Long Term Favorable Prognostic Value of Negative Treadmill Echocardiogram in the Setting of Abnormal Treadmill Electrocardiogram: A 95 Month Median Duration Follow-Up Study

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Background: The aim of this retrospective study was to assess if negative treadmill echocardiographic (NTME) results retained their favorable prognosis over a long period of follow-up (median, 95 months) in the setting of ischemic stress electrocardiographic (ISECG) results.

Methods: Consecutive patients with NTME results were analyzed as 2 groups (those with ISECG results and those with normal stress electrocardiographic results). Patients were followed up for a median duration of 95 months to identify major adverse cardiac events (MACEs), including all-cause death, myocardial infarction, and coronary revascularization.

Results: Six hundred seventy-seven patients fulfilled the inclusion criteria. Fifty-eight patients had MACEs (8.6%). The annual event rate was 1%. There was an increased unadjusted rate of MACEs among patients with ISECG results (15% vs 8%; $P = .025$). After adjusting for clinical and stress variables, ISECG results were not independently predictive of MACEs ($P = .2$). Female gender, prior coronary artery disease, metabolic equivalents achieved, and chest pain at stress were the independent predictors of MACEs.

Conclusions: Patients with NTME results had excellent long-term outcomes, regardless of ISECG results, over a median 95-month follow-up period. The findings of this study reaffirm the importance of benign long-term outcomes in the setting of good exercise capacity. (J Am Soc Echocardiogr 2008;21:1018-1022.)

Keywords: Treadmill electrocardiography, Treadmill echocardiography, Exercise echocardiography, Ischemia, Prognosis

Treadmill echocardiography is a well-validated technique for the diagnosis and assessment of coronary artery disease (CAD). Negative treadmill echocardiographic (NTME) results have good negative predictive value (annualized event rate, 1%-2%), regardless of the presence or absence of stress electrocardiographic (SECG) changes over a 2-year to 4-year follow-up period.[1,2] This strong prognostic value has been documented independent of age and gender.[3,4] Nevertheless, prior work has also suggested that ischemic SECG (ISECG) results do have some independent prognostic value.[5,6] Others have also shown that exercise-induced ISECG results add incremental prognostic value over stress echocardiography or myocardial perfusion imaging.[7-9] The objective of the study was to evaluate the prognostic value of NTME results with particular reference to whether an ISECG finding affects prognosis over a long follow-up period beyond what has been studied.

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METHODS

Study Population

This study was approved and monitored by the study center's institutional review board. This was a retrospective study of consecutive patients who had NTME results from January to December 1997 for the evaluation of known or suspected CAD. Patients were excluded from the study if they were aged < 18 years or had echocardiographic evidence of ischemia. Patients with left bundle branch block or abnormal baseline electrocardiographic results making ischemia uninterpretable by electrocardiographic criteria (digoxin therapy, left ventricular hypertrophy by voltage with ST-segment or T-wave abnormalities, ST depression ≥ 1 mm at baseline, preexcitation, or paced rhythm) were also excluded.

SECG Protocol

All patients underwent symptom-limited treadmill testing, according to the Bruce protocol. Patients underwent 12-lead electrocardiography at rest and continuous rhythm monitoring throughout the stress echocardiographic protocol using a commercially available treadmill console. Twelve-lead electrocardiography and blood pressure measurements were obtained at baseline, at each stage of the stress protocol, and during recovery. Electrocardiographic findings during peak stress were graded as normal or abnormal by experienced echocardiographers. SECG results were considered to be abnormal if there was ≥1-mm ST-segment horizontal or down-sloping depression measured at 80 ms after the J point in 2 contiguous leads during peak stress or immediately after recovery.

Treadmill Echocardiographic Protocol

Two-dimensional echocardiographic images were obtained from standard parasternal long-axis and short-axis and apical 4-chamber, 3-chamber, and 2-chamber windows before and immediately after exercise. Quad-screen digitized images displaying rest and immediate postexercise images were interpreted side by side. Supplementary videotape recordings of the entire studies were used in cases of suboptimal digital capture and for the analysis of the recovery phase as needed in selected cases. Regional wall motion was assessed by experienced echocardiographers according to a 16-segment model.[10] Ischemia was defined as new or worsening wall motion abnormalities on the postexercise views. NTME results were defined as either normal baseline and postexercise contractile response or as the absence of new or worsening wall motion abnormalities in the postexercise images.[11] The exercise level was considered to be adequate if the patient achieved ≥ 85% of the age-predicted maximal heart rate and a peak rate-pressure product (double product) > 25,000. Baseline demographics and treadmill echocardiographic variables were obtained through electronic medical record review at our institution.

Follow-Up

Patients were divided into 2 groups on the basis of whether or not they had ISECG results. Baseline demographics and exercise variables were obtained through electronic medical record review and the treadmill stress test reports. Patients were followed up for a median duration of 95 months to identify major adverse cardiac events (MACEs), including death, myocardial infarction, coronary angioplasty, and coronary artery bypass surgery. Follow-up for mortality was complete, with confirmation of patients' vital status using the National Death Index (accessed in September 2005). The 25th and 75th percentiles of the follow-up duration for the other endpoints were 65.1 and 98.5 months, respectively. Only 30 patients without future events had < 1 year of follow-up.

Statistical Methods and Analysis

Group comparisons were conducted for baseline characteristics and comorbidities, exercise variables, and outcomes between groups using Pearson's χ^2 or Fischer's exact test for categorical variables and Student's *t* test or analysis of variance for continuous variables. Continuous variables are described as mean ± SD. A *P* value ≤ .05 was considered statistically significant. Kaplan-Meier curves for MACE-free survival were constructed, and the curves were compared using log-rank testing. Multivariate Cox proportional-hazard regression models were used to identify independent predictors of follow-up events. The selection of variables for entry consideration was based on both univariate statistical significance and clinical judgment. Variables were selected in a stepwise forward selection manner, with entry and retention set at a significance level of .05. Variables included in the model were age, gender, race, history of hypertension, diabetes, prior CAD (myocardial infarction, coronary percutaneous angioplasty, and coronary artery bypass surgery), β-blocker use, metabolic equivalents (METs) achieved, ejection fraction, smoking history, positive electrocardiographic changes, and chest pain at peak exercise. Incremental and global χ^2 values were reported at every step. All analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, IL).

Table 1 Baseline characteristics

Variable	Normal SECG and NTME results (n = 598)	ISECG and NTME results (n = 79)	*P* value
Age ≥ 65 yr	98 (16%)	25 (32%)	.001*
Men (%)	304 (51%)	39 (49%)	.8
Hypertension (%)	45 (8%)	7 (9%)	.7
Diabetes (%)	49 (8%)	4 (5%)	.3
Prior myocardial infarction (%)	50 (8%)	5 (6%)	.5
Prior coronary artery disease (%)	80 (13%)	11 (14%)	.9
Achieving ≥85% PMHR	460 (79%)	67 (86%)	.20
METs achieved	9.6 ± 2.9	9.1 ± 2.3	.17
Heart rate product	22,829 ± 10,575	22,520 ± 11,294	.81
Mean resting ejection fraction	54 ± 4	54 ± 6	.91
Chest pain during exercise	28 (5%)	12 (15%)	<.001*

ISECG, Ischemic stress electrocardiographic; *MET*, metabolic equivalent; *NTME*, negative treadmill echocardiographic; *PMHR*, age-predicted maximal heart rate; *SECG*, stress electrocardiographic.
*Significant.

RESULTS

Patient Characteristics

A total of 677 patients fulfilled the inclusion criteria and served as the study population. Of these, 79 patients (12%) had ISECG results. Baseline characteristics are shown in Table 1. Patients with ISECG results were more often aged > 65 years but otherwise did not differ in the prevalence of other comorbidities or rate-slowing medications compared with the group with normal SECG results.

Stress Testing

The treadmill stress test results are also shown in Table 1. No differences were found between the 2 electrocardiographically based groups in achieving adequate heart rate response (≥85% of the age-predicted maximal heart rate) or in METs achieved. Patients with ISECG results were more often documented as having chest pain during exercise. The baseline ejection fraction was comparable between both groups.

Follow-Up

After a median follow-up period of 95 months, 58 (8.6%) patients with NTME results had MACEs. The distribution of MACEs in both groups studied is shown in Table 2. There was an increased unadjusted MACE rate among patients with ISECG results (15% vs 8%; *P* = .02) at the end of follow-up. However, as shown in Figures 1 and 2, no significant difference was found in the MACE rate between both groups in the first 5 years of follow-up.

Multivariate Predictors of Outcomes

Table 3 shows the independent predictors of MACEs. Using Cox proportional-hazard analysis, female gender, prior CAD, METs achieved, and chest pain at peak exercise were independent predictors of MACEs in this patient cohort after adjusting for age, history of hypertension, myocardial infarction, percutaneous intervention, coronary artery bypass surgery, diabetes, ejection fraction, smoking history, and positive electrocardiographic changes. Figure 3 shows the