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Research article

Factors Associated with False Positive Treadmill Exercise Stress Test Results

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Abstract

Background: The treadmill exercise stress test (EST) is predominantly performed in patients who are symptomatic or suspected of having ischemic heart disease. This study was conducted to study the factors associated with false positive EST results for CAD.

Methods: This was a cross-sectional study. Patients who obtained a positive EST result at the Cardiovascular Division, Department of Internal Medicine, Phramongkutklao Hospital, and who subsequently underwent coronary angiography (CAG) or coronary computed tomography angiography (CCTA) between October 2013 and October 2016 were included. Patients were divided into two groups, true positive and false positive, depending upon the CCTA and CAG data. The two groups were compared with each other.

Results: One hundred and seventy-two patients were included, 67% of whom were male. Ninety-five (55.2%) patients, most of whom were male (65.3%), had a false positive EST result. The mean age in the true positive group was 64.6 years, and that in the false positive group was 59.7 years. There was no significant difference in blood pressure response between the two groups. In the univariate analysis, in female patients, risk factors, including diabetes and dyslipidemia, appropriate heart rate responsiveness, upslope ST depression, and downslope ST segment depression confined to the inferior leads, had a statistically significant correlation between groups. Multivariate analysis to determine the independent predictors of a false positive EST result identified female sex (odds ratio [OR], 3.90; 95% confidence interval [CI], 1.36–11.18; p = 0.011) and upslope ST segment depression (OR, 74.03; 95% CI, 7.74–707.65; p < 0.001). The most commonly involved vessel was the left anterior descending artery (62, 81.58%), followed by the right coronary artery (52, 67.53%), and the left circumflex artery (49, 63.64%).

Conclusions: Female sex and upslope ST segment depression are associated with false positive EST results.

Keywords: EST= exercise stress test, CCTA= coronary computed tomography angiography, CAG= coronary angiography

Introduction

Coronary artery disease (CAD) is one of the most common contemporary health problems. Coronary angiography (CAG) is the investigation of choice for the diagnosis of significant CAD. A meta-analysis of about 58 published papers involving approximately 12,000 patients with no prior myocardial infarction who underwent CAG found a broad variability in specificity and sensitivity. The mean sensitivity and specificity were 67% and 72%, respectively.[1] However, CAG is an invasive technique. Therefore, exercise stress testing (EST), in which heart rate, blood pressure, and electrocardiogram (ECG) are monitored, is often used to screen for CAD in patients who are symptomatic or suspected of having heart disease. It is widely used because it is cost effective and widely available in tertiary care centers.

This study was performed to compare two groups based on their EST results, either true positive or false positive, to identify the factors that can lead to a false positive EST result for CAD.

Methods

This was a cross-sectional study, and was performed at Phramongkutklao Hospital from October 1, 2013 to September 30, 2016. All patients who had a positive EST result and underwent coronary computed tomography angiography (CCTA) or CAG during this period were included in the study.

All patients underwent EST according to the Bruce protocol. ST segment depression >0.1 mV at 80 ms after the J point (ST 80) in three consecutive beats in any lead during the test or in the recovery phase was considered a positive EST result. Furthermore, ST segment elevation >0.1 mV (1 mm) for three consecutive beats in any leads except AVR was also considered a positive EST test result.[2] Results were categorized as positive or negative. The exclusion criteria included abnormal baseline ECG, such as WPW, LBBB, and ST segment depression >1 mV, and patients who were taking digoxin.

Patients who had a positive EST were advised to undergo CCTA or CAG. Significant coronary vessel stenosis was defined as narrowing of 70% or more in any coronary artery as seen on CAG.[3] In the case of luminal narrowing of 50% or more on CCTA, patients were advised to undergo subsequent CAG.

The results were divided into two groups: a true positive group if CAG revealed luminal stenosis more than 70%, and a false positive group if CAG revealed luminal stenosis less than 70%, or if CCTA revealed minimal or mild luminal stenosis.

Descriptive statistics were compared between the two groups using the independent t test and proportions were compared between the two groups using Fisher's exact test; multivariate statistical analysis was performed using logistic regression analysis. Statistical significance was set at a confidence interval of 95%.

Results

In this study, 479 patients had a positive EST result. All patients were assigned to undergo CAG or CCTA. Only 172 patients, 129 (75%) men and 43 (25%) women, underwent CCTA or CAG. One hundred patients underwent CAG, and 72 underwent CCTA, of whom eight were recommended to undergo CAG because of significant luminal narrowing (50% or more).

The mean age of patients in this study was 62.12 years. The mean age of the true positive group was 64.58 years while it was 59.65 years in the false positive group (Table 1). Of the 172 patients, 77 (44.8%) patients had coronary artery disease and were included in the true positive group, while 95 (55.2%) patients had normal or mild CAD and were included in the false positive group (Figure 1).

In the true positive group, 67 (87.01%) were male and 10 (12.99%) were female, while 62 (65.26%) men and 33 (34.74%) women were included in the false positive group. Apart from diabetes mellitus, other strong risk factors, such as hyperlipidemia, hypertension and a history of coronary artery disease, were statistically significantly different between the two groups (Table 1).

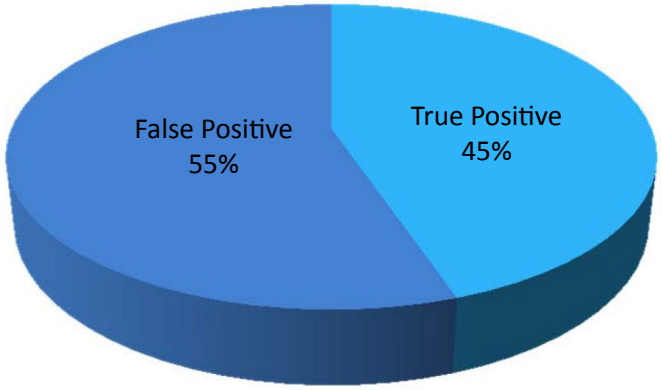

Figure 1. Percentage of true and false positives among patients with a positive EST result

Table 1. Baseline characteristics of the participants

Characteristics	True positive group (N=77)	False positive group (N=95)
Mean age (years)	64.58	59.65
Gender		
Male	67 (87.0)	62 (65.3)
Female	10 (13.0)	33 (34.7)
Underlying disease		
Diabetes	25 (32.5)	19 (20.0)
Hypertension	59 (76.6)	51 (53.7)
Dyslipidemia	58 (75.3)	56 (59.0)
History of CAD	24 (31.2)	10 (10.5)
BP response during EST		
Appropriate	67 (87.0)	77 (87.1)
Exaggerated response	10 (13.0)	18 (19.0)
ECG changes during EST		
Upslope	1 (1.3)	30 (31.6)
Horizontal	49 (63.6)	53 (55.8)
Downslope	27 (35.1)	12 (12.6)
Coronary finding results		
CAD < 50% stenosis from CTA	0	64 (67.4)
CAD < 70% stenosis from CAG	0	31 (32.6)
CAD ≥ 70% stenosis from CAG	77 (100)	0

In the univariate analysis, more women were present in the false positive group than in the true positive group (p = 001). Blood pressure response was not significantly different between the two groups. There were significant differences in risk factors, including hypertension (p = 0.002), dyslipidemia (p = 0.024), and history of coronary artery disease (p = 0.001), between the two groups.

In the false positive group, 21 participants had inappropriate heart rate responsiveness (HRR), while nine participants had inappropriate HRR (P = 0.002). There were 53 participants (55.8%) in the true positive group and 20 participants (26%) in the false positive group (p < 0.001) who achieved high EST workload.

There were statistical differences between the two groups regarding the number of participants with chest pain during exercise, with 21 participants (27.3%) in the true positive group and four (4.2%) in the false positive group. Upslope ECG changes during exercise were found in 30 participants (31.6%) and 1 participant (1.3%) in the true positive group ($p < 0.001$). Abnormal ECG findings confined to the inferior lead were revealed on 12 participants (15.58%) in the true positive group and 28 participants (44%) in the false positive group ($p = 0.001$) as shown in Table 2.

Table 2. Univariate analysis of factors associated with false positive EST results

Independent factors	True positive group (N=77)	False positive group (N=95)	Odds ratio (95% CI)	P value
Sex				
Male	67 (87.0)	62 (65.3)	0.63 (0.49–0.80)	0.001*
Female	10 (13.0)	33 (34.7)	1.60 (1.25–2.04)	0.001*
Underlying disease				
Diabetes	25 (32.5)	19 (20.0)	0.73 (0.50–1.05)	0.062
Hypertension	59 (76.6)	51 (53.7)	0.65 (0.51–0.84)	0.002*
Dyslipidemia	58 (75.3)	56 (59.0)	0.73 (0.56–0.95)	0.024
History of CAD	24 (31.2)	10 (10.5)	0.48 (0.28–0.82)	0.001*
BP response during EST				
Appropriate	67 (87.0)	77 (87.1)	0.83 (0.61–1.14)	0.292
Exaggerated response	10 (13.0)	18 (19.0)	1.20 (0.88–1.65)	0.292
Heart rate recovery				
Appropriate	56 (72.7)	86 (90.5)	2.02 (1.15–4.54)	0.002*
Inappropriate	21 (27.3)	9 (9.5)	0.50 (0.28–0.87)	0.002*
EST workload				
High	20 (26.0)	53 (55.8)	1.17 (1.31–2.24)	<0.001*
Moderate	30 (39.0)	33 (34.7)	0.92 (0.69–1.23)	0.568
Low	27 (35.0)	9 (9.5)	0.40 (0.22–0.71)	0.001*
Symptom during exercise				
No symptoms	19 (24.7)	35 (36.9)	1.27 (0.98–1.66)	0.087
Leg discomfort	8 (10.4)	11 (11.6)	1.05 (0.70–1.59)	0.805
Shortness of breath	29 (37.7)	45 (47.4)	1.19 (0.91–1.56)	0.201
Chest pain	21 (27.3)	4 (4.2)	0.26 (0.10–0.64)	<0.001*
ECG change during exercise				
Upslope	1 (1.3)	30 (31.6)	2.10 (1.74–2.54)	<0.001*
Horizontal	49 (63.6)	53 (55.8)	0.87 (0.66–1.13)	0.298
Downslope	27 (35.1)	12 (12.6)	0.49 (0.30–0.80)	0.001*
Abnormal leads during exercise				
Anterior	8 (10.39%)	6 (6.3)	0.76 (0.41–1.41)	0.331
Inferior	12 (15.58%)	28 (44.0)	1.63 (1.27–2.08)	0.001*
Lateral	18 (23.38%)	13 (13.7)	0.82 (0.62– 1.09)	0.163
Others	39 (50.65%)	38 (40.0)	0.72 (0.47–1.12)	0.100

CAD, coronary artery disease; BP, blood pressure; EST, exercise stress test; ECG, electrocardiography; EST, exercise stress test

Multivariate analysis to determine the independent predictors of false positive EST results identified female sex (OR, 3.90; 95% CI, 1.36–11.18; p = 0.011), high EST workload (OR, 5.21; 95% CI, 1.27–21.26; p=0.022), and upslope ST segment depression (OR, 74.03; 95% CI, 7.74–707.65; p < 0.001) (Table 3).

CAG revealed that 24 (31.17%) patients had single vessel disease, 19 (24.68%) patients had double vessel disease, and 34 (44.16%) patients had triple vessel disease. The coronary vessels that were affected included the left main coronary artery (12, 15.58%), left anterior descending artery (LAD; 62, 81.58%), left circumflex artery (LCX; 49, 63.64%), and right coronary artery (RCA; 52, 67.53%) as shown in Table 4.

Table 3. Multivariate analysis of factors associated with false positive EST results

Independent factors	Odds ratio (95% CI)	P Value
Female sex	4.96 (1.59–15.51)	0.006*
Hypertension	0.64 (0.23–1.83)	0.505
Dyslipidemia	0.42 (0.15–1.19)	0.103
History of CAD	0.69 (0.23–2.05)	0.505
BP response during EST	0.57 (0.16–2.28)	0.387
Heart rate recovery	0.60 (0.16–2.28)	0.454
EST workload		
Low	1	
Moderate	2.45 (0.68–8.90)	0.172
High	5.21 (1.27–21.26)	0.022*
Symptoms during exercise		
No symptoms	1	
Leg discomfort	1.76 (0.44–7.11)	0.426
Shortness of breath	1.07 (0.41–2.82)	0.884
Chest pain	0.21 (0.04–1.14)	0.071
ECG change during exercise		
Downslope	1	
Horizontal	2.08 (0.74–5.85)	0.167
Upslope	50.62 (4.72–543.24)	0.001*
Abnormal leads during exercise		
Anterior	1	
Inferior	1.04 (0.21–5.27)	0.962
Lateral	0.46 (0.08–2.49)	0.364
Other	0.82 (0.19–3.62)	0.791

CAD, coronary artery disease; BP, blood pressure; EST, exercise stress test; ECG, electrocardiography; EST, exercise stress test

Table 4. Coronary computed tomography angiography findings

Characteristics	True positive N = 77	False positive N = 95	P value
Number of diseased vessels			**<0.001**
None	0	95 (100%)	
Single	24 (30.17%)	0	
Two	19 (24.68%)	0	
Three	34 (44.16%)	0	
Individual vessel			**<0.001**
LM	12 (15.58%)	0	
LAD	62 (81.58%)	0	
LCX	49 (63.64%)	0	
RCA	52 (67.53%)	0	

LM, left main coronary artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery

Discussion

Although CAG is the investigation of choice in CAD, it is invasive. Therefore, exercise ECG as a part of EST has become commonly used as an initial investigation in CAD and plays an important role as a diagnostic test at present. However, one of the greatest disadvantages of exercise ECG is the occurrence of false positive tests. If we can identify the factors resulting in false positives, we can improve the accuracy of the test.

The study reviewed 3 years of data from patients who underwent an exercise ECG test followed by CCTA and/or CAG.

The univariate analysis revealed that many factors are related to a false positive result, including sex; strong risk factors such as hypertension, dyslipidemia, and a history of CAD; heart rate recovery, EST workload, symptoms during exercise, ECG ST-T changes during exercise, and lead abnormalities during the EST. However, after multivariate analysis, factors correlating with a false positive EST result were female sex, high EST workload, and upslope ST depression.

The results from this study are consistent with those of a prior study that found lower specificity of the EST in women when compared with that in men.[4-5] As a result of the low specificity of the EST in women, many investigators have tried to improve the diagnostic accuracy using ST/heart rate slope, computer-generated algorithms, and special guidelines for women.[6-8]. Additionally, some researchers have recommended that women should undergo stress imaging instead of EST.[9-12] Alexander KP found that the Duke treadmill score can improve the accuracy of the EST in women.[13] However, although female sex correlated with false positive EST results, the test is still useful for screening in patients who are symptomatic or suspected of having CAD. In particular, a negative EST can exclude a diagnosis of coronary artery disease.

Our result reveals that patients who can achieve high EST workload are associated with false positive EST results. This is consistent with a previous study that showed that patients who can achieve >10 METs are associated with a very low prevalence of significant ischemia.

Upslope ST depression in this study showed strong correlation with false positive EST results. The result is consistent with a previous study, which showed that the sensitivity and specificity of horizontal and downslope ST depression for diagnosis of ischemic heart disease were 50% and 90%, respectively.[14]

This study had a few limitations. The study population was small. We calculated that the

sample size needed for this trial would be 305 participants; however, only 172 participants were enrolled. Out of 479 potential participants with a positive EST result, only 172 underwent CAG and/or CCTA; this number could not be increased because CAG is an invasive procedure, and the risks of the procedure were not acceptable to all participants. In addition, some participants were lost to follow-up after completing the EST.

Conclusion

Among patients who have a positive EST result for CAD, those who are female and have high EST workload and upsloping ST depression are more likely to be associated with a false positive test result.

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