Stress testing in women: sexual discrimination or equal opportunity?

Riccardo Bigi1* and Lauro Cortigiani2

1 Cardiology Unit, Department of Medicine and Surgery, University School of Medicine, via A. di Rudinì 8, Milan 20142, Italy
2 Cardiovascular Unit, 'Campo di Marte' Hospital, Lucca, Italy

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This editorial refers to ‘Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4234 women and 6898 men† by L.J. Shaw et al., on page 447

Cardiovascular disease is the leading cause of death among women in the majority of industrialized countries, accounting for 54% of total cardiovascular mortality in the United States.1 Between the ages of 45 and 64, one in nine women develops symptoms of some form of cardiovascular disease; the ratio climbs to one in three women after age 65.2 The number of cardiovascular deaths is increasing in women but declining in men. Most of this is due to ischaemic heart disease and stroke. In particular, the 49% of overall mortality due to coronary artery disease (CAD) is observed in the female population.1 This problem is expected to increase according to population aging, as obesity, metabolic syndrome, as well as diabetes disproportionately affect women, and CAD generally becomes clinically evident at least 10 years later in women as compared with men. Women demonstrate more symptoms and non-invasive test findings suggesting ischaemia, yet have a lower prevalence of luminal obstructive coronary disease on angiography. However, once presenting with obstructive coronary disease, women will have more adverse outcomes than men, particularly if coronary revascularization is needed as bypass surgery is associated with approximately two-fold increased mortality in women compared to age-matched men. Several reasons may explain poor outcomes observed in women. First, an incomplete understanding of the disease and its pathophysiological mechanisms which include more microvascular involvement, perhaps more inflammation, and still undefined vascular and metabolic abnormalities different to that seen in the usual male variant. Secondly, women with CAD generally present with more co-morbidities, and finally, biases in patient care have also been suggested. On the other hand, management of CAD in women has major economical implications: in the United States, more than $400 billion are annually spent for care,3 whereas women with unknown CAD, who present with signs and symptoms of ischaemia have an estimated lifetime cost approaching $750 000.3 Thus, the early recognition of CAD in the female population as well as the identification of subjects at increased risk of major cardiac events represent an emerging point in contemporary cardiology. Several aspects, however, concur to compound the problem: (i) diagnostic work-up in women may be limited or prematurely terminated because of clinical misperception of a lower pre-test probability of CAD by the physician and/or the patient; (ii) there is still concern about validated gender-neutral testing procedures with equivalent diagnostic accuracies in men and women; (iii) gender-based discrepancies exist in the availability, use, and accuracy of existing diagnostic studies; (iv) diminished diagnostic accuracy with various non-invasive testing modalities when given to women may have led to a lack of physician confidence and, in turn, to underuse of available diagnostic procedures. Whether, and to what extent, the underestimation of clinical coronary risk in women and the limited diagnostic accuracy of some non-invasive tests may have contributed to the increased mortality is not clear. Anyhow, the concept that a sort of sexual discrimination affects the accuracy of stress testing in women represents a widespread belief among clinical cardiologists, as demonstrated by the low rate of reports in the literature till the mid-1990s. In fact, a diminished diagnostic accuracy with various non-invasive cardiac tests has been reported in women as compared to men.

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Although exercise ECG represents the most used strategy for the non-invasive evaluation of CAD, it is recognized that exercise-induced ST segment depression has less diagnostic value in women than in men, mainly due to a high rate of false positive responses. Weighted mean sensitivity and specificity of 61 and 70%, respectively, were reported in a meta-analysis of 19 studies including 3721 women. Epidemiological (lower prevalence of CAD and more frequent conditions potentially associated with false positive results, such as syndrome X, mitral valve prolapse, and coronary vasospasm) as well as physiological (ECG voltage, hormonal fluctuations, and lower exercise ability) causes have been advocated to explain the gender-related difference in exercise ECG accuracy. Because of the limited value of exercise ECG, interest has grown in the last years in the use of imaging techniques for assessing CAD in women. Unfortunately, false positive results mainly due to breast attenuation and small left ventricular chamber size also limit diagnostic accuracy of nuclear imaging among women. In particular, a 64% weighted mean specificity has been reported. Moreover, high costs, availability, and radiation exposure may represent further limitations to the general application of nuclear techniques.

Combining echocardiography with exercise or pharmacologic challenge proved to be an equal opportunity modality, providing encouraging results for both diagnostic and prognostic purposes in women. Comparable sensitivity but significantly higher specificity and accuracy for detecting CAD was demonstrated with exercise echocardiography as compared to exercise ECG in women without prior Q-wave myocardial infarction. On the basis of avoidance of unnecessary angiography, stress echocardiography proved to be a cost-effective testing modality. From a prognostic standpoint, although cardiac events occur more frequently in men, the incremental value of exercise echocardiography was shown to be comparable in both genders. In the same way, dipyridamole stress echocardiography demonstrated similar sensitivity but significantly better specificity and accuracy when compared with exercise ECG in chest pain women with suspected CAD. The diagnostic value of stress echocardiography in women translates into effective prognostic information. In a consecutive cohort of women complaining of chest pain, ischaemia at pharmacologic stress echocardiography was an independent indicator of hard as well as all spontaneous cardiac events. Of interest, the negative test result was associated with 3-year event rate less than 1%. Moreover, stress echocardiography proved to add incremental prognostic information over clinical and exercise ECG.

In the present issue of the Journal, Shaw et al. report on 5-year mortality in 4234 women and 6898 men undergoing exercise and dobutamine stress echocardiography and provide convincing evidence that inducible wall motion abnormalities can similarly predict long-term outcome in women and men. Their findings reinforce previous observations of smaller series and emphasize the strong prognostic potential of echocardiographic ischaemia. Obvious organizational and economical implications could be derived from this study into clinical practice. Of interest, the authors found a significant interaction between male gender and ischaemia for both exercise and dobutamine stress, thus concluding that, even though gender per se was not predictive of outcome, overall survival was differently affected by the extent of ischaemia in women and men. That is not surprising as it reflects the main characteristics of this as well as other consecutive study populations. Indeed, although women were on average older and had higher prevalence of risk factors, men more often had a known CAD, including more frequent history of prior myocardial infarction and/or chest pain and more compromised left ventricular function at rest. These differences are especially evident among those undergoing dobutamine stress where the recourse to a pharmacological stressor seems mainly related to the generally reduced physical performance in women and to the poor heart function in men. This clinical background is expected to worsen the impact of inducible ischaemia by turning into a more unfavourable prognostic outcome. It should be interesting to know whether these results could also apply to more selected populations of women and men with similar risk characteristics as, for instance, those evaluated for chest pain under suspicion of CAD. Another factor to be considered in evaluating gender differences in the results of cardiovascular studies is represented by the racial and/or socio-economical distribution of the study population. Important differences are known to exist in morbidity and mortality as well as in the prevalence of individual risk factors for CAD among racial and socio-economical subgroups. Many differences are also expected to exist at every point along the medical chain leading from presentation to evaluation, detection, and treatment of CAD. High-risk minorities are less likely to be referred to undergo for invasive diagnostic and therapeutic procedures; moreover, they are less involved in awareness campaigns as well as in primary and secondary prevention and are also less represented in clinical trials. Which, if any, role these factors could play in defining the prognostic value of stress testing is not fully established.

References
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