Prognostic value of heart rate recovery in patients with heart failure

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Background The rate in which heart rate recovers from exercise has recently been shown to be a strong predictor of mortality in patients suspected of having coronary disease, but its prognostic value in patients with heart failure (HF) has not been explored. We sought to assess the prognostic utility of heart rate recovery (HRR) in patients with HF.

Methods Eighty-seven subjects diagnosed with compensated HF underwent cardiopulmonary exercise testing (CPX). Mean age and ejection fraction were 50.0 (±13.9) years and 28.1% (±13.6%), respectively. Heart rate at 1-minute post-CPX was subtracted from maximal heart rate during the exercise test to produce a measure of HRR_1 in beats per minute. Subjects were followed for a combined death/hospitalization end point for 1-year after CPX.

Results The mean peak respiratory exchange ratio, peak oxygen consumption (V_{O_2}), minute ventilation/carbon dioxide production (V_E/V_{CO_2}) slope, and HRR_1 were 1.06 (±0.11), 14.8 (±4.7) mL · kg^{-1} · min^{-1}, 36.6 (±8.6), and 11.0 (±10.4) beat/min, respectively. Although all three variables were significant univariate predictors of the composite end point ($P < .001$), multivariate Cox regression analysis only retained the V_E/V_{CO_2} slope ($\chi^2 = 33.5$, $P < .001$) and HRR_1 (residual $\chi^2 = 15.0$, $P < .001$) in the equation. The hazard ratio for subjects having both an abnormal V_E/V_{CO_2} slope (>34.4) and HRR_1 (<6.5 beat/min) value was 9.2 (95% CI 4.5-18.5, $P < .0001$).

Conclusions These results indicate that HRR provides additional prognostic information in patients with HF undergoing CPX. Moreover, given the independent prognostic value of HRR, this variable alone may provide valuable clinical information when ventilatory expired gas analysis is not available. (Am Heart J 2006;151:851.e7-851.e13.)

Heart failure (HF) poses a significant health care burden in the United States and many other countries. Annual hospitalizations with HF as a primary or secondary diagnosis number approximately 900 000 and 2 million, respectively.[1] Currently, HF is the primary or contributory cause in approximately 300 000 deaths each year.[1] Moreover, the incidence of HF is expected to accelerate in coming decades as the population ages. Given the magnitude of this problem, it is important to identify clinical markers that accurately predict adverse events, particularly mortality and hospitalization, in patients with HF.

Several variables derived from cardiopulmonary exercise testing (CPX) have consistently demonstrated prognostic value in the HF population. Peak oxygen consumption (V_{O_2}) and the minute ventilation/carbon dioxide production (V_E/V_{CO_2}) slope are the two most frequently applied CPX variables for assessing prognosis. The application of these variables for this purpose is supported by a number of recent investigations demonstrating the ability of both peak V_{O_2} and the V_E/V_{CO_2} slope to predict hospitalization[2] and mortality[3-5] in subjects with HF. The strength of this body of evidence has led to the endorsement of CPX as a standard of care in the HF population.[1]

Several other CPX variables have the potential to provide additional prognostic value to established exercise responses. The degree of heart rate recovery (HRR) after a bout of maximal aerobic exercise has been shown to significantly predict cardiovascular mortality, independent of coinciding conditions such as ischemic burden and chronotropic incompetence.[6-8] Cole et al,[6] for example, found that HRR was a significant predictor of mortality in a group of 2428 adults with no history of CHF or coronary revascularization. Vivekananthan et al[8] also found that HRR was a significant predictor of mortality, independent of coronary artery disease severity, in 2935 subjects undergoing exercise testing. Possible mechanisms and major factors influencing variations in HRR have been studied by several

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groups.[9-11] Accrued evidence from these studies suggests that the rate at which parasympathetic tone increases after the cessation of exercise appears to heavily influence the time course of HRR.

Although several previous investigations have found that HRR after maximal exercise testing is a significant predictor of mortality, assessment of its value in the HF population is lacking. Thus, the purpose of the present study was to assess the prognostic value of HRR, independently and in combination with other CPX variables, in a group of subjects diagnosed with compensated HF.

Methods

Eighty-seven subjects, assessed between May 13, 1997, and October 18, 2004, were included in the study. The subjects were tested and followed by the HF program at the Medical College of Virginia in Richmond. All subjects underwent CPX on an outpatient basis and were instructed to maintain their normal pharmacological regimen. None of the subjects were participating in a cardiac rehabilitation or secondary prevention program at the time of testing. The exercise tests were conducted as part of subjects standard of care (initial assessment or follow-up) or as part of a prior research study. Regardless of the reason for testing, all procedures with respect to the exercise protocol and mode, monitoring, and data collection were consistent in the data set. Written informed consent was obtained from all subjects before testing. Approval from the Medical College of Virginia Institutional Review Board was obtained for those subjects undergoing an exercise test as part of a prospective research project. Subject clinical and pharmacological characteristics are listed in Table I.

Inclusion criteria consisted of a diagnosis of HF and evidence of left ventricular dysfunction by echocardiogram or cardiac catheterization. None of the subjects included in this analysis had a history of pulmonary or peripheral vascular disease. Twenty subjects who underwent CPX did not have HRR data collected in their records and were thus excluded from the analysis. Subjects without HRR data retained in their records were not different from those included in the analysis with respect to CHF severity, pharmacological regiment, or CPX performance. The sample was a consecutive series with HRR data evaluated over the specified period who met the inclusion criteria. Selection bias was therefore not a concern.

Equipment calibration

Ventilatory expired gas analysis was obtained through one of two metabolic systems depending on the time frame for CPX (Medgraphics CPX-D, Minneapolis, Minn/Sensormedics Vmax29, Yorba Linda, CA). The oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen, and carbon dioxide concentrations before each test. The flow sensor was also calibrated before each test.

Testing procedure and data collection

Symptom-limited exercise testing with ventilatory expired gas analysis was conducted with the use of a treadmill. The modified ramping protocol selected for testing consisted of approximately 2 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ increases in workload every 30 seconds.[12-14] Stage 1 began at 1.0 mph and a 0% grade. Stages increased by 0.1 mph and 0.5% grade thereafter. The same conservative treadmill protocol was used to test all subjects. Monitoring consisted of continuous electrocardiography (ECG), manual blood pressure measurements, heart rate recordings every stage via the ECG, and rating of perceived exertion (Borg 6-20 scale) every third stage. Test termination criteria followed AHA guidelines.[15] At the completion of CPX, all subjects performed an active recovery for a period no shorter than 1 minute and 30 seconds. The workload for this active recovery was 1 mph at a 0% grade.

Table I. Subject characteristics

No. of subjects	87 (52 male/35 female)
HF etiology (ischemic/nonischemic)	37/50
Age (y)	50.0 ± 13.9
LVEF (%)	28.1 ± 13.6
ACE inhibitor	67
Cardiac glycoside	60
Diuretic	67
β-Blocker	41

VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$), VCO_2 (L/min), and VE (L/min) were collected throughout the exercise test. All subjects had these parameters, averaged over 10-second intervals, in computerized format. Peak VO_2 and peak respiratory exchange ratio (RER) were expressed as the highest 10-second average value obtained during the last stage of the exercise test. Ten-second–averaged VE and VCO_2 data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope). Previous work by our group has shown this method of calculating the VE/VCO_2 slope to be optimal for predicting risk.[16] Heart rate data were averaged over 10-second intervals for the HRR_1 calculation. Heart rate at 1 minute post-CPX was subtracted from maximal heart rate during the exercise test to produce a measure of HRR_1 in beats per minute.

End points

Subjects were followed for cardiac-related events (mortality or hospitalization) 1 year after exercise testing via medical chart review. Cardiac-related mortality was defined as death directly resulting from failure of the cardiac system. An example fitting this definition is myocardial infarction followed by cardiac arrest. Cardiac-related hospitalization was defined as a hospital admission directly resulting from cardiac dysfunction requiring inpatient care to correct. An example fitting this definition is decompensated HF requiring the use of an intravenous inotropic agent and/or diuretic. Any death or hospital admission with a cardiac-related discharge diagnosis, confirmed by diagnostic tests or autopsy, was considered an event. The most common causes of mortality, as per discharge diagnosis, were cardiac arrest, myocardial infarction, and HF. The most common causes of hospitalization were decompensated HF and coronary artery disease. Subjects in whom mortality or hospitalization was of a noncardiac etiology were treated as censored cases.

Table II. Univariate and multivariate Cox regression results

CPET variable	χ^2	*P*
Univariate analysis		
LVEF	3.6	.06
HF etiology (ischemic vs nonischemic)	8.6	.003*
Peak V_{O_2}	16.6	<.001*
VE/V_{CO_2} slope	33.5	<.001*
HRR_1	17.2	<.001*
Multivariate analysis		
VE/V_{CO_2} slope	33.5	<.001*
HRR_1	12.9 (residual χ^2)	<.001*
Peak V_{O_2}	0.90 (residual χ^2)	.32
LVEF	2.1 (residual χ^2)	.15
HF etiology (ischemic vs nonischemic)	3.3 (residual χ^2)	.07

*Statistically significant.

Table III. Receiver operating characteristic curve analysis results

	Area under ROC curve	*P*	Optimal threshold value	Sensitivity (%)	Specificity (%)
VE/V_{CO_2} slope	0.85	<.001*	≤/>34.4	77	89
HRR_1 (beat/min)	0.82	<.001*	</≥6.5	82	67

*Statistically significant.

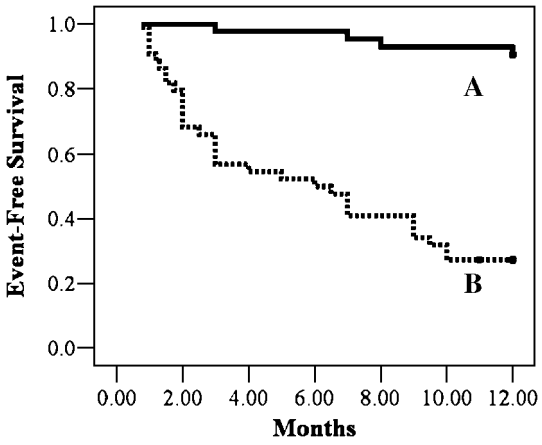
Statistical analysis

Pearson product moment correlation was used to assess the relationships between HRR_1 and peak V_{O_2}, VE/V_{CO_2} slope, age, and left ventricular ejection fraction (LVEF). Univariate Cox regression analysis was used to assess the independent prognostic value of LVEF, HF etiology, peak V_{O_2}, VE/V_{CO_2} slope, and HRR_1. Multivariate Cox regression analysis (forward stepwise method), using LVEF, HF etiology, peak V_{O_2}, VE/V_{CO_2} slope, and HRR_1, was used to assess the combined ability of these variables to predict 1-year cardiac-related events. Entry and removal *P* values for the multivariate analyses were set at .05 and .10, respectively. Receiver operating characteristic (ROC) curves were constructed for variables retained in the multivariate Cox regression analysis. Optimal threshold values (highest combination of sensitivity/specificity) were identified for the 1-year end points via ROC curve analysis and used to determine a composite hazard ratio for subjects possessing high-risk CPX values. Kaplan-Meier analysis was used to assess differences in cardiac-related events between subjects above or below CPX threshold values as determined by ROC curve analysis. The log-rank test was used to determine differences in event-free survival between groups. In a post hoc analysis, unpaired *t* testing was used to assess differences between key baseline and CPX data in those with normal and abnormal HRR_1 subgroups. Statistical tests with $P < .05$ were considered significant.

Table IV. Hazard ratios for VE/V_{CO_2} slope and HRR_1

	Hazard ratio	95% CI	*P*
Univariate			
VE/V_{CO_2} slope	11.6	4.1-33.0	<.001
HRR_1	4.6	2.3-9.3	<.001
Multivariate			
VE/V_{CO_2} slope	10.2	3.5-29.1	<.001
HRR_1	3.7	1.8-7.6	<.001

Figure 1



Kaplan-Meier analysis for 1-year cardiac-related events: VE/V_{CO_2} slope only.

Group	Characteristics	Subjects meeting criteria	Events	Percent event free
A	VE/V_{CO_2} slope ≤34.4	43	4	90.7
B	VE/V_{CO_2} slope >34.4	44	32	27.3

Log-rank = 39.1, $P < .0001$, • = censored cases

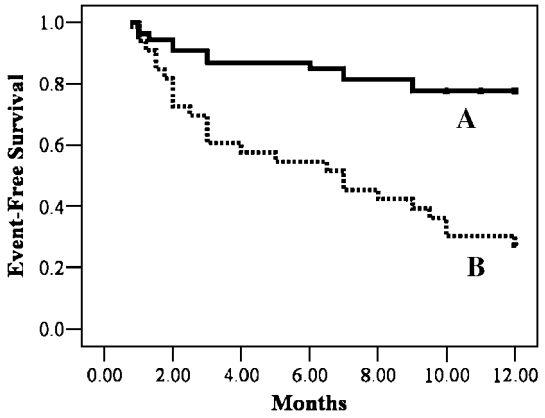
Results

Termination of exercise was due to volitional fatigue for all subjects. No subject demonstrated an abnormal physiological response to exercise (ECG signs of ischemia, new onset of arrhythmias, or excessive hypotensive/hypertensive response) warranting test termination before subject request.

The mean peak RER, peak V_{O_2}, VE/V_{CO_2} slope, and HRR_1 were 1.06 (±0.11), 14.8 (±4.7) mL · kg^{-1} · min^{-1}, 36.6 (±8.6), and 11.0 (±10.4) beat/min, respectively. HRR_1 was significantly correlated with peak V_{O_2} ($r = 0.31$, $P = .004$) and the VE/V_{CO_2} slope ($r = -0.28$, $P = .009$). HRR_1 was not significantly related to age ($r = -0.18$, $P = .09$), LVEF ($r = 0.17$, $P = .12$), or peak RER ($r = -0.05$, $P = .65$).

There were 9 cardiac-related deaths and 27 cardiac-related hospitalizations during the 1-year tracking period.

Figure 2



Kaplan-Meier analysis for 1-year cardiac-related events: HRR_1 only.

Group	Characteristics	Subjects meeting criteria	Events	Percent event free
A	HRR_1 ≥6.5 beat/min	54	12	77.8
B	HRR_1 <6.5 beat/min	33	24	27.3

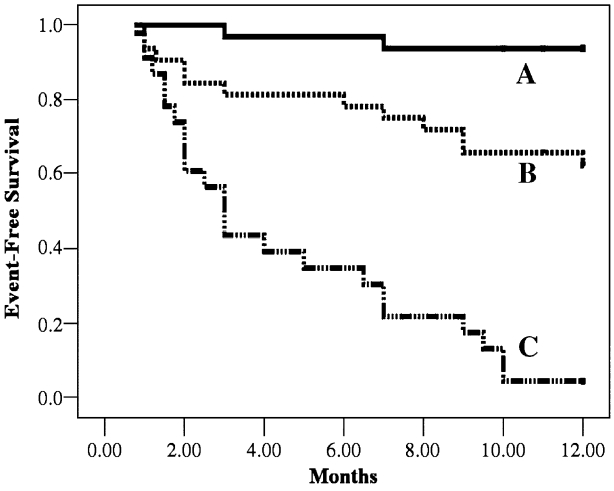
Log-rank = 22.7, $P < .0001$, • = censored cases

Univariate and multivariate Cox regression analyses are listed in Table II. Heart failure etiology (ischemic = worse prognosis), peak Vo_2, VE/VCO_2 slope, and HRR_1 were all significant univariate predictors of cardiac-related events. Left ventricular ejection fraction was not a significant univariate predictor of cardiac-related events. In the multivariate analysis, VE/VCO_2 slope was the strongest predictor of cardiac-related events. HRR_1 added additional predictive value and was retained in the regression. Heart failure etiology, LVEF, and peak Vo_2 did not add additional predictive value and was not retained in the multivariate regression.

Receiver operating characteristic curve analysis results are listed in Table III. Both the VE/VCO_2 slope and HRR_1 prognostic classification schemes were statistically significant; the optimal threshold values were ≤/>34.4 and </≥6.5, respectively. Univariate and multivariate hazard ratios for the optimal VE/VCO_2 slope and HRR_1 threshold values are listed in Table IV. Hazard ratios for both variables were highly significant. In a post hoc analysis, we assessed the prognostic classification scheme of HRR_1 in subgroups based upon β-blocker use. Area under the ROC curve for the subgroups not receiving and receiving a β-blocker were 0.85 ($P < .001$) and 0.79 ($P = .001$), respectively.

Kaplan-Meier analysis results are illustrated in Figures 1, 2, and 3. Based on the VE/VCO_2 slope and HRR_1 threshold values, there was a significant difference in event-free survival between groups. When combining VE/VCO_2 slope and HRR_1, a significant difference between subjects having one or two abnormal values was apparent. Furthermore, subjects with both an abnormal VE/VCO_2 slope and HRR_1 had the worst event-free survival.

Figure 3



Kaplan-Meier analysis for 1-year cardiac-related events: VE/VCO_2 slope and HRR_1.

Group	Characteristics	Subjects meeting criteria	Events	Percent event free
A	VE/VCO_2 slope ≤34.4 and HRR_1 ≥6.5 beat/min	32	2	93.8%
B	VE/VCO_2 slope ≤34.4 or HRR_1 ≥6.5 beat/min	32	12	62.5%
C	VE/VCO_2 slope >34.4 and HRR_1 <6.5 beat/min	23	22	4.4%

Log-rank = 59.4, $P < .0001$, • = censored cases

Table V. Unpaired *t* testing results for HRR_1 subgroups

	<6.5 beat/min (n = 33)	≥6.5 beat/min (n = 54)	*P*
Age (y)	52.5 (±11.4)	48.5 (±15.2)	.19
Ejection fraction (%)	24.1 (±11.8)	30.5 (±14.1)	.03*
Peak RER	1.07 (±0.11)	1.05 (±0.12)	.26
Peak Vo_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	13.1 (±4.1)	15.8 (±4.8)	.007*
VE/VCO_2 slope	39.6 (±8.6)	34.7 (±8.2)	.01*

*Statistically significant.

Given that HRR_1 was found to have significant prognostic value, unpaired *t* testing was used to assess differences in baseline and CPX values based on the optimal HRR_1 threshold value determined by ROC curve analysis. These results are presented in Table V. Age and peak RER were not significantly different between HRR_1 subgroups. However, peak Vo_2 and LVEF were

significantly lower and the VE/VCO_2 slope was significantly higher in the HRR_1 <6.5 beat/min subgroup.

Discussion

The results of the present study indicate that HRR provides valuable prognostic information in patients diagnosed with HF. This finding is consistent with previous investigations demonstrating the ability of HRR to predict adverse events in populations other than HF.[17-20] To our knowledge, the current study is the first to be conducted in subjects with compensated HF. Importantly, HRR_1 appears to outperform peak VO_2, LVEF, and HF etiology in predicting risk of death or hospitalization and adds significantly to the prognostic value of the VE/VCO_2 slope. Heart rate recovery may therefore provide important additive information to traditional exercise test variables during the clinical examination of patients diagnosed with HF.

The significant correlation between HRR_1 and both peak VO_2 and the VE/VCO_2 slope also appears to be a novel finding. Conversely, the relationships between HRR_1 and age, LVEF, and peak RER were not significant. The poor relationship between HRR_1 and LVEF is not surprising given the weak relationship between LVEF and other CPX variables, such as peak VO_2, in subjects diagnosed with HF.[21,22] Dividing the overall sample into subgroups according to an HRR_1 threshold value of </≥6.5 beat/min, peak VO_2 and LVEF were higher whereas the VE/VCO_2 slope was lower in patients with a more rapid HRR. Again, the difference in age and peak RER did not reach statistical significance between the HRR_1 subgroups. Collectively, these results indicate the following: (1) HRR_1 alone is a significant predictor of adverse events and is related to other prognostic CPX variables (peak VO_2 and VE/VCO_2 slope); (2) age and LVEF do not appear to modulate HRR_1, although subjects with a lower HRR_1 also tended to have a lower LVEF; and (3) subject effort did not appear to impact the HRR_1 response given it had no correlation with peak RER.

Possible mechanisms influencing variations in HRR have been studied by several groups.[9-11] Evidence from these studies suggests that the rate at which parasympathetic tone increases after the cessation of exercise appears to heavily influence the time course of HRR. Stated differently, a blunted decrease in heart rate after the cessation of exercise is indicative of an abnormal autonomic balance favoring the sympathetic system. The HF population is heterogeneous in many respects, including the distribution of sympathetic tone. In fact, higher sympathetic tone, measured by elevated sympathetic neurohormones, has previously been found to be a significant prognostic marker in subjects with HF.[23] The reason HRR has been shown to be a strong risk marker is likely because it reflects autonomic balance. Previous investigations have also examined the mechanism(s) precipitating an elevated VE relative to CO_2 elimination in patients diagnosed with HF. Several investigators have linked an abnormally elevated VE/VCO_2 slope to poor pulmonary perfusion[24,25] and decreased cardiac output, both at rest[26] and during maximal exercise.[27] Others have found a significant positive correlation between an abnormally elevated VE/VCO_2 slope and increased chemosensitivity.[28,29]

The ability of HRR and VE/VCO_2 slope to provide stronger prognostic value when assessed in combination may reflect the fact that they represent different pathophysiologic mechanisms. For example, a patient with HF who presents with both an abnormally low HRR (increased sympathetic tone) and an abnormally elevated VE/VCO_2 slope (decreased cardiac output, decreased pulmonary perfusion, and/or increased chemosensitivity) during CPX is likely to have more severe HF and therefore a poorer prognosis compared with individuals with only one abnormal response (HRR or VE/VCO_2 slope). It furthermore seems plausible to hypothesize that individuals with both a normal HRR and VE/VCO_2 slope during CPX would have fewer physiological abnormalities underlying their HF and thus a better short-term prognosis.

Forty-seven percent of the subjects in the present study were prescribed a β-blocking agent as part of their pharmacological management, and it could be argued that β-blockade could influence HRR and its interaction with prognosis. Racine et al[30] examined the effect of β-blocker therapy on HRR in a group of subjects with HF. Twenty-three subjects underwent maximal exercise testing, which was followed by use of a β-blocking agent (metoprolol or carvedilol) for 6 months. Subjects then underwent repeat exercise testing. After 6 months of β-blockade, the authors reported no significant difference in HRR measured at 1, 2, or 3 minutes after maximal exercise relative to baseline values. From these results, Racine et al[30] hypothesized that while improving left ventricular function and prognosis, β-blocker therapy may not influence the balance between sympathetic and parasympathetic tone during the acute phase of exercise recovery. The results of the study of Racine et al[30] suggest that controlling for β-blocker use in the evaluation of HRR may not be necessary. In addition, a post hoc ROC curve analysis in the current study demonstrated that the HRR_1 classification scheme remained prognostically significant irrespective of β-blocker use. Future research with larger subject samples and a greater number of events should examine this issue further.

Heart rate recovery was acquired during an active recovery period in the present investigation. All subjects ambulated at the same workload (1 mph/0% grade) for a minimum of 1 minute and 30 seconds. The optimal threshold value we observed may therefore not apply to exercise tests using a different intensity during active recovery or those that use an immediate supine position

in recovery. In fact, optimal calculation and clinical utilization of HRR has been a source of recent debate.[31] Given the differences in methodology for acquiring HRR, the current findings should be used to support the potential prognostic value of HRR in patients with HF and not to establish a threshold value for clinical application.

The small sample size of the present study is a limitation that must be rectified in future investigations. Although we were able to control for pulmonary and peripheral vascular disease, we were unable to control for differences in all aspects of pharmacological therapy and compliance (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists) or the impact of additional interventions (cardiac resynchronization therapy) and patient education during the 1-year follow-up period. In light of the paucity of data on HRR in HF and the limitations of our study, future research is required to confirm the results of the present investigation. Future investigations should also be directed toward assessing the impact of different exercise test recovery procedures (active recovery vs rest) and different exercise modes (treadmill vs bicycle) on HRR in patients with HF. These analyses are required before a standardized HRR recovery threshold value defining an abnormal vs normal response can be supported. The optimal period for acquiring HRR should also be determined. We were only able to calculate HRR at 1 minute because of the short duration of active recovery. Previous investigations in subjects not diagnosed with HF have shown that HRR measured at 1,[17,20] 2,[20] and 5[19] minutes after termination of exercise testing all have prognostic value. In these studies, both the optimal threshold values and time points of measurement differed, and these issues require further study, particularly in patients with HF. Lastly, volitional fatigue was the termination criteria for all exercise tests. The prognostic characteristics of HRR may differ in subjects whose exercise test is terminated secondary to ischemia or cardiac arrhythmias and should be the focus of future investigations. Clearly, a substantial amount of research in the area of HRR and HF is still required.

In conclusion, HRR is an easily attained exercise variable that appears to have significant prognostic value independently and in combination with previously established CPX variables in patients with HF. If the findings of the present study are confirmed, HRR, as a prognostic marker, may be used to help guide clinical decisions such as heart transplant listing and titration of pharmacological therapy. Continued research in this area is certainly warranted.

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