

Noninvasive Diagnostic Evaluation for Chest Pain in Women

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Women are eight times less likely to develop myocardial infarction than men are; nonetheless, when myocardial ischemic disease is present, it has a worse evolution^{1,2}. No explanations for this fact are available, although speculations exist about the inadequate manner of diagnosis.

It is worth emphasizing that in studies about coronary disease, women are either a minority or excluded from the study protocols. Therefore, most of the information regarding coronary disease in women comes from studies conducted in men. In fact, invasive cardiovascular procedures - either diagnostic or therapeutic - are frequently less indicated for women who bear confirmed coronary disease. However, it is not yet clearly established whether this difference is due to a larger use of such procedures in men or to a smaller indication in women.

Typical angina is more prevalent in women, although angiographic studies have revealed that all forms of angina, including the typical type, are associated on a smaller scale with coronary disease in women when compared with that men. The CASS³ study reveals that 62% of women with defined angina had ischemic disease compared with 40% of those with probable angina and 4% with nonischemic pain.

We propose to critically evaluate the main noninvasive diagnostic methods for chronic coronary disease in women.

Electrocardiogram - The association between electrocardiographic abnormalities at rest and a higher incidence of cardiovascular diseases is well documented in men but not in women. When ranking different levels of rest electrocardiographic abnormalities in men and women aged 40 to 64 years and with higher risk of cardiovascular disease-induced death, De Bacquer et al⁴ observed higher relative risk for men. High-degree abnormalities were directly associated with mortality in both sexes, but low-degree abnormalities were not. The abnormalities considered as high

degree were the presence of depression of the ST segment, T-wave inversion, complete or 2nd degree atrioventricular block, branch (left or right) block, frequent extrasystoles and atrial fibrillation or flutter; low-degree abnormalities were a deviated QRS axis complex with high or low voltage and other alterations in ventricular repolarization. De Bacquer et al⁴ demonstrated that depression of the ST segment in the rest electrocardiogram was associated with higher cardiovascular mortality, and was equally important in both sexes. The T-wave abnormalities were also more predictive for men, whereas arrhythmias were more predictive for women. It is worth emphasizing that low-degree abnormalities did not have predictive values for either sex.

Stress test - Several studies³⁻⁷ have revealed a reduced amount of noninvasive diagnostic interventions for coronary disease in women. This is so because of the lower prevalence of ischemic disease in women, in addition to a higher number of false-positives⁸, ie, the specificity of the conventional effort test is lower in women, compared with that observed in men. It is important to consider the probability that coronary disease in women, based on age and symptoms, frequently is between low and medium, especially if it is considered before menopause. Low probability induces patients with an estimated <20% to have the disease, and is limited to women who do not have any major risk factor and who do not have more than a medium risk factor or two minor risk factors for coronary disease, for instance women of child-bearing age with atypical angina. Patients with high probability, with an estimated >80% chance of having the disease, have two or more major risk factors or a major one associated with a medium or minor risk factor. Moderate probability is defined as risk between 20 and 80%⁹. The classification of risk factors for coronary disease in women is presented in Table I.

In patients with low pretest probability, no indication exists for diagnostic testing, because the posttest probability, in case of a positive result, will not be high enough to indicate an invasive examination, as seen by Bayes theorem⁸ that observed frequent false-positive results.

On the other hand, the exercise test should be indica-

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ted in women with a high probability of coronary disease. In this situation, the imaging tests add little information, because false-positive results are not frequent, in addition to the low probability of false-negatives in females.

The use of imaging tests, such as nuclear imaging and echocardiography associated with the exercise test is restricted to situations where the conventional exercise test is not conclusive.

In patients with moderate pretest probability, the exercise test is initially indicated; if positive, an additional noninvasive examination should be indicated, such as an imaging test or coronariography, depending of the patient's individual conditions (Fig. 1).

The exercise test is the most used noninvasive method

Table I - Risk factors for coronary disease in women	
Major	Typical angina Postmenopause without hormone replacement Diabetes mellitus Peripheral vascular disease
Moderate	Arterial hypertension Smoking Dyslipidemias, especially low HDL-cholesterol
Minor	Age >65 years Obesity, especially central obesity Sedentary habits Family history of coronary disease Other factors (psychosocial, hemostatic, etc.)
Adapted from Douglas and Ginsburg ⁹ .	

for the evaluation of ischemic heart disease. However, it is less accurate and has a greater potential for false-positives in women, which is at least partially explained by the Bayesian principles, based on the fact that, in most female patients with pretest probability for coronary disease, the performance on the exercise test is relatively low. Among the likely responsible mechanisms, to be indicate a higher prevalence of mitral valve prolapse, syndrome X, microvascular dysfunction, and possible hormone influence.

In regard to steroid hormones, Jaffe ¹⁰ showed that estrogen taken orally increases the possibility of ST segment depression, which is different from that seen with androgens; Glasser and Clark ¹¹, on the other hand, correlated the ST fluctuations with estrogen and progesterone levels, concluding that only the fluctuations of estrogen levels occur on the ST segment during exercise.

Kusumi et al ¹², studying the left ventricular function of healthy women with ST segment depression compared with others with normal responses, showed that the hemodynamic stress induced by augmented intraventricular pressure was responsible for the abnormal tests.

Women with syndrome X, especially those using nitrates whose angina has been alleviated and with a normal coronariography may show a reduction in coronary reserve ¹³, which explains the false-positives of the exercise test.

Abnormalities in the ST segment in young people are more frequent in women than in men. ST segment depression on induced exercise is less sensitive and less specific in women, reflecting a smaller prevalence of severe coronary disease and also because many patients are unable to exercise at the maximum aerobic capacity.

In a metaanalysis ⁸ of 147 studies on the conventional exercise test for diagnosis of coronary disease in 24,047 wo-

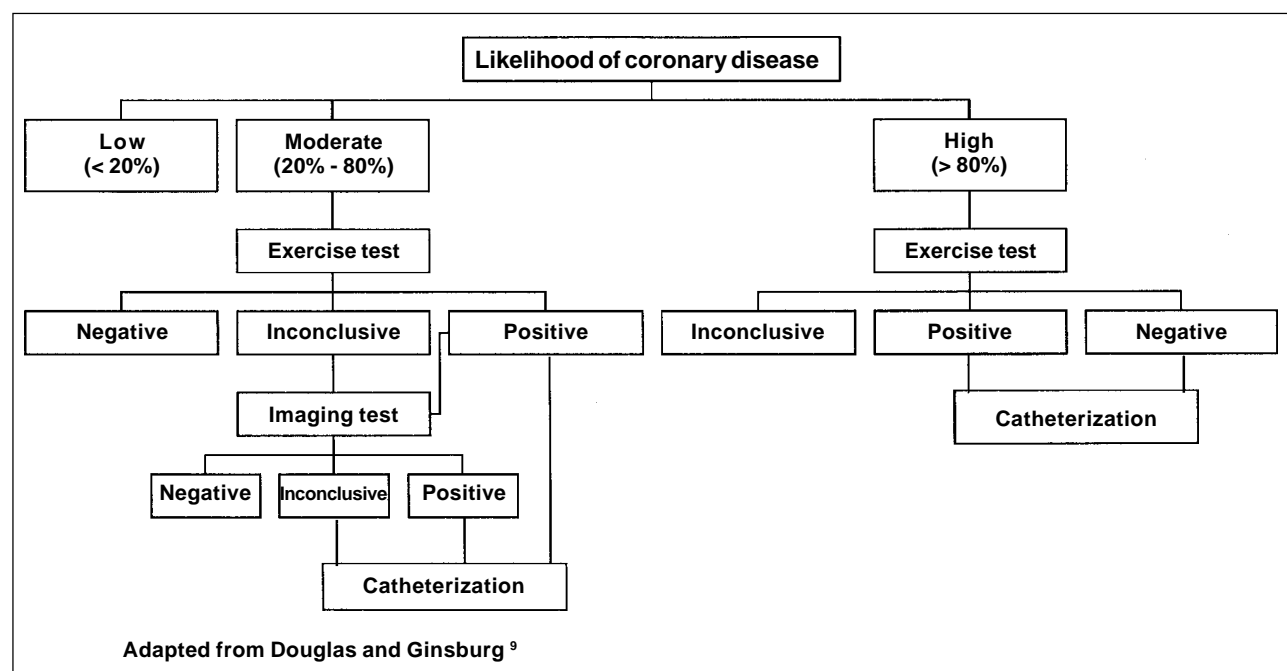


Fig. 1 - Algorithm of diagnostic tests in women with chest pain.

men, 68% sensitivity and 77% specificity were detected. Table II summarizes some studies that show the accuracy of the ST segment for diagnosis of coronary disease in women, with mean sensitivities of 66% and specificities of 67%. Variations among the studies are due to the different criteria used to define coronary disease, to the selection of patients (inclusion of previous heart attack, multi-vessel diseases), and to the different characteristics of the test, including the ST segment-based positivity and the type of exercise accomplished⁸.

At the Heart Institute¹⁴ of the HC-FMUSP, the tests considered positive or to indicate ischemia had ST segment depression of horizontal or downsloping morphology or both ≥ 1 mm for men and 2mm for women, when the upsloping with a 2mm for men and 3mm for women situated at 80ms of the J point. The ST segment elevation 1mm is also considered a positive response. Using these criteria, up to a 40% reduction in false-positive results has been noticed, confirmed by the normal results of the myocardial perfusion scintigraphy.

The accuracy of the exercise test in women may be higher if the levels of ST segment depression are analyzed with other parameters.

The exercise test provides other parameters of major importance for the diagnosis and prognosis of coronary disease, including physical capacity, hemodynamic response, and the presence or absence of cardiac symptoms on exercise, which must be analyzed together with electrocardiographic alterations.

Another strategy to differentiate true from false results is the retest with a beta-blocker. Marcomichelakis et al²⁹ studied 100 patients with positive effort tests, 50 of which did not have obstructive coronary disease. The retest with a beta-blocker normalized the ST segment modifications in all patients with false-positive results.

Because it is difficult to foresee the probability of coronary disease in women, some authors have preferred the association of exercise testing with imaging as an initial alternative.

The need for an additional test must always be based on the analysis of clinical parameters and results of the initial exercise test. Although a large number of false-positive results occur due to the physical stress, not enough data are available to justify the incorporation of imaging tests with the initial routine for the diagnosis of coronary disease. Women with moderate risk and negative exercise tests have a low probability of coronary disease; therefore an additional test is not necessary. If, however, the test is positive, another test is required, due to the elevated incidence of heart attack or heart disease-induced death. If the result is inconclusive for any reason, another method must be indicated, for instance, pharmacological stress for patients who cannot adequately accomplish the physical stress test.

Myocardial perfusion scintigraphy - Myocardial perfusion scintigraphy with tomography slices (SPECT, Single Photon Emission Computed Tomography) is more accurate for diagnosis of coronary disease than the conventional exercise test. Few studies have been conducted concerning the use of myocardial perfusion scintigraphy as a noninvasive method for diagnosis of coronary artery disease in women. For SPECT³⁰ with²⁰¹ TI, the sensitivity varies from 71% to 86% and the specificity from 81% to 91%. Just as with men, several factors may affect the accuracy of myocardial perfusion scintigraphy in women: choice of patients, percentage of maximum heart rate reached during the exercise, type of image acquisition (the plain, not currently in use or in tomography slices), criteria of interpretation, and level of tissue attenuation.

Artifacts suggestive of irreversible defects may arise as a consequence of tissue attenuation; thus, in women, the left breast may attenuate the antero-lateral wall on the plain study, and the apical-lateral wall on the tomography. Fat deposits on the thoracic left lateral wall may lessen the inferior left ventricle area, especially in obese patients. When the persistent defect of the antero-lateral region was considered an artifact due to attenuation of mammary tissue, Friedman and co-workers³¹ observed an increase in specificity from 88% to 97%, and, similarly, in Hung et al³², the specificity

Table II - Sensitivity and specificity of the exercise test in women

Author (year)	N	Mean Age	CAD definition	Sensitivity	Specificity
Guiteras ¹⁵ (1972)	112	49	>70%	79%	66%
Linhart ¹⁶ (1974)	98	46	>50%	71%	78%
Sketch ¹⁷ (1975)	56	50	>75%	50%	78%
Barolsky ¹⁸ (1979)	92	50	>50%	60%	68%
Weiner ¹⁹ (1979)	580		>70%	76%	64%
Ilsley ²⁰ (1982)	62	51	>50%	67%	74%
Hung ²¹ (1984)	92	51	>70%	75%	59%
Hlatky ²² (1984)	613		>75%	57%	86%
Melin ²³ (1985)	93	51	>50%	58%	80%
Robert ²⁴ (1991)	135	53	>50%	68%	48%
Chae ²⁵ (1993)	114		>50%	66%	60%
Williams ²⁶ (1994)	70	60	>50%	67%	51%
Marwick ²⁷ (1995)	118	60	>50%	77%	56%
Morise ²⁸ (1995)	264	56	>50%	46%	74%
Mean				66%	67%

CAD- Coronary artery disease.

varied from 81% to 91%. Different strategies have been proposed to improve the specificity of images with ²⁰¹Tl in women; however, the breast size, position, and density still limit test performance.

Myocardial perfusion scintigraphy with ^{99m}Tc-SESTAMIBI may diminish the tissue attenuation-induced artifact; in fact, the high-energy ^{99m}Tc compared with ²⁰¹Tl causes the former to reduce these artifact effects in approximately 15% of patients. SPECT specificity with ^{99m}Tc-SESTAMIBI in women is significantly better than that obtained with ²⁰¹Tl. In Taillefer and colleagues' study³⁰, where 115 women were evaluated, the specificities were 84.4% for ^{99m}Tc-SESTAMIBI and 62.7% for ²⁰¹Tl; however, the sensitivities for detection of stenosis in coronary arteries 70% were similar, ie, 84.3% and 80.4%, respectively. In this same study, when Gated-SPECT was analyzed, the specificity changed from 84.4% to 92.2%. Gated-SPECT is a technique that joins two methods; thus, with a single approach to the patient, it evaluates simultaneously the myocardial perfusion and the qualitative and quantitative parameters of ventricular function, improving therefore the test's accuracy. This technique may be performed by both perfusion markers; however, with ²⁰¹Tl, acquisition time must be bigger in order to obtain better image quality.

Echocardiogram - In addition to allowing the diagnosis of coronary disease, the stress (physical or pharmacological) echocardiogram helps to recognize artifacts, specifically those caused by the mammary tissue. Nonetheless, the echocardiographic imaging in obese patients, those with thoracic deformities, or lung diseases is technically more difficult to interpret and of poorer quality.

For the diagnosis of coronary disease, both echocardiography and myocardial perfusion scintigraphy may be performed in association with the exercise test or to pharmacological stress testing.

The sensitivity of the echocardiogram associated with physical stress is comparable between both sexes, but is influenced by the modality of exercise used. For instance, with the treadmill, the echocardiographic imaging is acquired before and immediately after the exercise, which is different from the exercise test with the ergometric bicycle; thus, Sawada et al³³ verified that in the exercise echocardiogram, the sensitivity was 80% with the treadmill and 100% with the bicycle, and the specificity was 94% and 73%, respectively. The accuracy, however, was similar, 87% for the treadmill and 84% for the bicycle.

The advantage of pharmacological stress over exercise associated with echocardiography includes obtaining higher quality images, due to the absence of movement and respiratory interference, and the easiness to control the

Table III - Noninvasive tests for the diagnosis of coronary disease in men and women³⁵

Method	Author	Year	# of Pts	Sensit.(%)	Specif.(%)
TE	Morise and Diamond	1995	M: 508	56	81
			W: 284	47	73
TE + MPS/ DIP + MPS	Santana-Boado and cols.	1998	M: 100	93	89
			W: 63	85	91
TE + Echo	Roger and cols.	1997	M: 244	78	37
			W: 96	79	34

Pts- patients; Sensit.- sensitivity; Specif.- specificity; TE- exercise test; M- men; W- women; MPS- myocardial perfusion scintigraphy with tomography slices; Dip- dipiridamol; Echo- echocardiogram.

stress reached. Recent studies show a sensitivity of pharmacological stress between 76 and 93%, the specificity of 43 to 94%, and accuracy of 58 to 95%³⁴.

Some studies suggest that the echocardiography and nuclear studies have similar sensitivity and specificity, but have greater sensitivity and specificity compared with the exercise test (Table III).

Another study³⁶, a metaanalysis to detect coronary disease in women, shows the preeminence of exercise echocardiography: 19 studies about the conventional exercise test for diagnosis of coronary disease in 3,721 women, reported 61% sensitivity and 70% specificity; in five studies on myocardial perfusion scintigraphy in 842 women, the sensitivity was 78% and the specificity 64%; in three studies about the exercise echocardiogram in 290 women, sensitivity was 86% and specificity was 79%.

Conclusion

The present review critically analyzes the main complementary examinations used to diagnose coronary disease in women. The stress electrocardiogram and myocardial perfusion scintigraphy are the most commonly used noninvasive methods for detecting coronary artery disease.

Stress echocardiography appears promising, requiring, however, more consistent studies.

Myocardial perfusion scintigraphy with tomography slices is still the method of choice for detection of coronary disease and, more recently, the Gated SPECT has gained favor, because in effort-induced ischemia, this method allows identification of the main events of the ischemic cascade, ie, the heterogeneity of coronary flow.

Other events, such as myocardial contractility, as a consequence of anaerobic metabolism, can be diagnosed by the stress echocardiography study (physical or pharmacological).

Electrocardiographic alterations appear later and may be observed in the exercise test.

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