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Provocative testing in women with suspected ischemic heart disease: an insight into daily clinical practice

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Summary. Ischemic heart disease (IHD) represents the major cause of death in women and early identification is crucial in evidence-based daily practice. An accurate pre-test risk assessment is required to identify the correct diagnostic pathway. In this setting a targeted choice of the best-matching index stress test plays a critical role in terms of both suitability and cost. Exercise electrocardiography (ECG) stress test represents the most widely available non-invasive method of diagnosing IHD in women. Because of good negative predictive value as well as the additional prognostic information, it should be the first-step test in a large number of symptomatic women. Stress imaging is represented especially by stress echocardiography (SE) and myocardial perfusion imaging (MPI). SE offers high diagnostic accuracy and is safe, with no significant gender differences. On the other hand, MPI allows some technical limitations of SE to be overcome by providing a slightly lower (SPECT) or slightly higher (PET) diagnostic accuracy in women, but radiation exposure and cost must be considered. Both SE and MPI offer an incremental prognostic value when compared to an exercise ECG stress test.

Key words: ischemic heart disease, coronary artery disease, women, risk, stress, exercise, electrocardiography, echocardiography, myocardial perfusion, imaging.

Test provocativi nella donna con sospetta cardiopatia ischemica: uno sguardo alla pratica clinica quotidiana

Riassunto. La cardiopatia ischemica (CI) è la più importante causa di morte della donna e la sua identificazione precoce è cruciale nella pratica quotidiana basata sull'evidenza. L'identificazione del percorso diagnostico corretto richiede un'accurata valutazione del rischio pre-test e la scelta mirata del miglior test provocativo indice è importante in termini di appropriatezza e di costi. L'elettrocardiogramma (ECG) da sforzo è il metodo non invasivo più diffuso nella diagnostica della CI nella donna. Grazie al suo buon valore predittivo negativo e alle informazioni prognostiche aggiuntive, tale test dovrebbe essere il primo step in una buona percentuale di pazienti sintomatiche. L'imaging da stress è rappresentato soprattutto da ecocardiografia da stress (ES) e imaging di perfusione (MPI). L'ES offre elevata accuratezza diagnostica e sicurezza senza significative differenze di genere. L'MPI invece permette di superare alcuni limiti tecnici dell'ES con un'accuratezza diagnostica di poco inferiore (SPECT) o superiore (PET), anche se l'esposizione radiologica ed i costi vanno tenuti in conto. Sia l'ES che l'MPI offrono un valore prognostico incrementale se confrontate con l'ECG da sforzo.

Parole chiave: cardiopatia ischemica, coronaropatia, donna, rischio, stress, sforzo, elettrocardiografia, ecocardiografia, perfusione miocardica, imaging.

1. Introduction

Ischemic heart disease represents the major cause of death in women, accounting for a third of all female deaths globally[1–3]. It affects 12.9 million women in Europe with an annual incidence of 2.7 million and nearly 855,000[4] deaths annually.

The term IHD describes a higher risk status associated with obstructive and non-obstructive coronary artery disease (CAD), including coronary microvascular dysfunction (CMD)[5]. Among patients with IHD, women experience relatively worse outcomes ranging from stable angina to acute coronary syndromes and heart failure, when compared with men. Early identification of women at risk for IHD is critical because sudden cardiac death contributes substantially to mortality in patients with and without obstructive CAD and is often the first manifestation of CAD in a significant proportion of patients[6-10].

In recent decades, gender equity in the evidence-based practice has been widely promoted to guide female-specific optimal management strategies for suspected and known IHD[5]. This has resulted in an impressive 30% decline in the number of women dying from cardiovascular disease[1,2].

Men and women share many "traditional" risk factors for IHD, but additional sex-based risk factors and different disease mechanisms have been shown recently to play an important role in women. There is also increasing evidence that biological differences may affect the expression of cardiovascular risk factors and modify their relative risk in women compared to men[11-13]. Common non-modifying risk factors in both genders are age, ethnicity and family history of ischemic heart disease at a young age. Among traditional risk factors, hypertension, diabetes mellitus and smoking seem to be more

potent risk factors for IHD in women than in men (odds ratio of 1.5, 1.6 and 1.3, respectively)[14]. Additionally, non-traditional cardiac risks unique to or predominant in women are early menopause or menarche, gestational diabetes mellitus, gestational hypertension, preeclampsia and eclampsia during pregnancy, systemic inflammatory disease and depression[1,15-18].

2. Pre-test risk assessment

Although chest pain can traditionally be classified as typical angina, atypical angina, or non-anginal chest pain, these definitions were derived from male-predominant populations[19-23].

Alternatively to the typical and most common symptomatic manifestations of myocardial ischemia, women may also describe atypical and non-chest-related pain symptoms that can be linked to a possible ischemic origin. Epigastric discomfort with nausea, dyspnea and/or fatigue, radiation of chest discomfort to arms, neck and interscapular areas can be considered ischemic equivalents in women. Compared with men, women's ischemic symptoms are additionally more often precipitated by mental or emotional stress and less frequently by physical exertion[5,24-28].

The non-specific clinical presentation complicates the evaluation of symptoms and a precise estimate of the pre-test probability of obstructive CAD can be difficult[22]. Consequently a more frequent referral for diagnostic testing is the most common clinical consequence in order to attempt to improve the IHD likelihood estimate[5,29]. Though, as defined by Bayesian theory, the post-test likelihood of disease is heavily influenced by a patient's pre-test risk estimate[30]. Therefore, as few women with a low pre-test likelihood of CAD have the disease, the result is only a slight shift from pre- to post-test assessment[31-33].

Given that IHD risk increases with age and is exacerbated in women with multiple risk factors or comorbidities[7-9,27,28,34], according to recent guidelines, the pre-test stratification of IHD risk refers to women who have chest pain symptoms (typical or atypical) or some suspected ischemic equivalent, including excessive dyspnea, with other cardiopulmonary comorbidities excluded[5,19,35].

According to the AHA consensus statement for clinical evaluation of women with suspected IHD[5], pre-menopausal women with symptoms should be considered at low risk, excluding those with diabetes mellitus. Symptomatic women over 50-years-old should be considered at low to intermediate IHD risk if they can perform routine activities of daily living (ADL). If this kind of activity is compromised, the patient is considered to be functionally limited. In this case a symptomatic woman in her 50s should be included in the intermediate IHD risk category. Symptomatic women over 60-years-old are considered at intermediate IHD risk and women ≥70 years old with ischemic symptoms are considered at high IHD risk. High-risk equivalent states (peripheral arterial disease, long-standing/poorly controlled diabetes mellitus in women aged >40 years) shift the patient's status into the high IHD risk category. Extensive comorbidity (in particular chronic obstructive lung disease, transient ischemic attacks or cerebrovascular accidents, chronic kidney disease), multiple risk factors or functional disability, elevate the IHD risk estimate by one category[5].

Pre-test risk categorization should be used to define the index diagnostic procedure through which further assessment of IHD risk is evaluated. Low-risk women are generally not candidates for further diagnostic testing. With some exceptions and according to a selective clinical judgement, a routine exercise ECG is the most appropriate test in women at low IHD risk. In case of low to intermediate or intermediate pre-test risk, an exercise ECG is indicated when rest ECG is normal (or at least interpretable) and functional capacity is normal. Women with intermediate to high IHD risk, mostly when the ECG at rest is abnormal (i.e. with resting ST-segment abnormalities), should be referred for provocative stress imaging (stress echocardiography or stress scintigraphy) or eventually for non-invasive imaging of the coronary arteries (coronary computed tomography angiography)[5]. Women at high IHD risk with stable symptoms should be directly referred for an invasive coronary angiography[35].

3. Exercise ECG stress test

Exercise electrocardiography (ECG) stress testing is the most commonly used and widely available method of diagnosing IHD in women and essentially the initial non-invasive exam of choice. According to ACC/AHA and ESC guidelines, bicycle or treadmill exercise stress testing (ETT) without imaging is the appropriate first-line testing for symptomatic women who[5,19,35,36]:

1. have an intermediate risk for IHD;
2. have a normal resting 12-lead ECG;
3. are capable of maximum exercise (i.e. routine ADL >5 METs; women who indicate difficulties in performing daily activities should be referred to pharmacological stress testing).

Basic reasons for using an exercise ECG without imaging as the index diagnostic procedure include[19,35,37]: good negative predictive value of exercise ECG; assessment of physical work capacity in functionally capable women; simplicity and widespread availability of this test.

I) Diagnostic criteria

The presence of IHD may be identified with ST-segment depression induced by exercise stress testing and interpreted as a sign of ischemia.

The hallmark of a positive test result is 1 mm or more of horizontal or downsloping ST-segment depression at 0.08 seconds after the J point that develops during or after exercise. ST-segment elevation >1 mm that develops in leads without Q waves occurs infrequently but also represents a positive test result[38]. T-wave changes such as inversion or pseudo-normalization when an inverted T-wave becomes upright are non-specific changes[39].

The exercise ECG is completely uninterpretable in the presence of left bundle branch block. The presence of right bundle branch block, low-degree non-specific intraventricular delay (QRS duration 100-120 ms) or non-specific resting ST-T abnormalities limits interpretability.

The leads that demonstrate ST depression do not accurately localize the site of myocardial ischemia. Moreover, standard stress testing does not accurately characterize the extent of ischemia and provides no direct information on other clinically important variables, such as left ventricular function[38].

II) Diagnostic accuracy

Exercise-induced ST-segment depression testing is well-known to be less accurate in identifying CAD in women than in men[40]. Differences in the accuracy of ST-segment depression for men and women may be explained by several factors (Table 1)[19,23,41-44].

Therefore, the use of traditional electrocardiography criteria for a positive ETT of ≥1 mm result in a consistent under-diagnosis of IHD in women. In a meta-analysis of 3721 women evaluated for IHD, positive ECG changes were shown to have a sensitivity and specificity in women of 61% and 70%, respectively, compared with men where both sensitivity and specificity were around 10% higher[9,45].

Table 1. Differences in accuracy of ST-segment depression in women.

1. Frequent baseline ST- and T-wave changes
2. More pronounced ST-segment depression with exercise testing
3. Digoxin-like effect on ST segments during exercise and increase the rate of exercise-induced ST-segment depression caused by estrogens (natural or pharmacological supply)
4. Variation in the extent of ST-segment depression during exercise in premenopausal women related to the menstrual cycle
5. Reduced exercise tolerance with a consequent decreased ability of the test to induce ischemia

The accuracy for detecting IHD depends also on the magnitude, morphology and duration of the ECG changes. Marked ST-segment changes (i.e. ≥2 mm horizontal or downsloping ST depression or ≥1 mm of ST-segment elevation in a non-Q-wave lead at low workloads and persisting into recovery for >5 minutes) have been shown to be more sensitive markers for critical CAD in women[5,46,47].

Although the diagnostic value of ST-segment depression with exercise is well-known, these same ECG changes did not prove to have significant prognostic value in women[40,48-50].

III) Prognostic value

A) Functional capacity

Exercise capacity, also known as functional capacity, is one of the most important prognostic markers that can be evaluated with exercise stress testing[51-56]. Exercise capacity is an estimate of the maximal oxygen uptake for a given workload and can be expressed in metabolic equivalents (METs)[57]. One MET is a unit of basal oxygen consumption and represents the consumption of 3.5 mL of oxygen per kilogram of body weight per minute (average adult). Poor exercise capacity has been shown to be an independent predictor of the presence of CAD in women[55,58], although it is not a diagnostic criterion.

Exercise capacity has strong prognostic implications in symptomatic women[48,59-61]. In a retrospective study of exercise stress testing in a symptomatic population of women, exercise capacity was the only exercise stress testing variable independent in predicting mortality. For every 1-MET increase in exercise capacity, there was a 25% reduction in risk of all-cause mortality and a 23% reduction in risk of cardiac events[60].

Exercise capacity has also been shown to be a strong independent predictor of all-cause mortality in asymptomatic women[48,59,62]. Women who achieve <5 METs are at an increased risk of death and related IHD events, independent of traditional cardiac risk factors[63,64]. Due to its strong prognostic value, the current recommendations[5] suggest incorporating fitness level into the interpretation of each exercise stress test.

B) Chronotropic response and heart rate recovery

The normal chronotropic response to exercise reflects the body's physiological requirement to increase cardiac output.

The peak heart rate (HR) achieved with maximal exercise testing is influenced by both age and gender[65,66]. A reduced HR response to exercise (or an abnormal chronotropic response) is defined as chronotropic incompe-

tence and is associated with poorer prognosis[66-69]. Measures of chronotropic response include the following:

1. peak HR, achieved with maximal exercise stress testing;
2. HR reserve (HRR) or change in HR with exercise (peak exercise HR minus resting HR);
3. ability to achieve at least 85% of the maximum age-predicted HR;
4. chronotropic index.

The last two parameters have been the most studied in women[40]. The achievement of 85% of age-predicted HR is the minimal requirement for the diagnostic significance of the test (otherwise the test may give a result of not evaluable[48,59,62]) and is not intended to be an endpoint of any stress test protocol[36,70].

In the diagnosis of IHD in women, inability to achieve 85% of the maximum age-predicted heart rate with exercise is associated with an increased likelihood of obstructive CAD[5,71].

The ability to reach target HR also has prognostic value in women. Lauer et al.[68] demonstrated that inability to achieve 85% of maximum age-predicted HR (defined as 220-age) was associated with decreased survival in both men and women.

Chronotropic index is another measure of chronotropic response that has relevant prognostic value[69,72]. It is defined as the ratio between HRR and metabolic reserve and in a healthy subject the chronotropic index is 1.0 because HRR and metabolic reserve are equal. An abnormal chronotropic index is defined as 0.80 and was shown to be an independent predictor of mortality[68]. Moreover, chronotropic index can account for differences in baseline resting HR and functional capacity[66,69] and for this reason it was shown to be a superior measure compared with the ability to achieve 85% of the maximum age-predicted HR in the prediction of cardiac death and all-cause mortality[67].

HR recovery, defined as peak HR achieved minus HR one minute into recovery, has been shown to have independent prognostic value in women. In a study that included 720 women who underwent exercise stress testing, 25% of them had an abnormal HR recovery (defined as a decrease in the HR of <12 bpm in the first minute of recovery) which resulted to be an independent predictor for all-cause mortality[64].

C) Blood pressure response

A hypotensive response to exercise, defined as a fall in systolic blood pressure of 10 mmHg, may reflect acute transient left ventricular dysfunction due to ischemia. Studies (involving predominantly male participants) demonstrated that a significant drop in systolic blood pressure with exercise may be a very specific marker of the presence of left main or severe triple-vessel CAD[73-75], particularly if ST-segment depression also occurs. Nevertheless, the diagnostic value of a drop in systolic blood pressure with exercise in women is uncertain. One study suggested that the specificity was lower in women because of the more frequent hypotensive response in women even in the absence of CAD[76], but other studies were unable to confirm this evidence[75].

In symptomatic populations, the relationship between a hypertensive response (≥190 mm Hg in women, ≥210 mm Hg in men) and risk of developing IHD remains conflicting[5,77,78].

D) Duke treadmill score (DTS)

The DTS, which was developed in 1987 by Mark et al.[79] is the most widely used of all risk scores in exercise stress testing and has diagnostic and prognostic value in both women and men. The use of the DTS in the interpretation of exercise stress testing is recommended in the current ACC/AHA guidelines for exercise stress testing[36]. The DTS includes exercise time (which is also a measure of exercise capacity), ST-segment depression, and the presence or absence of angina. DTS allows risk to be categorized into three categories: low, moderate and high risk. The DTS has been shown to have diagnostic value and to be an excellent prognostic tool in symptomatic women as well as men. A low DTS is associated with an annual mortality rate of ≈0.25% in contrast to an annual mortality rate of ≈5% in those with a high-risk DTS, with lower mortality rates among women than men[40,46,79-81].

4. Stress echocardiography

In intermediate pre-test probability for IHD, current guidelines[35] and consensus statements for the clinical evaluation of women with suspected IHD[5] emphasize the use of non-invasive imaging in women because of its significantly higher diagnostic accuracy.

Conducting pharmacological stress echocardiography (SE) should be the diagnostic test of choice in cases of[35,82]:

1. uninterpretable resting ECG (left bundle branch block);
2. less interpretable resting ECG (right bundle branch block, low-degree non-specific intraventricular delay, non-specific resting ST-T abnormalities);
3. conditions lowering the interpretability of the ECG during exercise stress (female gender, repolarization abnormalities on ECG under resting conditions or after hyperventilation, and the need to continue drugs such as digitalis or antiarrhythmics that potentially induce ST-segment and T-wave changes);
4. non-diagnostic/ambiguous result of exercise ECG;
5. intermediate to high pre-test probability (if local expertise and availability permit);
6. reduced left ventricular ejection fraction (EF <50%) without typical angina;

When feasible, exercise SE should be the test of choice[35]. Exercise provides a more physiological environment than pharmacological tests and provides supplementary data (functional capacity, heart rate response, blood pressure response and ECG changes) that offer additional diagnostic and prognostic information[35,60]. Nowadays it is performed using a tilt-table ergometer.

For patients in whom the exercise stress test is contraindicated (severe arterial hypertension) or not feasible (inability to exercise), pharmacological stress testing may be performed, with dobutamine or with a vasodilator (dipyridamole or adenosine). Dobutamine has an inotropic effect on the myocardium by acting as a direct β1 stimulant, consequently increasing oxygen demand and causing an ischemic response where an imbalance with blood supply occurs. Conversely, thanks to vasodilation and the subsequent increased blood flow into non-critical or healthy coronary vessels, dipyridamole and adenosine favor a steal phenomenon on the stenosed epicardial arteries that results in ischemia. Both dipyridamole and dobutamine have good overall tolerance and feasibility.

Combining ultrasound imaging with stress testing, SE has the diagnostic aim of inducing a transient ischemic change in regional function of the left ventricle. Thus myocardial ischemia is identified as reduced segmental wall motion during stress and real-time data on left ventricular global and regional systolic function, as well as the extent of stress-induced myocardial ischemia is therefore easily provided[82]. The most common limitation of this technique is the poor acoustic window (if >2 segments cannot be adequately viewed at rest), significantly decreasing accuracy. This problem can be easily overcome to obtain diagnostic-quality images by using intravenous contrast, obtaining greater than 97% feasibility[35,83].

I) Diagnostic criteria

For the assessment of regional LV function, the ventricle is divided into myocardial segments. Segmentation diagrams reflect coronary perfusion territories, result in segments with comparable myocardial mass and allow standardized communication with other imaging methods. Accordingly, a 17-segment model is commonly used[84].

All stress echocardiographic diagnoses can be summarized into four response patterns centered on regional wall function at rest and then during stress[85] (Table 2):

- normal response (no variation in contractility);
- ischemic response (worsening contractility during stress from normokinesia to hypokinesia, akinesia or dyskinesia);
- necrotic response (no increase in contractility in an akinetic segment);
- viability response (increase in contractility in an akinetic segment; both dobutamine and vasodilators, as well as exercise, exploit the same pathophysiological principle: a contractile reserve can be evoked by an inotropic challenge, either using catecholamines or flow-mediated[86]) suggestive of a non-jeopardized myocardium (hibernating).

II) Diagnostic accuracy

Two meta-analyses of 55 studies and of 5 studies, respectively, compared the accuracy of SE using the different stressors available in clinical practice (exercise, dobutamine, dobutamine plus atropine, dipyridamole, dipyridamole plus atropine, adenosine)[87,88] (Table 2). Exercise SE was shown to be the most balanced test with sensitivity of 83% and specificity of 84%. Dobutamine plus atropine and dipyridamole plus atropine showed higher sensitivity (84%), whereas the highest specificity was achieved by dipyridamole (95%).

Another meta-analysis evaluating the diagnostic accuracy of dobutamine SE showed that the sensitivities for detecting one-, two-, and three-vessel(s) coronary artery disease were 74%, 86%, and 92%, respectively. Furthermore, the sensitivity for detection of disease in the left circumflex coronary artery was lower (55%), compared with the left anterior descending (72%) and right coronary arteries (76%)[89]. Similar data has been reported for exercise echocardiography[90]. The higher prevalence of single-vessel CAD among women may potentially impact the diagnostic accuracy of SE in women and contribute to false-negative results[91], although some other meta-analyses showed that gender does not impact the accuracy of SE[92-94].

The positive predictive value (PPV) for SE is, however, lower in women than men, although the sensitivities and specificities are comparable[95]. The lower PPV is consistent with the lower prevalence of obstructive epicardial CAD in women[8,96]. Furthermore, compared with men, a higher rate of false-positive SE result has been reported in women[97]. This later observation may be ex-

Table 2. Diagnostic accuracy of echocardiographic stressors in women.

Stressor	Sensibility (%)	Specificity (%)
Exercise	83	84
Dobutamine	81	84
Dobutamine + atropine	84	92
Dipyridamole	72	95
Dipyridamole + atropine	84	87
Adenosine	79	91

plained by the presence of gender-specific differences in IHD pathophysiology[93].

The choice of one test over the other depends on patient characteristics, local availability and the physician's preferences. Antianginal drug therapy significantly affects the diagnostic accuracy of all forms of stress; therefore, it is recommended, whenever possible, to withhold it at the time of testing to avoid a false-negative result[85,98].

In women, SE provides similar sensitivity but a better specificity as compared to MPI[99]. The choice of an imaging test in this setting should take into account the radiation burden, particularly in young women[82]. Additionally, SE may be especially useful for the sub-population of women who may have a high incidence of false-positive results with other non-invasive evaluations[100].

III) Prognostic value

A normal stress echocardiogram yields an annual risk of 0.4-0.9%[101], the same as for a normal stress myocardial perfusion scan. In symptomatic women, a normal test is associated with <1% event-rate at 3 years of follow-up[102]. Thus in women with suspected IHD, the excellent prognosis related to a normal SE allows coronary angiography to be safely avoided.

On the opposite end, a positive SE response in women has a high and increasingly negative prognostic value compared to clinical, rest echocardiographic and exercise ECG data[103]. Moreover, in women with abnormal SE, not only the presence of abnormality, but also the extent of wall motion abnormalities (WMA), left ventricular dilation, decrease in systolic function at maximal stress and a low threshold at which ischemia develops all predict an unfavorable outcome[90,93]. In particular, presence of stress ischemia affecting >4-5 segments, evidence of multi-vessel ischemia, resting WMA with remote ischemia, decrease in stress EF and/or increase in end-systolic volume indicate >4-fold increased risk of a cardiac event compared to low-risk women[93].

When compared with men, the prognostic value of stress echocardiography in women is similar[104], but in the presence of SE myocardial ischemia the female gender is an independent and adjunctive predictor of cardiac events[94].

IV) Coronary flow reserve

More than half of women who attend for coronary angiography due to suspected angina do not have significant coronary stenosis, but they still have increased risks of future cardiovascular events[8,28,105]. CMD has been recently considered as the primary pathophysiological explanation for women symptomatic for angina without critical epicardial CAD[106]. In this specific setting the clinical utility of traditional stress echocardiography is limited[107].

In the last two decades, the evaluation of coronary flow reserve (CFR) by combining transthoracic Doppler assessment of coronary flow velocities with vasodilator stress, which has shown to have a diagnostic and prognostic role, has been increasingly developed and introduced into clinical practice.

Impaired CFR during dipyridamole stress testing was detected in almost one third of 919 symptomatic women without significant CAD. CFR was shown to be an independent parameter in the risk evaluation of these women, not being associated with other cardiovascular risk factors and suggesting that coronary microvascular dysfunction plays a role in the development of angina pectoris[108].

The use of CFR therefore offers additional diagnostic value over conventional wall motion analysis[82], but its use as a stand-alone method is limited by two relevant factors. Firstly, only the left anterior descending artery is sampled with a very high success rate. Secondly, Doppler CFR is not able to distinguish between microvascular and macrovascular critical coronary disease. For these reasons, Doppler CFR usually needs to be accompanied by a dipyridamole SE.

CFR of left anterior descending artery has moreover revealed to be a strong and independent indicator of mortality, giving incremental prognostic value over wall motion analysis[109]. CFR yields useful prognostic information also in the specific subset of normal or near normal coronary arteries[110,111]. Finally, a negative stress echocardiography result with a normal CFR confers an annual risk of death <1%[109].

Current guidelines therefore recommend the routine application of CFR to perform dual imaging (flow and function) when a vasodilator stressor is used[82,85].

5. Stress myocardial perfusion imaging

The diagnostic evaluation of symptomatic women with intermediate or intermediate to high IHD risk can also be performed using stress myocardial perfusion imaging (MPI), especially in the case of abnormal rest ST-segment changes or functional disability[5,35,112].

Exercise and pharmacological stress gated myocardial perfusion imaging (MPI) can be performed with single-photon emission computed tomography (SPECT) imaging or with positron emission tomography (PET) imaging. Stress MPI allows the extent and severity of rest and stress myocardial perfusion to be accurately defined by directly viewing them[5,113].

Women capable of maximal exercise should undergo an exercise MPI due to the well-known pathophysiological advantages. Alternatively a pharmacological stress

test with a vasodilator agent (i.e. dipyridamole, adenosine or regadenoson) can easily be performed[5].

As MPI with SPECT and PET involve exposure to non-ionizing radiation, recommendations by the ACC appropriate use criteria must be strictly followed in the selection of women on whom to use these techniques[114-116], in order to reduce unnecessary testing and consequent radiation exposure.

It is preferable to optimize the use of isotopes with lower radioactivity, including resting/stress 99m Tc SPECT (effective dose, ≅12 mSv) or resting/stress 82 Rb PET (effective dose, ≅3 mSv)[117]. Recent projected estimates in women report a small increase in cancer risk after exposure to ionizing radiation with MPI[118,119]. Cancer risk after exposure to ionizing radiation varies with age and is related to life expectancy and the latency period for oncogenesis[120]. Thus, the use of MPI in premenopausal women, who would have a higher than expected risk when compared with elderly women[113], should be minimized.

A) SPECT

The most commonly performed imaging procedure in nuclear cardiology is MPI SPECT imaging and there is strong evidence of its utility in women[5,9,19,27,37,121-124].

After injection of the chosen radiotracer, the isotope is extracted from the blood by viable myocytes and retained within the myocyte for some time. Photons are emitted from the myocardium in proportion to the magnitude of tracer uptake (i.e. perfusion). A multi-detector gamma camera system acquires tomographic ECG-gated images of single emitted photons. The final result of SPECT imaging is the creation of multiple slices of the left ventricle representing radiotracer distribution in stress and rest phases[125,126].

^{201}Tl, ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are the most commonly used myocardial perfusion imaging tracers.

I) Diagnostic criteria

As for echocardiography, SPECT MPI also uses the 17-segment model of the left ventricle[127]. Segmental radiotracer activity in rest and stress scans is scored as follows: 0-normal; 1-mild; 2-moderate; 3-severe; 4-absent. Segmental scores within the stress and rest scans are added together to generate summed stress scores (SSS) and summed rest scores, respectively. The summed difference score (SDS) is calculated from the sum of the segmental difference scores between stress and rest scans. Abnormal MPI is defined as SSS ≥4, while stress-induced ischemia is defined as SDS ≥2[128,129]. A myocardial mass distribution of 35%, 35%, and 30% is considered respectively for the basal, mid-cavity and apical thirds of the heart[127].

A quantitative post-stress gated-SPECT left ventricular ejection fraction (LVEF) of <50% is considered abnormal[128].

II) Diagnostic accuracy

Traditional limitations of SPECT (in particular photon attenuation due to breast attenuation artefact and limited spatial resolution with undetected minor perfusion defects in smaller hearts) reduced its diagnostic accuracy in women, particularly when obese or with large breasts. In recent decades, continuous technical advances including novel high-speed SPECT cameras, ECG gating, attenuation correction protocols, use of prone imaging, and use of higher-energy radioisotope technetium have significantly improved image quality and reduced radiation exposure[112,130-132].

SPECT MPI now offers high diagnostic accuracy for detection of physiologically significant CAD. The sensitivity of contemporary SPECT MPI exercise techniques in women ranges from 78% to 88%, with a specificity of 61% to 91%[37,112]. Vasodilator stress has a reported sensitivity of 85% to 93% and specificity of 78% for detecting critical coronary artery stenosis[112,133].

Despite a high sensitivity of 90% to 94% in detecting the presence of significant CAD (i.e. at least one significant stenosis) in patients with multi-vessel coronary disease, however, conventional SPECT imaging has a limited sensitivity of 60% to 76% for detecting isolated significant single-vessel disease and identifying correctly the extent of critical coronary artery disease[134-136] (Table 3). The presence of critical diffuse disease in all three coronary vessels may decrease the sensitivity for

Table 3. Sensitivity of dobutamine SE and adenosine SPECT for detection of CAD by number and type of critical-diseased vessels.

Number/ type of critical vessel(s)	Dobutamine SE sensibility* (%)	SPECT sensibility* (%)	SPECT sensibility in women (%)
1 vessel	74	72	60-76
2 vessels	86	95	90-94
3 vessels	92	94	
LAD	72	83	n.r.
LCX	55	72	
RCA	76	75	

*both genders; SE: stress echocardiography; SPECT: single-photon emission computed tomography; CAD: coronary artery disease; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; n.r.: not reported.

each individual vessel, and a "balanced ischemia" may mask the presence of disease altogether[137-140].

In addition to perfusion, MPI also allows the evaluation of segmental kinesis and ejection fraction, but accuracy is significantly lower when compared with echocardiography.

III) Prognostic value

The excellent prognostic accuracy of exercise and pharmacological stress MPI in women with incremental value over clinical variables, ECG data, and LVEF in symptomatic women at risk of IHD has been demonstrated[112,141]. The size and severity of SPECT perfusion defects relate directly to the annual risk of a cardiac event, independently of sex[112,142,143]. High-risk stress MPI markers include a summed stress score >8, ≥10% of abnormal myocardium at stress, left ventricular dilation, and peak stress or post-stress LVEF ≤45%[5]. In a study of 2225 women, abnormal SPECT MPI was associated with a threefold increase in death rate compared to normal scans[141]. In contrast, a normal SPECT MPI predicts an excellent prognosis, with 99% event-free survival in both genders[144].

B) PET

PET imaging differs from conventional radionuclide imaging because it uses radionuclides that decay with positron emission. When the positron interacts with an electron the two undergo mutual annihilation, resulting in the production of two photons, 180° apart from each other. PET imaging consists of detection of these photons in coincidence and offers high-quality sequential images[138].

The widespread use of PET MPI has, however, been limited by the shortcomings of the current perfusion tracers (^{15}O water, ^{13}N ammonia, ^{82}Rb, ^{18}F-FDG, C-11 acetate). The availability of these tracers is limited by the need for an on-site or nearby cyclotron or commitment to costly generators. Owing to the short half-lives, their use in conjunction with treadmill exercise stress testing is either not possible or not practical[145]. For this reason vasodilator stress agents like dipyridamole or adenosine are commonly used[138].

I) Diagnostic criteria

The assessment of myocardial perfusion follows the same criteria for SPECT MPI[129].

II) Diagnostic accuracy

Stress myocardial perfusion PET has several advantages over the more commonly performed SPECT imaging in women[6,116]:

1. improved spatial and temporal resolution;
2. high diagnostic and prognostic accuracy[146-149];
3. segmentation of sub-epicardial and epicardial perfusion;
4. quantification of absolute myocardial blood flow (MBF) and CFR[150].

Table 4. Diagnostic accuracy of myocardial perfusion imaging techniques in women.

Technique	Sensibility (%)	Specificity (%)
Exercise SPECT	78-88	61-91
Vasodilator SPECT	85-93	78
Vasodilator PET	90	89

Recent meta-analyses have confirmed incremental improvement in diagnostic accuracy with PET compared to SPECT for the diagnosis of obstructive CAD[151,152] (Table 4), with an average sensitivity of 90% and specificity of 89% for detecting angiographically significant coronary stenosis (vs. 78%-93% and 61%-99% with SPECT, respectively)[116,152,153]. Moreover, no gender difference in diagnostic accuracy emerged[153].

III) Prognostic value

Data from over 7000 patients (47% women) demonstrates that a normal PET scan is associated with excellent prognosis and the extent and severity of perfusion defects provide valuable risk stratification of patients with suspected IHD[112,154-156]. Specifically, a normal PET indicated low risk, whereas an abnormal scan indicated worsening prognosis (<1% vs 4.2% annual cardiac event rate)[112,116]. This data reveals a similar prognostic pattern with PET and SPECT, although no formal comparison has been made[6].

IV) Coronary flow reserve

PET CFR measures absolute MBF into the perfused myocardium and is affected by the extent and severity of atherosclerotic plaque within the epicardial coronary arteries, arterial remodeling and CMD. In patients with a reduced CFR, the frequency of non-obstructive CAD is greater in women, whereas obstructive CAD is more common in men[157]. A PET CFR of two or lower is a consistent threshold of higher adverse events[158,159]. In short-term follow-up of 1 year, a higher hazard ratio (≅5) for a reduced CFR suggests a temporal relationship to CAD events[158].

Importantly, there is a synergistic relationship among ischemia severity, CFR and major CAD events. In patients with ischemia, a reduced CFR doubles their CAD death rate[159,160].

V) Assessment of viable myocardium

Whereas a normal, non-ischemic, myocardium uses both fatty acids and glucose to meet its energy needs, glucose is the major energy source for an ischemic myocardium. Fluorine-^{18}fluorodeoxyglucose (^{18}F-FDG), a radiolabeled glucose analogue, is the most commonly used PET tracer to identify hibernating myocardium. Hibernating myocardium is viable, but ischemic and dysfunctional, and a potential functional improvement can occur with appropriate treatment. ^{18}F-FDG PET imaging is highly sensitive in detecting viable hibernating myocardium and has the highest sensitivity in predicting the recovery of regional function after revascularization[161-164]. The mean sensitivity and specificity ^{18}F-FDG PET for the prediction of improvement in regional function after revascularization are 92% and 63%, respectively[161].

Carbon-11 acetate (C-11 acetate) is a PET tracer for measuring oxidative metabolism and has the advantage of evaluating both viability and perfusion. Myocardial oxidative metabolism is required to support contractile function under physiologic conditions and its maintenance is required for subsequent functional recovery in case of an hibernating myocardium salvaged by reperfusion[165-167]. In patients with acute myocardial infarction, measurements of myocardial oxidative metabolism by C-11 acetate predicted more accurately myocardial functional recovery after coronary revascularization when compared to ^{18}F-FDG PET[168,169].

6. Conclusions

Despite new pathophysiological knowledge, increased medical gender equity and advancements in non-invasive diagnostic techniques, the evaluation of women with suspected IHD still remains a subtle field in which provocative testing plays an intricate role. The combination of pitfalls involving atypical symptomatology, growing cost of healthcare and clinical suitability may complicate the correct diagnostic approach.

An accurate pre-test risk stratification in women is the fundamental basis for a cost-effective and rational first step into the diagnostic pathway of IHD.

Current recommendations[5,6,35,36] strongly highlight the central role of exercise ECG stress testing as an index test, not only due to its low cost and the widespread availability, but also because it offers an excellent negative predictive value and an additional body of prognostic information. The lower diagnostic sensitivity of exercise ECG stress testing in women is well-known but should not be assumed to justify a shift to stress imaging without critical analysis. According to guidelines, stress imaging should be used as the first choice only in specific settings (functional disability, expected non-interpretable exercise ECG, intermediate to high pre-test probability).

Thanks to its high accuracy, feasibility and safety, SE represents to date the most used method of stress imaging in women worldwide. The possibility of evaluating CFR as well offers a complete non-invasive assessment of IHD, rapidly available and potentially accessible in every echo lab. On the other hand, beyond higher cost, use of radiotracers and limited local availability, MPI still plays an important role as an alternative to SE in specific circumstances, such as extremely poor acoustic windows due to obesity, large breasts or lung disease, evaluation of absolute CFR, precise definition of viable myocardium.

Therefore, the best way to improve both the diagnostic process and the prognostic categorization of women with suspected IHD is to provide a customized approach that considers the personalized pattern of advantages and disadvantages of every provocative test in each single patient.

Key messages

- Ischemic heart disease represents the major cause of death in women, accounting for a third of all female deaths globally.
- An accurate pre-test risk stratification in women is the fundamental basis for a cost-effective and rational first step into the diagnostic pathway of ischemic heart disease.
- Exercise ECG stress testing should be the main diagnostic procedure in intermediate-risk symptomatic women because of its good negative predictive value, ability to assess physical work and widespread availability.
- Stress echocardiography offers high accuracy, safety and widespread availability with no significant diagnostic differences between genders.
- Myocardial perfusion imaging plays a fundamental role as an alternative to stress echocardiography especially in cases of extremely poor acoustic windows due to obesity, large breasts or lung disease.

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