Original Article

Usefulness of standard treadmill stress testing in women

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Abstract

Objective: To determine the usefulness of stress test to detect coronary artery disease in women in local population.

Methods: Patients coming for stress test were evaluated clinically and 835 patients were enrolled, 69.6% were men and 30.4% were women. Chest pain was the main reason for referral for treadmill stress testing. Bruce protocol was used for stress.85% of the maximum predicted heart rate was considered significant.

Results: Higher numbers of male patients were able to achieve the desired metabolic equivalents (METs) as compared to females. Diabetes was equally prevalent in both men and women while higher number of male patients had higher systolic blood pressure. Males were relatively older while females were relatively overweight. CAD was detected in 9.3% of men and 5.5% of women. The number of cancelled and non conclusive results was significantly higher in women. Gender, age and BMI were predictors of positive results.

Conclusion: The guidelines recommend using stress test as initial modality in most of women and this study validates this belief (JPMA 59:197; 2009).

Introduction

Coronary artery disease is the leading cause of mortality and morbidity in men and women.[1] The diagnosis of CAD in women is problematic due to many reasons.[2] At the same time prompt diagnosis of CAD in women is important to avoid the complications of unrecognized and untreated ischaemia.[3]

Numbers of investigations are available to diagnose CAD including resting electrocardiogram (ECG), 24 hour ambulatory ECG monitoring, resting echocardiogram, stress echocardiogram, myocardial perfusion imaging, electron beam computerized tomography (EBCT), multislice computed tomography (MSCT) and treadmill stress test. The standard treadmill stress testing is the most widely used, non invasive modality for evaluation of CAD. It is easy to perform, safe and less costly in comparison to other investigations.[4] The sensitivity of stress testing for CAD is 63% and specificity is 74%. For prognostic implications of serious disease like left main or severe triple vessel disease the sensitivity improves to 86%.[5] The pre test likelihood of the disease is an important consideration before subjecting any individual for stress testing. The number of false positive results is expected to be high in population with pretest likelihood of disease of <20% and number of false negative results is large in population with high pretest likelihood of>80%. The optimum results are obtained only if pretest likelihood of the disease ranges in between 20%-80%.[6] A test with 80% sensitivity and specificity will have 50% predictive value if the prevalence of the disease is 20% and predictive value of above 80% if the prevalence of disease is >50%.[7]

Proper selection of patients, functional response, electrocardiographic changes, adequacy of exercise and treadmill exercise scoring are important factors to validate the effectiveness of stress test. The treadmill test becomes more useful if the patient selected is male who is more than 40 years of age and has multiple associated risk factors.[8] It has been reported previously that stress test is associated with 40% false positive ST segment depression in women versus 10% in men.[9] Similarly the predictive value of test is poor in women. When the test has sensitivity of 68% and specificity of 61%, the positive predictive value is 0.61 and negative predictive value is 0.68.[10] Another important limitation in effectiveness of stress test in women is their inability to exercise to maximum aerobic capacity.[11] This has been proved from the previous studies that females tend to have low false negative results which approves the regular use of stress testing in females to rule out CAD.[12] Present study was a comparative study between men and women to determine the usefulness of standard treadmill exercise testing in women.

Patients and Methods

This was a prospective and comparative study including both males and females referred for stress testing during year 2006-2007 to non invasive cardiac lab in a university hospital in Saudi Arabia. Written informed consent was obtained from all patients. The study was approved by local ethical committee of the institution. Brief history was obtained from all patients. Those patients who had angina Canadian class 11-V1, evidence of decompensated heart

failure, sustained arrythmias, pregnant women, clinically detectable aortic stenosis of unknown severity, severe aortic stenosis as defined by mean gradient of 40 mm of Hg and aortic valve area of <1cm^2, advanced osteoarthritis of knee or hip joints or any other disability leading to inability to perform exercise and patients receiving digoxin were not allowed to proceed further. Those patients whose baseline ECG had already ST segment deviation or were having left or right bundle branch block were also excluded. All patients had detailed clinical examination including supine and standing blood pressure measurements, cardiac auscultation and measurement of oxygen saturation by pulse oximetery. Those patients whose blood pressure was >220/120 and <80 mm of Hg systolic were not subjected for the stress test and were referred back to treating physician to optimize the treatment. Those patients, who did not stop beta blockers 48 hours before the test or they were using rate lowering calcium channel blockers, were postponed.

Adequate skin preparation was undertaken. Resting 12 lead ECG was performed. Torso ECGs were performed in supine and standing positions. The protocol used for stress testing was Bruce. Each stage had standard duration of three minutes. The test was performed on GE advanced system which was a dedicated stress test unit and had automatic speed acceleration starting from 1.7 to 2.5, 3.4, 4.2, 5.0 and 5.5 MPH. Similarly the inclination started at grade of 10% and automatically progressed further with each three minutes increment to 12%, 14%, 16%, 18% and 20% respectively. The exercise capacity was defined in terms of metabolic equivalents (METs); one MET was equivalent to 3.5mlO2/Kg/min.Stage one was equivalent to 5 METs and subsequent stages were equivalent to 7,10,14,16 and 18 METs. Maximum predicted heart rate (MPHR) was calculated as 220-age and 85% of MPHR was considered significant. The ECG was automatically recorded after completion of each stage and blood pressure was recorded one minute before the end of each stage and thereafter every minute in recovery for five to ten minutes. The exercise was stopped if the ST deviation recorded was more than three millimeters or systolic blood pressure exceeded 220mm of Hg or diastolic exceeded120mm of Hg or abnormal blood pressure response and heart rate response was obtained. This abnormal response was defined as more than 10 mm of Hg drop in blood pressure or drop in heart rate of more than 20 beats per minute. Abnormal response of the test was termed as positive which was defined as having ST deviation of >1mm in three adjacent complexes with stable baseline ,having horizontal or down sloping configuration and occurring 80 milliseconds after J point. The test was declared negative if there were no significant changes and non conclusive if exercise was sub maximal. Cancelled test were those where patients could not complete even one minute of exercise or could not continue in warm up stage. The recovery was continued for five minutes or delayed till normalization of ECG changes.

The ECG was continuously obtained after every minute for first 5 minutes and thereafter every three minutes.

Comparison between men and women was performed using the 2-sample t test for continuous variables and chi-square test for categorical variables. A p value of <0.05 was considered significant. Exact test P values were computed using StatsDirect Statistical software version 1.9.

Results

Eight hundred and thirty five patients were subjected for stress testing commencing from February 2006 till July 2007. Predominantly male patients (69.6%) were sent for stress testing as compared to smaller percentage (30.4) of women. Various baseline characteristics comparing both groups are shown in Table-1. The male patients were slightly older as compared to females but there was no statistically significant difference. Higher numbers of women were significantly overweight or obese as compared to men. Chest pain was the most common reason for referral of these patients for evaluation for CAD but higher number of women had significantly associated symptoms of dyspnoea and palpitation. Diabetes was equally prevalent in both groups while systolic blood pressure was significantly higher in males. The diastolic blood pressure in both groups was nearly the same. The resting heart rate was significantly higher in females. However the overall maximum predicted heart rate (MPHR) achieved in males was superior to females. But at the same time the maximum heart rate in males (158 ± 21) was lower than the desired MPHR. The exercise capacity was better in males achieving upto 14 metabolic equivalents (METs) while women had significantly lower exercise threshold achieving maximum of 10 METs. Table 2 compares the treadmill results in both groups.439 (75.6%) male patients had negative test as compared to females, 142 (55.9%). Number of positive results were 56 (9.3%) in men versus 14 (5.5%) in women. Nonconclusive results were obtained in 72 (12.4%) men and in significantly higher number of women 69 (27.4%). The cancellation was 16 times (2.6%) in men as compared to 29 times (11.4%) in women.

Discussion

Non invasive diagnosis of CAD in women is difficult as women have lower prevalence of CAD thereby increasing the chances of false positive results and lower sensitivity because of milder disease.[13] Atypical chest pain is a very common symptom in women making the decision very difficult as to which patient has genuine chest pain and which

Table 1: Baseline characteristics of two groups.

Variables	Men N (581) 69.6%	Women N (254) 30.4%	P value
Age(yrs,mean± SD)	49.06±10.88	47.17±9.89	NS
BMI	26±2.8	29±5.8	<0.001
Chest pain	63%	66%	NS
Dyspnoea	43%	62%	<0.001
Palpitation	37%	57%	<0.001
Syncope	3.2%	2.8%	NS
Diabetes	23%	24%	NS
Hypertension	32%	25%	<0.001
Resting hart rate (beats/min)	82.9±16.7	88.2±17.08	<0.001
Resting systolic BP (mm/Hg)	130±16	118±15	<0.001
Resting diastolic BP (mm/Hg)	81±8	80±8	<0.001

Data is expressed as Mean ± SD

one of these patients need further testing.[14] At the same time it is well documented that lesser number of female patients with chest pain are referred for further testing leading to under diagnosis and under treatment of CAD.[15] Coronary artery surgery study (CASS) showed poor correlation between chest pain and significant CAD in women.[16] Gender difference in evaluation of CAD is compounded by the lack of confidence in the diagnostic testing in women.[17] Patients with poor exercise capacity have poor overall prognosis irrespective of ST segment changes during stress test.[18] Poor exercise capacity in women was demonstrated in our study as they were unable to achieve MPHR and desired METs. These results correlated well with the results from previous studies in term of inability of women to complete the exercise to maximum aerobic capacity and strengthening the belief of this factor as one of the important reasons of false positive, false negative results or non conclusive results.[19] The non diagnostic rate of 12.4% in men and 27.6% in women in this study is well comparable to previously reported rate in literature of18%-31%.[20] The significant cancellations and

Table 2: Treadmill stress test results.

Variables	Men N (581) 69.6%	Women N (254) 30.4%	P value
Exercise			
Maximum heart rate	158.79± 20.74	159.00± 22.20	NS
Maximum systolic BP(mm of Hg)	172 ±15	146 ±20	<0.001
Maximum diastolic BP(mm of Hg)	85± 8	84± 8	NS
METs	9.6± 3.5	6.9 ±2.8	<0.001
Test Results			
Negative	439(75.6%)	142(55.9%)	<0.001
Positive	56(9.3%)	14(5.5%)	<0.001
Non conclusive	72(12.4%)	69(27.4%)	<0.001
Cancelled	16(2.6%)	29(11.4%)	<0.001

Data is expressed as Mean± SD
BP (Blood pressure); METs (Metabolic Equivalents).

subsequent course in this study did not demonstrate any disparity between this study and previous reported study showing women are less likely to undergo further testing and coronary angiography irrespective of result of the initial stress test.[21] The history of co existing risk factors or baseline investigations to exclude unknown hyperglycaemia and dyslipidaemia is mandatory in order to investigate CAD as male gender, hypertension, abnormal BMI, diabetes and current smoking are strongly related to higher chances of positivity of non invasive test to detect CAD.[22] This study did not include the history of smoking as it was difficult to ask about smoking from females due to social reasons. However the prevalence of diabetes was equal in both sexes and it also matched the overall prevalence of diabetes of around 23% in Saudi Arabia.

An interesting finding as a result of this study revealed that after nearly 18 months of stress testing in a university hospital only 14 females were discovered to have positive result. It is not clear that how many of them will have false positive results and how many of those who have true positive results will have non significant CAD. Here the concern arises that is it worth to send women for stress testing as an initial test? This study correlated well with the prevalence of CAD in women as reported in previous studies where the prevalence was reported to be 7%.[23] This picture overall is depressing and throws doubts on this modality and shatters the confidence of doctors in reliance on this test to evaluate CAD in women. This study has demonstrated significant disparity between males and females in terms of number of patients referred, prevalence of obesity, uncontrolled systolic hypertension, lower number of positive results in both males and females and very low number of positive cases in women.

To improve the out come of stress testing in women recommended is the incorporation of QRS scoring in standard protocols in addition to assessment of pretest likelihood of the disease.[24] In women with low pretest likelihood stress test is the modality of choice while in intermediate and high likelihood group there is no cost difference between myocardial perfusion imaging and standard stress test therefore the choice should be perfusion imaging.[25]

Limitations:

Unfortunately the major limitation of this study was that Duke scoring was not incorporated at the time of stress testing. The second important observation was that the number of women was roughly one third of total participants, thereby creating difference in number of participants very obvious and this may throw doubts on the impact of study as it was a comparative study between men and women. The number of the patients were not prespecified however the

period was prespecified and all those patients whether male or female were enrolled if they were eligible. It would have been better if the females enrolled were either more or at least equal in number as compared to men.

Conclusion

Treadmill stress test is most useful in subjects who can perform adequate exercise to achieve 85% of MPHR. It remains the modality of choice in most of women till the issue of appropriate first line non invasive test in women is addressed in further large studies.

References

1. Lerner DJ, Kanne WB. Patterns in coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986; 111:383-90.
2. Herlitz J, Bang A, Karlson BW, Hartford M. Is there a gender difference in aetiology of chest pain and symptoms associated with acute myocardial infarction? Eur J Emerg Med 1999; 6:311-5.
3. Khan SS, Nessim S, Gray R, Czer LS, Chaux A, Matloff J. Increased mortality of women in coronary artery bypass surgery: evidence for referral bias. Ann Intern Med 1990; 112:561-7.
4. Braunwald E, Mark DB, Jones RH, Brown J, Brown L, Cheitlin MD, Concannon CA, Cowan M, Edwards C, Fuster V. Unstable angina: diagnosis and management. Clinical Practice Guidelines Number 10. AHCPR Publication No. 94-0602. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, Public Health Service, US Department of Health and Human Services. March 1994.
5. Wackers FJ, Asymptomatic patients with diabetes mellitus should be screened for coronary artery disease. J Nucl Cardiol 2006; 13:609-15.
6. Hennessy TG, Codd MB, Kane G, McCarthy C, McCann HA, Sugrue DD. Dobutamine stress echocardiography in the detection of coronary artery disease: importance of pretest likelihood of disease. Am Heart J 1997; 134:685-92.
7. Severi S, Michelassi C. Prognostic impact of stress testing in coronary artery disease. Circulation 1991; 83:III: 82-8.
8. Crouse LJ, Kramer PH. Are there gender differences related to stress or pharmacological echocardiography? Am J Card Imaging 1996; 10:65-71.
9. 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; 83:660-6.
10. Curzen N, Patel D, Clarke D, Wright C, Mulcahy D, Sullivan A, et al. Women with chest pain: is exercise testing worthwhile? Heart 1996; 76:156-60.
11. Josephson Me. Treatment of ventricular arrhythmias after myocardial infarction. Circulation 1986; 74:653-8.
12. Weiner DA, Ryan TJ, Parsons L, Fisher LD, Chaitman BR, Sheffield LT, 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; 75:865-70.
13. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility,safety and diagnostic accuracy of dobutamine stress echocardiography.J Am Coll Cardiol 1997; 30:595-606.
14. Sheps DS, Kaufmann PG, Sheffield D, Light KC, McMahan RP, Bonsall R, 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.
15. Tobin J N, Wassertheil-Smoller S, Wexler JP, Steingart RM, Budner N, Lense L, et al. Sex bias in considering coronary bypass surgery. Ann Intern Med 1987; 107:19-25.
16. Chaitman BR, Bourassa MG, Davis K, Rogers WJ, Tyras DH, Berger R, et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981; 64:360-7.
17. Sketch MD, Mohiuddin SM, Lynch JD, Zencka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. Am J Cardiol 1975; 36:169-73.
18. Peterson PN, Magid DJ, Ross C, Ho PM, Rumsfeld JS, Lauer MS, et al. Association of exercise capacity on treadmill with future cardiac events in patients referred for exercise testing. Arch Int Med 2008; 168:174-9.
19. Guiteras P, Chaitman BR, Water DD, Bourassa MG, Scholl JM, Ferguson RJ, et al. Diagnostic accuracy of exercise ECG lead systems in clinical subsets of women. Circulation 1982; 65:1465-73.
20. Dewey M, Du¨bel HP, Schink T, Baumann G, Hamm B. Head-to-head comparison of multislice computed tomography and exercise electrocardiography for diagnosis of coronary artery disease. Eur Heart J 2007; 28: 2485-90.
21. Daugherty SL, Peterson PN, Magid DJ, Ho PM, Bondy J, Hokanson JE, et al. The relationship between gender and clinical management after exercise stress testing. Am Heart J 2008; 156:301-7.
22. Raimond Esbel, Joseph et al, Signs of sub clinical coronary atherosclerosis in relation to risk factors distribution, Eur Heart J 2008; doi 10:1093-439.
23. Sheffield LT, Maloof JA, Sawyer JA, Roitman D. Maximal heart rate and treadmill performance of healthy women in relation to age. Circulation 1978; 57:79-84.
24. Michaelides AP, Fourlas CA, Chatzistamatiou EI, Andrikopoulos GK, Soulis D, Psomadaki ZD, Stefanadis CI. QRS score improves diagnostic ability of treadmill exercise testing in women. Coron Artery Dis 2007; 18:313-8.
25. Nikhant K, Soman P, Udelson JE. The price for probability: comparing the costs of diagnostic testing. J Nucl Cardiol 2007; 14: 142-4.