EDITORIAL

Stress Myocardial Perfusion SPECT in Women: Is It the Cornerstone of the Noninvasive Evaluation?

But as to women, who can penetrate
The real sufferings of their condition?
Lord Byron

Coronary artery disease (CAD) is the leading cause of death among American women (*1*). Despite the flood of information available on this condition, the medical community has not fully resolved Lord Byron's question. Debate persists about basic issues, and understanding of the real sufferings of women with coronary disease remains incomplete. How does coronary disease differ between women and men? Are the tests used in the evaluation of patients with known or suspected CAD equally efficacious in men and women? Should men and women with similar conditions be treated the same? Three characteristics—the epidemiology of CAD, the efficacy of testing and the utilization of test results—define the way CAD is approached within a patient subset. These three facets are inextricably linked and must be considered to understand the use of testing in a population. Further, it is only when all three facets are understood that a rational clinical testing algorithm can be proposed.

CORONARY ARTERY DISEASE IN WOMEN

The Framingham Heart Study (*2*) introduced the striking differences in the cardiovascular epidemiology of women and men and ultimately raised the difficult issue of understanding these differences. CAD occurs later in women than in men. The mean age of initial clinical manifestation of coronary disease was 10 yr later for women than for men; the manifestation of initial myocardial infarction occurs 20 yr later. Despite the 10-yr lag in age between genders with respect to cardiovascular mortality rates, the "relative health advantage that is possessed by women, however, is buffered by a case fatality rate from coronary attacks that exceeds the male rate" (*2*). Although women developed CAD at a later age than men, women with documented CAD fared worse than men, having a greater cardiovascular mortality rate. This finding, although confirmed by a number of studies and clinical trials, has also been challenged as a spurious finding due to the confounding effect of the older age of women with heart disease.

In the Framingham Study, women developed angina more frequently than did men. These symptoms were relatively more benign and were complicated by myocardial infarction or cardiac death less often in women than in men. It was not until data from the Coronary Artery Surgery Study Registry (*3*) demonstrated the striking frequency of normal or near normal coronary arteries at the time of catheterization in women with angina (50% versus 17% in men) that the differential implications of typical angina pectoris in men and women were first elucidated.

Additionally, interventional therapy does not favor women. Vascular complications and mortality rates are higher in women undergoing percutaneous revascularization, although success and late outcomes in women are similar to men (*4*). Likewise, women undergoing coronary bypass surgery have higher mortality rates, more incomplete revascularization and more operative complications such as heart failure, perioperative infarctions and hemorrhage. These event rates are likely related to the increased comorbidities in women and technical factors such as smaller body size and coronary artery diameter (*5*).

Thus, the management goal of CAD in women, as in men, should be prevention and early detection. Cardiovascular risk factors associated with the greatest risk in men are also predictive of risk in women—age, family history, tobacco use, hypertension and diabetes. These factors, however, are not equally weighted in men and women; although symptoms such as typical angina and exertional dyspnea are less predictive in women than in men, diabetes confers a much worse prognosis in women compared to men. Increasing age confers a greater risk in women than in men. Elevated total cholesterol and low-density lipoprotein levels are only weakly associated with coronary disease in women, whereas elevated triglycerides and low high-density lipoprotein levels are independent predictors of disease in women (*6*).

EFFICACY OF NONINVASIVE TESTING IN WOMEN

Several investigators have shown the accuracy of SPECT imaging to be similar in men and in women. Van Train et al. (*7*), as part of a multicenter trial of quantitative analysis, demonstrated similar sensitivity, specificity and normalcy rates in men and women. In 1991, Iskandrian et al. (*8*) found the sensitivity of SPECT ^{201}Tl during pharmacologic stress to be similar in both genders. Using SPECT exercise thallium imaging, the sensitivity was 52% in women with one-vessel disease compared to 87% in men. In multivessel disease, the sensitivity was 82% in women compared to 93% in men. The authors postulate that the low sensitivity in women with single-vessel disease may be due to submaximal exercise and heart rate response in half of the women. They also postulate that some perfusion defects may be misinterpretations of breast attenuation artifacts in women with ^{201}Tl imaging (*9*). The same group demonstrated that SPECT exercise thallium imaging accurately identifies high-risk women with left main or three-vessel disease. Multivariate analysis reveals that low peak exercise heart rate and multivessel defects are independent predictors of more severe disease (*10*).

The advent of ^{99m}Tc agents, such as sestamibi, promised to further enhance the accuracy of SPECT in women. Amanullah et al. (*11*) determined a sensitivity of 93% in women catheterized after SPECT adenosine technetium imaging. Specificity was 78% and the overall diagnostic accuracy was determined to be 88%. In women with nonanginal symptoms, the sensitivity was 93% and the specificity was 69%. In women with symptoms of angina, the sensitivity and specificity were 92% and 83%, respectively. Sensitivity was similar in those women with low, intermediate and high likelihood of disease. The same authors using the same diagnostic technique further describe a sensitivity of 91% and specificity of 70% for the diagnosis of severe or extensive coronary disease in women (*12*).

Assessment of stress myocardial perfusion can be used for prognostic purposes

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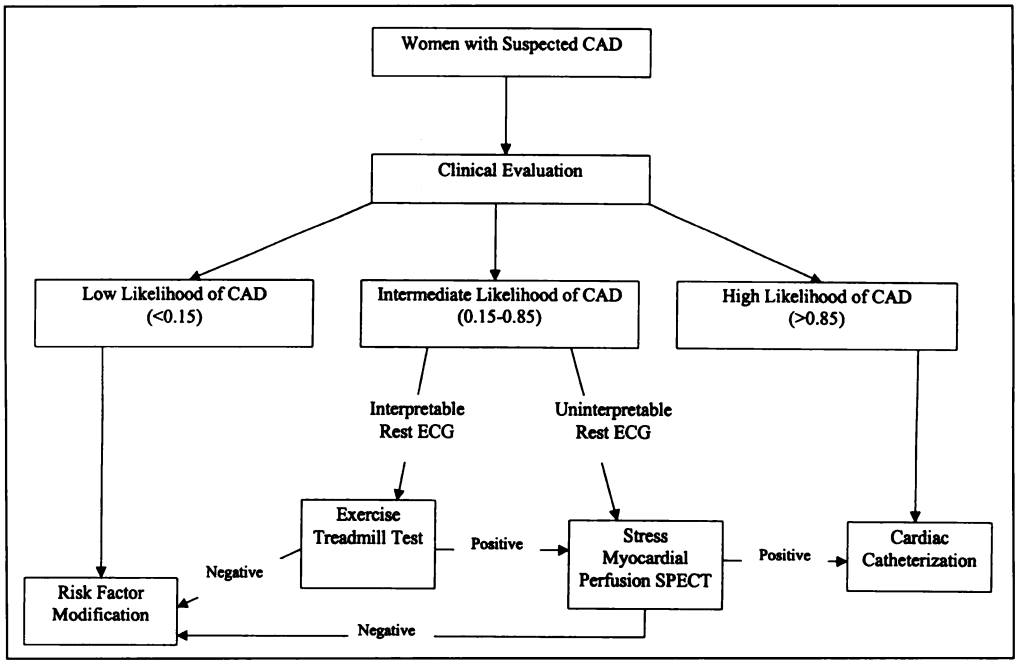

FIGURE 1. Clinical algorithm for the diagnostic evaluation of women with suspected CAD using an anatomic approach to testing. ECG = electrocardiogram.

in addition to diagnostic purposes. Pancholy et al. (*13*) identified an independent and incremental prognostic value of SPECT exercise ^{201}Tl imaging in women. The extent of the perfusion abnormality was the most important predictor of prognosis. Women with a large perfusion defect had an event rate (cardiac death or myocardial infarction) of 7% per year; in the setting of small perfusion defects or no perfusion defects, event rates were 2% and 1% per year, respectively.

Hachamovitch et al. (*14*) directly compared the incremental prognostic value of nuclear testing in men and women using SPECT exercise dual-isotope perfusion imaging. Normal nuclear scans with no perfusion defects had a low event rate in women and men, but women with an abnormal scan had a higher event rate than men. SPECT imaging demonstrated a greater discrimination for the detection of women than of men at high risk for adverse outcomes. Further, similar prognostic value was present in men and in women for exercise treadmill testing (ETT), with greater incremental prognostic gains (increase in chi-square) in women than in men after consideration of SPECT data. Thus, the cardiovascular test was shown to be more accurate in women than men. The efficacy of stratification was also shown to be greater in women than in men using dual isotope SPECT.

OTHER IMAGING MODALITIES

The benefits of nuclear stress myocardial perfusion imaging for detection of coronary disease and prognostication are clear. Nevertheless, other noninvasive strategies are available to clinicians including ETT, ultrafast CT, exercise radionuclide angiography and stress echocardiography. The diagnostic and prognostic value of these techniques should also be clarified.

ETT in women has a lower sensitivity and specificity compared to men, with a higher false-positive rate, ranging from 38%–67% compared to 7%–44% in men in the same studies (*15*). However, women referred for cardiovascular stress testing usually have a lower prevalence of CAD as well. Several investigators have shown that after adjusting for the prevalence of CAD, the sensitivity and specificity of ETT is similar in men and women (*6*). Prognostically, ETT is similarly predictive in men and women; however, in men, symptoms and ST segment changes are the most predictive variables, whereas in women, exercise duration is a more powerful predictor of outcomes.

Three examinations used by noninvasive imaging specialists—ultrafast CT, exercise radionuclide angiography and PET—can be used for the detection of coronary disease. Sex-specific differences in the diagnostic efficiency of coronary artery calcifications by ultrafast CT may be related to differences in disease prevalence. Nevertheless, Naito et al. (*16*) suggest that coronary calcification indicates a more adverse prognosis in women compared to men. Exercise radionuclide angiography has little diagnostic efficiency because many normal women fail to increase their ejection fraction during exercise. There is also little prognostic information in women using this technique. There is no information regarding gender differences at this time in PET imaging.

Stress echocardiography is emerging as a powerful noninvasive diagnostic tool in women with the best sensitivity and specificity reported to date as 86% and 84%, respectively (*17*). The technology is improving but remains very operator dependent. The use of this modality is widespread, but the greatest diagnostic accuracy occurs only in very skilled and experienced laboratories. There is limited prognostic information available regarding women with very few, small studies. Nevertheless, the technique is promising and the addition of contrast echo agents will undoubtedly enhance its diagnostic accuracy. The prognostic accuracy of this modality to date, however, remains questionable.

The implications of understanding the risk and prevalence of coronary disease in women and the limitations of noninvasive testing result in the need for a delineated clinical strategy for the treatment of heart disease in women. One approach is based on the anatomic diagnosis of the presence of coronary disease (Fig. 1; a testing approach with the goal of CAD detection irrespective of underlying risk), whereas the other is based on a prognostic risk assessment (Fig. 2; a testing approach with the goal of identifying those patients at risk of adverse outcomes irrespective of underlying anatomy). Both approaches are feasible, ap-

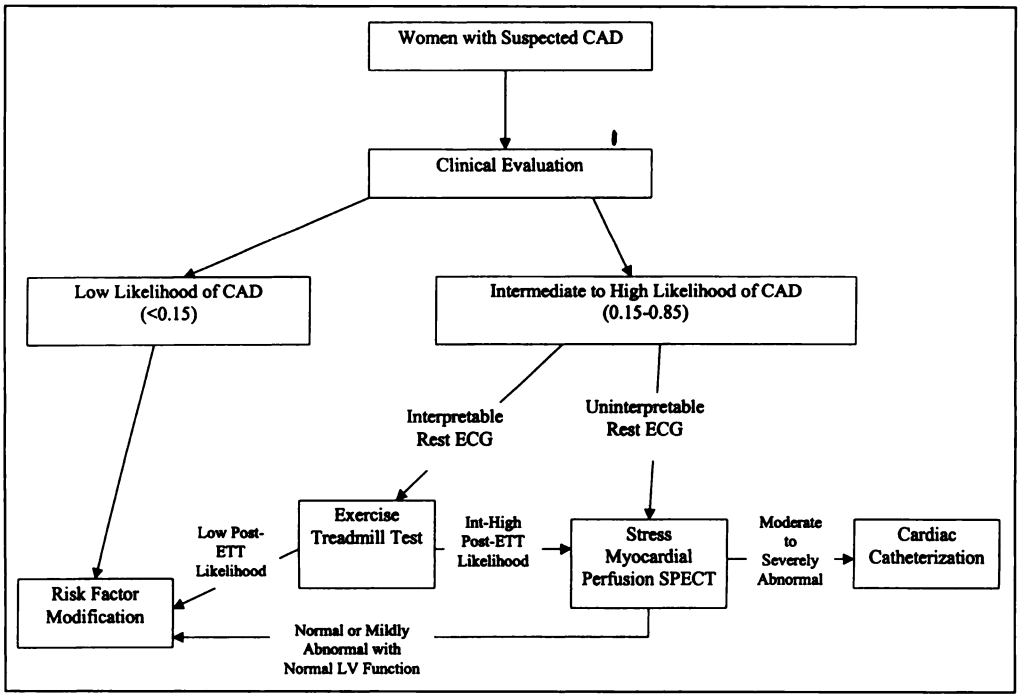

FIGURE 2. Clinical algorithm for the prognostic evaluation of women with suspected CAD using a risk-based approach to testing. ECG = electrocardiogram; LV = left ventricle; ETT = exercise treadmill testing.

plicable to most diagnostic centers and potentially cost-effective.

IS THERE A SEX-RELATED DIFFERENCE IN THE MANAGEMENT OF PATIENTS?

Since the study of Tobin et al. (*18*) in 1987 first pointed out an overwhelming referral bias favoring more aggressive testing of men compared to women, a number of studies have investigated further the issue of sex-related referral biases. In a Duke University study, Mark et al. (*19*) reported a significantly lower rate of referral to cardiac catheterization in women than in men after exercise testing. This difference was attributed to the lower pretest likelihood of coronary disease and the lower rate of positive ETT results. Thus, the authors declared an absence of gender bias in referrals to cardiac catheterization. Furthermore, Shaw et al. (*20*), found that men were more likely to undergo additional noninvasive testing and be referred to catheterization than women even after adjusting for confounding covariates. When referral rates to catheterization and revascularization after nuclear testing were examined, a lack of gender referral bias to catheterization or revascularization was also demonstrated once the extent and severity of stress perfusion abnormalities were taken into account (*21*). In fact, a greater rate of referral to catheterization was present in women with severe ischemia compared to men with similar amounts of defects. This reverse referral bias appears to be appropriate because women with severely abnormal scan results had a significantly higher event rate than men (17.5% versus 6.3%, $p < 0.0001$) (*21*). Nevertheless, investigators more recently showed that a sex-related bias can be present in referral to catheterization: The direction of the bias is dependent on whether the patient had known CAD at the time of testing (*22*). Consequently, whether or not a referral bias exists is not completely certain. Its presence may vary between institutions. Physicians' confidence in testing modalities and the level of work-up that is being considered are additional factors that contribute to potential biases. Although the risk of premature cardiac events is greater in men, women have a greater risk of adverse outcomes when coronary disease is present. Thus, when referral rates are considered, it is unclear whether actual referral bias is present when a result is obtained and appropriate treatment is implemented.

The article in this issue of *The Journal of Nuclear Medicine* by Santana-Boado et al. (*23*) evaluates the sensitivity and specificity of stress ^{99m}Tc-sestamibi myocardial SPECT imaging in women and men. The authors find that the prevalence of coronary disease and the probability of positive SPECT imaging results are lower in women compared to men. Although these findings are not original, the novelty is in the authors' analysis. Diamond's (*24*) alternative calculation to Bayes' theorem is used with analysis of the "silent majority" and "select minority." Diamond's (*24*) approach allows the authors to confirm the diagnostic value of SPECT perfusion imaging in women and to reconfirm its use in the management of coronary disease in women.

The patients in the study undergoing coronary angiography after a SPECT perfusion stress test were labeled the "select minority," whereas those who did not were labeled the "silent majority." The calculation of sensitivity and specificity applies the known diagnostic efficiency of SPECT stress perfusion imaging in the select minority, which has been confirmed with the gold standard of cardiac catheterization, to the silent majority, which has undergone SPECT stress perfusion imaging, but the prevalence of coronary disease is unknown. Using Diamond's (*24*) formulation, the sensitivity of SPECT stress perfusion imaging was lower in women of the select minority compared to men (85% versus 93%, $p < 0.01$), whereas the specificity in the select minority and the sensitivity and specificity in the silent majority were not statistically different. This study confirms previous studies addressing sensitivity and specificity in the detection of coronary disease in women and men.

CONCLUSION

The diagnostic and prognostic accuracy of nuclear stress myocardial perfusion imaging is very powerful in assessing coronary disease in women. Santana-Boada et al.'s (*23*) use of Diamond's

(*24*) alternative calculation of Bayesian analysis joins previous studies that confirm nuclear SPECT imaging with ^{99m}Tc-sestamibi as an accurate diagnostic modality in women and men. As women present to their physicians with symptoms suggesting coronary disease, this diagnostic technique can reliably enhance their treatment and assist in preventive strategies; thus, becoming the cornerstone of the noninvasive evaluation.

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