Treadmill Exercise Stress Echocardiography in Patients With No History of Coronary Artery Disease: A Single-Center Experience in Korean Population

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ABSTRACT

Background and Objectives: Treadmill exercise stress echocardiography (TSE) has superior diagnostic accuracy than exercise electrocardiography (ECG). The objectives of the study are 1) to define the diagnostic accuracy and safety of TSE in patients without a history of coronary artery disease (CAD), 2) to identify the clinical characteristics that predict positive TSE results and 3) to assess the differential predictive value between TSE and concomitant exercise ECG in a Korean population. **Subjects and Methods:** A total of 1,287 patients among 1,500 consecutive patients with no prior history of CAD and who were referred for TSE during a 4-year 3-month period were enrolled. **Results:** Of the 1,287 patients, 95 (7.4%) showed positive TSE results (newly developed regional wall motion abnormality). Among the 154 patients with coronary angiography, 94 patients (61%) showed significant CAD (30 of 77 patients with negative TSE results and 64 of 77 patients with positive TSE results). The TSE positive population had more cardiovascular risk factors and showed a higher Duke treadmill score and wall motion score index than the TSE negative group. TSE showed relatively good sensitivity (68%), specificity (78%) and positive and negative predictive values (83% and 61%, respectively), and TSE also had higher diagnostic accuracy than concomitant exercise ECG (72% vs. 64%, respectively). **Conclusion:** TSE is safe and offers greater diagnostic power for CAD than exercise ECG in Korean population without a history of CAD. Its prognostic value in this population needs to be confirmed in a larger prospective study. **(Korean Circ J 2011;41:528-534)**

KEY WORDS: Echocardiography, stress; Electrocardiography; Exercise test; Coronary artery disease.

Introduction

Several diagnostic methods are currently being used in deciding clinically to apply coronary angiography (CAG) or for early detection of coronary artery disease (CAD) even in patients without chest pain. Because the treadmill exercise test can give extra load to the heart and increase the myocardial oxygen consumption, exercise electrocardiography (ECG) is widely used for the initial assessment of patients with chest pain once the diagnosis of acute coronary syndrome has been excluded. Treadmill exercise stress echocardiography (TSE) has superior diagnostic accuracy than exercise ECG, and TSE has been used as a noninvasive method for diagnosis, risk stratification and predicting the prognosis in patients with known or suspected CAD.[1-7]

TSE provides similar diagnostic and prognostic accuracy as radionuclide stress perfusion imaging, but at a substantially lower cost, and TSE is without environmental impact and with no biohazards for the patient and the physician.[4)8)] Despite TSE being an ideal physiological stress, TSE is technically much more demanding than pharma-cologic stress and TSE is not commonly used in Korea.

The objectives of the present study are 1) to define the diagnostic accuracy and safety of TSE for detecting ischemia in patients without a history of CAD, 2) to identify the clinical characteristics that predict positive TSE results and 3) to assess the differential diagnostic power between TSE and concomitant exercise ECG in a Korean population.

Subjects and Methods

Study subjects

Consecutive patients who had undergone TSE at our institution from March 2006 to May 2010 were enrolled. Patients were excluded if 1) they had a history of myocardial infarction or ischemic heart disease, had undergone a percutaneous coronary intervention (PCI) procedure or a coronary artery bypass graft before the test, 2) they had significant valvular heart disease, hypertrophic cardiomyopathy, left ventricular dysfunction (an ejection fraction <45%), regional wall motion abnormality on resting echocardiography and 3) they had atrial fibrillation on ECG. We also excluded those patients who could not perform maximal exercise.

Framingham's risk score (10-year mortality) was calculated for all the patients based on their age, gender, smoking status, the presence of diabetes mellitus, blood pressure, and the cholesterol level.[9] The percentage of risk was then calculated. The clinical variables, including hypertension (defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg or the use of antihypertensive drugs), diabetes or insulin requirement or oral hypoglycemic agents, dyslipidemia (defined as fasting plasma total cholesterol level ≥240 mg/dL, triglyceride level ≥400 mg/dL or the use of lipid-lowering agents) and the smoking status (current smoker, never smoker or former smoker) were assessed from the medical records and by interviewing the patients. Written informed consent was obtained from all subjects, and this study was approved by the Institutional Review Board of our institution.

Treadmill exercise test protocol

The study participants underwent maximal treadmill exercise using the Bruce protocol with a 12-lead ECG monitor, and a physician trained in Basic Life Support and Advanced Cardiac Life Support attended the exercise test.[4] The clinical symptoms and blood pressure were monitored throughout the study. Treadmill exercise was terminated if the target heart rate (85% of the maximal age predicted heart rate) was reached, if the patients developed limiting symptoms (significant chest pain, dyspnea), serious ventricular arrhythmia, severe hypertension (systolic >220 mmHg; diastolic >120 mmHg), significant blood pressure depression (<90 mmHg for the systolic blood pressure) or marked ST-segment depression or elevation as per the standard recommendations.[2-4]

Before and immediately after exercise, two-dimensional echocardiography with harmonic imaging was obtained in the left lateral decubitus position from the apical four-, and two-chamber views and from the parasternal long- and short-axis views.[2)4)] The post-exercise echocardiographic images were acquired within 30 to 60 seconds after the termination of peak exercise by an experienced echocardiographer. The images were digitalized, recorded and analyzed by visual inspection. The early post-exercise images with the best endocardial definition were selected for comparison with the resting images.

Interpretation of exercise electrocardiography and echocardiography

Positive exercise ECG was defined as positive in cases of horizontal or downsloping ST-segment depression or elevation ≥1 mm at 80 ms after the J point in two or more contiguous leads. Duke treadmill score taking into account the patient's symptoms, extent of ST-segment shift during exercise and total exercise time was calculated.[10] The rate-pressure product, which is an indicator of the oxygen requirements of the heart, was calculated as the product of the maximal heart rate and the maximal blood pressure during the treadmill exercise.[11] The exercise ECG results were confirmed by a cardiologist who was blinded to the echocardiographic results.

The 17-segment model of the left ventricle was used and a 4-point scale was used to assess wall motion after exercise (1, normal; 2, hypokinesis; 3, akinesis; 4, dyskinesis).[12] The TSE results were interpreted by a cardiologist who was blinded to the ECG results. A positive TSE result was defined as newly developed regional wall motion abnormalities.[1-4]

Coronary angiography and revascularization

The attending cardiologist decided to proceed with CAG after considering both the TSE result and the clinical status within 30 days after the test. Standard techniques were used by the physician performing the CAG by utilizing a visual qualitative scoring system for image analysis with CAD defined as >50% luminal diameter narrowing. PCI, including balloon angioplasty and stent insertion, was performed based on the decision of the attending cardiologist.

Statistical analysis

Continuous variables are expressed as means±SDs and categorical variables are expressed as percentages. To compare between the positive TSE group and negative TSE group, the continuous variables were analyzed using Student's t-test and the categorical variables were analyzed using the Chi-square test. A p<0.05 was used to reject the null hypothesis. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 13.0 (SPSS Inc., Chicago, IL, USA). For the calculation of the sensitivity, specificity, the predictive value and the diagnostic accuracy of the exercise tests,

the numbers of patients were assessed according to the TSE results or the concomitant exercise ECG and the presence of significant CAD on CAG.

Results

Patient characteristics

Among the 1,500 participants referred for TSE to our institution during the 4-year 3-month period, 15 patients with a history of previous PCI, 1 patient who underwent coronary bypass surgery before TSE, 43 patients with significant valvular heart disease with more than a moderate degree of regurgitation or stenosis, 5 patients with hypertrophic cardiomyopathy, 25 patients with left ventricular dysfunction (an ejection fraction <45%), 23 patients with wall motion abnormalities seen on resting echocardiography, 2 patients with atrial fibrillation on the initial ECG and 99 patients with suboptimal exercise (early stop) (55 with leg discomfort, 44 with dyspnea) were excluded (Fig. 1).

A total of 1,287 participants met the inclusion criteria for this study. Of the 1,287 patients, 95 (7.4%) showed positive TSE results and 154 patients (12%) underwent CAG. Among the 1,192 patients who showed negative TSE results, 77 underwent CAG due to continued chest pain (n=16), positive results for other cardiovascular imaging modalities (45 patients showed positive results on coronary multi-detector computed tomography, 6 patients showed positive results on a nuclear scan) and the patient's request (n=10). Of the 154 patients with CAG, 94 patients (61%) showed significant CAD (30 of 77 patients with negative TSE results and 64 of 77 patients with positive TSE results) and finally 91 patients (59%) underwent successful revascularization therapy.

Comparison between the patients with positive treadmill exercise stress echocardiography results and negative treadmill exercise stress echocardiography results

The baseline characteristics of the subjects are described in Table 1. The mean age was 53.2±10.7 years. A total of 523 (41%) of the 1,287 patients were referred for TSE due to typical chest pain. The patients with positive TSE results were more often older in age and were males, and had diabetes and hypertension more often as compared to those with negative TSE results.

The TSE positive group showed a higher Framingham risk score, a lower total cholesterol level and higher blood pressure, and a lower high density lipoprotein-cholesterol level than the TSE negative group. There was no significant difference in the incidence of dyslipidemia, current smokers and the reasons for the TSE test.

Treadmill exercise stress echocardiography and exercise electrocardiography findings

The TSE parameters according to the TSE results are presented in Table 2. The TSE positive group showed a significantly higher diastolic blood pressure, a higher Duke treadmill score and a higher wall motion score index, but a lower maximal heart rate, exercise time, maximal achieved work load and rate-pressure product than the TSE negative group. The TSE positive group had a higher incidence of exercise limiting chest pain and positive results for concomitant exercise ECG than the TSE negative group. Adverse events, except for chest pain during the test, were reported in 4 patients (0.3%) among the 1,287 patients, and this included 1 patient with paroxysmal atrial fibrillation and a rapid ventricular response, 1 patient
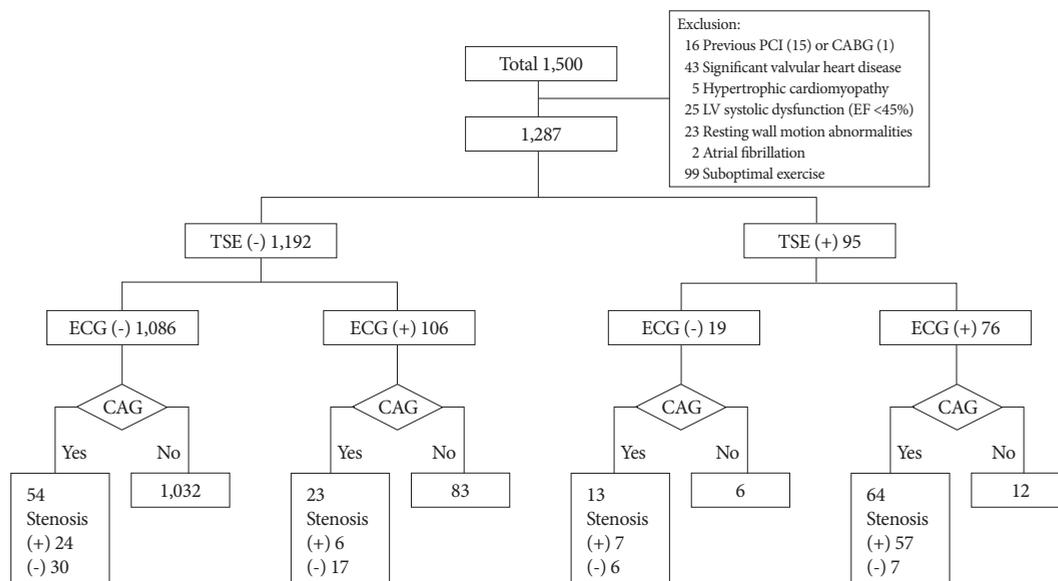

Fig. 1. Schematic diagram of the study population according to the exercise test and coronary angiography results. PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, LV: left ventricular, EF: ejection fraction, ECG: electrocardiography, TSE: treadmill exercise stress echocardiography, CAG: coronary angiography.

with paroxysmal supraventricular tachycardia, 1 patients who fainted (near-syncope) due to hypotension and 1 patient with vomiting immediately after peak exercise. All of them recovered spontaneously. No fatal ventricular arrhythmias or acute myocardial infarction occurred during the testing.

Comparison between treadmill exercise stress echocardiography and concomitant exercise electrocardiography

We analyzed the patient numbers according to the TSE results or concomitant exercise ECG and the presence of significant CAD on CAG to compare the sensitivity, specificity,

Table 1. Baseline characteristics of the subjects according to the results of treadmill exercise stress echocardiography (TSE)

Variables	Total (n=1,287)	TSE (-) (n=1,192)	TSE (+) (n=95)	p
Age (years)	53.2±10.7	52.7±10.7	59.0±8.8	<0.001
Male sex, n (%)	743 (58)	668 (56)	75 (79)	<0.001
Body mass index (kg/m^2)	24.9±3.0	24.9±3.1	25.4±2.9	0.087
Diabetes mellitus, n (%)	159 (12)	133 (11)	26 (27)	<0.001
Hypertension, n (%)	473 (37)	424 (36)	49 (52)	0.002
Dyslipidemia, n (%)	144 (11)	133 (11)	11 (17)	0.900
Smoking, n (%)				0.086
Non and former	1,023 (80)	954 (80)	69 (73)	
Current	264 (21)	238 (20)	26 (27)	
Framingham risk score	8.7±7.1	8.1±6.7	14.7±8.2	<0.001
Reasons for performing the test, n (%)				0.108
Typical chest pain	523 (41)	477 (40)	46 (48)	
Atypical chest pain	348 (27)	330 (28)	18 (19)	
Others*	416 (32)	385 (32)	31 (33)	
Total cholesterol (mg/dL)	192.0±38.2	192.9±38.2	182.2±36.5	0.013
Triglyceride (mg/dL)	146.6±114.1	146.1±115.3	151.4±99.4	0.687
HDL-C (mg/dL)	49.3±11.6	49.7±11.7	44.6±10.2	<0.001
LDL-C (mg/dL)	118.9±31.9	119.1±31.9	117.2±31.7	0.588
LVEF (%)	64.8±4.8	64.9±4.8	64.6±5.1	0.661
Heart rate (beats/min)	67.1±9.7	67.1±9.6	68.0±10.4	0.343
Systolic blood pressure (mmHg)	118.8±16.6	118.1±16.4	127.0±15.9	<0.001
Diastolic blood pressure (mmHg)	71.2±12.0	70. 9±11.8	74.2±13.0	0.010

The data is expressed as means±SDs or as the numbers (%). *Patients without symptoms, but who were suspicious of having ischemic heart disease on electrocardiography, or coronary calcium and/or stenosis on cardiac multi-detector computed tomography. HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, LVEF: left ventricular ejection fraction, TSE: treadmill exercise stress echocardiography

Table 2. Treadmill exercise parameters according to the results of treadmill exercise stress echocardiography (TSE)

Variables	Total (n=1,287)	TSE (-) (n=1,192)	TSE (+) (n=95)	p
Maximal HR (beats/min)	167.9±19.4	169.3±18.5	149.0±20.9	<0.001
Maximal systolic BP (mmHg)	171.9±24.4	171.6±24.5	174.8±22.5	0.228
Maximal diastolic BP (mmHg)	77.6±14.8	77.3±14.8	80.8±13.4	0.028
Exercise time (minutes)	10.5±1.9	10.6±1.8	8.9±2.5	<0.001
Rate-pressure product	28,892.7±5,471.0	29,107.0±5,392.1	26,203.6±5,763.4	<0.001
Work load, METs	12.2±2.1	12.4±2.0	10.5±2.9	<0.001
Limiting chest pain, n (%)	21 (1.6)	2 (0.2)	19 (20)	<0.001
Duke Treadmill score	8.3±6.3	9.3±4.7	-3.5±10.2	<0.001
Exercise ECG positive, n (%)	182 (14)	106 (9)	76 (80)	<0.001
Wall motion score index	1.0±0.1	1.0±0.0	1.2±0.2	<0.001
Events after exercise,* n (%)	4 (0.3)	4 (0.3)	0 (0)	0.572

The data are expressed as means±SDs or as the numbers (%). *Events after exercise; 1 PAF, 1 PSVT, 1 Near-syncope, 1 Vomiting. HR: heart rate, BP: blood pressure, METs: metabolic equivalents, ECG: electrocardiography, PAF: paroxysmal atrial fibrillation, PSVT: paroxysmal supraventricular tachycardia, TSE: treadmill exercise stress echocardiography

predictive value and diagnostic accuracy of the tests (Table 3). TSE showed relatively good sensitivity (68%), specificity (78%) and positive and negative predictive value (83 and 61%, respectively), and it also had higher diagnostic accuracy than concomitant exercise ECG (72% vs. 64%, respectively).

Concordance in the coronary artery territory between induced ischemia during treadmill exercise stress echocardiography and coronary artery disease on coronary angiography

Among the 95 patients who showed positive TSE results, 77 (81%) underwent CAG. According to the coronary artery territory, 46 of 77 patients with positive TSE results showed newly developed wall motion abnormality in the left anterior descending artery territory, 28 patients showed newly developed wall motion abnormality in the right coronary artery territory and 3 patients showed newly developed wall motion abnormality in the left circumflex artery territory (Table 4). The concordance rate between induced ischemia during TSE and CAD on CAG was 93% (43/46) for the left anterior descending artery, 57% (16/28) for the right coronary artery and 67% (2/3) for the left circumflex artery, respectively. The

Table 3. Comparison of the sensitivity, specificity, predictive value and diagnostic accuracy between treadmill exercise stress echocardiography (TSE) and exercise electrocardiography (ECG) to predict significant coronary artery disease

	TSE	ECG
Sensitivity (%)	68	67
Specificity (%)	78	60
Positive predictive value (%)	83	72
Negative predictive value (%)	61	54
Diagnostic accuracy (%)	72	64

Table 4. Concordance in the coronary artery territory between induced ischemia during treadmill exercise stress echocardiography (TSE) and significant stenosis noted on coronary angiography (CAG) in the patients with positive TSE test

Induced ischemia during TSE	Stenosis on CAG	Remarks (%)
Left anterior descending artery, 46	Left anterior descending artery, 43	Concordance, 43/46 (93)
	No stenosis, 3	False-positive, 3/46 (7)
Right coronary artery, 28	Right coronary artery, 16	Concordance, 16/28 (57)
	Other vessel, 3	Discordance, 3/28 (11)
	No stenosis, 9	False-positive, 9/28 (32)
Left circumflex artery, 3	Left circumflex, 2	Concordance, 2/3 (67)
	No stenosis, 1	False-positive, 1/3 (33)

rate of false positivity for induced ischemia (positive TSE results for a specific coronary artery territory, but without stenosis of that coronary artery on CAG) was 7% (3/46) for the left anterior descending artery, 32% (9/28) for the right coronary artery and 33% (1/3) for the left circumflex artery, respectively.

Discussion

This study demonstrates that TSE is safe and it has higher diagnostic power than exercise ECG for CAD in Korean population without a history of CAD. To the best of our knowledge, this is the first and largest study on TSE in a Korean population.

Diagnostic accuracy and safety of treadmill exercise stress echocardiography to predict coronary artery disease and comparison with exercise electrocardiography

In this study, we excluded the patients with a previous history of CAD (PCI or bypass surgery) and silent ischemic wall motion abnormalities seen on resting echocardiography. TSE showed a relatively good sensitivity, specificity and positive and negative predictive values, and it also had higher diagnostic accuracy than concomitant exercise ECG (72% vs. 64%, respectively).

Induced myocardial ischemia results in a typical cascade of events that occur in a time sequence; perfusion heterogeneity is followed by metabolic changes, changes in the regional mechanical function and only at a later stage is global left ventricular dysfunction, ECG changes and pain noted.[13] The concept of the ischemic cascade is translated clinically into a gradient of sensitivity of the different available clinical markers of ischemia, with chest pain being the least sensitive and regional malperfusion being the most sensitive.[4] This is the conceptual basis of the advantages of a perfusion scan or stress echocardiography over exercise ECG.[13] Wall motion abnormalities occur earlier than ECG changes and angina in the ischemic cascade, and therefore they provide a particular advantage in patients with submaximal stress test in whom the duration or the severity of ischemia may not be enough to induce ECG changes or angina.[2][4]

The diagnostic yield of exercise testing largely depends on the clinical risk profile, and the latter constitutes the pre-test probability of an individual patient.[14][15] It is well known that the pre-test probability for CAD is mainly related to the patient's history, age, gender and the characteristics of chest pain. In the present study, the TSE positive population had more cardiovascular risk factors and a higher Framingham risk score, and showed a higher Duke treadmill score and wall motion score index, and a lower achieved work load, which was mainly due to the higher incidence of exercise limiting chest pain than that in the TSE negative group. Based on the results

of the study, it appears that to select TSE or to refer a patient for CAG to detect significant CAD, individualized stratification using the Framingham risk score and Duke treadmill score is also important in patients with suspected angina even though the treadmill exercise ECG has shown negative results.

As for the issue of safety, exercise is usually safer than pharmacological stress. In the present study, only 4 cases of adverse events occurred among 1,287 patients and these adverse events resolved spontaneously. TSE is a safe test to evaluate CAD.

The diagnostic role of treadmill exercise stress echocardiography in other cardiovascular diseases

TSE is usually used as a non-invasive diagnostic technique in patients with suspected CAD. In addition, it provides assessment of additional cardiac abnormalities that cause chest pain such as hypertrophic cardiomyopathy, significant valvular disease and silent ischemia even in patients without symptoms, and is sometimes used for assessing life-threatening conditions like aortic dissection, pulmonary embolism and even acute myocardial infarction in patients with vague symptoms, although these can be the contraindications for exercise testing. Among the 1,500 patients referred for TSE in the present study, we found 43 patients with significant valvular heart disease with more than a moderate degree of regurgitation or stenosis, 5 with hypertrophic cardiomyopathy, 25 with left ventricular dysfunction (ejection fraction <45%) and 23 with wall motion abnormalities on resting echocardiography.

Technical considerations during performance of stress echocardiography

Echocardiographic scanning during treadmill exercise is not feasible, so immediate post-exercise imaging should be done as soon as possible within 1 minute from cessation of exercise. To accomplish this, the patient is moved immediately from the treadmill to an imaging bed and placed in the left lateral decubitus position, so TSE is technically much more challenging than pharmacological stress or supine bicycle exercise. Furthermore, in terms of the concordance of the coronary artery territory between induced ischemia during TSE and CAD on CAG, TSE results might be acceptable for the left anterior descending artery (93%), but not for the right coronary artery (57%) and left circumflex artery (67%). The false positivity for induced ischemia (positive TSE results for a specific coronary artery territory, but without stenosis of that coronary artery on CAG) was relatively high for the right coronary artery and left circumflex artery. Localized basal inferior wall abnormalities, a hypertensive response to exercise and other factors are related to false-positive or false-negative results during stress echocardiography, and patients with these factors should be carefully managed.[16-18]

Study limitations

There were several limitations to this study that should be noted. This was a single-center, retrospective observational study. Hence, several inherent limitations to this study may be unavoidable. Secondly, CAG was performed in only 154 participants, and all patients who had abnormal stress echocardiographic results did not undergo CAG. If all participants, and especially the TSE positive population, were evaluated for CAD, then the sensitivity and specificity might change. Thirdly, the survival status of all participants was not documented and the mortality or major adverse cardiac events were not obtained, so a further prospective study is needed. Fourthly, the known factors that may lead to false-positive or false-negative TSE results were not thoroughly assessed, as has been mentioned earlier.

In conclusion, TSE is safe and it has greater diagnostic power than exercise ECG for CAD in Korean population without a history of CAD. The prognostic value of TSE in this population needs further confirmation in a larger prospective study.

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