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 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, predicts increased risk for sudden and nonsudden cardiac death after myocardial infarction 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. 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. The latter 2 studies have brought a new dimension to the inexpensive and frequently used exercise testing. So far, all attempts by ourselves and others 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 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
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 ≥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 β-blocker therapy 1 week in advance.

Assessment of HR Response
During EST, HR increases were calculated at 1 minute after the beginning of exercise (ΔHR1 minute), at the end of each stepwise increment, and at peak exercise. For the purpose of the analysis, ΔHR1 minute was dichotomized according to the median value of its distribution (<12 bpm, ≥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.9

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 ± 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 ΔHR1 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 ΔHR1 minute dichotomized at 12 bpm as a risk factor for the combined end point and for cardiac death. To further clarify the role of ΔHR1 minute in predicting adverse events, we also evaluated the risk of death and myocardial infarction of our study population according to the third (ΔHR1 minute from 12 to 18 bpm) and fourth (ΔHR1 minute ≥18 bpm) quartiles of its distribution. Other known clinical and EST potential risk factors were also assessed, as was their interaction with ΔHR1 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 ΔHR1 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 ΔHR1 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, β-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 ΔHR1 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 ± 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 β-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 ΔHR1 minute was ≥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 β-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 ΔHR1 minute, those with ΔHR1 minute ≥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 ΔHR1 minute ≥12 bpm and only 13 over 1370 person-years among patients with ΔHR1 minute <12. Thus, the event rate per 100 person-years of those with lower ΔHR1 minute was 0.8 (95% CI 0.5 to 1.4), whereas it was 4.2 (95% CI 3.3
to 5.5) in patients with higher ΔHR1 minute. The findings show that ΔHR1 minute ≥12 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 shown in Figure 2B. With respect to those with ΔHR1 minute 5 bpm (fourth quartile) with respect to those with ΔHR1 minute <12 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, ΔHR1 minute ≥12 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, β-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 ΔHR1 minute ≥12 bpm was present in each subgroup. Of note, ΔHR1 minute ≥12 bpm was predictive of adverse outcome both in patients taking β-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 ΔHR1 minute was not significantly different.

### Cardiac Death

ΔHR1 minute ≥12 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 ΔHR1 minute are shown in Figure 2B. With respect to those with ΔHR1 minute...
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; \( \Delta HR_{1 \text{ minute}} \) 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, and may even predict rapid progression of coronary artery disease. Indeed, after several experimental studies, the value of autonomic imbalance in predicting susceptibility to cardiac death has become evident among patients with diverse cardiovascular diseases. Recently, HR variability has been used successfully for risk stratification in a large, prospective clinical trial. 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 \( \Delta HR_{1 \text{ minute}} \leq 12 \text{ bpm} \), it was 4.2 in patients with \( \Delta HR_{1 \text{ minute}} \geq 12 \text{ bpm} \), 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. 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;
Falcone et al Early HR Increase During Exercise Predicts Risk 1963

TABLE 2. Association Between ΔHR1 minute ≥12 bpm and Adverse Events (Cardiac Death and Nonfatal Myocardial Infarction) in Considered Subgroups and Interaction Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Adverse Events/No. of Patients (%)</th>
<th>ΔHR1 minute &lt;12 bpm</th>
<th>ΔHR1 minute ≥12 bpm</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
<th>P for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>10/196 (5.1)</td>
<td>50/188 (26.6)</td>
<td>5.1 (2.6–10.0)</td>
<td>&lt;0.0001</td>
<td>0.79</td>
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<tr>
<td>≥65 y</td>
<td>3/48 (6.2)</td>
<td>8/26 (30.8)</td>
<td>6.5 (1.7–24.6)</td>
<td>&lt;0.01</td>
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<td>Previous myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>6/90 (6.7)</td>
<td>24/82 (29.3)</td>
<td>4.3 (1.7–10.4)</td>
<td>&lt;0.001</td>
<td>0.64</td>
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<td>Yes</td>
<td>7/154 (4.5)</td>
<td>34/132 (25.8)</td>
<td>5.7 (2.5–12.8)</td>
<td>&lt;0.0001</td>
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<td>History of coronary revascularization</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8/114 (7.0)</td>
<td>29/112 (25.9)</td>
<td>3.2 (1.5–7.0)</td>
<td>&lt;0.01</td>
<td>0.14</td>
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<td>Yes</td>
<td>5/130 (3.8)</td>
<td>29/102 (28.4)</td>
<td>8.3 (3.2–21.3)</td>
<td>&lt;0.0001</td>
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<td>Previous percutaneous coronary intervention</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>11/152 (7.2)</td>
<td>35/131 (26.7)</td>
<td>3.5 (1.8–6.9)</td>
<td>&lt;0.001</td>
<td>0.08</td>
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<td>Yes</td>
<td>2/92 (2.2)</td>
<td>23/83 (27.7)</td>
<td>13.3 (3.1–56.4)</td>
<td>&lt;0.001</td>
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<td>Previous CABG</td>
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<tr>
<td>No</td>
<td>10/199 (5.0)</td>
<td>51/193 (26.4)</td>
<td>4.8 (2.4–9.5)</td>
<td>&lt;0.0001</td>
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<td>Yes</td>
<td>3/45 (6.7)</td>
<td>7/21 (33.3)</td>
<td>6.0 (1.5–23.3)</td>
<td>&lt;0.01</td>
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<td>No</td>
<td>8/126 (6.3)</td>
<td>38/114 (33.3)</td>
<td>5.3 (2.5–11.3)</td>
<td>&lt;0.0001</td>
<td>0.81</td>
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<td>Yes</td>
<td>5/118 (4.2)</td>
<td>20/100 (20.0)</td>
<td>4.7 (1.8–12.6)</td>
<td>&lt;0.001</td>
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<tr>
<td>EST on therapy</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>9/162 (5.6)</td>
<td>42/154 (27.3)</td>
<td>5.0 (2.4–10.2)</td>
<td>&lt;0.0001</td>
<td>0.99</td>
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<td>Yes</td>
<td>4/82 (4.9)</td>
<td>16/60 (26.7)</td>
<td>4.9 (1.6–14.8)</td>
<td>&lt;0.01</td>
<td></td>
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</tr>
</tbody>
</table>

Cole et al showed that an HR decrease ≥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.

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.

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 ΔHR1 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 ΔHR1 minute ≥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 ΔHR1 minute and other common risk factors was limited by the size of the present study population. Nevertheless, ΔHR1 minute ≥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 β-blockers. Specifically, exercise training titrated to...
Acknowledgment

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References

Rapid Heart Rate Increase at Onset of Exercise Predicts Adverse Cardiac Events in Patients With Coronary Artery Disease
Colomba Falcone, Maria Paola Buzzi, Catherine Klersy and Peter J. Schwartz

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