1   **Title:** Ventilatory Response to Carbon Dioxide Output in Patients with Chronic Heart

2   Failure and in Patients with Chronic Obstructive Pulmonary Disease with Comparable

3   Exercise Capacity

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15   **Short title:** Ventilatory Response to CO_2 in CHF and COPD during exercise

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1 **ABSTRACT**

2 BACKGROUNG: Patients with Chronic Heart Failure (CHF) or with COPD may share

3 an increased response in minute ventilation (VE) to carbon dioxide output (VCO_2)

4 during exercise. OBJECTIVE: To ascertain whether or not the VE/VCO_{2slope} and

5 $VE/VCO_{2intercept}$ values may discriminate CHF from COPD patients at equal peak

6 oxygen uptake (VO_{2peak}). METHODS: We studied 46 patients with CHF (mean age:

7 61 ± 9 years) and 46 COPD patients (mean age: 64 ± 8 years), who performed a

8 cardiopulmonary exercise test. RESULTS: The VE/VCO_{2slope} values were significantly

9 higher in CHF than in COPD patients (39.5 ± 9.5 vs 31.8 ± 7.4; $p<0.01$) at $VO_{2peak} < 16$

10 ml/kg/min, but not ≥ 16 ml/kg/min (28.3 ± 5.3 vs 28.9 ± 6.6). The $VE/VCO_{2intercept}$ values

11 were significantly higher in both subgroups of COPD patients, as compared to the

12 corresponding values of the CHF patients (3.60 L/min ±1.7 vs -0.16 L/min ±1.7; $p<0.01$

13 and 3.63 L/min ± 2.7 vs 0.87 L/min ± 1.5; $p<0.01$). According to ROC curve analysis,

14 when all patients with a $VO_{2peak} < 16$ ml/kg/min were considered, COPD patients had a

15 highest likelihood to have a $VE/VCO_{2intercept}$ value greater than 2.14 L/min (0.92

16 sensitivity, 0.96 specificity). Regardless of VO_{2peak} value, the end-tidal pressure of CO_2

17 ($PETCO_2$) values at peak exercise were not different in CHF ($p=0.42$) and significantly

18 higher in COPD ($p<0.01$) patients, as compared to the corresponding unloaded $PETCO_2$

19 values. CONCLUSIONS: The ventilatory response to VCO_2 during exercise was

20 significantly different between CHF and COPD patients in terms of VE/VCO_{2slope}

21 values in patients with moderate to severe reduction in exercise capacity, and in terms

22 of $VE/VCO_{2intercept}$ values, regardless of the exercise capacity.

23

1   **Key Words:** CHF, COPD, Exercise, Ventilatory Response

2

3   **ABBREVIATIONS**

4   AT: anaerobic threshold

5   AUC: area under curve

6

7   BMI: body mass index

8   CHF: chronic heart failure

9   COPD: chronic obstructive pulmonary disease

10   CPET: cardiopulmonary exercise test

11   DP: double product

12   FEV_1: forced expiratory volume in 1st second

13   FFM: fat-free mass

14   HR: heart rate

15   LVEF: left ventricular ejection fraction

16   O_2Pulse: oxygen pulse

17   $PETCO_2$: end-tidal pressure of CO_2

18   TLC: total lung capacity

19   VAS: visual analogue scale

20   VC: vital capacity

21   VCO_2: carbon dioxide output

22   VE: minute ventilation

23   VE/VCO_2: ventilatory equivalent for CO_2

24   VO_2: oxygen uptake

1 **INTRODUCTION**

2

3 Poor exercise tolerance, given by a reduction in peak oxygen uptake (VO_{2peak}) during a

4 rapidly incremental cardiopulmonary exercise testing (CPET), may occur in chronic

5 cardiopulmonary disabling conditions, such as chronic heart failure (CHF) and chronic

6 obstructive pulmonary disease (COPD).

7

8 Interestingly, while performing a CPET, both CHF [1,2] and COPD [3,4] patients may

9 share a different than normal ventilatory response to carbon dioxide output (VCO_2). The

10 mechanisms underlying the control of exercise hyperpnoea are complex and still under

11 investigation both in healthy subjects [5] and in cardiopulmonary patients [6,7]. At any

12 rate, the minute ventilation (VE) for a given metabolic rate (VE/VCO_2), also known as

13 ventilatory equivalent for CO_2 [8], may be increased both in CHF and COPD during

14 exercise. Notably, the slope of the VE/VCO_2 linear relationship is considered as the

15 strongest prognostic marker (including VO_{2peak}) in patients with CHF, regardless of the

16 aetiology of cardiomyopathy [9] and was found to be a significant post-surgical

17 prognostic marker in patients with COPD undergoing lung resection [10]. Moreover, it

18 has been recently recognized that even the intercept of the VE/VCO_2 relationship may

19 be relevant in fully understanding ventilatory control mechanisms in health [7] and in

20 disease [6,7].

21

22 Up to now, no study has been aimed to compare the ventilatory response to VCO_2 in

23 CHF and COPD patients with comparable exercise capacity and to assess the possible

24 discriminating value of VE/VCO_2 measurement among these patients. The aim of the

1   present study was, therefore, to measure the VE/VCO$_2$ value, both in terms of slope and

2   in terms of intercept, in a cohort of CHF and COPD patients and to ascertain whether or

3   not the VE/VCO$_2$ slope and intercept values may discriminate these patients at equal

4   VO$_{2peak}$.

5

1 **METHODS**

2

3 *Patients*

4 We consecutively enrolled over a 6-month period, from November 2012 to April 2013,

5 patients affected by CHF due to ischemic or idiopathic dilated cardiomyopathy referred

6 for cardiopulmonary exercise test (CPET), as part of a comprehensive heart failure

7 evaluation, and patients with COPD, who were admitted to a pulmonary rehabilitation

8 program.

9

10 All CHF patients had a history of at least 1 unequivocal clinical episode of heart failure

11 and an echocardiographic left ventricular ejection fraction (LVEF) < 50%. CHF patients

12 with uncontrolled atrial fibrillation or with history of sustained ventricular tachycardia,

13 recent syncope or myocardial infarct were excluded (11). COPD was diagnosed

14 according to the GOLD criteria (12) and patients with moderate to severe airflow

15 obstruction, i.e. Forced Expiratory Volume in 1 Second/Vital Capacity ratio (FEV_1/VC)

16 < 70% and FEV_1 < 80% of predicted value, were included.

17
18 For all patients eligibility criteria were: 1) age range 40 to 75 years; 2) BMI $\leq$ 30 kg/m^2;

19 3) stable clinical condition for at least 8 weeks; 4) absence of any comorbidity affecting

20 exercise performance (anaemia, neuromuscular disorders or malignancies); 5) ability to

21 perform a CPET with a peak of respiratory exchange ratio $\geq$ 1.05 in order to exclude

22 poor motivation (11); 6) CPET stopped for muscle fatigue and/or dyspnoea.

23

24 All the procedures and their risks were explained to the patients, who gave their written

25 informed consent to enter the study, which was conducted according to the Declaration

1   of Helsinki. The protocol was approved by the ethical committee of the University

2   Hospital of Parma. All participants' data were analysed and reported anonymously. No

3   extramural funding was used to support the study.

4

5   ***Measurements***

6   *Pulmonary function testing*

7   Pulmonary function tests were performed according to the international

8   recommendations (13,14). A flow-sensing spirometer and a body plethysmograph

9   connected to a computer for data analysis (Vmax 22 and 6200, Sensor Medics, Yorba

10   Linda, U.S.A.) were used for these measurements. Total Lung Capacity (TLC), VC,

11   FEV_1 and FEV_1/VC were recorded. TLC, VC, and FEV_1 were expressed as a percentage

12   of the predicted values (15).

13

14   *Cardiopulmonary exercise test*

15   CPET was performed according to a standardized procedure (11). Briefly, the exercise

16   protocol started with initial 3 minutes of rest, followed by unloaded cycling for 3

17   minutes and a subsequent increment of 5 to 15 W each minute, depending on the

18   anthropometric data and the degree of individual functional impairment, with the aim to

19   perform a total exercise time ranging 8-12 min. Patients were asked to maintain a

20   pedalling frequency of 60 rpm indicated by a digital display placed on the monitor of

21   the cycle ergometer (Corival PB, Lobe Bv, Groningen, The Netherlands). Breath-by-

22   breath VO_2 (in L/min), VCO_2 (in L/min) and VE (in L/min) were recorded during the

23   test (CPX/D; Medical Graphics, St Paul, MN, U.S.A.). Patients were continuously

24   monitored by a 12-lead electrocardiogram (Welch Allyn CardioPerfect, Delft, the

1   Nederlands) and a pulse oximeter (Pulse Oximeter 8600, Nonin Medical Inc, MPLS,

2   Mn U.S.A.). Blood pressure was measured in mmHg at 2 min intervals. Stopping

3   criteria consisted of symptoms such as unsustainable dyspnoea or leg fatigue, chest pain,

4   ECG significant ST-segment depression, a drop in systolic blood pressure or oxygen

5   saturation (SaO_2) $\leq 84\%$.

6

7   Workload peak and VO_{2peak} were recorded as the mean value of watts and VO_2 (in

8   mL/kg/min) during the last 20 s of the test. Anaerobic threshold (AT) was non

9   invasively determined by both V-slope and ventilatory equivalents methods ("dual

10   method approach") and was expressed in mL/kg/min of VO_2 ($VO_2@AT$) (11). The

11   ventilatory response during exercise was expressed as a linear regression function by

12   plotting VE against VCO_2 obtained every 10 seconds, excluding data above the

13   ventilatory compensation point (11), and by measuring slope (VE/VCO_{2slope}) and Y

14   intercept ($VE/VCO_{2intercept}$) values. The end-tidal pressure of CO_2 ($PETCO_2$, in mm Hg)

15   was recorded as mean value of $PETCO_2$ during the 3-minute rest period

16   ($PETCO_{2unloaded}$), during the last 20 s of the test ($PETCO_{2peak}$) and as the difference

17   between $PETCO_{2peak}$ and $PETCO_{2unloaded}$ ($PETCO_{2peak-unloaded}$), respectively.

18

19   The cardiovascular response to exercise was expressed by the following parameters:

20   oxygen pulse (O_2Pulse) and double product (DP). The O_2Pulse (in mL/bpm) was

21   calculated by dividing instantaneous oxygen uptake by heart rate (11) and was recorded

22   at peak of exercise. The DP at rest and at maximal exercise was calculated by the

23   product of systolic blood pressure and heart rate and expressed as DP reserve (DP at

24   maximal exercise minus DP at rest, in mmHg·bpm) (16).

1

2   *Functional status, dyspnoea and muscle fatigue*

3   The functional status of the CHF patients was categorized according to the New York

4   Heart Association (NYHA) functional classification system (I-IV) (17). Briefly, NYHA

5   classification places patients with cardiac disease in one of four categories based on

6   physical activity limitation: Class I, patients without limitation of physical activity, i.e.

7   ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal

8   pain; Class II, patients with slight limitation of physical activity, i.e. they are

9   comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea

10   or anginal pain; Class III, patients with marked limitation of physical activity, i.e. they

11   are comfortable at rest, but less than ordinary activity causes fatigue, palpitation,

12   dyspnea or anginal pain; Class IV, patients with inability to carry on any physical

13   activity without discomfort, symptoms of heart failure or the anginal syndrome may be

14   present even at rest and if any physical activity is undertaken, discomfort increases.

15

16   In COPD patients, the daily living activity-related dyspnoea was evaluated with the

17   Italian version of five-point MRC scale modified by the ATS (18). In all patients,

18   dyspnoea and muscle fatigue induced by CPET were measured at the end of the

19   incremental exercise by a visual analogue scale (VAS dyspnea and VAS fatigue,

20   respectively in mm), as previously described (19). Briefly, the VAS scale consisted of a

21   horizontal line with the word "none" placed at the left end of the scale and the word

22   "very severe" placed at the right of the scale. The VAS was scored from 0 to 100, but

23   the subjects were unaware of the numbers.

24

1 *Echocardiography*

2 In CHF patients, a complete Doppler echocardiographic evaluation was performed

3 within a three week-period before pulmonary function tests and CPET.

4 Echocardiograms were recorded using a commercially available machine (System five

5 CFM, GE) equipped with 2.5- and 3.5-MHz electronic transducers and harmonic

6 imaging. Left ventricular chamber dimensions were measured according to the

7 recommendations of the American Society of Echocardiography (20). Left ventricular

8 systolic function was evaluated and left ventricular ejection fraction (LVEF, %) was

9 recorded according to the single-plane area-length method.

10

11 *Body Composition*

12 Body height and weight were measured anthropometrically in all patients. Body

13 composition was assessed by a bioelectrical impedance analysis (BIA) method, that is

14 based on the conductance of an electrical sinusoidal alternating current through body

15 fluids. BIA measures the impedance or resistance to the signal as it travels through the

16 water that is found in muscle and fat. Foot-to-foot BIA was measured using a SC-331S

17 Body Composition analyzer (TANITA CO., Tokyo, Japan). Patients were measured in

18 standing position with bare feet on the analyzer footpads. The algorithms used to

19 estimate lean body mass from impedance are those given by Segal et al (21). The fat-

20 free mass (FFM) was standardized for height similar to BMI: FFM index (FFMI:

21 $FFM/height^2$, kg/m^2).

22

23

24

1   *Statistical analysis*

2   Data are reported as mean ± standard deviation (SD), unless otherwise specified. Due to

3   the explorative nature of the study no formal sample size calculation was performed.

4   The distribution of variables was assessed by means of Kolmogorov-Smirnov

5   Goodness-of-Fit test. Relationships between variables were assessed by the Pearson's

6   correlation coefficient (r) and linear regression analysis. Comparisons between variables

7   were determined by unpaired t test and χ^2 test, when appropriate.

8

9   According to the VO_2 peak, the population sample was divided in patients with

10   moderate to severe reduction in exercise capacity (VO_{2peak} < 16 mL/kg/min) and

11   patients with mild reduction in exercise capacity (VO_{2peak} ≥16 mL/kg/min) (22).

12

13   The receiver operating characteristic (ROC) curve method (23) was used to plot the true

14   positive rate (sensitivity) in function of the false-positive rate (100-specificity) for

15   different cutoff points of VE/VCO_{2slope} and $VE/VCO_{2intercept}$ values in order to

16   discriminate CHF from COPD patients.

17

18   A p value of less than 0.05 was taken as significant.

19

1 **RESULTS**
2

3 Of the 130 consecutive patients who agreed to participate in the study, eight-teen

4 patients were excluded because of their BMI > 30 kg/m^2, seven because of age > 75

5 years, 13 because of comorbidities. Ninety-two stable patients (46 CHF and 46 COPD),

6 aged between 42 and 75 years were included in the study. CHF patients did not differ in

7 gender (33/13 vs 34/12 male/female ratio; p = 0.815) and tended to be younger (61 ± 9

8 vs 64 ± 8 years; p = 0.068), as compared to COPD patients.

9

10 In CHF patients, NYHA class ranged between I to IV (median II) and their LVEF value

11 was 32 % ± 9, ranging from 15% to 48%. At the moment of the study, CHF patients

12 were receiving regular therapy with β-blockers (98%), diuretics (83%), and angiotensin-

13 converting enzyme (ACE) inhibitors (76%), whereas COPD patients were receiving

14 inhaled steroids (65%), long-acting beta$_2$-agonists (61%) and Tiotropium (43%). All of

15 COPD patients were ex-smokers and among them a wide range of daily living activity-

16 related dyspnoea (MRC from 0 to 4) was found. As expected, CHF patients

17 significantly differed from COPD patients in terms of TLC (94 % ± 16 vs 118 %± 25),

18 FEV_1 (91 % ± 17 vs 52 ± 16) and FEV_1/VC (75 % ± 6 vs 48 % ± 12) (p < 0.001 for all

19 comparisons).

20

21 All the included patients completed the exercise test without any complication. VO_{2peak}

22 values ranged from 7.2 to 31.0 ml/kg/min and from 7.7 to 30.2 ml/kg/min in CHF and

23 in COPD patients, respectively. Twenty-three out of 46 CHF patients and 24 out of 46

24 COPD patients had a VO_{2peak} < 16 ml/kg/min, whereas 23 CHF patients and 22 COPD

25 patients had VO_{2peak} ≥ 16 ml/kg/min. The two subgroups of patients categorized

1   according to the VO_{2peak} did not significantly differ in terms of age, gender and FFMI

2   (p>0.05 for all comparisons; Table 1). COPD patients with lower VO_{2peak} tended to

3   show worse resting lung function without reaching a statistical significance (TLC:

4   124 % ± 25 vs 113 % ± 24, p = 0.145; FEV_1: 49 % ± 14 vs 54 ± 15, p = 0.181;

5   FEV_1/VC: 45 % ± 11 vs 52 % ± 12, p = 0.056). No significant difference was found in

6   resting lung function between CHF patients with VO_{2peak} < 16 ml/kg/min and CHF

7   patients with $VO_{2peak} \geq 16$ ml/kg/min (TLC: 93 % ± 19 vs 96 % ± 13, p = 0.548; FEV_1:

8   88 % ± 20 vs 94 ± 11, p = 0.185; FEV_1/VC: 75 % ± 5 vs 75 % ± 7, p = 0.942). In the

9   group of patients with VO_{2peak} < 16 ml/kg/min, the VO_2@AT values were significantly

10   lower in CHF patients than in COPD patients (p=0.028; Table 1).

11

12   The VE/VCO_{2slope} values were significantly higher in CHF patients with VO_{2peak} < 16

13   ml/kg/min as compared to the corresponding values of the COPD group, but were not

14   different when CHF and COPD patients with $VO_{2peak} \geq 16$ ml/kg/min were compared

15   (Table 1, Figure 1). On the other hand, the $VE/VCO_{2intercept}$ values were significantly

16   higher in COPD patients, both in those with VO_{2peak} < 16 ml/kg/min and in those with

17    $VO_{2peak} \geq 16$ ml/kg/min, as compared to the corresponding values of the CHF patients

18   (Table 1, Figure 1). Furthermore, the $VE/VCO_{2intercept}$ values were positive in 43 out of

19   46 COPD patients and in 28 out of 46 CHF patients.

20

21   In order to discriminate CHF from COPD patients categorized according to the VO_{2peak}

22   value, the ROC curve analysis showed that VE/VCO_{2slope} had a significant cutoff point

23   only for patients with VO_{2peak} < 16 ml/kg/min, whereas $VE/VCO_{2intercept}$ had significant

1   cutoff points for both subgroups of patients and showed higher values in sensitivity and

2   specificity, as compared to the corresponding values of VE/VCO_{2slope} (Table 2).

3

4   The $PETCO_{2peak}$ values were not different as compared to the corresponding

5    $PETCO_{2unloaded}$ values in CHF patients (p = 0.423), whereas were significantly higher in

6   COPD patients (p < 0.001). The $PETCO_{2peak-unloaded}$ values were also significantly

7   different between CHF and COPD patients, both in the patients with VO_{2peak} < 16

8   ml/kg/min and in those with $VO_{2peak} \geq 16$ ml/kg/min (Table 1).

9

10   CHF patients differed from COPD patients in DP reserve, but not in O_2Pulse, both at

11   mild and at moderate to severe reduction in functional capacity (Table 1). With respect

12   to the exercise-induced symptoms, CHF patients experienced more leg fatigue than

13   COPD patients, when moderate to severe reduction in functional capacity was

14   considered (Table 1).

15

16   In all CHF and in all COPD patients, the VE/VCO_{2slope}, but not $VE/VCO_{2intercept}$ values

17   were significantly related to the VO_{2peak} (r = - 0.587; p < 0.0001 and r = - 0344; p =

18   0.022) and to the workload peak (r = -0.463, p = 0.001 and r = -0.509, p = 0.001)

19   values. The $VE/VCO_{2intercept}$, but not the VE/VCO_{2slope} values were significantly related

20   to the FEV_1/VC values in COPD patients (r = -0.377, p = 0.009) (Fig. 2).

21

1 **DISCUSSION**

2

3 The main finding of the present study is that CHF patients are significantly different in

4 ventilatory response to CO_2 output during exercise, as assessed by VE/VCO_{2slope}, when

5 compared to COPD patients, at moderate to severe, but not at mild reduction in exercise

6 capacity. By contrast, they are significantly different in comparison with COPD patients,

7 regardless of the reduction in exercise capacity, when the ventilatory response to CO_2

8 during exercise is assessed by $VE/VCO_{2intercept}$. Our results also showed that, according

9 to ROC curve analysis when patients with a $VO_{2peak} < 16$ ml/kg/min are considered,

10 COPD patients have a highest likelihood to have a $VE/VCO_{2intercept}$ value greater than

11 2.14 L/min (0.92 sensitivity, 0.96 sensitivity). Additionally, regardless of the reduction

12 in exercise capacity degree, the $PETCO_{2peak}$ values were not different in CHF patients,

13 whereas were significantly higher in COPD patients, as compared to the corresponding

14 $PETCO_{2unloaded}$ values. Finally, this study shows that the ventilatory response to CO_2

15 output is inversely related to resting lung function in COPD patients, when assessed by

16 $VE/VCO_{2intercept}$, and to the exercise capacity, both in in CHF and in COPD patients,

17 when assessed by VE/VCO_{2slope}.

18

19 An increase in VE/VCO_{2slope} may occur in several clinical conditions, including CHF

20 (1,2,9) COPD (3,4) and pulmonary arterial hypertension (24). A previous study by

21 Deboeck et al (25) showed that at the same functional capacity, patients with pulmonary

22 arterial hypertension had significantly higher values of VE/VCO_{2slope} than patients with

23 CHF. Similarly, our study showed that in presence of a moderate to severe decrease in

24 exercise tolerance, the VE/VCO_{2slope} measurement may differentiate CHF from COPD,

1   by finding the lowest values in COPD patients. It is of note that, taken together the

2   study by Deboeck et al (25) and ours, suggest that the ventilatory dysfunction, as

3   assessed by VE/VCO_{2slope}, is of minor extent in COPD than in patients with CHF or

4   pulmonary arterial hypertension.

5

6   In the present study, we provided the evidence that the $VE/VCO_{2intercept}$ measurement

7   can discriminate CHF from COPD, regardless of the reduction in exercise capacity and

8   that the $VE/VCO_{2intercept}$ value was on average near zero in CHF and positive in COPD

9   patients, respectively. Notably, our data show that the $VE/VCO_{2intercept}$ mean value was

10   3.60 L/min and 3.63 L/min in COPD patients and $-$ 0.16 L/min and 0.87 L/min in CHF

11   patients, when patients with $VO_{2peak} < 16$ ml/kg/min and with $VO_{2peak} \geq 16$ ml/kg/min

12   are considered. The positive intercept on the linear VE/VCO2 relationship is considered

13   by Whipp (26) as a dependent parameter that is secondary to a mechanistic coupling of

14   VE to changes in dead space to tidal volume ratio (VD/VT) during exercise. According

15   to the Whipp's law, a significant intercept can result from a decrease in VD/VT with

16   increasing exercise VE and, in this case, from an increasing mechanical constraint with

17   increasing exercise VE in order to conserve the work of breathing (7). It is of note that

18   in our COPD patients the $VE/VCO_{2intercept}$ values were inversely related to the

19   corresponding FEV_1/VC values.

20

21   In this study, $PETCO_{2peak}$ values, considered as an estimate of the $PaCO_2$ values (27), as

22   subtracted by the corresponding $PETCO_{2unloaded}$ values were significantly different in

23   CHF patients as compared to COPD patients, regardless of the reduction in exercise

24   capacity. These values were on average near zero in CHF and 7 mm Hg in COPD

1   patients. In CHF patients, an augmented hyperpnoea may occur and may reflect a neural

2   compensation for the increased pulmonary ventilation/perfusion mismatch during

3   exercise, which increases the apparent metabolic CO_2 load, as perceived by the central

4   respiratory controller (7). These patients may also experience an exercise-induced

5   hyperventilation, which is mainly due to early onset of systemic lactic acidosis (9)

6   and/or to overactive reflexes from metaboreceptors, baroreceptors and chemoreceptors,

7   as part of deranged cardiorespiratory reflex (28), though none of these reflexes has

8   lasting effects on ventilatory control (7). In COPD patients, the increase in VD/VT

9   caused by gas exchange abnormalities resulting from deformed acinii does not

10   necessarily result in hypercapnia, which can occur, however, with excessive mechanical

11   constraints (7).

12

13   A limitation to our noninvasive study consists in the use of $PETCO_2$ as estimate of

14     $PaCO_2$. $PETCO_2$ has the potential of underestimating $PaCO_2$, in particular in patients

15   with lung disease (27). Notably, our finding of resting $PETCO_2$ values, that were

16   significantly lower in COPD patients than in CHF patients, might be due to the fact that

17     $PETCO_2$ could underestimate in a greater extent the corresponding $PaCO_2$ value in

18   COPD patients. In addition, the finding of the resting $PETCO_2$ values, that were

19   significantly lower in CHF patients with lower VO_2peak values, could be explained by

20   the increase in $PaCO_2$-$PETCO_2$ gradient due to an increase in VD/VT, as reported in

21   CHF patients (29) and in animal models (30). Therefore, on the basis of our results we

22   can only infer, but not establish the mechanisms underlying the ventilatory response to

23   carbon dioxide output of the patients during exercise. Thus, a further study with $PaCO_2$

24   measurements is needed.

1   In summary, in this study we demonstrate that the ventilatory response to carbon

2   dioxide output during progressive exercise is significantly different between CHF and

3   COPD patients in terms of the slope of the VE/VCO_2 linear relationship in patients with

4   moderate to severe reduction in exercise capacity, and in terms of intercept of the

5   VE/VCO_2 linear relationship, regardless of the exercise capacity. Notably, we found

6   that the intercepts were positive in 93% of COPD patients and in 61% of CHF patients

7   and that in patients with $VO_{2peak} < 16$ ml/kg/min a $VE/VCO_{2intercept}$ value of 2.14 L/min

8   can highly discriminate COPD from CHF patients.

9

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17

1 **Legend for figures**

2

3 **Figure 1.** Mean, standard deviation and range values of VE/VCO$_{2slope}$ (*left panels*) and

4 VE/VCO$_{2intercept}$ (*right panels*) in 23 CHF and 24 COPD patients with VO$_2$peak < 16

5 ml/kg/min (*upper panels*) and in 23 CHF and 22 COPD patients with VO$_2$peak ≥ 16

6 ml/kg/min (*lower panels*).

7

8 **Figure 2.** Relationship between VE/VCO$_{2intercept}$ and FEV$_1$/VC in 46 COPD patients.

9

10

1 **Table 1.** Exercise characteristics of CHF and COPD patients categorized according to

2 the VO_{2peak} value

3
4

	Patients with $VO_{2peak} < 16$ ml/kg/min			Patients with $VO_{2peak} \geq 16$ ml/kg/min		
	CHF No. 23	COPD No. 24	*p*	CHF No. 23	COPD No. 22	*p*
Age (years)	63±8	67 ± 6	0.061	59 ± 10	61 ± 8	0.400
Gender (M/F)	14/9	14/10	0.859	19/4	20/2	0.413
FFMI (kg/m^2)	17.9±2.0	16.9±1.7	0.107	19.2±1.4	18.6±1.9	0.295
VO_{2peak} (ml/kg/min)	12.1±2.1	12.9±1.9	0.139	20.0±4.1	19.8±3.3	0.851
VO_2@AT (ml/kg/min)	8.6±1.5	9.8±1.7	*0.028*	13.4±4.2	13.7±3.2	0.825
Workload (watt)	63.9±18	67.5±21	0.530	119.6±38	111±39	0.481
VE (L/min)	38.9±11	36.8±12	0.547	53.9±14	50.2±14	0.375
VE/VCO_{2slope}	39.5±9.5	31.8±7.4	*0.004*	28.3±5.3	28.9±6.6	0.709
$VE/VCO_{2intercept}$ (L/min)	-0.16±1.7	3.60±1.7	*0.001*	0.87±1.5	3.63±2.7	*0.001*
$PETCO_{2unloaded}$ (mm Hg)	32.7±4.7	31.7±5.4	*0.526*	38.9±5.2	33.8±7.2	*0.009*
$PETCO_{2peak}$ (mm Hg)	31.8±5.8	38.2±7.02	*0.002*	38.8±6.7	41.4±9.1	0.295
$PETCO_{2peak-\ unloaded}$ (mm Hg)	-0.83±2.9	6.46±4.35	*0.002*	-0.13±4.9	7.54±5.9	*0.001*
O_2Pulse (mL/bpm)	9.53±2.7	8.46±2.1	0.130	12.7±2.9	11.9±2.7	0.389
DP reserve (mmHg·bpm)	6017±3379	9032±4056	*0.008*	10460±4622	13065±3731	*0.044*
VAS Dyspnea (0-100)	80(80-90)	90(72-100)	0.561	80(60-90)	80(80-90)	0.297
VAS Fatigue (0-100)	90(80-100)	80(62-90)	*0.047*	90(80-100)	85(70-90)	0.246

5

6 AT: anaerobic threshold; CHF: chronic heart failure; COPD: chronic obstructive

7 pulmonary disease; DP: Double product; FFM: fat-free mass; O_2Pulse: oxygen pulse;

8 $PETCO_2$: end-tidal pressure of CO_2; VAS: visual analogue scale; VCO_2: carbon dioxide

9 output; VE: minute ventilation ; VE/VCO_2: ventilatory equivalent for CO_2; VO_2:

10 oxygen uptake

11

1   **Table 2.** Receiver Operating Characteristic curve analysis of VE/VCO_{2slope} and

2     $VE/VCO_{2intercept}$ values in order to discriminate CHF from COPD patients chategorized

3   according to the VO_{2peak} value

4

	Patients with $VO_{2peak} < 16$ ml/kg/min		Patients with $VO_{2peak} \geq 16$ ml/kg/min	
	VE/VCO_{2slope}	$VE/VCO_{2intercept}$	VE/VCO_{2slope}	$VE/VCO_{2intercept}$
AUC	0.732	0.951	0.509	0.820
p value	*0.006*	*0.0001*	0.919	*0.0001*
Cutoff point	36.5	2.14 L/min	...	2.72 L/min
Sensitivity	0.62	0.92	...	0.64
Specificity	0.79	0.96	...	0.96

5

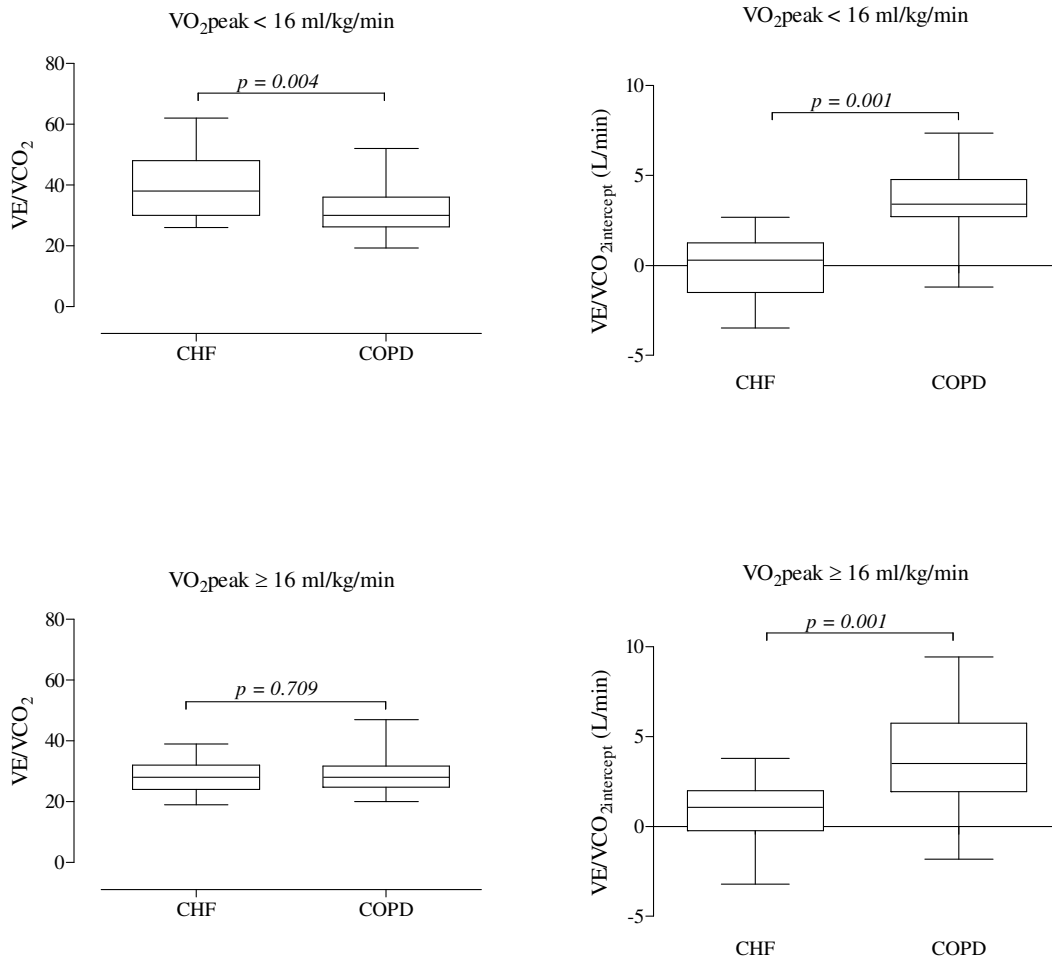6   AUC: Area Under Curve; VE/VCO_2: ventilatory equivalent for CO_2; VO_2: oxygen
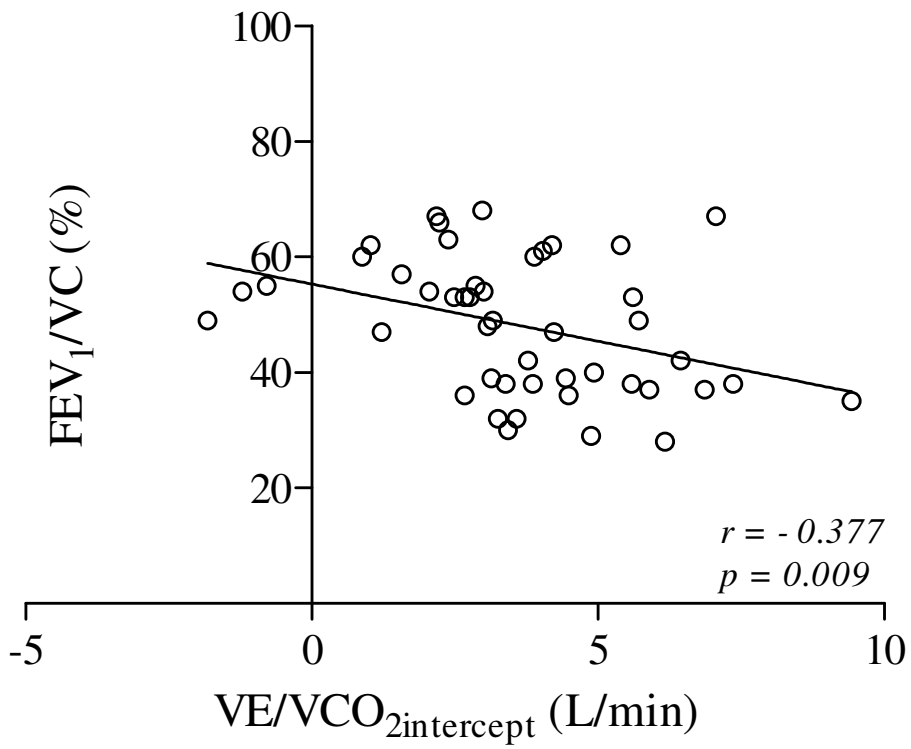
7   uptake

Figure 1

Figure 2