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Original Article

Echocardiographic and Clinical Factors Related to the False Results of the Exercise Tolerance Test

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ABSTRACT

Background: We aimed to identify the clinical and echocardiographic factors related to false results in the exercise tolerance test (ETT).

Methods: The present study included all patients who underwent transthoracic echocardiography and the ETT, followed by coronary angiography, within 6 months prior to echocardiography between March 2008 and March 2013. Clinical, 12-lead resting ECG, ETT, transthoracic echocardiography, and coronary angiography data were extracted. The multivariable logistic regression analysis was used to investigate the independent predictors of the false results of the ETT.

Results: Totally, 4057 patients, who underwent transthoracic echocardiography, ETT, and angiography, were enrolled. From 1132 patients with no significant coronary stenosis on angiography, 979 (84%) had false-positive results in the ETT and 153 (14%) had true-negative ETT results. In patients with significant coronary artery disease (CAD), there were 2728 (93%) true-positive and 197 (7%) false-negative ETT results. In our univariate analysis, the patients with false ETT results were more likely to be female and younger than the group with true ETT results. In our multivariable model, female gender increased and right bundle branch block and dilated left ventricular diastolic internal dimension (LVID) decreased the likelihood of a false-positive result in the ETT. The probability of a false-negative result in the ETT was increased by resting ECG changes, hemiblocks, and dilated LVID.

Conclusions: The diagnostic value of the ETT in patients with suspected CAD should be adjusted according to sex, presence of resting ECG changes, CAD risk factors, and traditional echocardiographic measurements. A dilated LV increases the risk of false-negative results and decreases the likelihood of a false-positive result in the ETT. ***(Iranian Heart Journal 2016; 17(3):36-45)***

Keywords: Exercise tolerance test ▪ False positive ▪ False negative ▪ Echocardiography

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The predictive power of normal as well as abnormal exercise tolerance test (ETT) results can provide us with a very useful tool in the clinical management of patients with coronary artery disease (CAD), not least those with chest pain.[1,2] As the ETT results are considered a decisive factor in performing angiography in patients with suspected CAD,[3] the false-positive results of the ETT can impose invasive procedures on patients with no obstruction in the coronary artery and lead to inattention to patients with false-negative ETT results. The accompanying clinical and paraclinical factors that increase the likelihood of false ETT results require further evaluation with other subsequent stress tests for a more precise discrimination of patients in need of angiography. In the previously published studies, the accuracy of the ETT varies broadly due to different factors such as heterogeneity in the population characteristics, methodological variations, technical factors, data interpretation methods, and drug consumption.[4,5]

The sensitivity, specificity, predictive value, and accuracy of the ETT have been accentuated in previous publications abundantly.[1,3,6,7] Nevertheless, to our knowledge, there is no study to feed all clinical and echocardiographic variations into analysis as a whole. The purpose of the present study was to identify the clinical and echocardiographic factors that are strongly in relation with false-positive ETT results on normal angiograms and patients with CAD.

METHODS

From March 2008 up to March 2013, this retrospective study recruited 4057 patients, who underwent transthoracic echocardiography, ETT, and angiography within 6 months prior to echocardiography. All the inclusion and exclusion criteria to perform the ETT were in accordance with the current guidelines.[8] Patients with the Wolff–Parkinson–White syndrome or a left ventricular hypertrophy (LVH) pattern on ECG or those using digoxin were excluded. The study protocol was approved by our institutional review board. All the patients signed a consent form prior to angiography, allowing the investigators of the hospital to use their data for research purposes.

The ETT was performed in accordance with the Bruce protocol—with continuous monitoring of blood pressure, heart rate, and 12-lead ECG up to 5 minutes into recovery. Drugs like β-blockers, calcium channel blockers, and nitrates were discontinued 2 days before the test. From the ECG point of view, ETTs with ≥1 mm horizontal or downsloping ST-segment depression 0.08 seconds after the J point were interpreted as positive. A nondiagnostic test result was defined as an exercise ECG without ischemic changes at a peak heart rate > 85% of the age-predicted maximum rate.[8] Patients with nondiagnostic test results were excluded from the present study.

Additionally, the patients' clinical data—comprising age, sex, symptoms, family history of CAD (first-degree relatives with CAD at age <55 y), current smoking (in the past month), history of dyslipidemia (total cholesterol >200 mg/dL or LDL ≥130 mg/dL or HDL <30 mg/dL or TG >150 mg/dL or taking lipid-lowering agents), hypertension (repeated blood pressure >140/90 mm Hg or under treatment with antihypertensive drugs), and diabetes (repeated fasting glucose >126 mg/dL or controlled by diet, tablet, or insulin)—were recorded systematically by physicians at the time of clinic visit. In sequence, paraclinical data such as 12-lead resting ECG, ETT, and transthoracic echocardiography were completed and merged with the clinical data if any or all of them were requested. 2D transthoracic echocardiography was conducted using a Vingmed-General Electric, Horten, Norway machine. The patients were asked to lie in the left lateral decubitus position, and echocardiography was conducted with a 3.5-MHZ phased-array transducer. Measurements were carried out in accordance with the guidelines of the American Society of Echocardiography.[9] Finally, the databank was completed with the results of coronary angiography recorded by the treating cardiologist. In the negative ETT cases, eligibility for angiography was based on the clinician's assessment and the results of other stress tests.

Within all the variables in the clinical component of the database, we extracted age, sex, family history of CAD, current smoking, history of dyslipidemia, hypertension, and diabetes. Additionally, we obtained ST-segment or T-wave changes, existence of Q wave, and conduction disorders such as right bundle branch block, left bundle branch block, and hemiblocks from the recorded resting 12-lead ECG variables.

Statistical Analysis

The data are presented as means ± SDs for the continuous variables and frequencies (%) for the categorical variables. The Pearson χ^2 test was used to compare the categorical variables, and the Student *t*-test or the Mann–Whitney test was employed to compare the continuous variables between the study groups, as required. Multivariable logistic regression models with the backward selection method for the factors associated with false, false-positive, and false-negative ETT results were constructed, and the associations between the independent predictors and false, false-positive, and false-negative ETT results in the final models were expressed as ORs with 95% CIs. Model calibration was estimated using the Hosmer–Lemeshow goodness-of-fit statistic. (A higher *P* implies that the model fits the observed data better.) The variables were incorporated into the multivariable model if there was a $P \leq 0.15$ in the univariate analysis. A $P < 0.05$ was considered statistically significant. The statistical analyses were conducted using SPSS, version 15 for Windows.

RESULTS

Of 45330 consecutive patients referred for coronary angiography between March 2008 and March 2013, a total of 4057 patients met our inclusion criteria and were enrolled in our study. The mean age of the patients was 57.39 ± 9.36 years. Sex distribution was 72% male and 28% female. Based on the angiographic results, 1132 (28%) patients had no or <50% stenosis in coronary arteries and 2925 (72%) had ≥50% stenosis of any coronary artery. From the 4057 patients, who underwent the ETT, 979 (24.1%) had false-positive, 2728 (67.2%) had true-positive, 197 (4.9%) had false-negative, and 153 (3.8%) had true-negative results.

Of the 1132 patients, who had no significant coronary stenosis on angiography, 979 (86.5%) patients had false-positive results in the ETT and 153 (13.5%) had true-negative ETT results. In the CAD group, there were 2728 (93%) true-positive and 197 (7%) false-negative ETT results. In the entire population—according to the angiographic results—2881 patients had true results and 1176 had false results in the ETT.

Table 1 depicts the clinical characteristics and echocardiographic findings of the patients with false ETT results in comparison to those of the patients with true ETT results. In the unadjusted analysis, the patients with false ETT results were more likely to be female and younger than those with true ETT results. All the traditional CAD risk factors—namely diabetes mellitus, smoking, hypertension, dyslipidemia, and family history of CAD—had a higher prevalence in the patients with true ETT results. Moreover, the patients with true ETT results had a significantly higher frequency of resting ECG changes than those with false ETT results.

Table 1. Baseline clinical characteristics and echocardiographic findings of the total study population according to the ETT results

	True Results (n=2881)	False Results (n=1176)	*P*
Female	636(22.1)	489(41.6)	<0.001
Age, mean ± SD	58.4±9.19	54.93±9.32	<0.001
BMI	27.39±3.92	27.91±4.12	<0.001
BSA	1.84±0.177	1.84±0.181	0.988
Symptomatic	2739(95.4)	1119(95.5)	0.953
Risk Factors			
Family history of CAD	663(23.3)	239(20.7)	0.075
Hypertension	1248(43.5)	473(40.3)	0.061
Dyslipidemia	2333(81.4)	899(76.9)	0.001
Current smoker	599(20.8)	197(16.8)	0.003
Diabetes mellitus	821(28.5)	218(18.6)	<0.001
ECG			
Resting ECG changes	1146(40)	356(30.5)	<0.001
Right bundle branch block	37(1.3)	19(1.6)	0.409
Left bundle branch block	31(1.1)	7(0.6)	0.156
Hemiblock	82(2.9)	35(3)	0.816
Echocardiography			
Abnormal LA size[a]	708(24.7)	283(24.1)	0.722
Abnormal LVIDd[b]	141(4.9)	77(6.6)	0.035
Abnormal IVST[c]	1489(52)	589(50.4)	0.344
Abnormal PWT[d]	1426(49.9)	577(49.4)	0.753
LVMI, g/m^2	97.45±27.49	92.69±27.36	<0.001
Left ventricular hypertrophy[e]	768(27.3)	263(22.9)	0.004
Moderate or severe MR	128(4.4)	48(4.1)	0.607
Moderate or severe AI	48(1.7)	19(1.6)	0.909
Moderate or severe TR	59(2)	34(2.9)	0.105

*Categorical variables are presented as frequencies (percentages) and the continuous variables as means ± SDs.
ETT, Exercise tolerance test; BMI, Body mass index; BSA, Body surface area; CAD, Coronary artery disease; LA, Left atrium; LVIDd, Left ventricular internal diastolic diameter; IVST, Interventricular septal thickness; PWT, Posterior wall thickness; LVMI, Left ventricular mass index ($0.8*[(LVIDd + PWT + IVST)^3 – LVIDd^3] + 0.6$)/body surface area); MR, Mitral regurgitation; AI, Aortic insufficiency; TR, Tricuspid regurgitation
a: male >4 cm, female >3.8 cm; b: male >5.9 cm, female >5.3 cm; c: male >1 cm, female >0.9 cm; d: male >1 cm, female >0.9 cm; e: male LVMI >115, female LVMI >95

One important interaction was found between female gender and diabetes mellitus in decreasing the likelihood of a false result in the ETT. Among the conventional echocardiographic measurements, dilated left ventricular diastolic internal dimension (LVID) was significantly more common in the patients with false ETT results. The mean of the left ventricular mass index (LVMI) in the group with true ETT results was significantly higher than that of the group with false ETT results. Accordingly, left ventricular hypertrophy (LVH) by echocardiography was also more prevalent in the group with true ETT results. In the multivariate model, the contribution of the above variables remained statistically significant in the same pattern (Table 4).

Table 2. Baseline clinical characteristics and echocardiographic findings of the patients with <50% stenosis on angiography according to the ETT results

	True Negative (n=153)	False Positive (n=979)	*P*
Female	55(35.9)*	450(46)	0.021
Age, y	52.22±10.1	54.66±9.17	0.012
Symptomatic	147(96.1)	926(95)	0.557
BMI, kg/m^2	29.22±4.99	27.94±4.15	0.003
BSA, m^2	1.91±0.20	1.83±0.18	<0.001
Risk Factors			
Family history of CAD	34(23.4)	182(18.9)	0.201
Hypertension	57(37.3)	379(38.8)	0.723
Dyslipidemia	116(76.3)	736(75.6)	0.857
Current smoker	20(13.1)	144(14.7)	0.593
Diabetes mellitus	24(15.7)	161(16.5)	0.809
ECG			
Resting ECG changes	48(31.4)	225(23.1)	0.028
Right bundle branch block	9(5.9)	14(1.4)	0.001
Left bundle branch block	2(1.3)	7(0.7)	0.455
Hemiblock	5(3.3)	24(2.5)	0.562
Echocardiography			
Abnormal LA size[a]	37(24.2)	237(24.3)	0.984
Abnormal LVIDd[b]	17(11.1)	52(5.3)	0.005
Abnormal IVST[c]	76(49.7)	489(50.3)	0.893
Abnormal PWT[d]	69(45.4)	491(50.5)	0.24
LVMI, g/m^2	94.79±34.1	90.95±26.35	0.279
Left ventricular hypertrophy[e]	38(25.5)	212(22.1)	0.36
Moderate or severe MR	10(6.5)	37(3.8)	0.117
Moderate or severe AI	5(3.3)	15(1.5)	0.139
Moderate or severe TR	6(3.9)	30(3.1)	0.575

*Categorical variables are presented as frequencies (percentages) and the continuous variables as means ± SDs.
ETT, Exercise tolerance test; BMI, Body mass index; BSA, Body surface area; LA, Left atrium; LVIDd, Left ventricular internal diastolic diameter; IVST, Interventricular septal thickness; PWT, Posterior wall thickness; LVMI, Left ventricular mass index (0.8*[(LVIDd + PWT + IVST)^3 – LVIDd^3] + 0.6)/body surface area); MR, Mitral regurgitation; AI, Aortic insufficiency; TR, Tricuspid regurgitation
a: male >4 cm, female >3.8 cm; b: male >5.9 cm, female >5.3 cm; c: male >1 cm, female >0.9 cm; d: male >1 cm, female >0.9cm; e: male LVMI >115 female LVMI >95

As the clinical and paraclinical conditions that accompany a false ETT result may differ between false-positive and false-negative ETT results, we classified the patients into 2 groups based on their angiographic results: patients with no stenosis or stenosis <50% on the angiogram and patients with ≥50% occlusion of any coronary artery. The results of the univariate comparison between the true-negative and false-positive ETT results and true-positive and false-negative results of the ETT in terms of clinical characteristics, ECG findings, and echocardiographic measurements are exhibited in Table 2 and Table 3—respectively. There were statistically significant differences between the true-negative and false-positive ETT results in female gender, resting ECG changes, right bundle branch block, and dilated LVID. After adjusting, female gender increased and right bundle branch block and dilated LVID decreased the likelihood of a false-positive result in the ETT (Table 5). A comparison of the true-positive and false-negative ETT results indicated that the probability of a false-negative result in the ETT was increased by resting ECG changes, hemiblocks, and dilated LVID (Table 6).

Table 3. Baseline clinical characteristics and echocardiographic findings of the patients with ≥50% stenosis on angiography according to the ETT results

	True Positive (n=2728)	False Negative (n=197)	*P*
Female	581(21.3)*	39(19.8)	0.619
Age, mean ± SD	58.74±9.02	56.23±9.98	0.001
Symptomatic	2592(95.4)	193(98)	0.090
BMI	27.30±3.83	27.75±4.00	0.108
BSA	1.84±0.18	1.90±0.18	<0.001
Risk Factors			
Family history of coronary artery disease	629(23.3)	57(29.7)	0.045
Hypertension	1191(43.8)	94(47.7)	0.288
Dyslipidemia	2217(81.7)	163(83.2)	0.605
Current smoker	579(21.3)	53(27)	0.059
Diabetes mellitus	797(29.2)	57(28.9)	0.928
ECG			
Resting ECG changes	1098(40.4)	131(66.8)	0.001
Right bundle branch block	28(1)	5(2.5)	0.062
Left bundle branch block	29(1.1)	0	0.998
Hemiblock	77(2.8)	11(5.6)	0.033
Echocardiography			
Abnormal LA size[a]	671(27.7)	46(23.6)	0.727
Abnormal LVIDd[b]	124(4.6)	25(12.7)	<0.001
Abnormal IVST[c]	1413(52.2)	100(51)	0.758
Abnormal PWT[d]	1357(50.2)	86(43.9)	0.087
LVMI, g/m^2	97.6±27.08	101.44±30.57	0.276
LVH[e]	730(27.4)	51(26.7)	0.843
Moderate or severe MR	118(4.3)	11(5.6)	0.408
Moderate or severe AI	43(1.6)	4(2)	0.624
Moderate or severe TR	53(1.9)	4(2)	0.939

*Categorical variables are presented as frequencies (percentages) and the continuous variables as means ± SDs.
ETT, Exercise tolerance test; BMI, Body mass index; BSA, Body surface area; LA, Left atrium; LVIDd, Left ventricular internal diastolic diameter; IVST, Interventricular septal thickness; PWT, Posterior wall thickness; LVMI, Left ventricular mass index; LVH, Left ventricular hypertrophy; MR, Mitral regurgitation; AI, Aortic insufficiency; TR, Tricuspid regurgitation
a: male >4 cm, female >3.8 cm; b: male >5.9 cm, female >5.3 cm; c: male >1 cm, female >0.9 cm; d: male >1 cm, female >0.9 cm; e: male LVMI >115 female LVMI >95

Table 4. Association between the ETT false results and the clinical characteristics and echocardiographic findings

Total Population (N=4058)	Univariate OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Female	2.51 (2.72-2.906)	<0.001	3.629 (2.986-4.410)	<0.001
Age (y)	0.960 (0.953-0.967)	<0.001	0.957 (0.949-0.966)	<0.001
Family history of coronary artery disease	0.859 (0.727-1.015)	0.075	0.627 (0.521-0.755)	<0.001
Hypertension	0.876 (0.763-1.006)	0.061	0.865 (0.738-1.014)	0.074
Dyslipidemia	0.761 (0.645-0.898)	0.001	0.696 (0.581-0.835)	<0.001
Current smoker	0.766 (0.641-0.914)	0.003	0.802 (0.655-0.983)	0.033
Diabetes mellitus	0.571 (0.483-0.675)	0.001	0.677 (0.532-0.861)	0.001
Female with diabetes mellitus			0.500 (0.347-0.723)	<0.001
Resting ECG changes	0.659 (0.570-0.762)	<0.001	0.688 (0.586-0.806)	<0.001
LVH[a]	0.792 (0.674-0.930)	0.004	0.769 (0.637-0.928)	0.006
Abnormal LVIDd[b]	0.812 (0.624-1.057)	0.035	1.451 (1.037-2.029)	0.030

ETT, Exercise tolerance test; LVH, Left ventricular hypertrophy; LVIDd, Left ventricular internal diastolic diameter
a: male LVMI >115 female LVMI >95; b: male >5.9 cm, female >5.3 cm
Area under the curve =69.8% (95% CI: 67.9 – 71.6%; *P* <0.001), *P* for Hosmer–Lemeshow goodness-of-fit statistic =0.383

Table 5. Association between the ETT false-positive results and the clinical characteristics and echocardiographic findings in the patients with <50% stenosis on angiography

Total Population (N=1132)	Univariate OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Female	1.516 (1.065-2.158)	0.021	1.483 (1.027-2.142)	0.035
Age (y)	1.029 (1.01-1.048)	0.003	1.030 (1.011-1.049)	0.002
Resting ECG changes	0.659 (0.454-0.956)	0.028	0.717 (0.488-1.054)	0.09
Right bundle branch block	0.234 (0.099-0.55)	0.001	0.213 (0.087-0.522)	0.001
Abnormal LVIDd[a]	0.7 (0.374-1.309)	0.005	0.455 (0.246-0.841)	0.012

ETT, Exercise tolerance test; LVIDd, Left ventricular internal diastolic diameter
a: male >5.9 cm, female >5.3 cm
Area under the curve =64.7% (95% CI: 59.8 – 69.5%; *P* <0.001), *P* for Hosmer–Lemeshow goodness-of-fit statistic =0.383

Table 6. Association of ETT false negative result with clinical characteristics and echocardiographic findings in patients with ≥50% stenosis in angiography

Total population (n=2925)	Univariable OR (95% CI)	p-value	multivariable OR (95% CI)	p-value
Age	0.970 (0.954-0.986)	<0.001	0.968 (0.952-0.984)	<0.001
Resting ECG changes	2.968 (2.183-4.033)	<0.001	2.600 (1.879-3.599)	<0.001
Hemi block	2.028 (1.06-3.882)	0.033	2.032 (1.011-4.087)	0.047
Abnormal LVIDd[a]	1.272 (0.785-2.061)	<0.001	2.295 (1.377-3.824)	0.001
Abnormal PWT[b]	0.775 (0.579-1.038)	0.087	0.755 (0.558-1.022)	0.069

ECG: electrocardiogram, LVIDd: left ventricular internal dimension diastolic, PWT: posterior wall thickness
a: male>5.9cm, female>5.3cm; b: male>1cm, female>0.9cm

DISCUSSION

The current study suggests that the utilization of clinical characteristics, ECG findings, and echocardiographic measurements could adjust the discriminatory ability of the ETT in CAD diagnosis.

Our results showed that female gender increased the likelihood of a false ETT result (both false-positive and false-negative) by threefold. This finding supports the results of the previous studies that reported a 36% frequency of false ETT results in women.[5,7,10,11] It has been discussed that this pattern can be in relation to the digitalis-like effects of estrogen, higher vascular resistance and increased oxygen demand, higher mean pulmonary pressure with exercise, limited vasodilator reserve, and decreased hematocrit in women.[12-14] It is recommended that for the diagnosis of CAD in women, physicians consider the patient's age, existence of CAD risk factors, and resting ECG changes and make the decision to apply the ETT or other stress tests such as myocardial perfusion scan or stress echocardiography.

We found that resting ECG changes and hemiblocks in ECG increased the likelihood of a false-negative ETT result by more than twofold in the patients with significant CAD compared to those without these changes. This can be due to the interference in the interpretation of the ETT results. The majority of the previous studies have published conflicting results.[15-17] Be that as it may, it seems that in these conditions, it is logical to classify patients according to the type and the level of ECG changes.[18,19] Since patients with ST-T abnormalities have a higher prevalence of CAD, severe CAD, LV dysfunction, and higher cardiac mortality and morbidity than those with normal resting ECG,[19-22] the value of further follow-up and other stress tests in patients with suspected CAD with resting ECG changes and negative ETT results is demonstrably highlighted.

The new finding in our study is that the probability of a false-negative ETT result was doubled in the patients with significant CAD and dilated LVID (males >5.9 cm and females >5.3 cm) compared to those with significant CAD and normal LVID. LV enlargement is associated with both systolic and diastolic dysfunction, giving rise to an increase in the end-diastolic and end-systolic volumes. The potassium shifting process, which is present in producing subendocardial current of injury and ST depression on ECG, may be altered by those changes and ischemic ST response is likely to be reduced.[23]

Previous studies have argued that LVH increases the probability of false-positive results in the ETT.[24,25] In our study, we did not obtain this result. It may be argued that in the previous studies, specific criteria accounting for the diagnosis of LVH were based on ECG and not on echocardiography. As it has been revealed that the sensitivity of ECG for ECG-defined LVH is only 6.9%,[26] ECG is a poor screening test for detecting LVH compared to echocardiography. To our knowledge, there is no study to report the role of echocardiographically defined LVH in the false-positive results of the ETT. Further studies are required to confirm our results.

Study Limitations

First and foremost among the limitations of the present study is its retrospective design. In addition, eligibility for angiography was based on the clinician's assessment in patients with negative ETT results. Therefore, coronary angiography was not performed on all the subjects and the patients with true-negative ETT results but without angiography were excluded. Another weakness of note is that although all the ETT examinations were done according to the current guidelines of the ACC/AHA, variables such as the Duke treadmill score were not included in the angiography registry—resulting in the unavailability of such variables for reporting. Moreover, because of the retrospective nature of the study, echocardiographic findings reported by different physicians were drawn upon—which may have influenced the results.

CONCLUSIONS

The diagnostic value of the ETT in patients with suspected CAD should be adjusted according to sex, presence of resting ECG changes, CAD risk factors, and traditional measurements on echocardiography. Based on clinical, paraclinical, and echocardiographic variables—other stress tests for the initial assessment of patients with suspected CAD or confirmation of the ETT results should be considered. A dilated LV increases the risk of false-negative results and decreases the likelihood of a false-positive result in the ETT.

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