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Heart rate recovery after the 6 min walk test rather than distance ambulated is a powerful prognostic indicator in heart failure with reduced and preserved ejection fraction: a comparison with cardiopulmonary exercise testing

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Aims Heart rate recovery (HRR) appears to be a robust prognostic marker in heart failure (HF). When using the 6 min walk test (6MWT) in HF, distance ambulated is generally the reference prognostic variable. We hypothesized that HRR after the 6MWT would be a better prognostic measure than distance ambulated.

Methods and results A 6MWT and cardiopulmonary exercise testing (CPX) were randomly performed in 258 HF patients [216 HF with reduced EF (HFrEF) and 42 HF preserved EF (HFpEF)], after which HRR was measured. HRR was defined as the difference between heart rate at peak exercise and 1 min following test termination. Patients were assessed for major cardiac events during a mean follow-up period of 22.8 $\pm$ 22.1 months. There were 50 major cardiac events during the tracking period. Univariate Cox regression analysis results identified HRR after both the 6MWT and CPX as a significant ($P < 0.001$) predictor of adverse events. Multivariate Cox regression analysis revealed that dichotomized HRR after the 6MWT and CPX was the strongest predictor of survival (χ^2 61.1 and 53.8, respectively; $P < 0.001$), with LVEF (residual χ^2 6.1, $P < 0.05$) adding significant prognostic value to the 6MWT model and ventilatory efficiency (the VE/VCO_2 slope) (residual χ^2 6.6, $P < 0$ .05) adding significant prognostic value to the CPX model.

Conclusions HRR after the 6MWT is a powerful prognosticator that performs similarly to HRR after maximal exercise. If confirmed in subsequent studies, 6MWT HRR should replace 6MWT distance as the reference criterion 6MWT measure to consider when grading cardiovascular risk in HF patients.

Keywords Heart failure • Heart rate recovery • 6 Min walk test • Cardiopulmonary exercise test

Introduction

The 6 min walk test (6MWT) is a functional performance measure that has received substantial attention as a tool to examine the functional status of patients with heart and lung disease.[1–3] The distance ambulated during the 6MWT has been most studied, with a distance of 300 m being a threshold below which a patient with heart failure (HF) appears to have poorer prognosis.[2,3] A 6MWT distance of 300 m was also recently found to be a significant predictor of all-cause mortality in a multivariate model

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examining predictors of clinical outcome in elderly patients with advanced HF.[4] Even so, cardiopulmonary exercise testing (CPX) is considered the clinical gold standard for the functional assessment of patients with systolic HF.[5,6] A variety of CPX measurements have been found to provide substantial prognostic value in the assessment of patients with HF, and include peak VO_2, the minute ventilation/carbon dioxide production (VE/VCO_2) slope, and exercise oscillatory ventilation (EOV).

An additional measurement which appears to have substantial prognostic value in patients with and without HF is the trajectory of heart rate (HR) decline after test termination, commonly referred to as heart rate recovery (HRR).[7–13] A low HRR value has consistently been observed to be a marker of increased mortality.[7–13] The rapid deceleration of the HR after exercise appears to reflect parasympathetic reactivation, providing a unique perspective regarding the health and function of the autonomic nervous system.[7–13] A HRR $\leq$12 beats at 1 min post-exercise has been proposed as a threshold to define an abnormal response,[12,13] which is supported by other investigators.[10,11]

The clinical utility of HRR does not appear to be dependent on maximal exercise since two previous large studies administering symptom-limited exercise tests (terminating exercise at 85–90% of age-predicted peak HR) found that an abnormal HRR remained a prognostic index despite achieving less than age-predicted maximal HR values.[14,15] Because of previous findings, we believed it important to examine the prognostic utility of HRR after an accepted submaximal functional assessment such as the 6MWT, testing the hypothesis that it may become a valuable submaximal variable in the prognostic work-up of HF patients.

Methods

This was a prospective study of patients with HF referred for functional assessment at San Paolo Hospital, Milan, Italy. Two hundred and fifty-eight patients diagnosed with HF who underwent a 6MWT and CPX between June 1999 and December 2008 were included in the study. Patients who were unable to perform either exercise assessment were excluded from the study. All patients were in NYHA functional classes II and III. Patients with both HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) were enrolled. HFpEF was defined using the following criteria: (i) signs and symptoms of HF; (ii) presence of preserved LV systolic function (LVEF $\geq$50%) as assessed by two-dimensional echocardiography;[16] and (iii) documentation of mitral inflow early (E) velocity to mitral annulus early velocity (E′) $\geq$ 8.[17] Approval by the institutional review board was obtained before the study was initiated, and all patients provided written informed consent to participate in the study. The investigation conforms with the principles outlined in the Declaration of Helsinki.

6 min walk test procedures

The 6MWT was performed on a level surface by a physician who was unaware of echocardiographic, CPX, and clinical results. Each subject underwent two 6MWTs performed on separate days. The first test was performed to familiarize the patient with the 6MWT and the second test was performed to obtain true functional performance. In 80 patients, a third 6MWT was performed to test day-to-day reproducibility. Patients were instructed to cover the greatest distance possible during the allotted time, at a self-determined walking speed, and were allowed to pause and rest when needed. The distance covered was measured by a body-borne pedometer with which the total number of steps taken during the 6MWT were used to calculate the 6MWT distance using the equation reported by Roul *et al.* ($d = y \times 10$ m/x; where d = distance ambulated in m; y = total number of steps during 6MWT; and x = number of steps for each subject to cover 10 m).[3] The distance ambulated in 6 min was also dichotomized using the commonly accepted threshold (6MWT distance $\leq$ / $>$ 300 m).[2,3] The HR was obtained while standing via electrocardiographic telemetry at rest before the 6MWT, at the end of the 6MWT, and 1 min after the 6MWT. The 6MWT HR reserve was calculated as the difference between the HR at the end of the 6MWT and the resting HR. The 6MWT HRR was defined as the difference between the HR at the end of the 6MWT and 1 min after the 6MWT. The recovery period following the 6MWT was passive and consisted of stationary standing.

Cardiopulmonary exercise testing procedures

Symptom-limited CPX was performed on a bicycle ergometer for all subjects. Pharmacological therapy was maintained during CPX. Individualized ramp protocols were designed to obtain a duration between 8 and 10 min. Ventilatory expired gas analysis was performed using a Sensormedics metabolic cart (Vmax, Yorba Linda, CA, USA). Before each test, the equipment was calibrated according to the manufacturer's specifications using reference gases.

Standard 12-lead ECGs were obtained at rest, each minute during exercise, and for at least 5 min during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. The HR was determined at rest, peak exercise, and at 1 min of recovery. The percentage age-predicted maximal HR achieved was determined by the following equation: [peak HR/(220 − age)] × 100. The CPX HR reserve was calculated as the difference between the peak HR and resting HR. The CPX HRR was defined as the difference between peak HR and HR at 1 min following test termination. An active cool-down period of at least 1 min was employed for all tests. In addition, minute ventilation [VE; body temperature, pressure, and saturated (BTPS)], oxygen uptake [VO_2; standard temperature, pressure, and dry (STPD)], and carbon dioxide output (VCO_2; STPD) were acquired breath-by-breath, averaged over 30 s, and printed using rolling averages every 10 s. The V-slope method was used to measure the anaerobic threshold.[18] Peak VO_2 and the peak respiratory exchange ratio (RER) were expressed as the highest 10 s averaged sample obtained during the last 20 s of testing. VE and VCO_2 values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA, USA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, where m = slope). Exercise oscillatory ventilation (EOV) during CPX was defined as previously described in detail.[19,20] Briefly, criteria for EOV included the presence of $\geq$3 regular oscillatory fluctuations in VE with a minimal average amplitude of 5 L/min persisting for at least 60% of the entire exercise test. The Modified Borg Rating of Perceived Exertion (RPE) was also obtained throughout the CPX.[21]

Test termination criteria consisted of symptoms (i.e. dyspnoea and/or fatigue), ventricular tachycardia, $\geq$2 mm of horizontal or downsloping ST-segment depression, or a drop of systolic blood pressure $\geq$20 mmHg during progressive exercise. A qualified exercise physiologist with physician supervision conducted each exercise test.

Echocardiography

The LV chamber dimensions were evaluated using standard procedures. The LVEF was calculated from two-dimensional apical images according to Simpson's method.

Endpoints

Subjects were followed for major cardiac-related events (i.e. cardiac death or urgent transplantation) by hospital and outpatient medical chart review to obtain the high likelihood that all major events were captured. Any death with a cardiac-related discharge diagnosis was considered an event. Clinicians conducting the study measurements were not involved in decisions regarding cause of death or heart transplantation.

Statistical analysis

A statistical software package (SPSS 19.0, Chicago, IL, USA) was used to perform all analyses. Continuous and categorical data are reported as mean ± standard deviation and percentages, respectively. Independent *t*-tests and χ^2 tests were used to assess differences in patient characteristics, 6MWT variables, and CPX variables between subjects who remained event free or suffered a major cardiac event during the tracking period and between patients with HFrEF and HFpEF. The area under the receiver operating characteristic (ROC) curve was compared between the 6MWT distance ambulated and 6MWT HRR, and between 6MWT HRR and CPX HRR. Additional diagnostic testing of HRR after the 6MWT and CPX was performed, and included the calculation of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Univariate Cox regression analysis was used to assess the prognostic value of key patient characteristics, 6MWT, and CPX variables. Multivariate Cox regression analysis (forward stepwise method; entry and removal value 0.05 and 0.10, respectively) was used to assess the prognostic value of the 6MWT vs. CPX by using two patient characteristics (age and LVEF), four 6MWT variables (6MWT distance, peak HR, 6MWT HR reserve, and dichotomous 6MWT HRR), and four CPX variables (peak VO_2, the VE/VCO_2 slope, EOV, and dichotomous CPX HRR) in two separate models using the 6MWT variables and CPX variables. Hazard ratios were also determined according to the established dichotomous classification of HRR ($\leq$ / $>$ 12 beats)[9–12] as well as 6MWT (6MWT distance $\leq$ / $>$ 300 m).[2,3] Kaplan–Meier analysis was used to assess the differences in survival among subjects according to dichotomous classification of HRR. The log-rank test determined statistical significance among the HRR categories for the Kaplan–Meier analyses. Separate univariate Cox regression analyses of survival in patients with HFrEF and HFpEF using the same 6MWT and CPX variables as above were performed. Separate multivariate Cox regression analyses of survival in patients with HFrEF using the same 6MWT and CPX variables as above were also performed. In patients with HFpEF, separate multivariate Cox regression analyses of survival using two 6MWT variables (6MWT distance and 6MWT dichotomous HRR) and two CPX variables

Table 1 Differences in patient characteristics, 6 min walk test, and cardiopulmonary exercise testing variables according to major cardiac event status

	Event free (n = 208)	Major cardiac event (n = 50)	*P*-value
Age (years)	61.4 ± 10.4	64.5 ± 7.0	0.02
Height (cm)	169.7 ± 7.4	169.9 ± 7.0	0.88
Weight (kg)	76.4 ± 14.6	74.7 ± 9.0	0.31
LVEF (%)	37.3 ± 10.9	32.7 ± 12.3	0.01
Female/male (%)	27	25	0.86
COPD (%)	24	38	0.05
6MWT distance (m)	357 ± 95	329.5 ± 77	0.05
6MWT resting HR (b.p.m.)	70.9 ± 8.3	74.2 ± 9.2	0.02
6MWT peak HR (b.p.m.)	123 ± 16.6	116.1 ± 12.1	0.001
6MWT HRR (beats)	12.9 ± 3.0	9.6 ± 1.9	<0.001
6MWT HR reserve (beats)	52.0 ± 18.2	41.9 ± 4.9	<0.001
CPX resting HR (b.p.m.)	73.2 ± 9.2	76.2 ± 9.1	0.03
CPX peak HR (b.pm.)	130.6 ± 17.1	122.9 ± 12.4	<0.001
CPX HRR (beats)	18.5 ± 3.2	14.8 ± 1.9	<0.001
CPX HR reserve (beats)	57.5 ± 19.4	46.6 ± 16.1	<0.001
CPX Borg RPE (0–10)	5.8 ± 1.1	7.2 ± 0.7	<0.001
CPX peak RER	1.06 ± 0.13	1.05 ± 0.12	0.86
CPX peak VO_2 (mL O_2/kg/min)	15.4 ± 4.8	13.5 ± 3.8	0.003
CPX VO_2AT (mL O_2/kg/min)	11.3 ± 3.6	9.6 ± 3.2	0.002
CPX VE/VCO_2 slope	34.1 ± 7.2	39.4 ± 8.5	<0.001
CPX EOV (%)	36.5	76.0	<0.001
ACE inhibitors (%)	82	76	0.42
Beta-blockade (%)	60	56	0.63
Anti-aldosterone (%)	36	60	<0.05

AT, anaerobic threshold; CPX, cardiopulmonary exercise testing; EOV, exercise oscillatory ventilation; HR, heart rate; HRR, heart rate recovery; 6MWT, 6 min walk test; RER, respiratory exchange ratio; RPE, rating of perceived exertion; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.

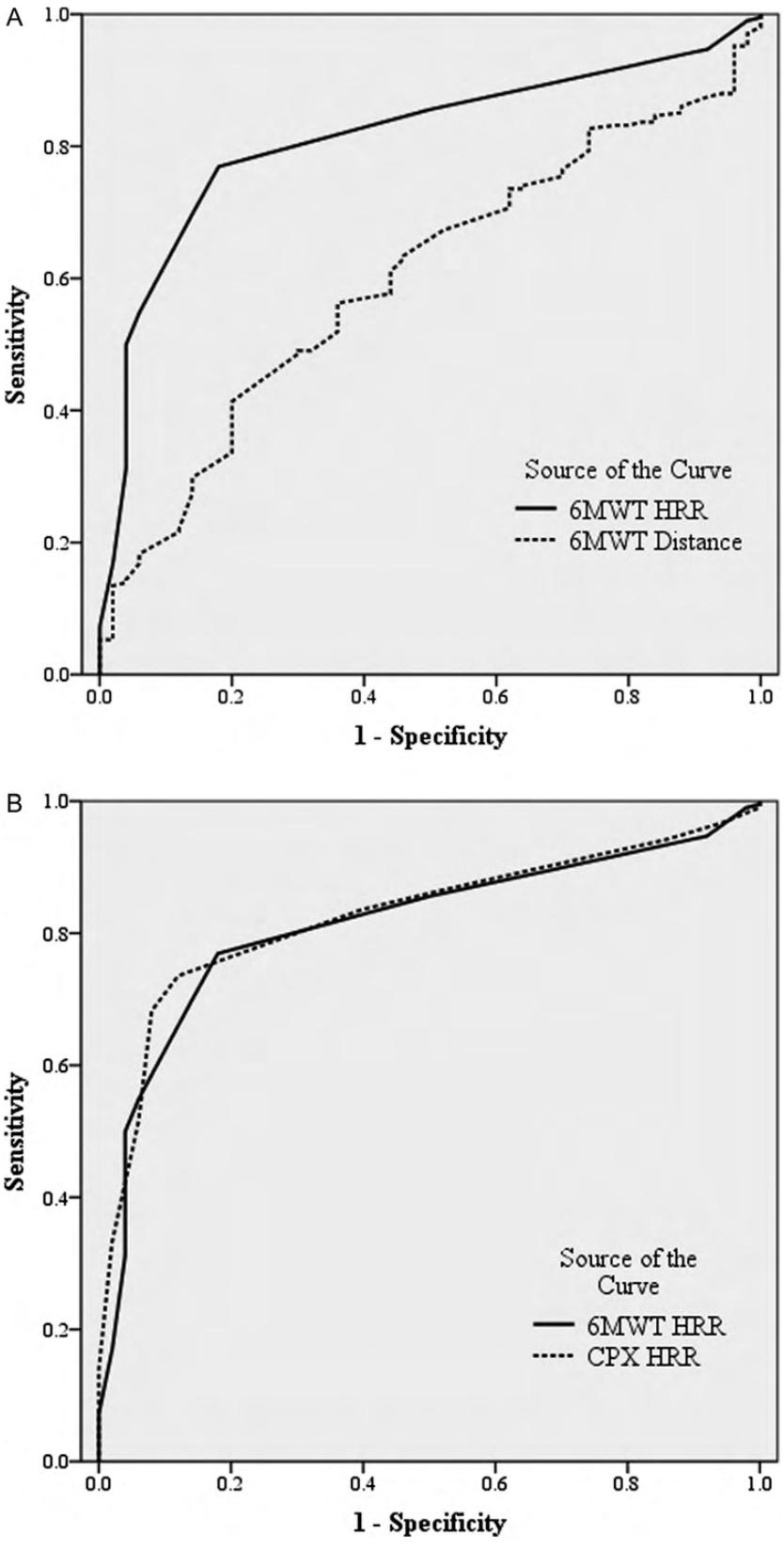

Figure 1 Receiver operating characteristic curve comparing (*A*) 6MWT HRR and 6MWT distance and (*B*) 6MWT HRR and CPX HRR. 6MWT, 6 min walk test; HRR, heart rate recovery; CPX, cardiopulmonary exercise testing.

(VE/VCO_2 slope and CPX dichotomous HRR) were also performed. A *P*-value <0.05 was considered statistically significant for all tests.

Results

Follow-up on survival

No patients were lost to follow-up during the mean follow-up period of 22.8 ± 22.1 months. There were 50 cardiac-related events (48 deaths and 2 urgent transplantations) during the tracking period, yielding an annual event rate of 9.3%. None of the subjects in the study experienced a non-cardiac-related death. The mortality rate of patients diagnosed with non-ischaemic vs ischaemic aetiology of HF was not significantly different between survivors and non-survivors (65%, 82/126 vs. 60%, 18/30; $P = 0.81$). The mortality rate of patients diagnosed with HFrEF (19.1%, 41 of 215) and HFpEF (17.1%, 7 of 41) was similar ($P = 0.76$).

Baseline characteristics

Table 1 lists patient characteristics as well as 6MWT and CPX variables between subjects who were event free and those who suffered a major cardiac event. Based on the patient characteristics and CPX results presented in *Table 1*, the patient population represents a mixed group with advanced and intermediate levels of HF. There were significant differences for all variables, with the exception of height, weight, 6MWT distance ambulated, and peak RER. Subjects who suffered a major cardiac event were significantly older, had poorer cardiac performance, and had a higher resting HR and lower peak HR (yielding a lower HR reserve). Moreover, subjects suffering a major cardiac event had significantly higher Borg RPE scores, a lower peak VO_2, and a greater VE/VCO_2 slope. A greater percentage of subjects suffering an event also presented with EOV. Although not statistically significant ($P = 0.75$), a greater number of patients with ischaemic HF ($n = 32$) experienced a major cardiac event compared with patients with non-ischaemic HF ($n = 18$).

The characteristics of patients with HFrEF ($n = 216$) and HFpEF ($n = 42$) were relatively similar except for significant differences in the LVEF ($32.8 \pm 8.3\%$ vs. $55.2 \pm 4.3\%$, respectively; $P < 0.001$) and peak RER (1.05 ± 0.13 vs. 1.10 ± 0.13, respectively; $P < 0.01$). No significant differences in the provision of medical therapies to patients with HFrEF and HFpEF were observed.

Receiver operating characteristic curves and related diagnostic analyses

Figure 1 presents the ROC curves comparing 6MWT HRR with 6MWT distance ambulated and the 6MWT HRR with CPX HRR. The area under the ROC curve for 6MWT HRR was 0.813 compared to 0.600 for the 6MWT distance. The area under the ROC curve for HRR after CPX was slightly greater (0.827) than that for HRR after the 6MWT (0.813). The sensitivity and specificity of 6MWT HRR were 0.94 and 0.55, respectively. The sensitivity and specificity of CPX HRR were 0.88 and 0.74, respectively. The positive and negative predictive values of 6MWT HRR were 0.33 and 0.97, respectively. The positive and negative predictive values of CPX HRR were 0.44 and 0.96, respectively. The accuracy of 6MWT HRR was 0.62 compared with 0.76 for CPX HRR.

Table 2 Univariate prognostic analysis for key 6 min walk test and cardiopulmonary exercise testing variables

	χ^2	Hazard ratio (95% CI)	*P*-value
6MWT variables			
Resting HR	1.37	–	0.24
Peak HR	23.9	0.95 (0.94–0.97)	<0.001
HR reserve	22.6	0.96 (0.95–0.98)	<0.001
HRR	56.3	0.69 (0.62–0.77)	<0.001
HRR*	60.9	22.7 (6.98–73.66)	<0.001
Distance	6.80	0.99 (0.99–0.99)	<0.01
Distance*	3.78	–	0.05
CPX variables			
VE/VCO_2 slope	21.3	1.07 (1.04–1.10)	<0.001
Peak VO_2	13.6	0.88 (0.82–0.94)	<0.001
VO_2AT	15.3	0.83 (0.75–0.92)	<0.001
EOV	35.9	6.15 (3.19–11.85)	<0.001
Borg RPE	63.0	2.91 (2.19–3.85)	<0.001
HR reserve	24.2	0.96 (0.95–0.98)	<0.001
Resting HR	2.5	–	0.12
Peak HR	26.0	0.95 (0.94–0.97)	<0.001
HRR	52.3	0.71 (0.64–0.78)	<0.001
HRR*	66.6	15.6 (6.61–36.77)	<0.001

AT, anaerobic threshold; CI, confidence interval; CPX, cardiopulmonary exercise testing; Distance*, dichotomized 6MWT distance (<300 m vs. ≥300 m); EOV, exercise oscillatory ventilation; HR, heart rate; HRR, heart rate recovery; HRR*, dichotomized HRR (≤12 beats vs. >12 beats); 6MWT, 6 min walk test; RPE, rating of perceived exertion; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.

Univariate Cox regression analyses

Table 2 lists the univariate Cox regression analyses for key 6MWT and CPX variables. With the exception of 6MWT resting HR and dichotomized 6MWT (6MWT distance $\leq$ / $>$ 300 m), all other variables were prognostically significant. The dichotomized HRR during the 6MWT (HRR at 1 min $\leq$ / $>$ 12 beats) was the strongest significant univariate predictor of major cardiac events (χ^2 60.9, $P < 0.001$) and the 6MWT distance was the least significant predictor of major cardiac events (χ^2 6.80, $P < 0.01$). Kaplan–Meier analysis for the HRR threshold of $\leq$ / $>$ 12 beats after the 6MWT is illustrated in *Figure 2A*.

Univariate Cox regression analysis results for key CPX variables are also listed in *Table 2*. With the exception of CPX resting HR, all other variables were prognostically significant. The dichotomized HRR during CPX (HRR at 1 min $\leq$ / $>$ 12 beats) was the strongest significant univariate predictor of major cardiac events (χ^2 66.6, $P < 0.001$). The Borg RPE at peak exercise was also a significant predictor of major cardiac events (χ^2 63.0, $P < 0.001$). Exercise oscillatory ventilation and the VE/VCO_2 slope were also highly significant predictors of major cardiac events (χ^2 35.9 and 21.3, respectively; $P < 0.001$). Kaplan–Meier analysis for the HRR threshold of $\leq$ / $>$ 12 beats after CPX is illustrated in *Figure 2B*.

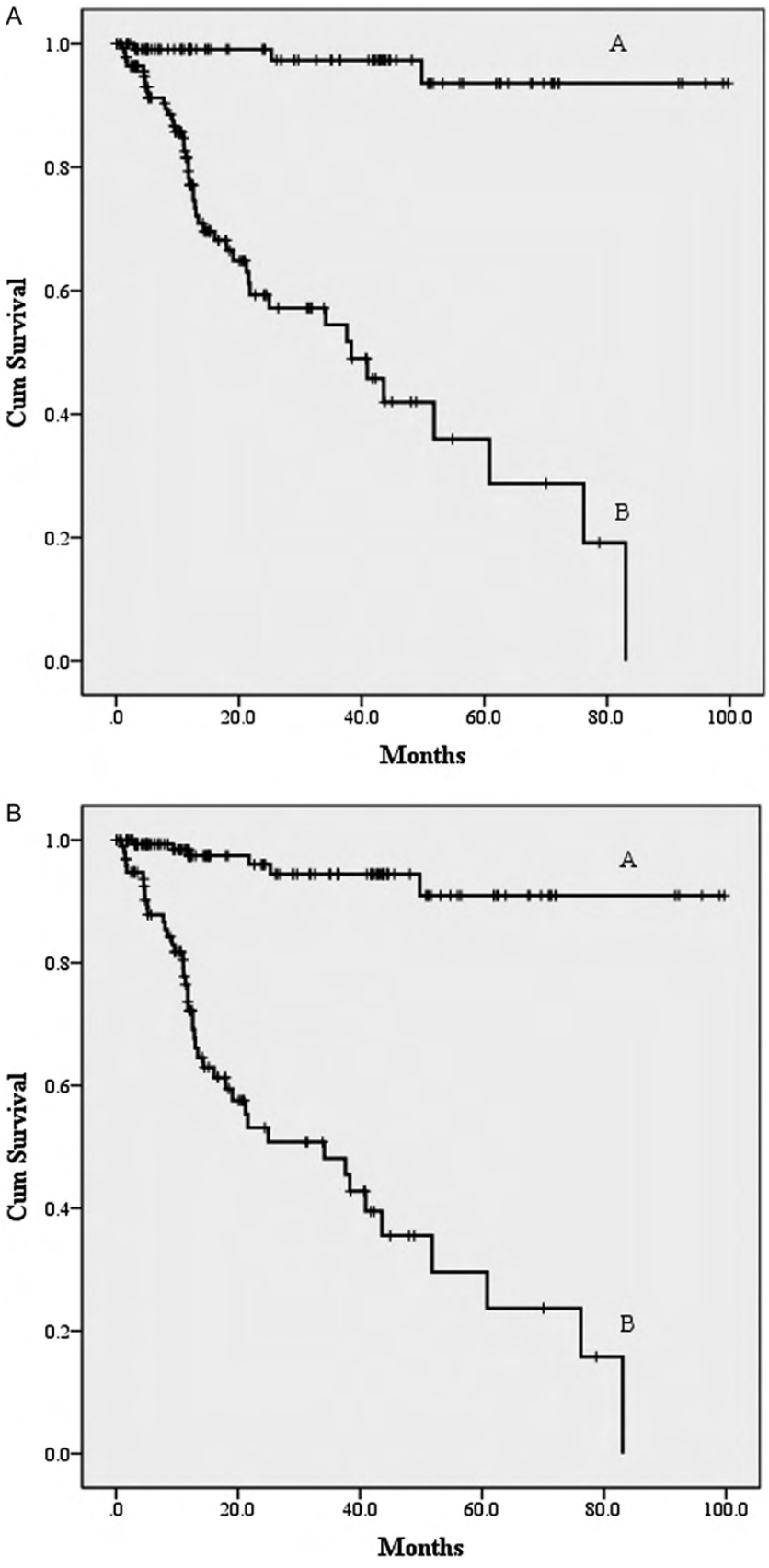

Figure 2 Kaplan–Meier analysis for (*A*) 6MWT HRR and (*B*) CPX HRR. 6MWT, 6 min walk test; HRR, heart rate recovery; CPX, cardiopulmonary exercise testing. A = HRR > 12 beats; B = HRR < 12 beats.

Table 3 Prognostic analysis for key patient characteristics, 6 min walk test, and cardiopulmonary exercise testing variables

	Univariate analysis		
	χ^2	Hazard ratio (95% CI)	*P*-value
Age	7.11	1.04 (1.01–1.08)	<0.01
HF aetiology	0.98	1.41 (1.0–1.0)	0.32
LVEF	5.99	0.03 (0.002–0.54)	<0.05
6MWT variables	**Multivariate analysis**		
	χ^2		*P*-value
HRR*	61.07		<0.001
	Residual χ^2		*P*-value
LVEF	6.12		<0.05
Age	2.15		0.14
Peak HR	0.82		0.36
HR reserve	0.59		0.44
6MWT distance	0.002		0.96
CPX variables	**Multivariate analysis**		
	χ^2		*P*-value
HRR*	53.82		<0.001
	Residual χ^2		*P*-value
VE/VCO_2 slope	6.65		<0.05
EOV	3.07		0.08
LVEF	2.23		0.13
Age	0.29		0.59
Peak VO_2	0.004		0.95

CI, confidence interval; CPX, cardiopulmonary exercise testing; EOV, exercise oscillatory ventilation; HF, heart failure; HR, heart rate; HRR*, dichotomized heart rate recovery (≤12 beats vs. >12 beats); 6MWT, 6 min walk test; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.

Multivariate Cox regression analysis

Table 3 lists the univariate and multivariate Cox regression analyses for key resting and exercise variables. Age and LVEF were significant univariate predictors of major cardiac events (χ^2 7.11 and 5.99, respectively; $P < 0.001$ and $P < 0.05$, respectively). Multivariate analysis of the 6MWT variables revealed that the dichotomous 6MWT HRR was the most robust prognostic marker (χ^2 61.07, $P < 0.001$), while LVEF added significant predictive value (residual χ^2 6.12, $P < 0.05$) and was retained in the regression, whereas HF aetiology and all other key 6MWT variables were not significant univariate or multivariate prognostic markers.

Multivariate analysis of the CPX variables revealed that the dichotomous CPX HRR was the most robust prognostic marker (χ^2 53.82, $P < 0.001$), while the VE/VCO_2 slope added significant predictive value (residual χ^2 6.65, $P < 0.05$) and was retained in the regression. HF aetiology and all other key CPX variables were not significant multivariate predictors of major cardiac events.

Univariate and multivariate Cox regression subanalyses of major cardiac events by heart failure type

Separate univariate and multivariate Cox regression analyses of major cardiac events in patients with HFrEF and HFpEF using 6MWT variables as well as CPX variables were performed and found many similar significant predictors of major cardiac events in patients with HFrEF and HFpEF (*Table 4*). Univariate Cox regression analyses of only patients with HFrEF found all previous 6MWT and CPX variables to be significant predictors of major cardiac events, but with lower χ^2 values. The HFrEF univariate Cox regression analysis results identified the dichotomized 6MWT HRR and CPX HRR as the most powerful predictors (χ^2 56.25 and 59.59, respectively; $P < 0.001$). Univariate Cox regression analyses of only patients with HFpEF found all previous 6MWT and CPX variables to be significant predictors of major cardiac events, except for 6MWT distance and CPX non-dichotomized HRR. Furthermore, the χ^2 values of all significant HFpEF 6MWT and CPX variables were lower than the χ^2 values of the HFrEF 6MWT and CPX variables. The most robust HFpEF 6MWT and CPX predictors of major cardiac events were peak HR and the VE/VCO_2 slope, respectively (χ^2 13.51, $P < 0.001$ and 10.52, $P < 0.01$, respectively). Age and LVEF were both significant univariate predictors of major cardiac events in patients with HFrEF, but only age was a significant univariate predictor of major cardiac events in patients with HFpEF (*Table 4*).

Multivariate Cox regression analysis of patients with HFrEF found identical multivariate predictors of major cardiac events for the 6MWT and CPX, with dichotomous HRR being the strongest predictor (χ^2 56.25 and 51.51, respectively; $P < 0.001$) and

Table 4 Prognostic analysis for key patient characteristics, 6 min walk test variables, and cardiopulmonary exercise testing variables in patients with reduced and preserved ejection fraction

	χ^2	Hazard ratio (95% CI)	*P*-value
Reduced EF			
Age	4.05	1.04 (1.00–1.07)	<0.05
LVEF	14.77	0.001 (0.000–0.025)	<0.001
6MWT variables			
HRR	57.09	0.66 (0.59–0.75)	<0.001
HRR*	56.25	30.19 (7.22–126.31)	<0.001
Distance	2.93	–	0.08
Distance*	0.73	–	0.39
Peak HR	13.75	0.96 (0.94–0.98)	<0.001
HR reserve	13.67	0.97 (0.95–0.98)	<0.001
CPX variables			
HRR	56.40	0.65 (0.58–0.74)	<0.001
HRR*	59.59	16.88 (6.59–43.18)	<0.001
VE/VCO_2 slope	14.38	1.06 (1.03–1.09)	<0.001
Peak VO_2	7.08	0.90 (0.83–0.97)	<0.01
EOV	28.61	5.87 (2.87–12.03)	<0.001
Preserved EF			
Age	4.46	1.09 (1.00–1.18)	<0.05
LVEF	0.18	–	0.67
6MWT variables			
HRR	2.92	–	0.08
HRR*	6.11	8.87 (1.05–74.94)	<0.05
Distance	5.45	0.99 (0.98–0.99)	<0.05
Distance*	5.24	0.18 (0.04–0.89)	<0.05
Peak HR	13.51	0.91 (0.85–0.97)	<0.001
HR reserve	11.02	0.93 (0.89–0.98)	<0.01
CPX variables			
HRR	2.68	–	0.10
HRR*	7.53	10.43 (1.26–86.18)	<0.01
VE/VCO_2 slope	10.52	1.16 (1.05–1.27)	<0.01
Peak VO_2	8.76	0.77 (0.63–0.95)	<0.01
EOV	7.18	7.64 (1.49–39.18)	<0.01

CI, confidence interval; CPX, cardiopulmonary exercise testing; Distance*, dichotomized 6MWT distance (<300 m vs. ≥300 m); EOV, exercise oscillatory ventilation; HR, heart rate; HRR, heart rate recovery; HRR*, dichotomized HRR (≤12 beats vs. >12 beats); 6MWT, 6 min walk test; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.

LVEF adding significant predictive value (residual χ^2 12.22 and 6.17, respectively; $P < 0.05$), which was retained in both the 6MWT and CPX regressions. Multivariate Cox regression analysis of patients with HFpEF using 6MWT distance and dichotomous 6MWT HRR as predictors found the dichotomous 6MWT HRR to be the only significant predictor of major cardiac events (χ^2 6.11, $P < 0.05$). Multivariate Cox regression analysis of patients with HFpEF using the CPX variables dichotomous CPX HRR and the VE/VCO_2 slope as predictors found the VE/VCO_2 slope to be the only significant predictor of major cardiac events (χ^2 10.52, $P < 0.01$).

Discussion

Our study provides new information by expanding the clinical and prognostic applicability of the 6MWT in a cohort of HF patients with both HFrEF and HFpEF. Specifically, this is the first study aimed at identifying whether the HR response during and after the 6MWT provides significant prognostic insights, challenging the distance ambulated as the reference measure in the assessment of cardiac-related functional limitation. Importantly, HRR after the 6MWT is a powerful prognosticator that performs better than distance ambulated and similarly to HRR after maximal exercise.

Initial studies examining the prognostic value of the 6MWT in patients with HF found that a distance ≤300 m was associated with poorer survival.[1–3] However, more recent investigations have observed that the 6MWT distance provides very little prognostic information unless patients have advanced HF.[22–25] This has been primarily interpreted as a consequence of beta-blocker therapy which was not standard therapy during earlier investigations,[25] but additional reasons may be advocated. Interestingly, in the current study, 6MWT distance was a significant univariate predictor of major cardiac events, but only as a continuous variable, and the threshold of 300 m was a near significant ($P = 0.05$) univariate predictor of major cardiac events. Furthermore, 6MWT distance was not retained as a significant predictor in multivariate analyses.

A previous study of the 6MWT in patients with HFrEF who were awaiting cardiac transplantation found that HRR at minute two of recovery was observed to be significantly lower in patients who died or underwent cardiac transplantation compared with patients surviving and not receiving cardiac transplantation.[26] This previous study of only patients with HFrEF did not extend their analyses to other HR measures.[26] Our study examined the prognostic value of several HR measures and found that most were significant predictors of major cardiac events in patients with both HFrEF and HFpEF, with 6MWT HRR being the strongest predictor.

Overall, the 6MWT seems to elicit a cardiac response that is similar to that observed during a maximal effort from CPX and is able to identify a greater percentage of patients with an abnormal HRR. In fact, the mean peak HR of the 6MWT was 122 ± 16 b.p.m. and the mean peak HR during CPX was 129 ± 17 b.p.m. In view of these findings, it is possible that beta-blocker therapy, which may be responsible for the decreased prognostic value of 6MWT distance, may also be responsible for the increased sensitivity of the 6MWT HRR.[25] It is also possible that the autonomic nervous system response during the 6MWT provides a more balanced sympathetic/parasympathetic drive that possibly better reflects parasympathetic reactivation in patients with HF.[6–14] At the very least, it appears that the 6MWT provides a sufficient stimulus to capture chronotropic incompetence, parasympathetic reactivation, and related symptoms in patients with HF.[27]

It is important to note that beta-blockade was included in the Cox regression models for both CPX and the 6MWT, and it was not observed to be a significant predictor of major cardiac events in either model. Furthermore, separate Cox regression models were analysed for patients with and without beta-blockade and there was no difference in the results for the separate models compared with the full models of the 6MWT and CPX. Thus, beta-blockade does not appear to influence the prognostic ability of

HRR in patients with HF as has been shown previously.[28] This study has expanded the clinical utility of HRR not only after CPX, but also after the 6MWT in patients with and without beta-blockade. However, due to the relatively small sample size, we are unable to make conclusive decisions regarding the effects of beta-blocker treatment on the major adverse events of the study.

Assessment of HRR during the 6MWT emerged as comparably valuable in patients with HFrEF and HFpEF. This finding is particularity relevant since HFpEF patients are more likely to be elderly and less prone to undergo a maximal symptom-limited evaluation. Also, elderly patients seem to be less tolerant of the mouthpiece and noseclip required for respiratory gas analysis during CPX. Additionally, the 6MWT is universally available, whereas CPX may only be available in more specialized centres.

A potential limitation to this study is that only 16% of the patients studied were patients with HFpEF. Despite our subanalyses finding almost identical univariate and multivariate prognostic indices in patients with HFpEF and HFrEF, further investigation of HRR in a larger population of patients with HFpEF is warranted. Also, although the methods we employed to measure 6MWT distance have been previously reported and found to be clinically useful and prognostic in patients with HF,[3] further examination of 6MWT distance using such methods is in need of investigation.

To our knowledge, this is the first study that identifies HRR, rather than distance ambulated, as the strongest prognostic variable derived from the 6MWT, thus making the 6MWT a relatively simple, but comprehensive functional performance measure that is readily available to most patients with HF. The predictive accuracy of HRR after the 6MWT is robust and comparable with HRR after maximal exertion during CPX and is equally applicable to the broad spectrum of HFpEF and HFrEF patients.

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References

1. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, Kronenberg MW, Kostis JB, Kohn RM, Guillotte M, Greenberg B, Woods PA, Bourassa MG. for the SOLVD Investigators. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. *JAMA* 1993;**270**:1702–1707.
2. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996;**110**:325–332.
3. Roul G, Germain P, Bareiss P. Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? *Am Heart J.* 1998;**136**: 449–457.
4. Manzano L, Babalis D, Roughton M, Shibata M, Anker SD, Ghio S, van Veldhuisen DJ, Cohen-Solal A, Coats AJ, Poole-Wilson PPA, Flather MD. Predictors of clinical outcomes in elderly patients with heart failure. *Eur J Heart Fail* 2011;**13**:528–536.
5. Fleg JL, Pina IL, Balady GJ, Chaitman BR, Fletcher B, Lavie C, Limacher MC, Stein RA, Williams M, Bazzarre T. Assessment of functional capacity in clinical and research applications. *Circulation* 2000;**102**:1591–1597.
6. Radford MJ, Arnold JMO, Bennett SJ, Cinquegrani MP, Cleland JG, Havranek EP, Heidenreich PA, Rutherford JD, Spertus JA, Stevenson LW. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Heart Failure Clinical Data Standards): Developed in Collaboration With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. *Circulation* 2005;**112**:1888–1916.
7. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, Takeda H, Inoue M, Kamada T. 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.
8. Pierpont GL, Voth EJ. Assessing autonomic function by analysis of heart rate recovery from exercise in healthy subjects. *Am J Cardiol* 2004;**94**:64–68.
9. Fisher JP, Seifert T, Hartwich D, Young CN, Secher NH, Fadel PJ. Autonomic control of heart rate by metabolically sensitive skeletal muscle afferents in humans. *J Physiol* 2010;**588**:1117–1127.
10. Huang PH, Leu HB, Chen JW, Cheng CM, Huang CY, Tuan TC, Ding YA, Lin SJ. Usefulness of attenuated heart rate recovery immediately after exercise to predict endothelial dysfunction in patients with suspected coronary artery disease. *Am J Cardiol* 2004;**93**:10–13.
11. Huang PH, Leu HB, Chen JW, Lin SJ. Heart rate recovery after exercise and endothelial function. Two important factors to predict cardiovascular events. *Prev Cardiol* 2005;**8**:167–170.
12. 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.
13. 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.
14. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascular healthy cohort. *Ann Intern Med* 2000;**132**:552–555.
15. 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.
16. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;**28**:2539–2550.
17. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschope C. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation* 2007;**116**:637–647.
18. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;**60**:2020–2027.
19. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J* 2007;**153**: 859–867.
20. Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga S, Pedretti R. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J Am Coll Cardiol* 2007;**50**:299–308.
21. Borg GAV. Psychophysical bases of perceived exertion. *Med Sci Sports Exer* 1982; **14**:377–381.
22. Ingle L, Rigby AS, Carroll S, Butterly R, King RF, Cooke CB, Cleland JG, Clark AL. Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. *Eur Heart J* 2007;**28**:560–568.
23. Lucas C, Stevenson LW, Johnson W, Hartley H, Hamilton MA, Walden J, Lem V, Eagen-Bengsten E. The 6-min walk and peak oxygen consumption in advanced heart failure: aerobic capacity and survival. *Am Heart J* 1999;**138**:618–624.
24. Opasich C, Pinna GD, Mazza A, Febo O, Riccardi R, Riccardi PG, Capomolla S, Forni G, Cobelli F, Tavazzi L. Six-minute walking performance in patients with moderate-to-severe heart failure: is it a useful indicator in clinical practice? *Eur Heart J* 2001;**22**:488–496.
25. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. *Circ Heart Fail* 2009;**2**:549–555.
26. Cipriano G, Yuri D, Bernardelli GF, Mair V, Buffolo E, Branco JNR. Analysis of 6-minute walk test safety in pre-heart transplantation patients. *Arq Bras Cardiol* 2009;**92**:294–300.
27. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation* 2011;**123**:1010–1020.
28. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M. The prognostic value of the heart rate response during exercise and recovery in patients with heart failure: influence of beta-blockade. *Int J Cardiol* 2010;**138**: 166–173.