Exercise versus recovery electrocardiography in predicting mortality in patients with uncomplicated myocardial infarction

Riccardo Bigia,*, Lauro Cortigianib, Dario Gregoric, Benedetta De Chiaraa, Cesare Fiorentinid

a CNR Institute of Clinical Physiology, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy
b Cardiovascular Unit, "Campo di Marte" Hospital, Lucca, Italy
c Department of Public Health and Microbiology, University of Turin, Italy
d Department of Cardiology, "S. Paolo" Academic Hospital, University of Milan, Milan, Italy

Received 17 September 2003; revised 27 January 2004; accepted 5 February 2004

Background Exercise testing after acute myocardial infarction has limited prognostic accuracy. We prospectively used stress-recovery, heart rate-adjusted, ST-segment analysis to predict cardiac death in this clinical setting.

Methods The stress-recovery index, defined as the difference in absolute values of the areas designated by ST depression in the heart-rate domain during exercise and recovery, was derived in 708 survivors of a first myocardial infarction. To assess whether it contributed additional prognostic information to routinely obtained information, clinical data, resting ejection fraction, and exercise testing data were entered into a sequential Cox model; the stress-recovery index was entered last. Model validation was performed by bootstrapping adjusted for the degree of optimism in estimates. Survival curves were set up using Kaplan–Meier analysis and compared by the log-rank test.

Results Hypertension (OR 1.3, 95%CI 0.9–4.6), exercise capacity (OR 0.6, 95%CI 0.3–1.1 for the interquartile difference in kilopounds per minute), and the stress-recovery index (OR 0.7, 95%CI 0.5–0.9 for the interquartile difference) were independent predictors of cardiac death at a median follow-up of 32 months. However, the stress-recovery index enhanced the prognostic power of the model on top of clinical and exercise testing variables in all diagnostic subgroups according to ST-segment analysis and significantly discriminated survival. A simple nomogram was generated from the fitted Cox model to estimate risk in individual patients.

Conclusions Stress-recovery, heart rate-adjusted, ST-segment analysis predicts cardiac death after acute myocardial infarction and provides additional prognostic information over clinical and exercise testing data.

KEYWORDS
Exercise electrocardiography; Coronary artery disease; Stress testing; Prognosis; Myocardial infarction

© 2004 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +39-02-64442605; fax: +39-02-66116990/6691909.
E-mail address: rbigi@tiscali.it (R. Bigi).
Exercise versus recovery electrocardiography in predicting mortality in patients

Introduction
The prognosis of patients who suffer from acute myocardial infarction has greatly improved with the extensive use of thrombolytic therapy and revascularisation. The mortality from six months to 1 year after discharge ranges from 3–4% in patients undergoing thrombolytic or invasive therapy to 8–9% in mixed populations. A patient’s inability to exercise or specific contraindications have been reported as the strongest negative prognostic indicators in this setting and call for an aggressive diagnostic and therapeutic approach. However, exercise electrocardiography still remains the most extensively used modality for prognostic assessment. Present international guidelines recommend submaximal or symptom-limited exercise testing before hospital discharge, or a maximal test soon after discharge. A weak point of this approach is the limited diagnostic and prognostic accuracy of ST-segment depression, the traditional electrocardiographic marker of exercise-induced ischaemia.

Adjustment of ST-segment depression for heart rate and analysis of the time course of ST-segment changes through exercise and recovery have been proposed to improve accuracy. In particular, improved identification of multivessel coronary artery disease after acute myocardial infarction has been reported with comparative analysis of ST-segment depression in the heart rate domain during exercise and recovery.

The aim of this study was to prospectively evaluate the prognostic significance of this approach in a consecutive series of postinfarction patients.

Methods
Patient population
The initial study population consisted of 924 consecutive patients eligible for symptom-limited postdischarge exercise testing following uncomplicated myocardial infarction who were recruited between March 1994 and February 1997. Seventy-five patients with features of complicated infarction (overt heart failure, complex arrhythmias, and recurrent ischaemia), 62 with prior myocardial infarction, 57 with electrocardiographic abnormalities at rest precluding the reading of exercise-induced changes (left ventricular hypertrophy, left bundle-branch block, ventricular pre-excitation or digoxin use, chronic atrial fibrillation, implantable pacemakers), and 22 with prognostically relevant comorbidities were excluded. Thus, the study cohort included 708 patients who gave their informed consent before being enrolled. The study protocol was approved by the local institutional Ethics Committee.

Clinical data and follow-up
All patients were in stable clinical condition. Hypertension was defined as resting systolic blood pressure ≥140 mm Hg, resting diastolic blood pressure ≥90 mm Hg, or treatment with anti-hypertensive drugs. Diabetes mellitus was diagnosed according to World Health Organisation criteria. Hypercholesterolaemia was defined as plasma total cholesterol >6.2 mmol/l 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). The ejection fraction was obtained by two-dimensional echocardiography using the Simpson rule.

Outcome was determined from patient interviews held at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient, a close relative, or the referring physician. Cardiac death was the only endpoint of the study. Death was defined as cardiac if it was strictly related to proven cardiac causes (fatal reinfarction, acute heart failure, or malignant arrhythmia), or if sudden and unexpected when occurring outside the hospital. Information on nonfatal reinfarction and myocardial revascularisation was also collected but was not considered as an endpoint. Patients undergoing revascularisation were censored at the time of the procedure.

Exercise testing
Exercise electrocardiography was performed 22 ± 4 days after the acute event using an upright, electromagnetically braked cycle ergometer with a 25-watt incremental load every 2 m. The 12-lead electrocardiogram was continuously monitored throughout the test for rhythm, rate, and ST-segment changes. The Mason-Linkart exercise adaptation of the 12-lead electrocardiogram was used. Blood pressure was measured by arm-cuff sphygmomanometry during the last 30 s of each work stage. Patients were encouraged to exercise maximally; the simple achievement of age-predicted maximal heart rate, defined according to the formula (220-age), was not considered a test endpoint. Exercise was continued until chest pain, repetitive arrhythmias, significant conduction abnormalities, ST-segment depression ≥0.3 mV, systolic blood pressure above 230 mmHg or that dropped ≥20 mmHg, or limiting symptoms occurred (such as dyspnoea, dizziness, fatigue, leg cramps). After exercise, patients recovered in a sitting position. Total work performed indicated the exercise capacity of the patient. ST-segment deviation in leads without pathological Q waves, excluding aVR, was measured 60 ms after the J point using the end of the P-R segment as reference. Electrocardiographic response was defined as positive in the case of a horizontal or downsloping deviation ≥0.1 mV in at least 2 contiguous leads, negative in the case of no deviation or an upsloping deviation, and nondiagnostic in the case of horizontal or downsloping deviation <0.1 mV. Decisions about discontinuing cardioactive drugs before testing and referring patients for invasive or conservative management strategy 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.

ST-segment analysis and stress-recovery index determination
Continuously updated, computer-derived measurements of ST-segment levels in each lead, based on incremental averaging of normal complexes, were obtained using a commercially available Marquette Case 15 System (Marquette Electronics, Inc., Milwaukee, WI, USA) and digitally stored for offline analysis. The accuracy of this measurement has been previously validated. Computer-calculated ST-segment amplitudes were obtained with a time constant of 12 s during exercise and up to 5 min during recovery. At the end of test, the lead exhibiting the greatest ST-segment change was selected for further analysis by a computerised algorithm technique. The area subtended to
Statistical analysis

Based on the results of our previous report, the present study was designed to detect a relative risk of 0.55 for a stress-recovery index value of $-5$ versus $0$ mV bpm. Assuming that 15–30% of subjects had a stress-recovery index $\leq -5$ mV bpm and a one-year case fraction of about 10%, with $\alpha$ level 0.05 and power 0.80, the planned enrolment was about 700 patients.

Continuous variables are expressed as means ± standard deviation. Differences between groups were compared using the Student $t$ and $\chi^2$ tests, as appropriate. The individual effects of clinical data (age, sex, hypertension, diabetes mellitus, hypercholesterolaemia, smoking habit, 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, exercise-induced chest pain, stress-recovery index) on survival were evaluated using Cox's proportional-hazards regression analysis. Proportional hazard assumption was carefully checked using both a visual approach (by plotting Schoenfeld results against fitted time and varying coefficients) and the Grambsch and Therneau test. Separate models were developed for each group of variables. Analysis was performed with all variables of a given model plus all variables from the preceding models that were identified as independent. In order to assess whether the stress-recovery index added prognostic information to routinely obtained information, clinical data were entered first (model 1), then resting ejection fraction and exercise testing data were added second (model 2), and finally the stress-recovery index was added last (model 3). All variables were entered into the model "as is" without any transformation or cutoffs. The functional form of the predictors was evaluated using a visual approach (by examining the Martingale residuals). Nonlinearity was formally assessed with the Wald test, comparing higher-order models with those including only linear terms. In the case of nonlinearity, a restrictive cubic spline was used to model a nonlinear effect of the covariate. The selection criterion was the Akaike Information Criterion applied backward for each model. Models were cross-validated by the bootstrap technique (200 runs). The discrimination index $D$ (the higher the better) and Somer's concordance index $Dxy$ (the closer to one the better), representing the concordance between predicted and observed outcome adjusted for data censoring, were obtained. Multivariate hazard ratios are presented with their 95% confidence intervals.

The receiver-operating-characteristic (ROC) curve method was used to assess the overall accuracy of the stress-recovery index according to ST-segment diagnostic subgroups. Cumulative survival curves as a function of time by quartiles of the stress-recovery index were generated with the Kaplan–Meier method and compared using the log-rank test. Estimated percent event rates were derived from the Kaplan–Meier estimates taking data censoring into account. Statistical significance was established at a $p$-value $<0.05$. The S-plus (Release 2000) statistical package and Harrell's Design and Hmisc libraries were used for analysis.

## Results

### Clinical characteristics and exercise test results

The clinical characteristics of the study population and exercise test results are summarised in Table 1.

Two hundred fifteen (30%) patients were on $\beta$-blockers, 48 (7%) on nondihydropyridinic calcium-channel

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Dead (n = 26)</th>
<th>Survivors (n = 682)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>60 [54; 65]</td>
<td>61 [54; 66]</td>
<td>60 [54; 65]</td>
<td>0.95 [0.57; 1.56]</td>
</tr>
<tr>
<td>Male</td>
<td>637 (90%)</td>
<td>21 (81%)</td>
<td>616 (90%)</td>
<td>0.46 [0.17; 1.23]</td>
</tr>
<tr>
<td>Inferior infarction</td>
<td>460 (65%)</td>
<td>18 (69%)</td>
<td>442 (65%)</td>
<td>2.69 [0.62; 11.59]</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>142 (20%)</td>
<td>2 (8%)</td>
<td>140 (21%)</td>
<td>0.32 [0.07; 1.32]</td>
</tr>
<tr>
<td>Non Q-wave infarction</td>
<td>104 (15%)</td>
<td>6 (23%)</td>
<td>98 (14%)</td>
<td>4.67 [0.94; 23.18]</td>
</tr>
<tr>
<td>CK (IU/l)</td>
<td>1221 [771; 2100]</td>
<td>1429 [805; 2842]</td>
<td>1215 [766; 2009]</td>
<td>1.17 [0.97; 1.41]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>58 (8%)</td>
<td>5 (19%)</td>
<td>53 (8%)</td>
<td>3.05 [1.14; 8.12]</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>426 (60%)</td>
<td>11 (42%)</td>
<td>415 (61%)</td>
<td>0.47 [0.21; 1.04]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>194 (27%)</td>
<td>12 (46%)</td>
<td>182 (27%)</td>
<td>2.64 [1.22; 5.71]</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>242 (38%)</td>
<td>7 (27%)</td>
<td>265 (39%)</td>
<td>0.55 [0.23; 1.32]</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>50 [48; 55]</td>
<td>49 [45; 55]</td>
<td>50 [48; 55]</td>
<td>0.72 [0.47; 1.10]</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>71 [63; 82]</td>
<td>71 [66; 88]</td>
<td>71 [62; 82]</td>
<td>1.41 [0.88; 2.26]</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mmHg)</td>
<td>130 [119; 140]</td>
<td>120 [120; 130]</td>
<td>130 [116; 140]</td>
<td>0.96 [0.58; 1.56]</td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>134 [117; 148]</td>
<td>129 [114; 138]</td>
<td>134 [118; 148]</td>
<td>0.54 [0.30; 0.99]</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mmHg)</td>
<td>190 [170; 200]</td>
<td>180 [160; 197]</td>
<td>190 [170; 200]</td>
<td>0.70 [0.45; 1.09]</td>
</tr>
<tr>
<td>Exercise capacity (kpm)</td>
<td>3900 [2700; 5250]</td>
<td>1800 [1350; 3300]</td>
<td>3900 [2700; 5250]</td>
<td>0.12 [0.05; 0.26]</td>
</tr>
<tr>
<td>Maximal ST-segment depression (mV)</td>
<td>0 [0; 1.72]</td>
<td>1.75 [0; 2.37]</td>
<td>0 [0; 0.17]</td>
<td>2.83 [1.72; 4.65]</td>
</tr>
<tr>
<td>Exercise-induced chest pain</td>
<td>83 (12%)</td>
<td>4 (15%)</td>
<td>79 (12%)</td>
<td>2.56 [0.96; 6.81]</td>
</tr>
<tr>
<td>Stress-recovery index (mV bpm)</td>
<td>-0.89 [-2.80; 0.27]</td>
<td>-3.05 [-6.49; -0.90]</td>
<td>-0.83 [-2.69; 0.29]</td>
<td>0.55 [0.46; 0.65]</td>
</tr>
</tbody>
</table>

Continuous variables are presented as medians (first and third quartile in square brackets). Categorical variables are presented as absolute numbers (percentages in parentheses). Univariate hazard ratios are presented with their 95%CI (in square brackets): values refer to the effect of an interquartile difference for continuous variables and to the category with the highest observed frequency for categorical variables.
blockers, 181 (26%) on angiotensin-converting enzyme inhibitors, and 250 (35%) on vasodilator agents; 262 (37%) patients were taking statins.

No major complication occurred. Causes for test interruption were muscular fatigue in 549 (78%), exhaustion in 61 (8.6%), orthopaedic limitation in 10 (1.4%) intolerable chest pain in 16 (2.3%), ST-segment depression $>0.3$ mV in 22 (3%), excessive increase in blood pressure in 31 (4.2%), decrease in blood pressure in 2 (0.3%), significant arrhythmias in 8 (1%), and patient request in 9 (1.2%).

Exercise testing was positive according to electrocardiographic criteria in 271 (38%) and negative in 437 (62%) patients ($p < 0.0001$). The median stress-recovery index was $-0.89$ mV bpm (interquartile range from $-2.8$ to $0.27$ mV bpm); in particular, it was $>0$ in 197 (28%), 0 in 57 (8%), and $<0$ in 454 (64%) patients.

**Prediction of mortality**

Follow-up information was obtained in all patients. The median follow-up time was 32 months (interquartile range from 30.4 to 33.6 months). Thirty-four deaths (7.5%) occurred during the follow-up period. Death was strictly related to proven cardiac causes (fatal reinfarction or irreversible heart failure) in 18 patients, whilst it occurred suddenly in 8. In addition, 8 patients died of noncardiac causes (6 cancer, 1 sepsis following abdominal surgery, and 1 suicide), 48 (19%) suffered a nonfatal reinfarction, and 194 (34%) underwent revascularisation procedures. Clinical and exercise testing data by outcome of the patients are reported in Table 1.

Multivariable analysis showed that, after adjusting for the most predictive clinical (model 1) and exercise testing (model 2) variables, hypertension (HR 1.3, 95%CI 0.9–4.6), exercise capacity (HR 0.6, 95%CI 0.3–1.1 for the interquartile difference), and stress-recovery index (HR 0.7, 95%CI 0.5–0.9 for the interquartile difference) correlated significantly and independently to outcome (model 3). However, the addition of the stress-recovery index further increased the power and discriminatory capacity of the model (Fig. 1). The effect of the stress-recovery index on overall mortality, as estimated by restricted cubic spline, is reported in Fig. 2: values $< -3$ mV bpm were associated with increasing risk; values of $-3$ to $3$ mV bpm identified a progressively decreasing risk and, finally, values $>3$ mV bpm, suggesting increasing but fast recovering ST-segment depression, yielded a new, smooth increase in risk.

The overall prognostic accuracy of the stress-recovery index, measured as the area under the ROC curve, was similar in patients with a negative (0.72 95%CI 0.67–0.77), positive (0.71 95%CI 0.66–0.76), and nondiagnostic (0.75 95%CI 0.64–0.83) ST-segment criterion, suggesting similar discriminatory capacity in the three subgroups.

The effect of the stress-recovery index on survival was analysed using the product-limit Kaplan–Meier method (Fig. 3): the lowest quartile was associated with a significantly lower survival rate than other quartiles.

**Assessment of individual risk**

In order to estimate the probability of death in the individual patient, a nomogram was generated from the fitted Cox model using the predictive variables of model 3.
Partial risk scores corresponding to each variable in a given patient are read on the upper scale, then their sum is reported on the total score scale and the corresponding risk can be estimated using the linear predictor.

**Discussion**

The results of this study demonstrate that the stress-recovery index significantly enhances the prediction of cardiac mortality in patients recovering from acute myocardial infarction when added to clinical and exercise testing variables and can be of value for discriminating risk in individual patients. This finding was confirmed in all diagnostic subgroups according to the usual interpretation of ST-segment changes. The index is easily calculated by means of a simple computerised algorithm and can be immediately obtained upon termination of the test at no additional cost, use of other equipment, or time expenditure.

Exercise electrocardiography is still the first-line modality for risk stratification of patients recovering from acute myocardial infarction, but the limitations of standard test criteria are well recognised. In particular, the improved prognostic profile of infarcted patients secondary to the use of more effective therapeutic tools has substantially reduced their positive predictive value in the last few years. Parameters of prognostic importance available from exercise electrocardiography essentially reflect the presence of inducible ischaemia and/or left ventricular dysfunction. The degree and extent of inducible ischaemia correlate with the extension of the myocardium at jeopardy, whilst left ventricular dysfunction can result from either exercise-induced ischaemia or pre-existing myocardial damage and indicates compromise of a critical mass of the left ventricle. Evidence of impaired haemodynamic or functional response to exercise has proved to be more prognostic of death than traditional electrocardiographic markers. Moreover, the ability of exercise-induced ischaemia to predict hard events in patients with normal or mildly impaired left ventricular function after an acute coronary syndrome has been questioned. Heart rate adjustment of ST-segment depression analysis can improve the diagnostic value of exercise testing in different clinical settings. However, even though different methodological approaches have been proposed, little attention has been devoted to assessing the prognostic utility of this analysis. An improved ability of the ST/heart rate index to predict future coronary events was demonstrated in asymptomatic, low-risk men and women in the Framingham Offspring Study and in higher-risk men in the Multiple Risk Factor Intervention Trial. No prognostic data, however, are available in patients with known CAD. Several considerations may explain the high prognostic value of the stress-recovery index observed in our study. First, it combines quantitative information (the amount of ST-segment depression normalised for the chronotropic response to exercise) with qualitative information (the relative rate of development and resolution of ST depression). Given its nonlinear relation to myocardial oxygen demand during early recovery, the resolution of ST depression lags behind its development in the case of extensive exercise-induced ischaemia. In addition, the stress-recovery index analysis is independent of achieving a critical threshold of ST-segment depression and, therefore, can provide information even in the case of a negative ST-segment criterion or blunted chronotropic response secondary to pharmacological interference.

In this study, the individual effect of clinical data, exercise testing variables, and the stress-recovery index on survival was evaluated sequentially to reproduce the flow of information as it becomes available to the phy...
Since no definite assessment of ischaemia was available, this approach has two main advantages: it serves to identify significant predictors of outcome within heterogeneous groups of variables and to sequentially assess the incremental prognostic yield of each group of variables. In keeping with established findings in the literature, exercise capacity, but not ST-segment depression, was an independent predictor of cardiac death. However, when comparatively analysed in the heart rate domain during exercise and recovery, ST-segment depression showed a strong prognostic capacity and significantly increased the discriminatory power of the model. This finding complements our previous observations on the superior ability of the stress-recovery index to identify multivessel disease after acute myocardial infarction and coincides with the results of stress echo studies showing the pivotal importance of time-domain analysis during both the stress and recovery phases in stratifying positive test results by diagnostic and prognostic endpoints. On the other hand, resting ejection fraction was not an independent predictor of death; possibly because ventricular function was only slightly compromised and varied within a narrow range in our study population.

Clinical implications

Present international guidelines recommend medical therapy and direct cardiac catheterisation, respectively, in infarcted patients with negative and markedly abnormal symptom-limited exercise testing. On the other hand, imaging studies are recommended in patients with mildly abnormal or nondiagnostic results. Imaging modalities were not used consecutively in this study population, so no correlation was made with the stress-recovery index. However, we have already demonstrated no predictive gain by imaging techniques in postinfarction patients with negative or low-threshold positive exercise testing by conventional ST-segment analysis. Conversely, a more than five-fold increase in risk definition was obtained in patients with a high-threshold positive or nondiagnostic exercise electrocardiogram. It is conceivable that more accurate analysis using the stress-recovery index may help to limit the need for imaging techniques, thus reducing the organisational and economical burden for risk-stratifying these patients, which account for up to 30% of the postinfarction population. Finally, the use of the simple nomogram shown in Fig. 3 allows the direct estimation of risk in individual patients. This substantially improves the applicability of the proposed statistical model by avoiding the oversimplification implicit in assigning patients to a few prognostic subgroups as well as the utilisation of overly complex regression equations in clinical practice.

Study limitations

Since no definite assessment of ischaemia was available, it was not possible to clarify the exact pathophysiological substrate of ST-segment changes. In addition, given the low-risk profile of the study population, our results cannot be extrapolated to different populations.

Possible interference of β-blocking therapy with the results of this study may be claimed. However, traditional ST-segment analysis and the stress-recovery index were compared on an intra-patient basis in the same clinical conditions. Moreover, we previously demonstrated that the diagnostic ability of the stress-recovery index, but not that of traditional ST-segment analysis, is not significantly affected by β-blockade.

Finally, the prognostic model was not evaluated using an external dataset. Nevertheless, a conservative approach was used to assess the predictive power of each model by adjusting indexes for the degree of optimism induced in our estimates by using the same dataset to estimate and evaluate the model.

References


