Predicting Factors for a False Positive Treadmill Exercise Stress Test

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Background: The present study was conducted to determine whether the exaggerated blood pressure (BP) response as well as other factors during exercise stress test (EST) is associated with false positive treadmill EST.
Material and Method: This is a retrospective (case-control) study. Patient upon whom EST was performed at Her Majesty Cardiac Center (HMCC), Siriraj Hospital, Mahidol University and for whom the result revealed positive EST and underwent coronary angiogram (CAG) during October 2007-July 2011.
Results: 272 patients were included. 61% was male gender. There were 65 false positive cases (23.9%). Most patients are female (60%). No significant difference in baseline systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) was noted between true and false positive group. Using Multiple logistic regression analysis to determining the independent predictors of false positive EST, exaggerated BP response did not result in false positive EST and factors that were associated with the occurrence of false positive EST are female (OR 2.604, 95% CI 1.109-5.952, p = 0.018), the use of statin (OR 0.402, 95% CI 0.194-0.835, p = 0.015), the difference between the peak and the baseline HR (OR 1.049, 95% CI 1.028-1.071, p < 0.001) and time from abnormal to baseline ECG (OR 0.725, 95% CI 0.641-0.820, p < 0.001).
Conclusion: The present study did not demonstrate that the exaggerated BP response during EST is associated with false positive EST.

Keywords: False positive EST, Exaggerated blood pressure response

Treadmill exercise stress test (EST) is a screening tool for patients with suspected coronary artery disease (CAD)[1-3]. When the result of EST revealed positive result for ischemia, coronary angiography (CAG) which is an invasive investigation is usually recommended for definite diagnosis[2]. However, CAG can cause morbidity and mortality[4]. Therefore, it should only be done in patients with appropriate indications.

According to American College of Cardiology and American Heart Association (ACC/AHA) 2002 Guideline Update for Exercise Testing[1], The EST can be interpreted as positive test for ischemia by the ECG during EST which shows horizontal or downsloping ST-segment depression or elevation of at least 1 mm at 60 to 80 milliseconds after QRS complex. But there are some factors that can cause false positive EST. For example, one study found that the exaggerated blood pressure (BP) response during EST was associated with ST segment depression[5]. Another study found that exaggerated BP response during EST can cause false positive EST[6]. However, some studies have found that the exaggerated BP response was not associated with a false positive, as the study of Lauer et al[7].

It was also found that there are other factors associated with the false positive EST test[8,9] such as sex, age, maximal heart rate, time of onset of ST depression, very high exercise rate-pressure product, etc.

The present study was conducted to determine whether the exaggerated BP response during EST, as well as other factors is associated with a false positive treadmill EST.

Material and Method
Study design
The present study was an observation clinical research; retrospective (case-control) study. The

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present study was approved by the Ethics committee of Siriraj Hospital.

Study group

The authors enrolled 272 positive EST patients whom EST was performed at Her Majesty Cardiac Center. Faculty of Medicine, Siriraj Hospital, Mahidol University from October 2007 to July 2011, and underwent CAG. Exclusion criteria were as follows: 1) age < 18 years 2) known coronary artery disease or having been previously treated with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) 3) abnormal baseline ECG that cannot be interpreted by EST such as left bundle branch block (LBBB), left ventricular hypertrophy (LVH) indicated by voltage, Wolff-Parkinson-White (WPW) pattern, resting ST segment depression, etc. 4) congenital heart disease. Flow of study is demonstrated in Fig. 1.

Exercise stress test

The authors used standard Bruce EST protocol according to the ACC/AHA 2002 Guideline Update for Exercise Testing[1]. The EST can be interpreted as positive test for ischemia by the ECG during EST if it showed horizontal or down sloping ST-segment depression or elevation of at least 1 mm at 60 to 80 milliseconds after QRS complex. The EST interpretation is based on the operator's judgment and reviewed by the investigator.

Coronary angiography

All patients underwent CAG at Her Majesty Cardiac Center, Faculty of Medicine, Siriraj Hospital, Mahidol University. Significant coronary artery disease was defined as coronary artery diameter stenosis more than 50% of any major epicardial coronary arteries.

Definition

Exaggerated BP response was defined as a maximum systolic blood pressure (SBP) during EST ≥ 200 mmHg or maximum diastolic blood pressure (DBP) ≥ 100 mmHg.

True positive was defined as a positive EST for ischemia and the CAG revealed a significant CAD. False positive was defined as a positive EST for ischemia but the CAG revealed non-significant CAD.

Outcomes

The primary outcome was to determine whether exaggerated BP response during EST was associated with a false positive EST. The secondary
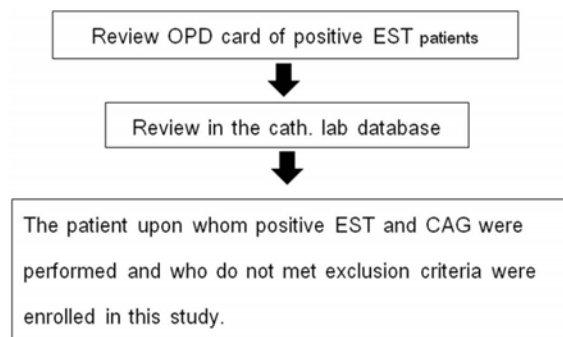

Fig. 1 Flow of study population

outcome was to determine other factors that were associated with a false positive EST.

Statistical analysis

Descriptive statistics was used to describe the demographic characteristics such as gender, age, BMI. Enumerated data type is presented as frequencies and percentages. The quantitative variables, such as age, are presented as mean $\pm$ SD, if the data was normal distribution. Median, Range (minimum, maximum) was used if the data was not normal distribution.

Statistical inference was used to determine the relationship between the factors that affect the occurrence of false positives treadmill EST by using Chi-square test or Fisher's exact test, if the factors were enumerated data type. The comparison between two independent groups was performed by using the independent t-test or Mann-Whitney U test. The factors which have a p-value < 0.1 were used to analyze the affect of the occurrence of false positive EST by using the multiple logistic regression analysis to determine the odds ratios (OR) with 95% confidence interval (95% CI).

All tests are performed by 2-sided test. A p-value of less than 0.05 was considered significant.

Results
Baseline characteristics

The authors enrolled 272 patients in this study. 61% were male. There were 65 false positive cases, representing 23.9% of patients; 60% are women. There was no significant difference between the diabetic condition and hypertension between true and false positive group, but the true positive group was more likely to have dyslipidemia, use of statin and beta-blocker was more than in the false positive group (Table 1).

Table 1. Baseline characteristics of 272 treadmill exercise stress test

Variables	Total (n = 272)	True positive (n = 207)	False positive (n = 65)	p-value
Male No. (%)	166 (61%)	140 (67.6%)	26 (40%)	<0.001
Age (years)	60.8 ± 8.3	61.1 ± 8.1	59.8 ± 8.7	0.248
Body weight (kg)	65.8 ± 11.2	66.6 ± 10.9	63.2 ± 11.9	0.035
Height (cm)	161.5 ± 7.6	162 ± 7	159 ± 8	0.002
BMI (kg/m²)	25.2 ± 3.5	25.2 ± 3.2	25.0 ± 4.5	0.771
Underlying disease No. (%)				
DM	75 (27.6%)	62 (30.0%)	13 (20.0%)	0.117
HT	221 (81.3%)	172 (83.1%)	49 (75.4%)	0.165
Dyslipidemia	198 (72.8%)	159 (76.8%)	39 (60.0%)	0.008
Current medication No. (%)				
ASA	202 (74.3%)	159 (76.8%)	43 (62.2%)	0.086
Diuretic	38 (14%)	30 (14.5%)	8 (12.3%)	0.658
Beta-blocker	157 (57.7%)	129 (62.3%)	28 (43.1%)	0.006
CCB	64 (23.5%)	50 (24.2%)	14 (21.5%)	0.664
ACEI or ARB	127 (16.7%)	99 (47.8%)	28 (43.1%)	0.503
Statin	187 (68.8%)	151 (72.9%)	36 (55.4%)	0.008

Values are the number (%), mean ± SD
BMI = body mass index, DM = diabetes mellitus, HT = hypertension, ASA = aspirin, CCB = calcium channel blocker, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker

Exercise stress test results

Fig. 2 shows an example of ECG during positive test in a false positive case. There were no significant differences in baseline SBP, DBP and heart rate (HR) between true and false positive group. There was more exaggerated BP response, maximum SBP, maximum HR, rate pressure product, exercise induced angina, maximum ST depression and time from abnormal to baseline ECG in false positive group. The Duke treadmill score is more negative in true positive group. But there was no significant difference in exercise time, Metabolic equivalent, total ST depression and number of ECG leads with ST depression between the two groups (Table 2).

Primary and Secondary outcomes

Using multiple logistic regression analysis to determine the independent predictors of false positive EST, exaggerated BP response did not result in false positive EST. Factors that were associated with a false positive were female (OR 2.604, 95% CI 1.109-5.952, p = 0.018), the use of statin (OR 0.402, 95% CI 0.194-0.835, p = 0.015), a difference between the peak and baseline HR (OR 1.049, 95% CI 1.028-1.071, p < 0.001) and time from abnormal to baseline ECG (OR 0.725, 95% CI 0.641-0.820, p < 0.001) (Table 3).

Fig. 2 ECG during peak exercise of false positive patient showed ST segment depression at II, III, aVF, V4, V5 and V6. The patient underwent CAG and showed non-significant CAD

Discussion

Exaggerated BP response during EST is considered as a cause of false positive EST[6]. It has been reported that worsening wall motion abnormalities may occur in patients without CAD who have an exaggerated BP response to exercise[3] but the data is still conflicted[7]. In the present study, there was no relationship between exaggerated BP response and the false positive EST. When comparing the results of the

Table 2. Comparison between true and false positive group

Variables	Total (n = 272)	True positive (n = 207)	False positive (n = 65)	p-value
Baseline				
SBP (mmHg)	145 ± 22	144 ± 22	147 ± 22	0.508
DBP (mmHg)	79 ± 11	79 ± 11	79±11	0.968
HR (bpm)	78 ± 15	78 ± 16	79 ± 15	0.542
Exaggerated BP response (%)	137 (57.4%)	95 (45.9%)	42 (64.6%)	0.008
Adequate HR response (> 85% predicted) (%)	101 (37.7%)	62 (30.0%)	39 (60%)	< 0.001
Maximum SBP (mmHg)	192 ± 32	189 ± 32	202 ± 32	0.006
SBP changes (mmHg)	47 ± 31	45 ± 31	55 ± 31	0.016
Maximum DBP (mmHg)	89 ± 16	88 ± 16	90 ± 16	0.379
DBP changes (mmHg)	10 ± 14	10 ± 13	12 ± 14	0.355
Maximum HR (bpm)	128 ± 21	125 ± 19	124 ± 21	< 0.001
HR changes (bpm)	51 ± 18	48 ± 16	61 ± 19	<0.001
Rate – pressure product (HR x SBP)	24,821 ± 6,433	23,732 ± 6053	28,289 ± 6,422	<0.001
Total exercise time (minutes)	4.9 ± 2.0	4.9 ± 2.0	5.2 ± 2.1	0.274
Metabolic equivalents	6.6 ± 1.7	6.5 ± 1.7	6.9 ± 1.9	0.143
Exercise induced angina (%)	109 (40.1%)	93 (44.9%)	16 (24.6)	0.004
Time to positive EST (minutes)	4.3 ± 2.1	4.3 ± 2.2	4.6 ± 1.8	0.036
Maximum ST depression (mm)	1.91 ± 0.80	2.0 ± 0.8	1.7 ± 0.7	0.021
Total ST depression (mm)	8.0 ± 4.6	8.2 ± 4.7	7.5 ± 4.0	0.243
Number of lead ECG depression	4.9 ± 1.6	4.9 ± 1.6	4.9 ± 1.5	0.854
Duke treadmill score	-7.0 ± 5.7	-7.7 ± 5.8	-4.9 ± 4.6	0.001
Time from abnormal to baseline ECG (minutes)	6.4 ± 3.9	7.1 ± 3.9	4.4 ± 3.3	<0.001

Table 3. Association between false positive EST and various baseline and EST parameters

Variables	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Male gender	0.319 (0.179-0.567)	<0.001	0.384 (0.174-0.851)	0.018
Body weight	0.971(0.945-0.998)	0.036		
Height	0.943 (0.907-0.980)	0.003		
Underlying dyslipidemia	0.453 (0.251-0.819)	0.009		
Use of antiplatelet	0.590 (0.322-1.082)	0.088		
Use of beta-blocker	0.458 (0.260-0.806)	0.007		
Use of statin	0.460 (0.258-0.820)	0.008	0.402 (0.194-0.835)	0.015
Exaggerated BP response	2.153 (1.209-3.833)	0.009		
Adequate HR response	0.285 (0.160-0.508)	<0.001		
Maximum SBP	1.012 (1.003-1.021)	0.007		
SBP changes	1.011 (1.002-1.019)	0.018		
Maximum HR	1.037 (1.022-1.052)	<0.001		
HR changes	1.043 (0.125-1.061)	<0.001	1.049 (1.028-1.071)	<0.001
Rate – pressure product	1.000 (1.000-1.000)	<0.001		
Exercise induced angina	0.400 (0.234-0.750)	0.004		
Maximum ST depression	0.607 (0.396-0.931)	0.022		
Duke treadmill score	1.103 (1.041-1.170)	0.001		
Time from abnormal to baseline ECG	0.762 (0.684-0.848)	<0.001	0.725 (0.641-0.820)	<0.001

present study to the previous studies, the authors result was consistent with the previous study of Lauer et al[7], but different from Chaing et al[5], which only studied healthy middle-aged Chinese men. The previous

study[5] demonstrated that exaggerated BP response during EST was associated with the ST segment depression, but they did not confirm a definite diagnosis by CAG to evaluate whether the population with ST segment depression had CAD or not. Another study from Miller et al[6] found that the exaggerated BP response during EST can cause false positive EST. However, a normal thallium image rather than coronary angiography was used to exclude CAD. So there may be some CAD undetectable by thallium scan. In the present study, we also found that female gender was a factor that can cause false positive EST, which is consistent with the study of Ellestad et al[8].

Another factor that was associated with the false positive EST from the present study was the HR changes. In the false positive group, there was a greater increase in HR. This result is similar with Pupita et al[2], which can be explained by the hypothesis of Taggart et al[10] that the ECG changes during EST resembling myocardial ischemia in the presence of normal coronary arteries are result of altered myocardial sensitivity to normal level of catecholamines. In the present study, time from positive test to baseline in the false positive group was significantly shorter than in those with true positive. Because exercise-induced ST-segment depression is a common manifestation of myocardial ischemia[11], the authors hypothesized that longer duration of persistent ST changes may indicate true positive.

The authors cannot explain the reason why the use of statin was associated with false positive EST. This may be incidental finding.

Study limitations

Although indirect BP measurement by cuff sphygmomanometer during EST is a standard practice and reasonably accurate during EST[12], it may be difficult to measure and may not be accurate in some patients. Another problem is that there are many doctors who performed EST. If the present study design had been a Inter and intra-observer variation test, it may have provided a more accurate outcome.

Conclusion

The present study does not demonstrate that the exaggerated BP response during EST is associated with false positive EST.

Acknowledgement

Potential conflicts of interest

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การศึกษาปัจจัยที่ทำให้เกิดผลบวกลวงด้วยการเดินสายพาน

กรกฏ โตวชิราภรณ์, รุ่งโรจน์ กฤตยพงษ์, อาทิตย์ ยินดีงาม

ภูมิหลัง*: การศึกษานี้จัดทำขึ้นเพื่อศึกษาว่าความดันโลหิตสูงอย่างมากขณะการตรวจด้วยการเดินสายพาน รวมถึงปัจจัยอื่นๆ สัมพันธ์กับการเกิดผลบวกลวงของการเดินสายพานหรือไม่*

วัสดุและวิธีการ*: การศึกษานี้เป็นแบบ retrospective (case-control) study. โดยผู้ป่วยที่เข้าร่วมการศึกษา คือผู้ป่วยที่มีผลการตรวจด้วยการเดินสายพานที่ศูนย์โรคหัวใจสมเด็จพระบรมราชินีนาถ คณะแพทยศาสตร์ ศิริราชพยาบาล*

ผลการศึกษา*: มีผู้ป่วยในการศึกษานี้ทั้งหมด 272 คน ร้อยละ 61 เป็นเพศชาย เกิดผลบวกลวง 65 ราย คิดเป็น ร้อยละ 23.9 ผู้ป่วยส่วนใหญ่เป็นเพศหญิง (ร้อยละ 60) ไม่พบความแตกต่างอย่างมีนัยยะสำคัญทางสถิติ ระหว่าง baseline systolic blood pressure (SBP) , diastolic blood pressure (DBP) และชีพจร (HR) ระหว่างกลุ่ม ที่มีผลบวกลวง กับกลุ่มที่มีผลบวกจริง เมื่อใช้ Multiple logistic regression เพื่อศึกษา independent predictors ในการเกิดผลบวกลวง พบว่า ความดันโลหิตสูงอย่างมากขณะการตรวจด้วยการเดินสายพาน ไม่ได้สัมพันธ์กับการเกิด ผลบวกลวง ส่วนปัจจัยสัมพันธ์กับการเกิดผลบวกลวงได้แก่ เพศหญิง (OR 2.604, 95% CI 1.109 – 5.952, p = 0.018), การใช้ statin (OR 0.402, 95% CI 0.194 – 0.835, p = 0.015) , ความแตกต่างระหว่าง peak และ baseline HR (OR 1.049, 95% CI 1.028 – 1.071, p <0.001) และระยะเวลาจาก abnormal to baseline ECG. (OR 0.725, 95% CI 0.641-0.820, p <0.001)*

สรุป*: การศึกษานี้ไม่พบว่า ความดันโลหิตสูงอย่างมากขณะออกกำลังกาย สัมพันธ์กับการเกิดผลบวกลวง ของการตรวจด้วยการเดินสายพาน*