

Noninvasive Evaluation of Symptomatic Women with Suspected Coronary Artery Disease

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ABSTRACT: Cardiovascular disease (CVD) is the leading cause of death in the United States, yet several factors make it challenging to diagnose in women. Although women have more frequent chest pain than men, atypical symptoms such as nausea, dyspnea, and fatigue make it difficult to determine their risk of coronary artery disease (CAD) before testing. Current guidelines recommend exercise electrocardiography (ex-ECG) as the initial test in symptomatic women with intermediate pretest probability who can exercise and have a normal resting ECG; however, treadmill ex-ECG testing has a significantly lower positive predictive value in women. In addition, women often have nonobstructive CAD in conjunction with microvascular dysfunction and other cardiovascular abnormalities that can decrease the accuracy of all noninvasive tests. The following provides an overview of exercise ECG, echocardiography, SPECT imaging, and various other available modalities and examines their effectiveness in diagnosing and managing symptomatic women with suspected CAD.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death among women in the United States.¹ Ischemic heart disease (IHD), which includes both obstructive and nonobstructive coronary artery disease (CAD), acute coronary syndromes, and angina, makes up the majority of this mortality.¹⁻⁴ The diagnosis of CAD in women is difficult for several reasons. Although the prevalence of CAD is significantly lower in women than in men, women have chest pain more frequently than men and have more atypical symptoms such as nausea, dyspnea, and fatigue, making it difficult to determine the pretest likelihood of CAD.⁵ Women frequently have nonobstructive CAD coexisting with microvascular or endothelial dysfunction, epicardial and microvascular spasm, myocardial bridging, and conduit vessel stiffening, all of which may contribute to myocardial ischemia. These factors decrease the diagnostic accuracy of all noninvasive tests.⁶ However, clinicians continue to rely heavily on the results of noninvasive tests to enhance their ability to correctly diagnose IHD in women.

Many types of noninvasive tests are available to clinicians, including exercise electrocardiography, exercise and pharmacologic echocardiography (echo), exercise and pharmacologic radionuclide myocardial perfusion imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET), stress myocardial perfusion and wall motion magnetic resonance imaging (CMR), and coronary computed tomography angiography (CCTA). This review touches on the role of each of these modalities in the diagnosis, prognosis, and management of symptomatic women with suspected IHD.

EXERCISE ELECTROCARDIOGRAPHY

Exercise electrocardiography (ex-ECG) is the least costly and most commonly used screening test for IHD.⁶ The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend ex-ECG for all symptomatic women at intermediate risk for IHD who can exercise > 5 METS and have a normal resting ECG.^{6,7} These recommendations are based on the fact that ex-ECG has a similar negative predictive value in women and men (78% and 81%, respectively) and provides important prognostic information, such as exercise capacity, heart rate recovery, and chronotropic response.⁶⁻⁹

Exercise capacity has been shown to be an independent predictor of death in women. For every 1 MET increase in exercise capacity, the Framingham Risk Score-adjusted mortality was reduced by 17% ($P < .001$).⁸ Impaired heart rate recovery, defined as < 12 beats/min drop in heart rate 1 minute after cessation of exercise, was an independent predictor of mortality in women (HR 1.6, $P < .0001$).¹⁰ Chronotropic incompetence, defined as failure to achieve 85% of the age-predicted maximum heart rate in the absence of beta blockade therapy, has also been associated with a poor prognosis in both women and men.¹¹ The Duke Treadmill Score (DTS), which incorporates exercise capacity, ST segment response, and angina score index, has likewise been shown to predict mortality in women, with annual mortality rates of 0.25% and 5% for DTS scores ≥ 5 or ≤ -11 , respectively.¹²

The ST segment response alone has been shown to be inaccurate in predicting obstructive CAD in women. A meta-analysis of 29 studies that included 3,392 women reported a

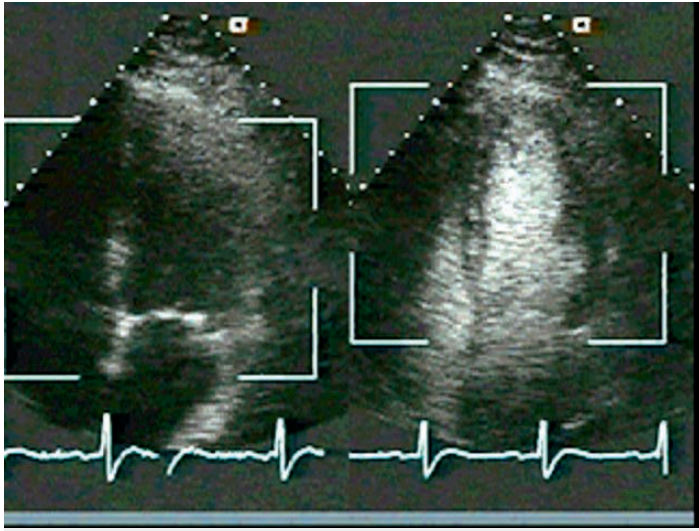


Figure 1.

Demonstration of improved endocardial detection using an echocardiographic contrast agent. The left image was captured using tissue harmonic imaging, but the endocardium is not well delineated. The right image was acquired after the injection of an echocardiographic contrast agent, and all of the endocardium is well visualized. Reprinted with permission.¹⁸

sensitivity and specificity of 62% and 68%, respectively, with a positive predictive value of only 47%.¹³ Some factors that may contribute to the inaccuracy of the ST response as a predictive tool include a lower prevalence of obstructive CAD in women compared to men and ST changes due to estrogen, mitral valve prolapse, coronary artery vasospasm, and microvascular disease, which are all more prevalent in women than men.^{14,15}

STRESS ECHOCARDIOGRAPHY

Multiple studies have demonstrated improved accuracy of stress echo over ex-ECG for diagnosing obstructive CAD in women.¹³ A meta-analysis from the Agency for Healthcare Research and Quality (AHRQ) that included 1,286 women undergoing exercise (treadmill or bicycle) or pharmacologic (dobutamine, dipyridamole, or adenosine) stress echo reported a sensitivity and specificity of 79% and 83%, respectively.¹³ Stress echo has also been shown to have comparable sensitivity and specificity for detecting CAD in both women and men.¹³

Exercise echo is recommended for symptomatic women at intermediate risk for CAD who have an abnormal resting ECG or an abnormal ex-ECG,¹⁶ while pharmacologic stress echo is recommended for the symptomatic, intermediate-risk women who cannot exercise.¹⁶ Dobutamine is the most commonly used pharmacologic stress agent simply because studies using a

vasodilator agent (dipyridamole or adenosine) have reported a lower sensitivity.¹⁷ The American Society of Echocardiography recommends the use of echocardiographic contrast for optimizing visualization of the endocardial border, which in turn improves wall motion analysis when two or more endocardial segments are not visualized at rest (Figure 1).¹⁸ Unlike ex-ECG, SPECT, and PET, stress echo can identify other reasons for the patient's symptoms, such as heart failure, valvular heart disease, pericardial diseases, pulmonary hypertension, or aortic dissection.⁶ Stress echo has been shown to effectively risk-stratify women into low- and high-risk groups. The event rate following a normal ex-echo is less than 1% annually.¹⁸ The annual event rate following a normal pharmacologic echo is slightly higher and likely reflects the increased comorbidities in this patient population.¹⁸ Stress echo allows clinicians to determine the extent of infarction or stress-induced ischemia, with ≥ 4 abnormal segments being associated with a high rate of future IHD events.¹⁸ Other high-risk stress echo features include resting left ventricular ejection fraction (LVEF) $\leq 40\%$, right ventricular ischemia, an increase in end-systolic size with stress, and a decrease in LVEF with stress.¹⁸

MYOCARDIAL PERFUSION IMAGING

Myocardial perfusion imaging (MPI) has been shown to have better accuracy compared to ex-ECG for diagnosing obstructive CAD in women.¹⁹ A 14-study meta-analysis from AHRQ that included 1,000 women undergoing exercise (treadmill or bicycle) or pharmacologic (dipyridamole, adenosine, or regadenoson) SPECT with technetium-99m (^{99m}Tc) or thallium (Tl-201) reported a sensitivity and specificity of 81% and 78%, respectively.¹³ Exercise MPI with SPECT is recommended for symptomatic women at intermediate risk for CAD who have an abnormal resting ECG or an abnormal ex-ECG.¹⁶ Pharmacologic MPI with SPECT is recommended for the symptomatic, intermediate-risk women who cannot exercise.¹⁶ Tl-201 is a low-energy radioisotope that is easily scattered and attenuated by densely fibrotic or large breasts.¹⁹ Different strategies have been proposed to improve the specificity of Tl-201 imaging in women—for example, using breast markers and prone imaging—but little improvement in specificity was seen.¹⁹ In addition to having higher energy and less scattering and attenuation, ^{99m}Tc radiotracers allow simultaneous acquisition of ECG-gated images of ventricular function. This helps to distinguish breast attenuation defects from true fixed perfusion defects, as the latter are associated with abnormal wall thickening and motion.¹⁹ Although Tl-201 and ^{99m}Tc SPECT have similar sensitivities for detecting CAD, ^{99m}Tc SPECT imaging has superior specificity and therefore is recommended for use in women (Figure 2).¹⁹ Perfusion defects of $\geq 10\%$ induced by ^{99m}Tc SPECT have been associated with a high risk of future IHD events.⁶ Other findings associated with high IHD risk include a summed stress score > 8 , LV dilation, and peak- or post-stress LVEF $< 45\%$.⁶

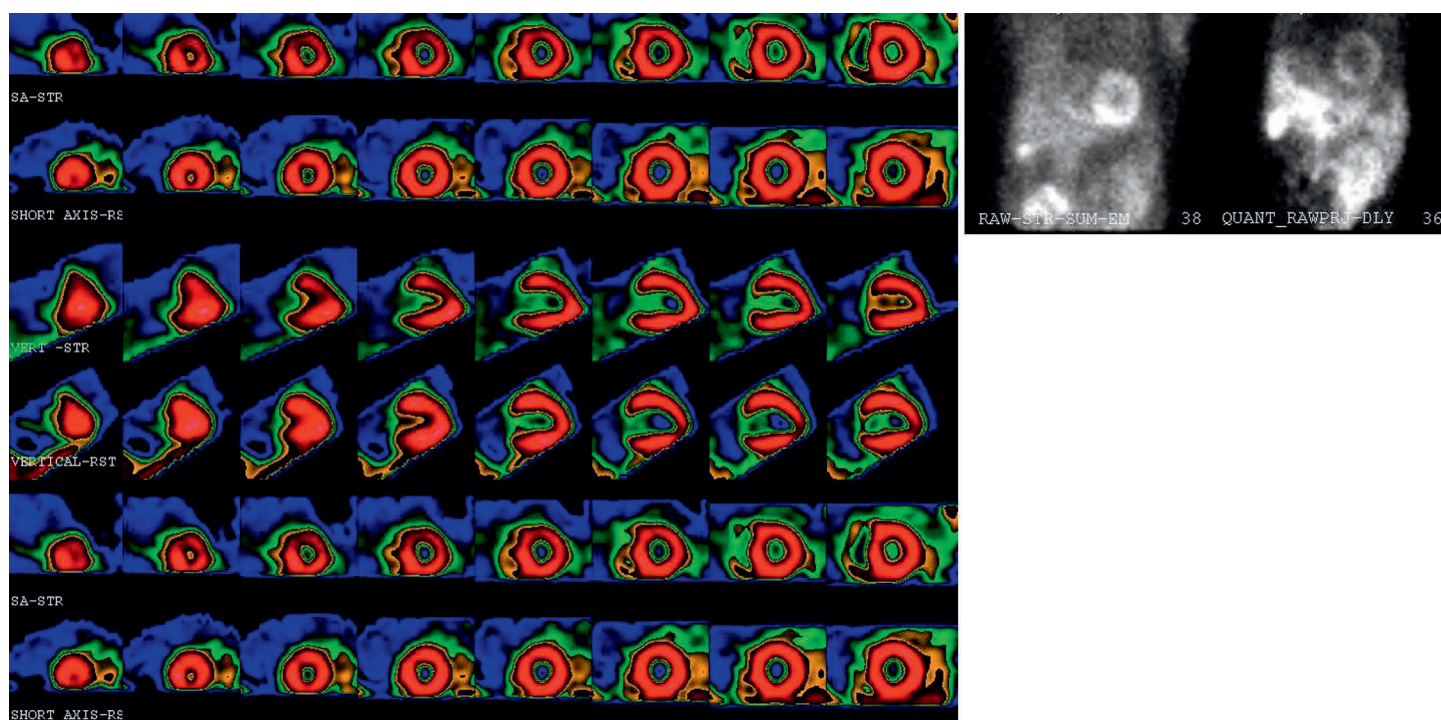


Figure 2.

Demonstration of a large breast attenuation defect masquerading as ischemia in the LAD distribution. Left panel: the top, third, and fifth rows are the short (SA), vertical (VERT), and horizontal (HORZ) axes images obtained at peak stress, which are compared to the corresponding rest images in the second, fourth, and sixth rows. At peak stress, a large defect is evident in the anteroseptal, anterior, and anterolateral walls. Right panel: comparison of the raw data at peak stress (RAW-STR-SUM-EM) to the raw data at rest (QUANT_RAWPRJ-DLY) reveals homogeneous attenuation of the heart by the breast tissue at rest, whereas at peak stress the breast attenuates only the upper half of the heart; this results in the illusion of a large ischemic defect in the LAD distribution. ECG gating (not shown here) demonstrated normal wall motion in all segments at peak stress.¹⁹ Reprinted with permission. LAD: left anterior descending artery; ECG: electrocardiogram

^{99m}Tc SPECT effectively risk stratifies women into low- and high-risk groups.¹⁹ Like ex-echo, the annual event rate following a normal exercise ^{99m}Tc SPECT is less than 1%. The annual event rate following a normal pharmacologic ^{99m}Tc SPECT is approximately 2-fold higher. The event rate following an abnormal ^{99m}Tc SPECT is dependent not only on the amount of ischemic myocardium and LVEF but also on age, functional disability, and other high-risk clinical features such as peripheral artery disease, diabetes mellitus, chronic obstructive lung disease, prior stroke, and chronic kidney disease.⁶ Comparative studies between stress echo and SPECT have shown comparable diagnostic and prognostic ability in the same patient population as well as in several meta-analyses.¹⁸ ACC/AHA guidelines recommend limiting radiation exposure as much as possible, particularly in premenopausal women and older women who are at low risk for obstructive CAD; in this patient population, ex-ECG or stress echo is preferable. If stress echo is unavailable, techniques to limit radiation exposure to < 3 mSv, such as stress-only MPI, rest-stress MPI PET, dose-reduction CCTA, or CMR, are recommended.⁶

In comparative studies between SPECT and PET, PET has demonstrated a statistically significant improvement in specificity for diagnosing obstructive CAD in women.²⁰ Although prognostic data for PET is limited, a recent meta-analysis indicated the event rate was 0.4% per year for a normal versus 11.5% per year for a moderately to severely abnormal stress Rb-82 PET.²¹ PET myocardial flow reserve remains an area of active research since it may be beneficial in detecting microvascular CAD and predicting future IHD events in women with nonobstructive CAD.²²

CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY

A wealth of data on the diagnostic and prognostic value of coronary computed tomographic angiography (CCTA) in patients suspected of having CAD has recently emerged. CCTA is currently recommended for symptomatic patients with an intermediate pre-test probability of CAD and an equivocal stress test result.²³ Compared to CMR, CCTA has a higher spatial resolution, is more widely available, and has better

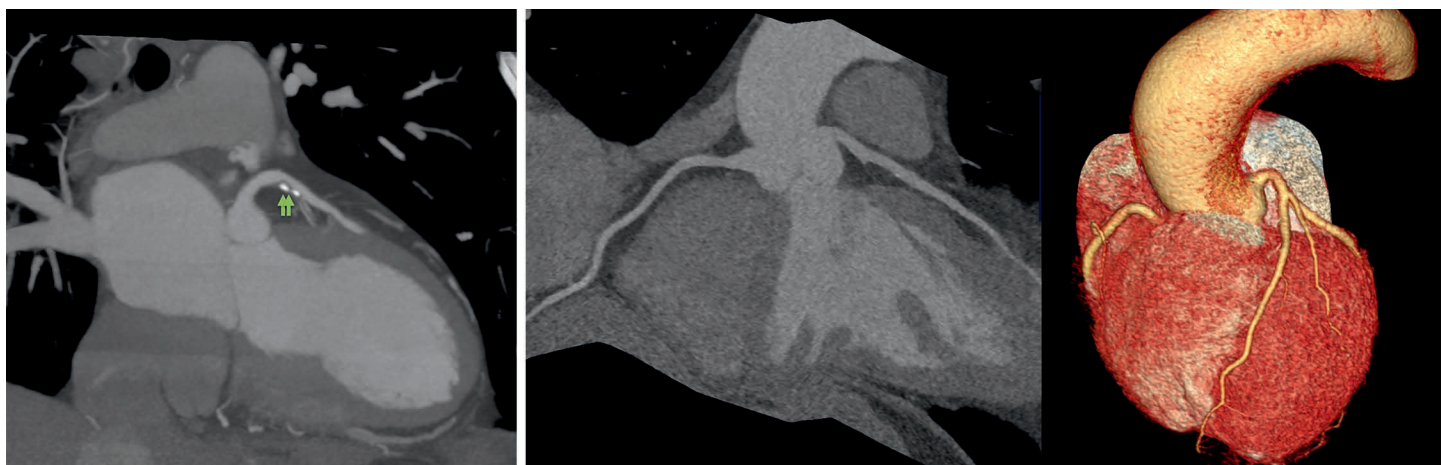


Figure 3.

(Left) Proximal left anterior descending coronary artery on CTA showing obstructive atherosclerotic plaque (>50% stenosis) with high-risk features including positive remodeling and spotty calcifications (arrows). (Right) Curved planar reformat and volume-rendered images on CTA showing essentially normal coronary arteries in a middle-aged female patient with risk factors and recurrent chest pains. CTA: computed tomography angiography

patient acceptance and shorter examinations.²³ In addition, CCTA can help to ascertain luminal narrowing, plaque location, plaque burden, advanced plaque characterization (low attenuation, noncalcified, calcified, or mixed), and the presence of arterial remodeling (Figure 3), all of which are instrumental in determining the prognostic significance of nonobstructive CAD in women.²⁴

A meta-analysis that included 474 symptomatic women, all of whom had no known CAD and who underwent CCTA, reported a sensitivity and specificity of 93% and 77%, respectively.¹³ This is similar to the sensitivity and specificity reported in studies that enrolled both men and women (85%-99% and 64%-90%, respectively). More importantly, there was no significant difference in the diagnostic accuracy of CCTA between the total 679 women and 1,173 men in these mixed-gender studies when compared to invasive angiography.⁶

In large multicenter registries, CCTA has been shown to effectively risk stratify women into low- and high-risk groups. For example, the CONFIRM registry reported outcomes on 23,854 symptomatic patients without known CAD, of which 12,128 were women. A normal CCTA was associated with a very low 0.28% annual mortality rate in both men and women. However, the mortality rate increased with the extent and severity of CAD, with a hazards ratio of 1.62 for nonobstructive disease, 2 for obstructive 1-vessel disease, 2.92 for obstructive 2-vessel disease, and 3.7 for obstructive 3-vessel or left main coronary artery disease, with obstructive disease being defined as greater than 50% stenosis.²⁵ Likewise, the annualized event rate, defined as death and myocardial infarction,

increased with the extent and severity of obstructive CAD and was not significantly different between men and women.²⁶ In nonobstructive CAD, the extent of disease also predicts mortality; 3-vessel nonobstructive disease is associated with the worst prognosis, followed by 2- and 1-vessel disease.²⁷ In one cohort study, the annualized event rate for patients with normal coronaries, nonobstructive CAD, and obstructive CAD was 0.2%, 1.2%, and 2.1%, respectively.²⁸ Plaque composition also predicts prognosis in patients with nonobstructive CAD, where noncalcified plaques are associated with a higher risk of death over 6 years (9.6%) than mixed plaque (3.3%) and calcified plaque (1.4%).²⁹ Another marker of high IHD risk in women is a coronary artery calcium score (CAC) ≥ 400 . In a subset of 2,820 symptomatic patients from the CONFIRM registry who had nonobstructive CAD—defined as 0% to 49% stenosis and a calculated CAC score—a CAC ≥ 400 was associated with a 13-fold increased risk of death compared to patients with a zero CAC score.³⁰

With technological advances, CCTA can now use fractional flow reserve (CT FFR) to delineate the severity of obstructive lesions by combining anatomical data with functional assessment of the stenosis. The DEFACTO trial is one of three studies that compared CT FFR to invasive FFR, and it demonstrated improved diagnostic accuracy for detecting lesion-specific ischemia compared to anatomic assessment by CCTA alone.³¹

CARDIAC MAGNETIC RESONANCE IMAGING

Growing evidence over the past decade demonstrates that stress cardiac magnetic resonance imaging (CMR) has

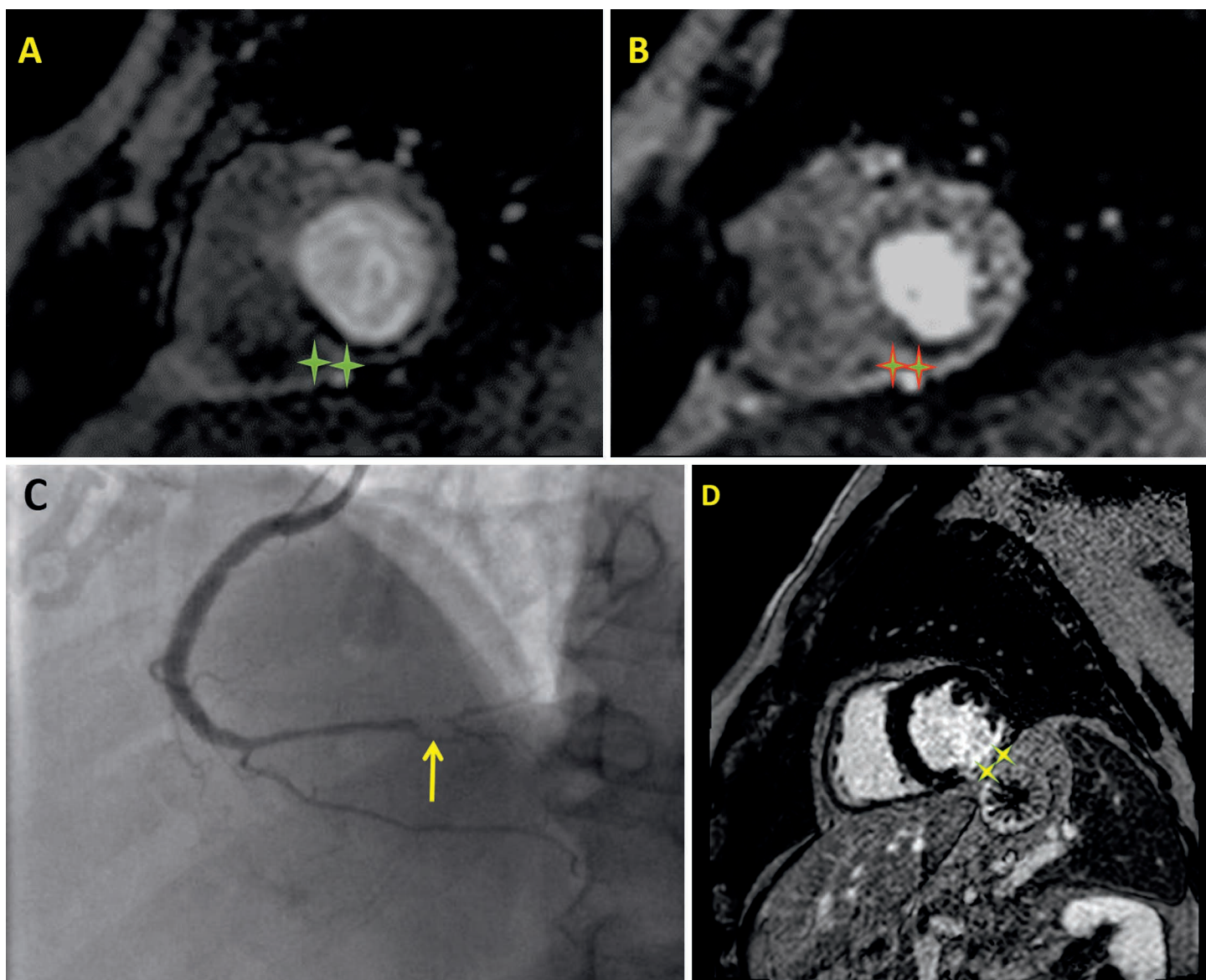


Figure 4.

(A-C) Short-axis views of the left ventricle on CMR showing basal to mid inferior and basal inferoseptal inducible ischemia on first-pass perfusion imaging. Hypoperfused myocardial segments are seen as dark regions (A and B asterisks) of low signal. Panel C demonstrates the lesion seen on invasive coronary angiography responsible for the CMR findings. (D) CMR-delayed contrast imaging showing hyperenhancement (asterisks) in the inferolateral wall, suggestive of myocardial fibrosis. CMR: cardiac magnetic resonance

good diagnostic accuracy and cost-effectiveness when evaluating patients for IHD. When compared to CCTA, CMR provides better temporal resolution, is radiation-free, and can assess epicardial and microvascular disease by detecting subendocardial ischemia, which makes it an ideal imaging modality for women. Diagnostic images can be obtained even in obese patients, whereas stress echo and SPECT would be limited by image quality.

In CMR, administration of a pharmacologic stressor (adenosine, regadenoson, dobutamine) is typically followed by contrast-enhanced imaging using gadolinium-based agents to assess regional wall motion, first-pass perfusion, and early and late gadolinium enhancement (Figure 4). However, in those patients who cannot receive gadolinium-based agents due to severely impaired renal function, wall motion can still be assessed using CMR following administration of

dobutamine in a dosing regimen similar to dobutamine stress echocardiography. Meta-analyses of stress myocardial perfusion and wall motion CMR studies using adenosine and dobutamine reported a sensitivity of 83% and specificity of 86% for diagnosing CAD in both men and women.^{32,33} In one meta-analysis that included 501 symptomatic women with no known CAD, stress CMR demonstrated a sensitivity of 72% and a specificity of 84%.¹³ A large single-center trial comparing stress CMR to stress MPI showed that CMR was more sensitive in women compared to men (88.7% vs 50.9%, respectively) and had superior diagnostic accuracy in both sexes.³⁴

Stress CMR prognostic data is limited compared to other noninvasive modalities but continues to emerge. One study of 208 symptomatic women demonstrated an event-free survival of 100% over 4 years in those with a negative stress CMR.³⁵ However, in another study of 168 women, a positive vasodilator stress CMR was associated with an annual event rate of 15%.³⁶ An LVEF $\leq 40\%$ has been identified as a marker of high IHD events in men and women and confers a hazard ratio of 4.1 for subsequent cardiovascular death and nonfatal MI compared to those with normal findings.³⁷ In addition, the extent of ischemia on stress CMR has been shown to predict IHD events, with ≥ 3 abnormal or ischemic CMR segments being associated with high risk.⁶ Finally, infarct size and the amount of transmural myocardial necrosis measured by late gadolinium enhancement has been shown to predict not only poor LV recovery but also major adverse cardiovascular events and all-cause mortality independent of LVEF and LV volumes.³⁸⁻⁴⁰

Stress CMR perfusion may be useful in detecting microvascular disease in women, which is a common cause of chest pain. Several small studies

evaluated patients with chest pain who had normal coronary arteries based on invasive angiography but abnormal functional stress tests. Two of the studies showed that subendocardial ischemia was frequently present on stress CMR,^{41,42} and another showed a notable association with increased IHD events such as anginal hospitalization and repeat catheterization.⁴³

CONCLUSIONS

The noninvasive diagnosis of CAD in women has proven to be particularly challenging secondary to limitations of the currently available noninvasive tests and the lower prevalence and severity of CAD in women. Due to its low specificity, ex-ECG in women may lead to increased cost and risk if cardiac catheterization is pursued rather than further noninvasive testing. However, current guidelines recommend it as the initial test in symptomatic women with intermediate pretest probability who have a normal resting ECG and can exercise. The other noninvasive imaging modalities give similar diagnostic and prognostic information in women that is comparable to men and are recommended in symptomatic women with intermediate pretest probability who have an abnormal resting or ex-ECG or are unable to exercise. Guidelines also recommend that factors such as radiation exposure, patient preference, renal function, body habitus, and the need for structural, functional, or hemodynamic information be taken into account when choosing the appropriate diagnostic test.

Conflict of Interest Disclosure

The authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest Statement and none were reported.

Keywords

coronary artery disease, women, ischemic heart disease, stress test, exercise ECG

KEY POINTS:

- Because of recent technological advances in noninvasive stress testing procedures, comparative studies have demonstrated similar accuracy in women and men with the exception of treadmill exercise ECG testing, which is more accurate in men.
- Treadmill exercise ECG testing has similar negative predictive value in women and men, but the positive predictive value is significantly lower in women.
- Women with a positive treadmill exercise ECG should be referred for stress testing with imaging because of the low positive predictive value of treadmill exercise ECG testing.
- The appropriate stress test with imaging needs to be individualized for each patient, taking into account radiation exposure, patient preference, renal function, body habitus, and the need for structural, functional, or hemodynamic information.

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