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 ($\Delta HR_{1\text{ minute}}$) 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, $\Delta HR_{1\text{ minute}} \geq 12$ 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, $\Delta HR_{1\text{ minute}}$ 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
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 ≥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 symp-
toms, 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. Compari-
sions 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
event 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 minutes, after
adjustment for potential confounders (age, hypertension, hypercho-
lerolemia, 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, accord-
ing 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 hyper-
tension, 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 fre-
quent 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 ΔHR$_{1 \text{minute}}$. The findings show that ΔHR$_{1 \text{minute}} \geq 12$ 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 reported in Figure 1A. On a continuous scale, the risk increased linearly by 40% for each increase in ΔHR$_{1 \text{minute}}$ 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 ΔHR$_{1 \text{minute}}$, we evaluated the event rate of patients with ΔHR$_{1 \text{minute}}$ from 12 to 18 bpm (third quartile) and $>18$ bpm (fourth quartile) with respect to those with ΔHR$_{1 \text{minute}} < 12$ 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, ΔHR$_{1 \text{minute}} \geq 12$ 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.

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

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

Values are mean±SD or n (%).
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;
study lies in the demonstration that ischemic or angina threshold. A major strength of the present functional capacity and limit the possibility of reaching an tone, pulmonary diseases, and self-motivation can reduce clinical status of the patients. Factors such as poor muscle morbidity can be predicted by the evaluation of ST-segment prognostic value, and it has become evident that mortality and in the past, several exercise variables have been assessed for exercise capacity, which has already been proven to be an independent risk stratifier.24

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, work-load), which suggests that it could be an expression of impaired exercise capacity, which has already been proven to be an independent risk stratifier.24

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 ΔHR 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 ΔHR 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 ΔHR minute and other common risk factors was limited by the size of the present study population. Nevertheless, ΔHR 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>ΔHR minute &lt;12 bpm</th>
<th>ΔHR 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>No. of Adverse Events/No. of Patients (%)</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>
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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>No</td>
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<td>29/112 (25.9)</td>
<td>3.2 (1.5–7.0)</td>
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<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>
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<td>Previous percutaneous coronary intervention</td>
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<td>23/83 (27.7)</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>
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<td>7/21 (33.3)</td>
<td>6.0 (1.5–23.3)</td>
<td>&lt;0.01</td>
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<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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<td>EST on therapy</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>
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</table>
effectively increase reflex vagal activity has already shown the potential of restoring autonomic balance and of reducing subsequent cardiovascular risk.  

Acknowledgment

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References


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