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The Role of Nuclear Cardiology in the Diagnosis and Risk Stratification of Women With Ischemic Heart Disease

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Ischemic heart disease (IHD) is the leading cause of death in women. Women present with coronary artery disease later in life than men, with greater number of risk factors and higher rate of angina. Women have higher mortality compared with age-matched men despite having less anatomical coronary artery disease. Distinct pathophysiologies are thought to account for sex-related differences in the presentation and prognosis of IHD. More women than men have chest pain secondary to coronary reactivity, microvascular dysfunction, and plaque erosion with distal microembolization. Sex-related factors such as lower exercise capacity, less specific ST-segment electrocardiographic changes, smaller left ventricular size, and breast attenuation can complicate the diagnosis of IHD in women. These sex-specific factors should be considered before determining the appropriate test to be performed in a woman with suspected IHD. Technological advances in nuclear cardiology including attenuation correction and coronary flow reserve measurement by PET hold promise in optimizing the diagnosis and risk stratification of women with IHD.
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Ischemic heart disease (IHD) is the leading cause of death for women in Western countries,[1] claiming a greater number of lives than breast cancer at all ages.[2] A greater number of women than men die of cardiovascular disease in the United States and Europe.[2,3] There are significant sex-related differences in the presentation and prognosis of IHD. Women present with IHD 10 years later in life than men do, with a greater number of risk factors, higher rate of angina, and a larger number of non-specific symptoms.[4] Women with IHD have greater rates of myocardial ischemia and mortality compared with age-matched men despite having less anatomical obstructive coronary artery disease (CAD), less ST-segment elevation myocardial infarction, and more preserved left ventricular ejection fraction.[5-12] Although differences in IHD progression between men and women are not completely understood, it appears that sex-specific pathophysiologies may play a role.

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The traditional diagnostic approach of IHD based on the evaluation for obstructive CAD is less effective in women compared with men. A large number of women have chest pain secondary to abnormal coronary reactivity,[13] microvascular dysfunction,[14] and plaque erosion with distal microembolization.[15,16] In fact, many women without obstructive CAD at coronary angiography continue to have chest pain, contributing to poor quality of life and greater use of health care resources.[17-19] Women with IHD have more office visits and greater rates of hospitalization than men have.[1]

Myocardial perfusion SPECT is often used in women with suspected or known IHD. The diagnostic accuracy of myocardial perfusion SPECT in women is adversely affected by sex-related factors such as lower exercise capacity, less specific ST-segment electrocardiographic (ECG) changes, higher prevalence of single-vessel obstructive CAD and microvascular dysfunction, smaller left ventricular size, and breast attenuation.

In Part I of this review, we describe the various challenges of IHD diagnosis in women referred for myocardial perfusion imaging (MPI) and examine imaging techniques that can increase the diagnostic value of nuclear cardiology in women. In Part II, we explore the role of MPI in the risk stratification and management of women with IHD.

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Challenges of IHD Diagnosis in Women and Potential Solutions

Exercise ECG

The diagnostic accuracy of exercise ECG is lower in women compared with men. When using ≥1.0-mm ST depression as threshold for diagnosis of obstructive CAD, the sensitivity and specificity of exercise ECG in women are 61% and 70%, respectively,[20] compared with 68% and 77%, respectively, in a meta-analysis including men and women.[21] The lower sensitivity of exercise ECG for obstructive CAD is related, in part, to impaired functional capacity, which prevents women from achieving adequate levels of exercise on the treadmill, either by not attaining maximal predicted heart rate or by developing an exaggerated heart rate response in the first few minutes of the Bruce protocol owing to deconditioning. Women unable to achieve 5 metabolic equivalents of exercise should be switched to pharmacologic stress testing.[22] An alternative for patients who cannot achieve a minimum 85% of maximum predicted heart rate is to combine low-level exercise testing with an intravenous injection of regadenoson. The combined exercise-regadenoson protocol is associated with fewer side effects and improved image quality compared with vasodilator-only stress because it increases the heart-to-liver and heart-to-lung count ratios.[23] A protocol combining regadenoson at peak exercise in patients unable to reach target heart rate also proved to be well tolerated, yielding comparable imaging results to standard regadenoson stress testing.[24] The lower sensitivity of exercise ECG in women compared with men is also, in part, attributed to a greater prevalence of single-vessel CAD (Bayesian theory).

Other sex-specific factors further decrease the diagnostic accuracy of exercise ECG in women. ST-segment abnormalities can vary according to the menstrual cycle. Endogenous estrogen levels in premenopausal women are highest in the mid-cycle, and studies have shown a reduced prevalence of chest pain and ischemia during this phase of the menstrual cycle.[25,26] Estrogen has a digoxinlike effect that may result in ST-segment depression, decreasing the specificity of exercise stress testing.[27]

Small Left Ventricular Size

Women have smaller body surface area and thus smaller hearts compared with men. The combination of smaller heart size and increased prevalence of mild-to-moderate 1-vessel obstructive CAD makes the identification of SPECT perfusion defects in women more difficult.[28] Because of limited spatial resolution of the SPECT cameras, small areas of hypoperfused myocardium may be missed. Hansen et al[29] reported a lower diagnostic accuracy of thallium myocardial perfusion SPECT in women vs men. However, after correcting for left ventricular size, there were no significant differences in diagnostic accuracy.

Patients with small hearts are more likely to have underestimation of end-systolic volumes and overestimation of the left ventricular ejection fraction. At end systole, the partial volume effect and the short distance between opposing left ventricular walls contribute to a smaller appearance of the left ventricular cavity. As a result, the left ventricular ejection fraction becomes overestimated. These errors are greater in women than in men.[30-35] Most commercially available software overestimate the left ventricular ejection fraction of patients with small hearts.[32,35] The low accuracy of gated SPECT in left ventricular end-systolic volume and ejection fraction assessment of small hearts is, in part, related to the algorithm used for left ventricular edge detection. Different acquisition and reconstruction methods have been proposed to overcome the challenges of imaging small hearts. Zoomed projection images and high-resolution collimators are used to optimize image acquisition. A high cutoff frequency of the Butterworth filter can improve the visualization of the endocardial borders.[31] Depth-dependent resolution recovery algorithms, now provided by all vendors, are more accurate in the estimation of the left ventricular volumes compared with traditional reconstruction algorithms.[36] Nakajima et al[37] have suggested a method to improve the accuracy of left ventricular volume assessment in small hearts. With their technique, the left ventricle is delineated based on a 3-dimensional heart-shaped model and an active shape algorithm instead of geometrical approximations.

Breast Attenuation

Breast tissue attenuation artifacts are more prevalent in women compared with men. Breast attenuation can give rise to regional count deficits that mimic a perfusion defect. Breast attenuation artifacts are most commonly localized to the anterior and anterolateral walls, but the location may vary depending on shape and size of the breast. In women with large breasts, apical defects can develop, and inferolateral wall defects are frequently seen in women with pendulous breasts. Breast attenuation artifacts are usually seen on both the stress and rest images, mimicking myocardial infarction. If the relative position of the attenuating soft tissue is altered between the stress and rest studies, it may give rise to a reversible count deficit mimicking myocardial ischemia. For example, an artifactual reversible count deficit may develop if a woman is imaged with her bra on during stress and her bra off during rest.

Several techniques are used to differentiate breast tissue attenuation artifact from a myocardial perfusion abnormality. Gated imaging is helpful because fixed count deficits associated with preserved left ventricular wall thickening and motion are more likely to represent an attenuation artifact. Gated imaging is less helpful in the differentiation of attenuation artifacts and subendocardial infarctions because preserved wall thickening is expected on both. Gated imaging is not useful in distinguishing shifting attenuation artifacts from true reversible perfusion defects. Prone imaging can be done to increase the diagnostic specificity of myocardial perfusion SPECT, but prone imaging is more helpful in men than in women.[38] The prone position has been shown to reduce diaphragmatic attenuation because of downward displacement of the diaphragm relative to the myocardium. On the contrary, the prone acquisition can also produce artifactual anteroseptal defects owing to the closer position of the heart to the sternum and ribs.[39]