Canadian Journal of Cardiology ■ (2013) 1–9

Review

Evaluation of Suspected Ischemic Heart Disease in Symptomatic Women

Leslee J. Shaw, PhD,[a] Suman Tandon, MD,[b] Stacey Rosen, MD,[c] and Jennifer H. Mieres, MD[c]

[a] *Emory University School of Medicine, Atlanta, Georgia, USA*

[b] *Yale University, New Haven, Connecticut, USA*

[c] *North Shore Long Island Jewish Hospital, Manhasset, New York, USA*

ABSTRACT

There is a wealth of evidence about the role of a variety of diagnostic testing modalities to define coronary artery disease (CAD) risk in women presenting for evaluation of suspected myocardial ischemia. The exercise electrocardiogram (ECG) is the core index procedure, which can define risk in women capable of performing maximal exercise. Stress imaging, using echocardiography or myocardial perfusion single-photon emission computed tomography/positron emission tomography, is useful for symptomatic women with an abnormal resting ECG or for those who are functionally disabled. For women with low-risk stress imaging findings, there is a very low risk of CAD events, usually < 1%. There is a gradient relationship between the extent and severity of inducible abnormalities and CAD event risk. Women at high risk are those defined as having moderate to severely abnormal wall motion or abnormal perfusion imaging findings. In addition to stress imaging, the evidence of the relationship between CAD extent and severity and prognosis has been clearly defined with coronary computed tomographic angiography. In women, prognosis for those with mild but nonobstructive CAD is higher when compared with those without any CAD. The current evidence base clearly supports that women presenting with chest pain can benefit from one of the commonly applied diagnostic testing modalities.

RÉSUMÉ

Il existe une multitude de données scientifiques sur le rôle des diverses modalités d'examens diagnostiques pour définir le risque de maladie coronarienne (MC) chez les femmes qui se présentent à l'évaluation pour une suspicion d'ischémie myocardique. L'électrocardiogramme (ECG) d'effort est la procédure d'indice de base, qui peut définir le risque chez les femmes en mesure de réaliser l'exercice maximal. L'imagerie à l'effort, au moyen de l'échocardiographie ou de l'imagerie de perfusion myocardique par tomographie par émission de photon unique/tomographie par émission de positons, est utile chez les femmes symptomatiques ayant un ECG anormal au repos ou chez celles ayant une anomalie fonctionnelle. Chez les femmes ayant des résultats d'imagerie à l'effort montrant un risque faible, le risque d'événements de MC est très faible, habituellement < 1 %. Il y a une relation de gradient entre l'étendue et la gravité des anomalies inductibles, et le risque d'événement de MC. Les femmes exposées à un risque élevé sont celles définies comme ayant un mouvement anormal de la paroi allant de modéré à grave ou des résultats d'imagerie de perfusion anormaux. En plus de l'imagerie à l'effort, les données scientifiques sur la relation entre l'étendue et la gravité de la MC, et le pronostic ont été clairement définies par la coronarographie par tomodensitométrie. Chez les femmes, le pronostic de celles ayant une MC bénigne, mais non obstructive est élevé lorsqu'il est comparé à celles n'ayant pas de MC. La base factuelle actuelle appuie manifestement le fait que les femmes ayant une douleur thoracique peuvent bénéficier de l'une des modalités d'examens diagnostiques les plus fréquemment appliquées.

For many decades, the diagnosis of the underlying burden of obstructive coronary artery disease (CAD) has been the focus of diagnostic evaluation algorithms for women and men presenting with chest pain. An abundance of clinical research has identified notable limitations in the diagnostic accuracy of an array of conventional stress testing and imaging modalities.[1] With the unfolding evidence of a higher case fatality rate for cardiovascular disease in women, there was a shift of primary focus in the noninvasive testing literature away from the diagnosis of obstructive disease and toward the detection of prognostically significant high-risk subsets of women. The hope of outcomes-based research was that the identification of at-risk women could further define female-specific evaluation algorithms and further define ischemic risk and, importantly, the role of nonobstructive atherosclerosis as a prominent factor precipitating symptoms and clinical event risk.[2]

Received for publication August 14, 2013. Accepted September 22, 2013.

Corresponding author: Dr Leslee J. Shaw, Emory Clinical Cardiovascular Research Institute, 1462 Clifton Rd NE, Room 529, Emory University School of Medicine, Atlanta, GA 30324. Tel.: +1-404-727-1484; fax: +1-404-727-6495.

E-mail: lshaw3@emory.edu

See page 7 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2013.09.019

The current article highlights the available evidence on the accuracy of a variety of commonly applied diagnostic testing modalities. Several systematic reviews have been published on this subject.[1,3] Although similar reviews have been published,[4] this article focuses on trends in stress imaging research that may proffer significant advantages in the identification of at-risk women. Before embarking on a review of the stress imaging literature, it is important to focus on the identification of clinical parameters that define CAD risk in women, as well as relevant safety issues within the diagnostic evaluation algorithm.

Detecting Clinical Risk in Women

The accurate identification of clinical risk in women is key to orchestrating appropriate referral patterns for diagnostic testing. In a 2005 expert consensus statement from the American Heart Association, there was an emphasis on defining angina in women from a very broad perspective, given the atypical nature of presentation for many women.[1] Using this approach, women targeted for a diagnostic evaluation include those who present with undiagnosed chest pain or excessive dyspnea on exertion, the latter of which may be termed an "ischemic equivalent." In addition to querying the patient regarding the quality and characteristics of the associated symptoms, a thorough understanding of provocative symptom stressors is important. For women, stressors may be not only physical exercise but also anxiety, depression, and financial stressors that may provoke angina.[5-7] The clinical history should also focus on the stability and frequency of angina symptoms. As such, typical angina generally occurs in older women but may also be defined with physical and emotional stressors.

An additional factor that is an essential factor in estimating CAD risk in women is age.[8] The prevalence of obstructive CAD increases with age for both women and men.[9] CAD risk is low for premenopausal women, but after menopause the prevalence of obstructive CAD increases. Although the average age of menopause is ~51 years, women with diabetes, polycystic ovary syndrome, human immunodeficiency virus, and the metabolic syndrome can go through menopause quite early, even before the age of 40 years.[10] A woman may be classified as being postmenopausal if menstruation has stopped for 1 year or more.[11] Thus, for the practicing clinician, understanding the delineation of postmenopausal status is clearly critical to optimal definition of at-risk women.

Importantly, for referral decisions about diagnostic testing, it remains important to categorize symptomatic women as being at low, intermediate, and high risk for CAD. Based on age, a woman generally does not approach intermediate risk of CAD until the sixth decade of life, whereas women in their 70s and those who are older may be categorized as having high risk. Additional high-risk subsets are based on the instability of presenting symptoms, peripheral artery disease, and CAD risk factors such as diabetes.

In general, the greater the number of traditional risk factors, the higher the expected CAD risk in any cohort. Although one may think that the use of a global risk score may be helpful, the use of such scores (eg, the Framingham risk score) has established limitations in symptomatic patients.[12] However, there are lessons to learn from how the risk scores categorize patients, eg, women with a 0 to 1 risk factor are generally low risk, whereas those with 3 or more CAD risk factors are generally at high risk for CAD.

Women at low risk are generally not candidates for stress testing, whereas women at intermediate to high risk of CAD form the core group of patients referred for diagnostic evaluation.[13] To choose the appropriate diagnostic test, 2 questions need to be answered: (1) Can the patient perform maximal exercise or does she have limitations in activities of daily living? (2) Does she have a normal resting electrocardiogram (ECG) without any significant ST-segment abnormalities? Women at intermediate to high risk and are functionally disabled or those with resting ST-segment changes are candidates for CAD imaging; this evidence will be highlighted in a later section of this article. However, women at intermediate risk who are capable of performing all regular activities of daily living should undergo an exercise tolerance test (ETT) without imaging.

ETT in Women

Clinical practice guidelines recommend the ETT as the index procedure for women at intermediate risk with a normal resting ECG and those capable of performing maximal exercise.[13] Many clinicians proceed directly to a stress imaging procedure because of the reported limitations of the ETT in women, which will be defined later in this section. However, a recent comparative effectiveness trial randomized 824 symptomatic women at low to intermediate risk to an index ETT compared with stress myocardial perfusion single-photon emission computed tomography (SPECT) with some interesting findings.[14] The results from the **W**hat Is the **O**ptimal **M**ethod for Ischemia **E**valuation in Wome**n** (WOMEN) trial reveals similar 2-year rates of major adverse CAD outcomes ($P = 0.59$) (Fig. 1).[14] These data support a strategy of using an index ETT with the potential for follow-up stress imaging for women with indeterminate or abnormal electrocardiographic markers or other ETT result abnormalities.

The rationale for supporting the ETT as the index procedure lies in the wealth of data on which CAD risk may be defined in women and men. There are numerous risk

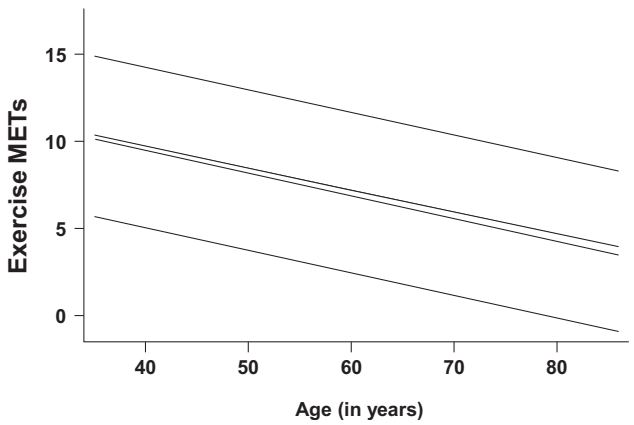

Figure 1. Nomogram for exercise capacity derived in a female population. The **double lines** are the mean and the outer lines indicate the range of metabolic equivalent (MET) values across patient ages.