

## Rapid Heart Rate Increase at Onset of Exercise Predicts Adverse Cardiac Events in Patients With Coronary Artery Disease

Colomba Falcone, MD; Maria Paola Buzzi, MD; Catherine Klersy, MD; Peter J. Schwartz, MD

**Background**—We previously demonstrated that reduced vagal activity and/or increased sympathetic activity identify post–myocardial infarction patients at high risk for cardiac mortality. Simple and inexpensive autonomic markers are necessary to perform autonomic screening in large populations. We tested our hypothesis that abnormally elevated heart rate (HR) responses at the onset of an exercise stress test, which imply rapid vagal withdrawal immediately preceding sympathetic activation, might predict adverse cardiac events in patients with documented coronary artery disease.

**Methods and Results**—The HR increase during the first minute ( $\Delta\text{HR}_{1\text{ minute}}$ ) of a symptom-limited exercise stress test was quantified in 458 patients with documented coronary artery disease. During a 6-year (interquartile range 3.7 to 9.0 years) follow-up, 71 patients experienced adverse cardiac events (21 cardiac deaths, 56 nonfatal myocardial infarctions). In univariate analysis,  $\Delta\text{HR}_{1\text{ minute}} \geq 12$  bpm (above the median value of its distribution) predicted both adverse outcome and cardiac death with a hazard ratio of 5.0 (95% CI 2.7 to 9.1;  $P < 0.0001$ ) and of 15.6 (95% CI 2.0 to 118.7;  $P < 0.001$ ), respectively. After adjustment for potential confounders,  $\Delta\text{HR}_{1\text{ minute}}$  remained predictive for both combined end points and for cardiac death.

**Conclusions**—A marked HR increase at the onset of a standard exercise stress test is a novel and easily available parameter that could be clinically useful as an independent predictor of adverse cardiac events, including death, among patients with documented coronary artery disease. (*Circulation*. 2005;112:1959-1964.)

**Key Words:** exercise ■ heart rate ■ mortality ■ nervous system, autonomic ■ risk factors

Early identification of individuals at high risk for cardiovascular mortality and morbidity is a cornerstone of modern medicine. The concept that alterations in the autonomic control of cardiac functions, characterized by augmented sympathetic and reduced vagal activity, play a major role in cardiovascular mortality<sup>1</sup> has had a wide impact. Indeed, the search for markers of “autonomic imbalance” has contributed to risk stratification in different patient populations.

The evidence that reduced ability to reflexly increase vagal activity, as quantified by baroreflex sensitivity,<sup>2</sup> predicts increased risk for sudden and nonsudden cardiac death after myocardial infarction<sup>3–6</sup> has stimulated the search for and testing of other markers of reduced vagal activity. Some of them, such as heart rate (HR) variability and HR turbulence, have validity in postinfarction patients.<sup>7,8</sup> Others, such as HR reduction and occurrence of ventricular arrhythmias in the recovery period of exercise, have focused more on the autonomic changes induced by exercise testing and have suggested that this period may provide important prognostic information.<sup>9,10</sup> The latter 2 studies have brought a new dimension to the inexpensive and frequently used exercise testing.<sup>11</sup> So far, all attempts by ourselves<sup>5,6,8</sup> and others<sup>7,9,10</sup>

have focused on markers of tonic or reflex vagal activity, searching for a correlation between cardiac events and impaired ability to increase the “protective” vagal activity. We have now examined a different facet of autonomic regulation, namely, the rapidity of vagal withdrawal at onset of exercise, because we postulate that the faster the vagal withdrawal in response to a stress, the greater will be the deleterious effect of sympathetic activation unopposed by vagal activity. Accordingly, in a cohort of patients with angiographically documented coronary artery disease, we tested our hypothesis that a novel autonomic marker—the rapidity of HR increase during the first minute of exercise—might predict major cardiovascular events.

### Methods

#### Patient Population

The study population consisted of 458 consecutive male patients referred in the 1990s at our center for coronary angiography, who subsequently underwent an exercise stress test (EST) and were scheduled for regular follow-up. Patients were included if coronary arteriography documented significant coronary artery disease ( $\geq 50\%$ ) and excluded if they had symptoms or signs of heart failure, previous evidence of impaired left ventricular ejection fraction, use of digoxin, valvular or congenital disease, a pacemaker, or a

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From the Department of Lung, Blood, and Heart (C.F., M.P.B., P.J.S.), University of Pavia, Pavia, Italy; Department of Cardiology (C.F., M.P.B., P.J.S.), IRCCS Policlinico S. Matteo, Pavia, Italy; and Biometry and Clinical Epidemiology Unit (C.K.), IRCCS Policlinico S. Matteo, Pavia, Italy.

Correspondence to Peter J. Schwartz, MD, Professor & Chairman, Department of Cardiology, Policlinico S. Matteo IRCCS, Via le Golgi, 19-27100 Pavia, Italy. E-mail PJQT@compuserve.com

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noninterpretable ECG. Before the EST, a structured interview gathered data on coronary risk factors, symptoms, medications, and previous cardiac events. All patients gave informed consent, and the study was approved by the institutional review board.

### Exercise Testing

Stress testing for detection of myocardial ischemia was performed in accordance with the American College of Cardiology/American Heart Association guidelines. A multistage symptom-limited EST was performed on a bicycle ergometer in the semisupine position. The initial workload was 25 W, with subsequent stepwise increments of 25 W every 2 minutes at a pedaling rate of 60 rpm; peak workload was followed by at least a 2-minute cool-down period. Standard 12-lead ECG and blood pressure were recorded in basal conditions, every minute during exercise, at peak exercise, and every minute during recovery. Frequent or complex ventricular arrhythmias were recorded. A positive ECG response was defined as the occurrence of ST-segment depression  $\geq 1$  mm compared with the baseline tracing. The EST was stopped when angina, dyspnea, muscle fatigue, ST-segment depression  $>3$  mm, or major arrhythmias occurred. The estimated workload was determined in metabolic equivalents (METS). Patients who performed their EST in pharmacological washout stopped use of calcium channel blocking agents and nitrates 48 hours before the EST or gradually reduced  $\beta$ -blocker therapy 1 week in advance.

### Assessment of HR Response

During EST, HR increases were calculated at 1 minute after the beginning of exercise ( $\Delta\text{HR}_{1\text{ minute}}$ ), at the end of each stepwise increment, and at peak exercise. For the purpose of the analysis,  $\Delta\text{HR}_{1\text{ minute}}$  was dichotomized according to the median value of its distribution ( $<12$  bpm,  $\geq 12$  bpm). HR recovery was defined as the difference in HR between the values recorded at the end of exercise and those recorded 1 minute after termination of exercise. A cutoff value of 12 bpm or less was considered abnormal.<sup>9</sup>

### Follow-Up

Patients were followed up for a median of 6 years (interquartile range 3.7 to 9.0 years). The end point of the study was a composite of cardiac death and nonfatal myocardial infarction. Most of the patients attended our center once or twice per year, according to clinical conditions; clinical data for those who interrupted their periodic follow-up were obtained through telephone calls. Out-of-hospital deaths were investigated by means of interview with the next of kin or patient's physicians or by analysis of death certificates. Myocardial infarction was diagnosed on the basis of clinical symptoms, ECG changes, and cardiac enzyme elevations.

### Statistical Analysis

Data are presented as mean  $\pm$  SD for continuous variables and as absolute and relative frequencies for categorical variables. Follow-up time is summarized with median and interquartile range. Comparisons between  $\Delta\text{HR}_{1\text{ minute}}$  groups were performed by means of the Student *t* test and Fisher exact test for continuous and categorical variables, respectively.

Kaplan-Meier estimates of event-free survival were plotted. Time origin was the time of EST. Patients undergoing revascularization or dying of other causes were censored at the time of revascularization when we analyzed the combined event and additionally at the time of myocardial infarction when we analyzed cardiac death. The event rate per 100 person-years was computed together with its 95% CI. Cox proportional hazard model was used to evaluate the role of  $\Delta\text{HR}_{1\text{ minute}}$  dichotomized at 12 bpm as a risk factor for the combined end point and for cardiac death. To further clarify the role of  $\Delta\text{HR}_{1\text{ minute}}$  in predicting adverse events, we also evaluated the risk of death and myocardial infarction of our study population according to the third ( $\Delta\text{HR}_{1\text{ minute}}$  from 12 to 18 bpm) and fourth ( $\Delta\text{HR}_{1\text{ minute}} >18$  bpm) quartiles of its distribution. Other known clinical and EST potential risk factors were also assessed, as was their interaction with  $\Delta\text{HR}_{1\text{ minute}}$  (which was excluded in all cases). The proportional

hazard assumption was tested based on Schoenfeld residuals. No violation was observed. Hazard ratios and 95% CIs were calculated. The role of  $\Delta\text{HR}_{1\text{ minute}}$  on a continuous scale was evaluated as well. Martingale residuals analysis indicated a linear effect. The Cox model was fitted to compute the hazard ratio for  $\Delta\text{HR}_{1\text{ minute}}$ , after adjustment for potential confounders (age, hypertension, hypercholesterolemia, diabetes, obesity, smoking, familial history of coronary artery disease, chronotropic incompetence, resting HR, abnormal HR recovery, exercise-induced frequent arrhythmias, exercise-induced ischemia, exercise-induced change in systolic arterial pressure, personal history of coronary heart disease, number of diseased coronary vessels,  $\beta$ -blocker therapy, and active drug therapy at the time of stress test evaluation). Backward stepwise selection was used, with *P*-to-remove of 0.2. Finally, subgroup analysis was performed by fitting Cox models for  $\Delta\text{HR}_{1\text{ minute}}$  within strata of some relevant patient characteristics.

Stata 8 (StataCorp) was used for computation. All probability values are 2 sided. Probability values for subgroup analysis are unadjusted.

### Results

The study cohort consisted of 458 male patients (mean age  $56 \pm 8.5$  years). At the time of stress test evaluation, 162 patients (35.4%) reported anginal pain during daily life (49% had exertion angina, 18% had angina at rest, and 33% had mixed angina), whereas 296 patients (64.6%) were asymptomatic; 286 patients (62.4%) had a prior MI; and 232 (50.6%) had a prior coronary revascularization. The EST was performed while patients were taking  $\beta$ -blocker therapy or nondihydropyridine calcium channel blocking agents in 142 cases (31.0%), whereas 316 patients (69.0%) were in pharmacological washout. An ischemic response to the EST was observed in 172 patients (37.5%).

The baseline and stress test characteristics of patients, according to whether their  $\Delta\text{HR}_{1\text{ minute}}$  was  $\geq 12$  bpm (above the median) or  $<12$  bpm (equal to or below the median), are shown in Table 1. These 2 groups were similar for most clinical features, with no observed differences in the presence of hypertension, hypercholesterolemia, or diabetes; use of  $\beta$ -blockers, calcium channel blocking agents, or nitrates; resting and peak systolic or diastolic blood pressures; presence of coronary artery disease; or ejection fraction. Compared with subjects with lower  $\Delta\text{HR}_{1\text{ minute}}$ , those with  $\Delta\text{HR}_{1\text{ minute}} \geq 12$  bpm were younger and had a lower resting HR; during exercise, they reached higher values of peak HR and were more likely to present abnormal ST-segment responses. No differences in the percentage of patients with abnormal HR recovery or exercise-induced frequent or complex arrhythmias were observed in the 2 groups.

### Cardiovascular Events

During a median follow-up period of 6 years (interquartile range 3.7 to 9.0 years), 71 patients (15.5%) had adverse cardiac events; 15 (3.3%) died, and 56 (12.2%) developed a nonfatal myocardial infarction, with 6 additional later deaths. Thus, there were 21 total cardiac deaths (4.6%). No patient underwent heart transplantation or implantation of an implantable cardioverter defibrillator during follow-up. We observed 58 adverse events over 1560 person-years among patients with  $\Delta\text{HR}_{1\text{ minute}} \geq 12$  bpm and only 13 over 1370 person-years among patients with  $\Delta\text{HR}_{1\text{ minute}} <12$ . Thus, the event rate per 100 person-years of those with lower  $\Delta\text{HR}_{1\text{ minute}}$  was 0.8 (95% CI 0.5 to 1.4), whereas it was 4.2 (95% CI 3.3

**TABLE 1. Clinical and Exercise-Related Characteristics of Patients According to  $\Delta\text{HR}_{1\text{ minute}}$** 

Variable	$\Delta\text{HR}_{1\text{ minute}} < 12\text{ bpm}$ (n=244)	$\Delta\text{HR}_{1\text{ minute}} \geq 12\text{ bpm}$ (n=214)	P
<b>Clinical characteristics</b>			
Age, y	57.4±8.6	55.4±8.3	0.01
Body mass index, kg/m <sup>2</sup>	26±3.2	25±2.7	<0.01
Hypertension	116 (47.5)	93 (43.4)	0.38
Hypercholesterolemia	148 (60.6)	117 (54.7)	0.19
Diabetes	22 (9.0)	23 (10.7)	0.53
Familial history of coronary artery disease	97 (39.7)	98 (45.8)	0.19
Smoking	193 (79.1)	152 (71.0)	0.04
Prior CABG	45 (18.4)	21 (9.8)	0.008
<b>Angiographic findings</b>			
1-Vessel disease	143 (58.6)	118 (55.1)	0.45
2-Vessel disease	53 (21.7)	58 (27.1)	0.18
3-Vessel disease	48 (19.7)	38 (17.8)	0.60
Ejection fraction	57±10	56±10	0.29
<b>Exercise-related characteristics</b>			
Resting heart rate, bpm	75±14	70±12	<0.0001
Resting systolic blood pressure, mm Hg	129±18	131±18	0.30
Resting diastolic blood pressure, mm Hg	83±8	83±4	0.62
Peak heart rate, bpm	125±21	129±20	0.047
Exercise capacity, METS	6.3±1	6.1±1	0.02
Exercise-induced ST-segment depression $\geq 1\text{ mm}$	75 (30.7)	97 (45.3)	0.001

Values are mean±SD or n (%).

to 5.5) in patients with higher  $\Delta\text{HR}_{1\text{ minute}}$ . The findings show that  $\Delta\text{HR}_{1\text{ minute}} \geq 12\text{ bpm}$  was strongly predictive of adverse outcome (hazard ratio [HR] 5.0, 95% CI 2.7 to 9.1;  $P < 0.0001$ ). Event-free survival curves for both groups are reported in Figure 1A. On a continuous scale, the risk increased linearly by 40% for each increase in  $\Delta\text{HR}_{1\text{ minute}}$  of 5 bpm (HR 1.4, 95% CI 1.2 to 1.5;  $P < 0.001$ ).

The only other predictor of death and myocardial infarction was hypercholesterolemia (HR 1.6, 95% CI 1.0 to 2.7;  $P < 0.05$ ). Abnormal HR recovery showed only a trend for association with cardiac events (HR 1.4, 95% CI 0.7 to 2.8;  $P = 0.30$ ). The following variables were nonpredictive for cardiovascular events: age, hypertension, diabetes, family history of coronary disease, and exercise-induced arrhythmias.

To further elucidate the prognostic role of  $\Delta\text{HR}_{1\text{ minute}}$ , we evaluated the event rate of patients with  $\Delta\text{HR}_{1\text{ minute}}$  from 12 to 18 bpm (third quartile) and  $> 18\text{ bpm}$  (fourth quartile) with respect to those with  $\Delta\text{HR}_{1\text{ minute}} < 12\text{ bpm}$ . The third and fourth quartiles were associated with an HR of 3.3 (95% CI 1.7 to 6.6) and 6.3 (95% CI 3.5 to 11.4), respectively (both  $P < 0.01$ ); the outcome was also found to differ between the third and fourth quartiles ( $P = 0.027$ ; Figure 1B). In a backward stepwise multivariate Cox analysis,  $\Delta\text{HR}_{1\text{ minute}} \geq 12\text{ bpm}$  remained predictive for cardiac adverse events (adjusted HR 5.8, 95% CI 3.1 to 10.9;  $P < 0.0001$ ) after adjustment for hypertension, hypercholesterolemia, diabetes, obesity, smoking, familial history of coronary artery disease, chronotropic incompetence, resting HR, abnormal HR recovery, exercise-induced frequent or complex arrhythmias, exercise-induced ischemia, exercise-induced change in

systolic arterial pressure, personal history of coronary heart disease, number of diseased coronary vessels, coronary revascularization,  $\beta$ -blocker therapy, and active drug therapy at the time of stress test evaluation.

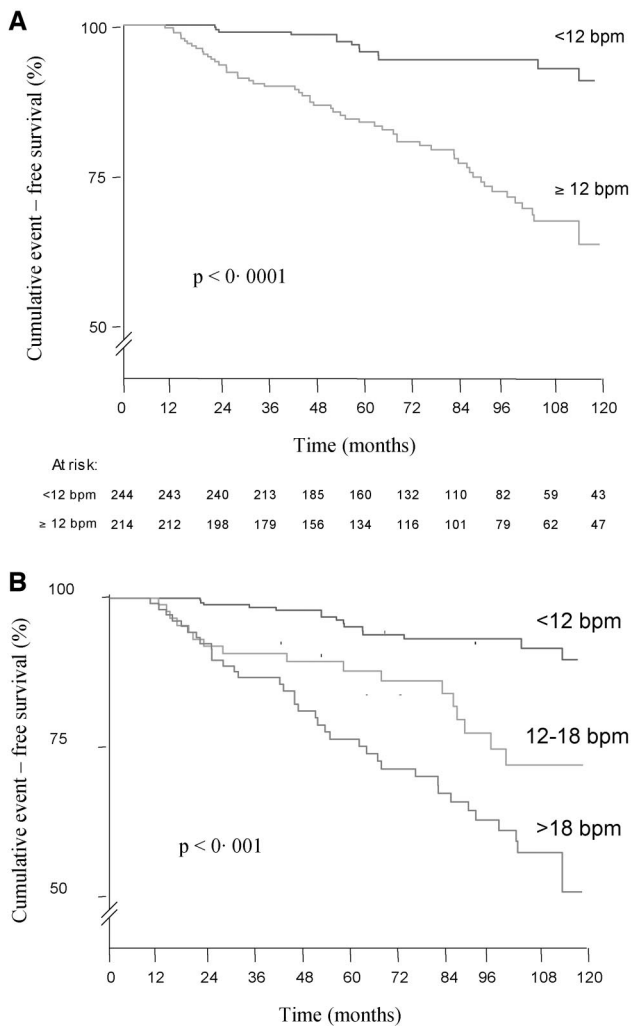
### Subgroup Analysis

The subgroup analyses (Table 2), none of which demonstrated a significant interaction, indicated that the effect of  $\Delta\text{HR}_{1\text{ minute}} \geq 12\text{ bpm}$  was present in each subgroup. Of note,  $\Delta\text{HR}_{1\text{ minute}} \geq 12\text{ bpm}$  was predictive of adverse outcome both in patients taking  $\beta$ -blockers or nondihydropyridine calcium-channel-blocking agents (HR 4.9, 95% CI 1.6 to 14.8;  $P < 0.001$ ) and in those not taking these drugs (HR 5.0, 95% CI 2.4 to 10.2;  $P < 0.0001$ ). Nonetheless, patients taking HR-lowering drugs had lower values for resting HR, peak HR, and peak systolic and diastolic blood pressures than patients not taking these drugs at the time of EST evaluation (all  $P < 0.001$ ), whereas  $\Delta\text{HR}_{1\text{ minute}}$  was not significantly different.

### Cardiac Death

$\Delta\text{HR}_{1\text{ minute}} \geq 12\text{ bpm}$  also showed a strong association with cardiac death (Figure 2A), both with univariate and adjusted Cox analysis (HR 15.6, 95% CI 2.0 to 118.7,  $P < 0.001$  and 13.5, 95% CI 1.8 to 103.7,  $P < 0.001$ , respectively). Given the relatively small number of cardiac deaths, this analysis could be regarded as exploratory.

Survival curves for the third and fourth quartiles of  $\Delta\text{HR}_{1\text{ minute}}$  are shown in Figure 2B. With respect to those with  $\Delta\text{HR}_{1\text{ minute}}$



**Figure 1.** A, Kaplan-Meier event-free (combined for cardiac death and nonfatal myocardial infarction) survival estimate according to  $\Delta HR_{1 \text{ minute}} \geq$  or  $< 12$  bpm. B, Kaplan-Meier event-free (combined for cardiac death and nonfatal myocardial infarction) survival estimate according to change in  $\Delta HR_{1 \text{ minute}}$ .

$< 12$  bpm, HRs for the third and fourth quartiles, respectively, were 14.7 (95% CI 1.7 to 125.9;  $P=0.014$ ) and 21.7 (95% CI 2.7 to 171.7;  $P=0.004$ ), with no significant difference between the 2 groups ( $P=0.48$ ).

## Discussion

The present study demonstrates that a rapid HR increase at the beginning of a standard EST is a strong and independent predictor of cardiac death and nonfatal myocardial infarction in patients with angiographic evidence of coronary artery disease. This finding has conceptual and practical implications.

From the point of view of cardiovascular pathophysiology, the fact that excessive vagal withdrawal is associated with adverse events contributes to the body of evidence indicating that autonomic imbalance increases cardiac risk.<sup>1,5,6,12-14</sup> It also raises the intriguing possibility of autonomic modulation, aimed at increasing vagal activity, as a means to reduce risk.

From the clinical perspective, compared with the complex and relatively expensive autonomic markers currently available,

$\Delta HR_{1 \text{ minute}}$  has significant advantages. They include universal in-hospital availability, simplicity, minimal cost, and above all the fact that valid data are obtained even when patients perform just the first minute of an EST. These considerations also suggest that  $\Delta HR_{1 \text{ minute}}$  could be used for autonomic screening in large populations.

## Rapid HR Increase and Risk Stratification

The underlying rationale for the assessment of possible autonomic imbalance is represented by the fact that sympathetic hyperactivity, as well as reduced vagal activity, increases electrical instability, thus enhancing life-threatening arrhythmias,<sup>15,16</sup> and may even predict rapid progression of coronary artery disease.<sup>17</sup> Indeed, after several experimental studies,<sup>3,4</sup> the value of autonomic imbalance in predicting susceptibility to cardiac death has become evident among patients with diverse cardiovascular diseases.<sup>5-7,18</sup> Recently, HR variability has been used successfully for risk stratification in a large, prospective clinical trial.<sup>19</sup> Measures of autonomic control, however, are only slowly entering the process of risk stratification on a routine basis because of the complexity and cost of most autonomic markers. This mismatch highlights the need for simple tools to allow autonomic screening in large patient populations.

The present data suggest that  $\Delta HR_{1 \text{ minute}}$  might represent a novel autonomic marker that could usefully contribute to a simpler and more accurate identification of high-risk coronary artery disease patients.  $\Delta HR_{1 \text{ minute}}$  relates to outcome whether measured as a continuous or a categorical variable. Although the event rate was only 0.8 per 100 person-years among individuals with  $\Delta HR_{1 \text{ minute}} < 12$  bpm, it was 4.2 in patients with  $\Delta HR_{1 \text{ minute}} \geq 12$  bpm, with a more than 4-fold increase in risk. Also, the risk of events increased linearly with increasing values of  $\Delta HR_{1 \text{ minute}}$ . Along the same lines, patients with  $\Delta HR_{1 \text{ minute}}$  between 12 and 18 bpm and above 18 bpm (third and fourth quartiles, respectively) had a 3- and 6-fold increase in risk for cardiac events compared with patients with  $\Delta HR_{1 \text{ minute}}$  below 12 bpm. A similar pattern was observed when we analyzed the risk for cardiac death. Importantly, the prognostic value of HR response at onset of exercise was present, with a risk of different magnitude, in all subgroups of patients with common risk factors for coronary artery disease (Table 2). Moreover,  $\Delta HR_{1 \text{ minute}}$  was independent of other EST-related clinical or therapeutic variables, such as resting HR, abnormal HR recovery, exercise-induced frequent or complex arrhythmias, hypercholesterolemia, previous myocardial infarction, coronary revascularization, and  $\beta$ -blocker therapy.

The recent report showing that the HR profile during an EST contains prognostic information about the long-term risk for sudden death among apparently healthy individuals points to an important role of the autonomic nervous system in determining cardiovascular outcomes, as does the present study.<sup>20</sup> The main difference between these 2 studies lies in the present finding that the essential information can be provided after just the first minute of exercise, with all the attendant implications for the many patients unable to perform a complete EST.

## Abnormal HR Recovery and Prognosis

A recent series of studies focused on HR recovery after exercise, which was used as a marker of vagal activation;

**TABLE 2. Association Between  $\Delta HR_{1\text{ minute}} \geq 12$  bpm and Adverse Events (Cardiac Death and Nonfatal Myocardial Infarction) in Considered Subgroups and Interaction Analysis**

Variables	No. of Adverse Events/No. of Patients (%)		Relative Risk (95% CI)	P	P for Interaction
	$\Delta HR_{1\text{ minute}} < 12$ bpm	$\Delta HR_{1\text{ minute}} \geq 12$ bpm			
<b>Age</b>					
<65 y	10/196 (5.1)	50/188 (26.6)	5.1 (2.6–10.0)	<0.0001	0.79
$\geq 65$ y	3/48 (6.2)	8/26 (30.8)	6.5 (1.7–24.6)	<0.01	
<b>Previous myocardial infarction</b>					
No	6/90 (6.7)	24/82 (29.3)	4.3 (1.7–10.4)	<0.001	0.64
Yes	7/154 (4.5)	34/132 (25.8)	5.7 (2.5–12.8)	<0.0001	
<b>History of coronary revascularization</b>					
No	8/114 (7.0)	29/112 (25.9)	3.2 (1.5–7.0)	<0.01	0.14
Yes	5/130 (3.8)	29/102 (28.4)	8.3 (3.2–21.3)	<0.0001	
<b>Previous percutaneous coronary intervention</b>					
No	11/152 (7.2)	35/131 (26.7)	3.5 (1.8–6.9)	<0.001	0.08
Yes	2/92 (2.2)	23/83 (27.7)	13.3 (3.1–56.4)	<0.001	
<b>Previous CABG</b>					
No	10/199 (5.0)	51/193 (26.4)	4.8 (2.4–9.5)	<0.0001	0.73
Yes	3/45 (6.7)	7/21 (33.3)	6.0 (1.5–23.3)	<0.01	
<b>Use of <math>\beta</math>-blockers</b>					
No	8/126 (6.3)	38/114 (33.3)	5.3 (2.5–11.3)	<0.0001	0.81
Yes	5/118 (4.2)	20/100 (20.0)	4.7 (1.8–12.6)	<0.001	
<b>EST on therapy</b>					
No	9/162 (5.6)	42/154 (27.3)	5.0 (2.4–10.2)	<0.0001	0.99
Yes	4/82 (4.9)	16/60 (26.7)	4.9 (1.6–14.8)	<0.01	

Cole et al<sup>9,21</sup> showed that an HR decrease  $\leq 12$  bpm within 1 minute of recovery after a symptom-limited Bruce protocol test was a predictor of overall mortality. Patients referred for an EST with radionuclide testing with an abnormal HR recovery had a 4 times greater 6-year mortality rate. These results were confirmed in subsequent studies by the same and other investigators.<sup>9,21–23</sup>

In the present study, HR recovery at the end of exercise did indeed show a trend toward increased risk, which, however, did not reach statistical significance. This may reflect an insufficient power of the study or the use of an end point (combined incidence of infarction and cardiac deaths) that was different from total mortality. Also, HR recovery is clearly related to other chronotropic variables (peak HR and percent peak HR, workload), which suggests that it could be an expression of impaired exercise capacity, which has already been proven to be an independent risk stratifier.<sup>24</sup>

**Clinical Implications**

In the past, several exercise variables have been assessed for prognostic value, and it has become evident that mortality and morbidity can be predicted by the evaluation of ST-segment depression, exercise-induced angina, and exercise capacity. All these variables are strongly related to and affected by the clinical status of the patients. Factors such as poor muscle tone, pulmonary diseases, and self-motivation can reduce functional capacity and limit the possibility of reaching an ischemic or angina threshold. A major strength of the present study lies in the demonstration that  $\Delta HR_{1\text{ minute}}$  is a useful

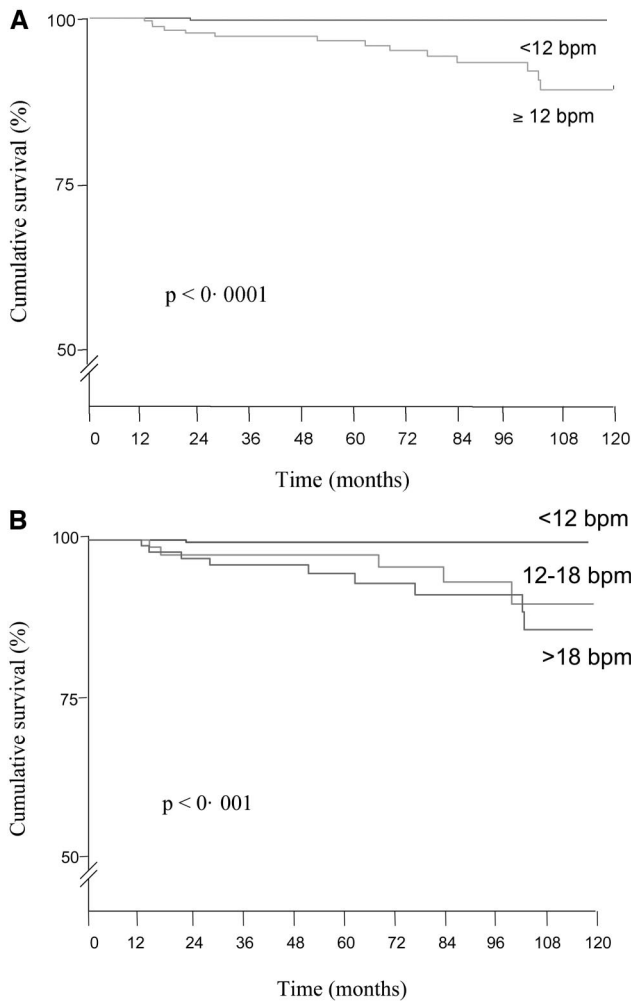
prognostic marker even in the presence of severe limitations of functional capacity because it requires a very short duration of exercise.

A limitation of the study is that the relatively small number of deaths has produced wide CIs, which affect the precision of the HR estimates without questioning the increased risk associated with  $\Delta HR_{1\text{ minute}} \geq 12$  bpm. This is not the case for the strong predictive value of the combined end point (cardiac death and nonfatal myocardial infarction).

The possibility of identifying a significant interaction between  $\Delta HR_{1\text{ minute}}$  and other common risk factors was limited by the size of the present study population. Nevertheless,  $\Delta HR_{1\text{ minute}} \geq 12$  bpm remained a significant predictor of adverse events in all subgroups, even if it was associated with a different degree of risk.

Whether our observations, obtained in a population of patients with documented coronary artery disease who were eligible for exercise stress testing, also apply to other populations, such as a community-based sample, requires further studies. Indeed, the present observations should be confirmed in a separate data set.

There are 2 main practical implications of the present study. One is the availability of a simple test, based on a solid background of experimental pathophysiology and of clinical evidence, that provides a novel autonomic marker capable of identifying patients with coronary artery disease at risk of major events. The other is that the nature of the abnormality unmasked by the test, autonomic imbalance, allows institution of effective preventive interventions beyond the obvious consideration for use of  $\beta$ -blockers. Specifically, exercise training titrated to



**Figure 2.** A, Kaplan-Meier survival estimate according to  $\Delta HR_{1 \text{ minute}} \geq$  or  $< 12$  bpm, limited to cardiac deaths. B, Kaplan-Meier survival estimate according to change in  $\Delta HR_{1 \text{ minute}}$ , limited to cardiac deaths (below the median and 3rd and 4th quartiles).

effectively increase reflex vagal activity has already shown the potential of restoring autonomic balance and of reducing subsequent cardiovascular risk.<sup>25</sup>

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