients with moderately or severely abnormal scans and high DTSs. In the study by Shaw et al. (16), which reported a cohort of 3,620 medically treated patients of whom 42% were female, more than 50% of patients with high DTSs had a normal perfusion scan. They had an annual cardiac death rate of 0.4% per year. In patients with high DTSs and high-risk scans showing defects in three vascular territories, there was a 10-fold higher annual cardiac death rate of 4.0%/year. Thus, MPI is able to further risk-stratify patients with a high probability of CAD after exercise ECG stress testing.

In the current article by Hachamovitch and colleagues (32), 1,270 consecutive patients with a pre-exercise stress test likelihood of ischemia of >85% were examined; 38% had adenosine stress imaging. Patients with normal MPI had a 0.6% mortality rate per year and a 1.3% combined death and nonfatal infarction rate per year. With increasing extent and severity of perfusion abnormalities, the risk of both cardiac mortality and combined events increased significantly. The authors found that the addition of the MPI data resulted in incremental prognostic value over pre-nuclear variable data. With respect to cost-effectiveness, the authors show that initial referral to MPI in this group of patients with a high pretest likelihood was more cost-effective than initial referral to either treadmill exercise testing or cardiac catheterization. They conclude that their results support the strategy of initial stress imaging in this high pretest-probability patient population, rather than direct referral to catheterization for coronary angiography or starting with treadmill exercise testing, as the first testing strategy.

Some limitations of both of these studies (31,32) deserve mention. First, neither study uniformly examined functional variables that are now easily measured from quantitative gated SPECT. The limitation may not be great, because the prevalence of CAD and previous infarction (the most common cause for a depressed LVEF and CAD) was probably quite low. In both studies, most patients had a
normal resting ECG. The Hachamovitch study (32) excluded patients with previous MI, and the study by Poornima et al. (31) comprised only those with low DTSs, although some did have a previous MI (12%). Several studies have shown that the prevalence of high-risk CAD is enhanced when functional variables, such as extent of regional wall motion or thickening abnormalities and resting LVEF, are obtained (21–25). This may be more relevant to the study by Hachamovitch et al. (32) in that some patients with extensive and diffuse CAD may have a normal perfusion pattern secondary to balanced ischemia or globally abnormal flow reserve (35) but have abnormal function because of hibernation or stunning. Thus, the addition of function variables would be expected to improve the separation of high- and low-risk subsets of patients with high pretest probability of CAD.

An interesting finding in the Hachamovitch et al. (32) study was the 47% prevalence of normal scans in their cohort of patients with >85% pretest likelihood of CAD. Ninety-five percent of the patients had typical angina; 56% had hypertension, and 48% had hyperlipidemia. Nearly 20% had diabetes. Thus, it is surprising that almost half of the patients judged to have a very high probability of CAD had normal scans. This finding highlights the poor predictive value of “typical angina” for predicting underlying ischemia.

In summary, these evidence-based studies by Poornima et al. (31) and Hachamovitch et al. (32) refine further our decision-making algorithms for use of radionuclide imaging in evaluating patients with suspected CAD and offer a rational basis for modifying practice guidelines. Patients with low-risk treadmill tests but high-risk clinical variables benefit from further noninvasive risk stratification with exercise MPI. Patients with a high pretest likelihood of CAD before any diagnostic testing benefit from undergoing stress SPECT imaging for further risk stratification rather than being referred directly for cardiac catheterization. Although clinical science is a good basis for policy for guidelines generation, practicing clinicians appreciate that individual patients can vary greatly from the average of their respective populations. The art and skill of medicine is the ability to recognize variants and to treat patients as individuals. While we strive to establish better evidence-based guidelines for deciding whether to refer patients for diagnostic testing and/or medical therapy versus coronary revascularization, we must continue to be aware of the limitations of population averages and correlations and continue to permit clinical experience and wisdom to play an appropriate role in medical management decisions.

Reprint requests and correspondence: Dr. George A. Beller, Cardiovascular Division, Department of Medicine, University of Virginia Health System, P.O. Box 800158, Charlottesville, Virginia 22908-0158. E-mail: gbeller@virginia.edu.

REFERENCES


