53 **Review**

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 855,000⁴ 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 patients⁶⁻¹⁰.

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 IHD⁵. This has resulted in an impressive 30% decline in the number of women dying from cardiovas-cular 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 men¹¹⁻¹³. 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 populations¹⁹⁻²³.

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 difficult²². 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 posttest likelihood of disease is heavily influenced by a patient's pre-test risk estimate³⁰. 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 assessment³¹⁻³³.

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 pretest 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 IHD⁵, 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 \geq 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 category⁵.

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 angiography³⁵.

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;
- 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 result³⁸. T-wave changes such as inversion or pseudo-normalization when an inverted T-wave becomes upright are non-specific changes³⁹.

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 function³⁸.

II) Diagnostic accuracy

Exercise-induced ST-segment depression testing is wellknown to be less accurate in identifying CAD in women than in men⁴⁰. 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

 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)

 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

women of 61% and 70%, respectively, compared with men where both sensitivity and specificity were around 10% higher^{9,45}.

The accuracy for detecting IHD depends also on the magnitude, morphology and duration of the ECG changes. Marked ST-segment changes (i.e. $\geq 2 \text{ mm}$ horizontal or downsloping ST depression or $\geq 1 \text{ mm}$ 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 testing⁵¹⁻⁵⁶. 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 events⁶⁰.

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 recommendations⁵ 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 prognosis⁶⁶⁻⁶⁹. Measures of chronotropic response include the following:

- 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 agepredicted HR;
- 4. chronotropic index.

The last two parameters have been the most studied in women⁴⁰. 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 mortality⁶⁸. 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 mortality⁶⁷.

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 mortality⁶⁴.

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 CAD⁷³⁻⁷⁵, 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 CAD⁷⁶, but other studies were unable to confirm this evidence⁷⁵.

In symptomatic populations, the relationship between a hypertensive response (\geq 190 mm Hg in women, \geq 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 testing³⁶. 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 guidelines³⁵ and consensus statements for the clinical evaluation of women with suspected IHD⁵ 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}:

- uninterpretable resting ECG (left bundle branch block);
- less interpretable resting ECG (right bundle branch block, low-degree non-specific intraventricular delay, non-specific resting ST-T abnormalities);
- 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;
- intermediate to high pre-test probability (if local expertise and availability permit);
- reduced left ventricular ejection fraction (EF <50%) without typical angina;

When feasible, exercise SE should be the test of choice³⁵. 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}. Now-adays 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 β 1 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 provided⁸². 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 used⁸⁴.

All stress echocardiographic diagnoses can be summarized into four response patterns centered on regional wall function at rest and then during stress⁸⁵ (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-mediated⁸⁶) suggestive of a non-jeopardized myocardium (hibernating). 57

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 echocardiography⁹⁰. The higher prevalence of single-vessel CAD among women may potentially impact the diagnostic accuracy of SE in women and contribute to false-negative results⁹¹, although some other meta-analyses showed that gender does not impact the accuracy of SE⁹²⁻⁹⁴.

The positive predictive value (PPV) for SE is, however, lower in women than men, although the sensitivities and specificities are comparable⁹⁵. 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 women⁹⁷. This later observation may be ex-

 Table 2. Diagnostic accuracy of echocardiographic stressors in women.

 Stressor
 Sensibility (%)

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 pathophysiology⁹³.

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 MPI⁹⁹. The choice of an imaging test in this setting should take into account the radiation burden, particularly in young women⁸². 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 evaluations¹⁰⁰.

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 followup¹⁰². 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 data¹⁰³. 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 women⁹³.

When compared with men, the prognostic value of stress echocardiography in women is similar¹⁰⁴, but in the presence of SE myocardial ischemia the female gender is an independent and adjunctive predictor of cardiac events⁹⁴.

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 CAD¹⁰⁶. In this specific setting the clinical utility of traditional stress echocardiography is limited¹⁰⁷.

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 pectoris¹⁰⁸.

The use of CFR therefore offers additional diagnostic value over conventional wall motion analysis⁸², 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 analysis¹⁰⁹. 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 performed⁵.

As MPI with SPECT and PET involve exposure to nonionizing radiation, recommendations by the ACC appropriate use criteria must be strictly followed in the selection of women on whom to use these techniques¹¹⁴⁻¹¹⁶, 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, $\cong 12$ mSv) or resting/stress 82 Rb PET (effective dose, $\cong 3$ 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 oncogenesis¹²⁰. Thus, the use of MPI in premenopausal women, who would have a higher than expected risk when compared with elderly women¹¹³, 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}.

²⁰¹Tl, ^{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 17segment model of the left ventricle¹²⁷. 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 \geq 4, while stress-induced ischemia is defined as SDS \geq 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 heart¹²⁷. A quantitative post-stress gated-SPECT left ventricular ejection fraction (LVEF) of <50% is considered abnormal¹²⁸.

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 disease¹³⁴⁻¹³⁶ (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 adenosineSPECT 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	00.04	
3 vessels	92	94	90-94	
LAD	72	83		
LCX	55	72	n.r.	
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 altogether¹³⁷⁻¹⁴⁰.

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

60

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 scans¹⁴¹. In contrast, a normal SPECT MPI predicts an excellent prognosis, with 99% event-free survival in both genders¹⁴⁴.

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 images¹³⁸.

The widespread use of PET MPI has, however, been limited by the shortcomings of the current perfusion tracers (¹⁵O water, ¹³N ammonia, ⁸²Rb, ¹⁸F-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 practical¹⁴⁵. For this reason vasodilator stress agents like dipyridamole or adenosine are commonly used¹³⁸.

I) Diagnostic criteria

The assessment of myocardial perfusion follows the same criteria for SPECT MPI¹²⁹.

II) Diagnostic accuracy

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

 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

- 1. improved spatial and temporal resolution;
- 2. high diagnostic and prognostic accuracy¹⁴⁶⁻¹⁴⁹;
- segmentation of sub-epicardial and epicardial perfusion;
- quantification of absolute myocardial blood flow (MBF) and CFR¹⁵⁰.

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 emerged¹⁵³.

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 made⁶.

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 men¹⁵⁷. 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 events¹⁵⁸.

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-18fluorodeoxyglucose (18F-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. ¹⁸F-FDG PET imaging is highly sensitive in detecting viable hibernating myocardium and has the highest sensitivity in predicting the recovery of regional function after revascularization¹⁶¹⁻¹⁶⁴. The mean sensitivity and specificity ¹⁸F-FDG PET for the prediction of improvement in regional function after revascularization are 92% and 63%, respectively¹⁶¹.

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 reperfusion¹⁶⁵⁻¹⁶⁷. 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 ¹⁸F-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.

References

- 1. Aggarwal NR, Patel HN, Mehta LS, et al. Sex differences in ischemic heart disease: advances, obstacles, and next steps. Circ Cardiovasc Qual Outcomes 2018; 11 (2): e004437.
- 2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017; 135 (10): e146-e603.
- Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. BMJ Glob Heal 2017; 2 (2): e000298.
- 4. Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: cardiovascular disease statistics 2017. Eur Heart J 2018; 39 (7): 508-79.
- Mieres JH, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. Circulation 2014; 130 (4): 350-79.
- Baldassarre LA, Raman SV, Min JK, et al. Noninvasive imaging to evaluate women with stable ischemic heart disease. JACC Cardiovasc Imaging 2016; 9 (4): 421-35.
- Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and prognostic implications of stable angina pectoris among women and men. JAMA 2006; 295 (12): 1404.
- 8. Shaw LJ, Shaw RE, Merz CNB, et al. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. Circulation 2008; 117 (14): 1787-801.
- 9. Shaw LJ, Bugiardini R, Merz CNB. Women and ischemic heart disease. J Am Coll Cardiol 2009; 54 (17): 1561-75.
- Davis MB, Maddox TM, Langner P, Plomondon ME, Rumsfeld JS, Duvernoy CS. Characteristics and outcomes of women veterans undergoing cardiac catheterization in the Veterans Affairs Healthcare System: insights from the VA CART Program. Circ Cardiovasc Qual Outcomes 2015; 8 (2 Suppl 1): S39-47.
- Wenger NK. Women and coronary heart disease: a century after Herrick: understudied, underdiagnosed, and undertreated. Circulation 2012; 126 (5): 604-11.
- Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: the Women's Heart Alliance. J Am Coll Cardiol 2017; 70 (2): 123-32.
- 13. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation 2016; 133 (9): 916-47.
- 14. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937-52.
- 15. Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying prema-

ture cardiovascular events in rheumatologic conditions. Eur Heart J 2015; 36 (8): 482-9.

- Tooher J, Thornton C, Makris A, Ogle R, Korda A, Hennessy A. All hypertensive disorders of pregnancy increase the risk of future cardiovascular disease novelty and significance. Hypertension 2017; 70 (4): 798-803.
- 17. Tobias DK, Stuart JJ, Li S, et al. Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. JAMA Intern Med 2017; 177 (12): 1735-42.
- Lubiszewska B, Kruk M, Broda G, et al. The impact of early menopause on risk of coronary artery disease (Premature Coronary Artery Disease in Women – PRECADIW case-control study). Eur J Prev Cardiol 2012; 19 (1): 95-101.
- 19. Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation 2005; 111 (5): 682-96.
- Pryor DB, Shaw L, McCants CB, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. Ann Intern Med 1993; 118 (2): 81-90.
- Pryor DB, Shaw L, Harrell FE, et al. Estimating the likelihood of severe coronary artery disease. Am J Med 1991; 90 (5): 553-62.
- 22. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979; 300 (24): 1350-8.
- 23. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing. Correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 1979; 301 (5): 230-5.
- Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2004; 109 (5): 672-93.
- 25. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update: a guideline from the American Heart Association. Circulation 2011; 123 (11): 1243-62.
- Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation 2011; 124 (19): 2145-54.
- 27. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol 2006; 47 (3 Suppl): S4-S20.
- 28. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and mac-

63

rovascular and microvascular coronary disease. J Am Coll Cardiol 2006; 47 (3 Suppl): S21-9.

- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol 2012; 60 (24): e44-e164.
- Diamond GA. Off Bayes: effect of verification bias on posterior probabilities calculated using Bayes' theorem. Med Decis Making 1992; 12 (1): 22-31.
- 31. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996; 334 (20): 1311-5.
- 32. Douglas PS. Is noninvasive testing for coronary artery disease accurate? Circulation 1997; 95 (2): 299-302.
- Hunink MGM, Begg CB. Diamond's correction method-a real gem or just cubic zirconium? Med Decis Mak 1991; 11 (3): 201-3.
- 34. Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation 2011; 124 (22): 2423-32.
- Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013; 34 (38): 2949-3003.
- 36. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002; 106 (14): 1883-92.
- 37. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation 2011; 124 (11): 1239-49.
- Mayo Clinic Cardiovascular Working Group on Stress Testing. Cardiovascular stress testing: a description of the various types of stress tests and indications for their use. Mayo Clin Proc 1996; 71 (1): 43-52.
- Banerjee A, Newman DR, Van den Bruel A, Heneghan C. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. Int J Clin Pract 2012; 66 (5): 477-92.
- 40. Kohli P, Gulati M. Exercise stress testing in women: going back to the basics. Circulation 2010; 122 (24): 2570-80.
- Cumming GR, Dufresne C, Kich L, Samm J. Exercise electrocardiogram patterns in normal women. Br Heart J 1973; 35 (10): 1055-61.
- Higgins JP, Higgins JA. Electrocardiographic exercise stress testing: an update beyond the ST segment. Int J Cardiol 2007; 116 (3): 285-99.
- Morise AP, Beto R. The specificity of exercise electrocardiography in women grouped by estrogen status. Int J Cardiol 1997; 60 (1): 55-65.

- 44. Grzybowski A, Puchalski W, Zieba B, et al. How to improve noninvasive coronary artery disease diagnostics in premenopausal women? The influence of menstrual cycle on ST depression, left ventricle contractility, and chest pain observed during exercise echocardiography in women with angina and normal coronary angiogram. Am Heart J 2008; 156 (5): 964.
- 45. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999; 83 (5): 660-66.
- 46. Alexander KP, Shaw LJ, Shaw LK, Delong ER, Mark DB, Peterson ED. Value of exercise treadmill testing in women. J Am Coll Cardiol 1998; 32 (6): 1657-64.
- 47. Vavas E, Hong SN, Henry S, Rosen SE, Mieres JH. Imaging Tests, Provocative Tests, Including Exercise Testing in Women with Suspected Coronary Artery Disease. Curr Cardiovasc Risk Rep 2012; 6 (5): 469-78.
- Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise Capacity and the Risk of Death in Women: The St James Women Take Heart Project. Circulation 2003; 108 (13): 1554-9.
- 49. Gulati M, Arnsdorf MF, Shaw LJ, et al. Prognostic value of the duke treadmill score in asymptomatic women. Am J Cardiol. 2005; 96 (3): 369-75. doi: 10.1016/j.amjcard.2005.03.078
- 50. Gordon DJ, Ekelund LG, Karon JM, et al. Predictive value of the exercise tolerance test for mortality in North American men: The Lipid Research Clinics Mortality Follow-up Study. Circulation. 1986; 74 (2): 252-61. http://www. ncbi.nlm.nih.gov/pubmed/3731417. Accessed April 29, 2018.
- 51. McNeer JF, Margolis JR, Lee KL, et al. The role of the exercise test in the evaluation of patients for ischemic heart disease. Circulation 1978; 57 (1): 64-70. http://www.ncbi. nlm.nih.gov/pubmed/618399. Accessed April 29, 2018.
- 52. Goraya TY, Jacobsen SJ, Pellikka PA, et al. Prognostic value of treadmill exercise testing in elderly persons. Ann Intern Med. 2000; 132 (11): 862-70.
- 53. Arena R, Myers J, Williams MA, et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation 2007; 116 (3): 329-43.
- Mark DB, Lauer MS. Exercise capacity: the prognostic variable that doesn't get enough respect. Circulation 2003; 108 (13): 1534-6.
- Robert AR, Melin JA, Detry JM. Logistic discriminant analysis improves diagnostic accuracy of exercise testing for coronary artery disease in women. Circulation 1991; 83 (4): 1202-9.
- 56. Al-Mallah M, Alqaisi F, Arafeh A, Lakhdar R, Al-Tamsheh R, Ananthasubramaniam K. Long term favorable prognostic value of negative treadmill echocardiogram in the setting of abnormal treadmill electrocardiogram: a 95-month median duration follow-up study. J Am Soc Echocardiogr 2008; 21 (9): 1018-22.
- Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973; 85 (4): 546-62.

- 58. Bourque JM, Holland BH, Watson DD, Beller GA. Achieving an exercise workload of ≥10 metabolic equivalents predicts a very low risk of inducible ischemia. J Am Coll Cardiol 2009; 54 (6): 538-45.
- 59. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. JAMA 2003; 290 (12): 1600-7.
- Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailey KR, Gersh BJ. Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota. Circulation 2018; 98 (25): 2836-41.
- 61. Weiner DA, Ryan TJ, Parsons L, et al. Long-term prognostic value of exercise testing in men and women from the Coronary Artery Surgery Study (CASS) registry. Am J Cardiol 1995; 75 (14): 865-70.
- Blair SN, Kohl HW, Barlow CE. Physical activity, physical fitness, and all-cause mortality in women: do women need to be active? J Am Coll Nutr 1993; 12 (4): 368-71.
- Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005; 352 (19): 1951-8.
- 64. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol 2003; 42 (5): 831-8.
- Sheffield LT, Maloof JA, Sawyer JA, Roitman D. Maximal heart rate and treadmill performance of healthy women in relation to age. Circulation 1978; 57 (1): 79-84.
- 66. Gulati M, Shaw LJ, Thisted RA, Black HR, Bairey Merz CN, Arnsdorf MF. Heart rate response to exercise stress testing in asymptomatic women: the St. James Women Take Heart Project. Circulation 2010; 122 (2): 130-7.
- 67. Azarbal B, Hayes SW, Lewin HC, Hachamovitch R, Cohen I, Berman DS. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. J Am Coll Cardiol 2004; 44 (2): 423-30.
- Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 1999; 281 (6): 524-9.
- 69. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996; 93 (8): 1520-6.
- Bruce R, Blackmon J, Jones J, Strait G. Exercising testing in adult normale subjects and cardiac patients. Pediatrics 1963; 32 (Suppl): 742-56.
- Pratt CM, Francis MJ, Divine GW, Young JB. Exercise testing in women with chest pain. Are there additional exercise characteristics that predict true positive test results? Chest 1989; 95 (1): 139-44.
- Okin PM, Kligfield P. Gender-specific criteria and performance of the exercise electrocardiogram. Circulation 1995; 92 (5): 1209-16.

- Thomson PD, Kelemen MH. Hypotension accompanying the onset of exertional angina. A sign of severe compromise of left ventricular blood supply. Circulation 1975; 52 (1): 28-32.
- Morris SN, Phillips JF, Jordan JW, McHenry PL. Incidence and significance of decreases in systolic blood pressure during graded treadmill exercise testing. Am J Cardiol 1978; 41 (2): 221-6.
- 75. Sanmarco ME, Pontius S, Selvester RH. Abnormal blood pressure response and marked ischemic ST-segment depression as predictors of severe coronary artery disease. Circulation 1980; 61 (3): 572-8.
- Levites R, Baker T, Anderson GJ. The significance of hypotension developing during treadmill exercise testing. Am Heart J 1978; 95 (6): 747-53.
- Allison TG, Cordeiro MA, Miller TD, Daida H, Squires RW, Gau GT. Prognostic significance of exercise-induced systemic hypertension in healthy subjects. Am J Cardiol 1999; 83 (3): 371-5.
- Lauer MS, Pashkow FJ, Harvey SA, Marwick TH, Thomas JD. Angiographic and prognostic implications of an exaggerated exercise systolic blood pressure response and rest systolic blood pressure in adults undergoing evaluation for suspected coronary artery disease. J Am Coll Cardiol 1995; 26 (7): 1630-6.
- 79. Mark DB, Hlatky MA, Harrell FE, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 1987; 106 (6): 793-800.
- Mark DB, Shaw L, Harrell FE, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991; 325 (12): 849-53.
- 81. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. Circulation 1998; 98 (16): 1622-30.
- Sicari R, Cortigiani L. The clinical use of stress echocardiography in ischemic heart disease. Cardiovasc Ultrasound 2017; 15 (1): 7.
- Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of Echocardiography. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 2007; 20 (9): 1021-41.
- 84. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Hear J - Cardiovasc Imaging 2015; 16 (3): 233-71.
- 85. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2008; 9 (4): 415-37.
- Picano E, Bento de Sousa MJ, de Moura Duarte LF, Pingitore A, Sicari R. Detection of viable myocardium by dobutamine and dipyridamole stress echocardiography. Herz 1994; 19 (4): 204-9.

- Heijenbrok-Kal MH, Fleischmann KE, Hunink MGM. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. Am Heart J 2007; 154 (3): 415-23.
- Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. Cardiovasc Ultrasound 2008; 6 (1): 30.
- 89. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997; 30 (3): 595-606.
- Armstrong WF, Zoghbi WA. Stress echocardiography: current methodology and clinical applications. J Am Coll Cardiol 2005; 45 (11): 1739-47.
- Stangl V, Witzel V, Baumann G, Stangl K. Current diagnostic concepts to detect coronary artery disease in women. Eur Heart J 2008; 29 (6): 707-17.
- Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA 1998; 280 (10): 913-20.
- Padang R, Pellikka PA. The role of stress echocardiography in the evaluation of coronary artery disease and myocardial ischemia in women. J Nucl Cardiol 2016; 23 (5): 1023-35.
- Cortigiani L, Gigli G, Vallebona A, Mariani PR, Bigi R, Desideri A. The stress echo prognostic gender gap. Eur J Echocardiogr 2001; 2 (2): 132-8.
- Roger VL, Pellikka PA, Bell MR, Chow CW, Bailey KR, Seward JB. Sex and test verification bias. Impact on the diagnostic value of exercise echocardiography. Circulation 1997; 95 (2): 405-10.
- 96. Sharaf BL, Pepine CJ, Kerensky RA, et al. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory). Am J Cardiol 2001; 87 (8): 937-41.
- Bach DS, Muller DW, Gros BJ, Armstrong WF. False positive dobutamine stress echocardiograms: characterization of clinical, echocardiographic and angiographic findings. J Am Coll Cardiol 1994; 24 (4): 928-33.
- Lattanzi F, Picano E, Bolognese L, et al. Inhibition of dipyridamole-induced ischemia by antianginal therapy in humans. Correlation with exercise electrocardiography. Circulation 1991; 83 (4): 1256-62.
- 99. Elhendy A, van Domburg RT, Bax JJ, et al. Noninvasive diagnosis of coronary artery stenosis in women with limited exercise capacity: comparison of dobutamine stress echocardiography and 99mTc sestamibi single-photon emission CT. Chest 1998; 114 (4): 1097-104.
- 100. McKeogh JR. The diagnostic role of stress echocardiography in women with coronary artery disease: evidence based review. Curr Opin Cardiol 2007; 22 (5): 429-33.
- 101. Poldermans D, Fioretti PM, Boersma E, et al. Dobutamine-atropine stress echocardiography and clinical data for predicting late cardiac events in patients with

suspected coronary artery disease. Am J Med 1994; 97 (2): 119-25.

65

- 102. Cortigiani L, Dodi C, Paolini EA, Bernardi D, Bruno G, Nannini E. Prognostic value of pharmacological stress echocardiography in women with chest pain and unknown coronary artery disease. J Am Coll Cardiol 1998; 32 (7): 1975-81.
- 103. Chaowalit N, McCully RB, Callahan MJ, Mookadam F, Bailey KR, Pellikka PA. Outcomes after normal dobutamine stress echocardiography and predictors of adverse events: long-term follow-up of 3014 patients. Eur Heart J 2006; 27 (24): 3039-44.
- 104. Cortigiani L, Sicari R, Bigi R, Landi P, Bovenzi F, Picano E. Impact of gender on risk stratification by stress echocardiography. Am J Med 2009; 122 (3): 301-9.
- 105. Shim WJ. Role of echocardiography in the management of cardiac disease in women. J Cardiovasc Ultrasound 2014; 22 (4): 173-9.
- 106. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010; 55 (25): 2825-32.
- 107. Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. Usefulness of a high-dose dipyridamole-echocardiography test for diagnosis of syndrome X. Am J Cardiol 1987; 60 (7): 508-12.
- 108. Mygind ND, Michelsen MM, Pena A, et al. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study. J Am Heart Assoc 2016; 5 (3): e003064.
- Cortigiani L, Rigo F, Gherardi S, et al. Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. JACC Cardiovasc Imaging 2012; 5 (11): 1079-85.
- 110. Cortigiani L, Rigo F, Galderisi M, et al. Diagnostic and prognostic value of Doppler echocardiographic coronary flow reserve in the left anterior descending artery in hypertensive and normotensive patients [corrected]. Heart 2011; 97 (21): 1758-65.
- 111. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive Prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. Am J Cardiol 2009; 103 (5): 626-31.
- 112. Taqueti VR, Dorbala S, Wolinsky D, et al. Myocardial perfusion imaging in women for the evaluation of stable ischemic heart disease-state-of-the-evidence and clinical recommendations. J Nucl Cardiol 2017; 24 (4): 1402-26.
- 113. Shaw LJ, Tandon S, Rosen S, Mieres JH. Evaluation of suspected ischemic heart disease in symptomatic women. Can J Cardiol 2014; 30 (7): 729-37.
- 114. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease. J Am Coll Cardiol 2014; 63 (4): 380-406.
- 115. Woodard PK, White RD, Abbara S, et al. ACR appropriateness criteria chronic chest pain-low to intermediate

probability of coronary artery disease. J Am Coll Radiol 2013; 10 (5): 329-34.

- 116. Aggarwal NR, Bond RM, Mieres JH. The role of imaging in women with ischemic heart disease. Clin Cardiol 2018; 41 (2): 194-202.
- 117. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? J Am Coll Cardiol 2012; 59 (6): 553-65.
- 118. Gerber TC, Gibbons RJ. Weighing the risks and benefits of cardiac imaging with ionizing radiation. JACC Cardiovasc Imaging 2010; 3 (5): 528-35.
- 119. Berrington de Gonzalez A, Kim KP, Smith-Bindman R, McAreavey D. Myocardial perfusion scans: projected population cancer risks from current levels of use in the United States. Circulation 2010; 122 (23): 2403-10.
- Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA 2007; 298 (3): 317-23.
- 121. Amanullah AM, Kiat H, Friedman JD, Berman DS. Adenosine technetium-99m sestamibi myocardial perfusion SPECT in women: diagnostic efficacy in detection of coronary artery disease. J Am Coll Cardiol 1996; 27 (4): 803-9.
- 122. Hachamovitch R, Berman DS, Kiat H, et al. Gender-related differences in clinical management after exercise nuclear testing. J Am Coll Cardiol 1995; 26 (6): 1457-64.
- 123. Hachamovitch R, Berman DS, Kiat H, et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. J Am Coll Cardiol 1996; 28 (1): 34-44.
- 124. Berman DS, Kang X, Hayes SW, et al. Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol 2003; 41 (7): 1125-33.
- 125. Bonow RO, Mann D, Zipes D, Libby Pl. Braunwald's heart disease. A textbook of cardiovascular medicine, 9th ed. Philadelphia: Elsevier Saunders, 2012.
- 126. Zamorano JL, Bax J, Knuuti J, et al. The ESC textbook of cardiovascular imaging, Oxford: Oxford University Press, 2010.
- 127. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002; 105 (4): 539-42.
- 128. Doukky R, Hayes K, Frogge N. Appropriate use criteria for SPECT myocardial perfusion imaging: are they appropriate for women? J Nucl Cardiol 2016; 23 (4): 695-705.
- 129. Tilkemeier PL, Cooke CD, Ficaro EP, et al. American Society of Nuclear Cardiology information statement: Standardized reporting matrix for radionuclide myocardial perfusion imaging. J Nucl Cardiol 2006; 13 (6): e157-71.
- 130. Sharir T, Ben-Haim S, Merzon K, et al. High-speed myocardial perfusion imaging initial clinical comparison with conventional dual detector anger camera imaging. JACC Cardiovasc Imaging 2008; 1 (2): 156-63.

- 131. Esteves FP, Raggi P, Folks RD, et al. Novel solid-state-detector dedicated cardiac camera for fast myocardial perfusion imaging: multicenter comparison with standard dual detector cameras. J Nucl Cardiol 2009; 16 (6): 927-34.
- 132. Gimelli A, Bottai M, Giorgetti A, et al. Comparison between ultrafast and standard single-photon emission CT in patients with coronary artery disease: a pilot study. Circ Cardiovasc Imaging 2011; 4 (1): 51-8.
- 133. Iskandar A, Limone B, Parker MW, et al. Gender differences in the diagnostic accuracy of SPECT myocardial perfusion imaging: a bivariate meta-analysis. J Nucl Cardiol 2013; 20 (1): 53-63.
- 134. Kong BA, Shaw L, Miller DD, Chaitman BR. Comparison of accuracy for detecting coronary artery disease and side-effect profile of dipyridamole thallium-201 myocardial perfusion imaging in women versus men. Am J Cardiol 1992; 70 (2): 168-73.
- 135. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Quantitative thallium-201 single-photon emission computed tomography during maximal pharmacologic coronary vasodilation with adenosine for assessing coronary artery disease. J Am Coll Cardiol 1991; 18 (3): 736-45.
- 136. Iskandrian AE, Heo J, Nallamothu N. Detection of coronary artery disease in women with use of stress single-photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol 1997; 4 (4): 329-35.
- 137. Bateman TM, Maddahi J, Gray RJ, et al. Diffuse slow washout of myocardial thallium-201: a new scintigraphic indicator of extensive coronary artery disease. J Am Coll Cardiol 1984; 4 (1): 55-64.
- 138. Machac J. Cardiac positron emission tomography imaging. Semin Nucl Med 2005; 35 (1): 17-36.
- 139. Aarnoudse WH, Botman KJ, Pijls NH. False-negative myocardial scintigraphy in balanced three-vessel disease, revealed by coronary pressure measurement. Int J Cardiovasc Intervent 2003; 5 (2): 67-71.
- 140. Martin W, Tweddel AC, Hutton I. Balanced triple-vessel disease: enhanced detection by estimated myocardial thallium uptake. Nucl Med Commun 1992; 13 (3): 149-53.
- 141. Cerci MSJ, Cerci JJ, Cerci RJ, et al. Myocardial perfusion imaging is a strong predictor of death in women. JACC Cardiovasc Imaging 2011; 4 (8): 880-8.
- 142. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004; 11 (2): 171-85.
- 143. Shaw LJ, Hage FG, Berman DS, Hachamovitch R, Iskandrian A. Prognosis in the era of comparative effectiveness research: where is nuclear cardiology now and where should it be? J Nucl Cardiol 2012; 19 (5): 1026-43.
- 144. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007; 49 (2): 227-37.
- 145. Maddahi J, Packard RRS. Cardiac PET perfusion tracers: current status and future directions. Semin Nucl Med 2014; 44 (5): 333-43.
- 146. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur SR, Reddy P, Carlos RC. Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a meta-analysis. Acad Radiol 2008; 15 (4): 444-51.

- 147. Kay J, Dorbala S, Goyal A, et al. Influence of sex on risk stratification with stress myocardial perfusion Rb-82 positron emission tomography: results from the PET (Positron Emission Tomography) Prognosis Multicenter Registry. J Am Coll Cardiol 2013; 62 (20): 1866-76.
- 148. Bateman TM, Heller G V, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. J Nucl Cardiol 2006; 13 (1): 24-33.
- 149. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging 2015; 8 (3): e002179-e002179.
- 150. Danad I, Raijmakers PG, Harms HJ, et al. Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: a [150] H2O PET study. Eur Heart J 2014; 35 (31): 2094-105.
- 151. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. J Am Coll Cardiol 2012; 60 (18): 1828-37.
- 152. Parker MW, Iskandar A, Limone B, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis. Circ Cardiovasc Imaging 2012; 5 (6): 700-7.
- 153. Di Carli MF, Dorbala S, Meserve J, El Fakhri G, Sitek A, Moore SC. Clinical myocardial perfusion PET/CT. J Nucl Med 2007; 48 (5): 783-93.
- 154. Dorbala S, Di Carli MF. Cardiac PET perfusion: prognosis, risk stratification, and clinical management. Semin Nucl Med 2014; 44 (5): 344-57.
- 155. Van Tosh A, Supino PG, Nichols KJ, Garza D, Horowitz SF, Reichek N. Prognosis of a normal positron emission tomography 82Rb myocardial perfusion imaging study in women with no history of coronary disease. Cardiology 2010; 117 (4): 301-6.
- 156. Marwick TH, Shan K, Patel S, Go RT, Lauer MS. Incremental value of rubidium-82 positron emission tomography for prognostic assessment of known or suspected coronary artery disease. Am J Cardiol 1997; 80 (7): 865-70.
- 157. Taqueti VR, Everett BM, Murthy VL, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation 2015; 131 (6): 528-35.
- 158. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol 2013; 62 (18): 1639-53.
- 159. Murthy VL, Lee BC, Sitek A, et al. Comparison and prognostic validation of multiple methods of quantification of myocardial blood flow with 82Rb PET. J Nucl Med 2014; 55 (12): 1952-8.
- 160. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation 2011; 124 (20): 2215-24.

- Schinkel AFL, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: diagnosis and patient outcomes. Curr Probl Cardiol 2007; 32 (7): 375-410.
- 162. Yoshida K, Gould KL. Quantitative relation of myocardial infarct size and myocardial viability by positron emission tomography to left ventricular ejection fraction and 3-year mortality with and without revascularization. J Am Coll Cardiol 1993; 22 (4): 984-97.
- 163. Tian M, Koyama K, Zhang H, Oriuchi N, Higuchi T, Endo K. Assessment of myocardial viability with a positron coincidence gamma camera using fluorodeoxyglucose in comparison with dedicated PET. Nucl Med Commun 2003; 24 (4): 367-74.
- 164. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002; 39 (7): 1151-8.
- 165. Graham TP, Covell JW, Sonnenblick EH, Ross J, Braunwald E. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. J Clin Invest 1968; 47 (2): 375-85.
- 166. Taegtmeyer H, Roberts AF, Raine AE. Energy metabolism in reperfused heart muscle: metabolic correlates to return of function. J Am Coll Cardiol 1985; 6 (4): 864-70.
- 167. Weinheimer CJ, Brown MA, Nohara R, Perez JE, Bergmann SR. Functional recovery after reperfusion is predicated on recovery of myocardial oxidative metabolism. Am Heart J 1993; 125 (4): 939-49.
- 168. Rubin PJ, Lee DS, Dávila-Román VG, et al. Superiority of C-11 acetate compared with F-18 fluorodeoxyglucose in predicting myocardial functional recovery by positron emission tomography in patients with acute myocardial infarction. Am J Cardiol 1996; 78 (11): 1230-35.
- 169. Sarikaya I. Cardiac applications of PET. Nucl Med Commun 2015; 36 (10): 971-85.

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