

Usefulness of Excellent Functional Capacity in Men and Women With Ischemic Exercise Electrocardiography to Predict a Negative Stress Imaging Test and Very Low Late Mortality



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Exercise electrocardiography (ExECG) is widely employed to assess patients for coronary artery disease but it has limited diagnostic accuracy. Many patients with positive (ischemic) tests based on exercise-induced ST depression undergo secondary evaluation by noninvasive stress imaging. We hypothesized that high functional capacity in patients with positive ExECG could predict: (1) negative results in secondary evaluation by exercise echocardiography (ESE) or myocardial perfusion scintigraphy (MPS) and (2) low mortality on late follow-up. We evaluated 511 consecutive patients (312 men, 199 women; age 51 ± 9 years) referred for ESE or MPS after an ischemic ExECG at a treadmill workload of ≥ 10 metabolic equivalents. All-cause mortality was also obtained. Of 511 patients, 401 underwent ESE and 110 had MPS for secondary study. ESE was negative in 94% (376 of 401) and positive in 6% (25 of 401). MPS was also negative in 94% (103 of 110) and positive in 6% (7 of 110). Total stress imaging results were negative in 92% (286 of 312) of men and 97% (193 of 199) of women. During follow-up of approximately 6 years, there were 3 deaths with total all-cause mortality of 0.6% and average annual mortality of 0.1%. In conclusion, high functional capacity in patients with an ischemic ExECG predicts a negative ESE or MPS in a large majority of patients and very favorable late survival in both men and women. These results suggest that patients with ischemic ExECGs and a workload of ≥ 10 metabolic equivalents during ExECG may not require additional noninvasive or invasive evaluation. © 2019 Published by Elsevier Inc. (Am J Cardiol 2019;124:661–665)

Exercise electrocardiography (ExECG) is widely used to evaluate individuals with coronary artery disease (CAD) or its symptoms.^{1,2} However, it has limited accuracy when its results are interpreted solely on the basis of the ST-segment response.^{1,3} Thus, many patients with positive results by this criterion undergo further evaluation by stress imaging modalities. Negative results with stress imaging are associated with a low frequency of obstructive CAD and excellent prognosis which may obviate need for further testing.^{4–10} In non-ECG variables used to enhance the utility of ExECG, functional capacity is one of the strongest predictors of prognosis.^{1,3,11–17} Previous studies on functional capacity focused on populations with high functional capacity rather than those with ischemic ECG changes.^{18–21} In our previous study, we reported that excellent functional capacity in patients with an ischemic ExECG was associated with a high rate of negative results on subsequent exercise

echocardiography (ESE).²² That study had important limitations, including a small patient cohort, and did not include follow-up testing by myocardial perfusion scintigraphy (MPS). In the current investigation, we included a large group of patients in whom secondary evaluation included ESE or MPS to further test our hypothesis that high functional capacity in patients with an ischemic ExECG predicts a negative stress imaging result and low subsequent mortality.

Methods

We reviewed our treadmill, echocardiographic, and nuclear cardiology databases to identify all consecutive patients referred for either ESE or MPS after a positive (ischemic) ExECG during which they achieved a workload of at least 10 metabolic equivalents (METs) at the University of California, Davis, Medical Center from November 1995 and August 2007. We chose a threshold of ≥ 10 METs as evidence of excellent functional capacity on the basis of previous studies that demonstrated a low risk for subsequent cardiac events or death in patients who achieved this level of exercise intensity.^{11,12,23–25}

Most of our patients were referred for evaluation of chest pain. Other indications included exertional dyspnea or preoperative risk stratification. All patients had normal baseline 12-lead electrocardiograms. Patients were excluded if they had (1) history of CAD on previous noninvasive

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testing or invasive coronary angiography, (2) history of myocardial infarction, and (3) ST-T abnormalities on resting ECG. Patient information, including demographics and CAD risk factors (diabetes, hypertension, smoking, dyslipidemia, and family history of premature CAD), was obtained from the electronic medical record and/or directly from the patient.

Initial ExECG was conducted according to the Bruce protocol and was symptom-limited. The procedure comprised 12-lead electrocardiography at rest, continuous ECG monitoring throughout the test, recordings during each 3-minute stage and during 3 to 6 minutes of recovery or later until return of original resting values. Brachial artery blood pressure was measured by sphygmomanometry at baseline, each minute of the stress protocol, and during recovery. The test was terminated if patients reported limiting symptoms such as dyspnea, fatigue, chest pain, or for systolic blood pressure >220 mm Hg or a decrease of ≥ 10 mm Hg in systolic blood pressure, ≥ 2.5 mm ST-segment depression, sustained supraventricular arrhythmia, or ≥ 3 consecutive ventricular ectopic complexes at a rate of >100/min. A positive (ischemic) result was defined as ≥ 1.0 mm horizontal or downsloping ST-segment depression for 60 to 80 ms after the J point.

The Duke treadmill score, an integrated approach to evaluating exercise treadmill test performance and prediction of cardiovascular risk and mortality, was calculated for all patients.^{16,17} Patients were identified as low, intermediate, and high risk based on this score, which has correlated with a 5 year mortality risk of 3%, 10%, and 35%, respectively.^{16,17}

ESE was performed according to the Bruce protocol and was symptom limited as described above and included rest echocardiography before ExECG and immediate postexercise acquisition of echocardiographic images. Complete postexercise echocardiography was acquired <90 seconds after termination of exercise. Rest and exercise images were displayed in standard quad-screen format for comparison of left ventricular wall motion in parasternal (long- and short-axis) and apical (2- and 4-chamber) views. All ESE included in the study were of diagnostic quality. Positive ESE was defined as ≥ 1 new exercise-induced left ventricular regional wall motion abnormalities.

Myocardial stress perfusion scintigraphy was performed with ECG-gated single photon emission computed tomography. Exercise MPS was performed with concurrent ECG monitoring. The isotope was Technetium-99m sestamibi. Rest scintigraphy was acquired, after which patients performed maximal treadmill testing (Bruce protocol as described above) and the isotope was injected at peak exercise. Polar and 3-dimensional quantitative images of the left ventricle were acquired. A study was considered positive if the stress image(s) demonstrated a new reversible perfusion defect(s) compared with the rest image.

All-cause mortality was determined from the electronic medical record and/or Social Security Administration Death Index. The Institutional Review Board of the University of California, Davis, approved this study.

Results

The study cohort comprised 511 consecutive patients including approximately 40% women (Table 1). Patient ages ranged from mid-thirties to almost 70 years old. Two or more CAD risk factors were present in 40% of patients. The mean exercise-induced ST segment depression for the study group was 1.5 ± 0.5 mm and over 30% of patients had >2 mm of ST depression on their ExECG. Over three-quarters had medium risk Duke treadmill scores (DTS). Average exercise capacity of the 511 patients was 11.7 METs, reflecting >3 full stages of the Bruce treadmill protocol. All patients had either ESE or MPS within 90 days after the initial positive ExECG and had no clinical cardiac events during the intervening interval.

Of the total study group, 401 (78%) underwent subsequent ESE and 110 (22%) patients had MPS. Of the patients who underwent ESE, 94% had a negative result, and of those who had MPS, 94% were also negative (Figure 1). Stress imaging tests were negative in 92% of men (286 of 312) and in 97% of women (193 of 199) (Figure 2).

Follow-up information regarding mortality was obtained in 100% of patients. The mean follow-up interval was 5.9 ± 3.3 years and the longest period was 12.4 years. There were 3 deaths (3 of 511) during the follow-up period for total all-cause mortality of 0.6% and average annual mortality of 0.1%.

Discussion

Our findings reveal that a high functional capacity in patients with a positive (ischemic) ExECG is associated with negative follow-up stress imaging results and excellent long-term survival. These findings suggest that further cardiac testing may not be mandatory for most such individuals. Our findings extend previous studies by providing data on either ESE or MPS. Although others have shown favorable prognosis with good functional capacity, very few have done so in patients with exercise-induced ischemia in a study of adequate size and follow up. Previous reports typically included a smaller cohort of patients with

Table 1
Baseline patient characteristics

Characteristic	All subjects (n = 511)
Age (years [mean \pm SD])	51 \pm 9
Men	312 (61%)
Women	199 (39%)
Number of atherosclerotic risk factors	
0	136 (26.6%)
1	171 (33.5%)
≥ 2	204 (39.9%)
Diabetes mellitus	44 (8.6%)
Exercise capacity, METs (mean \pm SD)	11.7 \pm 1.9
Low risk DTS	115 (22.5%)
Intermediate risk DTS	395 (77.3%)
High risk DTS	1 (0.2%)
Mean ST segment deviation (mm \pm SD)	1.51 \pm 0.54

DTS = Duke treadmill score; ETT = exercise treadmill test; METs = metabolic equivalents.

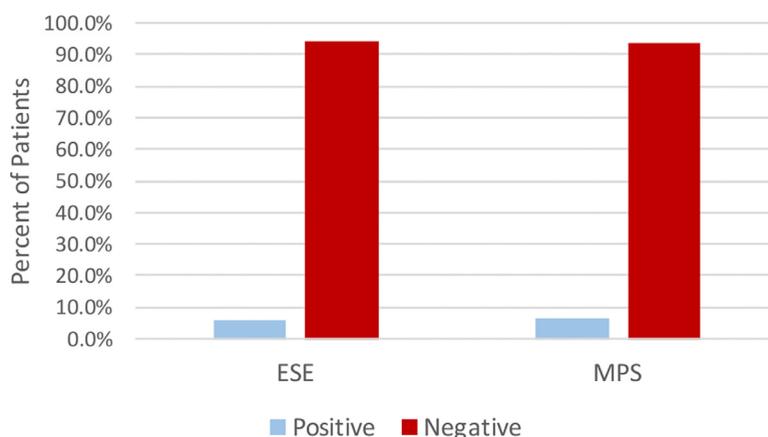


Figure 1. Imaging stress test results. ETT = exercise treadmill test (electrocardiography); ESE = exercise stress echocardiography; MPS = myocardial stress perfusion scintigraphy.

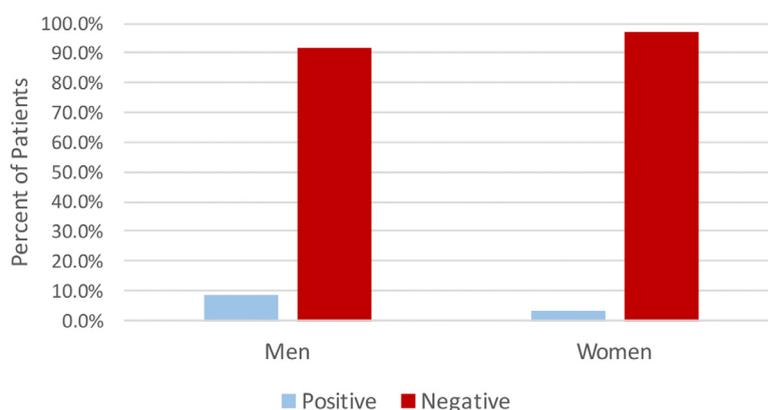


Figure 2. Imaging stress test results by sex. ETT = exercise treadmill test (electrocardiography); ESE = exercise stress echocardiography; MPS = myocardial stress perfusion scintigraphy.

high workloads associated with a positive (ischemic) ExECG.^{20,22,24} Duration of follow-up for our patients was unique, with an average follow-up of almost 6.0 years and a maximum >12 years which, to our knowledge, is the longest reported in studies of this type.^{20,21,24} Our study group includes patients of a wide age range, extending from mid-thirties to almost 70 years. Importantly, women who achieved a peak of ≥ 10 METs exercise intensity comprised nearly 40% of our patients, a substantially greater proportion than previously reported, which supports the applicability of our findings to women.^{20,21,24} Almost 40% of patients had ≥ 2 cardiac risk factors and over three-quarters had medium risk Duke treadmill scores.

Functional capacity is an established, independent predictor of prognosis for cardiovascular events and death even in patients with type II diabetes.^{2,12,13,23} The Coronary Artery Surgery Study demonstrated that excellent exercise capacity (≥ 10 METs) was associated with less benefit from bypass surgery than in those with lower functional capacity.^{26,27} Other studies have shown that lower functional capacity is associated with increased risk for myocardial infarction, unstable angina, and coronary revascularization.² More recently, Bourque et al showed that a high workload (≥ 10 METs) predicted a low rate of inducible ischemia on myocardial perfusion scintigraphy²⁰ but the study comprised only 43 patients with high workloads and

ischemic ExECG. In another recent report it was shown that high treadmill workload correlated with a favorable prognosis, although patients with ischemic ST depression were not the focus of their study.²¹ In addition to the aforementioned limitations, previous investigations may have had surrogate end points and some did not include further risk stratification tests of patients with ischemic treadmill tests. Many also did not perform separate analyses of outcomes in men and women^{20,24} or did not report the Duke treadmill score.^{20,21,24} Those studies that did employ further testing to risk stratify such patients reported only ESE or MPS.^{20–22}

Our findings extend current understanding of the prognostic utility of ExECG even in patients with exercise-induced evidence of myocardial ischemia. These results reflect the low positive predictive value of ExECG when interpreted by ST changes alone compared with imaging stress tests.²⁸ Notably, outcomes were favorable even in the sizable minority of our patients (over 30%) who developed over 2 mm of exercise-induced ST depression, a finding that has been reported in only one study²⁴ in addition to our previous report.²² Our results further develop the findings of our previous study²² and are unique in including either ESE or MPS for secondary evaluation. We also have extended previous studies that addressed the prognostic value of treadmill exercise capacity.^{3,16,17}

Approximately 94% of our population who achieved treadmill workloads of ≥ 10 METs had negative subsequent noninvasive cardiac stress imaging. Those patients who had an intermediate risk Duke treadmill score (DTS) comprised a sizable majority ($>77\%$) of our study cohort population. An intermediate risk DTS has suggested an average 5 year cardiac mortality of 10% in previous studies yet our patients had an overall mortality rate of only 0.6% (3 of 511) during almost 6 years of follow-up.^{16,17} These findings suggest that the DTS overestimates risk in patients who achieve high exercise workloads. The DTS was derived several decades ago previous to contemporary advances in prevention and treatment for CAD. In the current era, patients with a DTS indicating intermediate risk including ischemic ECG changes who achieve high exercise workloads may have an excellent prognosis and may not require further cardiac evaluation. Importantly, these findings applied not only to women and men but also elderly patients >65 years old.

This study has certain limitations. It is a retrospective investigation with the inherent limitations of that method. However, the study group is relatively large, the age range is wide, follow-up duration is the longest in this type of investigation, the proportion of women is substantial, and almost 40% of patients had multiple cardiac risk factors. The study cohort is representative of patients frequently referred for cardiac stress imaging. Additionally, although we have no data regarding cause of death and adverse cardiovascular events, all-cause mortality is a critical end point. Finally, negative stress imaging results, as in our patients, have been associated with a very low frequency of cardiovascular events in multiple studies.^{5-8,25,29}

In conclusion, high functional capacity in patients with an ischemic treadmill testing predicts a negative subsequent ESE or MPS in a very large majority of patients and excellent late survival in both men and women. Thus, these patients may not require further noninvasive or invasive evaluation.

Disclosures

The authors have nothing to disclose.

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