

## HEART-RATE RECOVERY IMMEDIATELY AFTER EXERCISE AS A PREDICTOR OF MORTALITY

CHRISTOPHER R. COLE, M.D., EUGENE H. BLACKSTONE, M.D., FREDRIC J. PASHKOW, M.D., CLAIRE E. SNADER, M.A., AND MICHAEL S. LAUER, M.D.

**ABSTRACT**

**Background** The increase in heart rate that accompanies exercise is due in part to a reduction in vagal tone. Recovery of the heart rate immediately after exercise is a function of vagal reactivation. Because a generalized decrease in vagal activity is known to be a risk factor for death, we hypothesized that a delayed fall in the heart rate after exercise might be an important prognostic marker.

**Methods** For six years we followed 2428 consecutive adults (mean [ $\pm$ SD] age,  $57 \pm 12$  years; 63 percent men) without a history of heart failure or coronary revascularization and without pacemakers. The patients were undergoing symptom-limited exercise testing and single-photon-emission computed tomography with thallium scintigraphy for diagnostic purposes. The value for the recovery of heart rate was defined as the decrease in the heart rate from peak exercise to one minute after the cessation of exercise. An abnormal value for the recovery of heart rate was defined as a reduction of 12 beats per minute or less from the heart rate at peak exercise.

**Results** There were 213 deaths from all causes. A total of 639 patients (26 percent) had abnormal values for heart-rate recovery. In univariate analyses, a low value for the recovery of heart rate was strongly predictive of death (relative risk, 4.0; 95 percent confidence interval, 3.0 to 5.2;  $P < 0.001$ ). After adjustments were made for age, sex, the use or nonuse of medications, the presence or absence of myocardial perfusion defects on thallium scintigraphy, standard cardiac risk factors, the resting heart rate, the change in heart rate during exercise, and workload achieved, a low value for heart-rate recovery remained predictive of death (adjusted relative risk, 2.0; 95 percent confidence interval, 1.5 to 2.7;  $P < 0.001$ ).

**Conclusions** A delayed decrease in the heart rate during the first minute after graded exercise, which may be a reflection of decreased vagal activity, is a powerful predictor of overall mortality, independent of workload, the presence or absence of myocardial perfusion defects, and changes in heart rate during exercise. (N Engl J Med 1999;341:1351-7.)

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**A**LTHOUGH attention has been given to the prognostic implications of changes in heart rate during exercise,<sup>1-3</sup> the prognostic value of the rate of decline in heart rate after the cessation of exercise has not been well characterized. The rise in heart rate during exercise is considered to be due to the combination of parasympathetic withdrawal and sympathetic activation.<sup>4</sup> The fall in heart rate immediately after exercise is

considered to be a function of the reactivation of the parasympathetic nervous system.<sup>5</sup> Because increased vagal activity has been associated with a reduction in the risk of death,<sup>6</sup> we hypothesized that the rate of recovery of the heart rate immediately after exercise may be an important prognostic marker.

The purpose of this study was to examine the usefulness of the heart-rate recovery after exercise as a long-term prognostic marker in a population of consecutive patients referred for exercise testing with single-photon-emission computed tomography and thallium scintigraphy at a single center. We specifically focused on overall mortality as an unbiased, objective end point.<sup>7</sup>

**METHODS****Patient Population**

The study cohort was made up of consecutive adult patients who were referred to the Cleveland Clinic Foundation for a first symptom-limited exercise test and single-photon-emission computed tomography with thallium scintigraphy between September 1990 and December 1993.<sup>8,9</sup> We included patients who were candidates for initial angiography.<sup>10</sup> Patients were excluded if they had a history of coronary angiography, previous cardiac surgery, an implanted pacemaker, congestive heart failure or use of digoxin, congenital or valvular heart disease, the preexcitation syndrome, or left bundle-branch block (because of the potential for false positive findings of myocardial perfusion defects on thallium scintigraphy during exercise in patients with these factors). Patients were also excluded if a valid Social Security number was not included in their registration or if data on the recovery of heart rate were not available. All patients gave informed consent before testing; the protocol was approved by the institutional review board of the Cleveland Clinic Foundation.

**Clinical Data**

Before the patients were tested, a review of each patient's chart and a structured interview were conducted to gather data on symptoms, medications, coronary risk factors, previous cardiac events, and other diagnoses.<sup>9</sup> Hypertension was defined as a systolic blood pressure of  $\geq 140$  mm Hg at rest, a diastolic blood pressure of  $\geq 90$  mm Hg at rest, or treatment with antihypertensive medication.<sup>11</sup> Diagnoses of diabetes mellitus and chronic lung disease were determined on the basis of chart review, interviews with the patients, and use of medication by the patients. A history of coronary disease was considered present when there were documented hospitalizations for myocardial infarction or unstable angina. The presence of a lipid disorder was defined by the use of lipid-lowering medication at the time of testing. Cardioactive medications

From the Departments of Cardiology (C.R.C., F.J.P., C.E.S., M.S.L.), Cardiothoracic Surgery (E.H.B.), and Epidemiology and Biostatistics (E.H.B.) and the George M. and Linda H. Kaufman Center for Heart Failure (M.S.L.), Cleveland Clinic Foundation, Cleveland. Address reprint requests to Dr. Lauer at the Section of Heart Failure and Cardiac Transplantation Medicine, Department of Cardiology, Desk F25, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195, or at lauerm@ccf.org.

were classified as beta-blockers, nondihydropyridine calcium-channel blockers (e.g., diltiazem and verapamil), or vasodilators (e.g., nifedipine, alpha-adrenergic blockers, and angiotensin-converting-enzyme inhibitors).

### Exercise Testing

Exercise testing of most of the patients was conducted according to the standard and modified Bruce protocols.<sup>12</sup> Whether cardioactive medications were used on the day of the test was left to the discretion of the referring physician. So that workload could be more accurately estimated, the patients were not allowed to lean on the handrails. Midway through each stage of exercise, at peak exercise, and one minute after the cessation of exercise, data on symptoms, heart rate and rhythm, blood pressure (as measured by indirect arm-cuff sphygmomanometry), and estimated workload (as determined on the basis of standard tables)<sup>12</sup> in metabolic equivalents (MET; 1 MET equals 3.5 ml of oxygen uptake per kilogram of body weight per minute) were collected and entered into a computer data base. The patients were encouraged to reach symptom-limited maximal exercise; the achievement of the target heart rate (based on age) alone was not a sufficient reason for the termination of testing. Chronotropic response during exercise was defined as the percentage of the heart-rate reserve (the difference between the maximal achievable heart rate [220 beats per minute minus age in years] and the resting heart rate) used at peak exercise. A failure to use 80 percent of the heart-rate reserve was considered to be evidence of an impaired chronotropic response.<sup>13</sup> This measure is an independent predictor of mortality.<sup>8</sup>

### Recovery of Heart Rate

After achieving peak workload, all the patients spent at least two minutes in a cool-down period during treadmill testing at a speed of 2.4 km (1.5 mi) per hour and a grade of 2.5 percent. This period was considered the recovery period. The value for the recovery of heart rate was defined as the reduction in the heart rate from the rate at peak exercise to the rate one minute after the cessation of exercise.

We determined an abnormal value for the recovery of heart rate by finding the maximal value for the log-rank chi-square test statistic for all possible cutoff points between the 10th and 90th percentiles for the study cohort.<sup>14</sup> A secondary abnormal value was based on the value for the 10th percentile for the study cohort.

### Thallium Scintigraphy

The scintigraphic methods used in our laboratory between 1990 and 1993 have been described in detail elsewhere.<sup>15</sup> We determined a modified summed score on the thallium stress test for each patient by dividing the number of segments of the left ventricle with either fixed or reversible perfusion defects during thallium scintigraphy by the total number of segments. We have previously reported on the associations between such defects and mortality.<sup>8,9,16</sup>

### End Points

The mean follow-up time was six years. The primary end point was death from all causes, identified through a search of the Social Security death index by Epidemiology Resources (Newton, Mass.). This index has previously been validated and is slightly less sensitive but more current and specific than the National Death Index.<sup>17</sup>

### Statistical Analysis

For descriptive purposes, the patients were divided into two groups on the basis of the value for the recovery of heart rate. Continuous variables are presented as means  $\pm$ SD. Differences between groups were compared with the use of Student's *t*-test, Wilcoxon's rank-sum test, and the chi-square test, as appropriate.

The value for heart-rate recovery was related to mortality from all causes by univariable and multivariable Cox regression analyses.<sup>18</sup> We performed stratified analyses of prespecified subgroups

defined according to age, sex, history of coronary disease, the chronotropic response during exercise, the presence or absence of perfusion defects on thallium scintigraphy, and the use or nonuse of medications. Logarithmic and quadratic transformations and potential interactions were assessed for improvement of fit. To assess further the association of heart-rate recovery with mortality, the population was divided according to quintiles of values for recovery, with relative risks and confidence intervals calculated on the basis of comparisons with the highest quintile. The Cox proportional-hazards assumption was confirmed by inspection of log[-log (survival function)] curves.

To assess the association between heart-rate recovery and exercise capacity, the study cohort was divided into sex-specific deciles of exercise capacity, measured in MET. Differences in the proportion of patients with an abnormal value for heart-rate recovery ( $\leq 12$  beats per minute) were compared with use of the chi-square test for trend.<sup>19</sup> Logistic-regression analysis was used to assess the effects of exercise capacity and medications on heart-rate recovery after adjustment for age, sex, and the presence or absence of perfusion defects on thallium scintigraphy.<sup>20</sup> All analyses were performed with the SAS statistical package (version 6.12, SAS Institute, Cary, N.C.).

## RESULTS

### Characteristics of the Patients at Base Line and during Exercise

There were 2428 patients who met all inclusion criteria. The median value for heart-rate recovery was 17 beats per minute, with a range from the 25th to the 75th percentile of 12 to 23 beats per minute. A cutoff value of 12 beats per minute was found to maximize the log-rank test statistic. An abnormal value for heart-rate recovery was found in 639 patients (26 percent).

The base-line characteristics of the patients according to whether their heart-rate recovery was normal or abnormal are summarized in Table 1. As compared with the patients with a normal value for heart-rate recovery, those with an abnormal value ( $\leq 12$  beats per minute) were older, had higher resting heart rates, were more likely to have hypertension or diabetes, were more likely to smoke, and were more likely to have Q waves on the electrocardiogram or a history of coronary artery disease. They were also more likely to take nondihydropyridine calcium-channel blockers or vasodilators. There were no marked differences between the groups in the use of beta-blockers.

During exercise, the patients with an abnormal value for heart-rate recovery, as compared with those with a normal value, had lower increases in heart rate from base line (an increase of  $61 \pm 21$  beats per minute vs. an increase of  $81 \pm 20$  beats per minute,  $P < 0.001$ ) and were more likely to have an impaired chronotropic response during exercise (45 percent vs. 23 percent of patients,  $P < 0.001$ ). They were also more likely to have perfusion defects on thallium scintigraphy (23 percent vs. 19 percent,  $P = 0.01$ ). There were no differences between the groups in the percentage of patients with abnormal ST-segment response (19 percent vs. 21 percent,  $P = 0.2$ ) or angina during treadmill testing (15 percent vs. 14 percent,  $P = 0.6$ ).

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO THE VALUE FOR THE RECOVERY OF HEART RATE AFTER EXERCISE.\*

CHARACTERISTIC	NORMAL (REDUCTION OF >12 bpm)	ABNORMAL (REDUCTION OF ≤12 bpm)	P VALUE
No. of patients	1789	639	
Age — yr	55±12	61±12	<0.001
Female sex — no. (%)	653 (37)	252 (39)	0.19
Resting heart rate — bpm	76±13	83±16	<0.001
Hypertension — no. (%)	680 (38)	334 (52)	<0.001
Diabetes — no. (%)	176 (10)	125 (20)	<0.001
Smoking — no. (%)	268 (15)	151 (24)	<0.001
Q waves on electrocardiogram — no. (%)	95 (5)	65 (10)	<0.001
Prior coronary artery disease — no. (%)	140 (8)	85 (13)	<0.001
Right bundle-branch block — no. (%)	136 (8)	54 (8)	0.49
Use of beta-blockers — no. (%)	224 (13)	88 (14)	0.42
Use of nondihydropyridine calcium-channel blockers — no. (%)	223 (12)	121 (19)	<0.001
Use of vasodilators — no. (%)	604 (34)	311 (49)	<0.001
Use of lipid-lowering medication — no. (%)	133 (7)	58 (9)	0.19

\*Plus-minus values are means ±SD. The abbreviation bpm denotes beats per minute.

### Heart-Rate Recovery and Mortality

During six years of follow-up, there were 213 deaths from all causes (9 percent). An abnormal value for heart-rate recovery was strongly predictive of death (mortality at six years, 19 percent vs. 5 percent; relative risk, 4.0; 95 percent confidence interval, 3.0 to 5.2;  $P<0.001$ ). Of the 213 patients who died, 120 (56 percent) had an abnormally low value for heart-rate recovery.

As a predictor of death, an abnormally low value for heart-rate recovery had a sensitivity of 56 percent, a specificity of 77 percent, a positive predictive value of 19 percent, and a negative predictive value of 95 percent. When the value for the 10th percentile (a decrease of eight beats per minute) was used as a cutoff, the sensitivity was 33 percent, the specificity 90 percent, the positive predictive value 24 percent, and the negative predictive value 90 percent; the relative risk was 4.1 (95 percent confidence interval, 3.0 to 5.4;  $P<0.001$ ).

Analyses stratified according to age, sex, history of coronary disease, the chronotropic response during exercise, the presence or absence of perfusion defects on thallium scintigraphy, and the use or nonuse of medications are presented in Table 2. A low value for heart-rate recovery was predictive of death in

**TABLE 2.** ASSOCIATIONS BETWEEN A LOW VALUE FOR THE RECOVERY OF HEART RATE AND MORTALITY IN PRESPECIFIED SUBGROUPS.\*

STRATIFYING VARIABLE	NORMAL (REDUCTION OF >12 bpm)	ABNORMAL (REDUCTION OF ≤12 bpm)	RELATIVE RISK (95% CI)	P VALUE	P VALUE FOR INTERACTION
	no. of deaths/no. of patients (%)				
All patients	93/1789 (5)	120/639 (19)	4.0 (3.0–5.2)	<0.001	—
Age					
<65 yr	41/1363 (3)	40/351 (11)	4.0 (2.6–6.2)	<0.001	0.11
≥65 yr	52/426 (12)	80/288 (28)	2.6 (1.8–3.6)	<0.001	
Sex					
Male	70/1136 (6)	84/387 (22)	3.9 (2.8–5.3)	<0.001	0.72
Female	23/653 (4)	36/252 (14)	4.4 (2.6–7.5)	<0.001	
History of coronary artery disease					
No	81/1649 (5)	99/554 (18)	4.0 (3.0–5.3)	<0.001	0.55
Yes	12/140 (9)	21/85 (25)	3.2 (1.6–6.6)	0.001	
Chronotropic response					
Normal	45/1375 (3)	50/353 (14)	4.7 (3.1–7.0)	<0.001	0.01
Impaired	48/414 (12)	70/286 (24)	2.3 (1.6–3.3)	<0.001	
Perfusion defects on thallium scintigraphy					
No	59/1452 (4)	74/489 (15)	4.0 (2.9–5.7)	<0.001	0.61
Yes	34/337 (10)	46/150 (31)	3.4 (2.2–5.4)	<0.001	
Use of beta-blockers					
No	77/1565 (5)	102/551 (19)	4.1 (3.1–5.6)	<0.001	0.74
Yes	16/224 (7)	18/88 (20)	3.1 (1.6–6.1)	0.001	
Use of nondihydropyridine calcium-channel blockers					
No	72/1566 (5)	103/518 (20)	4.8 (3.5–6.4)	<0.001	0.002
Yes	21/223 (9)	17/121 (14)	1.6 (0.8–3.0)	0.15	
Use of vasodilators					
No	48/1185 (4)	60/328 (18)	4.9 (3.4–7.2)	<0.001	0.04
Yes	45/604 (7)	60/311 (19)	2.8 (1.9–4.2)	<0.001	

\*CI denotes confidence interval, and bpm beats per minute.

**TABLE 3. RISK OF DEATH ACCORDING TO UNIVARIABLE ANALYSIS.\***

PREDICTOR	RELATIVE RISK (95% CI)	CHI-SQUARE	P VALUE
Value for heart-rate recovery (for each decrease of 9 bpm)	2.1 (1.8–2.5)	99	<0.001
Log-transformed value for heart-rate recovery (for each decrease of 0.21)	1.4 (1.4–1.5)	169	<0.001
Defects on thallium scintigraphy (for each additional segment)†	1.2 (1.2–1.3)	62	<0.001
Exercise capacity (for each decrease of 2.5 MET)	2.6 (2.2–3.0)	145	<0.001
Heart-rate increase during exercise (for each decrease of 22 bpm)	2.4 (2.0–2.7)	164	<0.001
Chronotropic response during exercise (for each decrease of 21 percent)	1.7 (1.5–1.9)	81	<0.001
Resting heart rate (for each increase of 14 bpm)	0.9 (0.8–1.0)	1.5	0.20

\*Except for the variable of perfusion defects on thallium scintigraphy, the relative risks were calculated for a change of 1 SD, as shown. CI denotes confidence interval, bpm beats per minute, and MET metabolic equivalents.

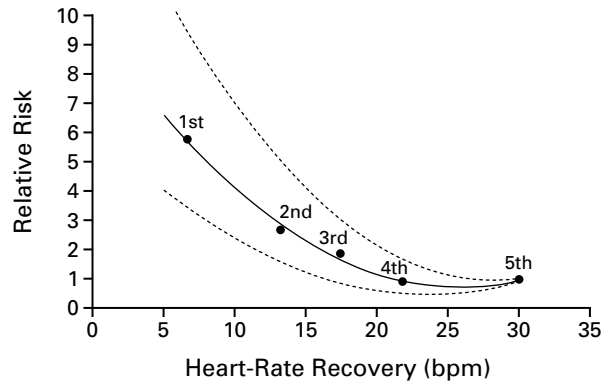
†Perfusion defects on thallium scintigraphy were considered abnormal, whether they were fixed or reversible, and were coded according to a 12-segment division of the left ventricle.

all subgroups, although the association was weaker among the patients with an impaired chronotropic response during exercise and those taking vasodilators or nondihydropyridine calcium-channel blockers.

A low value for heart-rate recovery was predictive of death when considered as a continuous variable, especially after logarithmic transformation; a decrease in exercise capacity, the presence of perfusion defects on thallium scintigraphy, and an impaired chronotropic response during exercise were also predictive of death (Table 3). Figure 1 shows the relative risk of death according to the quintile of heart-rate recovery; once this value dropped below 10 to 15 beats per minute there was a marked increase in the risk of death. Values above 15 to 20 beats per minute, however, were not associated with further improvements in prognosis.

**Multivariable Cox Regression Analyses**

After adjustments were made for age; sex; resting heart rate; heart-rate increase during exercise; exercise capacity; the presence or absence of hypertension, smoking, chronic lung disease, diabetes, Q waves on the electrocardiogram, a history of coronary artery disease, right bundle-branch block, and angina during treadmill testing; the use or nonuse of beta-blockers, nondihydropyridine calcium-channel blockers, lipid-lowering therapy, and vasodilator medications; and perfusion defects on thallium scintigraphy, a low value for heart-rate recovery emerged as the strongest pre-



**Figure 1.** Estimates of the Relative Risk of Death within Six Years According to Heart-Rate Recovery One Minute after Cessation of Exercise.

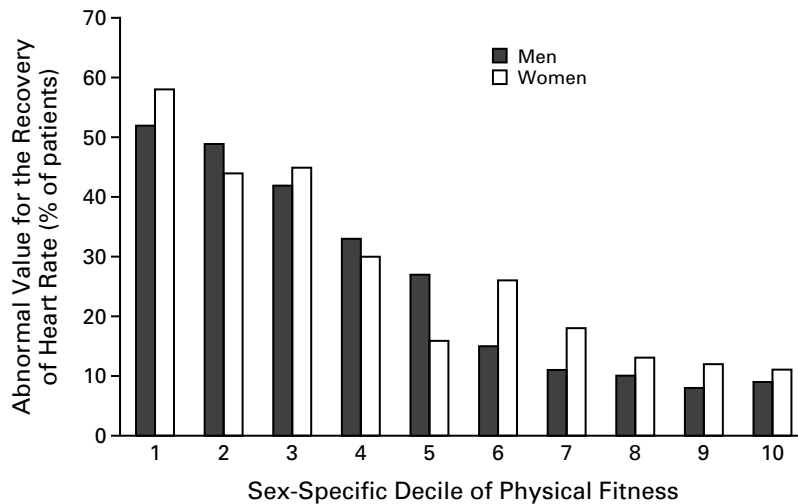
Circles represent the relative risk of death for each of the quintiles as compared with the quintile with the greatest reduction (5th). Dashed lines represent the 95 percent confidence interval. The abbreviation bpm denotes beats per minute.

dicator of death (adjusted relative risk, 2.0; 95 percent confidence interval, 1.5 to 2.7;  $P < 0.001$ ). Other independent predictors included decreased exercise capacity ( $P < 0.001$ ), male sex ( $P < 0.001$ ), increased age ( $P < 0.001$ ), the presence of perfusion defects on thallium scintigraphy ( $P = 0.006$ ), and a smaller increase in heart rate during exercise ( $P = 0.006$ ).

If an impaired chronotropic response during exercise was substituted in the regression model for the change in the heart rate during exercise, a low value for heart-rate recovery remained independently predictive of death (adjusted relative risk, 2.0; 95 percent confidence interval, 1.8 to 2.7;  $P < 0.001$ ), whereas an impaired chronotropic response during exercise was not as strongly predictive (adjusted relative risk, 1.7; 95 percent confidence interval, 1.2 to 2.3;  $P = 0.002$ ). Similar results were obtained when the value for heart-rate recovery was considered as a continuous variable. When the value for the 10th percentile (eight beats per minute) was used as the cutoff for an abnormal value for heart-rate recovery, it emerged as an independent predictor of mortality (adjusted relative risk, 1.7; 95 percent confidence interval, 1.3 to 2.4;  $P < 0.001$ ).

**Effects of Revascularization**

During the first three months after exercise stress testing, 79 patients (3 percent) underwent coronary-artery bypass grafting and 41 (2 percent) underwent percutaneous revascularization. The inclusion of any revascularization procedure — or of coronary-artery bypass surgery only — in supplementary multivariable Cox regression analyses had no effect on the associations between the value for heart-rate recovery and mortality from all causes.



**Figure 2.** Association between Sex-Specific Deciles of Physical Fitness and Abnormal Values for the Recovery of Heart Rate One Minute after the Cessation of Peak Exercise.

A value of  $\leq 12$  beats per minute for the recovery of heart rate was considered abnormal. Increasing levels of physical fitness were strongly correlated with decreasing rates of abnormal values for the recovery of heart rate among men and women (for men: chi-square for trend=207,  $P<0.001$ ; for women: chi-square for trend=97,  $P<0.001$ ).

#### Determinants of Heart-Rate Recovery

There was a strong association between decreasing exercise capacity and an abnormal value for heart-rate recovery in both men and women (Fig. 2). Among the patients with a normal result on thallium scintigraphy, exercise capacity was lower in the presence of an abnormal value for heart-rate recovery (men, 7.9 MET vs. 9.8 MET in patients with a normal value; women, 6.0 MET vs. 7.4 MET;  $P<0.001$  for both comparisons). In a logistic-regression analysis in which adjustments were made for age, sex, and the presence or absence of perfusion defects on thallium scintigraphy, independent predictors of an abnormal value for heart-rate recovery included a decrease in exercise capacity (adjusted odds ratio for a decrease of 2.5 MET, 2.4; 95 percent confidence interval, 2.1 to 2.8;  $P<0.001$ ) and the use of vasodilators (adjusted odds ratio, 1.3; 95 percent confidence interval, 1.1 to 1.6;  $P=0.01$ ). There were no independent associations between the use of beta-blockers or calcium-channel blockers and an abnormal value for heart-rate recovery.

#### Recovery of Systolic Blood Pressure

The median reduction in systolic blood pressure during the first minute of recovery was 8 mm Hg (25th and 75th percentiles, 0 and 20 mm Hg). There was no association between the recovery of systolic blood pressure and mortality (relative risk of death associated with a fall of 5 mm Hg in systolic blood pressure, 1.01; 95 percent confidence interval, 0.97 to 1.05;  $P=0.70$ ).

#### DISCUSSION

Among the patients undergoing exercise testing and single-photon-emission computed tomography with thallium scintigraphy, all of whom were candidates for initial coronary angiography, the failure of the heart rate to fall rapidly during early recovery after exercise was associated with increased overall mortality, even after adjustments were made for standard cardiovascular risk factors, changes in the heart rate during exercise, the use or nonuse of medications, exercise capacity, and the presence or absence of myocardial perfusion defects. Whether measured as a categorical or a continuous variable, a low value for heart-rate recovery was among the strongest predictors of death. Although only 26 percent of the population we studied had an abnormally delayed decrease in the heart rate, the majority of the patients who died (56 percent) had an abnormally low value. This is in sharp contrast with most risk factors, which, although they identify high-risk groups, predict only a minority of deaths.

A low value for heart-rate recovery was predictive of death in a number of important subgroups, including the elderly, women, patients with a normal chronotropic response during exercise, and those taking beta-blockers. It is noteworthy that the patients who had both a normal chronotropic response during exercise and a normal heart-rate recovery had a six-year mortality rate of only 3 percent, or 0.5 percent per year. The association between heart-rate recovery and mortality was weaker among the patients taking nondihydropyridine calcium-channel

blockers and vasodilators; it is possible that these medications may have blunted heart-rate recovery by causing a marked fall in blood pressure after exercise.

The mechanisms by which impaired heart-rate recovery confers an increased risk of death, even among patients without heart failure or myocardial perfusion defects, are not clear. Imai et al. examined the physiologic characteristics of heart-rate recovery after exercise in healthy adults, athletes, and patients with chronic heart failure.<sup>5</sup> They demonstrated that, in all three groups, vagal reactivation was the principal determinant of the decrease in heart rate during the first 30 seconds of recovery and that this mechanism was independent of age and the intensity of exercise. Heart-rate recovery was rapid in athletes but was blunted in patients with heart failure and was completely abolished by the administration of atropine. In our study, we also found a marked inverse association between heart-rate recovery and exercise capacity. Because increased vagal activity has been associated with a reduction in the risk of death,<sup>6</sup> we hypothesized that the heart rate after exercise may be an important predictor of mortality.

The Autonomic Tone and Reflexes after Myocardial Infarction study<sup>21</sup> was a large, prospective, multicenter study in which patients who had had myocardial infarctions were stratified according to markers of autonomic control. Both markers used — variability in heart rate and baroreflex sensitivity — proved to be strong predictors of outcome. Our study extends these findings in two important ways. First, we demonstrated the prognostic importance of an autonomic marker in a broader population. Second, the value for the recovery of heart rate is a simple marker that is easily calculated on the basis of data already contained in a standard exercise test and does not require 24-hour Holter monitoring or specialized baroreflex-sensitivity testing.

Because this study was performed at a single tertiary care center, it is possible that there were biases with respect to patient referral and population sampling. The thallium scintigraphic techniques in this study were those in use during the early 1990s, and the techniques of today may yield better prognostic results. Two important predictors of prognosis, dilatation of the left ventricular cavity and increased lung uptake of thallium with exercise,<sup>22</sup> could not be included in the analysis because of the very small number of patients in this low-risk cohort who had these findings.

Formal measures of left ventricular function, an important predictor of mortality, were not available. To decrease the effect of impaired cardiac function, we purposely excluded patients with a history of heart failure, revascularization, or use of digoxin. In addition, consideration of the total number of abnormal segments on thallium scintigraphy may also have part-

ly accounted for the effects of left ventricular dysfunction.

A reduction in the heart rate of 12 beats per minute after the cessation of exercise was used as the definition of a low value for the recovery of the heart rate. This cutoff was determined by calculating the maximal value for the log-rank chi-square test statistic for all possible cutoff points between the 10th and 90th percentiles. One disadvantage of this method is that it overstates the association as compared with what would be seen in an independent data set. Therefore, it is essential that these findings be confirmed in other populations. If the 10th percentile (indicating a decrease in the heart rate of eight beats per minute) is used as the cutoff, the specificity and positive predictive value of this method for mortality are improved. However, the improvement comes at the expense of a higher mortality rate (2 percent per year vs. 1 percent per year) in the group with what is defined as a normal value for heart-rate recovery; this mortality rate may be unacceptably high for some clinicians.

A low value for heart-rate recovery after exercise testing, which has been previously shown to be a marker of decreased vagal activity, is a powerful and independent predictor of the risk of death. This marker is simple to calculate from data that are already contained in the results of standard exercise tests and may be valuable for the assessment of risk in routine clinical practice.

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