Original Article

Predictors of outcome in exercise testing for new onset cardiac ischemia

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Objectives: To determine the predictors of outcome of exercise treadmill test (ETT) for the diagnosis of coronary artery disease with a view to develop a model to identify those best suited for a conclusive treadmill result.

Methodology: Data of consecutive 502 patients referred for ETT by local general practioners with chest pain was collected prospectively. Various cardiovascular risk factors were assessed.

Results: Significant predictors of positive ETT result included elderly males, diabetes mellitus, typical chest pain and abnormal resting electrocardiogram ($p<0.05$). ETT results were significantly negative for young and middle aged, normotensives, non-diabetics, atypical chest pain and normal resting electrocardiogram ($p<0.05$). The results were inconclusive for females, obese and very elderly ($p<0.05$).

Conclusion: Males, elderly, diabetes mellitus, typical chest pain and abnormal resting electrocardiogram had the highest probability to have positive ETT results in coronary artery disease. (Rawal Med J 2014;39: 128-132).

Key words: Exercise stress test, coronary artery disease, angina.

INTRODUCTION

Exercise treadmill test (ETT) is a relatively simple, non-invasive and cost effective procedure commonly used for assessment of cardiovascular disease. The diagnostic and prognostic value of this test has been widely accepted.[1,2] It is the second most frequently performed investigation after electrocardiography (ECG).[1-3] Common indications for ETT include patients with probability of coronary artery disease (CAD), vasospastic angina, determination of functional capacity and risk assessment in CAD.[1-4] While ETT has been recognized as a sensitive and specific modality for diagnosis and prognosis of cardiovascular disease, the knowledge of predictors of outcome is limited. The purpose of this study was to determine the predictors of different outcomes of ETT with a view to develop a model to differentiate those best suited for a conclusive treadmill result from those better suited for imaging techniques.

METHODOLOGY

Data of consecutive 502 patients referred by local general practioners (GPs) with chest pain for ETT to the Department of Cardiorespiratoty Medicine, Leighton Hospital, Crewe, United Kingdom was collected prospectively over a period of four years. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the declaration of Helsinki 1975, as revised in 2000.

Individuals aged $\geq$18 years, without a previous diagnosis of cardiovascular disease, with chest pain were included in the study. Patients with ST depression >1mm, pathological Q waves or left bundle branch block on baseline ECG, patients on β-blockers, patients with organic valvular and/ or congenital heart disease were excluded from the study. All those with contraindications to ETT and with baseline abnormalities that may obscure ECG changes during exercise were also excluded.[1-6] The presence of recognized cardiovascular risk factors including gender, age, history of smoking, hypertension, dyslipidemia, diabetes mellitus, obesity and family history of cardiovascular disease was documented for all patients.[7-12] ECG was defined as 'abnormal resting ECG' if with ST changes suggesting is chemia.[1,13] Exercise treadmill was performed according to standard Bruce

protocol with target heart rate defined as 85% of the age-predicted maximal heart rate (APMHR) using the formula: (APMHR = 220- age).[1-3]

Results of ETT were recorded as positive (abnormal), negative (normal) or inconclusive (non-diagnostic).[1-3] The data were analyzed using statistical software NCSS (Number Cruncher Statistical Systems) 1997 for Windows.[14] Univariate analysis was performed using Pearson's chi-square and student t-test. Multivariate analysis was conducted via forward stepwise logistic regression. $P < 0.05$ was taken as statistically significant.

RESULTS

Out of 502 patients, 255 (50.79%) were females and 247 (49.20%) were males. Mean age was 56.32±4.21 years. Resting 12 lead ECG was normal in 358 (71.31%) individuals and abnormal in 144 (28.68%). Typical chest pain was experienced by 201 (40.03%) while 301 (59.96%) had atypical chest pain. History of smoking, hypertension and family history of coronary artery disease were the most frequent risk factors (Table 1).

Table 1: Baseline characteristics of study population.

Characteristics	Total individuals with relevant characteristic % (n)	Gender distribution of baseline characteristics	
		Males % (n)	Females % (n)
Smoker	57.96 (291)	56.01 (163)	43.98 (128)
Hypertension	40.83 (205)	44.87 (92)	55.12 (113)
Diabetes Mellitus	8.96 (45)	60.00(27)	40.00 (18)
Obesity	29.88 (150)	47.33 (71)	52.66 (79)
Family History of CAD	54.98 (276)	43.84 (121)	56.15 (155)
Dyslipidemia	38.04 (191)	47.12 (90)	52.87 (101)
Abnormal resting ECG	28.68 (144)	56.25 (81)	43.75 (63)
Typical chest pain	40.03 (201)	73.13 (147)	26.86 (54)

ETT was positive in 94 (18.72%) individuals, negative in 229 (45.61%) and inconclusive in 179 (35.65%) (Table 2). Abnormal resting ECG, typical chest pain, smoking and diabetes were relatively more common in males while obesity, hypertension, dyslipidemia and family history of coronary artery disease were common in females (Table 1).

Table 2: Odds of having different ETT outcomes with different risk factors.

Variable	OR	CI	P value
Regression analysis for positive ETT			
Age	-	-	0.00*
Gender	1.75	1.04 – 2.93	0.03*
Obesity	0.48	0.26 – 0.87	0.01*
Smoking	1.30	0.78 – 2.19	0.30
Hypertension	1.34	0.80 – 2.24	0.26
Diabetes Mellitus	3.63	1.71 –7.71	0.00*
Dyslipidemia	1.33	0.79 – 2.23	0.27
Family history of CAD	1.51	0.90 – 2.53	0.11
Typical chest pain	3.17	1.97 – 5.63	0.00*
Abnormal resting ECG	3.02	1.81 – 5.03	0.00*
Regression analysis for negative ETT			
Age	-	-	0.00*
Gender	1.27	0.83 – 1.93	0.25
Obesity	0.71	0.45 – 1.12	0.13
Smoking	0.73	0.48 – 1.11	0.14
Hypertension	0.55	0.36 – 0.84	0.00*
Diabetes Mellitus	0.20	0.08 –0.49	0.00*
Dyslipidemia	1.28	0.84 – 1.96	0.25
Family history of CAD	0.98	0.65 – 1.49	0.93
Typical chest pain	0.64	0.41 – 0.97	0.00*
Abnormal resting ECG	0.55	0.34 – 0.87	0.01*
Regression analysis for inconclusive ETT			
Age	-	-	0.00*
Gender	0.49	0.33 – 0.75	0.00*
Obesity	2.14	1.39 – 3.28	0.00*
Smoking	1.17	0.78 – 1.76	0.42
Hypertension	1.48	0.99 – 2.22	0.05
Diabetes Mellitus	1.24	0.64 –2.39	0.51
Dyslipidemia	0.71	0.47 – 1.08	0.11
Family history of CAD	0.75	0.50 – 1.11	0.15
Typical chest pain	0.68	0.38 – 1.24	0.30
Abnormal resting ECG	0.74	0.48 – 1.17	0.20

Odds of having different ETT outcomes with different risk factors. OR = odds ratio; CI = confidence interval; ETT = Exercise treadmill test; CAD = coronary artery disease; ECG = Electrocardiogram; $p < 0.05$ = significant = *

On univariate analysis, atypical chest pain was mostly conclusive of a negative or inconclusive test result while typical chest pain was coherent with a positive result (Table 2,3). ETT results were significantly positive for males but inconclusive for majority of females and hypertension was consistent with a positive or inconclusive result. The results of ETT for diabetics and abnormal resting ECG mostly showed positive outcomes. Obesity was associated with inconclusive results while history of smoking, dyslipidemia and family history were statistically insignificant on univariate

analysis. Those between 60-80 years were the ones with most consistent positive ETT outcome (Table 2,3).

Table 3: Regression analysis showing relationship of various factors with outcome of ETT.

Category	Negative % (n)	Inconclusive % (n)	Positive % (n)	Total % (n)	P value
Gender					
Male	52.40 (120)	38.54 (69)	61.70 (58)	49.20 (247)	0.00*
Female	47.59 (109)	61.45 (110)	38.29 (36)	50.79 (255)	
Age (years)					
Up to 40	14.41 (33)	2.79 (5)	0.00 (0)	7.56 (38)	0.00*
40-60	66.37 (152)	50.27 (90)	43.61 (41)	56.37 (283)	
60-80	19.21 (44)	45.81 (82)	56.38 (53)	35.65 (179)	
>80	0.00 (0)	1.11 (2)	0.00 (0)	0.39 (2)	
Resting ECG					
Abnormal	17.90 (41)	30.16 (54)	52.12 (49)	28.68 (144)	0.00*
Normal	82.09 (188)	69.83 (125)	47.87 (45)	71.31 (358)	
Chest pain					
Typical	29.69 (68)	39.10 (70)	67.02 (63)	40.03 (201)	0.00*
Atypical	70.30 (161)	60.89 (109)	32.97 (31)	59.96 (301)	
Obesity					
Obese	25.89 (57)	39.66 (71)	23.40 (22)	29.88 (150)	0.00*
Non-obese	75.10 (172)	60.33 (108)	76.59 (72)	70.11 (352)	
Smoking					
Smokers	52.83 (121)	62.01 (111)	62.76 (59)	57.96 (291)	0.10
Non-smokers	47.16 (108)	37.98 (68)	37.23 (35)	42.03 (211)	
Blood Pressure					
Hypertensive	29.25 (67)	50.27 (90)	53.19 (50)	41.23 (207)	0.00*
Normotensive	70.74 (162)	49.72 (89)	46.80 (44)	58.76 (295)	
Diabetes Mellitus					
Diabetic	3.05 (7)	11.73 (21)	19.14 (18)	9.16 (46)	0.00*
Non-diabetic	96.94 (222)	88.26 (158)	80.85 (76)	90.83 (456)	
Dyslipidemia					
Dyslipidemic	35.37 (81)	36.31 (65)	45.74 (43)	37.64 (189)	0.19
Non-dyslipidemic	64.62 (148)	63.68 (114)	54.25 (51)	62.35 (313)	
Family history of CAD					
Positive	58.07 (133)	50.27 (90)	56.38 (53)	54.98 (276)	0.22
Negative	41.92 (96)	49.72 (89)	43.61 (41)	45.01 (226)	

Regression analysis showing relationship of various factors with outcome of ETT. ETT = Exercise treadmill test; ECG = Electrocardiogram; CAD = coronary artery disease; $p < 0.05$ = significant = *

On multivariate analysis, significant predictors of a positive ETT result included males, elderly and those with diabetes mellitus, typical chest pain and abnormal resting ECG ($p<0.05$). The results of ETT were mostly negative for young and middle aged, normotensives, non-diabetics, atypical chest pain and normal resting ECG ($p<0.05$). The results were mostly inconclusive for females, obese and very elderly ($p<0.05$). Dyslipidemia, history of smoking and family history were statistically insignificant ($p>0.05$).

DISCUSSION

Our study revealed that history of smoking to be the most frequent risk factor followed by family history of CAD and hypertension. Atypical chest pain was conclusive of a negative or inconclusive test result while typical chest pain was predictive of a positive result. It has been suggested that an individual presenting with typical chest pain should have an ETT performed.[15] We found that ETT results were significantly positive for males but inconclusive for females. Most researchers have proposed that ETT is a misleading predictor for both the presence and absence of CAD in women.[3,16] Few have reported equivocal results.[3,17]

We found hypertension to be consistent with a positive or inconclusive ETT. This is consistent with study by Cha.[15] The value of ETT as a diagnostic tool for CAD in hypertensive individuals is dependent on associated risk factors and therefore, hypertension alone is not a strong predictor of conclusive ETT. On the other hand, normotensives without other risk factors are expected not to benefit much from ETT and either should be evaluated for other causes of chest pain or offered imaging modalities based on individual characteristics.[14,16-18]

The results of ETT for those with diabetes mellitus and abnormal resting ECG mostly showed positive outcomes. Rezaii et al. documented similar results.[17] Contrary to this, a study conducted by Adekunle et al. concluded that differences in results of ETT may be attributed to gender differences for exercise capacity in diabetics.[1] Nevertheless, it should be noted that ischemic changes in ETT are more consistent with diabetes and ETT seems to be a good tool in diabetics for the diagnosis of CAD.

Decreased exercise capacity, a delayed decrease in heart rate during the first minute of graded exercise and increased peak pulse pressure have been reported by Pitsavos et al. as contributing factors for positive ETT in dyslipidemia.[18] This might be the

reason why dyslipidemia was insignificant in predicting ETT results in our study and therefore is a poor predictor despite the fact that it is a well recognized risk factor for development of CAD. It has been suggested that smoking is associated with positive ETT results, however, there is lack of clinical trials to support this hypothesis and we suggest that smoking and family history are poor predictors of ETT results.[19]

Our study showed that those between 60-80 years of age were the ones most consistent with positive ETT outcome. The results were mostly inconclusive for very elderly. Our findings were similar to that of Curzen et al. who emphasized upon low predictive value of ETT for the elderly, particularly older women.[3] Although increasing age itself limits a conclusive ETT due to decreased exercise capacity, Framingham study subjects attaining 80 years of age without developing CAD were unlikely to have low HDL cholesterol. This explains the lower risk of new onset CAD in very elderly and might be the reason why ETT results in our study were mostly negative for very elderly.[20]

CONCLUSION

Males, elderly, diabetes mellitus, typical chest pain and abnormal resting ECG are the ones with highest probability to have abnormal ETT. Individuals under 40 years of age with no cardiovascular risk factors are liable to have a normal ETT and hence should be investigated for non-ischemic causes of chest pain. Also, the inconclusive ETT in case of females and very elderly signifies the early need of alternative tests to diagnose coronary artery disease.

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