Importance of the First Two Minutes of Heart Rate Recovery After Exercise Treadmill Testing in Predicting Mortality and the Presence of Coronary Artery Disease in Men

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We retrospectively analyzed exercise treadmill and coronary angiographic data of 2,193 men to compare heart rate (HR) recovery with angiographic and mortality data during a follow-up study of 7 ± 2.7 years. Only the first 2 minutes of HR recovery predicted mortality ($p < 0.001$), and the HR decrease during the second minute of recovery predicted the presence of coronary artery disease ($p < 0.05$). ©2004 by Excerpta Medica, Inc.

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Heart rate (HR) recovery as a marker of prognosis has been validated in both asymptomatic persons[1] and patients being evaluated for chest pain.[2–4] These studies found that patients with a reduced HR recovery were at greater risk of dying than patients with a HR that rapidly decreased after exercise. Vagal reactivation plays an integral part in reducing HR after exercise, especially during the first 30 seconds.[5] Although the role of autonomic imbalances in cardiac mortality has been studied,[6,7] the effects of β blockers on HR recovery have only been investigated comparing patients with known coronary artery disease (CAD), patients with a very low risk of having CAD, and patients who received a prior heart transplant.[8] Although HR recovery has previously been shown not to be a strong predictor of CAD presence,[3] recent data have revealed that rapid HR recovery immediately after exercise is associated with a lower risk of CAD and cardiovascular disease events.[9] The goal of this study was to investigate how angiographically significant CAD, myocardial infarction, β blockers, and target HR achievement influence HR recovery in patients being evaluated for chest pain, and to determine whether the change in HR during individual minutes of recovery predicts the presence of CAD and prognosis.

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In all, 8,000 male patients underwent treadmill testing at 2 Veterans Affairs Medical Centers between 1987 and 1998. Of these, 3,454 were evaluated for chest pain with coronary angiography within 3 months of treadmill testing. Patients who had previous cardiac surgery or angiography, valvular heart disease, left bundle branch block, paced rhythms, or Wolff-Parkinson-White syndrome on their electrocardiograms at rest were excluded from the study. The remaining 2,193 patients were selected for survival analysis; after excluding those with previous myocardial infarction (MI) by history or by Q waves, there was a diagnostic subgroup of 1,281 patients. Although the total remaining patients are appropriate for prognostic assessment, evaluation of the diagnostic properties of a test should be performed in the subgroup without MI.[10]

Patients underwent symptom-limited treadmill testing using the US Air Force School of Aerospace Medicine protocol[11] or an individualized ramp treadmill protocol.[12] The physiologic distinction of these protocols is that the patient is subjected to small, frequent increments in workload rather than abrupt increases every 3 minutes. Information gathered from a questionnaire enabled maximal exercise to be reached at approximately 10 minutes.[13] Patients reached their target HR if their maximum HR on treadmill testing was ≥85% of their estimated physiologic maximum HR. This study evaluated 2 equations for age-adjusted maximum HR. The first method of calculating age-adjusted HR is 220 − age and the alternative method uses 210 − (age × 0.80). Although these equations perform similarly, this study used the formula maximum HR/(220 − age) ≥0.85 as an achievement of target HR to allow comparison with previous studies.[2,4,14] Patients did not perform a cooldown walk, but were placed in the supine position as soon as possible after exercise. The reasons for termination of exercise were angina, 2 mm of abnormal ST depression, a decrease in systolic blood pressure, or ominous arrhythmias. Visual ST-segment depression was measured at the J junction and corrected for pre-exercise ST-segment depression. An abnormal response was defined as ≥1 mm of horizontal or downsloping ST-segment depression. Blood pressure was measured manually, and metabolic equivalents were estimated from treadmill speed and grade. No test was classified as indeterminate[15]; medications were not withheld, and maximal HR target was not used as an end point. The exercise tests were performed, analyzed, and reported with a standard protocol using a computerized database.

HR was measured with the patients in the supine and standing positions, during each minute of exercise, at maximum exercise, and in the recovery room at 1, 2, 3, and 5 minutes. HR recovery was defined as

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TABLE 1 Comparison of Clinical Characteristics of Patient Subgroups Divided by β-blocker and Coronary Artery Disease (CAD) Status

β Blocker CAD	+ + (n = 577)	+ 0 (n = 167)	0 + (n = 959)	0 0 (n = 488)
Age	60 ± 10	55 ± 11	62 ± 9	56 ± 11
Body mass index (kg/m^2)	27.9 ± 4.4	28.1 ± 4.7	28 ± 12.7	27.9 ± 5
Death	21%	7%	24%	11%
Prior myocardial infarct	60%	26%	45%	18%
Severe CAD	41%	0%	53%	0%
Target HR achievement	13%	20%	38%	52%
Angina pectoris	295 (51%)	42 (25%)	408 (43%)	109 (22%)
Diabetes mellitus	16%	10%	17%	13%
Current smoker	36%	37%	32%	37%
Chronic obstructive pulmonary disease	5.0%	4.2%	6.9%	7.0%
Hypertension	57%	70%	52%	43%
Hypercholesterolemia (total cholesterol ≥220 mg/dl)	48%	41%	41%	33%
Stroke	4%	2%	5%	3%
Digoxin	2%	2%	6%	5%
Congestive heart failure	4%	3%	6%	6%
Left ventricular hypertrophy	3%	3%	3%	3%
Ejection fraction (%)	60 ± 13	65 ± 11	61 ± 14	65 ± 11

Values are expressed as mean ± SD or percentages.

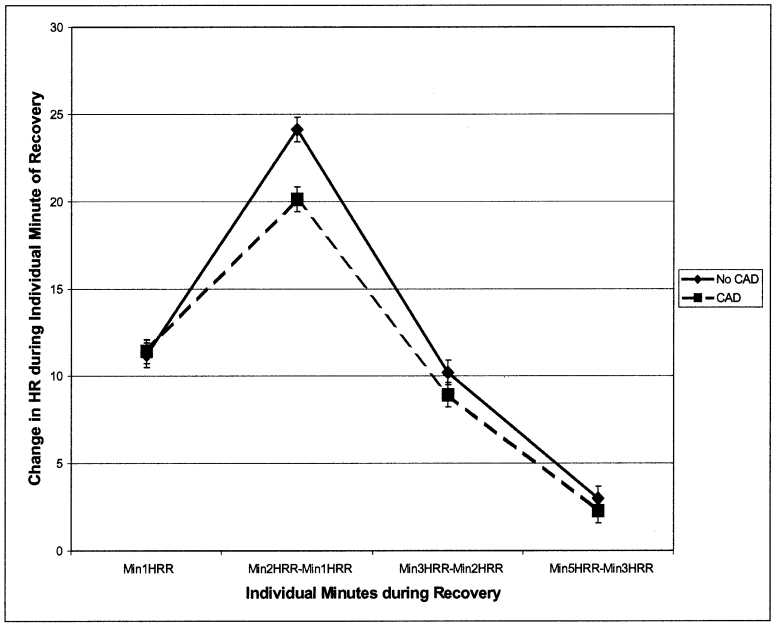

FIGURE 1. Comparison of the decrease in HR at individual minutes during recovery in patients with and without CAD. HRR = heart rate recovery; Min = minute.

(maximum HR − HR at a specified time period during recovery) and represented the decrease in HR during that time interval. HR recovery during individual minutes of recovery was measured by calculating the difference between HR at 1 time point and HR at the previous minute. Therefore, HR recovery during the second minute was calculated by (HR at 1 minute after exercise − HR at 2 minutes after exercise). Therefore, this is different from HR recovery after 2 minutes, which equals (maximum HR − HR at 2 minutes after exercise).

Coronary artery narrowing was visually estimated and expressed as percent lumen diameter stenosis. Patients with a 50% diameter narrowing of the left main, left anterior descending, left circumflex, or right coronary arteries or their major branches were considered to have significant angiographic CAD. Severe CAD was considered to be 2-vessel disease if the proximal left anterior descending artery was involved; otherwise, 3-vessel or left main disease was considered severe. The 50% criterion was chosen to be consistent with definitions used by the Coronary Artery Bypass Graft Surgery Trialists' Collaboration.[16] In addition, the Duke coronary artery jeopardy score was calculated.[17] Ejection fractions were estimated from biplane left ventricular angiograms. Decisions for cardiac catheterization were consistent with clinical practice.

The Social Security Death Index was used to match all of the patients' names to their Social Security numbers. The index was updated weekly, and the most current records were used. Death status was determined as of July 2000 and was 100% complete. No other information regarding hospitalizations, cardiac interventions, or cause of death during follow-up was known.

All-cause mortality was considered the end point for follow-up, and coronary angiography was performed to diagnose the presence of CAD. Student's *t* test analysis for continuous variables and chi-square analysis for categorical variables were performed to determine the effects of β blockers on HR recovery in groups with and without CAD and in those who did and did not die. Results are shown as mean ± SD. Survival analysis was performed using Kaplan-Meier curves to compare variables and cut points. Cox proportional-hazards function and logistic regression were already performed in this population[3] and repeated to measure the effects of β blockers and target HR achievement. How well the models separated patients with and without a given outcome (abnormal angiogram or death) was assessed by means of the area under a receiver-operating characteristic (ROC) curve, which ranged from 0 to 1, with 0.5 corresponding to no discrimination (i.e., random performance) and 1.0 to perfect discrimination. Multiple regression and proportional-hazards regression analyses were performed to determine whether variables significantly predict end points and whether they rank

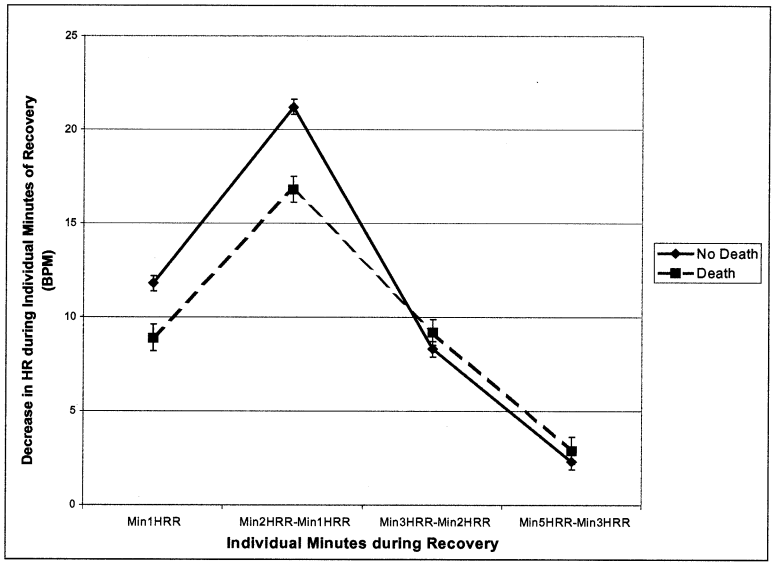

FIGURE 2. Comparison of the decrease in HR at individual minutes during recovery in patients who either died during follow-up or survived. BPM= beats per minute; other abbreviations as in Figure 1.

TABLE 2 Variables Selected for Multiple Regression Analysis for Prediction of Coronary Artery Disease

Variables	Regression Coefficient (95% CI)	p Value
2-min HR recovery	−0.003 (−0.005–−0.0003)	0.045
Age	0.008 (0.006–0.01)	0.000000
ST depression	0.13 (0.1–0.15)	0.000000
Hypercholesterolemia (total cholesterol ≥220-mg/dl)	0.13 (0.08–0.18)	0.000000
Chest pain	−0.07 (−0.1–−0.04)	0.00001
Maximum HR	−0.003 (−0.004–−0.002)	0.00007
Metabolic equivalents	−0.008 (−0.017–0.001)	0.10
Diabetes mellitus	0.06 (−0.01–0.13)	0.07

CI = confidence interval.

over other variables. The NCSS 2001 Statistical Analysis Sytem (Keysville, Utah) was used for all statistical analyses.

This male study population had a mean ± height of 69.6 ± 2.9 in, a mean weight of 191 ± 34 lbs, and a mean body mass index of 28 ± 9 kg/m^2. Average HR at rest was 76 ± 14 beats/min, with a corresponding mean systolic blood pressure of 125 ± 20 mm Hg. With regard to medications, 4.4% reported taking digoxin, and 34% were taking β blockers. No significant differences in these parameters were noted between those who survived and those who died. Over the mean 7-year follow-up (median 6), 413 patients died. There was an average annual mortality of 2%. Characteristics based on β-blocker and CAD status of the patients are listed in Table 1.

Of the 744 patients taking β blockers, only 14.2% achieved their target HR, whereas 42.6% of 1,447 patients not taking β blockers achieved their target HR ($p < 0.000001$). When patients with prior MI were removed from the analysis, 16.6% of the 355 patients taking β blockers achieved target HR, whereas 47.2% of 926 patients not taking β blockers achieved their target HR ($p < 0.0001$). The percentage of patients who achieved target HR was significantly decreased in patients taking β blockers and in patients with CAD not taking β blockers. In a similar analysis, β blockers significantly decreased the percentage of patients that achieved their target HR regardless of whether they died (14% for those taking vs 43% for those not taking β blockers; $p < 0.0001$). Among patients not taking β blockers, a significantly smaller percentage of patients who died achieved their target HR compared with those who survived (37.3% for those who died vs 43.9% for those who survived; $p < 0.03$). However, there was no difference in achieving target HR between patients taking β blockers who either died or did not die during follow-up.

The differences in HR between 1 and 2 minutes into recovery, 2 and 3 minutes into recovery, and 3 and 5 minutes into recovery were calculated for each patient. The decrease in HR during the second minute of recovery is equal to the HR at 1 minute into recovery minus the HR at 2 minutes into recovery, and equal to the HR recovery at 2 minutes minus the HR recovery at 1 minute (minute 2 HR recovery − minute 1 HR recovery). This allowed a comparison of the rate at which HR decreases at individual minutes during recovery. Figure 1 demonstrates how HR decreases at individual minutes during recovery for patients with and without CAD. Figure 2 demonstrates how HR decreases at individual minutes during recovery for patients who either died during follow-up or survived. When this same analysis was performed matching for β blockers and target HR achievement, only the decrease in HR during the second minute of recovery was significantly less in patients with than without CAD ($p < 0.05$). Similarly, when matching for β blockers and target HR achievement, only the decrease in HR during the first and second minutes of recovery was significantly reduced in patients who died during follow-up ($p < 0.05$). When multivariable regression analysis was performed, the decrease in HR for the second minute of recovery predicted the presence of CAD ($p < 0.05$) along with patient age, chest pain history, hypercholesterolemia, and maximum HR. Table 2 displays the multiple regression analysis for predicting the presence of CAD. The ROC curve analysis, which shows a decrease in HR during the second minute of recovery, significantly discriminates which patients will have CAD (area under the curve

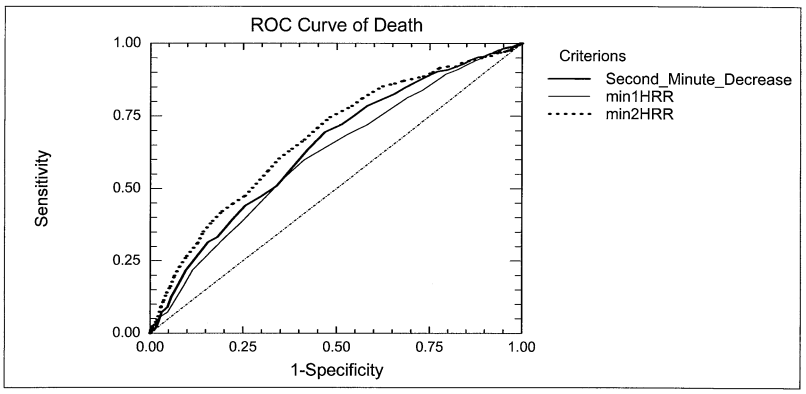

FIGURE 3. ROC curve analysis comparing the ability of HR recovery (HRR) at 1 and 2 minutes, with the decrease in HR during the second minute of recovery determining which patients died during follow-up.

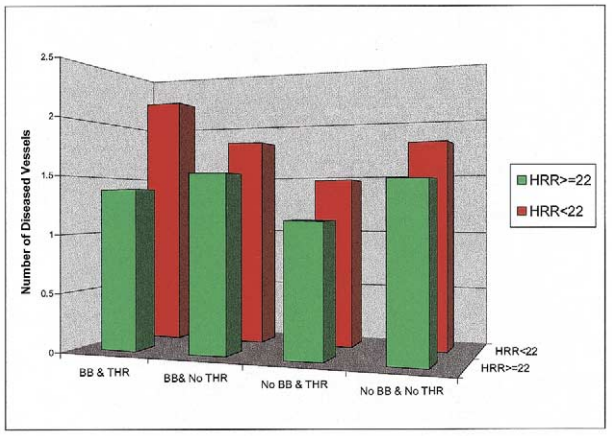

FIGURE 4. Comparison of the average number of diseased vessels in patients who were above or below the 2-minute HR recovery (HRR) cut point of 22 beats, depending on whether the patient was taking β blockers (BB) or achieved a target HR (THR).

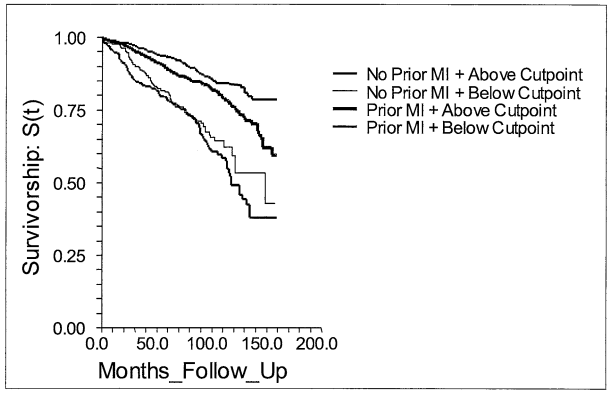

FIGURE 5. Kaplan-Meier curves comparing prognostic survival outcomes in patients separated by whether they had achieved a HR recovery of 22 beats at 2 minutes and whether the patient had a prior MI.

0.61, p <0.001). When performing ROC curve analysis with death during follow-up as an end point, only HR recovery at 2 minutes performed better at determining which patients would die than the decrease in HR during the second minute of recovery (HR recovery at 2 minutes, area under the curve 0.67; second minute HR decrease, area under the curve 0.64; HR recovery after 1 minute, area under the curve 0.61). The area under the curves for the 3 variables were significantly different from each other, indicating that HR recovery after 2 minutes performs better than HR recovery during the second minute, and that HR recovery during the second minute predicts death better than HR recovery after 1 minute. These data are illustrated in Figure 3. Proportional-hazards regression analysis revealed that the second-minute recovery was a significant independent predictor of mortality (p <0.00001) along with age, metabolic equivalents, maximum HR, and HR recovery after 2 minutes. When comparing average HR recovery, patients with CAD had a significantly decreased HR recovery at 2 (31.5 vs 35.3, p <0.001), 3 (40.4 vs 45.5, p <0.001), and 5 (42.7 vs 48.5, p <0.001) minutes of recovery. HR recovery at 1 minute was not significantly affected by whether CAD was present. When controlling for β blockers and target HR achievement, HR recovery at 2, 3, and 5 minutes was significantly less in patients with CAD (p <0.05).

To evaluate whether HR recovery is affected by greater disease burden, the average number of vessels with significant disease was calculated using previously selected cut points. Using the HR recovery cut point for 2 minutes, patients with a decrease of <22 beats in 2 minutes had a significantly greater number of vessels with disease than patients with a HR recovery of ≥22 beats in all patients except those taking β blockers who achieved target HR (p <0.05). These data are presented in Figure 4. Results were the same when using the 5-minute recovery cut point of 30 beats (p <0.05). HR recovery was not significantly affected by which coronary artery was diseased, but only by how much disease was present.

Prior MI significantly reduced HR recovery during the second minute (prior vs no prior MI, 18.7 vs 21.7 beats/min, respectively; p <0.001). Three- and 5-minute HR recovery was reduced in patients with prior MI regardless of whether they were taking β blockers or achieved target HR (p <0.05). Kaplan-Meier curves were also calculated comparing the influence on survival of prior MI with HR recovery at 2 minutes. Figure 5 illustrates the influence on survival of prior MI and HR recovery at 2 minutes. The main findings are that prior MI does not significantly affect survival in patients with a reduced HR recovery using the 22-beat, 2-minute recovery cut point, but significantly decreases survival in patients whose HR decreased by >22 beats after exercise testing.

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The main finding of this study is that the rate of decrease in HR during the first 2 minutes of recovery

predicts mortality. However, changes in the rate of decrease in HR after the first 2 minutes of recovery are not predictive of mortality. Another important finding is that the decrease during the second minute of recovery predicts the presence of angiographically significant CAD. This helps explain why HR recovery is significantly reduced in patients with angiographically significant CAD at 2, 3, and 5 minutes after exercise testing, but not after 1 minute. This finding is also true regardless of whether the patients were taking β blockers or achieved target HR during exercise testing. Patients with reduced HR recovery, as defined by previously established cut points, had a significantly greater number of narrowed coronary arteries than those without reduced HR recovery. This was shown to be true regardless of whether the patients were taking β blockers or whether they achieved a target HR during exercise testing. This study also reveals that prior MI decreases HR recovery at 2, 3, and 5 minutes regardless of whether the patient was taking β blockers or the target HR was achieved. Prior MI decreased survival in patients with a normal HR recovery, but not in patients with a decreased HR recovery. These findings need to be validated in the general population and in populations that undergo a cooldown period after exercise testing. These prognostic findings support previous studies and reveal that HR recovery is a strong predictor of mortality independent of other variables. Our data also support the belief that a decreased HR recovery in the first 2 minutes predicts mortality and the presence of CAD because of a reduced parasympathetic return.

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