International Journal of Physical Medicine & Rehabilitation

White, et al., Int J Phys Med Rehabil 2014, 2:6
DOI: 10.4172/2329-9096.1000240

Research Article Open Access

Characterization and Functional Implications of Heart Rate Increase and Heart Rate Recovery on Maximal and Submaximal Exercise Capacity in Patients with Advanced Heart Failure

Michel White[1*], Jonathan Myers[2], Marie-Claude Guertin[3], Annik Fortier[3], Anique Ducharme[1], François Harel[4], Eileen O'Meara[1], Geneviève Gravel[1] and Bernard Thibault[1]

[1]*Department of Medicine, Montreal Heart Institute and Université de Montréal, Montreal, Quebec, Canada*

[2]*VA Palo Alto Medical Center, Stanford University, Palo Alto, Canada*

[3]*Montreal Heart Institute Coordinating Center, Montreal, Quebec, Canada*

[4]*Department of Nuclear Medicine, Montreal Heart Institute and Université de Montréal, Montreal, Quebec, Canada*

[*]**Corresponding author:** Dr. Michel White, Department of Medicine, Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada, Tel: 514-376-3330; Fax: 514-376 1355; E-mail: m_white@icm-mhi.com

Received date: 31 July 2014; **Accepted date:** 24 Oct 2014; **Published date:** 29 Oct 2014

Abstract

Objective: Heart rate increase early after the initiation of exercise has not been characterized nor related to exercise capacity, heart rate recovery, and gas exchange analyses in patients with advanced heart failure. One hundred and forty-one patients including 121 patients randomized in the GREATER-EARTH trial were investigated.

Methods: Exercise capacity was assessed using a treadmill ramp exercise protocol with gas exchange analyses, a fix-load endurance exercise protocol, and a 6-minute walk test. Heart rate increase was computed at 1-, 2-minutes, and 1/3 of exercise time while heart rate recovery was measured at 1- and 2-minutes following maximal exercise.

Results: Heart rate increase early after the initiation of exercise test was not related to exercise capacity. In contrast, heart rate recovery was significantly related to maximal and submaximal exercise capacity. Among gas exchange responses, only the VE/VCO_2 slope and $PetCO_2$ at peak exercise were significantly associated with maximal but not submaximal exercise capacity.

Conclusions: Heart rate increase early after the initiation of exercise yields no relationship with maximal and submaximal exercise capacity in patients with advanced heart failure. Among gas exchange parameters, only some markers of ventilatory inefficiency have significant associations with maximal exercise capacity in patients with heart failure.

Keywords: Exercise test; Gas exchange analyses; Heart failure; Heart rate

Introduction

Heart rate increase at the onset of exercise testing has been associated with adverse outcomes in patients with or without documented coronary artery disease (CAD) [1,2]. However, the prognostic value of an increase vs. an attenuation of heart rate increase early after the initiation of exercise has been a matter of debate. Leeper et al. [1] reported that a rapid initial heart rate increase was associated with an improved survival in a large cohort of subjects referred for clinical exercise testing while Falcone et al. [2] reported that a rapid increase in heart rate at 1-minute following the initiation of exercise testing was associated with adverse outcomes in patients with documented CAD. The characterization of heart rate increase at the onset of exercise testing and its association with exercise capacity assessed concomitantly with gas exchange analyses and submaximal exercise duration have not been reported in a large cohort of patients with symptomatic heart failure.

Similar to heart rate increase, heart rate recovery within the first minutes following maximal exercise is regulated by sympathetic and parasympathetic balance [3]. Attenuation of heart rate recovery within the first 2-minutes of exercise testing has been related to adverse outcomes in high-risk patients without heart failure [4-7]. In addition, heart rate recovery has been related to adverse events both independently and when assessed multivariately as part of heart failure scores in patients with symptomatic heart failure [8-13]. The relationships between heart rate increase, heart rate recovery, and functional capacity assessed both by maximal and submaximal exercise tests have not been investigated in a large cohort of patients with advanced heart failure with a wide QRS complex referred to CRT (cardiac resynchronization therapy) [14]. Accordingly, the primary objective of this study was to characterize the changes in heart rate increase at the onset of exercise testing in patients with advanced heart failure. The secondary objective was to assess the relationship between maximal and submaximal exercise capacity and parameters with both heart rate increase and recovery in this study population.

Subjects and Methods

The GREATER-EARTH study was a randomized, double-blind, crossover study involving 141 patients in 11 sites across Canada [14,15]. Patients with a clinical indication for an implantable cardioverter defibrillator (ICD), left ventricular ejection fraction (LVEF) <35% and a QRS duration >120 msec, symptoms of heart failure, and a 6-minute walk test (6MWT) <400 meters were eligible for this study. Patients in permanent atrial fibrillation, those who were limited to exercise by non-cardiac conditions or who had a recent (<6 weeks) myocardial infarction and/or cardiac intervention were excluded. Other exclusion criteria included left ventricular (LV) dysfunction associated with reversible causes such as post-partum cardiomyopathy, active cancer and end-stage renal failure. All patients were required to receive optimal treatment for heart failure including a maximally tolerated dose of ACE inhibitors or angiotensin-receptor blockade for at least 4 weeks. The design and rationale for the EARTH study have been previously reported [15]. For the purpose of this study only data collected at baseline (prerandomizations resynchronization turned-OFF) were analysed in the 141 patients who completed the initial exercise evaluation. All patients have given their consent and the Montreal Heart Institute Research Center Ethics Committee has approved the study protocol.

Maximal and submaximal exercise testing

As part of the baseline evaluation, 2 exercise tests were performed (minimum of 2 hours between sub-max and the 6MWT and 24 hours between max and the others). The maximal cardiopulmonary exercise test consisted of a continuous and incremental exercise test performed on a treadmill using an individualized ramp protocol as originally reported by Myers [16]. Oxygen uptake was determined continuously on a breath by breath basis by an automated cardiopulmonary exercise system. Cardiopulmonary data were recorded at rest, during graded exercise and during a 2-minute recovery period. The maximal cardiopulmonary exercise test lasted until the attainment on the primary maximal criteria: respiratory exchange ratio (RER)>1.01, or 1 of 2 secondary maximal criteria: 1) inability to maintain exercise, and 2) patients' exhaustion due to fatigue, or cessation due to other clinical symptoms.

The submaximal constant load exercise test was performed on a treadmill using a fixed load protocol at an intensity corresponding to 75% of VO_2 peak measured during the maximal exercise test [15,17,18]. After a 2-minutes warm-up at 30% of the maximal load, the slope and speed observed at 75% of the VO_2 peak as measured during the ramp protocol was applied. The test was terminated for exhaustion or at 30 minutes of exercise. The 6MWT was completed as previously published by Guyatt et al. [19]. Heart rates were computed in the standing position state and at 1- 2- 3-minutes, at 1/3 of exercise time, and at peak exercise during the maximal exercise test [1,2]. The absolute change in heart rate at these specific time-points was defined as the observed heart rate minus standing/resting heart rate. Heart rate recovery was computed as the difference from peak exercise to heart rate measured at 1- and 2-minutes following peak exercise.

Statistical analyses

Characteristics of the study population (Table 1) and hemodynamic and gas exchange parameters (Table 2) are expressed as mean ± SD or median (Q1, Q3) for continuous variables and as frequency (%) for categorical variables. The normality of the continuous variables was assessed using Shapiro-Wilk and Kolmogorov-Smirnov tests. Stem-and-leaf and normal probability plots were also used to support tests for normality. Spearman correlations were used to investigate the relations between selected hemodynamic and gas exchange parameters, and the technique of locally weighted scatterplot smoothing (LOWESS) was used for further graphic representation. All analyses were done with SAS 9.2 or higher (SAS Institute, Cary, North Carolina) and conducted at the 0.05 significance level.

Age (years)	61.8 ± 8.9
BMI (units)	28.8 ± 5.5
Diabetes, n (%)	48 (34%)
NYHA class III-IV, n (%)	46 (32.6%)
LVEF, (%)	23.6 ± 5.7
6-minute walk test, (meters)	360 ± 69
Ischemic etiology, n (%)	76 (53.9%)
QRS duration, (ms)	155 ± 23
IV delay ECHO, (ms)	42.7 ± 27.2
Intra LV delay (basal) – ECHO, (ms)	16.4 ± 69.2
β-blocker therapy, n (%)	137 (97.2%)
ACE inhibitors / ARBs, n (%)	137 (97.2%)
Digoxin, n (%)	63 (44.7%)
Loop diuretic, n (%)	117 (83.0%)
Spironolactone, n (%)	67 (47.5%)

Table 1: Characteristics of the study population. BMI: Body Mass Index; NYHA: New York Heart Association; n: Number; LVEF: left Ventricular Ejection Fraction; ms: minutes; IV: Interventricular; LV: left Ventricle; ACE: Angiotensin Converting Enzyme; ARBs: Angiotensin Receptor Antagonists.

Results

The clinical characteristics of the study population are presented in Table 1. One hundred and forty-one patients with advanced heart failure were included in the present subanalysis. About 33% of patients experienced NYHA class III symptoms and most patients had heart failure caused by ischemic heart disease. Echocardiographic findings were consistent with advanced heart failure, with reduced LVEF and LV dyssynchrony. More than 95% received a β-blocker and an angiotensin modulating agent, while 47.5% received an aldosterone antagonist.

The parameters of interest analysed for the ramp exercise test and the constant load exercise duration are presented in Table 2. In response to the ramp exercise test, heart rate reserve achieved was 41.2 bpm corresponding to only 69% of maximal heart rate predicted for age. Heart rates increase at 1-minute and at 1/3 of exercise times were lower when compared with report from Leeper et al. Peak heart rate achieved during the submaximal exercise test was 101 bpm, equivalent to 87% of peak heart rate measured at peak exercise during the ramp exercise test. Mean peak VO_2 was below 15 ml per kg per minute. Heart rate recovery at 1minute was 15.4 bpm and 24.9 bpm at 2-

minutes. Submaximal exercise time was 679 seconds (median=526 seconds) excluding warm-up time.

Baseline HR (bpm)	70.3 ± 13.8
Peak exercise HR (bpm)	110 ± 21
Δ Exercise HR (bpm)	40.4 ± 16.6
Δ HR – 1 min (bpm)	10.1 ± 8.6
Δ HR – 2 min (bpm)	18.2 ± 10.1
Δ HR – 1/3 exercise (bpm)	18.5 ± 10.5
Peak VO_2 (m/kg/min)	14.7 ± 4.5
VE/VCO_2 slope (units)	35.6 ± 13.6 (32.3; 27.5-39.8)
HR recovery – 1 min (bpm)	15.4 ± 15.8
HR recovery – 2 min (bpm)	24.9 ± 13.3
CL exercise duration (seconds)	679 ± 532 (526; 269-923)

Table 2: Hemodynamic and gas exchange parameters. HR: Heart Rate; CL: Constant Load. Δ Exercise HR: increase exercise HR during the RAMP exercise test; Δ HR: increase in heart rate at 1-minute (Δ HR – 1 min), 2-minutes (Δ HR – 2 min) and at 1/3 of exercise time (Δ HR – 1/3 exercise). Values in parentheses are median, Q1-Q3 for parameters not distributed normally.

	Peak VO_2	**CL duration**	**6-minute walk test**	**$PetCO_2$ (rest)**	**$PetCO_2$ (peak)**
HR Peak	0.29 (0.0005)	0.21 (0.014)	0.25 (0.003)	0.03 (0.82)	0.16 (0.14)
HR Increase	0.39 (<0.0001)	0.38 (<0.0001)	0.31 (0.0003)	0.03 (0.77)	0.17 (0.14)
Δ HR 1-min	0.15 (0.12)	0.14 (0.13)	0.02 (0.84)	-0.17 (0.17)	-0.10 (0.39)
Δ HR 2-min	-0.03 (0.77)	0.14 (0.14)	0.02 (0.85)	-0.24 (0.05)	-0.22 (0.07)
Δ HR 1/3 Ex	0.21 (0.03)	0.32 (0.0007)	0.15 (0.13)	0.03 (0.79)	0.02 (0.9)
HRR 1-min	0.42 (<0.0001)	0.21 (0.02)	0.16 (0.09)	0.27 (0.02)	0.30 (0.01)
HRR 2-min	0.46 (<0.0001)	0.29 (0.004)	0.32 (0.001)	0.30 (0.02)	0.40 (0.001)

Table 3: Spearman correlation coefficients between selected hemodynamic and gas exchange parameters. HRR: Heart Rate Recovery.

The relationships between gas exchange parameters, hemodynamics and maximal and submaximal exercise capacity are presented in Table 3 and Figures 1 and 2. There was a significant relationship between peak VO_2 and constant load exercise time (r=0.37; p<0.0001) and between peak VO_2 and 6MWT (r=0.40; p<0.0001). Peak VO_2 was significantly associated with the minute ventilation-carbon dioxide production relationship (VE/VCO_2) slope and heart rate recovery at 2-minutes (Figure 1). Constant load exercise time and 6MWT were weakly yet significantly related to the VE/VCO_2 slope (r=0.26, p=0.002; and r=0.26, p=0.003 respectively).

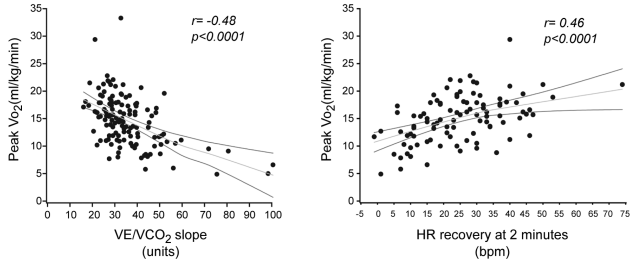

Figure 1: Relationships between peak VO_2 and VE/VCO_2 slope [left panel], and between peak VO_2 with heart rate recovery at 2-minutes following maximal exercise [right panel].

Spearman correlation coefficients between selected hemodynamics and gas exchange parameters are presented in Table 3. Peak heart rate achieved was significantly associated with both maximal and submaximal exercise performance assessed by the constant load exercise test and the 6MWT. Heart rate increase at 1- and 2-minutes yielded no relationship with neither exercise performance nor partial pressure of end-tidal carbon dioxide ($PetCO_2$). Heart rate recovery at 2-minutes was significantly associated with maximal and submaximal exercise performance and with $PetCO_2$ measured at rest and at peak exercise. The relationship between $PetCO_2$ measured at peak exercise and some selected gas exchange, hemodynamic and exercise parameters are presented in Figures 2 and 3. $PetCO_2$ yielded a significant inverse relationship with VE/VCO_2 slope (r=-0.65, p ≤ 0.0001) and with heart rate recovery at 2-minutes (r=0.40, p=0.001) (Figure 2). Similarly, a significant relationship was observed between $PetCO_2$ and peak exercise oxygen consumption (r=0.47, p<0.001). There was no significant relationships between $PetCO_2$ and exercise duration measured with the constant load exercise test (r=0.08, p=0.47) (Figure 3).

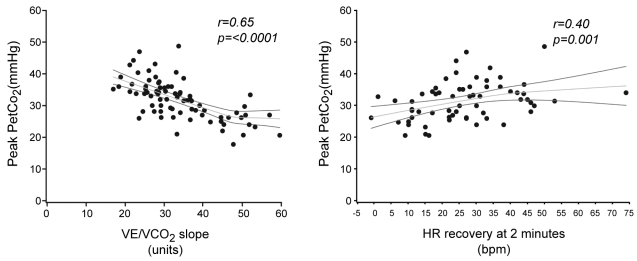

Figure 2: Relationships between $PetCO_2$ measured at peak exercise (peak PetCO2) with VE/VCO_2 slope [left panel], and with heart rate recovery at 2-minutes [right panel].

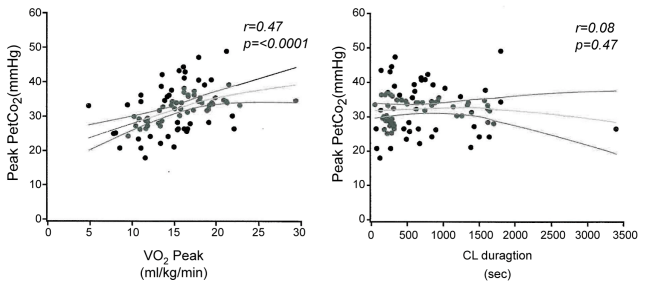

Figure 3: Relationships between $PetCO_2$ measured at peak exercise with peak VO_2 [left panel], and with constant load exercise duration [right panel].

Discussion

In this investigation, we reported the characteristics of heart rate increase and heart rate recovery concomitantly with maximal exercise capacity with gas exchange analyses, and submaximal exercise performance assessed by a fixed load protocol and a 6MWT in a large cohort of patients with advanced heart failure with a wide QRS complex. Compared with previous investigations in high risk patients, the current sample of patients with heart failure exhibited a significant attenuation in heart rate increase at the onset of exercise. There were no significant relationships between the increase in heart rate during the first 2-minutes of exercise or with any of the other exercise parameters. In contrast, heart rate recovery at 1- and 2-minutes was significantly associated with both maximal and submaximal exercise capacity. Among gas exchange parameters, only the VE/VCO_2 slope and $PetCO_2$ both at rest and stress were correlated with maximal exercise capacity. There was a significant relationship between maximal and submaximal exercise performance measured with a fixed load exercise protocol and the 6MWT. Thus, in contrast to patients with CAD and normal LV function, heart rate attenuation provides little additional information in comparison with heart rate recovery. In addition, there is a significant relationship between peak VO_2 and exercise time in these patients. Finally these results confirmed the value of selected parameters of ventilator inefficiency for both maximal and sub-maximal exercise performance in patients with heart failure.

The significance and prognostic value of heart rate increase at the onset of exercise testing has not been extensively studied and has recently been debated in patients with CAD. Leeper et al. [1] reported that a rapid increase in heart rate at the initiation of exercise testing was associated with improved survival in patients referred for clinical treadmill testing. In contrast, Falcone et al. [2] reported that a faster increase in heart rate at the onset of exercise testing (≥12 bpm at 1-minute) predicted both adverse outcome and cardiac death in patients with documented coronary heart rate disease. In the Leeper study, 20.7% of patients were taking a β-blocker at the time of enrolment while 31% of subjects performed the exercise test while on a β-blocker or a calcium-channel blocker in the Falcone study. The characterization and the relationship between heart rate increases with functional capacity in patients with advanced heart failure chronically treated with β-blockers have not been previously reported.

In this study, we report values for heart rate increase at the onset and peak exercise in a large population of heart failure patients. Our observations at 1-minute, 2-minutes, and at 1/3 of the exercise time are in general agreement with the values reported by Leeper et al. [1] and Falcone [2]. In fact, the values reported herein are similar to those observed in the high risk group (e.g. patients who experienced cardiovascular (CV) death) in the cohort studied by Leeper et al. [1]. The mechanisms related to an impaired heart rate increase in early exercise in patients with heart failure are likely multifactorial. The use of β-blockers in the current study was >97%, which contrasts with the much lower use of β-blockers in the studies of both Leeper et al. [1] and Falcone et al. [2]. In addition, patients with heart failure are known to exhibit β-1 receptor down-regulation [20]. The magnitude of beta receptor down-regulation is proportional to the severity of heart failure [21] and likely underlies the low heart rate values during exercise in this specific population. Similar to that reported by Leeper et al. [1], we found minimal associations between heart rate increases in the first 2-minutes of exercise and both maximal and submaximal exercise performance. The reasons for this are likely explained in part by the slow increase in heart rate related to β-blockade and β-1 receptor down-regulation. Nevertheless, heart rate increase from baseline to peak exercise was significantly related to both maximal and submaximal exercise performance confirming the importance of heart rate reserve in increasing cardiac output in these patients with poor left ventricular function.

We also investigated the changes in heart rate recovery at 1- and 2-minutes following maximal exercise testing. Heart rate recovery has been extensively studied in high-risk patients with coronary disease, but to a lesser extent in patients with heart failure. The heart rate recovery data reported in the present study are in agreement with the observations published previously by our group [8] but slightly lower compared to data reported by others [22,23] in patients with heart failure. No study to our knowledge has investigated the relationship between heart rate recovery at 1- and 2-minutes following maximal exercise along with hemodynamic responses, both maximal and submaximal exercise performance and gas exchange parameters. In heart failure, heart rate recovery has demonstrated significant prognostic value when analysed alone [11,12] or when included in a heart failure score [9,10,22,23]. We observed a significant relationship between both maximal and submaximal exercise performance and heart rate recovery at 1- and 2-minutes. However, the correlation was greater with maximal exercise capacity. Heart rate recovery is mediated by an increase in parasympathetic tone coupled with sympathetic withdrawal following exercise [3]. The significant relationships between heart rate recovery at 1- and particularly at 2-minutes following exercise with maximal and submaximal exercise capacity and gas exchange parameters have not been previously reported. These observations suggest that heart rate recovery and thus autonomic regulation following exercise is more closely related to functional capacity than the chronotropic response early after the initiation of exercise in patients with advanced heart failure.

Here, we also studied the relationships between selected gas exchange parameters, maximal and submaximal exercise performance, and exercise hemodynamics. The relationships between peak of VO_2, constant load exercise duration and 6MWT was significant but weak ($r=0.40$; $p<0.001$). Similar level of relationship (unadjusted $r=0.54$; adjusted $r=0.33$) was recently reported by Forman et al in the HF-ACTION Trial [24] Among gas exchange parameters, only the VE/VCO_2 slope and $PetCO_2$ measured at peak exercise exhibited significant relationships with most of the exercise hemodynamic parameters. Patients with advanced heart failure exhibit an increased ventilatory response to exercise [25,26], and the magnitude of

ventilatory inefficiency has been related to the severity of heart failure [27-30]. A decrease in cardiac output during exercise causes a decrease in peripheral muscular flow, acidemia, and thus an exaggerated ventilatory response to exercise [31-33]. Similarly, pulmonary congestion and ventilation/perfusion mismatching lead to an increase in the ratio of physiologic dead space to tidal volume [26]. The most widely studied indicator of ventilator inefficiency has been the minute-ventilation/carbon dioxide production slope (VE/VCO_2 slope) [27-29]. This parameter has been repeatedly associated with adverse outcomes when analysed solely [27] or when integrated as a part of multivariate exercise scores [9,34]. Similarly, $PetCO_2$ is frequently reduced in heart failure [30,35]. Rest and exercise $PetCO_2$ has been related to ventilation/perfusion mismatching and to a reduction in cardiac output [30]. In addition, $PetCO_2$ measured at peak exercise has been correlated with maximal exercise capacity and a decrease in cardiac output during exercise [30]. We extended these previous observations by showing that these indices of ventilatory inefficiency are related to both maximal but not submaximal exercise capacity in patients with heart failure. The reasons for this remain unclear. However, this suggests that submaximal exercise capacity relies also on the peripheral arterial and muscular functions as opposed to mostly cardiopulmonary reserve for maximal exercise performance. Finally, the significant relationships between ventilatory inefficiency and heart rate recovery suggest that these ventilatory abnormalities may be associated with autonomic dysregulation in patients with advanced heart failure.

Study Limitations

This investigation was a retrospective study analysis from the GREATER-EARTH study. As such, these were not a priori analyses. Nevertheless, the patients recruited were fairly homogenous and presented with advanced heart failure with a wide QRS complex. In addition, treatment of heart failure was optimal with more than 97% of patients treated with a β-blocker. The study was also performed at multiple sites and consequently the degree of encouragement and support given to the patients during the endurance tests were likely variable. Nevertheless, this was minimized by the use of a standard protocol in all participating centers.

Conclusions

We have characterized the limited value of heart rate increase at the onset of exercise testing in patients with advanced heart rate failure chronically treated with a β-blocker. In contrast, heart rate recovery at 1- and more so at 2-minutes was significantly associated with maximal and submaximal exercise capacity. Among gas exchange parameters, markers of ventilatory inefficiency (the VE/VCO_2 slope and $PetCO_2$) were significantly associated with both maximal and submaximal exercise capacity. These parameters warrant further investigation among responders vs. non responders to cardiac resynchronization therapy.

Acknowledgement

This study was supported by the Canadian Institutes of Health Research and St-Jude Medical Canada.

References

1. Leeper NJ, Dewey FE, Ashley EA, Sandri M, Tan SY, et al. (2007) Prognostic value of heart rate increase at onset of exercise testing. below Circulation 115: 468-474.
2. Falcone C, Buzzi MP, Klersy C, Schwartz PJ (2005) Rapid heart rate increase at onset of exercise predicts adverse cardiac events in patients with coronary artery disease. below Circulation 112: 1959-1964.
3. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, et al. (1994) Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. below J Am Coll Cardiol 24: 1529-1535.
4. Shetler K, Marcus R, Froelicher VF, Vora S, Kalisetti D, et al. (2001) Heart rate recovery: validation and methodologic issues. below J Am Coll Cardiol 38: 1980-1987.
5. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS (2000) Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. below JAMA 284: 1392-1398.
6. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS (1999) Heart-rate recovery immediately after exercise as a predictor of mortality. below N Engl J Med 341: 1351-1357.
7. Cole CR, Foody JM, Blackstone EH, Lauer MS (2000) Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. below Ann Intern Med 132: 552-555.
8. Racine N, Blanchet M, Ducharme A, Marquis J, Boucher JM, et al. (2003) Decreased heart rate recovery after exercise in patients with congestive heart failure: effect of beta-blocker therapy. below J Card Fail 9: 296-302.
9. Myers J, Arena R, Dewey F, Bensimhon D, Abella J, et al. (2008) A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. below Am Heart J 156: 1177-1183.
10. Ritt LE, Oliveira RB, Myers J, Arena R, Peberdy MA, et al. (2012) Patients with heart failure in the "intermediate range" of peak oxygen uptake: additive value of heart rate recovery and the minute ventilation/carbon dioxide output slope in predicting mortality. below J Cardiopulm Rehabil Prev 32: 141-146.
11. Cahalin LP, Forman DE, Chase P, Guazzi M, Myers J, et al. (2013) The prognostic significance of heart rate recovery is not dependent upon maximal effort in patients with heart failure. below Int J Cardiol 168: 1496-1501.
12. Cahalin LP, Arena R, Labate V, Bandera F, Lavie CJ, et al. (2013) 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. Eur J Heart Fail 15: 519-527.
13. Cahalin LP, Arena R, Labate V, Bandera F, Guazzi M (2013) Predictors of abnormal heart rate recovery in patients with heart failure reduced and preserved ejection fraction. Eur J Prev Cardiol 21: 906-914.
14. Thibault B, Harel F, Ducharme A, White M, Frasure-Smith N, et al. (2011) Evaluation of resynchronization therapy for heart failure in patients with a QRS duration greater than 120 ms (GREATER-EARTH) trial: rationale, design, and baseline characteristics. Can J Cardiol 27: 779-786.
15. Thibault B, Ducharme A, Harel F, White M, O'Meara E, et al. (2011) Left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex ≥120 milliseconds. Circulation 124: 2874-2881.
16. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, et al. (1991) Comparison of the ramp versus standard exercise protocols. below J Am Coll Cardiol 17: 1334-1342.
17. Blanchet M, Sheppard R, Racine N, Ducharme A, Curnier D, et al. (2005) Effects of angiotensin-converting enzyme inhibitor plus irbesartan on maximal and submaximal exercise capacity and neurohumoral activation in patients with congestive heart failure. Am Heart J 149: 938.e1-7.
18. Blanchet M, Ducharme A, Racine N, Rouleau JL, Tardif JC, et al. (2003) Effects of cold exposure on submaximal exercise performance and adrenergic activation in patients with congestive heart failure and the

effects of beta-adrenergic blockade (carvedilol or metoprolol). Am J Cardiol 92: 548-553.

19. Guyatt GH, Thompson PJ, Berman LB, Sullivan MJ, Townsend M, et al. (1985) How should we measure function in patients with chronic heart and lung disease? J Chronic Dis 38: 517-524.
20. Bristow MR, Ginsburg R, Umans V, Fowler M, Minobe W, et al. (1986) Beta 1- and beta 2-adrenergic-receptor subpopulations in non-failing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta1-receptor down-regulation in heart failure. Circ Res 59: 297-309.
21. Bristow MR, Minobe W, Rasmussen R, Larrabee P, Skerl L, et al. (1992) Beta-adrenergic neuroeffector abnormalities in the failing human heart are produced by local rather than systemic mechanisms. J Clin Invest 89: 803-815.
22. Arena R, Myers J, Abella J, Pinkstaff S, Peberdy MA, et al. (2010) Prognostic characteristics of heart rate recovery according to sex in patients with heart failure. Int J Cardiol 145: 293-294.
23. Arena R, Guazzi M, Myers J, Peberdy MA (2006) Prognostic value of heart rate recovery in patients with heart failure. Am Heart J 151: 851.
24. Forman DE, Fleg JL, Kitzman DW, Brawner CA, Swank AM, et al. (2012) 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. J Am Coll Cardiol 60: 2653-2661.
25. Buller NP, Poole-Wilson PA (1990) Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. Br Heart J 63: 281-283.
26. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, et al. (1997) Lung function and exercise gas exchange in chronic heart failure. Circulation 96: 2221-2227.
27. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA (2004) Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. Am Heart J 147: 354-360.
28. Robbins M, Francis G, Pashkow FJ, Snader CE, Hoercher K, et al. (1999) Ventilatory and heart rate responses to exercise : better predictors of heart failure mortality than peak oxygen consumption. Circulation 100: 2411-2417.
29. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, et al. (2000) Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation 101: 2803-2809.
30. Matsumoto A, Itoh H, Eto Y, Kobayashi T, Kato M, et al. (2000) End-tidal CO2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. J Am Coll Cardiol 36: 242-249.
31. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP (1982) Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. below Circulation 65: 1213-1223.
32. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR (1989) Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation 80: 769-781.
33. Ingram R Jr, McFadden ER Jr (1976) Respiratory changes during exercise in patients with pulmonary venous hypertension. Prog Cardiovasc Dis 19: 109-115.
34. Guazzi M, Boracchi P, Arena R, Myers J, Vicenzi M, et al. (2010) Development of a cardiopulmonary exercise prognostic score for optimizing risk stratification in heart failure: the (P)e(R)i(O)dic (B)reathing during (E)xercise (PROBE) study. J Card Fail 16: 799-805.
35. Sue DY, Oren A, Hansen JE, Wasserman K (1987) Diffusing capacity for carbon monoxide as a predictor of gas exchange during exercise. N Engl J Med 316: 1301-1306.