The role of treadmill exercise testing in women

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Treadmill exercise electrocardiogram (ECG) is one of the most commonly used noninvasive tests for the assessment of ischemic heart disease (IHD). Sex-specific challenges in diagnostic and prognostic tests methods for IHD outlined the importance of pretest probability evaluation and referral bias using risk-prediction charts available for both asymptomatic and symptomatic women. Accordingly, exercise ECG has been indicated as the initial test for the symptomatic women at intermediate risk of IHD who has a normal resting ECG and is capable of maximal exercise. However, the difficulties of using exercise testing for diagnosing IHD in women have led to an initial speculation that stress imaging may be preferred to standard stress testing. This editorial analyzed a large body of evidence on the diagnostic and prognostic powers of treadmill ECG and exercise myocardial perfusion imaging (MPI) according to new advanced imaging technologies. (J Nucl Cardiol 2016;23:991–6.)

Key Words: Exercise: stress testing • women • ischemic heart disease

Abbreviations

ECG	Exercise electrocardiogram
IHD	Ischemic heart disease
DTS	Duke treadmill score
MPI	Myocardial perfusion imaging
SPECT	Single photon emission computed tomography
DASI	Duke activity status index
CZT	Cadmium zinc telluride

Treadmill exercise electrocardiogram (ECG) is one of the most commonly used noninvasive tests for assessment of ischemic heart disease (IHD). Its simplicity and availability have led to its widespread use, and over a long time, it has been recommended as the initial test in patients with suspected IHD and intermediate probability of disease.[1] However, exercise ECG diagnostic accuracy has been demonstrated as gender related, showing lower values in women compared with men in detecting IHD.[2] Different studies with the same prevalence of IHD in men and women have confirmed the demonstrated lower exercise ECG accuracy in women,[3,4] excluding that the lower prevalence of disease in women can be responsible of these results. Important differences in the symptom presentation and functional capacity between women and men have an impact on the diagnosis of IHD. Women have a higher prevalence of angina than men do and more functional impairment from the pain.[5] Women are more likely to have atypical symptoms compared with men. Moreover, functional capacity was higher in men than in women, and tended to decrease with age for both the genders.[6] The performance of exercise ECG for the diagnosis of IHD has shown variable diagnostic yield, according to the threshold selected for the diagnosis. The main diagnostic ECG abnormalities during exercise testing consist of horizontal or down-sloping ST-segment depression $\geq$0.1 mV, persisting for at least 0.06-0.08 s after the J-point, in one or more ECG leads. To obtain

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maximal diagnostic information from exercise ECG testing, the latter should be symptom/sign-limited and performed without the influence of anti-ischemic drugs. However, the sensitivity and specificity of ST-segment depression with an exercise ECG in symptomatic women vary, with sensitivity generally being worse than specificity. In a meta-analysis of exercise ECG testing in women, the sensitivity and specificity for ST-segment depression in symptomatic women, at intermediate-risk were 61% and 70%, respectively.[2] These values compared reasonably well with the sensitivity and specificity of 68% and 77%, respectively, obtained in a meta-analysis of predominantly male participants.[7] Positive predictive value of ST-segment depression with exercise testing has been demonstrated to be significantly lower in symptomatic women than in symptomatic men, while negative predictive value of ST-segment depression showed similar results. Different factors can interfere with the ECG response to exercise in women. Autonomic and hormonal influences, inappropriate catecholamine release during exercise[8] and estrogen that has molecular similarities to digitalis, can cause a digitalis-like false-positive response. Moreover, women showed a lower performance to exercise with an inability to attain maximal stress and less exercise-induced angina than men did.[9] Thus, Duke Treadmill Score (DTS), a combination of several variables from testing into a single composite score, has been proposed as the optimal parameter to define as positive the interpretation of exercise test in both symptomatic and asymptomatic women, demonstrating significant ability to diagnose disease accompanied by an effective stratification power. Predictive value of DTS in women was demonstrated to be entirely due to exercise capacity considering that both ST-segment changes and occurrence of angina pectoris do not appear to add any additional information beyond the prognostic value of exercise capacity.[9,10] In fact, women have the same frequency of angina on treadmill as men do, but exercise angina in women is less often correlated with the presence of obstructive coronary artery disease. Interestingly, a nomogram has been proposed to predict a woman's expected exercise capacity at any given age, and the resulting measure was shown to predict the risk of death in both asymptomatic and symptomatic cohorts.[11] Also heart rate recovery, defined as peak heart rate minus heart rate at two minutes after exercise, has been shown to aid in the estimation of near- and long-term outcomes in large cohorts of women, making a contribution to confer a significant prognostic power to exercise ECG.[12] The inclusion of all available parameters in our interpretation of the response to exercise, such as the description of maximal exercise capacity measurements, as well as the integrative test scores, leads to a standardized improvement in our knowledge on how to optimize the diagnostic power of exercise ECG in women.

Sex-specific challenges in diagnostic and prognostic tests for IHD outlined the importance of pretest probability evaluation and referral bias using risk-prediction charts available for both asymptomatic and symptomatic women. Accordingly, exercise ECG has been indicated as initial test for the symptomatic women at intermediate risk of IHD, who have a normal resting ECG and are capable of maximal exercise.[1,13] The definition of intermediate pretest risk is referred to individuals aged 30-59 years presenting typical angina, aged $\geq$50 with atypical angina, or aged $\geq$60 with nonanginal chest pain.[1] However, it should be considered that the predictive value of positive exercise ECG result in women is significantly altered by age and certain exercise responses. In 111 symptomatic women aged <65 years, a <2.0-mm ST-segment depression during exercise and a <3.0 min in recovery suggest a false-positive response in more than half of the cases.[14] The positive predictive value increases to nearly 70% in women $\geq$65 years old, in younger women and in women at intermediate-age with ST-segment depression $\geq$2.0 mm and/or prolonged exercise-induced ischemic ST-segments shifts.[14]

EXERCISE TREADMILL TEST WITH MPI FOR ISCHEMIA IN WOMEN

The difficulties of using exercise testing for diagnosing IHD in women have led to an initial speculation that stress imaging may be preferred to standard exercise treadmill test. Myocardial perfusion imaging (MPI) by single-photon emission computed tomography (SPECT) provides a more sensitive and specific prediction of the presence of IHD than exercise ECG does. Without correction for referral bias, the reported sensitivity of exercise MPI has generally been placed in the range of 85%-90% and specificity in the range of 70%-75%.[15]

The first randomized trial to identify what is the optimal method for ischemia evaluation in women (WOMEN) showed us important findings regarding the claimed possibility to improve the diagnostic accuracy of standard treadmill exercise ECG combining exercise test with MPI in women.[16] Symptomatic women with suspected IHD, an interpretable ECG, and $\geq$5 metabolic equivalents on Duke Activity Status Index (DASI) were randomized to exercise ECG or exercise MPI and were followed for the incidence of primary major adverse cardiac events (composed of cardiac death, nonfatal myocardial infarction, or hospital admission for an acute coronary syndrome or heart failure) and secondary end points (such as hospitalization for any chest pain,

follow-up worsening of health status measurements, and all-cause death). No incremental benefit of an initial diagnostic strategy by exercise MPI compared with treadmill-only strategy has been observed in predicting clinical outcomes at 2 years of follow-up. In this study, women enrolled were at intermediate risk of IHD, aged ≥50 years with typical or atypical angina, or aged ≥60 years with nonangina symptoms. The representative enrollment included one half of the women aged ≥50 years and one quarter aged ≥65 years. Moreover, an important caveat of the findings reported was that the observed event rates, during only 2 years of follow-up, were lower than the rates that would have been expected and that the potential benefits of MPI have been missed. In fact, published evidence derived from observational registries supported the superiority of exercise MPI over standard ECG in women with suspected or known IHD.[17] Despite there being no data of direct comparison in a larger size with a longer follow-up demonstrating the superiority of initial diagnostic strategy by combined MPI with treadmill exercise vs exercise ECG alone in women, the former is often the preferred modality of testing to evaluate IHD in women. In the recently published guidelines, more weight is given to testing patients according to pretest probability, age, and sex using the most recent estimates of IHD prevalence as the basis of clinical algorithm (Figure 1).[18,19] A noninvasive imaging functional test has been recommended for making a diagnosis of IHD in women with a pretest probability of disease between 66% and 85% (women aged ≥70 years with typical angina). Moreover, the indications are that women with a 15%-65% pretest probability of disease (women aged 30-69 years with typical angina and aged 60-80 years with atypical angina or nonangina pain) could have an exercise ECG if feasible as the initial test.[18] However, the guidelines clearly outlined that if local expertise and availability could permit a noninvasive imaging test for ischemia, this would be preferable given the superior diagnostic capabilities of such test.

WHY PREFER EXERCISE MPI TO TREADMILL ECG IN WOMEN?

As with all stress imaging techniques, MPI provides superior diagnostic performance to predict the presence of IHD compared with the exercise ECG.[20,21] Advanced imaging technologies have overcome the limitations of using MPI in women. The use of MPI by ECG-gated SPECT imaging with 99-technetium-labeled agents, with a view to reducing the breast tissue attenuation defects to the minimal level, significantly improved specificity to 91%-92% in detecting disease in women, showing results comparable to those of men.[22,23] Moreover, all the functional information obtained, acquired using the ECG-gated method, as transient ischemic dilatation and reduced poststress ejection fraction, revealed important nonperfusion predictors of severe disease providing important findings for the interpretation of imaging results. Recent advances have been performed also to overcome the challenges of imaging small hearts in women using new depth-dependent resolution recovery algorithms.[24] New solid-state detector with cadmium zinc telluride (CZT) cameras, always more frequently used for MPI studies with protocols increasing the diagnostic accuracy while decreasing the test duration and radiation exposure, also showed that several patients with breast attenuation on conventional SPECT have no significant loss of counts in the anterior wall as observed on the CZT camera.[25] Although no evidence has indicated higher diagnostic capability of CZT SPECT in diagnosing IHD in women, data suggested different breast attenuation patterns between traditional and CZT cameras (Figure 2).

While choosing exercise MPI, it should be also emphasized that in this modern era, it is not possible to refer a patient to stress testing for ischemia only for diagnostic purpose, considering that it is widely recognized that the estimation of prognosis with any given modality allows for a more precise linkage with patient-risk-reduction and therapeutic-risk-reduction efforts.[26] The prognostic accuracy of exercise MPI in the assessment of IHD in women has been demonstrated to be extremely powerful. The prognostic values of normal exercise MPI in 17 exercise MPI studies covering 8008 subjects with a mean age of 54 years, of whom 34% were women, have been evaluated in a recent meta-analysis. The negative predictive value for myocardial infarction and cardiac death in women was 99% over a follow-up period of 32 months, against that shown in men, with an annualized event rate of 0.3%.[27] In the presence of abnormal exercise MPI, an increased risk of cardiac events has been indicated in 1394 women according to the extent of MPI defects.[28] In particular, women with definitely abnormal scan response had a significant twofold higher event rate than men (14% vs 7%). Nuclear testing significantly stratified both men and women irrespective of their rest ECG, showing a superior discriminative power in identifying high-risk women than men. Interestingly, nuclear testing revealed incremental prognostic values in both men and women after inclusion of the most predictive clinical and exercise variables.[28]

It has to be considered that in both performing exercise ECG alone and combining with MPI, the women present some limitations in reaching a maximal exercise considering the demonstrated lower exercise capacity compared with men. The DASI demonstrated

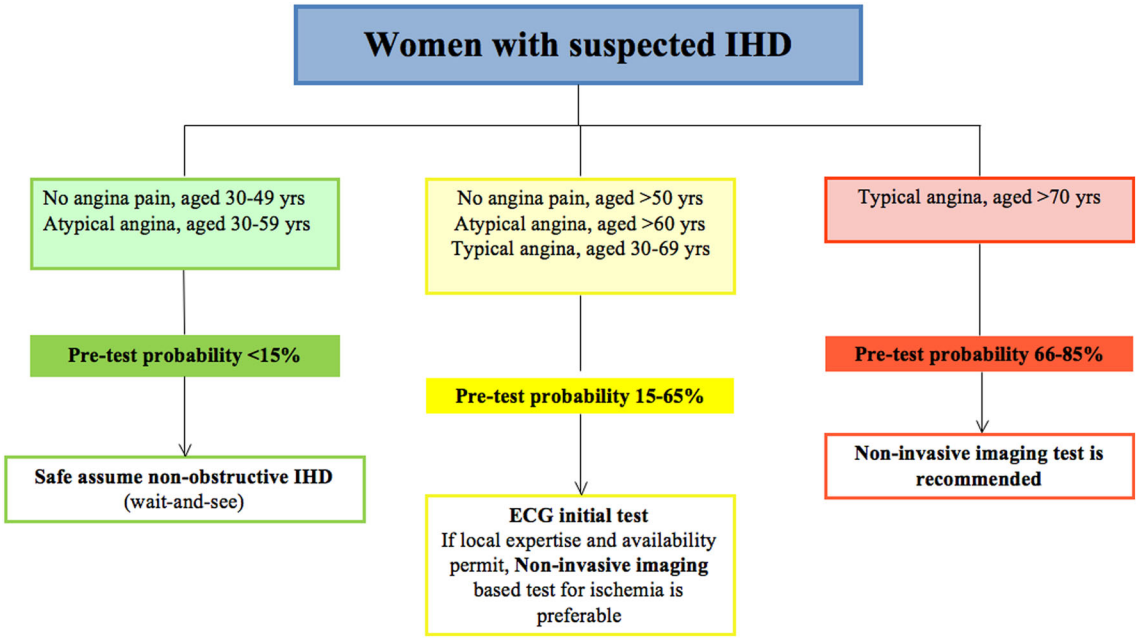

Figure 1. Initial diagnostic management of women with suspected ischemic heart disease (IHD) according to clinical pretest probability[18].

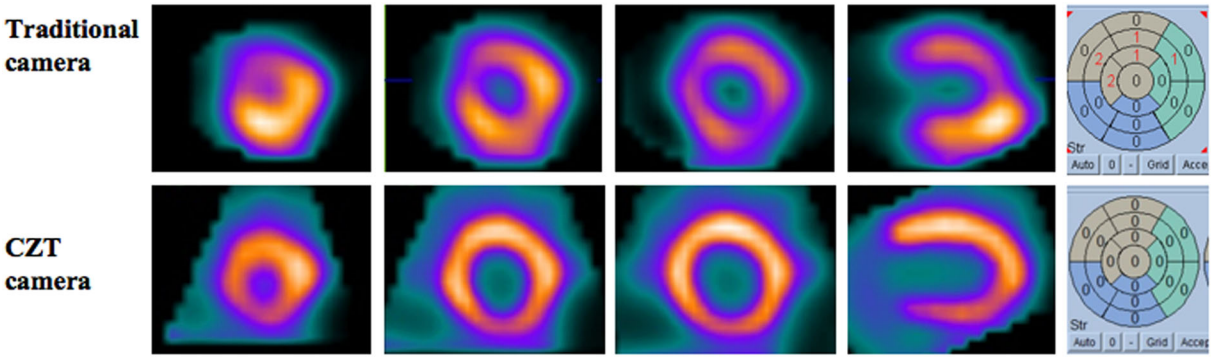

Figure 2. Myocardial perfusion imaging by the traditional (*upper panel*) and the CZT (*bottom panel*) cameras in a woman with intermediate pretest probability.

to guide the selection of exercise treadmill vs pharmacologic stress MPI, predicting exercise capacity in Mets and determining patients' eligibility for exercise stress testing.[29]

The indications for cardiac imaging in symptomatic cohort of women include obese patients, elderly and those with orthopedic limitations as challenging candidates for the exercise ECG. In fact, <60% of the obese subjects met criteria for maximal exercise ECG.[30] In general, in all female patients in whom exercise is limited by orthopedic or other noncardiac problems, an alternative noninvasive imaging test with pharmacologic stress should be selected. New pharmacological agents such as regadenoson demonstrated safety and efficacy in all patients regardless of age, gender, and body mass index. Thus, the possibility to perform pharmacologic stress MPI in women after an appropriate selection adds great flexibility in stress-testing strategies and affords greater availability of the stress MPI to virtually all female population referred for the assessment of IHD.

NEW KNOWLEDGE GAINED

Exercise ECG has been indicated as the initial test for the symptomatic women at intermediate risk of IHD who have a normal resting ECG and is capable of maximal exercise. The difficulties of using exercise testing for diagnosing IHD in women have led to an initial speculation that stress imaging may be preferred to standard stress testing. This editorial viewpoint

recommends to select a noninvasive imaging-based test for ischemia, combining exercise ECG with MPI, for women at intermediate pretest probability of disease, according to published evidence.

CONCLUSION

The studies cited in this editorial viewpoint strongly suggest that exercise ECG remains the recommended method of initial evaluation only in selected symptomatic women suspected with IHD. In women at intermediate pretest probability of disease, a noninvasive imaging-based test for ischemia, combining exercise ECG with MPI, is preferred, whenever local expertise and availability could permit. A large body of evidence on the diagnostic and prognostic powers of exercise MPI according to new advanced imaging technologies supports this approach.

Disclosure

The author declares no conflict of interest.

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