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Cardiopulmonary Exercise Testing in Mild Heart Failure: Impact of the Mode of Exercise on Established Prognostic Predictors

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Key Words
Cardiopulmonary exercise testing · Heart rate recovery · Heart failure

Abstract
Objectives: In patients with heart failure (HF), peak oxygen consumption (peak VO_2), the relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope) and heart rate recovery (HRR) are established prognostic predictors. However, treadmill exercise has been shown to elicit higher peak VO_2 values than bicycle exercise. We sought to assess whether the VE/VCO_2 slope and HRR in HF also depend on the exercise mode. ***Methods:*** Twenty-one patients with mild HF on chronic β-blocker therapy underwent treadmill and bicycle cardiopulmonary exercise testing for measurement of peak VO_2 and the VE/VCO_2 slope. In patients with sinus rhythm (n = 16), HRR at 1 (HRR-1) and 2 min (HRR-2) after exercise termination was assessed. ***Results:*** Peak VO_2 was higher during treadmill as compared with bicycle testing (21.7 ± 4.6 vs. 19.6 ± 3.4 ml/kg/min; p = 0.006). HRR-1 tended to be slower (15 bpm, interquartile range 8–19, vs. 18 bpm, interquartile range 11–22; p = 0.16), and HRR-2 was significantly slower after treadmill exercise (26 bpm, interquartile range 20–39, vs. 31 bpm, interquartile range 22–41; p = 0.04). In contrast, VE/VCO_2 slope values did not differ between the test modes (32.9 ± 5.5 vs. 32.3 ± 5.0; p = 0.56). ***Conclusions:*** In contrast to peak VO_2 and HRR, the VE/VCO_2 slope is not affected by the exercise mode in patients with mild HF.

Introduction

The value of cardiopulmonary exercise testing (CPET) in the management of patients with chronic heart failure (HF) is well established. Peak oxygen consumption (VO_2) [1], the relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope) [2] and heart rate recovery (HRR) [3] have been shown to be prognostic predictors in these patients. In daily practice, peak VO_2 is a response that significantly influences decisions regarding the management of patients with HF. However, peak VO_2 depends on the mode of exercise, and higher peak VO_2 levels are commonly reported during treadmill testing as compared with bicycle testing among both healthy subjects and patients with heart disease [3–5],

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particularly HF [6–9]. However, most of these studies were performed before β-blockers were widely used in HF, and it is not known whether the same findings apply for patients in the current treatment era.

In addition to peak VO_2, the VE/VCO_2 slope and HRR have gained interest in recent years because of their prognostic power independent from peak VO_2 [2, 3, 10], but only a few studies [9, 11] have explored whether these parameters are also influenced by the mode of exercise. Proper interpretation of CPET results for risk stratification in HF would be optimized by more precise knowledge of the impact of the mode of exercise on these prognostic markers. Accordingly, we performed an intra-individual comparison of peak VO_2, the VE/VCO_2 slope and HRR in a typical population of patients with mild HF under currently prescribed medication including chronic β-blocker therapy undergoing treadmill and bicycle exercise testing within a few days.

Methods

This is a prospective, cross-sectional study. The local ethics committee approved the study protocol, and all patients gave oral and written informed consent to participate in the study.

Patients

We studied 21 patients with systolic HF defined as breathlessness on exertion corresponding to New York Heart Association class ≥II in the absence of other causes of dyspnea and a left ventricular ejection fraction (LVEF) ≤45%. To be included in the study, chronic β-blocker therapy and unchanged medication within the last month were required. Patients with hospitalization for HF, acute coronary syndrome, percutaneous coronary intervention or cardiac surgery within the last 3 months, significant peripheral arterial occlusive disease, orthopedic problems or other conditions limiting exercise capacity unrelated to HF were excluded.

Laboratory Analyses

Before each test, 3–5 ml of blood was drawn into an ethylenediamine-tetra-acetate-containing tube for B-type natriuretic peptide (BNP) analysis. BNP was determined using the established and well characterized Triage BNP test (Biosite Diagnostics Inc., San Diego, Calif., USA).

Cardiopulmonary Exercise Testing

All participants performed a treadmill ramp (CS-200, Schiller, Baar, Switzerland) and a bicycle ramp (Ergo 500S, Schiller) test on 2 different days in alternating sequence. All tests were performed between 4.00 and 6.00 p.m. All protocols were individualized based on a pretest interview. For the bicycle tests, protocols starting with a workload between 15 and 30 W and using continuous increments of 5–10 W/min were employed, depending on the subject's severity of disease, level of fitness, age and gender. For the treadmill tests, a set of 7 ramp protocols for exercise capacities ranging from 4 to 10 metabolic equivalents – as estimated from the speed and grade of the treadmill [12] – to achieve a test duration of approximately 10 min was employed. Patients were advised not to hold on to the handrails during treadmill exercise.

During the tests, a 12-lead electrocardiogram was recorded continuously, and blood pressure (by indirect arm cuff sphygmomanometer) was assessed every 2 min. Expired gases were acquired continuously, and VO_2 and carbon dioxide (VCO_2) output were recorded in rolling 30-second averages (ErgoScope, Ganshorn, Niederlauer, Germany). Calibration of the system was performed before each test. During the tests, subjects were verbally encouraged to exercise until exhaustion. All tests were terminated upon patient request. No test was terminated due to an untoward exercise response.

The respiratory exchange ratio (RER), defined as VCO_2 divided by VO_2, was determined at rest (sitting on the bicycle or standing on the treadmill) and at peak exercise. For each test, the relation between minute ventilation and VCO_2 was plotted to determine the VE/VCO_2 slope. All data points from the beginning to the end of exercise were included to determine the VE/VCO_2 slope [13, 14].

After achieving peak workload, participants spent at least 2 min in a cool-down period on the treadmill or the bicycle at low workload (10–25 W, 1.6 km/h and 0% inclination, respectively), and HRR data were obtained. The heart rate at 1 min after CPET was subtracted from the peak heart rate to obtain HRR at 1 min (HRR-1) [3], and the heart rate at 2 min after CPET was subtracted from the peak heart rate to obtain HRR-2. Only patients with sinus rhythm (n = 16) were included in the HRR analysis.

Statistical Analysis

Statistical analysis was performed using a commercially available software package (SPSS Inc., version 10.1, Chicago, Ill., USA). Categorical data were expressed as numbers and percentages. Continuous data were expressed as the mean ± standard deviation or the median (interquartile range), as appropriate. The χ^2 test was used to compare categorical data. For comparison of continuous data, the paired t test or the Wilcoxon rank sum test was used, as appropriate. For correlations between variables, Pearson or Spearman correlation coefficients were calculated as appropriate. A p value ≤0.05 was considered statistically significant.

Results

Patients

Baseline characteristics of the study population are shown in table 1. The median interval between the two tests was 5 days (interquartile range 3–8). There were no changes in symptoms, clinical examination, self-reported body weight or medication between the two test days. Values for BNP obtained before the two tests were similar (before treadmill, 253 pg/ml, interquartile range 118–554, vs. before bicycle, 317 pg/ml, interquartile range 131–539; p = 0.33).

Peak Oxygen Consumption

Results of CPET are shown in table 2. Exercise time, peak heart rate and peak rate-pressure product were similar in the two tests. Peak VO_2 was significantly higher when using the treadmill as compared with the bicycle, although peak RER as a measure of subject effort was lower with the treadmill as compared with the bicycle. Seventeen of 21 (81%) subjects achieved a higher peak VO_2 with the treadmill compared with 4/21 (19%) participants with the bicycle ($p = 0.005$). There was a moderate-to-good correlation between peak VO_2 levels achieved during treadmill and bicycle testing ($r = 0.73$; $p < 0.001$).

In patients undergoing the treadmill test first (n = 11), peak VO_2 was higher during treadmill as compared with bicycle exercise (20.3 ± 4.9 vs. 18.1 ± 3.5 ml/kg/min), and in those undergoing the bicycle test first (n = 10), peak VO_2 was also higher during treadmill as compared with bicycle exercise (23.4 ± 3.9 vs. 21.3 ± 2.5 ml/kg/min). Due to the small number of patients in this analysis, these differences just failed to reach statistical significance ($p = 0.06$ for both comparisons).

Table 1. Baseline characteristics (n = 21)

Age, years	72 ± 8
Gender, female	2 (10)
Body mass index, kg/m^2	25.9 ± 3.6
Main cause of heart failure	
Coronary artery disease	8 (38)
Hypertensive heart disease	8 (38)
Dilated cardiomyopathy	5 (24)
LVEF, %	31 ± 7
Rhythm	
Sinus rhythm	16 (76)
Atrial fibrillation	5 (24)
Medication	
ACE-I or ARB	20 (95)
β-Blocker	21 (100)
Digoxine	5 (24)
Spironolactone	7 (33)
Loop diuretic	16 (76)
Dyspnea functional class	
New York Heart Association class II	16 (76)
New York Heart Association class III	5 (24)

Data are given as number of patients, with percentage in parentheses, or mean ± standard deviation.

ACE-I = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 2. Comparison of exercise responses in the two test modes (n = 21)

	Treadmill	Bicycle	p value
Test order (1st test)	11 (52)	10 (48)	0.9
Exercise time, s	501 (365–688)	492 (461–554)	0.66
Exercise time 8–12 min	10 (48)	14 (67)	0.4
Exercise time <8 min	8 (38)	6 (28)	0.7
Exercise time >12 min	3 (14)	1 (5)	0.6
Resting heart rate, bpm	65 ± 11	67 ± 12	0.34
Peak heart rate, bpm	125 ± 22	124 ± 22	0.28
Systolic blood pressure at rest, mm Hg	122 ± 21	118 ± 26	0.42
Systolic blood pressure at peak exercise, mm Hg	151 ± 28	151 ± 25	0.98
Diastolic blood pressure at rest, mm Hg	72 ± 11	73 ± 14	0.71
Diastolic blood pressure at peak exercise, mm Hg	77 ± 22	82 ± 17	0.29
Peak rate-pressure product, mm Hg · bpm	19,144 ± 5,260	18,744 ± 4,648	0.47
Respiratory exchange ratio at rest	0.77 ± 0.07	0.80 ± 0.07	0.26
Peak exercise respiratory exchange ratio	1.03 ± 0.08	1.08 ± 0.08	0.006
Peak workload			
Estimated metabolic equivalents	6.0 ± 1.9	5.2 ± 1.2	<0.001
Watts	109 ± 40	91 ± 28	0.001
Peak VO_2, ml/kg/min	21.7 ± 4.6	19.6 ± 3.4	0.006
Peak VCO_2, ml/kg/min	22.4 ± 5.4	21.2 ± 4.1	0.10
Peak VE, l/min	59.3 ± 13.1	56.7 ± 12.7	0.16
VE/VCO_2 slope	32.9 ± 5.5	32.3 ± 5.0	0.56

Data are given as number of patients, with percentage in parentheses, mean ± standard deviation, or median, with interquartile range in parentheses.

Table 3. Comparison of HRR in the two modes of exercise in patients with sinus rhythm (n = 16)

	Treadmill	Bicycle	p value
Test order (1st test)	7 (44)	9 (56)	0.8
Exercise time, s	495 (428–690)	492 (459–554)	0.8
Resting heart rate, bpm	64 ± 12	64 ± 11	0.8
Peak heart rate, bpm	119 ± 19	118 ± 19	0.6
HRR-1, bpm	15 (8–19)	18 (11–22)	0.16
HRR-2, bpm	26 (20–39)	31 (22–41)	0.04
Peak rate-pressure product, bpm · mm Hg	17,683 ± 5,163	18,270 ± 5,026	0.2
Peak VO_2, ml/kg/min	21.6 ± 4.9	19.6 ± 3.6	<0.001
Peak exercise respiratory exchange ratio	1.03 ± 0.09	1.08 ± 0.08	0.009
VE/VCO_2 slope	33.6 ± 5.3	32.7 ± 5.5	0.53

Data are given as number of patients, with percentage in parentheses, mean ± standard deviation, or median, with interquartile range in parentheses.

Ventilatory Response to Exercise

In contrast to peak VO_2, there was no significant difference in the VE/VCO_2 slope between the two modes of exercise (table 2). In 12/21 (57%) patients, the VE/VCO_2 slope was higher during treadmill exercise, and in 9/21 (43%) patients, it was higher during bicycle exercise (p = 0.5). There was a moderate correlation between VE/VCO_2 slope values in the two modes of exercise (r = 0.49; p = 0.02). During treadmill testing, there was a significant inverse relationship between peak VO_2 and the VE/VCO_2 slope (r = –0.62; p = 0.003), whereas this was not the case for bicycle testing (r = –0.24; p = 0.3). The RER at peak exercise was not related to the VE/VCO_2 slope in either exercise mode (treadmill, r = –0.25, p = 0.28; bicycle, r = –0.36, p = 0.1).

When looking at patients undergoing the treadmill test first (n = 11) and those undergoing the bicycle test first (n = 10), there were again no differences between the VE/VCO_2 slope values during the two test modes (treadmill first, 33.7 ± 5.2 vs. 32.8 ± 4.4, p = 0.5; bicycle first, 32.1 ± 5.9 vs. 31.6 ± 5.7, p = 0.8).

Heart Rate Recovery

Results of the comparison of heart recovery data for the two exercise modes in the subgroup of patients in sinus rhythm (age 71 ± 9 years, body mass index 25.2 ± 2.8 kg/m^2, LVEF 31 ± 8%) are presented in table 3.

Despite a similar peak heart rate, HRR-1 tended to be lower, and HRR-2 was significantly lower during treadmill as compared with bicycle exercise. The workload after treadmill exercise was 1.8 metabolic equivalents in all patients, and the workload after bicycle exercise was 19 ± 6 W, which corresponds to 1.9 ± 0.3 metabolic equivalents [15]. Thus, the workload during the recovery period was similar after treadmill and bicycle exercise (1.8 ± 0.0 vs. 1.9 ± 0.3 metabolic equivalents; p = 0.1).

During treadmill exercise, HRR-1 was related to the VE/VCO_2 slope (r = –0.75; p = 0.001), but not to peak VO_2 (r = 0.40; p = 0.12), and HRR-2 was related to both peak VO_2 (r = 0.63; p = 0.01) and the VE/VCO_2 slope (r = –0.57; p = 0.02). During bicycle exercise, there was no significant association between peak VO_2 and both HRR-1 (r = 0.41; p = 0.12) or HRR-2 (r = 0.30; p = 0.26), whereas both HRR-1 (r = –0.51; p = 0.04) and HRR-2 (r = –0.53; p = 0.04) were related to the VE/VCO_2 slope.

During treadmill exercise, there was no significant association between RER at peak exercise and both HRR-1 (r = 0.11; p = 0.63) and HRR-2 (r = 0.25; p = 0.27). During bicycle exercise, RER at peak exercise and HRR-1 (r = –0.003; p = 1.0) and HRR-2 (r = 0.18; p = 0.42) were not related either.

Discussion

The present study demonstrates that in patients with mild HF on chronic β-blocker therapy, peak VO_2 and HRR depend on the mode of exercise, whereas the VE/VCO_2 slope is not significantly influenced by the exercise mode.

Peak Oxygen Consumption

In accordance with previous studies in healthy subjects and patients with heart disease [6–9], we have shown

that the majority of HF patients achieve a higher peak VO_2 on the treadmill as compared with the bicycle. The present data extend the findings of Page et al. [7] from the pre-β-blocker era to HF patients under modern medical therapy including β-blockers, and confirm the findings of a recently published smaller study (n = 11) [9].

The majority of earlier studies dealing with the prognostic impact of peak VO_2 in patients with HF have used treadmill protocols, e.g., the landmark paper by Mancini et al. [1], but more recent studies evaluating the association between peak VO_2 and prognosis have used bicycle testing [16, 17]. Although peak VO_2 values obtained during bicycle and treadmill testing have been shown to provide comparable prognostic information [11], one can assume that peak VO_2 values in studies using bicycle exercise was lower than the 'true' peak VO_2 levels in a significant proportion of patients.

These findings are clinically relevant given the fact that in Europe (except for Great Britain), bicycle exercise testing is the preferred mode of exercise in most centers. Thus, interpretation of peak VO_2 should not only consider the absence of current medical therapy in most studies that established the value of peak exercise testing [18], but also the mode of exercise testing. Individually, this may be very difficult, and a given peak VO_2 value in an individual patient should only be compared with one obtained using the same exercise mode.

Ventilatory Response to Exercise

Patients with HF exhibit an increased ventilatory response to exercise expressed as an increased VE/VCO_2 slope. Several recent studies have shown that the VE/VCO_2 slope is an independent prognostic marker in HF patients [2, 10, 19].

In a recent small study in HF patients with a similar functional capacity as ours (n = 11) undergoing CPET using step protocols, the VE/VCO_2 slope was found to be significantly higher when using the treadmill as compared with the bicycle in HF patients [9]. The authors speculated that a weight-bearing activity such as walking on a treadmill would cause higher ergoreflex activation and thus higher ventilatory response to exercise in HF [9]. In contrast, we found that in a larger study group undergoing CPET using ramp instead of step protocols, there was a minimal difference between VE/VCO_2 slope values obtained during the two modes of exercise.

The increased ventilatory response to exercise in HF is thought to be due to both increased dead space ventilation and abnormal ventilatory control secondary to premature metabolic acidosis or heightened sensitivity of chemoreceptors and muscle ergoreceptors [20, 21]. It has been a debate for a long time to which extent each of these mechanisms contributes to the increased VE/VCO_2 slope in HF [22]. Whether the magnitude of these mechanisms depends on the mode of exercise is not known. The type and amount of muscles involved in a type of exercise might influence the ergoreflex response. Notably, arm exercise is known to lead to a greater ventilatory response to exercise than leg exercise at the same workload [23], and patients were advised not to hold on to the handrails during treadmill exercise in the current study. In the study by Witte and Clark [9], it is not specified whether holding the handrails was allowed. If it was, this could have contributed to the higher VE/VCO_2 slope during treadmill exercise. In addition, one could speculate that the use of step protocols with fix increments in workload [9] as compared with individualized ramp protocols (present study) might account for the discrepant findings. In the former study [9], a modified Bruce protocol and a bicycle protocol increasing workload by 25 W every 3 min were used for all patients. The increments in the Bruce protocol might have been relatively more demanding than the steps during bicycle exercise and might have provoked a more pronounced ergoreflex activation, which could explain differences in the ventilatory response. In contrast, workload was continuously increased in the present study. On the other hand, there is no reason to assume that chemoreceptor activation and dead space ventilation differ significantly in the two exercise modes. Interestingly, the VE/VCO_2 slope has been shown to be superior to peak VO_2 with respect to its prognostic prediction in HF [2, 10], and in contrast to peak VO_2, it does not depend on effort. The value of this variable for prognostic assessment in HF is further strengthened by the fact that in contrast to peak VO_2, it does not depend on the mode of exercise as shown in the present study.

Heart Rate Recovery

The decline in heart rate following exercise is a reflection of vagal tone, and a delayed HRR is a marker of poor prognosis both in subjects with suspected or known coronary artery disease and patients with HF [3, 24]. HRR and peak VO_2 are weakly related in patients with HF [25], but HRR is an independent predictor of death in these patients [3]. To the best of our knowledge, the impact of the mode of exercise on HRR in HF patients has not been previously studied. In the present study, we observed a trend toward higher HRR-1 and significantly higher HRR-2 values after bicycle exercise, indicating that CPET using bicycle exercise might lead to an overestimation of

HRR-1 and HRR-2 values relative to the treadmill. This difference was observed although the workload during the recovery period was similar after the two tests. Of note, a recent study suggested that HHR-2 is an even stronger prognostic predictor than HRR-1 in the HF population [26], which may underscore the impact of our findings. Because of the differences between the modes of exercise, HRR-1 and HRR-2 values obtained by bicycle exercise cannot be directly compared with data from studies employing treadmill exercise for prognostic assessment. Similarly, a recent study randomizing patients with suspected or known coronary artery disease and normal LVEF to treadmill or bicycle exercise testing found a slower HRR-1 after treadmill exercise [27]. However, in that study, no intra-individual comparisons were made, and small differences between the two groups could not be completely excluded.

Study Limitations

The number of patients in our study was small. Because we did not investigate transplant candidates, the results require confirmation in larger studies including sicker patients. Nonetheless, our data can serve as a model to demonstrate the impact of the mode of exercise on important CPET parameters. A second limitation is the lack of a familiarization procedure before the tests [28]. However, as none of the patients recently had an exercise test with either test mode, this might not have had major impact on the findings. In addition, it is unknown whether repeated testing influences exercise responses other than peak VO_2, i.e. the VE/VCO_2 slope and HRR. In addition, current exercise testing guidelines suggest ramp rather than staged protocols, and exercise times between 8 and 12 min [29], which we attempted to achieve by individualizing the protocol. Unfortunately, in approximately 50% of the tests, we failed to achieve the target test duration. However, overall exercise time was similar in the two test modes, and the number of patients with a too short exercise duration (<8 min), which may be associated with underestimation of peak VO_2 [30], was similar for the two test modalities, and therefore, the potential bias introduced by this factor may be balanced across the test modes. Importantly, test mode sequence was randomized and the differences of peak VO_2 between the two tests were as expected.

Conclusions

In patients with mild HF on chronic β-blocker therapy, bicycle testing may lead to an underestimation of peak VO_2 and an overestimation of HRR when compared with values obtained during treadmill exercise. In contrast, the mode of exercise has minimal impact on the VE/VCO_2 slope, and thus, both modes of exercise may be equally suitable to assess this parameter.

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