

Comparison of the Prognostic Value of the Stress-Recovery Index Versus Standard Electrocardiographic Criteria in Patients With a Negative Exercise Electrocardiogram

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To verify whether the stress recovery index (SRI) improves risk stratification in patients with a negative exercise electrocardiogram (ECG) using standard criteria, the SRI was derived in 708 consecutive patients with a negative exercise ECG. All-cause mortality and the combination of death or nonfatal myocardial infarction were target end points. The individual effect of clinical and exercise testing data on outcome was evaluated using Cox regression analysis with separate models for each group of variables. Model validation was performed using bootstrap adjusted by degree of optimism in estimates. Survival analysis was performed using a product-limit Kaplan-Meier method. During a 37-month follow-up, 22 deaths and 40 nonfatal acute coronary syndromes occurred. After adjusting for confounding variables, age (hazard ratio 1.62, 95% confidence interval [CI] 1.14 to 2.31 for interquartile difference), hypertension (hazard ratio 1.74, 95% CI 1.04 to 2.89), and SRI (hazard ratio 0.75, 95% CI 0.65 to 0.86 for interquartile difference) were predictive of death or nonfatal myocardial infarction. Moreover, SRI increased the prognostic power of the model on top of clinical and exercise testing variables and provided significant discrimination of survival. In conclusion, the SRI may help refine the prognostic stratification of patients with a negative exercise test result using standard electrocardiographic criteria. © 2007 Elsevier Inc. All rights reserved. (*Am J Cardiol* 2007;100:605–609)

Heart-rate adjustment of ST-segment depression is a well-established modality to improve the accuracy of an exercise electrocardiogram (ECG).^{1,2} More recently, the stress recovery index (SRI) was shown to improve the diagnostic³ and prognostic accuracy of standard ST-segment depression criteria in general populations,⁴ as well as in specific clinical settings.^{5–7} We aimed to verify whether the SRI may improve risk stratification of patients with a negative exercise ECG using standard criteria.

Methods

The study cohort consisted of 708 consecutive outpatients with a negative exercise ECG that was defined based on the absence of a ≥ 0.1 -mV ST-segment depression. Patients were tested from December 1998 to January 2001 for evaluation of chest pain and/or prognostic assessment and prospectively included in a follow-up program. Of these patients, 198 (28%) had suspected and 510 (72%) had known coronary artery disease (CAD) that was defined as previous myocardial infarction and/or revascularization procedure or presence of a $>50\%$ stenosis in ≥ 1 major epicardial vessel. Exclusion criteria were a recent (<1 month) acute coronary

syndrome, significant congenital or valvular heart disease, congestive heart failure, left branch bundle block, chronic atrial fibrillation, implantable pacemaker, digoxin use, and prognostically relevant co-morbidity. Informed consent was obtained from all patients before testing, and the study protocol was approved by the institutional ethical committee. Complete follow-up information was not available for 8 patients; therefore, the present analysis refers to 700 patients.

All patients were in stable clinical condition. Hypertension was defined as systolic blood pressure at rest of ≥ 140 mm Hg, diastolic blood pressure at rest of ≥ 90 mm Hg, or treatment with antihypertensive drugs.⁸ Diabetes mellitus was diagnosed according to World Health Organization criteria.⁹ Hypercholesterolemia was defined as fasting plasma total cholesterol >6.2 mmol/L¹⁰ or treatment with cholesterol-lowering drugs. Ejection fraction was obtained using 2-dimensional echocardiography using Simpson's rule.¹¹ Clinical characteristics of the study population are listed in Table 1.

Patients exercised on a cycle ergometer with 25-W incremental loading every 2 minutes. The 12-lead ECG was continuously monitored throughout the test for rhythm, rate, and ST-segment changes. Blood pressure was measured using arm-cuff sphygmomanometry during the last 30 seconds of each work stage. Exercise was continued until chest pain, repetitive arrhythmias, significant conduction abnormalities, ST-segment depression >0.3 mV, systolic blood pressure >230 mm Hg or a decrease >20 mm Hg, or limiting symptoms (dyspnea, dizziness, fatigue, or cramp in legs) occurred. After exercise, patients recovered in a sitting position. Total work performed indicated the exercise capacity of the patient. ST-segment deviation in leads without

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Table 1
Clinical characteristics and exercise electrocardiography results

Variable	All Patients (n = 700)	Event (n = 62)	No Event (n = 638)	Hazard Ratio
Age (yrs)	59 (53,64)	62 (57,66)	68 (52,64)	1.85 (1.31–2.61)
Men	595 (85%)	53 (85%)	542 (85%)	0.96 (0.47–1.95)
Patients with known CAD	510 (72%)	46 (74%)	464 (72%)	1.40 (0.64–3.07)
Diabetes mellitus	49 (7%)	5 (8%)	44 (7%)	1.32 (0.53–3.31)
Smoker	327 (47%)	31 (50%)	244 (38%)	1.98 (1.20–3.27)
Blood pressure >140/90 mm Hg	277 (40%)	33 (53%)	182 (27%)	2.64 (1.22–5.71)
Total cholesterol >6.2 mmol/L	276 (39%)	18 (29%)	258 (40%)	0.62 (0.36–1.07)
Ejection fraction (%)	50 (48,55)	50 (48,55)	50 (48,55)	0.77 (0.61–0.97)
Heart rate at rest (beats/min)	73 (63,84)	74 (63,86)	72 (63,84)	1.01 (0.71–1.43)
Systolic blood pressure at rest (mm Hg)	130 (120,140)	130 (120,150)	130 (120,140)	1.28 (0.98–1.68)
Peak heart rate (beats/min)	136 (120,150)	136 (119,149)	136 (120,151)	0.82 (0.58–1.16)
Percent maximal predicted heart rate	85 (74,92)	86 (75,92)	85 (74,92)	1.01 (0.70–1.46)
Peak systolic blood pressure (mm Hg)	190 (170,200)	190 (170,210)	190 (170,200)	1.08 (0.80–1.46)
Exercise capacity (kpm)	4,087 (2,700,6,000)	4,200 (2,275,6,750)	4,012 (2,700,5,650)	1.08 (0.78–1.50)
Exercise time (min)	11 (9,13.5)	11 (9,15)	11 (9,13.5)	1.11 (0.79–1.54)
Exercise-induced chest pain	95 (14%)	7 (11%)	88 (14%)	0.96 (0.44–2.11)
Maximal ST-segment depression (mV)	0.4 (0,0.7)	0.5 (0,0.8)	0.4 (0,0.7)	1.03 (0.72–1.65)
SRI (mV beats/min)	-0.82 (-2,6.6)	-6 (-16,0)	-0.5 (-12,7.7)	0.84 (0.71–0.99)

Continuous variables presented as median (first and third quartile). Categorical variables presented as absolute number (percent). Univariate hazard ratios are presented with their 95% confidence intervals; values refer to the effect of interquartile difference for continuous variables and to the category with the highest observed frequency for categorical variables.

pathologic Q waves, excluding aVR, was measured 60 ms after the J point using the end of the PR segment as reference. Electrocardiographic response was defined as positive in the case of a horizontal or downsloping deviation >0.1 mV compared with the ECG at rest in ≥ 2 contiguous leads. Decisions about discontinuing cardioactive drugs before testing and patient management after testing were made independently by the attending physician, who was unaware of the study aim. Only exercise testing data reported as part of patient care were available as test results.

Details about determination of the SRI were described extensively elsewhere.^{3,4} Briefly, computer-calculated ST-segment amplitudes were obtained with a time constant of 12 seconds during exercise and up to 5 minutes during recovery. At the end of the test, the area subtended to baseline and limited by the ST-segment trend against heart rate during exercise and recovery was calculated in the lead with the greatest ST-segment shift. The SRI was defined as the difference in absolute values between areas defined by ST-segment depression in the heart-rate domain during exercise and recovery, respectively.³

Outcome was determined by telephone calls to patients' families and primary physicians, with review of outside records, if necessary. Study end points were all-cause mortality and occurrence of a nonfatal acute coronary syndrome, diagnosed according to the present international guidelines.¹² Patients undergoing revascularization were censored at the time of the procedure. End points were assessed by an independent noninstitutional review board blinded to the study aim.

Continuous variables are presented as median with the corresponding interquartile difference. Categorical variables are presented as absolute number with corresponding percentages. Univariate hazard ratios refer to the effect of being in the highest compared with the lowest quartile for continuous variables or in the category with the highest

observed frequency for categorical variables, respectively. The individual effect of clinical data, resting ejection fraction, and exercise testing results on survival was evaluated using Cox proportional hazards regression analysis. The proportional hazard assumption was checked by plotting Schoenfeld results against fitted time and varying coefficients and using the Grambsch and Therneau test.¹³ To assess whether the provided additional prognostic information, clinical data, ejection fraction at rest, and exercise ECG data were entered first (model 1), whereas SRI was entered last (model 2). All variables were entered into the model without transformation or cutting off. Nonlinearity was assessed using the Wald test comparing higher order models with that including only linear terms. In case of nonlinearity, a restrictive cubic spline was used to model a nonlinear effect of the covariate. To account for potential risk differences in patients with known CAD compared with those with suspected CAD, baseline hazards were assumed different in each group of patients and modeled using a CAD-stratified Cox model. Selection criteria were the Akaike information criterion¹⁴ applied backward for each model. Models were cross-validated using a bootstrap technique.¹⁵ Multivariable hazard ratios are presented with their 95% confidence intervals. Areas under the receiver-operating characteristic curves¹⁶ of estimated cumulative hazard functions were compared with provide evidence of a significant increase in predictive accuracy of the model after addition of the SRI.

Cumulative survival curves as a function of time by quartiles of were generated using the Kaplan-Meier method and compared using log-rank test. Estimated percentage of event rates were derived from Kaplan-Meier estimates to take censoring of data into account. Statistical significance was settled at $p < 0.05$. The S-Plus (release 2000, Insightful Corporation, Seattle, Washington) statistical package and Harrell's Design and Hmisc libraries (Insightful Corporation) were used for analysis.

Table 2
Multivariable analysis result

Predictor	Hazard Ratio
Model 1	
Age	1.73 (1.21–2.45)
Hypertension	1.68 (1.01–2.80)
Model 2	
Age	1.62 (1.14–2.31)
Hypertension	1.74 (1.04–2.89)
SRI	0.52 (0.28–0.96)

Values expressed as hazard ratio (95% confidence interval). Values refer to the effect of interquartile difference for continuous variables and to the category with the highest observed frequency for categorical variables.

Results

Exercise testing was performed off therapy in 525 patients (75%). Beta-blocker therapy was discontinued for at least 48 hours before testing in all patients. Of those who were tested on therapy, 35 patients were using calcium channel blockers; 17 patients, nitrates; 103 patients, angiotensin-converting enzyme inhibitors; and 20 patients, angiotensin-receptor blockers. Cause for test interruption was muscular fatigue in 648 patients (92.5%), dyspnea in 14 patients (2%), chest pain in 28 patients (4%), and excessive blood pressure increase in 10 patients (1.5%). Exercise testing results according to outcome and in the overall study group are listed in Table 1.

During a median follow-up of 37 months (interquartile difference 24 to 52), 22 patients (3.1%) died, whereas 40 patients (5.7%) were admitted to the hospital because of an acute coronary syndrome. A cardiac cause of death was ascertained in 18 of 22 patients. The yearly event rate was 3%. In addition, 103 patients (14.8%) underwent myocardial revascularization using bypass surgery or percutaneous coronary intervention. Univariate analysis of outcome predictors is listed in Table 1.

Multivariable analysis results according to both prognostic models are listed in Table 2. Age, hypertension, and SRI were multivariable predictors of outcome; however, addition of the SRI was associated with improved accuracy of the prognostic model, proved by the significant increase in area under the receiver operating characteristic curve (Figure 1). The effect of the SRI on outcome is further demonstrated using survival analysis (Figure 2). The percentage of event rate over time was accurately stratified using the SRI; in particular, the highest quartile reflected a very favorable outcome, whereas the lowest quartile was associated with the highest event rate.

To estimate the likelihood of event-free survival in individual patients, a nomogram was generated from the fitted Cox model using the multivariable predictors of outcome (Figure 3).

Discussion

Although use of the SRI needs further prospective testing in other populations, results of the present study confirm the definition of negative exercise ECG crudely based on a fixed-threshold ST-segment depression to provide unsatisfactory prognostic information. However, a more compre-

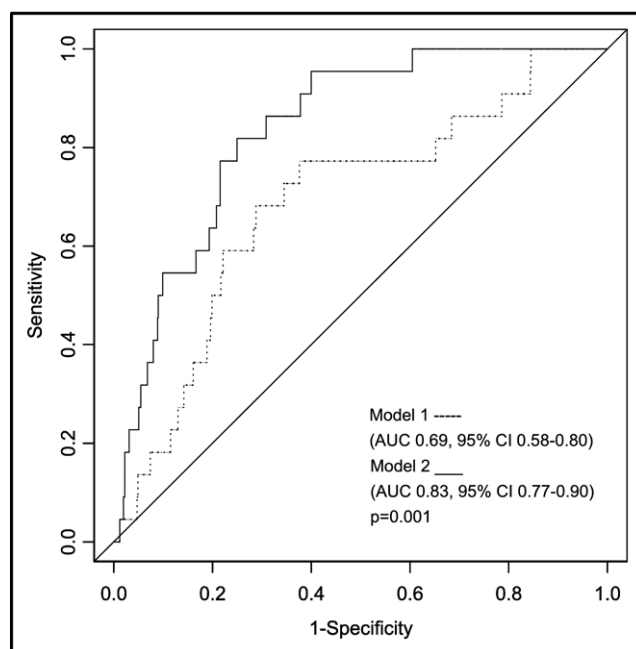


Figure 1. Comparison of areas under the receiver-operating characteristic curve (AUCs) by model 1 (0.68, 95% confidence interval 0.57 to 0.80) and model 2 (0.84, 95% confidence interval 0.77 to 0.90) for prediction of outcome. The area of model 2 including the SRI was significantly ($p = 0.001$) wider, showing superior predictive accuracy.

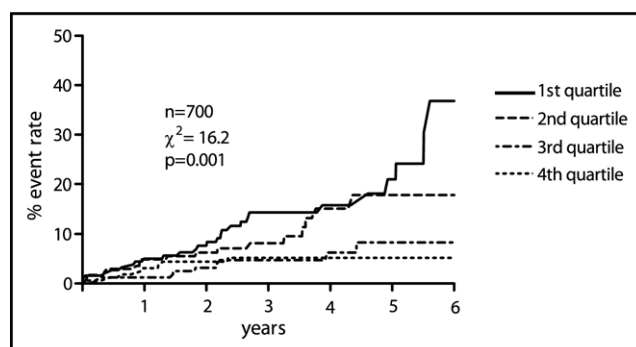


Figure 2. Kaplan-Meier plots associating SRI by quartiles with event rate.

hensive analysis of heart rate-adjusted ST-segment depression during exercise and recovery yields relevant prognostic discrimination on top of clinical and exercise testing data.

The electrocardiographic hallmark of exercise-induced ischemia is horizontal or downsloping ST-segment depression ≥ 0.1 mV. Intrinsic limitations of this standard criterion for diagnostic and prognostic purposes are well recognized. Nevertheless, it has been representing the “central dogma” of exercise electrocardiographic interpretation during the last decades.¹⁸ Accordingly, the majority of clinical studies dealing with the diagnostic and prognostic accuracy of exercise ECG in comparison to different noninvasive modalities relied on this standard definition. In particular, although increasing cardiac risk is known to parallel increasing exercise-induced ST-segment depression beyond the threshold of 0.1 mV,¹⁹ an evenly favorable interpretation is generally assigned to all deviations less than this

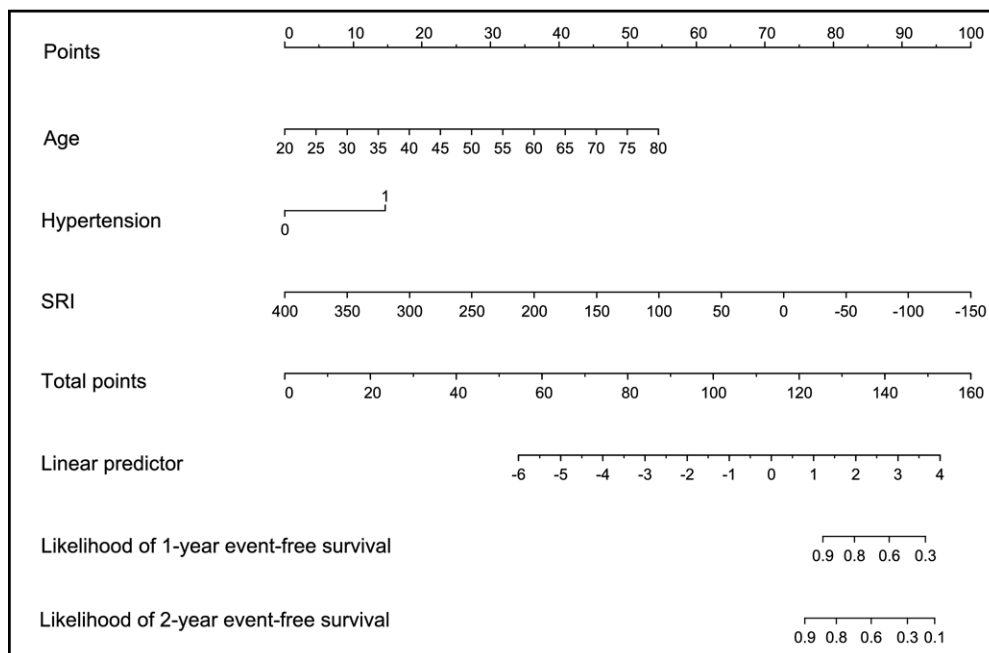


Figure 3. Nomogram for calculating the likelihood of event-free survival in individual patients from multivariate predictors of the fitted Cox model. To derive the likelihood, partial points relative to each predictor are read on the upper scale, their sum is then reported on the total points scale, and the corresponding 1- or 2-year likelihood can be read on the lower scales.

cut-off value. This is based on the observation that minor ST-segment shifts increase sensitivity for angiographic CAD, but with substantial decreases in specificity. However, coronary angiography provides a partial look at CAD so that the apparent diagnostic mistake, represented by the lack of correlation between exercise ECG and coronary angiography findings,²⁰ may translate into a prognostic truth because of the inadequacy of the coronary angiogram to best describe all aspects of CAD.²¹ A prognostic significance of exercise-induced ST-segment shifts ≤ 0.1 mV was shown previously in symptomatic populations.²² This was not confirmed in the selected population of asymptomatic volunteers participating in the Baltimore Longitudinal Study of Aging (BLSA).²³ However, to the best of our knowledge, no prospective study including a consecutive unselected population of patients was specifically designed to address this issue. Moreover, the interpretation of exercise ECG was traditionally based on observations made during exercise despite the known evidence that those made during the recovery period provide important information.²⁴

Some years ago, the SRI was suggested to improve the diagnostic ability of exercise ECG for the detection of extensive CAD.³ Afterward, the SRI was shown to add relevant prognostic information to that obtained from clinical data and standard exercise electrocardiographic analysis.³⁻⁷ Results of the present study reinforce these findings and extend their clinical relevance to the setting of patients with known or suspected CAD who are able to undergo symptom-limited exercise testing with no evidence of significant ST-segment depression. The physiologic basis of comparative stress-recovery adjustment of ST-segment depression grounds on earlier observations.³ In particular, resolution of exercise-induced ST depression was shown to lag behind its development given the nonlinear relation to myo-

cardial oxygen demand during the recovery phase.²⁵ SRI analysis is independent of achievement of a critical threshold of ST-segment depression and therefore is able to convey information throughout the entire spectrum of heart rate-adjusted ST-segment deviation occurring during the different phases of exercise.

A progressive increase in the use of procedures for the diagnosis of CAD during the last decades recently was reported.²⁶ In particular, the use of imaging stress tests increased substantially, whereas the use of nonimaging stress tests decreased, although this increase is unlikely to be related to an increase in underlying prevalence of the disease. The economic consequences of that are extraordinary relevant and are going to challenge the sustainability of reimbursement systems in the coming years. Thus, physicians will have increasing responsibility to ensure that expensive cardiac procedures are used effectively and efficiently to maximize their value for improving health.²⁷ Exercise electrocardiography is a time-honored modality with a favorable clinical profile for assessing CAD. In particular, it is low cost, generally available, and safe. Therefore, any attempt to improve its diagnostic and prognostic accuracy is expected to have major implications in term of pay-for-performance measures.

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