

## Original Scientific Paper

# Comparison of the chronotropic response to exercise and heart rate recovery in predicting cardiovascular mortality

Jonathan Myers, Swee Y. Tan, Joshua Abella, Vikram Aleti and Victor F. Froelicher

Cardiology Division, Veterans Affairs Palo Alto Health Care System, Stanford University, Palo Alto, California, USA

Received 11 August 2006 Accepted 4 January 2007

**Background** Both an impaired capacity to increase heart rate during exercise testing (chronotropic incompetence), and a slowed rate of recovery following exercise (heart rate recovery) have been shown to be associated with all-cause mortality. It is, however, unknown which of these responses more powerfully predicts risk, and few data are available on their association with cardiovascular mortality or how they are influenced by  $\beta$ -blockade.

**Methods** Routine symptom-limited exercise treadmill tests performed on 1910 male veterans at the Palo Alto Veterans Affairs Medical Center from 1992 to 2002 were analyzed. Heart rate was determined each minute during exercise and recovery. Chronotropic incompetence was defined as the inability to achieve  $\geq 80\%$  of heart rate reserve, using a population-specific equation for age-predicted maximal heart rate. An abnormal heart rate recovery was considered to be a decrease of  $<22$  beats/min at 2 min in recovery. Cox proportional hazards analyses including pretest clinical data, chronotropic incompetence, heart rate recovery, the Duke Treadmill Score (abnormal defined as  $<4$ ), and other exercise test responses were performed to determine their association with cardiovascular mortality.

**Results** Over a mean follow-up of  $5.1 \pm 2.1$  years, there were 70 deaths from cardiovascular causes. Both abnormal heart rate recovery and chronotropic incompetence were associated with higher cardiovascular mortality, a lower exercise capacity, and more frequent occurrence of angina during exercise. Both heart rate recovery and chronotropic incompetence were stronger predictors of risk than pretest clinical data and traditional risk markers. Multivariately, chronotropic incompetence was similar to the Duke Treadmill Score for predicting cardiovascular mortality, and was a stronger predictor than heart rate recovery [hazard ratios 3.0 (95% confidence interval 1.9–4.9), 2.8 (95% confidence interval 1.7–4.8), and 2.0 (95% confidence interval 1.1–3.5) for abnormal Duke Treadmill Score, chronotropic incompetence, and abnormal heart rate recovery, respectively]. Having both chronotropic incompetence and abnormal heart rate recovery strongly predicted cardiovascular death, resulting in a relative risk of 4.2 compared with both responses being normal. Beta-blockade had minimal impact on the prognostic power of chronotropic incompetence and heart rate recovery.

**Conclusion** Both chronotropic incompetence and heart rate recovery predict cardiovascular mortality in patients referred for exercise testing for clinical reasons. Chronotropic incompetence was a stronger predictor of cardiovascular mortality than heart rate recovery, but risk was most powerfully stratified by these two responses together. The simple application of heart rate provides powerful risk stratification for cardiovascular mortality from the exercise test, and should be routinely included in the test report. *Eur J Cardiovasc Prev Rehabil* 14:215–221 © 2007 The European Society of Cardiology

European Journal of Cardiovascular Prevention and Rehabilitation 2007, 14:215–221

Keywords: autonomic function, exercise testing, heart rate recovery, mortality

Correspondence to Dr Jonathan Myers, PhD, Cardiology Division (111C), VA Palo Alto Health Care System, 3801 Miranda Ave, Palo Alto, CA 94304, USA  
Tel: +1 650 493 5000 ext. 64661; fax: +1 650 852 3473;  
e-mail: djr993@aol.com

## Introduction

The standard exercise test is one of the most powerful tools for risk stratifying patients with or suspected of having cardiovascular disease [1,2]. Although the

electrocardiographic response, symptoms, and exercise tolerance have traditionally been applied to estimate risk for cardiac events or mortality, recent studies have observed that heart rate provides both independent and complementary information for estimating prognosis [3,4]. Both an attenuated heart rate response to exercise [termed chronotropic incompetence (CI)] and slowed recovery of heart rate following exercise [termed heart rate recovery (HRR)] have been associated with all-cause mortality and cardiac events [5–12]. The observation made over the last decade that simply applying heart rate during and after an exercise test powerfully stratifies risk has provided support for the continued use of the standard exercise test despite advances in related technologies [1–4,13].

Few previous studies have, however, measured both CI and HRR in predicting mortality; thus, their relative prognostic power is uncertain. It is also uncertain how these two responses compare with the Duke Treadmill Score (DTS), a widely used and established marker of risk. In addition, although  $\beta$ -blockade has a marked effect on resting and exercise heart rate, this issue has only recently been explored in the context of CI, HRR and outcomes [6,10,12]. The majority of previous studies have also focused on all-cause mortality; the extent to which CI and HRR responses predict cardiovascular mortality is less certain. The aim of this study was to assess the relative prognostic utility of CI and HRR in predicting cardiovascular mortality in patients referred for exercise testing for clinical reasons. A secondary purpose was to evaluate the effect of  $\beta$ -blockade on the association between CI, HRR and mortality.

## Methods

### Population

The study sample consisted of 1910 patients who underwent maximal exercise testing for clinical reasons at the Veterans Affairs Palo Alto Medical Center between 1992 and 2002. Historical information that was recorded at the time of the exercise test included previous myocardial infarction (MI) by history or Q wave, heart failure, hypertension, family history of heart disease, hypercholesterolemia ( $> 220$  mg/dl), claudication, chronic obstructive pulmonary disease, diabetes, stroke, smoking status (current, past, and pack-years), use of digoxin or a  $\beta$ -blocker, and cardiac arrhythmias. The presence of each condition was defined by history and medical record review at the time of the test. The sample was 78% Caucasian, 13% African-American, and 6% Hispanic.

### Exercise testing

Patients underwent symptom-limited treadmill testing using an individualized ramp treadmill protocol [14]. A pretest questionnaire was used to set an individualized

ramp rate on the treadmill such that test duration was targeted between 8 and 12 min [15]. Patients did not perform a cool-down walk but were placed supine as soon as possible after exercise. Standard criteria for termination were employed, including moderately severe angina,  $> 2.0$  mm abnormal ST depression, a sustained drop in systolic blood pressure, or serious rhythm disturbances [1]. The Borg 6–20 perceived exertion scale was used to quantify degree of effort [16]. Visual ST-segment depression was measured at the J-junction, corrected for pre-exercise ST depression, and considered abnormal if it was  $\geq 1.0$  mm and horizontal or downsloping. Blood pressure was taken manually and exercise capacity [in metabolic equivalents (METs)] was estimated from peak treadmill speed and grade.

Heart rate was measured supine, standing, during each minute of exercise, at maximum exercise, and in recovery at 1, 2, 3, and 5 min. HRR was defined as (maximum heart rate – heart rate at specified time period after exercise) and represented the drop in heart rate during that time interval. An abnormal HRR was considered a decrease of  $< 22$  beats after 2 min of recovery as we previously reported this criteria to be the optimal HRR cut point for predicting mortality in our population [10]. CI was defined as the inability to achieve 80% of heart rate reserve, using the regression equation that best fit the population [ $174 - 0.54$  (age)]. Thus, the equation used to define percentage heart rate reserve was  $[(\text{maximal heart rate} - \text{resting heart rate}) / (174 - 0.54 \times \text{age}) - (\text{resting heart rate}) \times 100]$ . The DTS was calculated as  $[\text{exercise capacity in METs} - (5 \times \text{maximal ST depression}) - (4 \times \text{angina index})]$  (angina index defined as 0 = no angina; 1 = nonlimiting angina; and 2 = exercise-limiting angina). A DTS  $< 4$  was considered abnormal. No test was classified as indeterminate [17], medications were not withheld, and age-predicted maximal target heart rates were not used as end points. The exercise tests were performed, analyzed, and reported using a standard protocol incorporating a computerized database with all definitions and measurements prospectively defined [18].

### Outcomes

The main outcome variable was cardiovascular mortality; noncardiovascular deaths were also recorded. The California Health Department Service and Social Security Death Indices were used to ascertain the vital status of each patient as of 31 December 2004. Accuracy of deaths was reviewed by two clinicians blinded to exercise test results and confirmed using the Veterans Affairs computerized medical records.

### Statistical analysis

NCSS software (Kayesville, Utah, USA) was used for all statistical analyses. Unpaired *t*-tests were used for comparisons of continuous variables, and  $\chi^2$  tests were

used to compare dichotomous variables between those patients with normal and abnormal HRR and CI. Survival analysis was performed using Cox proportional hazards analysis to determine which clinical and exercise test variables were independently and significantly associated with time to cardiovascular death. Analyses were adjusted for age. Automatic selection of variables was performed with a *Z* value cut-off of 2 and 20 iterations. Hazard ratios were calculated along with their 95% confidence intervals. The proportional hazards assumption was evaluated and confirmed using the scaled Schoenfeld residual.

Initially, age-adjusted CI and HRR were assessed separately with pretest variables (including the dichotomous variables history of angina, smoking, diabetes, hypertension, and hyperlipidemia). Exercise test variables were assessed in a second analysis. The DTS (which incorporates exercise capacity) was used as a standard to compare the relative prognostic power of CI and HRR. Given the limited number of cardiovascular outcomes (70), no more than seven independent variables were used in the multivariate models. Kaplan–Meier curves using normal and abnormal HRR, DTS, and CI were constructed; the log-rank test was used to compare these responses at specified cut points. Receiver operator characteristic (ROC) curves were constructed to compare CI and abnormal HRR in terms of their discriminatory accuracy in predicting survival, using the abnormal cut points mentioned above. The ROC curves were compared using the *Z*-statistic.

## Results

The mean age of the population was  $57 \pm 12$  years and the mean body mass index was  $29 \pm 5 \text{ kg/m}^2$  (Table 1). Less than 3% were taking digoxin and approximately one-fifth were taking  $\beta$ -blockers. Cardiovascular disease was present in 526 of the patients (28% of the population). Of the 1910 patients, 167 (8.7%) had an abnormal HRR. Those with an abnormal HRR response were older and had a greater prevalence of heart failure, hypertension, and  $\beta$ -blocker use than those with a normal HRR. During exercise, patients with an abnormal HRR had a lower maximal heart rate and systolic blood pressure, lower exercise capacity ( $9.3 \pm 3.3$  vs.  $6.9 \pm 2.9$  METs,  $P < 0.0001$ ), a lower DTS, and a greater proportion of patients with abnormal HRR exhibited CI.

Clinical and exercise test responses of patients with and without CI are presented in Table 2; 526 patients (27.5%) demonstrated CI. Patients with CI more commonly had a history of myocardial infarction, heart failure, stroke, hypertension, claudication, smoking, and diabetes. Exercise test responses also differed between those with and without CI, including a lower exercise capacity, lower DTS, slower HRR, and more frequent occurrence of ST

**Table 1** Baseline and exercise test data in patients with normal vs. abnormal heart rate recovery

	Total ( <i>n</i> = 1910)	Normal HRR ( <i>n</i> = 1743)	Abnormal HRR ( <i>n</i> = 167)	<i>P</i> value
Demographic and historical data				
Age	$57 \pm 12$	$57 \pm 11$	$60 \pm 12$	0.002
BMI	$29.4 \pm 5.3$	$28.9 \pm 5.2$	$29.2 \pm 5.3$	0.60
Previous MI	145 (7.6)	127 (7.3)	18 (10.8)	0.12
History of typical angina	175 (9.2)	154 (8.8)	21 (12.6)	0.12
Heart failure	61 (3.2)	51 (2.9)	10 (6.0)	0.04
Stroke	46 (2.4)	42 (2.4)	4 (2.4)	0.99
Hypertension	824 (43)	738 (4.2)	86 (51.5)	0.03
Claudication	71 (3.7)	55 (3.1)	16 (9.6)	0.002
Smoking	1079 (56.5)	975 (55.9)	104 (62.3)	0.12
Diabetes	259 (13.6)	230 (13.2)	29 (17.4)	0.15
Digoxin	52 (2.7)	44 (2.5)	8 (4.8)	0.13
Beta-blocker	374 (19.6)	324 (18.6)	54 (32.3)	0.001
LBBB	12 (0.6)	8 (0.4)	4 (2.4)	0.02
RBBB	68 (3.6)	59 (3.4)	9 (5.4)	0.19
Exercise test responses				
Peak HR (beats/min)	$143 \pm 23$	$146 \pm 22$	$118 \pm 26$	0.0001
Peak SBP (mmHg)	$175 \pm 27$	$177 \pm 26$	$163 \pm 30$	0.0001
Peak METs	$9.0 \pm 3.3$	$9.3 \pm 3.3$	$6.9 \pm 2.9$	0.0001
Duke Treadmill Score	$7.7 \pm 5.1$	$7.9 \pm 5.2$	$5.6 \pm 4.7$	0.0001
HRR (beats/min)	$43 \pm 19$	$45 \pm 13$	$14 \pm 8.4$	0.0001
ST $\downarrow$ > 1 mm, no. (%)	151 (7.9)	136 (7.8)	15 (9.0)	0.54
Angina, no. (%)	193 (10.1)	179 (10.3)	14 (8.4)	0.12
CI, no. (%)	526 (27.5)	414 (23.8)	152 (91.0)	0.0001

Data are shown as mean  $\pm$  SD or no. of patients (%). BMI, body mass index; CI, chronotropic incompetence; HR, heart rate; HRR, heart rate recovery at 2 min after exercise; LBBB, left bundle branch block; MI, myocardial infarction; Peak METs, peak estimated metabolic equivalents; RBBB, right bundle branch block; SBP, systolic blood pressure; ST  $\downarrow$ , ST depression.

depression and angina among those with CI. A total of 134 patients exhibited both CI and abnormal HRR.

## Survival results

Over a mean follow-up of  $5.1 \pm 2.1$  years, there were 157 deaths; 70 (45%) were cardiovascular and 87 (55%) were noncardiovascular. Most historical data and exercise test responses were significantly different between those who died of cardiovascular causes compared with the remainder of the cohort. Those who died of cardiovascular causes had a greater prevalence of cardiovascular disease, and during exercise testing more frequently exhibited ST depression, CI, abnormal HRR, angina, and had lower exercise capacity and lower DTS values. Notably, 8.2% of those with CI died of cardiovascular causes, whereas 10.2% of those with abnormal HRR died of cardiovascular causes during the follow-up.

In age-adjusted multivariate analyses, CI and HRR were stronger predictors of risk than pretest risk markers (history of angina, smoking, diabetes, hyperlipidemia, hypertension) and exercise test responses (occurrence of angina, ST depression) [hazard ratios 4.9 (95% confidence interval 2.8–8.5) and 4.0 (95% confidence interval 2.2–7.4) for CI and HRR, respectively,

**Table 2** Baseline and exercise test data in patients with and without chronotropic incompetence

	Total (n=1910)	Normal chronotropic response (n=1384)	Chronotropic incompetence (n=526)	P value
<b>Demographic and historical data</b>				
Age	57 ± 12	57 ± 12	58 ± 12	0.40
BMI	29.4 ± 5.3	29.1 ± 5.2	28.7 ± 5.1	0.17
Previous MI	145 (7.6)	76 (5.5)	69 (13.1)	<0.0001
History of typical angina	175 (9.2)	95 (6.9)	80 (15.2)	<0.0001
Heart failure	61 (3.2)	35 (2.5)	26 (4.9)	0.008
Stroke	46 (2.4)	22 (1.6)	24 (4.6)	0.0003
Hypertension	824 (43.1)	517 (37.4)	307 (58.4)	<0.0001
Claudication	72 (3.8)	18 (1.3)	54 (10.3)	<0.0001
Smoking	1079 (56.5)	753 (54.4)	326 (62.0)	<0.003
Diabetes	254 (13.3)	165 (11.9)	94 (17.9)	0.013
Digoxin	52 (2.7)	26 (1.9)	26 (4.9)	0.0004
Beta-blocker	358 (18.7)	157 (11.3)	221 (42.0)	<0.0001
LBBB	12 (0.6)	4 (0.2)	8 (1.5)	0.05
RBBB	68 (3.6)	41 (3.0)	27 (5.1)	0.03
<b>Exercise test responses</b>				
Peak HR (beats/min)	144 ± 24	154 ± 16	114 ± 14	<0.0001
Peak SBP (mmHg)	175 ± 27	179 ± 26	165 ± 27	<0.0001
Peak METs	9.1 ± 3.3	9.8 ± 3.3	7.1 ± 2.5	<0.0001
Duke Treadmill Score	7.7 ± 5.2	8.6 ± 4.9	5.3 ± 4.9	<0.0001
HRR (beats/min)	43 ± 15	47 ± 14	32 ± 13	<0.0001
ST ↓ > 1 mm, no. (%)	151 (7.9)	100 (7.2)	51 (9.7)	0.09
Angina, no. (%)	193 (10.1)	119 (8.6)	74 (14.1)	<0.0001

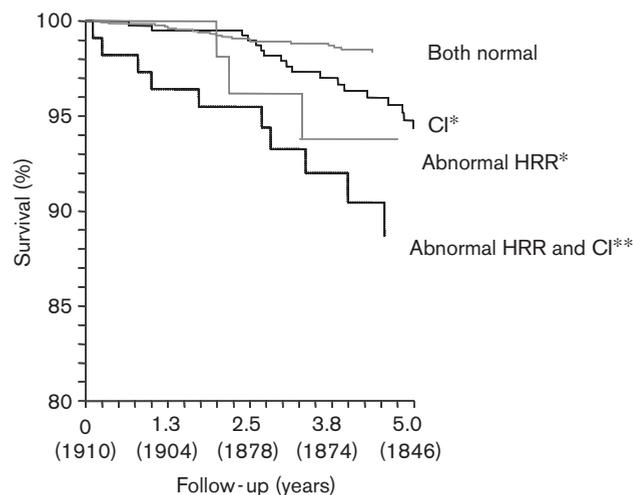
Data are shown as mean ± SD or no. of patients (%). BMI, body mass index; HR, heart rate; HRR, heart rate recovery at 2 min after exercise; LBBB, left bundle branch block; MI, myocardial infarction; Peak METs, peak estimated metabolic equivalents; RBBB, right bundle branch block; SBP, systolic blood pressure; ST ↓, ST depression.

**Table 3** Age-adjusted multivariate predictors of cardiovascular mortality

Variable	Hazard ratio	95% confidence interval	P value
Duke Treadmill Score	3.0	1.9–4.9	<0.0001
Chronotropic incompetence	2.8	1.7–4.8	<0.0001
Heart rate recovery	2.0	1.1–3.5	0.02

Abnormal response for chronotropic incompetence was defined as inability to achieve ≥ 80% of age-predicted maximal heart rate reserve; for heart rate recovery, abnormal was considered ≤ 22 beats/min at 2 min in recovery, and an abnormal Duke Treadmill Score was defined as < 4.

$P < 0.001$ ]. Age-adjusted multivariate predictors of cardiovascular mortality comparing presence of confidence interval, abnormal HRR, and abnormal DTS are presented in Table 3. CI, abnormal HRR, and abnormal DTS were all significant predictors of cardiovascular death. The DTS and CI had similar predictive power [hazard ratio 3.0 (95% confidence interval 1.9–4.9,  $P < 0.0001$ ) for the DTS and 2.8 (95% confidence interval 1.7–4.8,  $P < 0.0001$ ) for CI], whereas the hazard ratio for HRR was 2.0 (95% confidence interval 1.1–3.5,  $P = 0.02$ ). Having both an abnormal HRR and CI resulted in a hazard ratio of 4.2 and an annual mortality rate of 2.0%. Conversely, exhibiting a normal HRR and a normal chronotropic response was highly specific; those exhibit-

**Fig. 1**

Kaplan-Meier survival curve comparing a normal response to exercise, chronotropic incompetence (CI), abnormal heart rate recovery (HRR), and both abnormal HRR and CI. \* $P < 0.05$  vs. normal response. \*\* $P < 0.05$  vs. abnormal CI, abnormal HRR, and both normal. Numbers in parentheses on the x-axis represent patients evaluated at each time point.

ing both these responses had a very low annual cardiovascular mortality rate of 0.25%. The area under the ROC curve for CI (0.68) was higher than that for abnormal HRR (0.57) ( $P < 0.01$ ). When considered as continuous variables (i.e. hazard ratio per heart beat), CI was similarly more powerful than abnormal HRR.

Kaplan-Meier curves illustrating rates of cardiovascular death for CI, abnormal HRR, having neither, or having both are presented in Fig. 1. Having either one of these responses was associated with a higher death rate than having neither (log-rank test  $P < 0.05$ ). Having both CI and an abnormal DTS was associated with a greater cardiovascular death rate than having either abnormality alone ( $P < 0.05$ ).

Presence or absence of  $\beta$ -blockade was not a significant predictor of cardiovascular mortality, and adding this variable to the model did not affect the prognostic power of CI, HRR, or the DTS. When only the 378 patients who were receiving  $\beta$ -blockers were assessed, the hazard ratios for abnormal CI and HRR were similar [2.7 (95% confidence interval 0.88–8.3,  $P < 0.001$ ) for CI and 2.0 (95% confidence interval 0.76–5.0) for abnormal HRR], whereas the hazard ratio for abnormal DTS was reduced to 1.9 (95% confidence interval 0.85–4.5). Similarly, ethnicity had no impact on the results.

## Discussion

The present results demonstrate that both an attenuated increase in heart rate during exercise and a reduced rate

of recovery of heart rate after exercise are associated with cardiovascular mortality in patients referred for exercise testing for clinical reasons. These responses independently predict risk after adjustment for age, established risk factors including hypertension, high cholesterol, smoking, and diabetes, as well as other exercise test variables known to be associated with risk (ST depression, angina, DTS). These findings concur with other recent studies, which underscore the importance of including the chronotropic response to exercise and rate of recovery in the exercise test report [5–12,19]. The simple application of heart rate during and after exercise provides powerful information regarding risk for cardiovascular mortality; having both an abnormal CI and HRR increased the risk of cardiovascular mortality more than four-fold.

Although numerous studies have assessed the prognostic utility of these two responses separately, few data are available regarding their relative prognostic power. In addition, one criticism of HRR [20] is that its incremental value for predicting risk has rarely been compared with the DTS, an established tool for stratifying risk with a compelling 20-year history [21]. Nishime *et al.* [11] studied 9454 patients referred for exercise testing at the Cleveland Clinic and reported that HRR predicted all-cause mortality beyond that estimated by the DTS. In this study, using cardiovascular mortality as the primary outcome, CI had prognostic power that was similar to the DTS, and both CI and the DTS more strongly predicted cardiovascular mortality than HRR. This is in accordance with previous findings from our group [10] and others [12] demonstrating that although HRR is a powerful predictor of all-cause mortality, it is not a strong marker of the presence or severity of angiographic disease.

An additional observation from this study was that the results were not greatly affected by  $\beta$ -blocker therapy. This is important in that many previous studies have removed patients on  $\beta$ -blockers, assuming the prognostic applications of CI and HRR would not apply to patients taking these agents. In particular, the role of CI in patients taking  $\beta$ -blockers has not been fully explored. Although our sample of patients taking  $\beta$ -blocking agents was limited (438, of whom 23 died of cardiovascular causes), the trend observed suggests that CI predicts risk regardless of  $\beta$ -blocker use. CI and HRR showed similar trends for predicting cardiovascular mortality when the model was adjusted for  $\beta$ -blocker use, when those taking  $\beta$ -blockers were assessed separately, and when they were excluded from the analysis. These findings also extend our previous observations regarding HRR, in which  $\beta$ -blockade had no impact on the prognostic impact of HRR [10], those of Vivekananthan *et al.* [12], who observed no interaction between  $\beta$ -blocker use and the association of HRR with mortality, and Khan *et al.* [6], who reported that CI predicted all-cause mortality

irrespective of  $\beta$ -blocker use, type of  $\beta$ -blocker, and half-lives elapsed since the last dose was taken.

### Effect of end point

We limited the current analysis to cardiovascular mortality, because we [10] and others [6–8,12,19,22] have previously reported associations between all-cause mortality and CI, HRR, or both. Although the association between HRR and all-cause mortality has been confirmed by numerous studies in recent years, studies assessing the association between HRR, presence of cardiovascular disease, and mortality have been mixed. We recently reported in preliminary form that HRR more strongly predicted all-cause mortality than cardiovascular mortality [23]. Conversely, Jouven *et al.* [5] found that HRR more strongly predicted sudden death from MI than other causes of death. Morshedi-Meibodi *et al.* [9] reported that among Framingham Study individuals undergoing routine treadmill testing, a rapid HRR was associated with a lower risk of cardiovascular disease events, but not all-cause mortality. Cheng and colleagues [24] observed that HRR was the only historical and exercise test predictor of cardiovascular mortality, whereas only fitness and body mass index predicted all-cause mortality among men who were relatively young at baseline (< 40 years).

Studies on the association between HRR and presence and extent of coronary artery disease have also varied widely. We previously observed that HRR was not associated with angiographic disease [10]. Georgoulis *et al.* [25], however, reported that patients with an abnormal HRR response were more likely to have myocardial perfusion defects. Diaz *et al.* [26] observed that patients with abnormal HRR were at high risk for death even with normal nuclear findings. Chen and colleagues [22] demonstrated that among patients with evidence of myocardial ischemia by perfusion imaging, an abnormal HRR had only a nonsignificant trend toward blunting the survival improvement associated with early revascularization. Other recent studies have reported associations between impaired HRR and cardiovascular events in men [9,24] and women [9,27–29]. Whether impaired HRR predicts mortality because it reflects underlying cardiovascular disease, or because it identifies a group with autonomic imbalance and therefore a propensity toward serious rhythm disturbances in the absence of cardiovascular disease [5], or both, requires further study.

### Previous studies including both chronotropic incompetence and heart rate recovery

Few studies have addressed both CI and HRR in the same analysis, and to our knowledge only one such study has evaluated cardiovascular mortality. In a detailed analysis including resting heart rate, degree of change in heart rate during exercise, and HRR, Jouven *et al.* [5]

reported that the strongest predictor of sudden death from MI was an impaired ability to increase heart rate during exercise. When these three variables were assessed multivariately and adjusted for confounding factors, resting heart rate and HRR were not significant predictors of risk, whereas CI had an adjusted relative risk of 4 (comparing highest vs. lowest quintile of heart rate increase). Conversely, studies from the Cleveland Clinic have demonstrated that HRR more strongly predicts all-cause mortality than CI. Vivekananthan *et al.* [12] reported that an abnormal CI (defined as achieving < 80% heart rate reserve, as in this study) in the absence of  $\beta$ -blocker use was associated with higher all-cause mortality even after adjustment for abnormal HRR. The association with mortality was markedly stronger for HRR than for CI. Cole and colleagues [8] observed that CI was a weaker predictor of mortality than HRR among patients referred for diagnostic single photon emission computed tomography (SPECT). In fact, the relative risk for all-cause mortality among patients with an abnormal HRR was actually lower among those with CI (hazard ratio 2.3 vs. 4.7 for presence and absence of CI, respectively). For those with a normal heart rate response during and after exercise (i.e. normal HRR and absence of CI), the mortality rate was only 0.5% per year. Similarly, in our study, a normal chronotropic response to exercise and recovery reflected a low cardiovascular mortality, having an event rate of 0.25% per year.

#### **Mechanisms underlying mortality with abnormal chronotropic incompetence and heart rate recovery**

The mechanisms underlying CI and impaired HRR have been the topics of a great deal of discussion in recent years. The mechanisms that have been proposed to explain CI largely involve abnormalities in autonomic balance, including an altered parasympathetic response to cardiac mechanoreceptors,  $\beta$ -receptor insensitivity, and postsynaptic desensitization of the sinoatrial node to sympathetic stimulation [30–32]. Other explanations include reduced myocardial viability and a protective response to permit greater myocardial perfusion in the presence of narrowed coronary arteries [30,32]. Although there have been efforts to exclude patients with an ‘inadequate’ physical response to exercise [33], the concept that CI in part reflects simply an inability to achieve a good exercise response and thus an adequate heart rate must be considered. The ability of heart rate to recover following exercise is related to the capacity of the cardiovascular system to reverse autonomic nervous system (withdrawal of vagal activity) and baroreceptor (detection of changes in blood pressure and inhibition of sympathetic discharge) adaptations that occur during exercise, often termed vagal reactivation [34,35]. This has been underscored by the long-established observation that recovery of heart rate is faster in athletes [36], and the fact that autonomic imbalance, particularly a deficiency in vagal tone, is associated with mortality [35,37].

#### **Limitations**

As this was a Veterans Affairs cohort, our findings were limited to men. CI was defined as the percentage of heart rate reserve achieved, but we did not use the chronotropic index, which expresses the ratio of heart rate reserve to the metabolic reserve at peak exercise [7,19,21]. The latter measure has been widely used in recent years as a measure of CI to predict all-cause mortality [7,19,21], but it requires the use of the Bruce protocol. We also employed a definition of HRR that best predicts outcomes in our population ( $\leq 22$  beats at 2 min recovery in the supine position [10]), but there have been various other definitions of abnormal HRR. The results may differ when applying different criteria for both CI and HRR. Our sample size was relatively small, which limited our subgroup analysis of patients taking  $\beta$ -blockers.

#### **Summary**

Both CI and HRR independently predict cardiovascular mortality in patients referred for exercise testing for clinical reasons. CI was similar to the DTS in estimating risk, and both the DTS and CI were stronger predictors of cardiovascular mortality than HRR. Patients exhibiting both CI and abnormal HRR have more than a four-fold risk of cardiovascular mortality; conversely, when both the heart rate response to and recovery from an exercise test are normal, cardiovascular mortality is extremely low. The simple application of heart rate provides powerful risk stratification from the exercise test, and should be routinely included in the test report.

#### **References**

- Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, *et al.* ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002; **106**:1883–1892.
- Ashley E, Myers J, Froelicher VF. Exercise testing in clinical medicine. *Lancet* 2000; **356**:1592–1597.
- Lauer MS, Froelicher V. Abnormal heart-rate recovery after exercise. *Lancet* 2002; **360**:1176–1177.
- Myers J. Beyond ST-segment displacement: newer diagnostic and prognostic markers from the exercise test. *Am J Med Sport* 2003; **5**:332–336.
- Jouven X, Empana JP, Schwartz PJ, Desnos M, Coubon D, Ducimetiere P, *et al.* Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005; **352**:1951–1958.
- Khan MN, Pothier CE, Lauer MS. Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers. *Am J Cardiol* 2005; **96**:1328–1333.
- Lauer MS, Mehta R, Pashkow FJ, Okin PM, Lee K, Marwick TH, *et al.* Association of chronotropic incompetence with echocardiographic ischemia and prognosis. *J Am Coll Cardiol* 1998; **32**:1280–1286.
- Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999; **341**:1351–1357.
- Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (The Framingham Heart Study). *Am J Cardiol* 2002; **90**:848–852.
- Shetler K, Marcus R, Froelicher VF, Vora S, Kalisetti D, Prakash M, Myers J. Heart rate recovery: validation and methodological issues. *J Am Coll Cardiol* 2001; **38**:1980–1987.

- 11 Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* 2000; **284**: 1392–1398.
- 12 Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. *J Am Coll Cardiol* 2003; **42**:831–838.
- 13 Morise AP. Heart rate recovery: predictor of risk today and target of therapy tomorrow? *Circulation* 2004; **110**:2778–2780.
- 14 Myers J, Buchanan N, Smith D, Neutel J, Bowes E, Walsh D, Froelicher VF. Individualized ramp treadmill: observations on a new protocol. *Chest* 1992; **101**:236S–241S.
- 15 Myers J, Do D, Herbert W, Ribisl P, Froelicher VF. A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. *Am J Cardiol* 1994; **73**:591–596.
- 16 Borg Gav. *Borg's Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics; 1998.
- 17 Reid MC, Lachs MS, Feinstein AR. Use of methodological standards in diagnostic test research: getting better but still not good. *JAMA* 1995; **274**:645–651.
- 18 Shue P, Froelicher VF. EXTRA: an expert system for exercise test reporting. *J Non-Invasive Test* 1998; **11**:4:21–27.
- 19 Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH, *et al.* Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA* 1999; **281**:524–529.
- 20 Gibbons RJ. Abnormal heart-rate recovery after exercise. *Lancet* 2002; **359**:1536–1537.
- 21 Lauer MS. Exercise electrocardiogram testing and prognosis. Novel markers and predictive instruments. *Cardiol Clin* 2001; **19**:401.
- 22 Chen MS, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery and impact of myocardial revascularization on long-term mortality. *Circulation* 2004; **110**:2851–2857.
- 23 Sandri M, Myers J, Engel G, Aleti V, Tan SY, Jannaureddy D, *et al.* Heart rate recovery predicts non-cardiovascular better than cardiovascular death. *Circulation* 2005; **112**:II-646.
- 24 Cheng YJ, Lauer MS, Earnest CP, Church TS, Kampert JB, Gibbons LW, Blair SN. Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. *Diabetes Care* 2003; **24**:2052–2057.
- 25 Georgoulas P, Orfanakis A, Demakopoulos N, Xaplanteris P, Mortzos G, Vardas P, Karkavitsas N. Abnormal heart rate recovery immediately after treadmill testing: correlation with clinical, exercise testing, and myocardial perfusion parameters. *J Nucl Cardiol* 2003; **10**:498–505.
- 26 Diaz LA, Brunken RC, Blackstone EH, Snader CE, Lauer MS. Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. *J Am Coll Cardiol* 2001; **37**: 1558–1564.
- 27 Pitsavos CH, Chrysohoou C, Panagiotakos DB, Kokkinos P, Skoumas J, Papaioannou I, *et al.* Exercise capacity and heart rate recovery as predictors of coronary heart disease events, in patients with heterozygous familial hypercholesterolemia. *Atherosclerosis* 2002; **173**:347–352.
- 28 Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, Blumenthal RS. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA* 2003; **290**: 1600–1607.
- 29 Mora S, Redberg RF, Sharrett AR, Blumenthal RS. Enhanced risk assessment in asymptomatic individuals with exercise testing and Framingham risk scores. *Circulation* 2005; **112**:1566–1572.
- 30 Ellestad MH. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?) *Circulation* 1996; **93**:1485–1487.
- 31 Colucci WS, Ribeiro J, Rocco MB, Quigg RJ, Creager MA, Marsh JD, *et al.* Impaired chronotropic response to exercise in patients with congestive heart failure; role of postsynaptic  $\beta$ -adrenergic desensitization. *Circulation* 1989; **2**:314–323.
- 32 Hammond HK, Froelicher VF. Normal and abnormal heart rate responses to exercise. *Prog Cardiovasc Dis* 1985; **27**:271–296.
- 33 Hammond HK, Kelly TL, Froelicher VF. Radionuclide imaging correlates of heart rate impairment during maximal exercise testing. *J Am Coll Cardiol* 1983; **2**:826–833.
- 34 Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, *et al.* Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *J Am Coll Cardiol* 1994; **24**:1529–1535.
- 35 Rosenwinkel ET, Bloomfield DM, Arwady MA, Goldsmith RL. Exercise and autonomic function in health and cardiovascular disease. *Cardiol Clin* 2001; **19**:369–387.
- 36 Winnick JP. The prediction of maximum oxygen intake from recovery heart rates. *Am Corr Ther J* 1972; **26**:19–23.
- 37 Curtis BM, O'Keefe JH. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc* 2002; **77**:45–54.