EXERCISE TOLERANCE TEST AS A SCREENING TOOL FOR CORONARY ARTERY DISEASE IN ASYMPTOMATIC ADULTS

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ABSTRACT

Objective: To determine the screening efficacy of exercise tolerance test in the diagnosis of coronary artery disease in asymptomatic physically active adults.

Study Design: Hospital-based cross-sectional validation study.

Place and Duration of Study: Department of Medicine, Combined Military Hospital Mangla Cantonment, from Jan 2019 to Nov 2019.

Methodology: Eight Hundred and Four patients fulfilling the inclusion criteria were included in study after obtaining informed written consent. All the enrolled subjects underwent an exercise tolerance test. Those subjects who had a normal exercise tolerance test were not assessed further and those who had an abnormal or inconclusive exercise tolerance test were referred to Armed Forces Institute of Cardiology/National Institute of Heart Diseases for coronary angiography. A database was maintained and used for further analysis.

Results: Exercise tolerance test positivity is very low in asymptomatic young and active males, which was established to be 9% in our study. Similarly it was found that the positive predictive value of an abnormal exercise tolerance test result is also unacceptably low i.e. 18%.

Conclusion: The diagnostic yield of exercise tolerance test remains low in view of a very high rate of false positive results, technical & procedural shortfalls and ethical constraints of subjecting asymptomatic persons to invasive and expensive coronary angiography.

Keywords: Atherosclerosis, Coronary artery disease, Mass screening.

INTRODUCTION

Coronary artery disease (CAD) is a very important public health issue worldwide with a high prevalence in South Asia including Pakistan[1,2]. The prevalence of this disease is on the rise as evidenced by population based studies carried out in the recent years[3]. The risk factors for CAD are well known and include hypertension, diabetes mellitus, hyperlipidemia, smoking, sedentary lifestyle, obesity and positive family history etc[4]. CAD has a lot of presentations which include chest pain, breathlessness and signs of heart failure etc. However many a times it presents for the first time with massive myocardial infarction or sudden cardiac death in a previously asymptomatic individual. Many screening tools are utilized to identify the individuals at risk to develop CAD. These include history, blood pressure measurements, blood sugar determinations, lipid profile measurements, serum uric acid quantification and resting ECG etc in addition to novel biomarkers[4-6]. Further evaluations including resting echocardiography, conventional exercise tolerance test (ETT), stress echocardiogram, Computerized Tomographic (CT) angiography, Thallium scan and conventional coronary angiography etc are usually carried out if the screening tools point to the presence of CAD [4]. A high coronary artery calcium score on CT angiography if followed by conventional coronary angiography can predict later morbidity and mortality[7]. However being an invasive and relatively expensive test angiography cannot be utilized as a screening test in asymptomatic individuals. It is therefore important to assess the diagnostic utility of a non-invasive and inexpensive test in asymptomatic individuals

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as CAD can present with catastrophic cardiac events even in this population. ETT is a relatively easy, non-invasive and cheaper test and it is been used as a screening tool in susceptible populations which include those with diabetes mellitus and those having chest pain etc. We have carried out this study to determine the diagnostic accuracy of this test as a supplement to history, physical examination and basic tests in previously asymptomatic individuals in order to ascertain its usefulness as a screening tool.

METHODOLOGY

This hospital-based cross-sectional validation study was carried out at Combined Military Hospital, Mangla Cantonment from 11 January 2019 to 7 November 2019. The Ethical Review Committee of the hospital reviewed the study proposal and found it to be ethically sound (EC Ref no. 21/Trg/CMH Mgl dated 03 Jan 2019). International prevalence of coronary artery disease is 6.7%. Keeping accuracy of 0.05, and a constant of 1.96 for 95% confidence interval, we applied NHS sample size calculator and found out minimum sample representative of 26264 (estimated population) to be 96. A total number of 804 individuals were selected by non-probability consecutive sampling after taking informed written consent.

We included male residents of Mangla and surrounding areas reporting to Combined Military Hospital, Mangla Cantonment with normal resting ECGs, 35-56 years of age. Individuals with atypical chest pain or minor changes in resting ECG (isolated T wave inversions in leads III, aVF, I or aVL) of 21-56 years of age were also included in the study. We excluded individuals having a note of CAD, valvular heart disease or grossly abnormal resting ECG findings (T wave inversion with ST segment changes in one or more groups of leads). Presence of significant systemic co-morbid conditions including uncontrolled hypertension and musculoskeletal disorders and patients taking beta blockers, non-dihydropyridine calcium channel blockers and anti-arrhythmic drugs were excluded from the study because of chances of interference with the ETT findings were excluded from study.

A detailed history was taken from each individual and clinical examination was carried out with emphasis on detecting heart murmurs and pulmonary findings such as wheezing and crackles, followed by resting ECG, complete blood count, blood sugar, renal and liver function tests, lipid profile and urine routine examination were carried out to identify the individuals who fulfilled the inclusion and exclusion criteria of this study. The individuals enrolled in the study underwent exercise tolerance test using modified Bruce Protocol. ETT results were analyzed and categorized into the following standard categories into 'negative for ischemia', 'borderline positive for ischemia', 'positive for ischemia', 'positive for arrhythmia', and 'inconclusive' on the basis of ST changes observed and any arrhythmia observed during the study:

The individuals with normal ETTs were documented as not requiring coronary angiography and were not taken to the next step. Those persons who had any other category of ETT were further referred to AFIC/NIHD (Armed Forces Institute of Cardiology/National Institute of Heart Diseases) a tertiary care center of excellence for further CT/conventional angiography and evaluation. After this step the whole study population was categorized as per table-I for analysis of the results:

We maintained the database in IBM-SPSS version-25. Descriptive statistics were applied to find out frequency variables. 2 x 2 table analysis was conducted to find out the positive predictive value of an abnormal exercise tolerance test in our subjects.

RESULTS

We performed exercise tolerance test on a cohort of 804 male subjects for routine evaluation of their cardiovascular status. Youngest individual was 21 years of age and maximum age was 56 years. Mean age was 40.39 ± SD 5.197, (figure). 732 (91%) recordings carried no evidence of ischemia or arrhythmia on ETT. 34 (4.2%) were

found to have the equivocal finding of borderline positivity for coronary ischemia. Out of the 804 individuals, only 27 (3.4%) were labeled to be positive for ischemia, and 5 (0.6%) exhibited signs of arrhythmia on their exercise tolerance test. We found out that 6 (0.7%) of all ETT recordings remained inconclusive.

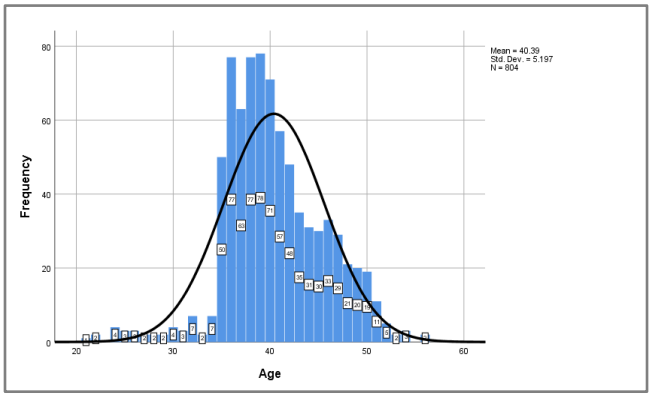

Figure: Age Histogram.

Coronary angiography was deemed to be unnecessary in 733 (91.1%) of our under-study subjects on the basis of a negative ETT. Subsequently, only 71 (8.8%) of our under-study subjects were referred to tertiary care cardiac centre for their angiographic assessment out of which 68 (8.5%) reported there and 3 (0.4%) lost to follow up. Angiography was conducted in 68 (8.4%) persons. 54 (6.7%) had normal coronaries. Only 13 (1.6%) and 1 (0.1%) of the cumulative percentage were revealed to have a positive angiographic evidence of coronary artery disease and muscle bridge on LAD, respectively. The distribution of CAD or lack thereof amongst the various positive/inconclusive ETT result groups is mentioned in table-I. It is obvious that coronary artery disease was confirmed in a very low percentage of the individuals even with abnormal ETT results i.e., 13 (18.1%). Positive predictive values of the different categories of ETT results were also calculated and are given in table-II. This table illustrates the low diagnostic yield of ETT in asymptomatic individuals.

However, sensitivity, specificity and negative predictive values of exercise tolerance test could not be ascertained on account of ethical restraints, which did not allow us to refer asymptomatic patients with normal ETT for coronary angiography. We therefore could not establish true negative and false negatives based on ETT findings (table-I).

Table-I: Exercise tolerance Test × Coronary Angiography Findings.

		Angiography Not Required	Normal Coronary Arteries	Coronary Artery Disease on Angiography	Muscle Bridge LAD on Angiography	Lost to follow up	Total
Exercise Tolerance test	Negative for Ischemia	732 (99.9%)	-	-	-	-	732 (91%)
	Borderline positive for Ischemia	-	25 (46.3%)	7 (53.8%)	-	2 (66.7%)	34 (4.2%)
	Positive for Ischemia	-	21 (38.9%)	5 (38.5%)	1 (100%)	-	27 (3.4%)
	Positive for arrhythmia	1 (0.1%)	4 (7.4%)	-	-	-	5 (0.6%)
	Inconclusive	-	4 (7.4%)	1 (7.7%)	-	1 (33.3%)	6 (0.7%)

Table-II: Positive Predictive Values of Abnormal Exercise Tolerance Test Results.

Category of Exercise Tolerance Test Abnormality	True positive results (coronary artery disease confirmed on angiography)	False positive results (coronary artery disease ruled out on angiography)	Positive Predictive Value	
a. Borderline positive for ischemia	7 (20.58%)	27 (79.41%)	Grand Total	21%
b. Positive for ischemia	5 (18.51%)	22 (81.48%)		19%
c. Positive for arrhythmia	-	4 (100%)		-
d. Inconclusive	1 (16.66%)	6 (100%)		14%
e. Overall positive predictive value of an abnormal exercise tolerance test	13 (18%)	59 (81.94%)	72	18%

DISCUSSION

Although age-adjusted mortality is decreasing in the United States, however coronary

artery disease is still increasing as the cause of death in developing countries[8]. CAD remains a top killer all over the world and especially in the South Asia with decreasing age of onset observed in recent years. Coronary heart disease is nevertheless the most preventable of all cardiovascular diseases. Annual cost of burden of its treatment would exceed $1 trillion by the year 2030[9]. It has been suggested that asymptomatic disease is far more prevalent[10]. In addition to community efforts to reduce the risk factors well known through the Framingham Study, a need has been felt to improve the screening procedures to avoid sudden cardiac death and morbidity in previously asymptomatic individuals. In our study we have tried to determine the efficacy of exercise tolerance test in terms of feasibility and diagnostic accuracy in screening the asymptomatic otherwise physically active males. We have found in our study that this procedure to be carried out in the general population as screening test is not feasible because of following two reasons. First of all a very low percentage of the tested population had an abnormal test result in our study 72 (9%). And secondly, that even when the ETT result was positive it translated to the presence of coronary artery disease in a very low percentage 14 (19.4%) of positive tests and 1.7% of the total study group). Due to specific procedural and ethical constraints, we failed to elaborate the yield of exercise tolerance test in terms of its negative predictive value. The same question has also been raised in literature showing conflicting results. Jean-Louis Megnein *et al* and cited by Attar *et al*[11]. Carried out an analysis of the prospective studies published on this subject. They concluded that in the asymptomatic population ETT has frequent false positive results but abnormal results can be used to predict future CAD as the population with positive ETT had a much higher rate of progression to CAD. In yet another citation by LaMonte, Gary. Balady *et al*[12] used ETT as an additional test in 3043 members of the Framingham Heart Study offspring cohort without CAD and after following them for 18.2 years found out that a positive test provided CAD prediction over and above the original Framingham risk factors in men but not in women. Rezaii[13] similarly concluded that ETT positivity is associated with CAD in asymptomatic elderly men, in a recent citation by Murrone. However ETT positivity was associated with significant CAD in females with co-existing hypertension or diabetes mellitus only. Dawood *et al*[14,15] found that in asymptomatic individuals especially females had a higher percentage of false positive results on ETT as compared to people with co-morbidities, especially males. Armin *et al*[11] worked on the possible cause of false positive ETT results and found that this phenomenon was found to be more common in people with left dominant coronary circulation. They found that left dominant coronary circulation was found in 27% of people with a positive ETT but a normal coronary angiogram as compared to 10.9% left dominance in the whole population. Considering the non-specificity of ETT positivity in the general population current guidelines including those from American College of Physicians and US Preventive Services Task Force propose that ETT should not be used as a screening test for CAD[16,17]. The use of ETT as a form of reassurance for the patients who are anxious that they may have CAD has been studied and found useful and therefore may be considered on a case to case basis[18].

More and more stress is aimed on instituted counseling, media campaigns and mass educational strategies highlighting the risks of coronary artery disease in the modern era. It has been proposed over the last one decade that adequately addressing the three major risk factors like cigarette smoke exposure, hyperlipidemia and hypertension brought down mortality in 66% of women and 69% of men[19]. In the guidelines of American College of Cardiology and American Heart Association a risk estimation score for 10-years regarding possible development of first atherosclerotic cardiovascular event has been promulgated[20]. These guidelines bring into account physical and biochemical parameters like age, total cholesterol (HDL-C), systolic blood pressure

(treated and untreated) diabetes mellitus and current smoking status for risk estimation.

On the contrary, the American College of Physicians (ACP) guidelines clearly demonstrate no evidence of benefit of cardiac screening on patient outcome in asymptomatic low risk adults[16]. The guidelines restrain cardiac screening in these active subjects on account of false positive results, low predictive value (possibly adversely affecting therapeutic decisions), and with regards invasiveness of these procedures. It is advocated that for patients in their 2nd till 7th decade of life, who do not have existing atherosclerotic coronary vascular event, clinical risk factors must be meticulously ruled out every 4 to 6 years.

A major limitation of our study is that females were not studied and therefore the recommendations cannot be generalized to the whole asymptomatic population through our study; although as pointed out in many studies females are even more likely to have false positive ETT results than males[21].

RECOMMENDATION

Owing to the inadequate yield of ETT, we recommend that exercise tolerance test should not be used as a routine screening test for CAD in asymptomatic active adults. Instead emphasis must be laid on preventing the onset of cardiovascular events by addressing the well known risk factors like diabetes mellitus, hypertension, smoking, hyperlipidemia, obesity and stress etc.

CONCLUSION

The diagnostic yield of exercise tolerance test remains low in view of a very high rate of false positive results, technical & procedural shortfalls and ethical constraints of subjecting asymptomatic persons to invasive and expensive coronary angiography.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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