Gender differences in diagnostic procedures

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This review examines the contribution of the literature to the controversial issue of diagnostic procedures in women affected by coronary artery disease (CAD), on which a large number of papers have been published. It has been reported that cerebro- and cardiovascular diseases represent the first cause of death in the New as well as in the Old World, Italy included. Some studies are conditioned by bias; one of these is the Framingham study, in which angina was reported and defined only clinically and for a relatively young age range, as a benign condition in women. Angiographic studies, such as the CASS, considered a super elected group of women referred to the hemodynamic laboratory for chest pain, which in the female gender often has atypical characteristics. In our opinion, it is mandatory to take into account: 1) what chest pain really means in women; 2) the fact that there are gender differences: women have a different biological and hormonal status, lifestyle, and perception of the disease; 3) that there is a different approach of the physicians to a woman with possible or suspected CAD. We suggest, therefore, a more peculiar and individualized diagnostic approach to women suspected as having CAD. This approach should also take the pre-test probability of disease into consideration. The first investigational step we recommend is the exercise ECG test; should this be unfeasible or not interpretable, an imaging and/or pharmacological stress test is advisable. In case of positive first test results, coronary angiography should be performed.

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Introduction

Several epidemiological sources show that half of all women in western countries will die of some cardiovascular event, and since women live longer than men, the absolute number of women dying of cardiovascular disease exceeds that of men. Therefore, diagnosis, treatment and prevention are as important in women as in men; and yet for many decades women have been under-diagnosed and under-treated in all cardiovascular procedures.

There certainly are gender-related differences in:
- the risk factor prevalence,
- the disease presentation and natural history,
- behavioral and psychosocial factors, quality of life, communication style, etc.

The global risk profile is important both in women and in men; nevertheless, diabetes is more aggressive, and menopause – especially when this occurs before age 40-45 – a unique risk factor in women. On the other hand, hormone replacement therapy may be considered as a unique antidote or as a bias for the evaluation of the natural history of the disease[1], although this issue is now still widely debated.

The evaluation of chest pain

The evaluation of chest pain is a critical step in the care of women with heart disease. Some misconceptions derive from important studies such as the Framingham study[2], where angina was defined as being benign when compared to men. The problems with this study were that angina was defined using clinical criteria and that the study group was relatively young.

Another bias derives from the CASS study[3] where the prevalence of coronary stenosis was 50% in men and 17% in women. All data were derived from hemodynamic assessments and we now know that, in virtually every angiographic series, women with chest pain have a lower prevalence of coronary stenosis than men. The problem with chest pain evaluation in women is due to the fact that women have:
• "atypical" chest pain, probably because the present description of the "typical" symptoms was developed and based on what referred by male patients;
• silent ischemia and dyspnea as well as diastolic dysfunction more frequently than in men.

Moreover, women tend to be older and less active than their male counterpart, and

often lack typical effort symptoms. Hence, many authors still believe that coronary artery disease (CAD) is a "widow maker disease" or a man's disease.

Taking a closer look at the CASS description of atypical angina pectoris we easily recognize women within these characteristics[3]. CASS defines "atypical" the pain located in the left or right chest, abdomen, back or arms in the absence of mid-chest pain; it may be sharp or fleeting, very prolonged and unrelated to exercise; it may be relieved by antacids, but not by rest or nitroglycerin. Moreover, the PIMI study[4] included 170 men and 26 women, each with documented CAD; women reported chest pain more often than men during their daily activities and during mental stress, but not during exercise. A higher proportion of women, as compared to men, referred marked pain sensitivity to graded heat applied to the skin. Another report[5] described a group of 98 patients (51 women) admitted with a diagnosis of myocardial infarction and among whom chest pain was the most common symptom reported by men and women. Four signs were also identical in both sexes: fatigue, rest pain, dyspnea and weakness, but women also reported a loss of appetite, paroxysmal dyspnea and back pain. Finally, Everts et al.[6] reported on 903 consecutive patients admitted to the coronary care unit for suspected myocardial infarction. According to these authors, women reported neck pain ($p < 0.05$) and back pain ($p < 0.01$) more frequently than men.

Use of diagnostic tests in women with chest pain

We agree with the opinions expressed in a classic study by Douglas and Ginsburg[7] stating that the pre-test probability of CAD in women is the most important guide to choose the ideal test. If there is a low likelihood of CAD (< 20%), no initial or subsequent test is recommended; with a moderate likelihood of CAD (20-80%) an exercise test should be performed. When the test is negative, no further investigations are required; in the presence of an inconclusive or positive exercise test, an imaging test or a coronary angiography is indicated. Finally, while a negative imaging stress test is decisive for the diagnosis, an inconclusive or positive one implies a coronary angiography. We should recommend the same aggressive approach to our female patients with a high likelihood of CAD (> 80%). Douglas' survey reported (Table I) the determinants of CAD in American women and the global risk profile, which does not reflect the risk we observed in the population of our study[8]. Our study involved 862 women (mean age 63 ± 8 years) who were hospitalized between January 1994 and December 1996 for a first episode of angina. These patients were divided into two groups: group 1 included 560 patients with angiographic evidence of CAD and group 2, 302 patients without CAD. At univariate analysis the following characteristics were significantly correlated with the presence of CAD: 1) age > 65 years ($p < 0.0001$), 2) positive rest ECG at least during one episode ($p < 0.0001$), and 3) hypertension ($p < 0.0001$) and diabetes ($p < 0.005$). At multivariate analysis, only a positive ECG during an anginal attack was an independent predictor of CAD.

Table I. Determinants of coronary heart disease (CHD) in women with chest pain.

Major
Typical angina
Postmenopausal status without HRT
Peripheral vascular disease
Diabetes
Intermediate
LDL cholesterol levels
Hypertension
Smoking
Minor
Age > 65 years
Central obesity (waist to hip ratio > 0.9)
Sedentary lifestyle
Family history of CHD

HRT = hormone replacement therapy.

Diagnostic test

The standard stress ECG test is reported to be less accurate in women because of: 1) a lower prevalence of CAD at any given age, and 2) a possible influence of autonomic and sex hormones on the ECG.

Given the fact that women are older and that the achievement of an adequate stress level can be a problem due to deconditioning or orthopedic limitations, this test is, in our opinion, the most accurate only when feasible and easily interpretable. Nonetheless, many studies have contributed to create skepticism. Sullivan et al.[9] reported on 1570 patients (886 females) referred for chest pain; 23% of women had normal coronary angiograms compared with 41% of men ($p < 0.01$) and diabetes was the only risk factor in women with CAD ($p < 0.0001$). The specificity and positive predictive value of the exercise test were significantly lower in women than in men (71 vs 93%, $p < 0.001$, and 76 vs 95%, $p < 0.001$, respectively). Again, Curzen et al.[10] reported, in 347 women with chest pain who underwent the ECG test, an overall low sensitivity (68%) and specificity (61%), with low positive (61%) and negative (68%) predictive values. The authors concluded that in 36% of women with chest pain the use of the ECG test was a misleading predictor of the presence or absence of CAD. This appears, in our opinion, a real misleading interpretation of an old, easily feasible, low-cost, accurate test. Chae et al.[11] described the ECG test and thallium stress scintigraphy as having the same sensitivity and specificity in women, when the exercise was well performed and the ECG was clearly interpretable. Women have a notoriously high rate of false positive exercise tests, but, as demonstrated by Pratt et al.[12] three independent exercise variables are associated

with a high likelihood of CAD: an exercise duration < 5 min, the inability to reach the target heart rate, and a time to ST-segment normalization ≥ 6 min. The ST-T change (91%) and a low maximum workload (84%) at the exercise test were reported by our group to have a high positive predictive value in women.

Imaging stress test

Women are under-represented in studies on the imaging stress test. Gender specific artifacts and physiological responses have been described in both nuclear and echocardiographic studies. The pre-test likelihood of disease is probably more important than the type of stress test for women just as and more than for men. Dipyridamole thallium-201 was described by Shaw et al.[13] to have a lower sensitivity and a much lower specificity in women compared to men (43 women and 71 men with angina pectoris), with less sensitivity for one vessel disease. With regard to stress echocardiography it appears in some reports to be very accurate in women. Davar et al.[14] described 135 women with a high pre-test probability of CAD. These were investigated by treadmill or dobutamine stress echo, with a mean follow-up of 20 months. Cox analysis revealed a positive stress echo as a unique predictor of future events (relative risk 8.9, confidence interval 1.0-76.5, p = 0.04). In this experience a negative stress echo test identified a subgroup of women with a low risk of cardiac events, and a positive stress echo a subgroup with an increased risk of events. Cortigiani et al.[15] investigated the prognostic value of pharmacological stress echocardiography in 456 women referred for chest pain, and unknown CAD. In that group of patients, the test proved to be safe and highly feasible for risk stratification. All these different, sometimes confusing results are the consequence of the approach of doctors to women with chest pain, characterized by a higher number of test requests in comparison to male patients. In conclusion, starting from the misconception that women have a lower probability of CAD, physicians feel justified in recommending all feasible tests rather than running the risk of a mistaken diagnosis. The consequence is that of non-homogeneous results in test sensitivity and specificity in women.

To test the accuracy of different tests, some years ago we studied[16] 200 patients (100 males, mean age 60 ± 6 years) who were hospitalized in the coronary care unit for a first episode of "definite" angina. All patients underwent coronary angiography and different stress tests before angiography: 1) dobutamine stress echocardiography: 42 males and 40 females; 2) stress thallium: 18 males and 17 females; and 3) the exercise test: 48 males and 52 females. Our results (Table II) revealed a very low sensitivity and specificity of all the tests in women, whereas dobutamine stress echocardiography was the most accurate test in men.

Conclusions

Our experience allows some recommendations for a correct non-invasive evaluation in women. If the endpoint of the diagnosis is the localization of ischemia, we recommend imaging techniques associated with stress testing. The choice of the imaging modality to be used should depend on the expertise of the individual institute. If the endpoint is the diagnosis of ischemia, we suggest an evaluation of the pre-test probability of the disease on the basis of the guidelines summarized in table III in which our own approach is outlined.

Table II. Comparison of three different non-invasive tests between females and males with coronary artery disease.

	DSE		STS		ECG test	
	Females	Males	Females	Males	Females	Males
Sensitivity (%)	67	87*	69	80**	65	77**
Specificity (%)	72	98*	60	93**	58	90**

DSE = dobutamine stress echocardiography; STS = stress thallium scintigraphy. * $p < 0.001$; ** $p < 0.01$.

Table III. Diagnostic work-up guidelines.

Pre-test probability of disease	*Low* No test
Pre-test probability of disease - interpretable ECG, possible exercise - uninterpretable ECG, possible exercise - uninterpretable ECG, impossible exercise	*Intermediate* Exercise test Exercise echocardiography or sestamibi Stress pharmacological with echo or sestamibi (or thallium)
Pre-test probability of disease	*High* Coronary angiography

References

1. Modena MG, Origliani G, Sansoni S, Turco V, Rossi R. La diagnosi di cardiopatia ischemica nella donna. Ital Heart J Suppl 2000; 1: 481-7.
2. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: the Framingham study. Am J Cardiol 1979; 44: 53-9.
3. 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: 230-5.
4. Sheps DS, Kaufmann PG, Sheffield D, et al. Sex differences in chest pain in patients with documented coronary artery disease and exercise-induced ischemia. Results from the PIMI study. Am Heart J 2001; 142: 864-71.
5. Penque S, Halm M, Smith M, et al. Women and coronary heart disease: relationship between descriptors of signs and symptoms and diagnostic and treatment course. Am J Crit Care 1998; 7: 175-82.
6. Everts B, Karlson BW, Wahrborg P, Hedner T, Herlitz J. Localization of pain in suspected acute myocardial infarction in relation to final diagnosis, age and sex, and site and type of infarction. Heart Lung 1996; 25: 430-7.
7. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996; 334: 1311-5.
8. Modena MG, Origliani G, Rossi R, et al. Le indicazioni alla coronarografia nella donna alla luce di nuove acquisizioni. Cardiologia 1996; 41: 239-44.
9. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. BMJ 1994; 308: 883-6.
10. Curzen N, Patel D, Clarke D, et al. Women with chest pain: is exercise testing worthwhile? Heart 1996; 76: 156-60.
11. Chae SC, Heo J, Iskandrian AS, Wasserleben V, Cave V. Identification of extensive coronary artery disease in women by exercise single-photon emission computed tomographic (SPECT) thallium imaging. J Am Coll Cardiol 1993; 21: 1305-11.
12. 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: 139-44.
13. Shaw L, Chaitman BR, Hilton TC, et al. Prognostic value of dipyridamole thallium-201 imaging in elderly patients. J Am Coll Cardiol 1992; 19: 1390-8.
14. Davar JI, Roberts EB, Coghlan JG, Evans TR, Lipkin DP. Prognostic value of stress echocardiography in women with high (≥ 80%) probability of coronary artery disease. Postgrad Med J 2001; 77: 573-7.
15. 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: 1975-81.
16. Modena MG, Rossi R, Muia N, et al. Sex differences in noninvasive diagnosis of multivessel coronary artery disease. (abstr) J Am Coll Cardiol 1997; 29: 164-5.