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# Work-rate affects cardiopulmonary exercise test results in heart failure

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**Abstract**

*Aims:* Cardiopulmonary exercise test (CPET) is used to evaluate patients with chronic heart failure (HF) usually by means of a personalized ramp exercise protocol. Our aim was to evaluate if exercise duration or ramp rate influences the results.

*Methods and results:* Ninety HF patients were studied (peak $\dot{V}_{O_2}$: >20 ml/min/kg, $n$=28, 15–20 ml/min/kg, $n$=39 and <15 ml/min/kg, $n$=23). Each patient did four CPET studies. The initial study was used to separate the subjects into three groups, according to their exercise capacity. In the remaining studies, work-rate was increased at three different rates designed to have the subjects reach peak exercise in 5, 10 and 15 min from the start of the ramp increase in work-rate, respectively. The order was randomized. The work-rate applied for the total population averaged 22.7±8.0, 11.6±3.7, 7.5±2.9 W/min with effective loaded exercise duration of 5 min and 16 s±29 s, 9 min and 43 s±49 s and 14 min and 32 s±1 min and 12 s for the 5-, 10- and 15-min tests, respectively. Peak $\dot{V}_{O_2}$ averaged 16.9±4.3*, 18.0±4.4 and 18.0±5.4 ml/min/kg for the 5-, 10- and 15-min tests, (*=$p$<0.001 vs. 10 min). The shortest test had the lowest peak heart rate and ventilation and highest peak work-rate. Peak $\dot{V}_{O_2}$ and heart rate were lowest in 5-min tests regardless of HF severity. The $\Delta\dot{V}_{O_2}$/Δwork-rate was lowest in 5-min tests and highest in 15-min tests. At all ramp rates, $\Delta\dot{V}_{O_2}$/Δwork-rate was lower for the subjects with the lower peak $\dot{V}_{O_2}$. The $\dot{V}_E/\dot{V}_{CO_2}$ slope and $\dot{V}_{O_2}$ at anaerobic threshold were not affected by the protocol for any grade of HF.

*Conclusions:* In chronic HF, exercise protocol has a small effect on peak $\dot{V}_{O_2}$ and $\Delta\dot{V}_{O_2}$/Δwork but does not affect $\dot{V}_{O_2}$ at anaerobic threshold and $\dot{V}_E/\dot{V}_{CO_2}$ slope.



*Keywords:* Exercise; Oxygen consumption; Heart failure

In chronic heart failure (HF), a cardiopulmonary exercise test (CPET) is frequently done to evaluate the severity of the disease, and thereby the patient's prognosis, or to test the efficacy of therapy [1–8]. For these purposes, several CPET parameters have been studied including oxygen uptake ($\dot{V}_{O_2}$) at peak exercise and at anaerobic threshold, work-rate achieved at peak exercise, slope of ventilation ($\dot{V}_E$) vs. carbon dioxide output ($\dot{V}_{CO_2}$), $\dot{V}_E/\dot{V}_{CO_2}$ ratio at anaerobic threshold, $\Delta\dot{V}_{O_2}$/Δwork-rate from unloaded cycling to peak, and the oxygen pulse ($O_2$p) at peak $\dot{V}_{O_2}$ [9]. Some of these parameters are independent of each other and have specific prognostic relevance; as a consequence their combined use improves our capability to evaluate prognosis in HF patients [9,10]. While it is generally recommended to use a personalized exercise protocol in which work-rate is increased in ramp pattern aimed at achieving target time to peak exercise within 8–12 min [9,11–13], the exercise protocol is rarely provided in clinical study reports. Because it is not known if and how the duration, or the rate of increase of exercise load, affects the results obtained by CPET in the general HF population, and in subgroups of patients divided by HF severity, we investigated the effect of rate of work-rate

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increase, selected to reach the subject's peak exercise tolerance in approximately 5, 10 and 15 min, on the major exercise parameters of aerobic function and ventilatory efficiency.

## 1. Methods

### 1.1. Patient population

We studied 90 patients, 70 male and 20 female (age 59.3±0.7 years), with chronic HF in stable clinical condition and stable drug treatment for at least 2 months. These patients were followed regularly at single specialized Heart Failure Unit. Mean left ventricular ejection fraction, evaluated by echocardiography, was 36.2±10.9%. Cause of heart failure was idiopathic cardiomyopathy in 43 cases, ischemic cardiomyopathy in 44 and valvular heart disease in 3. All patients were on an optimized drug regimen, which included diuretics (72 cases), ACE-inhibitors (75 cases), angiotensin 1 receptor (AT1)-blockers (16 cases), beta-adrenergic receptor blockers (43 cases), anti-aldosteronic drugs (41 cases), digitalis (25 cases), and amiodarone (29 cases). Forty-seven and 43 patients were in New York Heart Association class II and III, respectively. According to the Weber classification [1], which is based on peak $\dot{V}_{O_2}$, 28 patients were in class A (peak $\dot{V}_{O_2}$>20 ml/min/kg, age 57.1±0.7 years), 39 in class B (peak $\dot{V}_{O_2}$ between 15 and 20 ml/min/kg, age 59.7±1.4) and 23 in class C (peak $\dot{V}_{O_2}$<15 ml/min/kg, age 61.1±4.9). Patients were studied between June 1998 and May 2002. All patients were evaluated by the same medical staff using the same instruments (V-Max, Ergo 800 S and 12-lead ECG recorder Max-1; Sensor Medics, Yorba Linda, CA). The study was approved by the Institutional Ethics Committee and each subject provided written informed consent to the study.

### 1.2. Study protocol

All subjects had previous experience with cycle ergometer CPETs in our laboratory [14]. The protocol consisted of four-cycle ergometer CPETs performed with a ramp protocol, with breath-by-breath analysis of expiratory $O_2$ and $CO_2$ concentrations and ventilation and 12-lead EKG recording. The first test was utilized to assess the patients exercise capacity. The work-rate of the ramp protocol of this first test was decided on the basis of each patient clinical evaluation and on previous tests. The work-rate reached by the patient in the first test was utilized to target the ramp work-rate for the other three remaining tests, with the aim of achieving peak exercise in 5, 10 and 15 min, respectively. The order of these three tests was randomized. In each test, the loaded cycling period was preceded by 3 min of unloaded cycling. Tests were performed at about 60 rpm. All four tests were done within 10 working days with a minimum test-to-test interval of 48 h. The patients determined when they reached their peak exercise tolerance; however, they were strongly encouraged to perform a maximal effort. Neither patients nor laboratory personnel knew the protocol in use or the time course of the test, both being concealed from the monitor.

### 1.3. Data analysis

Data were collected breath-by-breath but specific time-related values are reported as means over 20 s. Peak exercise was considered the highest $\dot{V}_{O_2}$ achieved during active exercise or early recovery. Anaerobic threshold was measured with the *V*-slope analysis of $\dot{V}_{CO_2}$ vs. $\dot{V}_{O_2}$. The anaerobic threshold value was confirmed by ventilatory equivalents (increase of $\dot{V}_E/\dot{V}_{O_2}$ with a constant $\dot{V}_E/\dot{V}_{CO_2}$) and end-tidal pressure (increase of end-tidal $P_{O_2}$ with constant end-tidal $P_{CO_2}$). Oxygen pulse was calculated as $\dot{V}_{O_2}$/heart rate at peak exercise. The slope of the $\Delta\dot{V}_{O_2}$/$\Delta$work-rate relationship was calculated by computerized linear regression analysis from $\dot{V}_{O_2}$ increase from the end of unloaded cycling to peak exercise [15]. The $\dot{V}_E/\dot{V}_{CO_2}$ slope was calculated as the slope of the linear relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ from the beginning of loaded exercise and the end of the isocapnic buffering period identified where end-tidal $P_{CO_2}$ starts to decrease. Periodic breathing was defined as exercise-induced oscillatory changes in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during exercise with a period of approximately 1 min. Two experts independently read each test.

### 1.4. Statistical Analysis

The data are reported as mean±S.D. Comparisons were made by one-way ANOVA followed by paired *t*-test as appropriated. The 10-min test was used as the reference work-rate protocol for the 5- and 15-min tests to which they were compared.

## 2. Results

All patients completed the trial. In three cases, some tests were postponed for a few days because of interceding reasons. The respiratory exchange ratio ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) at peak exercise was >1.0 in all subjects suggesting that, at least, a near maximal exercise was performed; the respiratory exchange ratio achieved was not significantly different among the three tests (1.05±0.2, 1.09±0.2 and 1.06±0.2, for the 5-, 10- and 15-min test durations, respectively). The average work-rate applied was 22.7±8.0, 11.6±3.7 and 7.5±2.9 W/min for the 5-, 10- and 15-min tests, respectively. Periodic breathing was observed in 13 patients (1 in class A, 4 in class B and 8 in class C) and, if present, was observed in all the tests

Table 1
Average±standard deviation of cardiopulmonary exercise testing parameters in 90 HF patients

| | 5 min | 10 min | 15 min |
|---|---|---|---|
| Peak heart rate (beats/min) | 128±24* | 137±24 | 137±25 |
| Peak $\dot{V}_{O_2}$ (ml/min/kg) | 16.9±4.3* | 18.0±4.4 | 18.5±5.4 |
| Peak work-rate (W) | 116±44 | 114±40 | 105±42* |
| Peak $O_2$p (ml/min/beat) | 10.1±3.3 | 10.1±3.3 | 10.1±3.2 |
| Ventilation (l/min) | 47±12* | 54±13 | 55±16 |
| Tidal volume (l) | 1.6±0.4 | 1.7±0.4 | 1.7±0.4 |
| Respiratory rate (breath×min) | 30±6* | 33±7 | 34±7 |
| $\dot{V}E/\dot{V}_{CO_2}$ slope | 32.9±6.7 | 32.7±6.1 | 32.7±6.3 |
| $\Delta\dot{V}_{O_2}$/Δwork-rate (ml/min/W) | 8.2±1.1* | 8.9±1.5 | 9.5±1.1* |
| Pet$O_2$ (mm Hg) at peak exercise | 115±11 | 117±11 | 118±6 |
| Pet$CO_2$ (mm Hg) at peak exercise | 35±6* | 33±6 | 33±5 |
| $\dot{V}_{O_2}$ at anaerobic threshold (ml/min/kg)§ | 12.3±4.1 | 12.3±5.5 | 12.4±3.9 |

HF=heart failure; $O_2$p=$O_2$ pulse; et=end-tidal.
* $p$<0.001 vs. 10-min test.
§ $n$=85 patients.

regardless of the exercise protocol. Exercise-induced periodic breathing disappeared during the test usually around anaerobic threshold. The effective loaded exercise duration was 5 min and 16 s±29 s, 9 min and 43 s±49 s and 14 min and 32 s±1 min and 12 s for the 5-, 10- and 15-min tests. Peak exercise measurements, $\Delta\dot{V}_{O_2}$/Δwork-rate and $\dot{V}_E/\dot{V}_{CO_2}$, for the entire study population are reported in Table 1. Peak $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and heart rate were lower in the 5-min test compared to both longer tests. In the 5-min test, $\dot{V}_E$ was the lowest due to a low respiratory rate and end-tidal $P_{CO_2}$ was the highest. The $\dot{V}_E/\dot{V}_{CO_2}$ slope and $\dot{V}_{O_2}$ at anaerobic threshold were not affected by the exercise protocol (Table 1).

Regardless of the exercise protocol used, the heart rate at peak exercise was lower in class B and C patients compared to class A patients ($p$<0.01 for class A vs. class B and class C) (Table 2). Heart rate and $\dot{V}_{O_2}$ at peak exercise were lowest in the 5-min test in all classes of patients (Table 2). In contrast, the work-rate achieved was lowest at peak exercise in the 15-min test for all three heart failure classes (Table 2). The $\Delta\dot{V}_{O_2}$/Δwork-rate was lowest in class C patients regardless of rate of increase in work-rate or exercise duration (Fig. 1). The $\Delta\dot{V}_{O_2}$/Δwork-rate had a progressively lower slope from the 15-min test to the 5-min test for all three heart failure classes (Fig. 2). At the 10-min test, peak $O_2$ pulse was 12.6±3.0*§, 10.0±2.9§ and 7.3±1.4* ml/min/beat in class A, class B and class C, respectively (*$p$<0.001 vs. class B patients, §$p$<0.001 vs. class C patients). The peak $O_2$ pulse value was not affected by the ramp protocol applied (Tables 1 and 2).

At peak exercise, $\dot{V}_E$ was: in class C highest with the 10-min protocol; in class B lowest for the 5-min protocol; and in class A lowest for the 5-min and highest for the 15-min protocols, respectively (Table 3). $\dot{V}_E$ differences among the exercise protocols were mainly due to respiratory rate changes (Table 3). As the functional class worsened, the slope of $\dot{V}_E/\dot{V}_{CO_2}$ was progressively higher; however, the exercise protocol did not influence the $\dot{V}_E/\dot{V}_{CO_2}$ slope (Table 3).

Anaerobic threshold was not clearly identified in five patients and, therefore, anaerobic threshold data refer to 85 of the 90 subjects (Table 4). The all-group average anaerobic thresholds were at 74±32*, 64±30 and 58±28§ W with the 5-, 10- and 15-min tests, respectively (*$p$<0.001, §$p$<0.01), with it being progressively reduced as

Table 2
CPET parameters at peak exercise and work-rate applied in the three tests in class C (peak $\dot{V}_{O_2}$<15 ml/min/kg), class B (peak $\dot{V}_{O_2}$ 20–15 ml/min/kg) and in class A patients (peak $\dot{V}_{O_2}$>20 ml/min/kg)

| Test | HR (beats/min) | Peak WR (W) | ET (s) | $\dot{V}_{O_2}$ (ml/min/kg) | Peak $O_2$p (ml/min/beat) | Ex Pr WR (W/min) | Pet$O_2$ (mm Hg) | Pet$CO_2$ (mm Hg) |
|---|---|---|---|---|---|---|---|---|
| *Class C patients (n=23)* | | | | | | | | |
| 5 min | 124±24* | 77±26 | 323±35 | 11.8±2.0§ | 7.2±1.4 | 15.0±4.9 | 120±6 | 30.4±5.3 |
| 10 min | 131±26 | 76±24 | 565±39 | 12.5±1.7 | 7.3±1.4 | 8.8±3.2 | 120±6 | 30.2±5.3 |
| 15 min | 126±23§ | 65±20* | 899±96 | 12.3±2.0 | 7.5±1.5 | 4.8±1.8 | 119±6# | 31.2±5.4# |
| *Class B patients (n=39)* | | | | | | | | |
| 5 min | 125±23* | 111±28§ | 311±24 | 16.4±1.7* | 10.0±3.0 | 21.6±5.3 | 114±14 | 34.6±5.0* |
| 10 min | 134±20 | 106±24 | 583±43 | 17.4±1.3 | 10.0±2.9 | 10.8±2.4 | 117±15 | 32.3±5.3 |
| 15 min | 132±23 | 97±27* | 860±62 | 17.6±1.7 | 10.1±2.7 | 7.9±1.9 | 119±5 | 32.2±4.8 |
| *Class A patients (n=28)* | | | | | | | | |
| 5 min | 136±24* | 154±41 | 318±31 | 21.9±2.3* | 12.6±2.8 | 30.5±6.1 | 112±5# | 39.5±4.8§ |
| 10 min | 146±24 | 154±30 | 600±58 | 23.2±2.0 | 12.6±3.0 | 14.9±3.3 | 114±5 | 37.4±4.0 |
| 15 min | 151±23§ | 150±32# | 868±58 | 23.4±2.4# | 12.3±3.5 | 10.4±2.3 | 115±6# | 35.8±4.9§ |

HR=heart rate; peak WR=peak work-rate; ET=endurance time; peak $O_2$p=oxygen pulse at peak; Ex Pr WR=exercise protocol work-rate; Pet$O_2$=end-tidal pressure for $O_2$; Pet$CO_2$=end-tidal pressure for $CO_2$.
* $p$<0.001 vs. 10-min test.
§ $p$<0.01 vs. 10-min test.
\# $p$<0.05 vs. 10-min test.

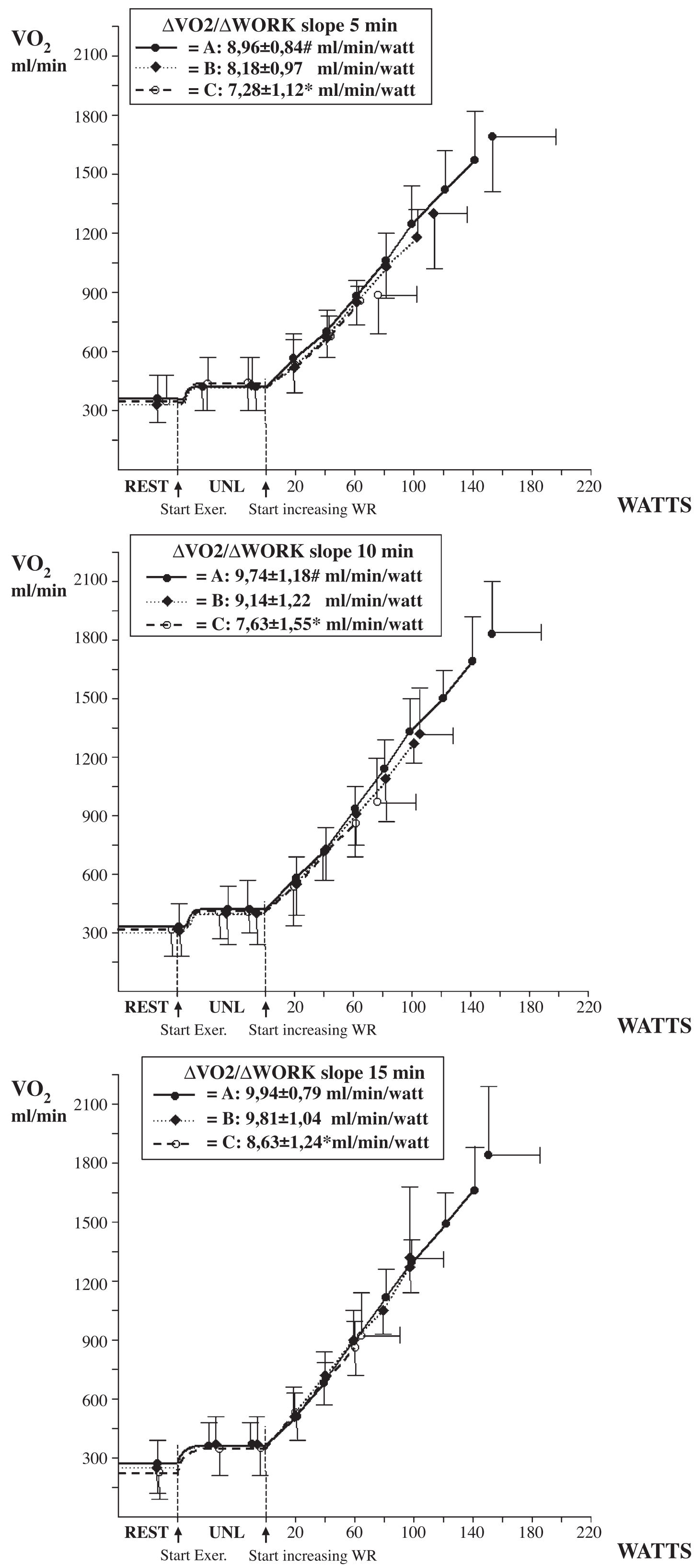


Fig. 1. From top to bottom the $\Delta\dot{V}_{O_2}$/Δwork-slope relationship for 5-min (upper panel), 10-min (middle panel) and 15-min tests (lower panel) in class A, class B and class C HF patients. The $\Delta\dot{V}_{O_2}$/Δwork-rate slope was most shallow in class C patients. *$p$<0.01 vs. class A and class B; #$p$<0.05 vs. class B. The last symbols on the right for each patients group are peak exercise data. UNL=unloaded cycling; WR=work-rate.

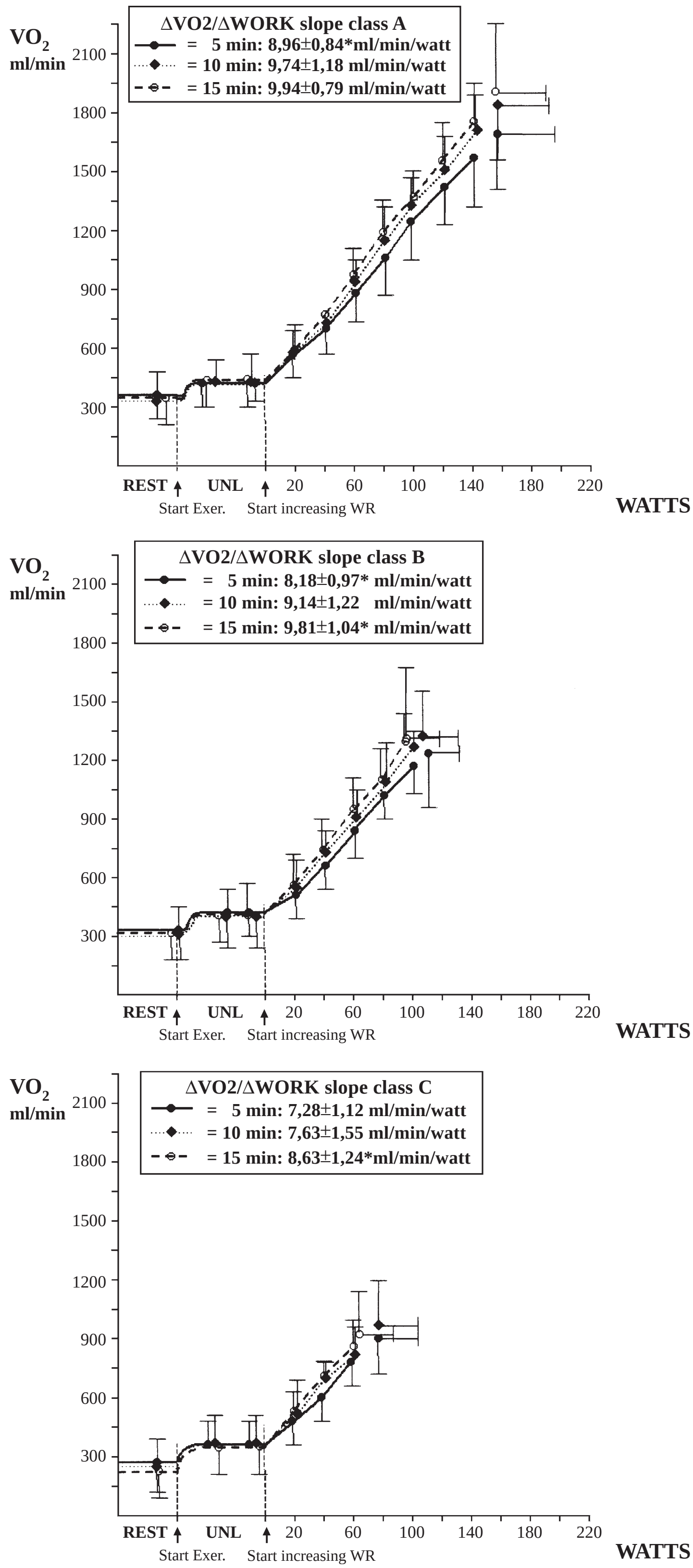


Fig. 2. From top to bottom, the effect of work-rate ramp on the $\Delta\dot{V}_{O_2}$/Δwork-rate slope relationship in class A ($n$=28, upper panel), class B ($n$=39, middle panel) and class C ($n$=23, lower panel). *$p$<0.001 vs. 10-min test. The last symbols on the right for each work-rate are peak exercise data. UNL=unloaded cycling; WR=work-rate.

Table 3
Ventilatory parameters in the three tests in class C (peak $\dot{V}_{O_2}$<15 ml/min/kg), class B (peak $\dot{V}_{O_2}$ 20–15 ml/min/kg) and in class A patients (peak $\dot{V}_{O_2}$>20 ml/min/kg)

| Test | Peak exercise ventilation (l/min) | Peak exercise tidal volume (l) | Peak exercise respiratory rate (breath/min) | $\dot{V}_E/\dot{V}_{CO_2}$ slope |
|---|---|---|---|---|
| *Class C patients (n=23)* | | | | |
| 5 min | 42±12[§] | 1.3±0.3 | 33±7[§] | 38.8±7.0 |
| 10 min | 46±13 | 1.4±0.3 | 35±8 | 38.0±7.1 |
| 15 min | 42±13[§] | 1.2±2.0[§] | 34±8 | 37.4±7 |
| *Class B patients (n=39)* | | | | |
| 5 min | 47±10* | 1.5±0.4 | 30±7* | 32.4±5.8 |
| 10 min | 54±10 | 1.6±0.3 | 34±7 | 32.3±4.7 |
| 15 min | 54±12 | 1.6±0.3 | 35±7 | 32.7±5.6 |
| *Class A patients (n=28)* | | | | |
| 5 min | 54±12* | 1.9±0.3 | 28±5[§] | 28.9±4.2 |
| 10 min | 61±13 | 2.0±0.4 | 30±5 | 28.9±3.5 |
| 15 min | 66±16[§] | 2.0±0.4 | 32±5[§] | 28.9±5.5 |

$p<0.05$ vs. 10-min test.
* $p<0.001$ vs. 10-min test.
§ $p<0.01$ vs. 10-min test.

the functional class worsened. However, $\dot{V}_{O_2}$ at the anaerobic threshold, $\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}_E/\dot{V}_{O_2}$ at anaerobic threshold were unaffected by the ramp protocol, in all groups of patients (Table 4).

## 3. Discussion

This study shows that, for any grade of HF, among the most relevant CPET measurements, $\dot{V}_{O_2}$ at anaerobic threshold and $\dot{V}_E/\dot{V}_{CO_2}$ slope are independent of the work-rate applied and test duration. Peak $\dot{V}_{O_2}$ was mildly reduced for the test in which work-rate was increased most rapidly. The shortest duration test was accompanied by the lowest peak exercise heart rate and ventilation (Table 1). Importantly, we showed that the $\Delta\dot{V}_{O_2}/\Delta$work-rate, which depends on the ability of the circulatory delivery of $O_2$ to keep pace with the $O_2$ requirement, was reduced as rate of work-rate increased and as heart failure worsened (Table 1; Figs. 1 and 2).

The exercise tests were done with different ramp protocols to achieve peak exercise in 5, 10 and 15 min. All of the possible problems related to patient familiarization with laboratory and staff [14] was avoided by studying patients who were regularly followed in a single Heart Failure Unit. All patients performed CPETs in the same laboratory including a formal familiarization test, and were repeatedly evaluated with the same instruments and by the same personnel. We used the 10-min test as reference for short, 5-min, and long, 15-min, tests. The 10-min test was chosen because 10 min is the duration considered optimal for CPET [12] and most frequently recommended [9,11,13]. The influence of a possible training effect on the results was minimized by performing tests in random order.

Heart failure severity was assessed according to peak $\dot{V}_{O_2}$ in the 10-min test, using the Weber classification [1]. CPET parameters varied according to HF severity, as expected. For the 10-min test, peak exercise heart rate, $O_2$ pulse and work-rate achieved were lower, the more severe the HF. Also, peak exercise ventilation and tidal volume were lowest in patients with the greatest HF severity [16]. Patients with the greatest severity of HF also showed a higher inappropriate ventilation as documented by a steeper $\dot{V}_E/\dot{V}_{CO_2}$ slope and a higher $\dot{V}_E/\dot{V}_{CO_2}$ at anaerobic threshold; as a consequence, peak exercise $PetO_2$ was higher and $PetCO_2$ was lower in the more severe HF patients (Table 2).

Peak $\dot{V}_{O_2}$ was significantly lower in the 5-min as compared to the 10- and 15-min tests. This may relate to the large work-rate increase in a short time period dictated by the 5-min protocol.

This imposes a heavy load early in exercise, forcing the patient to stop exercising early because of limited $O_2$ transport. The inability to regenerate adenosine triphosphate (ATP), aerobically, may account for the failure to sustain muscle contraction and cause early muscle fatigue. Indeed, the more shallow $\Delta\dot{V}_{O_2}/\Delta$work-rate for the more rapid rates of increase in work-rate (Table 1), undoubtedly relates to the failure of the cardiac output to increase at the rate required to provide the muscles with the $O_2$ needed to regenerate ATP aerobically. The $\Delta\dot{V}_{O_2}/\Delta$work-rate slope is frequently utilized to assess the adequacy of $O_2$ flow and utilization in the periphery [15]. The exercise protocol affected the $\Delta\dot{V}_{O_2}/\Delta$work-slope with its value being lower with greater work increments (Fig. 2). This was a trend in all classes of HF and similar to changes in normal subjects, as described by Hansen et al. [15]. Albeit we have not partitioned the $\Delta\dot{V}_{O_2}/\Delta$work-rate relationship between above and below anaerobic threshold, the reason for the observed differences might be due to

Table 4
CPET parameters at anaerobic threshold in the three tests in class C (peak $\dot{V}_{O_2}$<15 ml/min/kg), class B (peak $\dot{V}_{O_2}$ 20–15 ml/min/kg) and in class A patients (peak $\dot{V}_{O_2}$>20 ml/min/kg)

| Test | Work-rate (W) | $\dot{V}_{O_2}$ (ml/min/kg) | $\dot{V}_E/\dot{V}_{O_2}$ | $\dot{V}_E/\dot{V}_{CO_2}$ |
|---|---|---|---|---|
| *Class C patients (n=21)* | | | | |
| 5 min | 42±21 | 8.0±2.9 | 38.3±8.1 | 42.9±8.1 |
| 10 min | 39±19 | 9.1±1.9 | 37.2±6.7 | 39.8±6.4 |
| 15 min | 32±16[#] | 8.4±2.1 | 37.0±6.7 | 40.5±6.4 |
| *Class B patients (n=37)* | | | | |
| 5 min | 69±22* | 12.1±2.1 | 30.2±5 | 35.6±5.0 |
| 10 min | 55±18 | 11.7±1.5 | 31.2±4.4 | 35.6±5.2 |
| 15 min | 53±18 | 12.0±2.0 | 30.2±4.7 | 34.6±5.0 |
| *Class A patients (n=27)* | | | | |
| 5 min | 106±21[#] | 16.2±2.7 | 26.2±3.2 | 31±3.4 |
| 10 min | 96±21 | 16.4±2.0 | 27.4±3.9 | 31.0±3.7 |
| 15 min | 86±20[#] | 16.3±2.7 | 27.2±3.7 | 30.9±3.5 |

$\dot{V}_E$=ventilation.
* $p<0.001$ vs. 10-min test.
\# $p<0.05$ vs. 10-min test.

the zone of work above the anaerobic threshold being $O_2$-flow-dependent, as described by Wasserman et al. [17] and thereby be subject to a decreasing $\Delta\dot{V}_{O_2}$/$\Delta$work-rate slope when the $O_2$ demand is faster than the circulation can transport $O_2$. As shown in Fig. 1, $\Delta\dot{V}_{O_2}$/$\Delta$work-rate is lowest for the most severely impaired patients in all the exercise protocols. The more shallow $\Delta\dot{V}_{O_2}$/$\Delta$work-rate for the fast ramp may bias the grading of HF severity and the decision of cardiac transplantation, if work-rate is used to grade the patient's impairment [18,19].

While the exercise protocol influenced peak exercise ventilation, it did not affect the $\dot{V}_E/\dot{V}_{CO_2}$ slope, which is an index of coupling of ventilation and lung perfusion. As previously described, the slope was higher as HF severity worsened [10,20,21]. The $\dot{V}_E/\dot{V}_{CO_2}$ relationship is calculated during exercise, in the range of work below the ventilatory compensation point for the exercise-induced lactic acidosis, thus avoiding the non-linearity to ventilation caused by lactic acidosis. The $\dot{V}_E/\dot{V}_{CO_2}$ slope is a relevant indicator of HF survival, independent of peak exercise $\dot{V}_{O_2}$ [10,22] as it is $\dot{V}_{O_2}$ at anaerobic threshold [19]. The absence of a change in $\dot{V}_E/\dot{V}_{CO_2}$ slope and $\dot{V}_{O_2}$ at anaerobic threshold with increasing rates of work-rate demonstrates the robust nature of both these measurements and their physiological significance. Indeed, our findings reinforce the observation of Gitt et al. [23] who suggests the combined use of $\dot{V}_E/\dot{V}_{CO_2}$ slope and $\dot{V}_{O_2}$ at anaerobic threshold for precise HF prognosis. Only the work-load at which anaerobic threshold was identified was influenced by the protocol. This is as expected because of the time lag between the change in work-rate and metabolic events in the muscle.

In conclusion, we showed that, when evaluating HF patients, the exercise protocol influences the peak imposed cycle ergometer work-load and, to a small degree, the $\Delta\dot{V}_{O_2}$/$\Delta$work-rate. Peak $\dot{V}_{O_2}$ is slightly reduced, only for the most rapid ramp protocol. $\dot{V}_E/\dot{V}_{CO_2}$ slope and $\dot{V}_{O_2}$ at anaerobic threshold are unaffected.

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