Prognostic Value of Heart Rate Increase at Onset of Exercise Testing

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Background—The initial response of heart rate to dynamic exercise has been proposed as having prognostic value in limited studies that have used modalities other than the treadmill. Our aim was to evaluate the prognostic value of early heart rate parameters in patients referred for routine clinical treadmill testing.

Methods and Results—The heart rate rise at the onset of exercise was measured in 1959 patients referred for clinical treadmill testing at the Palo Alto (Calif) Veterans Affairs Medical Center from 1997 to 2004. Multivariable Cox survival analysis was performed for 197 all-cause and 74 cardiovascular deaths that accrued during a mean follow-up of 5.4 ± 2.1 years. Decreased heart rate changes at all initial relative exercise workloads were associated with significantly increased all-cause mortality. The heart rate rise at one-third total exercise capacity, however, was the only early heart rate variable that significantly predicted both all-cause and cardiovascular risk after adjustment for confounders. Failing to reach 1 SD in the heart rate rise at one-third total exercise capacity was associated with a 28% increased all-cause mortality rate (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P = 0.001) and a 35% cardiovascular mortality rate (hazard ratio, 0.65; 95% CI, 0.49 to 0.86; P = 0.003). Of all heart rate measurements considered (initial and recovery), the heart rate increase at peak exercise was the most powerful predictor of cardiovascular prognosis after adjustment for potential confounders. The Duke treadmill score, however, was superior to all heart rate measurements in the prediction of cardiovascular mortality.

Conclusions—In the present study population, a rapid initial heart rate rise was associated with improved survival, but the heart rate rise at peak exercise and other conventional measurements such as exercise capacity and the Duke treadmill score were more powerful predictors of prognosis. (Circulation. 2007;115:468-474.)

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

Clinical researchers have attempted to enhance the ability of the standard exercise test to predict adverse cardiovascular (CV) outcomes. Early efforts focused largely on exercise test responses such as hemodynamic and ECG parameters, leading to the establishment of variables such as exercise capacity and ischemic ST-segment depression as determinants of morbidity and mortality. Recent research, however, has elucidated that the autonomic nervous system also plays a significant role in cardiac arrhythmia and survival.1 Studies of markers for vagal tone and autonomic imbalance have shown that an elevated resting heart rate (HR), impaired HR recovery from exercise, suppressed peak HR, low HR variability, and decreased baroreflex sensitivity predict CV events.2-4

The exercise test provides an opportunity to examine the interaction of the autonomic nervous system and the CV system at various phases of rest, exercise, and recovery. Initial investigations considered the maximal HR response,
equivalents [METs] in nonobese patients) in the first minute of semisupine cycle exercise test in patients with angiographically documented coronary artery disease. The authors reported a hazard ratio of 15 for CV death for an HR rise exceeding 12 bpm in the first minute of exercise. The prognostic value of early HR measurements during treadmill testing remains to be investigated. We aimed to comprehensively evaluate the prognostic value of early HR measurements in 1959 patients referred for treadmill testing for routine clinical indications.

Methods

Study Population

The study population consisted of 1959 subjects referred to the Palo Alto (Calif) Veterans Affairs Medical Center from 1997 to 2004 for clinical treadmill testing who were tested on a device (QUEST, Burdick Corp, Milwaukie, Wis) that enabled continuous digital ECG recording. This represented approximately half of the initial tests referred to our Cardiology Service during this time period, with the choice of devices for testing made only by availability and convenience. Data on coronary risk factors, symptoms, medications, and prior cardiac events were gathered before exercise testing. All subjects gave written informed consent, and the study was approved by the Stanford University Institutional Review Board.

Exercise Testing

Subjects underwent symptom-limited treadmill testing using an individualized ramp treadmill protocol and exercised to maximum exertion. All tests began at a uniform speed of 2 mph at 0% grade. A pretest questionnaire was used to predict a target maximal MET level that would be reached within 10 minutes. HR targets were not used as an end point or to judge the adequacy of the test. Subjects were placed in the supine position immediately after exercise. No medications were changed or stopped before testing, and no test was classified as indeterminate. The senior authors (V.F., J.M.) read all exercise studies. Blood pressure was taken manually every 2 minutes, and exercise capacity (in METs) was calculated from treadmill speed and grade. The Duke treadmill score was calculated by converting METs estimated from the individualized ramp protocol to treadmill score using the Bruce protocol.

ECG Study

Twelve-lead ECG data were recorded at 500 samples per second during the exercise test. Visual ST-segment depression was measured at the J junction; ST slope was measured over the following 60 ms and classified as upsloping, horizontal, or downsloping. The ST response considered was the greatest horizontal or downsloping ST-segment depression in any lead except aVR during exercise or recovery. An abnormal response was defined as ≥1 mm of horizontal or downsloping ST-segment depression.

Mean average HRs were computed for 15-second intervals by sorting the R-R intervals longest to shortest and averaging the middle half. Because all treadmill tests began at an identical speed and grade before increasing according to individualized protocols, multiple early HR parameters were measured to study both uniform absolute workload end points (very early time points at fixed MET levels) and uniform relative workload end points (at peak exertion and by ratio to peak exercise). HRs were computed in the pretest standing state, at 15 seconds of exercise, at 2 METs, at 1 minute of exercise, at one-third the total exercise time, at peak exercise, and at each minute of recovery. The absolute change in HR at each time point was defined as follows:

- ΔHR15 sec is HR at 15 seconds minus standing resting HR.
- ΔHR2METs is HR at 2 METs minus standing resting HR.
- ΔHR1 minute is HR at 1 minute minus standing resting HR.
- ΔHR2 minutes is HR at two minutes minus standing resting HR.
- ΔHR3 minutes is HR at three minutes minus standing resting HR.

resting HR; HR increase is peak HR minus standing resting HR; and HR recovery is peak HR minus HR at 2 minutes of recovery.

Follow-Up

Cardiovascular mortality was the main outcome considered. Mortality data were gathered from the Social Security Death Index and California Death Registry, and cause of death was determined from the registry classification and confirmed by Veterans Affairs medical records. Death status was determined as of March 2006. Cardiovascular mortality was defined as death from a clearly identifiable CV cause or death of subjects with a history of CV disease and no identifiable non-CV cause for death. Classification was made with the observers blinded to the test results and resolved by consensus of 2 observers; conflicts were resolved by the senior author (V.F.).

Statistical Analysis

Clinical and exercise variables for survivors and nonsurvivors were compared through the use of χ² tests (categorical variables) and unpaired t tests (continuous variables). HR measurements were nonnormally distributed and thus were compared by use of the Mann-Whitney U test. To evaluate the relationship between HR measurements and exercise test responses, a correlation matrix was constructed using the Spearman-Rank correlation.

The relationship between tertiles of ΔHR15 sec and CV mortality was evaluated according to the Kaplan-Meier method. Separate multivariable Cox proportional hazards analyses adjusted for age, β-blocker use, history of congestive heart failure, smoking history, and Duke treadmill score were used to evaluate associations between HR measurements and all-cause and CV mortality. All continuous variables were standardized and included as such in Cox survival analysis to avoid artifacts of dichotomization, and hazard ratios are reported for a 1-SD increase in each variable. Given 197 total all-cause deaths, 74 total CV deaths, and a 2-sided error rate of 5%, we estimated that the study had a statistical power of 80% to detect a 22% change in the relative risk of all-cause mortality and a 38% change in the relative risk of CV mortality per SD of each HR parameter. Discriminative accuracy was assessed through the right-sided concordance index (C index), and predictive power was evaluated using χ² analysis of deviance. The proportional hazards assumption was evaluated with the scaled Schoenfeld residual, and linearity of associations was assessed with the Martingale residual. No violations were observed.

Survival analyses were repeated in the subgroup of subjects with documented coronary artery disease (prior coronary intervention, prior myocardial infarction, abnormal coronary catheterization, typical angina, or abnormal ST-segment response to exercise). In this subgroup analysis, we estimated that the present study had a statistical power of 80% to detect a 35% change in relative risk of all-cause mortality and a 49% change in the relative risk of CV mortality per SD of each HR parameter. No adjustments were made for multiple comparisons. Subjects were not removed from observation at the time of interventions or infarction because this information was not available. Statistical analyses were performed with NCSS (NCSS, Inc, Salt Lake City, Utah) and the Design and Hmisc libraries in S-Plus 6.0 (Insightful Corp, Seattle, Wash). A 2-sided value of P<0.05 was considered statistically significant.

The authors had full access to the data and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

The study cohort consisted of 1959 subjects (mean age, 57±12 years); 95% were male. A subgroup analysis was performed for 578 subjects with documented coronary artery disease (prior coronary intervention, prior myocardial infarction, abnormal coronary catheterization, typical angina, or abnormal ST-segment response to exercise). Baseline char-
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire Population</th>
<th>Subjects With CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivors (n=1762)</td>
<td>All-Cause Deaths (n=197)</td>
</tr>
<tr>
<td>Age</td>
<td>56.6±11.6</td>
<td>65.1±12.2*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131±19</td>
<td>136±22*</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>88 (5)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>261 (15)</td>
<td>37 (19)</td>
</tr>
<tr>
<td>Claudication, n (%)</td>
<td>80 (5)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>52 (3)</td>
<td>28 (14)*</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>44 (2)</td>
<td>11 (6)*</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>679 (39)</td>
<td>100 (51)*</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical, n (%)</td>
<td>188 (11)</td>
<td>34 (17)*</td>
</tr>
<tr>
<td>Atypical, n (%)</td>
<td>469 (27)</td>
<td>46 (23)</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>393 (22)</td>
<td>52 (26)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>80 (5)</td>
<td>85 (4)</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease. Results are presented as mean±SD when appropriate.

*P<0.05 vs survivors in each population.
†P<0.05 vs survivors and subjects who died of non-CV causes in each population.

Characteristics for both groups according to outcome are described in Table 1. At the time of testing, 222 subjects (11.3%) reported typical angina pectoris, and 515 subjects (26.3%) had atypical chest pain symptoms. There were 278 subjects who had suffered a prior myocardial infarction (14.2%), and a similar number (14.1%) had been revascularized. There were 298 diabetics (15%), 497 subjects (25.4%) were current smokers at the time of testing, and 1276 subjects (65.1%) had ever smoked. There were 465 subjects (23.7%) who were taking β-blockers at the time of enrollment.

Subjects were followed up for a mean period of 5.4±2.1 years, during which time there were 197 total deaths and 74 CV deaths. Nonsurvivors were significantly older; had higher resting systolic blood pressures, prevalence of congestive heart failure, β-blocker use, and angina, and were more likely to have ever smoked than survivors (P<0.05). In the subgroup with a documented history of coronary artery disease, nonsurvivors were significantly older and had a significantly higher prevalence of congestive heart failure, angina, and β-blocker use than survivors (P<0.05).

Exercise Test Responses

Exercise test responses according to outcome status and coronary artery disease status are described in Table 2. Nonsurvivors achieved lower estimated MET values and Borg perceived exertion scores and exhibited lower Duke treadmill scores than survivors; subjects who died of CV causes also had a higher prevalence of abnormal ST-segment deviation than survivors and subjects who died of non-CV causes (P<0.05). Similar differences in exercise responses between subjects who died of CV causes were observed in the coronary artery disease subgroup (Table 2).

TABLE 2. Exercise Test Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire Population</th>
<th>Subjects With CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivors (n=1762)</td>
<td>All-Cause Deaths (n=197)</td>
</tr>
<tr>
<td>Exercise capacity, METs</td>
<td>8.8±3.4</td>
<td>6.2±3.2*</td>
</tr>
<tr>
<td>ST-segment deviation ≥1 mm, n (%)</td>
<td>177 (9)</td>
<td>155 (8)</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurred</td>
<td>153 (9)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Stopped the test</td>
<td>61 (3)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Duke treadmill score</td>
<td>7.3±5.2</td>
<td>3.5±5.9*</td>
</tr>
<tr>
<td>Borg's perceived exertion score</td>
<td>17.0±2.4</td>
<td>16.7±2.3*</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease. Results are presented as mean±SD when appropriate.

*P<0.05 vs survivors in each population.
†P<0.05 vs survivors and subjects who died of non-CV causes in each population.
Heart Rate Responses and Outcome

The HR responses to exercise according to selected outcomes and coronary artery disease status are described in Table 3. Survivors had significantly greater ΔHR at 1 minute and one third of exercise, HR increase at peak exercise, and HR recovery at 2 minutes than nonsurvivors, regardless of coronary artery disease status \((P<0.05)\). There was no significant difference in median values of ΔHR$_{15}$ seconds or ΔHR$_{2METs}$. 

The Spearman-Rank correlation between HR variables and exercise responses is shown in Table 4. Early HR variables were modestly interrelated \((r=-0.33 \text{ to } 0.71, P<0.001)\) and correlated with HR increase at peak exercise \((r=0.31 \text{ to } 0.58, P<0.05)\) but did not significantly correlate with other exercise test variables considered. HR increase at peak exercise was strongly correlated with HR recovery \((r=0.72, P<0.001)\) and peak estimated METs \((r=0.63, P<0.001)\) and weakly correlated with perceived exertion score \((r=0.16, P<0.001)\).

Results of Kaplan-Meier analysis of the relationship between ΔHR$_{1}$ minute and CV mortality are shown in Figure 1. There was a significant association between tertiles of ΔHR$_{1}$ minute and CV mortality in the population as a whole, with a protective effect observed for greater ΔHR$_{1}$ minute; there was a similar nonsignificant trend in the subgroup of subjects with coronary artery disease. Results of multivariable Cox survival analysis are shown in Figures 2 and 3. Lower ΔHR$_{15}$ seconds and ΔHR$_{1}$ minute were significantly associated with increased all-cause mortality \((P<0.05)\) and showed similar nonsignificant trends toward increased CV mortality in the population as a whole. A decrease of 1 SD in ΔHR$_{15}$ seconds was associated with a 28% increase in all-cause mortality \((\text{hazard ratio, 0.72; 95\% CI, 0.61 \text{ to } 0.85; } P<0.001)\) and a 35% increase in CV death \((\text{hazard ratio, 0.65; 95\% CI, 0.49 \text{ to } 0.86; } P=0.003)\).

In subjects with coronary artery disease, ΔHR$_{15}$ seconds was the only early HR parameter that significantly predicted prognosis \((P<0.05)\). Reduced ΔHR$_{15}$ seconds and ΔHR$_{1}$ minute, however, were associated with nonsignificant trends toward increased all-cause and CV mortality. The HR increase at the uniform absolute workload of 2 METs \((\Delta \text{HR}_{2\text{METs}})\) was not significantly associated with all-cause or CV mortality in the population as a whole or in subjects with coronary artery disease.

After adjustment for potential confounders, the HR increase at peak exercise and HR recovery at 2 minutes significantly predicted all-cause and CV mortality in both the population as a whole and the subgroup of subjects with coronary artery disease. Of all HR change variables considered, the HR increase at peak exercise was the most powerful and accurate predictor of all-cause \((\text{hazard ratio, 0.62; 95\% CI, 0.52 \text{ to } 0.73; } P<0.001)\) and CV \((\text{hazard ratio, 0.68; 95\% CI, 0.52 \text{ to } 0.89; } P=0.005)\) mortality in multivariable Cox survival analysis. The Duke treadmill score was a marginally more powerful and accurate predictor of CV mortality than
the HR increase at peak exercise (χ², 12.7 versus 8.0; C index, 0.63 versus 0.61 for Duke treadmill score and HR increase at peak exercise, respectively). In an alternative multivariable Cox regression substituting peak estimated METs for the Duke treadmill score, peak METs performed similarly.

Discussion

The present study reports the largest and most comprehensive evaluation of the early HR response to treadmill testing in a clinical population. We did not find that a rapid HR rise in the first minute of exercise is predictive of increased CV mortality, as was recently reported for a semisupine cycle ergometry protocol. This was true in both a general population referred for clinical exercise testing and a subset of these subjects with documented coronary artery disease. In fact, we have demonstrated the contrary to be the case, i.e., that a greater rise in HR early in exercise was associated with increased survival.

Although we discovered several HR parameters that predict survival, we found that they all are associated with the degree of HR increase with exercise that ultimately proved to be the most powerful HR prognostic indicator. This absolute change from baseline likely reflects the level of basal vagal tone and the capacity of the heart to respond to maximal sympathetic drive after parasympathetic withdrawal. Heart rate increase was directly related to HR recovery, further implicating the role of both components of the autonomic nervous system in the slowing of HR after exercise.

Our results contrast with a recently published report that found that a rapid HR rise in the first minute of a cycle ergometry exercise protocol was associated with worse outcomes. Differences in exercise protocols between the 2 studies might have contributed to these divergent findings. In their study, Falcone et al used a nonindividualized semisupine cycle protocol and measured the HR change at 1 minute at a uniform absolute workload (25 W, roughly 2 METs in a 70-kg person). Patients with a rapid HR rise at this fixed absolute workload ultimately achieved lower total METs, and the HR change in this protocol may simply be a surrogate...
marker for exercise capacity. We used an individualized ramp treadmill protocol, which, in addition to its demonstrated superiority in the determination of the relationship between work rate and oxygen uptake, requires a similar relative workload for each subject at each time point. Because the relative workload has been shown to be strongly associated with the physiological HR response to exercise, this protocol minimizes possible differences in HR that arise solely from different relative exercise workloads. We believe that our individualized ramp protocol adequately controls for differences in exercise capacity. Nevertheless, to control for possible force function differences between these exercise protocols, we measured HR changes at uniform absolute exercise workloads, at uniform relative exercise workloads, and at uniform time intervals in the individualized protocol. We found that a greater early rise in HR in response to uniform relative exercise workloads and uniform time intervals in the individualized protocol was associated with better prognosis. We found no association between the HR rise at the uniform absolute workload of 2 METs and prognosis.

Falcone et al recently reported a significantly increased risk for CV mortality in subjects with coronary artery disease who had a $\Delta HR_{min}$ of $\geq 12$ during nonindividualized semisupine cycle testing. They postulated that this early HR change was associated with an increased risk of death related to sympathetic hyperactivity or premature vagal withdrawal. Furthermore, they postulated that a blunted HR rise in exercise is a marker for persistent protective parasympathetic tone that antagonizes the deleterious effects of the adrenergic system.

On the other hand, others believe that a rapid HR rise is a marker of rapid vagal withdrawal and high resting vagal tone. In an interesting approach, Almeida et al studied the response to a 4-second exercise test. They defined the cardiac vagal tone index as the ratio of the R-R intervals at rest and at 4 seconds of resistance-free maximal effort stationary cycling. The cardiac vagal tone reflects vagotonia and CV fitness and importantly was found to correlate with HR recovery, another prognostic indicator thought to partially reflect vagal activity. The authors postulated that a brisk HR rise reflects the rapid removal of vagal tone, not the early application of sympathetic activity. This hypothesis is supported by pharmacological experiments in which blockade of the parasympathetic system with atropine blunts the cardiac vagal tone, whereas inhibition of the sympathetic system with propranolol fails to suppress the HR rise in this exercise interval. Taken together, these findings suggest that the HR profile early in exercise is dominated by the parasympathetic nervous system. The relationship between autonomic modulation, early HR changes in response to exercise, and prognosis remains to be demonstrated in humans, however.

**Study Limitations**

Our present study population was predominantly male and older, and these results may not be generalizable to other populations. Although our coronary artery disease subgroup had signs and symptoms of coronary artery disease, only $\approx 20\%$ had angiographically confirmed coronary artery disease. In addition to the differences in exercise protocols described above, other methodological issues between the present study and the report by Falcone et al may make direct comparisons between the 2 studies difficult. Unlike the Falcone et al investigators, we did not provide a pharmacological washout before enrollment, nor did we have access to revascularization data; thus, we were unable to evaluate the predictive power of the early chronotropic parameters after adjusting for these factors. The present study was a retrospective, hypothesis-generating study designed primarily to evaluate associations between chronotropic parameters and outcome. As is the case in all exploratory retrospective cohort studies, the possibility remains that unmeasured clinical factors were unaccounted for. Prospective studies are needed.
to confirm these results and to elucidate the pathophysiological basis for these findings.

Clinical Implications
The present study shows that the HR changes early in exercise are weakly associated with CV mortality and do not add to conventional measurements or the Duke treadmill score. Contrary to prior evidence, it appears that a faster rise predicts improved survival and may represent overall resting vagal tone and its natural release. Several early time points for HR measurement were prognostic, but the total HR rise ultimately was the most powerful HR variable for predicting CV mortality. Future studies should continue to investigate additional markers for autonomic tone, and particular attention should be paid to the very onset of exercise. For the time being, the initial HR response to the standard exercise test should not be used for clinical decision making.

Disclosures
Dr Hadley is an employee of Cardiac Science. The other authors report no conflicts.

References