Should Exercise Myocardial Perfusion Imaging Be the Standard Noninvasive Approach for the Initial Evaluation of Symptomatic Women With Suspected Coronary Artery Disease?

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Exercise ECG (SECG) is one of several noninvasive test procedures routinely used to diagnose coronary disease presence and to estimate prognosis. Unfortunately, like all current noninvasive procedures used for this type of risk stratification, test accuracy is imperfect. A common approach to improve test sensitivity is to implement an additional modality, such as exercise myocardial perfusion imaging (MPI). However, the additional procedure adds cost, may lead to false-positive results that necessitate downstream testing, and, in the case of MPI, adds radiation exposure (≈11 mSv for rest-stress 99mTc sestamibi and ≈29 mSv for dual isotope 201Tl/99mTc sestamibi studies).1,2 Very few studies have examined the cost-effectiveness of using either SECG or MPI as the initial exercise test procedure to assess symptomatic women with suspected coronary disease. Risk stratification with SECG/MPI is considerably more difficult in women than men, in part because of a greater frequency of abnormal SECG, more soft-tissue attenuation on MPI (ie, breast artifacts), and, in general, a lower pretest risk of coronary disease.3 The likelihood of finding obstructive coronary disease in a woman seen for the initial evaluation of stable chest pain is strongly influenced by the character of chest pain (typical angina, atypical angina, nonspecific chest pain), age, and risk factors that are used to estimate the pretest risk of coronary disease and the likelihood of future cardiac events.3,4

Pretest Risk of Coronary Disease

The importance of considering the pretest coronary disease risk is illustrated by data from the Coronary Artery Surgery Study (CASS) registry.5 The prevalence of obstructive coronary disease in women referred for coronary angiography without a prior history of an acute coronary syndrome or revascularization was 72% in 401 women with typical angina, 36% in 1012 with atypical chest pain, and 6% in 1397 women with nonspecific chest pain. Of those <60 years of age with nonspecific chest pain, none had left main or 3-vessel coronary disease (Figure). Thus, searching for prognostic high-risk coronary anatomy in lower-risk symptomatic women with a noninvasive functional test, such as SECG or MPI, is not likely to be productive.

Myocardial Perfusion Imaging in Lower-Risk Patients

Peak exercise capacity is one, if not the most important, determinant of prognosis when SECG testing is used in symptomatic men and women.5,6 Several investigators have found minimal incremental prognostic information by adding an MPI study to SECG in symptomatic patients with good exercise capacity.7-10 Bourque et al7 studied 974 intermediate- to high-risk patients who achieved ≥85% of age-predicted maximum heart rate and underwent quantitative exercise gated 99mTc sestamibi MPI. Of 430 who reached ≥10 metabolic equivalents (METs) without exercise ST-segment depression, none had ≥10% left ventricular ischemia, and there were no cardiac deaths over a 1-year follow-up. This group of patients represented 31% (430 of 1396) of all exercise SPECT studies done at this institution. In an earlier study of 299 symptomatic patients able to exercise into Bruce stage 3 and followed up an average of 4.2 years, Fagan et al9 reported 185 (62%) with a normal exercise ECG. The cardiac event rate in this group of patients was 3% when the MPI was normal and 0% when the MPI was abnormal. Similar data have been reported by other investigators.8-10 In a direct comparison that tested an initial strategy of SECG versus MPI to detect coronary disease, Fazel and colleagues10 randomized 457 patients with stable chest pain (44% women) to SECG or MPI and analyzed the cost-effectiveness of each approach stratified by the American College of Cardiology/American Heart Association guideline pretest likelihood of coronary disease. In low-risk patients, an initial strategy of SECG for the diagnosis of coronary disease was significantly more cost-effective than an initial strategy of MPI. In intermediate- to high-risk patients, the MPI approach significantly reduced the need for downstream procedures, but there were no differences in cost of diagnosis between the 2 strategies. After an average 1.5 years of follow-up, there were 3 deaths resulting from cancer and 1 cardiac death resulting from myocardial infarction.

Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Imaging

A major limitation of prior research in this area is the absence of randomized, controlled trials comparing an initial strategy of SECG with MPI that provides outcome data, particularly in women, and the inability to accurately estimate current...
cardiac events rates with modern medical therapy versus those obtained in an earlier era. In this week’s Circulation, Shaw and colleagues\textsuperscript{11} address both issues by reporting results from the What’s the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. A total of 824 symptomatic women with suspected coronary disease presenting for initial evaluation were randomized to either SECG or MPI at 43 medical centers. Entry criteria required an interpretable baseline ECG and ability to do at least 5 METS estimated with the Duke Activity Status Index. The primary end point was 2-year incidence of major adverse cardiac events, defined as cardiac death or hospitalization for an acute coronary syndrome or heart failure. Major adverse cardiac events occurred in 17 patients (1 sudden death, 3 nonfatal myocardial infarctions, 12 admissions for unstable angina, and 1 heart failure hospitalization). The incidence of abnormal or indeterminate tests was 36\% for SECG compared with 9\% for MPI. 18\% of the SECG group crossed over to MPI during follow-up, and 9\% of the MPI group had repeat MPI. There were no significant differences in the major adverse cardiac event rate and no difference in major adverse cardiac event–free survival between the 2 strategies. For women with abnormal findings, the 2-year primary end point was 5.1\% for the SECG strategy and 13.1\% for the MPI strategy. Six patients died of noncardiac causes (0.5\% for SECG and 1\% for MPI). From a cost-effectiveness standpoint, index testing costs were significantly greater for an initial MPI approach, and downstream procedural costs were slightly less. Whereas no differences in prognostic outcomes of interest were seen with the MPI approach, cumulative cost savings were 48\% lower for SECG as the initial ETT approach compared with MPI (P<0.001). In light of these findings and those from earlier studies, how should the data from this important cost-effectiveness trial be applied to current clinical practice?

First, protocol study entry criteria for WOMEN required that patients have an intermediate to high pretest coronary disease likelihood based on American College of Cardiology/American Heart Association chronic stable angina and exercise test guidelines that use age, sex, and character of chest pain to determine low-, intermediate-, and high-risk groups. The protocol added to these criteria by requiring that subjects be capable of performing physical activity levels of at least 5 METS with the Duke Activity Status Index questionnaire. The sample of elderly patients (median age, 62 years) was limited by design, and those with markedly abnormal rest ECGs were excluded. At randomization, 19\% of the patients were taking β-blockers and 3\% were taking nitrates, even though 60\% of the women reported typical angina symptoms. The relatively low use of antianginal medication could be explained by the fact that testing was performed for the initial evaluation for chest pain, although one might question how convinced the referring doctor was about the diagnosis of typical angina. Nonspecific chest pain was the indication for testing in 27\% of the patients. The peak workload achieved was relatively high (8.4 METS); 88\% of the women reached at least 85\% of their age-predicted maximum; and chest pain was the indication for stopping exercise in only 12\% of the patients. A preselection bias to exclude higher-risk patients may have occurred because only 29\% of the original 2859 eligible women were actually randomized into the trial. The observed primary event rates were very low (1.7\% for SECG and 2.3\% for MPI), and hard end points were even fewer (1 sudden cardiac death, 3 nonfatal myocardial infarctions). Thus, even though the original aim of the study was to recruit intermediate- to high-risk women with coronary disease, the study population actually enrolled was low risk. Therefore, the results are not applicable to intermediate- or high-risk women unless future studies in this type of patient population replicate the findings in the WOMEN trial.

Second, comparison of SECG and MPI may have been biased by the fact that the SECG interpretation was limited to only ECG findings (normal, abnormal, indeterminate). The use of additional variables, such as hemodynamic response to exercise, peak METS, heart rate recovery, and classic angina during testing to the ECG finding would likely have improved diagnostic and prognostic estimates.\textsuperscript{12} Exclusion of these commonly measured variables may have resulted in a significant underestimation of the value of using an initial SECG approach.

Third, the study had limited power to detect outcome differences. The estimated sample size calculation for major adverse cardiac events in this superiority-designed trial based on observational data reported in the older literature was 3.2\% for SECG and 1\% for MPI, yet the observed primary event rates using adjudicated data were 47\% less for SECG. The reasons for the greater observed (2.3\%) than predicted (1\%) event rate in the MPI strategy are not immediately clear. Downstream coronary revascularization that could potentially influence later cardiac outcomes was performed in 1\% and 2.2\% of women randomized to SECG and MPI.

Conclusions

A strength of the WOMEN trial is the pragmatic real-world approach to interpretation of the noninvasive test data. Although a core laboratory was used to standardize and control the quality of the MPI data before the trial started, subsequent interpretations were site dependent, reflecting existing practice patterns in the 43 participating sites. Thus, the findings allow broader applicability of the results for the 2 strategies tested to the general community. The data from the WOMEN trial and from earlier studies firmly support guideline recommendations that,
when noninvasive testing is being used for appropriate diagnostic or prognostic purposes in low-risk women initially evaluated for chest pain, SECG should be selected as the initial test procedure. The use of MPI in this clinical setting should be reserved for those with abnormal, equivocal, or nondiagnostic studies, when clinically indicated, and as recommended in current guidelines. Substantial cost savings would be achieved if noninvasive testing (MPI, stress echocardiography, and exercise treadmill testing) in \( \approx 10,000 \) middle-aged or older low- to intermediate-risk patients in terms of hard cardiac end points and cost-effectiveness over an average 2.5-year follow-up. The Randomized Evaluation of Patients With Stable Angina Comparing Diagnostic Examinations (RESCUE) trial will test two strategies, cardiac computed tomography angiography or MPI in diagnosing cardiac disease in patients with stable angina or angina equivalent. The diagnostic imaging results will guide subsequent therapy. Participants with abnormal findings will be considered for optimal medical therapy or diagnostic invasive coronary angiography and possible revascularization, depending on extent and location of disease. The trial is expected to enroll 4300 patients without prior revascularization over a 2-year follow-up. Finally, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial will test the hypothesis that elimination or reduction of at least moderate myocardial ischemia by an approach of usual care (optimal medical therapy and prompt revascularization when feasible) versus optimal medical therapy alone with deferred revascularization when clinically indicated (excluding left main disease detected by cardiac computed tomographic angiography) reduces the likelihood of hard cardiac events over an average 3-year follow-up (personal communication, Drs Judith Hochman and David Maron, study chair and co-chair, http://www.ischemiatrial.org, August 17, 2011). ISCHEMIA is expected to enroll \( \approx 8000 \) patients. The results of these key cost-effectiveness clinical trials that compare noninvasive risk stratification with anatomic or functional testing (PROMISE and RESCUE) and the potential prognostic benefit of reducing ischemia on noninvasive testing (ISCHEMIA) will not be available for several years but should be critical contributions that will be helpful in determining alternative or superior cost-effective approaches (anatomic/functional or combination approaches) for risk stratification in the future.  

Disclosures

None.

References


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