



Original article

The clinical usefulness of carotid ultrasonography in patients with an inconclusive exercise treadmill stress test result



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ABSTRACT

Background: Although a treadmill exercise stress testing (EST) is often the first-line screening procedure for subjects with an intermediate probability of coronary artery disease (CAD), one limitation of this test is the high rate of inconclusive tests that result from borderline exercise-induced ST changes. The carotid intima media thickness (CIMT) correlates well with atherosclerosis. The purpose of this study was to evaluate the clinical usefulness of performing CIMT measurements in patients with an inconclusive EST. **Methods:** Symptomatic patients without history of vascular disease and with inconclusive EST result were included. Inconclusive results were defined as the presence of horizontal or downsloping ST-segment depression between 0.5 and 0.9 mm or 1.0 and 1.4 mm upsloping ST-segment depression. After inconclusive EST regarding electrocardiographic changes, the measurements of the CIMT and myocardial perfusion imaging study (MPS) were performed in all patients. The CIMT was measured at the posterior wall of the common carotid artery. The diagnosis of CAD was based on the presence of reversible perfusion defects on exercise MPS.

Results: A total of 87 patients (57 men) with a mean age of 58.9 ± 7.2 years were enrolled. The MPS was positive in 18 patients. The CIMT in patients with positive MPS was significantly greater than in patients with negative MPS. The CIMT was 0.82 ± 0.33 mm in patients with positive MPS and 0.63 ± 0.21 mm in patients with negative MPS ($p = 0.004$). Receiver operating characteristic curve analyses revealed that the greatest specificity was obtained when the cut-off value of CIMT was set at 0.66 mm (sensitivity 39%; specificity 72.5%; positive predictive value 27%; negative predictive value 82%).

Conclusion: In patients with inconclusive electrocardiographic changes during EST, CIMT was a useful measurement to prevent alternative more expensive and invasive tests. Additionally, mean CIMT is useful for screening patients with an inconclusive EST result to exclude CAD.

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Introduction

Exercise treadmill stress testing (EST) is a useful diagnostic tool for primary assessment of symptomatic patients with an intermediate probability of coronary artery disease (CAD) based on clinical findings [1]. However, one limitation is the high rate of nondiagnostic tests. EST results have been classified as negative (no evidence of reversible ischemia), positive (moderately or severely abnormal), or equivocal (reported as nondiagnostic, sub-optimal, equivocal, possibly artifactual or minimally abnormal) [2]. While the most determined reason for the high rate of nondiagnostic tests that result from patients' failure to reach the target heart rate, another reason results from inconclusive electrocardiographic

abnormalities. In case of nondiagnostic EST, patients are referred for more expensive and invasive stress tests and consequently, it causes prolonged hospital evaluation [3].

Carotid intima media thickness (CIMT) measurement has been used as a surrogate index of atherosclerosis. Several studies have found an association between increased CIMT and the incidence of cardiovascular disease in the general population [4–7]. Exercise testing and arterial ultrasonography are able to improve significantly the accuracy of the risk stratification over conventional risk factors [8].

The purpose of this study was to evaluate the clinical usefulness of performing CIMT measurements in patients with an inconclusive stress test.

Methods

Patient population

The study population consisted of patients referred to an outpatient clinic with stable chest pain and suspected CAD. The sample

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comprised 87 (57 male, mean age 58.9 ± 7.2 years) consecutive symptomatic patients with no previous history of overt atherosclerotic disease (cerebral, peripheral, or CAD, which was defined as any degree of CAD on previous angiogram or history of myocardial infarction or angina) who underwent exercise test with an 'inconclusive' result. Age ranged from 36 to 74 years.

A complete history was taken and a physical examination [measurement of weight, height, body mass index (BMI) and systolic and diastolic blood pressure in the supine position after 10 min rest] and 12-lead electrocardiography (ECG) at rest were performed. Blood samples were taken for fasting blood glucose and cholesterol level.

After the medical examination, patients with an intermediate pretest probability of CAD on the basis of gender, age, and symptoms (nonangina, atypical angina, or typical angina) were prepared for treadmill exercise stress testing (EST) for evaluation of symptoms of possible coronary artery disease [9].

Patients with a history of stroke, unstable angina pectoris, myocardial infarction, peripheral artery disease, valvular disease, arrhythmia, abnormal ECGs that would preclude adequate interpretation of changes or taking digoxin were excluded. Patients were excluded if they were pregnant or lactating women. Since the extent of CAD may be underestimated when calcium channel blockers and β blockers are given, these medications were discontinued for 48 h.

Informed consent was obtained from each patient. The study protocol was approved by the ethical committee of the hospital.

Treadmill exercise stress testing

EST was performed using a modified Bruce protocol exercise treadmill test. The protocol for EST has been previously reported [9,10]. Briefly, modified Bruce protocol was employed. Since our institution uses a heart rate of at least 85% of the adjusted age-predicted maximal heart rate ($220 \text{ beats/min} - \text{age}$) to indicate adequate stress, the patients were encouraged to continue until 85% of maximal heart rate was achieved. All participants reached this 85% target. During exercise, a 12-lead ECG and blood pressure were recorded at the end of each 3-min stage and at peak exercise. Post-exercise ECGs were obtained after 5 min. Based on clinical or ECG response, the test was considered as normal (negative), ischemic (positive), and inconclusive.

The EST was considered ischemic if there was horizontal or downsloping ST-segment depression of at least 1.0 mm or 1.5 mm upsloping ST-segment depression, 80 ms after the J point in ≥ 1 lead was observed. However, in the presence of horizontal or downsloping ST-segment depression from 0.5 to 0.9 mm or 1.0 to 1.4 mm upsloping ST-segment depression, the test was considered as 'inconclusive.' Patients with 'inconclusive' ECG findings were assessed.

Besides the ECG findings, blood pressure response to exercise is an important finding. Hypertensive blood pressure response was defined as systolic blood pressure of $>220 \text{ mmHg}$ and/or a diastolic blood pressure of $>95 \text{ mmHg}$.

Myocardial perfusion imaging study

Eighty-seven subjects with an 'inconclusive' treadmill EST were referred for exercise myocardial perfusion single-photon emission tomography (SPECT) imaging. Studies were performed using the treadmill (Series 2000 Treadmill; GE Marquette Medical Systems, Milwaukee, WI, USA) according to a Bruce protocol. The isotope used was $^{99\text{m}}\text{Tc}$ (technetium)-sestamibi. At 1 min before peak exercise, the stress dose of sestamibi was injected intravenously. The patient exercised for at least 1 min longer after the injection. Stress and rest studies were performed using a 1-day protocol "one-day rest/stress Tc-99m protocols" for exercise stress

according to the consensus report [11]. Resting and peak exercise $^{99\text{m}}\text{Tc}$ sestamibi injection with perfusion imaging was performed using a gamma camera (Infia; H300WE, VC [GE Medical System, Tirat Hacarmel, Israel]). A positive test was defined as the presence of one or more reversible perfusion defects during stress.

Measurement of carotid intima-media thickness

All carotid ultrasonographic examinations were performed with the same device (Logic S8; GE Medical Systems) equipped with an 8-MHz linear probe. Patients were examined in the supine position with the head 45° away from the side being scanned.

Digital images were stored directly from the ultrasound system. Far-wall CIMTs were measured in the distal of each carotid artery in the proximal 1 cm of carotid bulb in areas free of plaque using B-mode imaging [12]. Measurements were repeated three times and results were averaged. Mean CIMT values from the far walls of the right and left common carotid arteries were reported. Plaque was defined as focal wall being 50% thicker than the surrounding wall. Presence of any calcification, plaque, and echocardiographically lucent components was noted.

Statistical analysis

Categorical and numeric variables are expressed in percentage and mean \pm standard deviations respectively. Numerical variables were tested with Mann–Whitney *U*-test, and categorical variables were tested using Fisher's exact test or Chi-square test whichever was suitable. Spearman's test was used for correlation analysis. Sensitivity and specificity values for positive MPS were calculated from receiver operating characteristic curve (ROC). A *p*-value of <0.05 was regarded significant for all analyses. All the statistical tests were done using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Reproducibility

Intra- and interobserver reproducibilities were assessed for CIMT values. For intraobserver variability, the same operator performed a second measurement more than a month after the initial analysis. The Bland–Altman analysis for interobserver reproducibility [mean difference – 95% confidence interval (CI)] and intraobserver reproducibility [intraclass correlation coefficient (ICC), 95% CI] were calculated. The interobserver and intraobserver reproducibility showed a perfect agreement for the CIMT – interobserver and intraobserver agreement were assessed as 0.04 (–0.09 to 0.11) and [(0.92), (0.89–0.94)], respectively.

Results

A total of 87 patients (males, 65.5%) with a mean age of 58.9 (± 7.2) years who had an intermediate pretest probability (10–90%) of CAD based on age, gender, and nature of symptoms were included. Among them, 59 patients had hypertension, 25 dyslipidemia, 55 were smokers, and 21 had diabetes mellitus. Baseline characteristics of the study population are shown in Table 1.

After inconclusive EST regarding ECG changes, the measurements of CIMT and myocardial perfusion imaging study (MPS) were performed in all patients.

All ultrasound examinations (100%) provided images good enough to allow the measurement of the CIMT. We did not observe any calcification or plaque. Mean CIMT was found to be $0.67 \pm 0.25 \text{ mm}$.

Coronary artery disease was diagnosed based on the MPS. The MPS was positive in 18 (21%) of the 87 patients. Patients with pathologic results of the perfusion study had a borderline difference in levels of low-density lipoprotein cholesterol and age (for both,

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