

Heart Rate Recovery and Treadmill Exercise Score as Predictors of Mortality in Patients Referred for Exercise ECG

Erna Obenza Nishime, MD

Christopher R. Cole, MD

Eugene H. Blackstone, MD

Fredric J. Pashkow, MD

Michael S. Lauer, MD

ATTENUATED HEART RATE RECOVERY after exercise, which is thought to be a marker of reduced parasympathetic activity,^{1,2} has been shown to be an independent predictor of mortality among patients referred for stress nuclear testing³ and among healthy adults enrolled in a population-based cohort study.⁴ The Duke treadmill exercise score, a composite of measures of functional capacity and stress-induced ischemia, has been shown to predict mortality risk in different patient subsets.⁵⁻⁷ It is unknown, however, whether or how heart rate recovery and the treadmill exercise score relate to each other as prognostic measures. The purpose of this study was to determine whether heart rate recovery adds to or interacts with the treadmill exercise score as a predictor of all-cause mortality⁸ among patients referred for exercise electrocardiography (ECG).

METHODS

Patient Population

The study population consisted of consecutive patients referred specifically for exercise ECG at the Cleveland Clinic Foundation between September 1990 and December 1997. Patients were ex-

Context Both attenuated heart rate recovery following exercise and the Duke treadmill exercise score have been demonstrated to be independent predictors of mortality, but their prognostic value relative to each other has not been studied.

Objective To assess the associations among abnormal heart rate recovery, treadmill exercise score, and death in patients referred specifically for exercise electrocardiography.

Design and Setting Prospective cohort study conducted in an academic medical center between September 1990 and December 1997, with a median follow-up of 5.2 years.

Patients A total of 9454 consecutive patients (mean [SD] age, 53 [11] years; 78% male) who underwent symptom-limited exercise electrocardiographic testing. Exclusion criteria included age younger than 30 years, history of heart failure or valvular disease, pacemaker implantation, and uninterpretable electrocardiograms.

Main Outcome Measures All-cause mortality, as predicted by abnormal heart rate recovery, defined as failure of heart rate to decrease by more than 12/min during the first minute after peak exercise, and by treadmill exercise score, defined as (exercise time) – (5 × maximum ST-segment deviation) – (4 × treadmill angina index).

Results Three hundred twelve deaths occurred in the cohort. Abnormal heart rate recovery and intermediate- or high-risk treadmill exercise score were present in 20% (n=1852) and 21% (n=1996) of patients, respectively. In univariate analyses, death was predicted by both abnormal heart rate recovery (8% vs 2% in patients with normal heart rate recovery; hazard ratio [HR], 4.16; 95% confidence interval [CI], 3.33-5.19; $\chi^2=158$; $P<.001$) and intermediate- or high-risk treadmill exercise score (8% vs 2% in patients with low-risk scores; HR, 4.28; 95% CI, 3.43-5.35; $\chi^2=164$; $P<.001$). After adjusting for age, sex, standard cardiovascular risk factors, medication use, and other potential confounders, abnormal heart rate recovery remained predictive of death (among the 8549 patients not taking β -blockers, adjusted HR, 2.13; 95% CI, 1.63-2.78; $P<.001$), as did intermediate- or high-risk treadmill exercise score (adjusted HR, 1.49; 95% CI, 1.15-1.92; $P=.002$). There was no interaction between these 2 predictors.

Conclusions In this cohort of patients referred specifically for exercise electrocardiography, both abnormal heart rate recovery and treadmill exercise score were independent predictors of mortality. Heart rate recovery appears to provide additional prognostic information to the established treadmill exercise score and should be considered for routine incorporation into exercise test interpretation.

JAMA. 2000;284:1392-1398

www.jama.com

Author Affiliations: Departments of Cardiology (Drs Nishime, Cole, Pashkow, and Lauer), Cardiothoracic Surgery (Dr Blackstone), and Biostatistics and Epidemiology (Dr Blackstone), Cleveland Clinic Foundation, Cleveland, Ohio.

Corresponding Author and Reprints: Michael S. Lauer, MD, Clinical Research and Exercise Laboratory, Department of Cardiology, Desk F25, Cleveland Clinic Foundation, Cleveland, OH 44195 (e-mail: lauem@ccf.org).

cluded if they were younger than 30 years old, had a history of heart failure, valvular or congenital disease, or had pacemaker implantation. No patients had uninterpretable ST segments due to left bundle-branch block, digoxin use, preexcitation syndrome, left ventricular hypertrophy, or more than 1 mm of resting ST-segment depression, and no patients were undergoing concurrent imaging studies. Patients were excluded if a valid Social Security number was not available or if they lived outside the United States. The protocol was approved by the foundation's institutional review board.

Clinical Data

Prior to exercise testing, each patient underwent a structured history taking and medical record review to document symptoms, past medical history, medication use, cardiac risk factors, and prior cardiac events and procedures.⁹ Patients were considered to be undergoing screening tests if they had no symptoms suggestive of coronary heart disease and had no notable cardiac history.

Resting tachycardia was considered present if the resting heart rate was 100/min or greater. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive medications.¹⁰ Diabetes was defined as documented prescription of a diabetic diet or use of insulin or other hypoglycemic medications. Prior coronary artery disease was considered present if diagnosed by prior coronary angiography; if there was a documented history of revascularization, myocardial infarction, or unstable angina; or if pathologic Q waves were present in at least 2 contiguous ECG leads. Total cholesterol values were routinely recorded if obtained within the previous 3 months and if they were 200 mg/dL (5.18 mmol/L) or higher. Hypercholesterolemia was defined as a documented total cholesterol level of 200 mg/dL (5.18 mmol/L) or higher or the use of lipid-lowering medications. Chronic obstructive pulmonary disease was based on documentation in the

medical record or use of inhaled or oral bronchodilators. Patients were considered smokers if they regularly smoked cigarettes within the past year.

To describe pretest risk of prognostically significant coronary artery disease, we used a validated Mayo Clinic risk index in which 1 point was added for each of the following: male sex, typical angina pectoris, prior myocardial infarction by history or ECG, diabetes, and insulin use.¹¹

All clinical and exercise data were recorded prospectively into a computerized database.⁹ All data fields were standardized with prespecified definitions; all personnel involved with administering tests were formally trained how to complete data fields. For quality control, we periodically performed random comparisons of exercise reports with chart reviews.

Exercise Testing

Patients underwent "symptom-limited" exercise treadmill testing using primarily Bruce or modified Bruce protocols.¹² Predicted peak heart rate was calculated as 220 – age. Patients were encouraged to exercise until they experienced limiting symptoms, even if 85% of maximum predicted heart rate was achieved. During each exercise stage and recovery stage, symptoms (eg, chest discomfort, shortness of breath, fatigue, dizziness, leg pain, and heart palpitations), blood pressure, heart rate, cardiac rhythm, and exercise workload in metabolic equivalents (METs) were recorded. An ischemic ST-segment response was defined as at least 1 mm of horizontal or downsloping ST-segment depression 80 milliseconds after the J point.

Heart Rate Recovery

Following peak exercise, patients walked for a 2-minute cool-down period at 1.5 mph at a 2.5% grade. Heart rate recovery was defined as the difference between heart rate at peak exercise and 1 minute later. A cutoff value of 12/min or less was considered abnormal, based on a previous study from our laboratory that involved a differ-

ent cohort.³ Chronotropic incompetence was considered present if less than 80% of the patient's heart rate reserve (calculated as 220 – age – resting heart rate) was used at peak exercise.^{13,14}

Treadmill Exercise Score

The Duke treadmill exercise score was calculated as previously described: [duration of exercise (in minutes)] – [5 × maximal ST-segment deviation during or after exercise (in millimeters)] – [4 × treadmill angina index (0=no angina, 1=nonlimiting angina, 2=exercise-limiting angina)]. A treadmill exercise score of 5 or greater was considered low risk; –10 to +4, intermediate risk; and less than –10, high risk.⁵⁻⁷

End Points

Patients were followed up for a median of 5.2 years (range for survivors, 1.4-8.7 years) through May 1999. The primary end point was all-cause mortality as reported by the Social Security Death Index,¹⁵ which has been shown to be more specific and possibly less biased than the National Death Index.¹⁶ Unlike "cardiac mortality," all-cause mortality is an objective and unbiased end point.⁸

The high specificity, exceeding 99%, of the Social Security Death Index has been established.¹⁷ To assess the likely sensitivity of this index in our population, we analyzed the outcomes of 873 patients who had undergone coronary artery bypass graft surgery and had subsequently an exercise thallium study at our institution between 1990 and 1993.¹⁸ Vital status was ascertained by contacting all patients or next of kin through 1998. There were 102 confirmed deaths linked to a Social Security number; of these, the Social Security Death Index correctly identified the decedent status of 99 (sensitivity, 97%, 95% confidence interval [CI], 91%-99%).

Statistical Analyses

The univariate associations of abnormal heart rate recovery, an intermediate- or high-risk treadmill exercise score, chronotropic incompetence, and other potential predictors of death were as-

sessed using Kaplan-Meier curves¹⁹ and Cox proportional hazards models.²⁰ Analyses of heart rate recovery and treadmill exercise score as continuous variables included tests of logarithmically transformed values. The Cox proportional hazards assumption was confirmed by examination of log (–log[survival]) curves. Additional analyses were performed to assess potential interactions with certain prespecified candidate covariates, including age, sex, use of β -blockers, use of calcium channel antagonists, smoking, hypertension, diabetes, known coronary artery disease, chronotropic incompetence, testing for screening, and abnormal treadmill exercise score. If an interaction was found, specific terms describing the concur-

rent presence of factors were defined such that separate hazard ratios could be estimated according to the presence of the effect-modifying factor.

An additional set of Cox analyses was performed to confirm the validity of the estimates for the model in which all exercise variables were considered in dichotomous terms. A series of bootstrap resamplings were performed.^{21,22} First, 250 resampling analyses were done for variable selection, using $P = .10$ for model entry and $P \leq .05$ for retention. Second, those variables that were still retained in at least half the models were considered in 1000 fixed variable resamplings.

All analyses were performed using SAS version 6.12 software (SAS Inc,

Cary, NC). Bootstrapping was performed using SAS macros written by one of us (E.H.B.; available on request).

RESULTS

Baseline and Exercise Characteristics

The study cohort consisted of 9454 patients. The median value of heart rate recovery was 19/min, with 25th and 75th percentile values of 14/min and 24/min, respectively. Twenty percent of the population ($n = 1852$) had abnormal heart rate recovery, and 21% ($n = 1996$) had an intermediate- to high-risk treadmill exercise score. Only 25 patients (<1%) had a high-risk treadmill exercise score, so they were considered together with patients with an intermediate score. There were 3565 potentially eligible patients who either did not have valid Social Security numbers recorded or lived outside the United States. Those patients had nearly identical distributions of age, functional capacity, ST-segment responses, and heart rate recovery as study patients.

Baseline characteristics of the study population are shown in TABLE 1. Patients with abnormal heart rate recovery had more adverse risk profiles. Cholesterol data were available in about 25% of patients, irrespective of heart rate recovery; there was no association between heart rate recovery and cholesterol level.

Exercise characteristics according to heart rate recovery are summarized in TABLE 2. Patients with abnormal heart rate recovery had lower functional capacity and lower peak heart rates, and they used less of their heart rate reserve at peak exercise. The 2 groups (abnormal and normal heart rate recovery) were similar with regard to measured ST-segment depression, ST-segment slope interpretation, and non-test-limiting angina.

Heart Rate Recovery and Mortality

During a median follow-up of 5.2 years, there were 312 deaths. The presence of abnormal heart rate recovery was strongly associated with death (8% vs 2% in patients with normal heart rate

Table 1. Baseline Characteristics According to Heart Rate Recovery*

Characteristic	Heart Rate Recovery		P Value
	Normal (>12/min) [n = 7602]	Abnormal (\leq 12/min) [n = 1852]	
Age, mean (SD), y	52 (10)	58 (11)	<.001
Male sex	5966 (79)	1365 (74)	<.001
Hypertension†	1570 (21)	714 (39)	<.001
Current or recent smoker‡	1090 (14)	387 (21)	<.001
Diabetes‡	356 (5)	257 (14)	<.001
Insulin use	93 (1)	86 (5)	<.001
Hypercholesterolemia‡	2193 (29)	612 (33)	<.001
Cholesterol data available‡	1888 (25)	484 (26)	.25
Cholesterol level, mean (SD), mg/dL‡	245 (33)	246 (33)	.41
Lipid-lowering drug use	598 (8)	217 (12)	<.001
Prior coronary artery disease‡	1004 (13)	513 (28)	<.001
Prior myocardial infarction	548 (7)	294 (16)	<.001
Prior coronary artery bypass graft surgery	460 (6)	306 (17)	<.001
Mayo risk index§			<.001
0	1434 (19)	365 (20)	
1	5429 (71)	1059 (57)	
≥2	199 (10)	428 (23)	
β -Blocker use	619 (8)	286 (15)	<.001
Nondihydropyridine calcium channel blocker use	464 (6)	214 (12)	<.001
Vasodilator use	782 (10)	378 (20)	<.001
Chronic obstructive pulmonary disease‡	71 (1)	64 (3)	<.001
Screening exercise test	5917 (78)	1178 (64)	.04
Resting heart rate, mean (SD), beats/min	74 (13)	81 (15)	<.001
Resting tachycardia	202 (3)	209 (11)	<.001
Resting systolic blood pressure, mean (SD), mm Hg	128 (18)	132 (20)	<.001

*Values are presented as No. (%) unless indicated otherwise.

†Definition of this finding is explained in the "Methods" section.

‡Cholesterol data were routinely recorded if obtained within the past 3 months and if 200 mg/dL or higher. To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259.

§Score ranges from 0 to 5 with 1 point each for male sex, prior myocardial infarction by history or electrocardiogram findings, diabetes, insulin use, and typical angina pectoris. This score has been shown to correlate with left main or 3-vessel coronary artery disease.¹¹

recovery; hazard ratio [HR], 4.16; 95% CI, 3.33-5.19; $\chi^2=158$, $P<.001$). Other univariate predictors of mortality included resting tachycardia (9% vs 3% in patients without tachycardia; HR, 2.76; 95% CI, 1.95-3.91; $\chi^2=33$, $P<.001$), an intermediate- or high-risk treadmill exercise score (8% vs 2% in patients with low-risk scores; HR, 4.28; 95% CI, 3.43-5.35; $\chi^2=164$, $P<.001$), and chronotropic incompetence (9% vs 2% in patients without chronotropic incompetence; HR, 4.68; 95% CI, 3.74-5.84; $\chi^2=184$, $P<.001$).

Stratified analyses relating normal and abnormal values for heart rate recovery to death among prespecified subgroups are shown in TABLE 3. Abnormal heart rate recovery was associated with death in all subgroups except for patients taking β -blockers. Abnormal heart rate recovery provided additive prognostic information to the tread-

Table 2. Exercise Characteristics According to Heart Rate Recovery

Characteristic	Heart Rate Recovery		P Value
	Normal (>12/min) [n = 7602]	Abnormal (\leq 12/min) [n = 1852]	
Peak metabolic equivalents, mean (SD)			
Men	11 (2)	9 (3)	<.001
Women	8 (2)	7 (2)	<.001
Peak heart rate, mean (SD), beats/min	164 (18)	150 (24)	<.001
Proportion of heart rate reserve used, mean (SD)	0.96 (0.16)	0.87 (0.25)	<.001
Chronotropic incompetence*	1001 (13)	620 (33)	<.001
Heart rate recovery, mean (SD), beats/min	22 (7)	8 (4)	<.001
ST-segment depression, mm			
<1	6457 (85)	1591 (86)	.64
1-1.4	626 (8)	150 (8)	
1.5-1.9	235 (3)	46 (2)	
2.0-2.4	191 (3)	46 (2)	
\geq 2.5	93 (1)	19 (1)	
Abnormal ST-segment changes	963 (13)	230 (12)	.77
Angina, not test limiting	42 (1)	10 (1)	.17
Angina, test limiting	12 (0.2)	7 (0.4)	
Duke treadmill score, intermediate/high*	1350 (8)	646 (35)	<.001

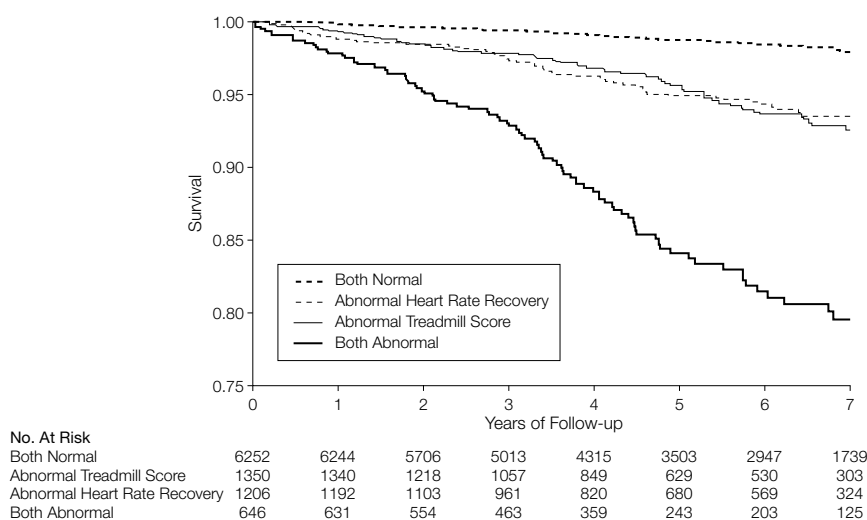
*For a definition of chronotropic incompetence, see the "Heart Rate Recovery" section of the "Methods." For an explanation of intermediate/high Duke treadmill score and how it was calculated, see the "Treadmill Exercise Score" section of the "Methods."

Table 3. Association of Abnormal Heart Rate Recovery With Mortality in Prespecified Subgroups*

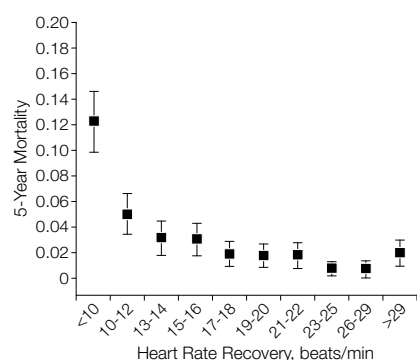
Group	Deaths, No./Total (%) by Heart Rate Recovery		Hazard Ratio (95% CI)	P Value	P Value for Interaction
	Normal (>12/min)	Abnormal (\leq 12/min)			
Age, y					
\geq 65	78/1003 (8)	97/612 (16)	2.36 (1.75-3.19)	<.001	.05
<65	81/6599 (1)	56/1240 (5)	3.73 (2.66-5.25)	<.001	
Sex					
Male	129/5966 (2)	115/1365 (8)	4.10 (3.19-5.27)	<.001	.80
Female	30/1636 (2)	38/487 (8)	4.39 (2.72-7.09)	<.001	
Known coronary heart disease					
Yes	56/1004 (6)	67/513 (13)	2.65 (1.86-3.78)	<.001	.04
No	103/6598 (2)	86/1339 (6)	4.25 (3.19-5.66)	<.001	
β -Blocker use					
Yes	38/619 (6)	23/286 (8)	1.53 (0.91-2.58)	.10	<.001
No	121/6983 (2)	130/1566 (8)	4.91 (3.83-6.28)	<.001	
Calcium channel blocker use†					
Yes	22/464 (5)	31/214 (14)	3.34 (1.93-5.76)	<.001	.47
No	137/7138 (2)	122/1638 (7)	4.09 (3.20-5.22)	<.001	
Vasodilator use					
Yes	30/782 (4)	53/378 (14)	4.11 (2.63-6.44)	<.001	.66
No	129/6820 (2)	100/1474 (7)	3.68 (2.83-4.77)	<.001	
Duke treadmill score					
Intermediate/high risk	67/1350 (5)	91/646 (14)	3.52 (2.55-4.85)	<.001	.63
Low risk	92/6252 (2)	62/1206 (5)	3.15 (2.30-4.32)	<.001	
Chronotropic incompetence					
Yes	59/1001 (6)	87/620 (14)	2.48 (1.78-3.45)	<.001	.09
No	100/6601 (2)	66/1232 (5)	3.66 (2.68-5.00)	<.001	
Screening test					
Yes	101/5917 (2)	78/1178 (7)	3.97 (2.95-5.34)	<.001	.34
No	58/1685 (3)	75/674 (11)	3.20 (2.27-4.50)	<.001	

*For an explanation of intermediate/high Duke treadmill score and how it was calculated, see the "Treadmill Exercise Score" section of the "Methods." For a definition of chronotropic incompetence, see the "Heart Rate Recovery" section of the "Methods." CI indicates confidence interval.

†Excluding dihydropyridines, which were counted as vasodilators.

Figure 1. Kaplan-Meier Survival Curves According to Heart Rate Recovery and Treadmill Exercise Score

Analyses using the log-rank test including both treadmill score and heart rate recovery were significant ($\chi^2_3=383$; $P<.001$).

Figure 2. Five-Year Kaplan-Meier Survival Estimates According to Deciles of Heart Rate Recovery

Error bars indicate 95% confidence intervals. Heart rate recovery was defined as the difference between heart rate at peak exercise and 1 minute later.

mill exercise score, with no interaction noted (Table 3 and FIGURE 1).

Heart rate recovery also was predictive of mortality when considered as a continuous variable. Heart rate recovery values less than 10/min to 12/min were associated with increasing risk of death (FIGURE 2).

Multivariate Cox Regression Analyses

In multivariate proportional hazards analyses, adjusting for potential con-

founders (listed in the footnote to TABLE 4), abnormal heart rate recovery was predictive of death. There were no interactions noted between heart rate recovery and either the treadmill exercise score or chronotropic incompetence; however, a significant interaction was noted such that heart rate recovery was not predictive of death among patients taking β -blockers. An intermediate- to high-risk treadmill exercise score and chronotropic incompetence were also predictive of mortality. There was no interaction noted between the treadmill exercise score and β -blocker use. When the 25 patients with an exercise treadmill score lower than -10 were excluded, the results were essentially unchanged.

When heart rate recovery and the exercise treadmill score were analyzed as continuous variables, similar results were noted; model fit was improved with logarithmic transformation of heart rate recovery, but not of treadmill exercise score. When the 3 components of the treadmill exercise score were analyzed separately, functional capacity was predictive of death (for each 2.5-MET decrease: adjusted HR, 1.57; 95% CI, 1.33-1.85; $P<.001$), but ST-segment changes (for each additional 1 mm of ST-

segment depression: adjusted HR, 1.09; 95% CI, 0.93-1.29; $P=.30$) and exercise-induced angina (adjusted HR, 1.14; 95% CI, 0.69-1.89; $P=.62$) were not. In this model, the association between heart rate recovery and death was similar to the primary model shown in Table 4.

Bootstrap Resampling Analyses

In 250 bootstrap resamplings, the only variables that entered at least 50% of models were age (100%), chronotropic incompetence (97%), resting tachycardia (97%), heart rate recovery (96%), current or recent smoking (96%), the treadmill exercise score (79%), sex (76%), and use of vasodilators (74%). No interaction term, including the β -blocker interaction term, entered even 50% of models. After 1000 subsequent fixed-model resamplings, abnormal heart rate recovery was still predictive of death (adjusted HR, 1.77; 95% CI, 1.39-2.28), as was chronotropic incompetence (adjusted HR, 2.13; 95% CI, 1.62-2.72) and a high- or intermediate-risk treadmill exercise score (adjusted HR, 1.52; 95% CI, 1.16-2.03).

Predictors of Death After Screening Exercise Tests

Among 7095 patients who were referred for screening exercise tests, 179 (3%) died during 5 years of follow-up. Abnormal heart rate recovery predicted death just as well in this group as among non-screening patients (Table 3). Abnormal heart rate recovery as an isolated finding was noted in 709 patients (10%), among whom 28 (4%) died (age- and sex-adjusted HR, 2.73; 95% CI, 1.71-4.34; $P<.001$). An additional 469 patients (7%) had abnormal heart rate recovery along with either chronotropic incompetence or a high- or intermediate-risk treadmill exercise score; 50 (11%) of these patients died (adjusted HR, 4.43; 95% CI, 2.88-6.81; $P<.001$).

Heart Rate Recovery, Treadmill Exercise Score, and Mortality in Women

Of 2123 women, 68 (3%) died. Heart rate recovery was associated with death in women, but there was no sex inter-

action noted (Table 3). Abnormal treadmill exercise score also was predictive of death (6% vs 2%; HR, 4.43; 95% CI, 2.69-7.29; $P < .001$). In a multivariate model independent predictors of mortality included abnormal heart rate recovery (adjusted HR, 2.73; 95% CI, 1.66-4.50; $P < .001$), age (for each 10 years, adjusted HR, 1.96; 95% CI, 1.54-2.48; $P < .001$), and Mayo risk index (for each additional risk factor, adjusted HR, 1.60; 95% CI, 1.20-2.13; $P = .001$). The treadmill exercise score was not independently predictive.

Achievement of Maximal Predicted Heart Rate

There were 4060 patients (43%) who achieved 100% or more of their age-predicted maximum heart rate. Among these, 70 patients (2%) died; abnormal heart rate recovery was associated with death (5% vs 1%; HR, 4.26; 95% CI, 2.65-6.68; $P < .001$). In a multivariate model the only independent predictors of mortality were age (for each 10 years, adjusted HR, 3.65; 95% CI, 2.82-4.73; $P < .001$) and abnormal heart rate recovery (adjusted HR, 2.30; 95% CI, 1.41-3.77; $P < .001$); the treadmill exercise score was not independently predictive.

COMMENT

Among patients referred for exercise ECG, heart rate recovery was a strong and independent predictor of all-cause mortality. Furthermore, heart rate recovery gave additional prognostic information over and above the Duke treadmill exercise score.

Multiple exercise variables obtained during stress testing have been assessed for prognostic value.^{5,23-29} The treadmill exercise score is an established exercise assessment that considers the duration of exercise, ST-segment deviation, and angina during exercise.⁵⁻⁷ Exercise heart rate response variables, specifically heart rate recovery and chronotropic incompetence, have been shown to have prognostic value.^{3,4,14,30-32} We have demonstrated that heart rate recovery was a predictor of mortality in a moderate-

Table 4. Results of Cox Multivariate Proportional Hazards Models*

Variable	Adjusted Hazard Ratio (95% CI)	P Value
Age (10 years)	2.23 (1.97-2.53)	<.001
Abnormal heart rate recovery without β -blocker use	2.13 (1.63-2.78)	<.001
Chronotropic incompetence	1.96 (1.52-2.53)	<.001
Resting tachycardia	2.39 (1.66-3.45)	<.001
Current or recent smoking	1.85 (1.41-2.44)	<.001
β -Blocker use	1.87 (1.28-2.75)	.001
Female sex	0.64 (0.49-0.84)	.002
High-/intermediate-risk Duke treadmill score	1.49 (1.15-1.92)	.002
Vasodilator use	1.48 (1.14-1.92)	.003
Abnormal heart rate recovery with β -blocker use	0.91 (0.54-1.52)	.79

*CI indicates confidence interval. Other variables considered included resting systolic blood pressure considered as a continuous variable, body mass index; use of nondihydropyridine calcium channel blockers, and lipid-lowering drugs; diabetes, insulin use, known hypercholesterolemia, documentation of total cholesterol value, known prior coronary heart disease, prior myocardial infarction, prior coronary artery bypass graft surgery, reason for test (screening or not), and presence of chronic obstructive pulmonary disease.

risk population undergoing symptom-limited exercise thallium testing.³ We also have found heart rate recovery to be predictive of death among healthy individuals in a population-based cohort study undergoing submaximal exercise testing.⁴

The current study extends previous findings in several respects. First, it confirms the prognostic value of heart rate recovery as a strong and independent predictor of mortality in a cohort of patients referred specifically for exercise ECG; our cohort is likely to be similar to patients seen in general medical practice. Of note, despite the very different risk profile of the population studied, the association between the level of heart rate recovery, assessed as a continuous variable (Figure 2), and risk of death was similar to that of the higher-risk population studied previously.³ When heart rate recovery decreases to less than 10/min to 12/min, risk of death increases markedly.

Second, heart rate recovery, along with treadmill exercise score and chronotropic response, were found to predict mortality among adults undergoing screening exercise testing, which is a controversial practice.³³ Our study suggests that by using heart rate response and treadmill exercise score, exercise tests can be used as a powerful marker of risk even in healthy patients. In fact, there was no difference in the predictive properties of heart rate

recovery in the screening and symptomatic groups.

Third, heart rate recovery further risk-stratified patients over and above the treadmill exercise score. Patients with intermediate- to high-risk treadmill exercise scores were found to have even higher mortality if abnormal heart rate recovery was also present (Figure 1). Patients with both low-risk treadmill exercise scores and normal heart rate recovery had very low risk of death.

We found that heart rate recovery was not predictive of mortality among patients taking β -blockers, which contrasts with our previous observation in a different, higher-risk population.³ This observation must be interpreted with caution given the small number of events that occurred among patients taking β -blockers and the failure of the β -blocker interaction term to be validated in a rigorous bootstrap analysis.

The mechanisms of adverse outcome associated with abnormal heart rate recovery are unclear. Parasympathetic activation is thought to be the underlying mechanism of heart rate recovery after exercise,^{1,2} and abnormalities in parasympathetic activation have been suggested as the link to mortality.³ Together, heart rate recovery and treadmill exercise score appear to be complementary, strengthening the predictive value of exercise stress testing.

Our current study has several limitations. It was an observational, single-

center experience, and it is not known if heart rate recovery is a modifiable risk factor. In addition, we had incomplete data on lipid abnormalities; only total cholesterol values were available for those patients who had blood samples drawn within 3 months of exercise testing and high-density lipoprotein cholesterol values were not recorded. Thus, we could not use the Framingham coronary heart disease index³⁴ to control for

baseline risk. Nonetheless, we found little if any association between lipid abnormalities and heart rate recovery. Previously we found no association between lipid abnormalities and heart rate recovery,⁴ so it is unlikely that the association between heart rate recovery and mortality was materially confounded by lipid disorders.

Heart rate recovery was a strong and independent predictor of mortality

among patients referred for exercise ECG. Heart rate recovery provides additional prognostic information to the established treadmill exercise score and should be considered for routine incorporation into exercise test interpretation.

Funding/Support: Dr Lauer is the recipient of an Established Investigator Grant from the American Heart Association.

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