Outcome by Exercise Echocardiography in Patients with Low Pretest Probability of Coronary Artery Disease

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Background: Recommendations for testing in patients with low pretest probability of coronary artery disease differ in guidelines from no testing at all to different tests. The aim of this study was to assess the value of exercise echocardiography (ExE) to define outcome in this population.

Methods: A retrospective analysis was conducted of 1,436 patients with low pretest probability of coronary artery disease (<15%) who underwent initial ExE. Overall mortality, major adverse cardiac events (MACEs), defined as cardiac death or nonfatal myocardial infarction, and revascularization during follow-up, were assessed. Ischemia (development of new wall motion abnormalities with exercise) and fixed wall motion abnormalities were measured.

Results: The mean age was 50 ± 12 years. Resting wall motion abnormalities were seen in 13 patients (0.9%) and ischemia in 108 (7.5%). During follow-up, 38 patients died, 10 of cardiac death (annualized death rate, 0.39%); 20 patients had MACEs (annualized MACE rate, 0.21%); and 48 patients (29 with ischemia) underwent revascularization (annualized revascularization rate, 0.51%). The number and percentage of MACEs in the abnormal and normal ExE groups were similar (two [1.7%] vs 18 [1.4%], $P = .70$), as was the annualized MACE rate (0.31% vs 0.21%, $P = .50$). Peak left ventricular ejection fraction exhibited a nonsignificant trend for predicting MACEs ($P = .11$). The number of studies needed to detect an abnormal finding was 12.6 and to detect a patient with extensive ischemia was 26.1.

Conclusions: ExE offers limited prognostic information in patients with low pretest probability of coronary artery disease. The small number of abnormal findings on ExE and low event rates and the large number of studies needed to detect an abnormal finding limit further the value of imaging in this population. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Low pretest probability, Coronary artery disease, Exercise echocardiography

Although functional noninvasive imaging has the highest reach in patients with intermediate pretest probability of coronary artery disease (CAD), there remains an important number of patients with low pretest probability (LPP) of the disease and clinical symptoms. Recommendations for testing in these patients differ in current guidelines from no testing at all in those with probabilities <15% according to European Society of Cardiology guidelines[1] or <10% according to National Institute for Health and Care Excellence guidelines[2] to exercise electrocardiography, stress echocardiography, or computed tomography according to American guidelines.[3,4] Also, stress echocardiography has been proposed in some guidelines for the assessment of chest pain with any pretest probability in case of wide availability and also for the assessment of atypical chest pain in women.[5] Overall, although the small number of cardiac events when the pretest probability of CAD is low is well known,[1,6] as well as the large number of false-positive results resulting from diagnostic testing in this population, clinicians may still choose imaging techniques to study these patients. This might be true particularly if the pretest probability is not taken into account before ordering the test, if the referring clinician is not aware of the limited performance of these tests in these patients, and if these techniques are widely available. We aimed to review our stress echocardiography database for patients with LPP of CAD to investigate if exercise echocardiography (ExE) has any value to define outcomes. We hypothesized that adverse event rates would be low for these patients and that higher event rates in those with abnormal results would be driven by revascularization, not by cardiac death or nonfatal myocardial infarction (MI).

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METHODS

Collected data from the University of A Coruña stress echocardiography laboratory data bank were retrospectively analyzed.

Abbreviations

CAD = Coronary artery disease

DTS = Duke treadmill score

ECG = Electrocardiographic

ExE = Exercise echocardiography

LPP = Low pretest probability

LV = Left ventricular

LVEF = Left ventricular ejection fraction

MACE = Major adverse cardiac event

MI = Myocardial infarction

WMA = Wall motion abnormality

WMSI = Wall motion score index

Patients

Data were obtained from 1,436 patients with LPP of CAD (<15%) who underwent initial treadmill ExE at our institution during a 20-year period from March 1995 to January 2015. Data were extracted from a database of 18,031 patients, with initial ExE performed in 14,906 patients. Patients with left ventricular (LV) dysfunction, defined as LV ejection fraction (LVEF) < 52% for men and < 54% for women,[7] were excluded ($n = 155$), as were patients with congenital heart disease ($n = 5$), moderate or severe valvulopathies ($n = 49$), and hypertrophic cardiomyopathy ($n = 281$). The pretest probability of CAD was determined retrospectively by an investigator who was blinded to the results of ExE.

Demographic and clinical data, as well as stress testing results, were entered into our database at the time of the procedures. Data were taken from the original ExE reports of the patients. The pretest probability of CAD was assessed according to Genders *et al.*[8] Clinicians referred these patients for ExE, instead of exercise ECG testing, because of the high availability of the former at our institution.

Whenever possible, β-blocker therapy was discontinued for ≥48 hours before testing. However, 6% of patients were still under the influence of β-blockers at the time of their tests.

Exercise Electrocardiography

Heart rate, blood pressure, and electrocardiography were obtained at baseline and at each stage of exercise. Patients were encouraged to perform a treadmill exercise test (Bruce protocol in 78.8%, Bruce protocol for fitness patients in 19%, modified Bruce protocol in 1.6%, Naughton protocol in 0.6%). Exercise end points included physical exhaustion, significant arrhythmia, severe hypertension (systolic blood pressure > 240 mm Hg or diastolic blood pressure > 110 mm Hg), severe hypotensive response (decrease > 20 mm Hg), and symptoms during exercise. Ischemic electrocardiographic (ECG) results were defined as the development of ST-segment deviation ≥ 1 mm that was horizontal or down-sloping away from the isoelectric line 80 ms after the J point in at least two leads, in patients with normal baseline ST segments. ECG results were considered nondiagnostic in the presence of left bundle branch block, preexcitation, paced rhythm, repolarization abnormalities, or treatment with digoxin. In patients with diagnostic ECG results, the Duke treadmill score (DTS) was calculated.[9] Positive exercise test results were defined as chest pain during the test and/or ischemic ECG abnormalities in patients with diagnostic ECG results.[10,11] A maximal test was defined as the achievement of ≥85% of the mean age-predicted heart rate; otherwise the test was considered submaximal. All patients gave informed consent.

Exercise Echocardiography and Echocardiographic Analysis

Echocardiography was performed in three apical views (long-axis, four-chamber, and two-chamber) and two parasternal views (long-axis and short-axis) at baseline, at peak exercise,[7-9] and in the immediate postexercise period. Peak exercise imaging on the treadmill has been previously described by our group.[11-13] It is performed with the patient still exercising, when signs of exhaustion are present or an end point is achieved. If the patient is running, he or she is asked to walk fast instead of running during acquisition. In addition, it may be necessary to keep steady the velocity of the treadmill. The transducer is firmly positioned on the apical and then parasternal area by applying pressure to the patient's back with the left hand, maintaining the patient between the transducer and the left hand, in order to diminish body and respiratory movements. A continuous imaging acquisition system is used. We have demonstrated higher heart rates during acquisition with peak than with postexercise imaging, and also higher sensitivity and prognostic value.[11-13]

Regional wall motion abnormalities (WMAs) were evaluated with a 16-segment model of the left ventricle.[7] Each segment was graded on a four-point scale: normal wall motion = 1, hypokinetic = 2, akinetic = 3, dyskinetic = 4, and nonvisualized = 0. However, isolated hypokinesia of the basal inferior or inferoseptal segments was not considered abnormal.[14] Wall motion score index (WMSI) and visually estimated LVEF[15] were calculated at rest, peak exercise, and postexercise.

WMSI was calculated as the sum of scores divided by the number of visualized segments. The worst WMSI and LVEF obtained on peak exercise or postexercise imaging were considered definitive values. The change in WMSI from rest to exercise was calculated. Ischemia was defined as the development of new or worsening WMA with exercise and a fixed WMA as a WMA that remained the same with exercise. Extensive ischemia was defined as new or worsening WMA involving three or more segments in the same or different coronary artery distribution territories. Abnormal results on ExE were defined as ischemia or fixed WMAs.

Follow-up and End Points

Follow-up in the entire study cohort of 1,436 patients was obtained by review of hospital databases, medical records, and death certificates, as well as by telephone interviews when necessary. We had complete access to the electronic health care system of our community and also electronic access to general practitioner consults. In case of death outside a hospital, the cause of death was provided by the mortality registry of our community. No patients were lost during follow-up.

Considered end points were overall mortality and major adverse cardiac events (MACEs). MACEs were considered in case of cardiac death or nonfatal MI. MI was defined as the appearance of new symptoms of myocardial ischemia or ischemic ECG changes accompanied by increases in markers of myocardial necrosis. Cardiac death was defined as death due to acute MI, congestive heart failure, life-threatening arrhythmias, or cardiac arrest. Unexpected sudden death without an identified cardiac cause was also considered cardiac death. Revascularization procedures during follow-up were identified, although they were not considered events, as the results of ExE might have influenced