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Post-Exercise Heart Rate Recovery Independently Predicts Mortality Risk in Patients with Chronic Heart Failure

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Abstract

Background—Post-exercise heart rate recovery (HRR) is an index of parasympathetic function associated with clinical outcomes in populations with and without documented coronary heart disease. Decreased parasympathetic activity is thought to be associated with disease progression in chronic heart failure (HF), but an independent association between post-exercise HRR and clinical outcomes among such patients has not been established.

Methods and Results—We measured HRR (calculated as the difference between heart rate at peak exercise and after 1 minute of recovery) in 202 HF subjects and recorded 17 mortality and 15 urgent transplantation outcome events over 624 days of follow-up. Reduced post-exercise HRR was independently associated with increased event risk after adjusting for other exercise-derived variables (peak oxygen uptake and V_E/VCO_2 slope), for the Heart Failure Survival Score (adjusted HR 1.09 for one beat/min reduction, 95% CI 1.05-1.13, $p<0.0001$) and the Seattle Heart Failure Model score (adjusted HR 1.08 for one beat/min reduction, 95% CI 1.05-1.12, $p<0.0001$). Subjects in the lowest risk tertile based on post-exercise HRR (≥ 30 beats/min) had low risk of events irrespective of the risk predicted by the survival scores. In a subgroup of 15 subjects, reduced post-exercise HRR was associated with increased serum markers of inflammation (interleukin-6 $r=0.58$, $p=0.024$, high sensitivity C-reactive protein $r=0.66$, $p=0.007$).

Conclusions—Post-exercise HRR predicts mortality risk in patients with HF and provides prognostic information independent of previously described survival models. Pathophysiologic links between autonomic function and inflammation may be mediators of this association.

Keywords

Parasympathetic nervous system; exercise; clinical outcomes

Neuroendocrine dysregulation plays a central role in the pathogenesis of chronic heart failure and is an important predictor of clinical outcomes among such patients.¹ Adaptations

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of the autonomic nervous system, including excess sympathetic activity and concomitant parasympathetic withdrawal, are among the manifestations of this maladaptive neuroendocrine imbalance.²⁻⁶

Heart rate deceleration during the first minute after peak exercise is mediated primarily by activation of the parasympathetic nervous system.^{7,8} Measurement of post-exercise heart rate recovery provides a noninvasive and clinically accessible means to quantitatively assess parasympathetic function. Impaired heart rate deceleration after exercise cessation is strongly associated with increased mortality in subjects referred for stress testing regardless of cardiovascular disease history.⁹⁻¹¹ While attenuated post-exercise heart rate recovery also confers higher mortality risk among patients with chronic heart failure, there is conflicting evidence as to whether this measurement provides independent prognostic information after accounting for previously identified clinical and exercise-derived prognostic variables.¹²⁻¹⁴ Multivariate clinical survival scores derived from and validated in larger heart failure populations represent the cumulative predictive capacity of many variables and may be useful to determine whether novel predictors yield independent additional information.^{15,16} It is unknown whether post-exercise heart rate recovery data provides prognostic information beyond that derived from validated survival scores developed for heart failure patients.

The current study was undertaken to determine the association between post-exercise heart rate recovery and subsequent risk of adverse clinical outcomes in a population of ambulatory patients with heart failure referred for exercise testing. We hypothesized that reduced post-exercise heart rate recovery would provide incremental independent prognostic information beyond that provided by validated heart failure prognostic scores. To test this hypothesis, the relationship between post-exercise heart rate recovery and outcome was determined after adjusting for other exercise-derived variables known to be associated with subsequent clinical outcomes (peak oxygen uptake (VO_2) and the V_E/VCO_2 slope) and two independently developed and validated prognostic scores: the Heart Failure Survival Score and the Seattle Heart Failure Model.¹⁵⁻¹⁷ To explore potential mechanisms linking parasympathetic function and mortality risk in heart failure, serum markers of inflammation were also measured in a subset of patients.^{6,18,19}

METHODS

Study Design

The study was conducted as a prospective follow-up of a retrospectively defined consecutive sample of 202 subjects with chronic heart failure (New York Heart Association Class I-III) referred for maximal exercise testing at the Yale Heart Failure and Transplantation Center between 2002 and 2007. For subjects with multiple exercise tests during this period, the earliest test data were used. Patients with atrial fibrillation and pacemaker dependency were excluded from the analysis. Clinical characteristics and exercise test results were obtained from medical record review. Outcome events (death or urgent cardiac transplantation procedures in UNOS status 1A patients or UNOS status 1B patients receiving continuous positive inotropic therapy at home or in the hospital) were determined from medical record review or by contact with the primary physician. Vital status at the end of study follow-up was determined in all subjects. The Heart Failure Survival Score and Seattle Heart Failure Model score were calculated from published formulae (variables included in the Heart Failure Survival Score are: presence/absence ischemic cardiomyopathy, resting heart rate, left ventricular ejection fraction, mean blood pressure, presence/absence widened intraventricular conduction delay, peak oxygen consumption, and serum sodium; variables included in the Seattle Heart Failure Model are: age, gender, New York Heart Association functional class, left ventricular ejection fraction, presence/absence ischemic

cardiomyopathy, systolic blood pressure, presence/absence of angiotensin converting enzyme inhibition therapy, diuretic dose, serum sodium, hemoglobin, percent lymphocytes, uric acid, and total cholesterol).^{15,16} Approval for this study, including the necessary waiver for access to private health information, was obtained from the Human Investigation Committee of the Yale School of Medicine.

Exercise testing protocol

Symptom-limited maximal exercise testing was performed on a motorized treadmill with graded increases in work rate according to standard Bruce (n=114) and modified Naughton protocols (n=88). Medications were not discontinued before exercise testing. Electrocardiographic data (Cardiocontrol Cardioperfect MD, Netherlands) were recorded continuously during a one-minute pre-exercise rest period, throughout exercise, and during the first minute of recovery. Expired gases were collected and analyzed on a breath-by-breath basis with a metabolic cart calibrated immediately before each test (Medgraphics, St. Paul, Minnesota, USA). The peak oxygen uptake was calculated as the highest value in the last minute of exercise based on the median five of seven breaths moving average filter. The VE/VCO₂ slope was calculated over its linear portion from the start of exercise to the anaerobic threshold (or the linear portion of the test until end of exercise in subjects without detectable ventilatory anaerobic threshold). After completion of exercise, the treadmill was immediately stopped and all subjects recovered in a seated position. Heart rate at maximal exercise and at one minute of recovery was calculated from the average of 3 consecutive sinus beats. Heart rate recovery (beats/min) was calculated by subtracting the heart rate obtained at one minute after exercise cessation from the heart rate at peak exercise. The reference value for post-exercise recovery in sedentary healthy subjects tested with this protocol in our laboratory is 41±11 beats/min.

Serum markers of inflammation

In a subgroup of 15 subjects, an indwelling catheter for blood sampling was placed into a medial antecubital vein. Prior to exercise testing, five milliliters of blood was obtained after 30 minutes of supine rest. Plasma and serum were separated by cold centrifugation and stored at -80° C. Plasma C-reactive protein (CRP) was measured with a high sensitivity immunoturbidimetric assay (Alfa Wasserman high-sensitivity CRP reagent, Caldwell NJ). The lower limit of detection for this CRP assay was 0.01 mg/dl. Serum interleukin-6 was measured in pg/ml with a commercially available enzyme-linked immunoabsorbant assay (R&D systems, Minneapolis MN).

Data analysis

Values for variables with normal distributions are expressed as mean ± standard deviation. Cox proportional hazards regression models were used for assessment of predictor variables in univariate and multivariate analyses (Stata version 10.1, College Station TX). Subject follow-up was censored at the time of cardiac transplantation. Proportional hazards assumptions were tested based on analysis of Schoenfeld residuals. Simple linear regression was used to determine the association between serum markers of inflammation and post-exercise heart rate recovery. Since the distribution of values for C-reactive protein and interleukin-6 significantly deviated from the normal distribution (by Shapiro-Wilk test), a log transformation was applied to these variables before inclusion in the regression analysis. For all analyses, a p-value <0.05 was used to infer statistical significance.

RESULTS

Post-exercise heart rate recovery in the study sample averaged 23±12 beats/min. There were 32 outcome events (17 deaths and 15 urgent cardiac transplantations) over a median follow-

up period of 624 days. Clinical characteristics of the study sample are summarized in Table 1. Reduced post-exercise heart rate recovery, peak heart rate, peak VO_2 , V_E/VCO_2 slope, the Heart Failure Survival Score, and the Seattle Heart Failure Model score were all significantly associated with increased risk of outcome events in univariate and multivariate models (Table 2). To further explore the clinical utility of post-exercise heart rate recovery as a prognostic indicator, subjects were grouped into tertiles based on the distribution of values for post-exercise heart rate recovery, the Heart Failure Survival Score, and the Seattle Heart Failure Model score (Figures 1 and 2). Subjects in the lowest risk tertile based on post-exercise heart rate recovery (≥ 30 beats/min) had a low risk of outcome events irrespective of the risk predicted by the multivariate prognostic scores. Among subjects with post-exercise heart rate recovery in this lowest risk tertile, only one adverse outcome event was recorded (negative predictive value of 98% (95% CI 96-100%)).

We also performed 2 post-hoc analyses to determine the impact of treadmill protocol and beta-blocker use on the association between post-exercise recovery and clinical outcomes. Treadmill protocol was significantly associated with post-exercise heart rate recovery (Bruce 26 ± 12 beats/min vs. modified Naughton 20 ± 12 beats/min, $p=0.001$). Treadmill protocol was significantly associated with outcomes in univariate analysis (increased risk with modified Naughton protocol, estimated HR 5.8 (95% CI 1.7-19, $p=0.004$)), but was not significantly associated with outcomes in a multivariate model that included post-exercise heart rate recovery and peak oxygen uptake (estimated HR 2.4 (95% CI 0.7-8.2, $p=0.16$)). Treadmill protocol did not modify the relationship between risk tertiles of post-exercise heart rate recovery and outcomes ($p=0.39$ for interaction term). Beta-blocker use was not associated post-exercise heart rate recovery (beta-blocker 23 ± 13 beats/min vs. no beta-blocker 24 ± 13 beats/min, $p=0.50$). Beta-blocker use was not significantly associated with outcomes in univariate analysis ($p=0.81$), and did not modify the relationship between tertile of post-exercise heart rate recovery and outcomes ($p=0.72$ for interaction term).

In the subgroup of 15 subjects who had provided written informed consent for blood sampling (14 men and 1 woman, mean age 54 years, mean ejection fraction 24%, mean peak VO_2 17.7 ± 6.8 ml/kg/min), venous blood samples were obtained immediately before exercise. Post-exercise heart rate recovery (23 ± 11 beats/min) in these subjects did not significantly differ from the remainder of the study cohort. High sensitivity C-reactive protein levels (median (IQR) 1.1(2.3) mg/dl) and interleukin-6 levels (median (IQR) 2.2(1.6) pg/ml) were significantly associated with post-exercise heart rate recovery (log C-reactive protein $r^2=0.44$, $p=0.007$; log interleukin-6 $r^2=0.33$, $p=0.025$).

DISCUSSION

Heart rate recovery measured one minute after cessation of exercise is significantly associated with increased risk of mortality or urgent cardiac transplantation in ambulatory patients with chronic heart failure referred for exercise testing. Even after adjusting for other exercise-derived predictor variables and previously validated heart failure survival scores, post-exercise heart rate recovery remained an independent predictor of adverse clinical events. Patients with preserved heart rate recovery had a low rate of adverse outcomes regardless of their multivariate prognostic score. In a subset of patients, attenuated heart rate recovery was significantly associated with increased serum markers of inflammation. These findings support our proposed hypothesis that post-exercise heart rate recovery yield incremental independent prognostic information beyond that provided by validated heart failure prognostic scores.

Our findings are consistent with previous studies that have demonstrated a significant association between post-exercise heart rate recovery and adverse clinical outcomes in both

heart failure and non-heart failure populations.⁹⁻¹⁴ Prior analyses have reached different conclusions regarding the ability of heart rate recovery to independently predict clinical outcomes in heart failure patients after adjusting for previously identified clinical and exercise test derived prognostic variables.¹²⁻¹⁴ These inconsistencies in previous reports may be partly attributable to inherent limitations of multivariate models applied to relatively small study samples from exercise testing laboratories. In the current study, we utilized exercise-derived measurements and validated multivariate survival scores to evaluate the independent prognostic value of post-exercise heart rate recovery.¹⁵⁻¹⁷ This approach allowed adjustment for a wide array of clinical and exercise-derived factors despite a relatively small study sample and number of events. Our findings both confirm the validity of the previously described predictor variables and indicate that post-exercise heart rate recovery provides additional, independent prognostic information.

In both animal models and in heart failure patients, reduction in parasympathetic control of heart rate is an early marker of ventricular dysfunction.^{4,20} The mechanisms underlying this reduction in vagal activity remain incompletely characterized and likely involve abnormalities in both afferent and efferent limbs of the parasympathetic neural pathways.^{6,21-24} Parasympathetic withdrawal, as assessed by decreased resting heart rate variability and baroreceptor sensitivity, is associated with increased risk of adverse outcomes in heart failure patients.²⁵⁻²⁷ Heart rate deceleration during the first minute of exercise recovery is mediated primarily by activation of the parasympathetic nervous system and therefore serves as a clinical tool to assess vagal activity.^{7,28,29} The association between reduced post-exercise heart rate recovery and adverse outcomes in our study cohort further implicates parasympathetic dysfunction in the pathogenesis of heart failure progression.

The parasympathetic nervous system regulates heart rate via muscarinic receptor signaling at the sino-atrial node. Vagal activity alters myocardial contractile function and susceptibility to ventricular arrhythmias through suppression of adrenergic signaling, G-protein interactions, and nitric oxide signaling.^{6,30-33} In animal heart failure models, chronic stimulation of the right vagus nerve is associated with improved ventricular pump function, evidence of decreased chamber remodeling, and reductions in mortality.³⁰ The parasympathetic nervous system is also linked to systemic inflammatory signaling pathways, possibly by activation of the alpha-7 subunit of the nicotinic receptor in macrophages.^{18,19} We found a strong correlation between attenuation of heart rate recovery and increased serum markers of inflammation. Independent association of high sensitivity C-reactive protein levels and post-exercise heart rate recovery have been reported in a population of sedentary elderly subjects,³⁴ while increased circulating levels of interleukin-6 and C-reactive protein have been associated with increased mortality risk in heart failure patients.^{35,36} It is therefore possible, but presently unproven, that changes in vagal activity are responsible for these observed alterations in inflammatory signaling. The cross-sectional design of our study precludes determination of causality with respect to these two neuroendocrine derangements, so our data must be considered as hypothesis generating for validation in future studies.

Beta-blocker therapy was not associated with post-exercise heart rate recovery and did not modify the association between heart rate recovery and adverse outcomes observed in our study sample. This finding is in accord with previous cross-sectional studies and a single prospective study that demonstrated no change in post-exercise heart rate recovery after initiation of beta-blockade in heart failure patients.³⁷⁻³⁹ In contrast, several investigators have reported that initiation of beta-blocker therapy in heart failure patients is associated with changes in resting heart rate variability consistent with increased parasympathetic tone.⁴⁰⁻⁴² This apparent discrepancy is consistent with previous reports that demonstrated that resting heart rate variability and post-exercise heart rate recovery provide distinct and

complementary information about parasympathetic function in healthy subjects.^{24,43} Taken together, these previous studies indicate that beta-blocker therapy may enhance phasic cholinergic signaling at the sinus node at rest, but does not increase the magnitude of mean cholinergic signaling at the sinus node at peak exercise.

Our findings indicate post-exercise heart rate recovery is an important measurement to obtain when assessing mortality risk in patients with heart failure. Calculation of heart rate recovery is straightforward and does not require specialized testing equipment beyond a treadmill and exercise electrocardiographic recording system. The high negative predictive value of a preserved post-exercise measurement in our cohort indicates heart rate recovery may prove valuable in the clinical management of heart failure patients. Post-exercise heart rate recovery could potentially identify a subset of the heart failure population unlikely to derive benefit from invasive and costly procedures, including cardioverter defibrillator implantation, due to low risk of sudden cardiac death. Predictive value could be further enhanced by assessment of heart rate recovery in tandem with multivariate prognostic scores, as subjects with a low risk based on these criteria had no adverse events in our study sample.

We acknowledge that our study sample was derived from a single academic referral center, with clinical characteristics (relatively young age, relatively well preserved aerobic capacity, predominance of males with non-ischemic cardiomyopathy) that may potentially limit widespread applicability of our findings. As our study cohort was selected from an exercise laboratory database, the potential for referral bias also exists. Furthermore, differences in exercise testing protocols, post-exercise recovery procedures, and heart rate recovery calculations among prior studies limits the quantitative comparison of our data to earlier results. The choice of treadmill protocol (Bruce vs. modified Naughton), medication use, home exercise regimens, or other unmeasured confounders may have also contributed to our study findings. Application of post-exercise heart rate recovery as a prognostic marker in clinical practice would require standardization of exercise and post-exercise recovery protocols and validation studies in a multicenter population.

In conclusion, reduced post-exercise heart rate recovery is independently associated with increased risk of adverse outcomes in chronic heart failure patients. This measurement provides prognostic information independent of other exercise-derived variables and previously validated multivariate heart failure survival scores. Increased levels of both CRP and interleukin-6 are associated with reduced post-exercise heart rate recovery, suggesting a possible pathologic link between autonomic dysfunction and systemic inflammation. Our findings highlight both the important relationship between parasympathetic withdrawal and heart failure progression and the need for a more complete understanding of the underlying causative mechanisms. Additional research is warranted to more precisely define the role of post-exercise heart rate recovery in the clinical management of patients with heart failure.

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Figure 1.
Number of outcome events plotted according to tertiles of increasing risk (Low, Medium (Med.) and High) for post-exercise heart rate recovery and Heart Failure Survival Score.

Figure 2.
Number of outcome events plotted according to tertiles of increasing risk (Low, Medium (Med.) and High) for post-exercise heart rate recovery and Seattle Heart Failure Model score.

Table 1

Clinical characteristics of study sample for all subjects and for subjects grouped by median value of heart rate recovery at 1 minute post-exercise (HRR1, 22 beats/min)

	All Subjects (n=202)	HRR1 above median (n=107)	HRR1 below median (n=95)	p-value *
Age (years)	45±15	41±15	50±15	<0.001
Gender (% male)	74	70	79	0.15
Etiology (% ischemic)	19	15	22	0.19
Ejection fraction (%)	24±9	25±10	23±9	0.29
NYHA Class (%)				<0.001
Class I	41	53	26	
Class II	30	32	28	
Class III	29	15	46	
Peak exercise heart rate (beats/min)	136±28	146±24	124±28	<0.001
Peak VO ₂ (ml/kg/min)	19.4±7	21.8±7	16.6±5.9	<0.001
RER at peak exercise	1.14±0.14	1.15±0.13	1.14±0.16	0.59
V _E /VCO ₂ slope	34.6±7.2	33.4±6.4	36.0±7.8	<0.01
Medications (%)				
Beta-Blockers	75	73	77	0.43
ACEI or ARB	71	70	71	0.98
Devices (%)				
ICD	31	22	42	0.004
CRT	10	8	12	0.31

Legend: ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; RER=respiratory exchange ratio

* indicates p-value for comparison between subjects above and below the median value for post-exercise heart rate recovery

Table 2

Estimated hazard ratios derived from Cox proportional hazards models for a one-beat/min decrease in post-exercise heart rate recovery, a one-beat/min decrease in peak heart rate, one ml/kg/min decrease in peak VO₂, one dimensionless unit increase in V_E/VCO₂ slope, and a one point increment in risk in the Heart Failure Survival Score and the Seattle Heart Failure Model. Results of 6 univariate models, and 5 multivariate models are shown.

Predictor Variable(s)	Hazard Ratio	95% Confidence Intervals	χ^2	p-value
Univariate Models				
HRR	1.09	1.06-1.13	28.43	<0.0001
Peak HR	1.04	1.02-1.06	24.18	<0.0001
Peak VO ₂	1.28	1.17-1.42	32.25	<0.0001
V _E /VCO ₂ slope	1.09	1.05-1.13	15.59	0.0001
HFSS	1.23	1.06-1.44	6.19	0.007
SHFM	1.32	1.14-1.52	11.90	0.0006
Paired Multivariate Models				
Model 1			40.78	<0.0001
HRR	1.09	1.05-1.14		<0.0001
Peak HR	1.03	1.00-1.04		0.002
Model 2			50.23	<0.0001
HRR	1.08	1.04-1.12		<0.0001
Peak VO ₂	1.26	1.14-1.40		<0.0001
Model 3			44.42	<0.0001
HRR1	1.10	1.06-1.14		<0.0001
V _E /VCO ₂ slope	1.10	1.05-1.15		<0.0001
Model 4			32.43	<0.0001
HRR	1.09	1.05-1.13		<0.001
HFSS	1.19	1.01-1.39		0.032
Model 5			34.21	<0.0001
HRR	1.08	1.05-1.12		<0.001
SHFM	1.22	1.04-1.42		0.012

Legend: HFSS=Heart Failure Survival Score; HR=heart rate; HRR=post-exercise heart rate recovery at 1 minute; SHFM=Seattle Heart Failure Model; V_E/VCO₂ slope=change in minute ventilation per change in carbon dioxide production, VO₂=oxygen uptake