Prognostic Value of Combined Exercise and Recovery Electrocardiographic Analysis

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Background: Heart rate–adjusted ST-segment depression (ST/HR) analysis improves the diagnostic accuracy of exercise testing, but its prognostic value has not been evaluated in unselected populations. We prospectively used comparative exercise-recovery ST/HR analysis to predict outcome in a consecutive cohort of outpatients referred for exercise testing.

Methods: The stress-recovery index, defined as the difference between ST/HR areas during exercise and recovery, was derived in 1163 patients (median age, 60 years; interquartile range, 54-65 years). 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 by Cox regression analysis using separate models for each group of variables. Model validation was performed using bootstrap methods adjusted by the degree of optimism in estimates. Survival analysis was performed with the product-limit Kaplan-Meier method.

Results: During a 33-month follow-up, 48 deaths and 72 nonfatal myocardial infarctions occurred. After adjusting for confounding variables, hypertension (hazard ratio, 1.80; 95% confidence interval, 1.26-2.59), ST/HR index (hazard ratio, 1.32; 95% confidence interval, 1.04-1.66; for interquartile difference), and stress-recovery index (hazard ratio, 0.75; 95% confidence interval, 0.65-0.86; for interquartile difference) were predictive of death or nonfatal myocardial infarction, whereas hypertension (hazard ratio, 3.67; 95% confidence interval, 2.00-6.73) and stress-recovery index (hazard ratio, 0.55; 95% confidence interval, 0.48-0.63; for interquartile difference) were predictive of all-cause mortality. In addition, stress-recovery index increased the prognostic power of the model on top of clinical and exercise-testing variables and provided significant discrimination for survival.

Conclusion: Combined evaluation of ST/HR analysis during exercise and recovery improves the prognostic capacity of standard exercise electrocardiography.

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DESPITE THE ENCOURAGING downward trend during the last decades, coronary artery disease (CAD) remains the major cause of death, disability, and economic loss in developed countries.[1,2] This accounts for the continuous effort to improve risk stratification strategies in patients with known or suspected CAD. Exercise electrocardiography is a well-established procedure that has been in widespread clinical use for many years. It is noninvasive, readily available, and generally safe and cheap; therefore, it still represents the most used diagnostic and prognostic tool for assessing CAD. Nevertheless, a weak point concerning its use is the limited accuracy of the electrocardiographic signal by conventional analysis.[3,4] The heart rate adjustment of ST-segment depression[5,6] and the analysis of the course of its modification through the exercise and recovery phase[7-10] have been proposed to improve this accuracy. However, the prognostic value of any heart rate adjustment method compared with standard ST-segment analysis has not been proved in nonselected populations specifically referred for exercise testing. This study aimed to prospectively evaluate the prognostic significance of heart rate–adjusted ST-segment depression (ST/HR) analysis during the exercise phase alone or the exercise and recovery phase in a consecutive series of outpatients with known or suspected CAD undergoing exercise electrocardiography.

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METHODS

PATIENT POPULATION

The study cohort consisted of 1163 consecutive outpatients referred to a single institution for exercise testing between December 1995 and January 1998 to evaluate known or suspected CAD. Known CAD was defined as a previous myocardial infarction and/or a revascularization procedure (986 patients, 85%), whereas suspected CAD (177 patients, 15%) was defined on the basis of clinical judgment of the referring physician. Patients were excluded if they had had acute coronary syndromes during the last 3 months, congenital or valvular heart disease,

Table 1. Clinical Characteristics and Exercise Test Results

Variable	Study Population (N = 1163)	Death or Nonfatal Myocardial Infarction			Death		
		Event (n = 120)	No Event (n = 1043)	Hazard Ratio (95% CI)*	Event (n = 48)	No Event (n = 1115)	Hazard Ratio (95% CI)*
Age, median (IQR), y	60 (54 to 65)	64 (58 to 68)	60 (54 to 65)	2.09 (1.61 to 2.72)	66 (60 to 70)	60 (54 to 65)	2.65 (1.73 to 4.06)
Male, No. (%)	1002 (86)	101 (84)	901 (86)	0.83 (0.51 to 1.36)	34 (71)	968 (87)	0.37 (0.20 to 0.70)
Diabetes, No. (%)	88 (8)	9 (8)	79 (8)	1.13 (0.57 to 2.23)	5 (10)	83 (7)	1.61 (0.64 to 4.07)
Smoking habits, No. (%)							
Current smokers	548 (47)	55 (46)	493 (47)	0.87 (0.62 to 1.27)	19 (40)	529 (47)	0.67 (0.38 to 1.20)
Previous smokers	61 (5)	2 (2)	59 (6)	0.30 (0.07 to 1.21)	0 (0)	61 (5)	NA
Hypertension, No. (%)	466 (40)	63 (52)	403 (39)	1.87 (1.31 to 2.68)	32 (67)	434 (39)	3.44 (1.89 to 6.28)
Hypercholesterolemia, No. (%)	418 (36)	39 (32)	379 (36)	0.84 (0.57 to 1.23)	16 (33)	402 (36)	0.87 (0.48 to 1.58)
Known CAD, No. (%)	986 (85)	103 (86)	883 (85)	1.02 (0.61 to 1.70)	39 (81)	947 (85)	0.73 (0.35 to 1.50)
Ejection fraction, median (IQR)	50 (48 to 55)	50 (48 to 55)	50 (48 to 55)	0.84 (0.70 to 1.01)	50 (48 to 55)	50 (48 to 55)	0.84 (0.63 to 1.12)
Resting heart rate, median (IQR), beats/min	72 (62 to 82)	72 (63 to 83)	71 (62 to 82)	1.08 (0.85 to 1.38)	76 (68 to 88)	71 (62 to 82)	1.48 (1.04 to 2.11)
Resting systolic blood pressure, median (IQR), mm Hg	130 (120 to 140)	130 (119 to 150)	130 (120 to 140)	1.19 (0.98 to 1.45)	135 (120 to 155)	130 (120 to 140)	1.49 (1.11 to 2.00)
Resting diastolic blood pressure, median (IQR), mm Hg	80 (80 to 90)	80 (80 to 90)	80 (80 to 90)	1.03 (0.84 to 1.26)	80 (80 to 90)	80 (80 to 90)	1.19 (0.87 to 1.63)
Peak heart rate, median (IQR), beats/min	133 (118 to 148)	134 (116 to 146)	133 (118 to 148)	0.74 (0.57 to 0.96)	134 (118 to 141)	133 (118 to 148)	0.74 (0.49 to 1.11)
Maximal heart rate, median (IQR), %	83 (73 to 92)	83 (73 to 92)	84 (73 to 91)	1.19 (0.70 to 2.04)	85 (75 to 92)	84 (73 to 91)	1.05 (0.69 to 1.61)
Peak systolic blood pressure, median (IQR), mm Hg	190 (170 to 200)	190 (170 to 200)	190 (170 to 200)	0.95 (0.73 to 1.24)	190 (170 to 210)	190 (170 to 200)	1.04 (0.73 to 1.47)
Peak diastolic blood pressure, median (IQR), mm Hg	100 (90 to 105)	100 (90 to 105)	100 (90 to 105)	0.91 (0.71 to 1.17)	100 (90 to 110)	100 (90 to 105)	1.06 (0.71 to 1.58)
Double product, median (IQR), $\times 10^{-3}$	24.8 (21.1 to 28.7)	25.1 (20.9 to 28.8)	24.8 (21.1 to 28.8)	0.79 (0.62 to 1.01)	25.3 (21.2 to 28.8)	24.8 (21.1 to 28.8)	0.83 (0.57 to 1.23)
Exercise time, median (IQR), min	10.5 (8.5 to 13)	10 (7 to 12.5)	11 (9 to 13)	0.66 (0.51 to 0.84)	7.75 (6.00 to 10.12)	11 (9 to 13)	0.27 (0.18 to 0.42)
Exercise capacity, median (IQR), kilopounds/min	3900 (2700 to 5250)	3450 (1800 to 4906)	3900 (2700 to 5250)	0.72 (0.57 to 0.90)	2138 (1350 to 3900)	3900 (2700 to 5400)	0.30 (0.19 to 0.48)
Maximal ST depression, median (IQR), mV	0.06 (0.0 to 0.17)	0.08 (0.0 to 0.20)	0.05 (0.0 to 0.17)	1.74 (1.35 to 2.25)	0.13 (0.0 to 0.23)	0.04 (0.0 to 0.17)	1.90 (1.14 to 3.15)
ST/HR index, median (IQR), μV/beats per minute	1.1 (0.0 to 2.95)	1.6 (0.0 to 3.53)	0.4 (0.0 to 2.76)	1.72 (1.41 to 2.09)	2.88 (0.0 to 4.80)	0.9 (0.0 to 2.82)	2.17 (1.66 to 2.85)
Chest pain during exercise, No. (%)	202 (17)	23 (19)	179 (17)	1.40 (0.89 to 2.21)	15 (31)	187 (17)	2.77 (1.50 to 5.11)
Stress-recovery index, median (IQR), mV × beats/min	−9.1 (−27.6 to 0.9)	−18 (−43.3 to −4.5)	−26.6 (−8.2 to 2.7)	0.44 (0.29 to 0.68)	−32.9 (−63.5 to −10.8)	−8.5 (−26.5 to 2.1)	0.06 (0.01 to 0.50)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; IQR, interquartile range; NA, not applicable; ST/HR, heart rate–adjusted ST-segment depression.
*Values refer to the effect of an interquartile difference for continuous variables and to the category with the highest observed frequency for categorical variables.

congestive heart failure, left bundle branch block, chronic atrial fibrillation, implantable pacemakers, digoxin use, and prognostically relevant comorbidity. Informed consent was obtained from all patients before testing, and the study protocol was approved by the institutional ethical committee.

CLINICAL DATA

All patients were in stable clinical conditions. Hypertension was defined as resting systolic blood pressure of 140 mm Hg or higher, resting diastolic blood pressure of 90 mm Hg or higher, or treatment with antihypertensive drugs.[11] Diabetes mellitus was diagnosed according to World Health Organization criteria.[12] Hypercholesterolemia was defined as a fasting plasma total cholesterol level of greater than 239 mg/dL (>6.2 mmol/L)[13] or treatment with cholesterol-lowering drugs. Cardioactive drugs were classified as β-blockers, nondihydropyridinic calcium antagonists, angiotensin-converting enzyme inhibitors, and vasodilators (dihydropyridinic calcium antagonists, nitrates, and α-adrenergic blockers). Ejection fraction was obtained by 2-dimensional echocardiography using the Simpson rule.[14] The clinical characteristics of the study population are given in **Table 1**.

EXERCISE ELECTROCARDIOGRAPHY

Exercise electrocardiography was performed using an upright, electromagnetically braked, cycle ergometer. After a 1-minute warm-up at a 15-W workload and 60 rpm, exercise began with 25-W incremental loading every 2 minutes. The 12-lead electrocardiogram was continuously monitored throughout the test for rhythm, rate, and ST-segment changes. The exercise adaptation developed by Mason et al[15] with a 12-lead electrocardiogram was used. Blood pressure was measured by indirect arm-cuff sphygmomanometry during the last 30 seconds of each work stage. Patients were encouraged to reach symptom-limited, maximal exercise; the simple achievement of their age-predicted maximal heart rate, defined according to the formula 220 minus age, was not considered as the test end point. Exercise was continued until chest pain, major arrhythmias, significant conduction abnormalities, ST-segment depression of 0.3 mV or higher, systolic blood pressure increase higher than 230 mm Hg or decrease of 20 mm Hg or higher, or limiting symptoms (such as dyspnea, dizziness, fatigue, and/or cramping in legs) occurred. After exercise, patients recovered in a sitting position. Total work performed during the test was measured in kilopounds per minute to indicate the exercise capacity of the patient. Decisions about discontinuing use of cardioactive drugs before exercise testing were made 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. Moreover, physicians responsible for acquiring data and electrocardiographic analysis were unaware of the study aim.

ST-SEGMENT ANALYSIS AND STRESS-RECOVERY INDEX DETERMINATION

ST-segment shift in leads without pathologic Q waves, excluding aVR, was measured 60 milliseconds after the J point using the end of the P-R segment as a reference point. The electrocardiographic response was defined as positive in case of horizontal or downsloping deviation of more than 0.1 mV and negative in case of no deviation or upsloping deviation. The ST/HR index was calculated to obtain standard heart rate adjustment of ST-segment depression during exercise only.[16]

Continuously updated, computer-derived measurements of ST-segment levels in each analyzed lead, based on incremental averaging of normal complexes, were obtained using the commercially available Marquette Case 15 System (Marquette Electronics Inc, Milwaukee, Wis) and digitally stored for offline analysis. The accuracy of this measurement has been previously validated.[17] 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 each test, the lead that exhibited the greatest depression was selected for further analysis by a computerized algorithm technique. The area subtended to baseline and limited by the ST-segment trend against heart rate during both exercise and recovery was then calculated by adding the single trapezoidal areas obtained for each 12-second period of recording. ST-segment shifts that lasted less than 1 minute were rejected to minimize the misleading effect of transient oscillations of the baseline. The stress-recovery index was defined as the difference between the absolute values of the areas defined by ST-segment depression in the heart rate domain during exercise and recovery, as previously described.[8] The stress-recovery index calculation in a typical patient with ST-segment depression is shown in **Figure 1**.

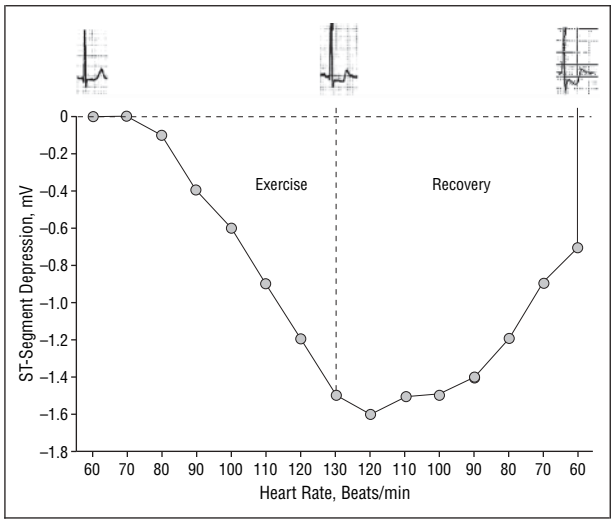

Figure 1. Stress-recovery index calculation in a typical patient with ST-segment depression. Stress-recovery index was defined as the difference between the areas subtended to baseline and limited by the ST-segment trend against heart rate during exercise and recovery.

FOLLOW-UP

Outcome was determined by telephone calls to patient families and primary care physicians with review of outside records if necessary. The primary end points were all-cause mortality[18] and the combination of death or nonfatal myocardial infarction. Nonfatal myocardial infarction was diagnosed based on a combination of symptoms, electrocardiographic changes, and cardiac enzyme changes. Patients undergoing revascularization were censored at the time of the procedure. End points were assessed by reviewers blinded to exercise-testing results who were not aware of the study aim.

STATISTICAL ANALYSIS

Continuous variables are expressed as median, with interquartile range as a measure of variability. The individual effect of clinical data (age, sex, diabetes mellitus, hypertension, hypercholesterolemia, smoking habits, known CAD, resting heart rate, and systolic blood pressure), resting ejection fraction, and exercise-testing results (peak heart rate, peak systolic blood pressure, exercise capacity, maximal ST-segment depression, ST/HR index, exercise-induced chest pain, and stress-recovery index) on survival was evaluated by Cox proportional hazards regression analysis.[19] Univariate estimate of hazard ratios were presented along with their 95% confidence intervals. Proportional hazard assumption was checked for each model (both univariate and multivariate) using the Grambsh and Therneau test[20] and diagnostic plots based on Shoenfeld residual. All variables considered were entered into the model as is, without any transformation or cutting off. Nonlinear effect of covariates was modeled using a restrictive cubic spline function, and its significance was assessed by the χ^2 Wald test. Separate models were developed for each group of variables. To account for potential risk differences in patients with known CAD compared with those with suspected CAD, baseline hazards were assumed to be different in each group of patients and were modeled using a CAD-stratified Cox model. The model strategy was determined following a rigid selection strategy. Separate models were developed for each group of variables, and Cox analysis was performed with all variables of a given model plus all variables that were significant for the antecedent model. After selecting significant clinical predictors (model 1), standard exercise-testing data and the ST/HR index were added (model 2). The stress-recovery index was entered last to verify whether it provided additional prognostic information to routinely available data. Thus, each model reflected the overall information available to the physician at that point and included only those variables that significantly improved model fit. At each step, a significance of .1 was required to enter into the model. Model fit was considered significantly improved on the basis of the Akaike Information Criterion applied backward for each model at a significance level of .05. To account for possible overfitting in the Cox model secondary to a high ratio between events and covariates, cross-validation and bootstrap (200 runs) techniques were applied. Discrimination Index D (the higher the better) and Somer Concordance Index D*xy* (the closer to 1 in absolute value the better) were obtained. In addition, the area under the receiver operating characteristic curve[21] of the estimated cumulative hazard function was obtained to evaluate the overall model accuracy at each step.

Cumulative survival curves as a function of time by quartiles of the stress-recovery index were generated with the Kaplan-Meier method and compared by the log-rank test. The statistical significance was set at $P < .05$. The S-plus (release, 2000) statistical package and the Harrells Design and Hmisc libraries (Insightful Corporation, Seattle, Wash) were used for analysis.

RESULTS

EXERCISE ELECTROCARDIOGRAPHY

No major complications occurred. Exercise testing was performed while the patients were not receiving therapy or after withdrawing cardioactive treatment for at least

Table 2. Multivariable Analysis Result

Predictor	Hazard Ratio (95% CI)*
Death or Nonfatal Infarction	
Model 1	
Age	1.98 (1.53 to 2.58)
Hypertension	1.60 (1.11 to 2.30)
Model 2	
Hypertension	1.67 (1.16 to 2.40)
Exercise capacity	0.82 (0.65 to 1.03)
ST/HR index	1.59 (1.31 to 1.94)
Model 3	
Hypertension	1.81 (1.26 to 2.59)
ST/HR index	1.32 (1.04 to 1.66)
Stress-recovery index	0.75 (0.65 to 0.86)
Death	
Model 1	
Age	2.25 (1.47 to 3.44)
Male sex	0.49 (0.26 to 0.92)
Hypertension	2.78 (1.51 to 5.11)
Model 2	
Hypertension	2.52 (1.37 to 4.65)
Exercise capacity	0.38 (0.24 to 0.61)
ST/HR index	1.73 (1.34 to 2.25)
Model 3	
Hypertension	3.67 (2.00 to 6.73)
Stress-recovery index	0.55 (0.48 to 0.63)

Abbreviations: CI, confidence interval; ST/HR, heart rate–adjusted ST-segment depression.

*Values refer to the effect of interquartile difference for continuous variables and to the category with the highest observed frequency for categorical variables. When considering the combination of death and nonfatal infarction, D and D*xy* were 0.051 and –0.41 for model 1, 0.079 and –0.55 for model 2, and 0.091 and –0.59 for model 3, respectively. When considering just death, these values were 0.052 and –0.418 for model 1, 0.078 and –0.556 for model 2, and 0.093 and –0.600 for model 3.

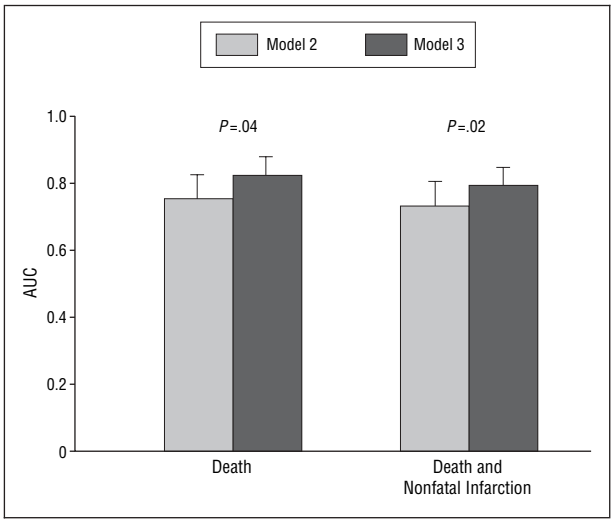

Figure 2. Comparison of the area under the receiver operating characteristic curve (AUC) by models 2 and 3 for the prediction of death and the combination of death and myocardial infarction. The area corresponding to model 3, which includes the stress-recovery index, is significantly wider, thus demonstrating a superior predictive accuracy. Error bars indicate SEM.

5 half-lives in 469 patients (40%). Conversely, 377 patients (32%) were taking β-blockers, 218 (19%) were taking calcium-channel blockers, 292 (25%) were taking angiotensin-converting enzyme inhibitors, and 348 (30%) were taking vasodilators. Cause for test interruption was muscular fatigue in 582 (50%), exhaustion in 228 (19%), chest pain in 174 (15%), ST-segment depression of 0.3 mV or more in 56 (5%), excessive increase in blood pressure in 57 (5%), claudication in 35 (3%), and miscellaneous in 31 (3%). Exercise test results were positive for electrocardiographic criteria in 463 patients (40%) and negative in 700 patients (60%). Median stress-recovery index was –9.1 mV × beats/min (interquartile difference, –27.6 to 0.9 mV × beats/min); in particular, it was more than 0 in 298 (26%), 0 in 90 (8%), and less than 0 in 775 patients (66%). Exercise test results in the overall population and according to outcome are reported in Table 1.

CLINICAL END POINTS

Follow-up information was obtained in all patients. During a median follow-up time of 33 months (interquartile difference, 16-48 months), 48 deaths (4.1%) and 72 nonfatal myocardial infarctions (6.2%) occurred; thus, a total of 120 clinical end points (10.3%) were observed. In addition, 272 patients (23.4%) underwent revascularization by means of bypass surgery or percutaneous coronary intervention. Univariate analyses of predictors of all-cause mortality and the combination of death or nonfatal myocardial infarction are given in Table 1.

PREDICTION OF OUTCOME

Multivariable analysis results according to each prognostic model are given in **Table 2**. After adjusting for the most predictive clinical and exercise-testing variables, hypertension, ST/HR index, and stress-recovery index were independent predictors of death or myocardial infarction, whereas hypertension and stress-recovery index were independent predictors of all-cause mortality. However, the addition of the stress-recovery index (model 3) yielded an additional increase in accuracy of the model for both considered end points, as demonstrated by the significant increase in the area under the receiver operating characteristic curve (**Figure 2**).

Finally, the effect of the stress-recovery index on outcome was analyzed using the product-limit Kaplan-Meier method (**Figure 3**). Survival and infarction-free survival were accurately stratified by stress-recovery index quartiles; in particular, the highest quartile was associated with favorable outcome, whereas the inferior quartile, reflecting negative values, was associated with the lowest survival and infarction-free survival, respectively.

COMMENT

The results of this study demonstrate that exercise vs recovery ST-segment analysis in the heart rate domain allows significant prediction of all-cause mortality and a combination of death and nonfatal myocardial infarction in patients with known or suspected CAD on top of clinical and exercise-testing variables and provides additional prognostic information that outperforms standard ST-segment depression criteria. Evaluation of ST-segment response to exercise on a standard electrocar-

diogram has been the most widely used laboratory method for the diagnostic and prognostic assessment of CAD for half a century. The availability, accessibility, and relatively simple technological requirements of exercise electrocardiography make it a useful tool for general internists and subspecialists, but the limitations of standard criteria based on achievement of a fixed magnitude of ST-segment depression for diagnostic[3] and prognostic[22-24] purposes are well recognized. In an attempt to overcome these limitations, the heart rate adjustment of ST-segment depression has been suggested as a more physiologic approach to the interpretation of ST-segment response to exercise[25] by several investigators using different analytical schemes.[5] Despite important methodologic differences among the studies, a significant increase in accuracy for assessing CAD presence and extension has been reported compared with standard ST-segment depression analysis.[5]

Conversely, little attention has been devoted to the assessment of the prognostic value of this approach. In a nonreferred group of low-risk, asymptomatic subjects within the Framingham Offspring Study cohort, an abnormal ST/HR index significantly concentrated the risk of future cardiovascular events.[24] Similar findings were obtained in a relatively high-risk population of asymptomatic middle-aged men without evidence of CAD from the Usual Care Group of the Multiple Risk Factor Intervention Trial.[26] No prognostic data, however, are available for patients with known CAD. More recently, the comparative analysis of ST/HR during the exercise and recovery phase has been suggested[7-9] to further improve diagnostic accuracy in different clinical settings, but few data have been reported concerning the prognostic capacity of this approach.[25,27] A comparative evaluation vs standard and heart rate–adjusted criteria that are derived from exercise phase data alone was performed in the Framingham Offspring Study.[24] Both heart rate adjustment modalities performed better than standard ST-segment analysis and showed similar ability to predict outcome; however, owing to the low-risk profile of the study population, 28 major events (4 deaths and 24 myocardial infarctions) and 37 incident cases of angina pectoris were observed among 3168 patients during 7-year follow-up.

In our study, both the ST/HR index and stress-recovery index were independently associated with the cumulative end point of death and nonfatal myocardial infarction, but the latter further increased the accuracy and discriminant capacity of the predictive model. When death was separately assessed, the stress-recovery index was the only exercise-testing variable significantly associated with the outcome. Several methodologic and pathophysiologic considerations can at least in part explain these findings.

The selected populations in which heart rate–adjusted methods have been tested so far represent only a segment of the possible populations usually referred for exercise testing in clinical practice. We addressed a nonselected population consecutively referred for exercise testing, based on a clear-cut clinical judgment, that was at much higher risk than those in previous studies. In addition, since the value of exercise testing for risk

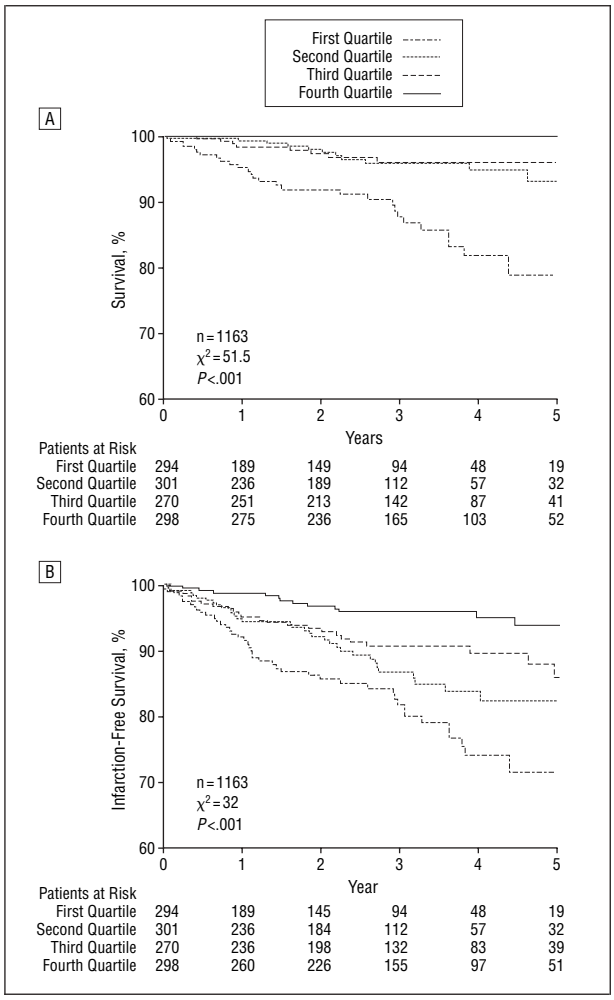

Figure 3. Kaplan-Meier plots associating stress-recovery index by quartiles with survival (A) and infarction-free survival (B).

stratification must be considered in light of what is already known about the patient's risk status, the individual effect of clinical data, exercise-testing variables, and stress-recovery index on outcome was evaluated according to a sequential procedure to reproduce the information flow as it becomes available to the physician. This allowed us to identify significant predictors of outcome within homogeneous groups of variables and to evaluate the incremental prognostic yield of each group of variables. Finally, to account for possible overfitting in the Cox model secondary to a high ratio between events and covariates, cross-validation and bootstrap techniques were applied; this has the major benefit of adjusting for the degree of optimism in evaluating predictive performance in the proposed models.

The physiologic foundation of comparative stress-recovery adjustment of ST-segment depression is based on earlier observations.[28-30] The stress-recovery index combines quantitative information, represented by the amount of ST-segment depression normalized for the chronotropic response to exercise, with qualitative information, represented by the relative rate of development and resolution of ST-segment depression. Given its nonlinear relation to myocardial oxygen demand during early recovery,[28] the resolution of ST-segment depression lags

behind its development in cases of extensive exercise-induced ischemia. In addition, because the stress-recovery index analysis is independent of the achievement of a critical threshold of ST-segment depression, it can provide information even in the case of a negative standard criterion or in the presence of blunted chronotropic response secondary to pharmacologic interference.[31] It is logical to assume that these characteristics could give the stress-recovery index a superior ability to identify exercise-induced myocardial ischemia with the greatest prognostic potential.

The results of this study may have relevant clinical implications. Owing to low cost, wide availability, and excellent negative predictive value, exercise electrocardiography still remains the cornerstone of the diagnostic and prognostic assessment of patients with known or suspected CAD. Patients with maximal negative and markedly positive test results by standard diagnostic criteria have a well-defined risk profile on Bayesian grounds; conversely, additional testing by either cardiac catheterization or exercise imaging study is suggested in those with an exercise test result that shows the patient to be at immediate risk of CAD.[32] The stress-recovery index could be helpful in improving the prognostic capacity of exercise electrocardiography and therefore in reducing the use of this more expensive and less available workup.

Since no definite assessment of ischemia was available in this study, it was not possible to clarify the exact pathophysiologic substrate of ST-segment changes. In addition, the stress-recovery index approach needs to undergo offline analyses that are not routinely available. Software implementation of commercial electrocardiogram analyzers could make this calculation more feasible in clinical practice.

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