Noninvasive cardiac imaging for the diagnosis of coronary artery disease in women

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ABSTRACT

Cardiovascular diseases are the foremost cause of morbidity and mortality for both genders worldwide. Appropriate diagnostic tests with increased accuracy and safety provide the decisive relationship between diagnosis and treatment of coronary artery disease (CAD). However, it has been known that women at risk for occurrence of CAD are less often conducted for the proper diagnostic tests compared to men. Many noninvasive diagnostic modalities (exercise/stress electrocardiogram, echocardiography, nuclear imaging, magnetic resonance imaging and coronary computerized tomography) are available for this purpose in the women. In this review, we present the current data on the role of both conventional and modern noninvasive diagnostic tests in the assessment of women with CAD suspicion.
(Anadolu Kardiyol Derg 2014; 14: 741-6)

Key words: coronary artery disease, women, noninvasive imaging techniques

Introduction

Cardiovascular diseases are the foremost cause of morbidity and mortality for both genders, and worldwide there are clear differences between genders both in admission, symptomatology, efficiency of diagnostic tests, response to treatment and outcomes (1-5). Due to the American Heart Association (AHA) data about one in three female adults have some patterns of the cardiovascular diseases. Also, women who have had an acute myocardial infarction (MI)-especially those > 55 years of age - have a poor prognosis than men, with a higher recurrence of MI and mortality. Indeed, females are more likely to have atypical anginal symptoms compared to men, which may promote the missed diagnoses of coronary artery disease (CAD) and increased risk of acute coronary events (6, 7). In addition, the frequency of CAD in females with chest pain is approximately 50%, compared with 80% in males, which makes difficult to diagnose CAD in female (8). AHA report is demonstrating that women with risk of CAD are less often referred for the convenient diagnostic test than are men (1, 9, 10). Coronary angiography is a gold standard test which identifies coronary pathophysiology in patients who have angina pectoris and are at high risk for CAD. In patients with intermediate-risk for CAD, clinicians have several noninvasive imaging tools to select from that can evaluate functional or anatomical properties. Functional evaluation methods consist of exercise electrocardiography (ECG), stress echocardiography and nuclear myocardial perfusion imaging [single-photon emission computed tomography (SPECT) and positron emission tomography (PET)]. Anatomic diagnostic tests include cardiac magnetic resonance imaging (MRI) and coronary computed tomography angiography (coronary CTA). The comparative safety and accuracy of these noninvasive modalities in women was uncertain, although substantial data exists for populations combining both men and women (1). Noninvasive diagnostic imaging techniques are particularly important choice for patients who have contraindications to invasive angiography or for those who are at high risk for complications with invasive tests (11). Noninvasive imaging tests should be used when necessary but is not applied in all women simply because of the fear of probable false-positive test results.

Diagnosing coronary artery disease in women

Diagnosis of CAD can be challenging in women, given the lower frequency of obstructive lesions, greater symptomatology,

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Accepted Date: 09.06.2014 **Available Online Date:** 23.06.2014

DOI:10.5152/akd.2014.5406

and lower functional capacity (5, 12). Establishing the pretest likelihood of disease in a women is key in the diagnosis of CAD, balancing the probability of false positives when the disease prevalence is low with the need to avoid unnecessary additional and/or invasive testing. Diamond et al.(13) analyzed the pretest probability of CAD as well as sensitivity and specificity in patients undergoing exercise electrocardiography. The prevalence of CAD by angiography was stratified into asymptomatic, nonanginal, atypical, and typical angina categories. Using this type of strategy can help further refine the likelihood of disease and hence direct the most appropriate testing, such as cardiac catheterization for high-risk individuals and exercise tolerance testing for low-risk individuals. In the WISE study, this strategy was found to overestimate the degree of obstructive disease (3).

Types of noninvasive tests

Because of the assessment techniques as an anatomical or functional, there are several noninvasive tests including:

• Functional tests

o Exercise/stress electrocardiography (ECG)

o Exercise/stress echocardiography

o Nuclear myocardial perfusion tests, including single photon emission computed tomography (SPECT) and positron emission tomography (PET)

• Anatomic tests

o Magnetic resonance imaging (MRI)

o Coronary computerized tomographic angiography (coronary CTA)

The AHA and the American College of Cardiology (ACC) recommend that women with suspicion of CAD should be categorized as either symptomatic or asymptomatic and further sorted as being at low, intermediate or high risk for CAD to direct the decision about which diagnostic tool to use initially. In 2005, the AHA developed a consensus statement on the role of noninvasive screening in the assessment of women with suspicion of CAD. In this statement, the AHA recommended that noninvasive diagnostic tests (i.e., exercise ECG and cardiac imaging tools) should be performed in women who have symptoms and intermediate-high risk for occurrence of CAD and that such noninvasive tests should not be applied in women who have no symptom and low risk for occurrence of CAD (1). The AHA consensus statement was a thorough synopsis of the available literature regarding the diagnosis of CAD in women with expert-guided recommendations for the work-up of symptomatic women but did not include a comparative effectiveness review of the accuracy of the various noninvasive modalities in women.

Functional modalities

Electrocardiographic modalities

Treadmill exercise ECG test is the older and most frequently used form of stress testing. It is extensively available, simplest and cheapest screening modality. According to the current AHA/ACC guidelines, women should undergo treadmill testing if they have an intermediate risk for occurrence of CAD (14). However, several confounding parameters that are unique to females (like hormonal changes) have been shown to result in ECG changes during exercise test and increase the false-positive rate of the test. Other challenging factors with treadmill testing in women include their lower functional capacity and the high prevalence of other comorbid conditions like obesity (12). Also, it has been reported that exercise ECG is less reliable in diabetic women (15), therefore treadmill exercise test alone may be particularly misleading.

A major disadvantage of exercise ECG is its reduced diagnostic power for obstructive CAD in women. The Coronary Artery Surgery Study (CASS) which was a milestone multicenter study affected clinical practice in CAD for many years showed that false-positive treadmill test results were 4.5 times higher in women even in the presence of anatomically normal coronary arteries (16). But that a normal exercise test result can effectively exlude a diagnosis of CAD. A meta-analysis reported by Kwok et al. (17) reported 15 studies with a sensitivity of 61% (46-79%) and specificity of 69% (51-86%). These testing results suggest a limited value of exercise ECG alone in the appropriate diagnosis of CAD in females. Moreover, aditional parameters may improve the diagnostic efficacy of the exercise test, like hemodynamic and chronotropic responses to exercise. Despite various limitations, available ACC/AHA guidelines suggest that impact of sex-specific factors is in adequate to displace the treadmill exercise ECG test as the first screening test for symptomatic women at intermediate risk for CAD who have normal resting ECG results and are able to exercise (1, 14). The AHA argues that combining other parameters into exercise scores (e.g., the ST/heart rate index, Duke Treadmill Score, ST/HR slope, blood pressure response) may improve the diagnostic and prognostic value in women (1). Exercise capacity is an important predictor of cardiovascular outcome in women, and unless functional capacity is significantly limited, all stress testing should be done with exercise (18).

Echocardiographic modalities

Exercise or stress echocardiography is another noninvasive technique for diagnosing CAD that provides data for the presence of left ventricular systolic and/or diastolic abnormality, valvular pathology, and the amount of infarction and stress-induced ischemia. The AHA claims that exercise or stress echocardiography yields significantly greater specificity and accuracy for detecting obstructive CAD in women compared to treadmill exercise test. Exercise stress echocardiography has an improved specificity and sensitivity compared to exercise ECG alone, increasing the specificity and sensitivity to 81% to 86% and 80% to 88%, respectively, for establishment of obstructive CAD in symptomatic females (19-22). Exercise or stress echocardiography is recommended for women who are symptomatic and are at intermediate-high risk for occurrence of CAD, and dobutamine stress

echocardiography is recommended for women with normal or abnormal ECG results who are inadequate to exercise (1). The important gain with stress echocardiography over resting ECG alone are higher diagnostic accuracy, capable of localizing ischemic regions, and the opportunity of applicating stress test on subjects who are incapable of exercise (23). The advantages over myocardial perfusion imaging with nuclear techniques include lack of radiation exposure, lesser charge, and concomitant delineation of cardiac structures. According to a recent review, the overall sensitivities for exercise or stress echocardiography are demonstrated to be a bit lesser in women compared to men, although the specificities seem to be similar (23).

Myocardial perfusion imaging techniques

From the view of myocardial ischemia pathophysiology, perfusion abnormalities come first compared to both ECG changes and segmental wall motion abnormalities (24). Exercise or stress myocardial perfusion techniques (PET, SPECT and scintigraphy) are nuclear-based methods which are more sensitive than treadmill test in the demonstration of ischemic coronary disease at an early period. Among the imaging tools, exercise PET, SPECT, and scintigraphy can be carried out by applying a treadmill or bicycle. In patients incapable to exercise, the pharmacologic stress agents are adenosine, dobutamine, and dipyridamole. Also, technetium Tc 99m sestamibi (MIBI), thallous chloride TL-201 (thallium) and fluorodeoxyglucose are the most commonly used radioactive materials in nuclear medicine for cardiovascular system.

SPECT is the most commonly performed stress imaging test in the United States, especially for men and women who are unable to exercise (1). Recently, the use of stress PET has increased. Parameters included in this modality are perfusion defects, global and regional left ventricular function, and left ventricular volumes. For myocardial perfusion imaging studies, a positive test is one that demonstrates reversible ischemia, and different scores can be used. The most frequently used is the summed stress score, which is a semiquantitative index obtained by adding the individual score derived from the 17 or 20 segments analyzed and scored during the stress study. Another score is based on the analysis of extent and severity of stress perfusion defect in the different segments of the left ventricle. This modality has been found to have technical limitations in women, including false-positive results, because of breast attenuation and a small left ventricular chamber size; however, recent advances in nuclear imaging have improved its accuracy (i.e., reduced the breast artifact) (1). Using exercise as the stress modality, radionuclide perfusion imaging with thallium (Tl)-201 has been shown to have on average a sensitivity of 83% and specificity of 88% using planar imaging. SPECT imaging studies have been shown to be more accurate than planar imaging in the diagnosis of CAD and in separating single-vessel from multivessel disease (25). In the diagnosis of CAD in symptomatic women, the sensitivity of exercise SPECT ranges from 78% to 88%, with a specificity of 64% to 91% (26-28). Imaging by using SPECT is recommended for symptomatic women with an intermediate-high risk for occurrence of CAD in the AHA 2005 consensus statement for the role of NIT in women (1). Because of the higher amount of single-vessel CAD among women, diagnostic accuracy of this imaging tool decreases (as well as the echocardiographic techniques) (8).

There was no study directly comparing the diagnostic accuracy of exercise SPECT and exercise echocardiography. In a systematic review of the literature, there has been no significant difference between exercise SPECT and exercise echocardiography in respect to sensitivity (77-81%) and specificity (63-73%) for the diagnosis of coronary heart disease in women (29).

Anatomic modalities

Anatomic assessment techniques directly assure noninvasive imaging of coronary anatomic structures similar to that of conventional coronary angiography. These modalities include cardiac magnetic resonance imaging (MRI) and coronary computerized tomographic angiography (coronary CTA). For cardiac MRI, a positive test is defined by the evidence of perfusion defects (extent and severity) and of wall motion abnormalities (at rest and/or at stress) in different left ventricular segments. For coronary CTA, a significant stenosis is defined quantitatively as at least a 50% narrowing (stenosis) of the coronary artery lumen. Meijboom et al. (30) reported that coronary CTA yielded a high diagnostic accuracy for imaging of the proximal segments of the coronary arteries of both genders but found reduced sensitivity in the detection of distal coronary artery stenosis in women. This finding was attributed to the physical factors of the women like smaller body size and relatively smaller coronary arterial size compared to men. Particularly, the spatial resolution of CTA is not adequate for direct visualization of small-vessel disease (microvascular disease), which is shown to develop more frequently in women. Accordingly, myocardial perfusion imaging modalities like cardiac PET and MRI should be applied to demonstrate small-vessel disease in women.

Although AHA published a scientific document regarding the recommendations for performance of cardiac MRI and coronary CTA in general population, it has no comment on applications in women specifically (31). The AHA indicates that both MRI and CTA are suboptimal in patients with cardiac arrhythmias like atrial fibrillation and poor image quality because of overweight and obesity. Eventually, the AHA recommends that the advantage of noninvasive coronary angiography is to be highest for symptomatic subjects who are at intermediate risk for occurrence of CAD, including patients with indefinite stress tests. Cardiac MRI or coronary CTA should not be performed as a screening tool in asymptomatic patients; in addition, radiation dose limits the application of coronary CTA especially in young and female patients with very low risk for occurrence of CAD (32). As well as, patients with a high risk for occurrence of CAD are likely to require conventional coronary angiography instead of noninvasive imaging. AHA concludes that the exact advantages of coronary CTA over cardiac MRI are higher availability, increased spatial resolution and lesser procedural time.

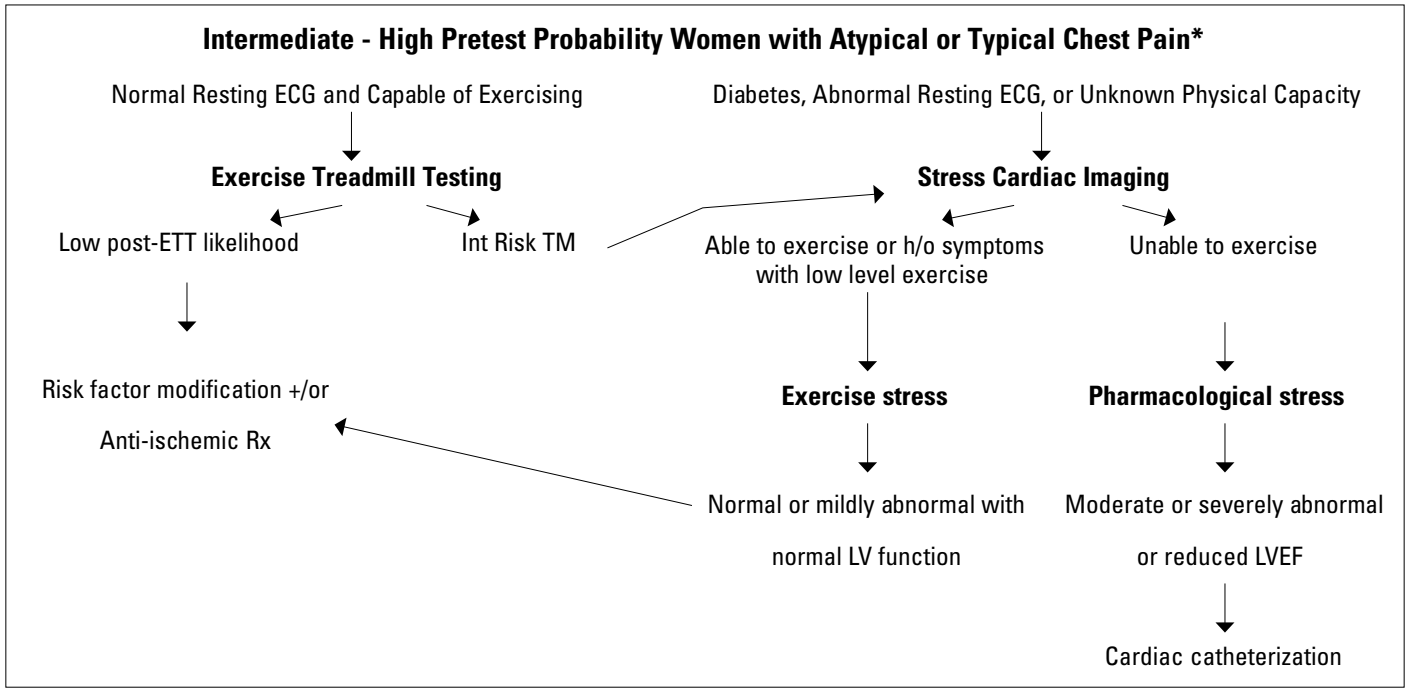

Figure 1. Algorithm for evaluation of symptomatic women using exercise ECG or cardiac imaging
*Pretest probability of CAD determined by age, sex, and symptoms.
The statement TM should be corrected as "ETT". ECG - electrocardiography; ETT - exercise treadmill test; LVEF - left ventricular ejection fraction; Rx - treatment

Advantages of cardiac MRI consist of no exposure to radiation and contrast media. However, the evidence for the differences due to safety and efficacy of either imaging modality among both genders is not adequate (8, 33). In a cohort of 103 subjects (51 women and 52 men), the diagnostic sensitivity and specificity of coronary CTA was similar by gender at 85% and 99%, respectively (34). In the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) study, coronary CTA revealed a sensitivity and specificity for demonstration of >50% stenosis of 95% and 83% and for >70% stenosis of 94% and 83% (35). In a subgroup analysis, both women and men did not differ in regard to detection of significant coronary stenosis. The only significant difference between the genders was in the positive predictive value of detecting a >70% stenosis, which was 77% in women and 90% in men. The negative predictive value was high (97%) for detection of both a >50% stenosis and a >70% stenosis in women and was same with men (36). Stress perfusion cardiac MRI also may take part in the evaluation of myocardial ischemia in women. Dobutamine cardiac MRI has shown to be a helpful noninvasive stress imaging tool for detection of stenotic CAD in women at risk, with a sensitivity of 85% and specificity of 86% (37). The advantages consist of absence of radiation exposure, increased diagnostic accuracy and no artifacts due to breast and diaphragmatic attenuation in compared to nuclear tests. These favourable advantages are especially important in assessment of microvascular disease and syndrome X, which were found more frequent in women (38, 39). WISE study including women with suspected myocardial ischemia in the absence of stenotic CAD revealed that the abnormal cardiac MRI stress test result by using phosphorus-31 nuclear was an important predictor of worse cardiovascular outcomes in women with chest pain. The test was capable of detecting women with persistent and worsening angina requiring unnecessary invasive angiography and hospitalization. These findings suggest that cardiac MRI may gain wide function in assessing women with chest pain, reduce the unnecessary coronary angiography and accelerates treatment before the ischemia worsens (40).

Recommendations

In symptomatic women with risk factors for CAD, physicians should initially assess the risk factors, symptoms and resting ECG to predict pretest probability of CAD. Additionally, functional capacity which was significantly associated with cardiovascular prognosis should be evaluated. Besides, functional capacity is also practical in selection of the appropriate noninvasive stress testing modality. Recent evidence endorses the use of the treadmill stress test as the initial test for the symptomatic women with a normal resting ECG and good physical capacity (capable of >5 METs).

Cardiac imaging by using modern SPECT myocardial perfusion imaging or stress echocardiography modalities ensures perfect diagnostic accuracy and risk stratification in symptomatic women with known or suspected CAD. In accordance with the recent AHA scientific document, symptomatic women with unknown physical capacity, an abnormal resting ECG, and diabetes mellitus, should undergo cardiac imaging with exercise or pharmacologic stress. In the context of an abnormal or equivocal stress cardiac imaging modalities, cardiac CTA can be used in accordance with the recent evidence. Cardiac MRI can be practical in assessing symptomatic women with no evidence of

stenotic CAD to investigate the subendocardial ischemia or abnormal coronary reserve. Figure 1 provides a diagnostic scheme based on current evidence for assessing symptomatic women at risk for CAD.

Conclusion

In conclusion, transitioning from a ''one size fits all'' model for the detection of CAD to an approach more tailored to risk prediction models and diagnostic tools should prove more effective at diagnosing CHD risk and hopefully lead to improved net health outcomes in women.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - N.Ö., U.C.; Design - N.Ö., U.C.; Supervision - N.Ö.; Data collection and/or processing - U.C.; Analysis and/or interpretation - N.Ö., U.C.; Literature search - N.Ö., U.C.; Writing - N.Ö., U.C.; Critical review - N.Ö.; Other - N.Ö.

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