

# Ventilatory Response to Carbon Dioxide Output in Subjects With Congestive Heart Failure and in Patients with COPD With Comparable Exercise Capacity

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**BACKGROUND:** Patients with congestive heart failure or COPD may share an increased response in minute ventilation ( $\dot{V}_E$ ) to carbon dioxide output ( $\dot{V}_{CO_2}$ ) during exercise. The goal of this study was to ascertain whether the  $\dot{V}_E/\dot{V}_{CO_2}$  slope and  $\dot{V}_E/\dot{V}_{CO_2}$  intercept can discriminate between subjects with congestive heart failure and those with COPD at equal peak oxygen uptake ( $\dot{V}_{O_2}$ ). **METHODS:** We studied 46 subjects with congestive heart failure (mean age  $61 \pm 9$  y) and 46 subjects with COPD (mean age  $64 \pm 8$  y) who performed a cardiopulmonary exercise test. **RESULTS:** The  $\dot{V}_E/\dot{V}_{CO_2}$  slope was significantly higher in subjects with congestive heart failure compared with those with COPD ( $39.5 \pm 9.5$  vs  $31.8 \pm 7.4$ ,  $P < .01$ ) at peak  $\dot{V}_{O_2} < 16$  mL/kg/min, but not  $\geq 16$  mL/kg/min ( $28.3 \pm 5.3$  vs  $28.9 \pm 6.6$ ). The  $\dot{V}_E/\dot{V}_{CO_2}$  intercept was significantly higher in both subgroups of subjects with COPD compared with the corresponding values in the subjects with congestive heart failure ( $3.60 \pm 1.7$  vs  $-0.16 \pm 1.7$  L/min,  $P < .01$ ;  $3.63 \pm 2.7$  vs  $0.87 \pm 1.5$  L/min,  $P < .01$ ). According to receiver operating characteristic curve analysis, when all subjects with peak  $\dot{V}_{O_2} < 16$  mL/kg/min were considered, subjects with COPD had a higher likelihood to have the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept  $> 2.14$  L/min (0.92 sensitivity, 0.96 specificity). Regardless of peak  $\dot{V}_{O_2}$ , the end-tidal pressure of  $CO_2$  ( $P_{ETCO_2}$ ) at peak exercise was not different in subjects with congestive heart failure ( $P = .42$ ) and was significantly higher in subjects with COPD ( $P < .01$ ) compared with the corresponding unloaded  $P_{ETCO_2}$ . **CONCLUSIONS:** The ventilatory response to  $\dot{V}_{CO_2}$  during exercise was significantly different between subjects with congestive heart failure and those with COPD in terms of the  $\dot{V}_E/\dot{V}_{CO_2}$  slope with moderate-to-severe reduction in exercise capacity and in terms of the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept regardless of exercise capacity. *Key words:* congestive heart failure; COPD; exercise; ventilatory response. [Respir Care 2014;59(7):1034–1041. © 2014 Daedalus Enterprises]

## Introduction

Poor exercise tolerance, demonstrated by a reduction in peak oxygen uptake (peak  $\dot{V}_{O_2}$ ) during a rapidly incremental cardiopulmonary exercise test (CPET), may occur in

chronic cardiopulmonary disabling conditions, such as congestive heart failure and COPD.

While performing a CPET, subjects with congestive heart failure<sup>1,2</sup> and COPD<sup>3,4</sup> may share a different from normal ventilatory response to carbon dioxide output ( $\dot{V}_{CO_2}$ ). The mechanisms underlying the control of exercise hyperpnoea are complex and still under investigation both in

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healthy subjects<sup>5</sup> and in cardiopulmonary patients.<sup>6,7</sup> Regardless of rate, the minute ventilation ( $\dot{V}_E$ ) for a given metabolic rate ( $\dot{V}_E/\dot{V}_{CO_2}$ ), also known as ventilatory equiv-

alent for CO<sub>2</sub>,<sup>8</sup> may be increased both in congestive heart failure and COPD during exercise. Notably, the slope of the  $\dot{V}_E/\dot{V}_{CO_2}$  linear relationship is considered as the strongest prognostic marker (including peak  $\dot{V}_{O_2}$ ) in patients with congestive heart failure, regardless of the etiology of cardiomyopathy,<sup>9</sup> and was found to be a significant post-surgical prognostic marker in patients with COPD undergoing lung resection.<sup>10</sup> Moreover, it has been recently recognized that even the intercept of the  $\dot{V}_E/\dot{V}_{CO_2}$  relationship may be relevant in fully understanding ventilatory control mechanisms in health<sup>7</sup> and in disease.<sup>6,7</sup>

Up to now, no study has aimed to compare the ventilatory response to  $\dot{V}_{CO_2}$  in subjects with congestive heart failure and COPD with comparable exercise capacity or to assess the possible discriminating value of  $\dot{V}_E/\dot{V}_{CO_2}$  measurement in these patients. The aim of the present study was to measure  $\dot{V}_E/\dot{V}_{CO_2}$  in terms of both slope and intercept in a cohort of subjects with congestive heart failure and COPD and to ascertain whether the  $\dot{V}_E/\dot{V}_{CO_2}$  slope and intercept may discriminate between these patients at equal peak  $\dot{V}_{O_2}$ .

## Methods

### Subjects

Over a 6-month period (from November 2012 to April 2013), we consecutively enrolled subjects affected by congestive heart failure due to ischemic or idiopathic dilated cardiomyopathy referred for CPET, as part of a comprehensive heart failure evaluation, and subjects with COPD, who were admitted to a pulmonary rehabilitation program.

All subjects with congestive heart failure had a history of at least one confirmed clinical episode of heart failure and an echocardiographic left-ventricular ejection fraction of < 50%. Subjects with congestive heart failure and uncontrolled atrial fibrillation or history of sustained ventricular tachycardia, recent syncope, or myocardial infarct were excluded.<sup>11</sup> COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease criteria,<sup>12</sup> and subjects with moderate-to-severe air-flow obstruction (ie, FEV<sub>1</sub>/vital capacity [VC]) < 0.70 and FEV<sub>1</sub> < 80% of predicted) were included.

For all subjects, eligibility criteria were: (1) age range of 40–75 y, (2) body mass index ≤ 30 kg/m<sup>2</sup>, (3) stable clinical condition for at least 8 weeks, (4) absence of any comorbidity affecting exercise performance (anemia, neuromuscular disorders, or malignancies), (5) ability to perform a CPET with a peak of respiratory exchange ratio of ≥ 1.05 to exclude poor motivation,<sup>11</sup> and (6) CPET stopped for muscle fatigue and/or dyspnea.

All procedures and their risks were explained to the subjects, who gave their written informed consent to enter the study, which was conducted according to the Decla-

## QUICK LOOK

### Current knowledge

The ventilatory response to carbon dioxide production ( $\dot{V}_E/\dot{V}_{CO_2}$ ) is a function of alveolar ventilation and ventilation/perfusion matching. Alterations in the response to an increased  $\dot{V}_{CO_2}$  can be diagnostic for cardiac and respiratory disease.

### What this paper contributes to our knowledge

The ventilatory response to  $\dot{V}_{CO_2}$  during progressive exercise was significantly different between subjects with congestive heart failure and those with COPD. The slope and intercept of the  $\dot{V}_E/\dot{V}_{CO_2}$  was altered, and this finding can be used to discriminate between cardiac and pulmonary disease.

ration of Helsinki. The protocol was approved by the ethics committee of the University Hospital of Parma. All participants' data were analyzed and reported anonymously. No extramural funding was used to support the study.

### Measurements

**Pulmonary Function Testing.** Pulmonary function tests were performed according to international recommendations.<sup>13,14</sup> A flow-sensing spirometer and a body plethysmograph connected to a computer for data analysis (Vmax 22 and 6200, SensorMedics, Yorba Linda, California) were used for these measurements. Total lung capacity (TLC), VC, FEV<sub>1</sub>, and FEV<sub>1</sub>/VC were recorded. TLC, VC, and FEV<sub>1</sub> were expressed as a percentage of the predicted values.<sup>15</sup>

**Cardiopulmonary Exercise Test.** CPET was performed according to a standardized procedure.<sup>11</sup> Briefly, the exercise protocol started with an initial 3 min of rest, followed by unloaded cycling for 3 min with a subsequent increment of 5–15 watts each minute, depending on the anthropometric data and the degree of individual functional impairment, with the aim to perform a total exercise time ranging 8 to 12 min. Subjects were asked to maintain a pedaling frequency of 60 rpm as indicated by a digital display placed on the monitor of the cycle ergometer (Corival PB, Lode BV, Groningen, The Netherlands). Breath-by-breath  $\dot{V}_{O_2}$  (L/min),  $\dot{V}_{CO_2}$  (L/min), and  $\dot{V}_E$  (L/min) were recorded during the test (CPX/D, Medical Graphics, Minneapolis, Minnesota). Subjects were continuously monitored by a 12-lead electrocardiogram (CardioPerfect, Welch Allyn, Delft, The Netherlands) and a pulse oximeter (model 8600, Nonin, Plymouth, Minnesota). Blood pressure

(mm Hg) was measured at 2-min intervals. Stopping criteria consisted of symptoms such as unsustainable dyspnea or leg fatigue, chest pain, electrocardiogram significant ST-segment depression, a drop in systolic blood pressure, or arterial oxygen saturation  $\leq$  84%.

Peak work load and peak  $\dot{V}_{O_2}$  were recorded as the mean value of watts and  $\dot{V}_{O_2}$  (mL/kg/min) during the last 20 s of the test. Anaerobic threshold was noninvasively determined by both V-slope and ventilatory equivalents methods (dual-method approach) and was expressed in mL/kg/min of  $\dot{V}_{O_2}$ .<sup>11</sup> The ventilatory response during exercise was expressed as a linear regression function by plotting  $\dot{V}_E$  against  $\dot{V}_{CO_2}$  obtained every 10 s, excluding data above the ventilatory compensation point,<sup>11</sup> and by measuring the slope ( $\dot{V}_E/\dot{V}_{CO_2}$  slope) and y intercept ( $\dot{V}_E/\dot{V}_{CO_2}$  intercept). The end-tidal pressure of CO<sub>2</sub> ( $P_{ETCO_2}$ , mm Hg) was recorded as the mean value of  $P_{ETCO_2}$  during the 3-min rest period (unloaded  $P_{ETCO_2}$ ), during the last 20 s of the test (peak  $P_{ETCO_2}$ ), and as the difference between peak and unloaded  $P_{ETCO_2}$ .

The cardiovascular response to exercise was expressed as oxygen pulse and double product. The oxygen pulse (mL of O<sub>2</sub> consumed/heartbeat) was calculated by dividing the instantaneous oxygen uptake by heart rate<sup>11</sup> and was recorded at the peak of exercise. The double product at rest and at maximum exercise was calculated by the product of systolic blood pressure and heart rate and expressed as double-product reserve (double product at maximum exercise minus double product at rest, mm Hg/beats/min).<sup>16</sup>

**Functional Status, Dyspnea, and Muscle Fatigue.** The functional status of the subjects with congestive heart failure was categorized according to the New York Heart Association functional classification system (classes I–IV).<sup>17</sup> Briefly, the New York Heart Association classification places patients with cardiac disease in one of 4 categories based on physical activity limitation: class I, patients without limitation of physical activity (ie, ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain); class II, patients with slight limitation of physical activity (ie, they are comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain); class III, patients with marked limitation of physical activity (ie, they are comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain); and class IV, patients with inability to carry on any physical activity without discomfort (symptoms of heart failure or the anginal syndrome may be present even at rest, and if any physical activity is undertaken, discomfort increases).

In subjects with COPD, the activity of daily living (ADL)-related dyspnea was evaluated using the Italian version of the 5-point Medical Research Council dyspnea scale mod-

ified by the American Thoracic Society.<sup>18</sup> In all subjects, dyspnea and muscle fatigue induced by CPET were measured at the end of incremental exercise by a visual analog scale (dyspnea and fatigue, respectively; mm) as described previously.<sup>19</sup> Briefly, the visual analog scale consisted of a horizontal line with the word “none” placed at the left end of the scale and the words “very severe” placed at the right end of the scale. The visual analog scale was scored from 0 to 100, but the subjects were unaware of the numbers.

**Echocardiography.** In subjects with congestive heart failure, a complete Doppler echocardiographic evaluation was performed within a 3-week period before pulmonary function testing and CPET. Echocardiograms were recorded using a commercially available machine (System five, GE Healthcare, Madison, Wisconsin) equipped with 2.5- and 3.5-MHz electronic transducers and harmonic imaging. Left-ventricular chamber dimensions were measured according to the recommendations of the American Society of Echocardiography.<sup>20</sup> Left-ventricular systolic function was evaluated, and left-ventricular ejection fraction (%) was recorded according to the single-plane area-length method.

**Body Composition.** Body height and weight were measured anthropometrically in all subjects. Body composition was assessed by a bioelectrical impedance analysis method that is based on the conductance of an electrical sinusoidal alternating current through body fluids. Bioelectrical impedance analysis measures the impedance or resistance to the signal as it travels through the water that is found in muscle and fat. Foot-to-foot bioelectrical impedance analysis was performed using an SC-331S body composition analyzer (Tanita, Tokyo, Japan). Subjects were measured while standing in bare feet on analyzer footpads. The algorithms used to estimate lean body mass from impedance are those given by Segal et al.<sup>21</sup> The fat-free mass was standardized for height similar to body mass index: fat-free mass/height<sup>2</sup> (kg/m<sup>2</sup>).

### Statistical Analysis

Data are reported as mean  $\pm$  SD unless specified otherwise. Due to the explorative nature of the study, no formal sample size calculation was performed. The distribution of variables was assessed by the Kolmogorov-Smirnov goodness-of-fit test. Relationships between variables were assessed by Pearson correlation coefficient (*r*) and linear regression analysis. Comparisons between variables were determined by unpaired *t* test and chi-square test when appropriate.

According to peak  $\dot{V}_{O_2}$ , the population sample was divided into subjects with moderate-to-severe reduction in

Table 1. Exercise Characteristics of Subjects with Congestive Heart Failure and COPD Categorized According to Peak  $\dot{V}_{O_2}$

	Peak $\dot{V}_{O_2} < 16$ mL/kg/min			Peak $\dot{V}_{O_2} \geq 16$ mL/kg/min		
	Congestive Heart Failure (n = 23)	COPD (n = 24)	P	Congestive Heart Failure (n = 23)	COPD (n = 22)	P
Age, mean $\pm$ SD (y)	63 $\pm$ 8	67 $\pm$ 6	.061	59 $\pm$ 10	61 $\pm$ 8	.40
Gender (male/female)	14/9	14/10	.86	19/4	20/2	.41
Fat-free mass index, mean $\pm$ SD (kg/m <sup>2</sup> )	17.9 $\pm$ 2.0	16.9 $\pm$ 1.7	.11	19.2 $\pm$ 1.4	18.6 $\pm$ 1.9	.29
Peak $\dot{V}_{O_2}$ , mean $\pm$ SD (mL/kg/min)	12.1 $\pm$ 2.1	12.9 $\pm$ 1.9	.14	20.0 $\pm$ 4.1	19.8 $\pm$ 3.3	.85
Anaerobic threshold, mean $\pm$ SD (mL/kg/min of $\dot{V}_{O_2}$ )	8.6 $\pm$ 1.5	9.8 $\pm$ 1.7	.03	13.4 $\pm$ 4.2	13.7 $\pm$ 3.2	.83
Work load, mean $\pm$ SD (watts)	63.9 $\pm$ 18	67.5 $\pm$ 21	.53	119.6 $\pm$ 38	111 $\pm$ 39	.48
$\dot{V}_E$ , mean $\pm$ SD (L/min)	38.9 $\pm$ 11	36.8 $\pm$ 12	.54	53.9 $\pm$ 14	50.2 $\pm$ 14	.38
$\dot{V}_E/\dot{V}_{CO_2}$ slope, mean $\pm$ SD	39.5 $\pm$ 9.5	31.8 $\pm$ 7.4	.004	28.3 $\pm$ 5.3	28.9 $\pm$ 6.6	.71
$\dot{V}_E/\dot{V}_{CO_2}$ intercept, mean $\pm$ SD (L/min)	-0.16 $\pm$ 1.7	3.60 $\pm$ 1.7	.001	0.87 $\pm$ 1.5	3.63 $\pm$ 2.7	.001
Unloaded P <sub>ETCO<sub>2</sub></sub> , mean $\pm$ SD (mm Hg)	32.7 $\pm$ 4.7	31.7 $\pm$ 5.4	.53	38.9 $\pm$ 5.2	33.8 $\pm$ 7.2	.009
Peak P <sub>ETCO<sub>2</sub></sub> , mean $\pm$ SD (mm Hg)	31.8 $\pm$ 5.8	38.2 $\pm$ 7.02	.002	38.8 $\pm$ 6.7	41.4 $\pm$ 9.1	.29
Peak P <sub>ETCO<sub>2</sub></sub> - unloaded P <sub>ETCO<sub>2</sub></sub> , mean $\pm$ SD (mm Hg)	-0.83 $\pm$ 2.9	6.46 $\pm$ 4.35	.002	-0.13 $\pm$ 4.9	7.54 $\pm$ 5.9	.001
Oxygen pulse, mean $\pm$ SD (mL of O <sub>2</sub> consumed/heartbeat)	9.53 $\pm$ 2.7	8.46 $\pm$ 2.1	.13	12.7 $\pm$ 2.9	11.9 $\pm$ 2.7	.39
Double-product reserve, mean $\pm$ SD (mm Hg/beat/min)	6,017 $\pm$ 3,379	9,032 $\pm$ 4,056	.008	10,460 $\pm$ 4,622	13,065 $\pm$ 3,731	.044
Visual analog scale						
Dyspnea (0-100)	80 (80-90)	90 (72-100)	.56	80 (60-90)	80 (80-90)	.30
Fatigue (0-100)	90 (80-100)	80 (62-90)	.047	90 (80-100)	85 (70-90)	.25

$\dot{V}_{O_2}$  = oxygen uptake  
 $\dot{V}_E$  = minute ventilation  
 $\dot{V}_{CO_2}$  = carbon dioxide output  
P<sub>ETCO<sub>2</sub></sub> = end-tidal pressure of CO<sub>2</sub>  
 $\dot{V}_E/\dot{V}_{CO_2}$  = ventilatory equivalent for CO<sub>2</sub>

exercise capacity (peak  $\dot{V}_{O_2} < 16$  mL/kg/min) and subjects with mild reduction in exercise capacity (peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min).<sup>22</sup>

The receiver operating characteristic curve method<sup>23</sup> was used to plot the true positive rate (sensitivity) in function of the false-positive rate (100 specificity) for different cut-off points of the  $\dot{V}_E/\dot{V}_{CO_2}$  slope and intercept to discriminate between subjects with congestive heart failure and those with COPD.  $P < .05$  was taken as significant.

**Results**

Of the 130 consecutive subjects who agreed to participate in the study, 18 subjects were excluded because their body mass index was  $> 30$  kg/m<sup>2</sup>, 7 subjects were excluded because they were  $> 75$  y old, and 13 subjects were excluded because of comorbidities. Ninety-two stable subjects (46 with congestive heart failure and 46 with COPD), 42-75 y old, were included in the study. Subjects with congestive heart failure did not differ in gender (33/13 vs 34/12 male/female ratio,  $P = .82$ ) and tended to be younger (61  $\pm$  9 vs 64  $\pm$  8 y,  $P = .068$ ) compared with subjects with COPD.

In subjects with congestive heart failure, New York Heart Association classes ranged from I to IV (median of

II), and their left-ventricular ejection fraction was 32  $\pm$  9%, ranging from 15 to 48%. At the moment of the study, subjects with congestive heart failure were receiving regular therapy with  $\beta$  blockers (98%), diuretics (83%), and angiotensin-converting enzyme inhibitors (76%), whereas subjects with COPD were receiving inhaled steroids (65%), long-acting  $\beta_2$  agonists (61%), and tiotropium (43%). All subjects with COPD were ex-smokers, and among them, a wide range of ADL or activity of daily living-related dyspnea (Medical Research Council dyspnea scale of 0-4) was found. As expected, subjects with congestive heart failure significantly differed from subjects with COPD in terms of TLC (94  $\pm$  16% vs 118  $\pm$  25%), FEV<sub>1</sub> (91  $\pm$  17% vs 52  $\pm$  16%) and FEV<sub>1</sub>/VC (0.75  $\pm$  0.06 vs 0.48  $\pm$  0.12,  $P < .001$  for all comparisons).

All subjects completed the exercise test without any complication. Peak  $\dot{V}_{O_2}$  ranged from 7.2 to 31.0 mL/kg/min and from 7.7 to 30.2 mL/kg/min in subjects with congestive heart failure and COPD, respectively. Twenty-three of 46 subjects with congestive heart failure and 24 of 46 subjects with COPD had peak  $\dot{V}_{O_2} < 16$  mL/kg/min, whereas 23 subjects with congestive heart failure and 22 subjects with COPD had peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min. The two subgroups of subjects categorized according to peak  $\dot{V}_{O_2}$  did not significantly differ in terms of age, gender, and

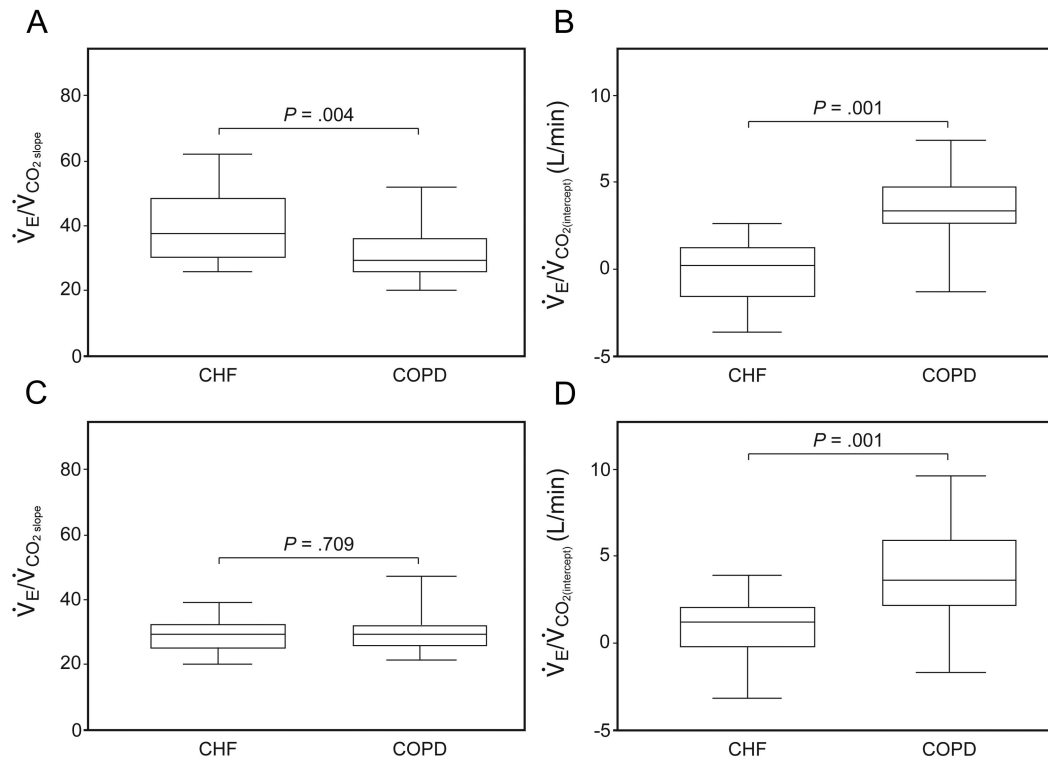


Fig. 1. Data are expressed as mean  $\pm$  SD and ranges for 46 subjects with congestive heart failure (CHF) patients and 46 subjects with COPD. A: minute ventilation ( $\dot{V}_E$ )/carbon dioxide output ( $\dot{V}_{CO_2}$ ) slope with peak  $\dot{V}_{O_2} < 16$  mL/kg/min. B:  $\dot{V}_E/\dot{V}_{CO_2}$  intercept with peak  $\dot{V}_{O_2} < 16$  mL/kg/min. C:  $\dot{V}_E/\dot{V}_{CO_2}$  slope with peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min. D:  $\dot{V}_E/\dot{V}_{CO_2}$  intercept with peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min.

fat-free index ( $P > .05$  for all comparisons) (Table 1). COPD subjects with lower peak  $\dot{V}_{O_2}$  tended to show worse resting lung function without reaching statistical significance (TLC:  $124 \pm 25\%$  vs  $113 \pm 24\%$ ,  $P = .15$ ; FEV<sub>1</sub>:  $49 \pm 14\%$  vs  $54 \pm 15\%$ ,  $P = .18$ ; FEV<sub>1</sub>/VC:  $0.45 \pm 0.11$  vs  $0.52 \pm 0.12$ ,  $P = .056$ ). No significant difference was found in resting lung function between congestive heart failure subjects with peak  $\dot{V}_{O_2} < 16$  mL/kg/min and those with peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min (TLC:  $93 \pm 19\%$  vs  $96 \pm 13\%$ ,  $P = .55$ ; FEV<sub>1</sub>:  $88 \pm 20\%$  vs  $94 \pm 11\%$ ,  $P = .19$ ; FEV<sub>1</sub>/VC:  $0.75 \pm 0.05$  vs  $0.75 \pm 0.07$ ,  $P = .94$ ). In the group of subjects with peak  $\dot{V}_{O_2} < 16$  mL/kg/min, the anaerobic threshold (mL/kg/min of  $\dot{V}_{O_2}$ ) was significantly lower in subjects with congestive heart failure than in those with COPD ( $P = .03$ ) (see Table 1).

The  $\dot{V}_E/\dot{V}_{CO_2}$  slope was significantly higher in congestive heart failure subjects with peak  $\dot{V}_{O_2} < 16$  mL/kg/min compared with the corresponding values in the COPD group, but were not different between congestive heart failure and COPD subjects with peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min (see Table 1 and Fig. 1). On the other hand, the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept was significantly higher in all subjects with COPD (peak  $\dot{V}_{O_2} < 16$  mL/kg/min and peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min) compared with the corresponding values in subjects with congestive heart failure (see Table 1 and Fig. 1). Furthermore, the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept was positive in 43 of 46 sub-

jects with COPD and in 28 of 46 subjects with congestive heart failure.

To discriminate between subjects with congestive heart failure and those with COPD categorized according to peak  $\dot{V}_{O_2}$ , the receiver operating characteristic curve analysis showed that the  $\dot{V}_E/\dot{V}_{CO_2}$  slope had a significant cutoff point only for subjects with peak  $\dot{V}_{O_2} < 16$  mL/kg/min, whereas the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept had significant cutoff points for both subgroups of subjects and showed higher values in sensitivity and specificity compared with the corresponding values of the  $\dot{V}_E/\dot{V}_{CO_2}$  slope (Table 2).

Peak  $P_{ETCO_2}$  was not different compared with the corresponding unloaded  $P_{ETCO_2}$  in subjects with congestive heart failure ( $P = .42$ ), but was significantly higher in subjects with COPD ( $P < .001$ ). The difference between peak and unloaded  $P_{ETCO_2}$  was also significantly different between subjects with congestive heart failure and those with COPD both with peak  $\dot{V}_{O_2} < 16$  mL/kg/min and peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min (see Table 1).

Subjects with congestive heart failure differed from those with COPD in double-product reserve, but not in oxygen pulse, at both mild and moderate-to-severe reduction in functional capacity (see Table 1). With respect to exercise-induced symptoms, subjects with congestive heart failure experienced more leg fatigue than subjects with COPD

Table 2. Receiver Operating Characteristic Curve Analysis of the  $\dot{V}_E/\dot{V}_{CO_2}$  Slope and Intercept to Discriminate Between Subjects with Congestive Heart Failure and Those With COPD Categorized According to Peak  $\dot{V}_{O_2}$

	Peak $\dot{V}_{O_2} < 16$ mL/kg/min		Peak $\dot{V}_{O_2} \geq 16$ mL/kg/min	
	$\dot{V}_E/\dot{V}_{CO_2}$ Slope	$\dot{V}_E/\dot{V}_{CO_2}$ Intercept	$\dot{V}_E/\dot{V}_{CO_2}$ Slope	$\dot{V}_E/\dot{V}_{CO_2}$ Intercept
Area under the curve	0.732	0.951	0.509	0.820
<i>P</i>	.006	.001	.92	.001
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

$\dot{V}_{O_2}$  = oxygen uptake  
 $\dot{V}_E/\dot{V}_{CO_2}$  = ventilatory equivalent for CO<sub>2</sub>

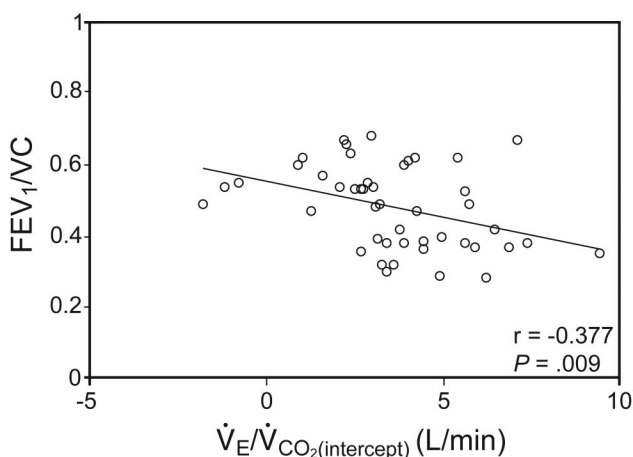


Fig. 2. Relationship between the minute ventilation ( $\dot{V}_E$ )/carbon dioxide output ( $\dot{V}_{CO_2}$ ) intercept and FEV<sub>1</sub>/VC in 46 subjects with COPD.

when moderate-to-severe reduction in functional capacity was considered (see Table 1).

In all subjects with congestive heart failure and COPD, the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, but not the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept, was significantly related to peak  $\dot{V}_{O_2}$  ( $r = -0.59$ ,  $P < .001$ ;  $r = -0.34$ ,  $P = .02$ ) and to peak work load ( $r = -0.46$ ,  $P = .001$ ;  $r = -0.51$ ,  $P = .001$ ). The  $\dot{V}_E/\dot{V}_{CO_2}$  intercept, but not the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, was significantly related to FEV<sub>1</sub>/VC in subjects with COPD ( $r = -0.38$ ,  $P = .009$ ) (Fig. 2).

### Discussion

The main finding of the present study is that subjects with congestive heart failure are significantly different in ventilatory response to  $\dot{V}_{CO_2}$  during exercise, as assessed by the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, compared with subjects with COPD

at a moderate-to-severe (but not mild) reduction in exercise capacity. In contrast, they are significantly different in comparison with subjects with COPD regardless of the reduction in exercise capacity when the ventilatory response to CO<sub>2</sub> during exercise is assessed by the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept. Our results also show that, according to receiver operating characteristic curve analysis when subjects with peak  $\dot{V}_{O_2} < 16$  mL/kg/min are considered, subjects with COPD have a higher likelihood to have a  $\dot{V}_E/\dot{V}_{CO_2}$  intercept  $> 2.14$  L/min (0.92 sensitivity, 0.96 specificity). In addition, regardless of the degree of reduction in exercise capacity, peak  $P_{ETCO_2}$  was not different in subjects with congestive heart failure, but was significantly higher in subjects with COPD compared with the corresponding unloaded  $P_{ETCO_2}$ . Finally, this study shows that the ventilatory response to  $\dot{V}_{CO_2}$  is inversely related to resting lung function in subjects with COPD, when assessed by the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept, and to exercise capacity in both subjects with congestive heart failure and those with COPD, when assessed by the  $\dot{V}_E/\dot{V}_{CO_2}$  slope.

An increase in the  $\dot{V}_E/\dot{V}_{CO_2}$  slope may occur under several clinical conditions, including congestive heart failure,<sup>1,2,9</sup> COPD,<sup>3,4</sup> and pulmonary arterial hypertension.<sup>24</sup> A previous study by Deboeck et al<sup>25</sup> showed that at the same functional capacity, subjects with pulmonary arterial hypertension had significantly higher  $\dot{V}_E/\dot{V}_{CO_2}$  slope values than subjects with congestive heart failure. Similarly, our study showed that, in the presence of a moderate-to-severe decrease in exercise tolerance, the  $\dot{V}_E/\dot{V}_{CO_2}$  slope measurement may differentiate between congestive heart failure and COPD by finding the lowest values in subjects with COPD. It is of note that, taken together, the study by Deboeck et al<sup>25</sup> and our study suggest that the ventilatory dysfunction, as assessed by the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, is minor in COPD compared with subjects with congestive heart failure or pulmonary arterial hypertension.

In the present study, we provided evidence that the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept measurement can discriminate between congestive heart failure and COPD regardless of the reduction in exercise capacity and that the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept was, on average, near zero in subjects with congestive heart failure and was positive in subjects with COPD. Notably, our data show that the mean  $\dot{V}_E/\dot{V}_{CO_2}$  intercepts were 3.60 and 3.63 L/min in subjects with COPD and  $-0.16$  and  $0.87$  L/min in subjects with congestive heart failure at peak  $\dot{V}_{O_2} < 16$  mL/kg/min and peak  $\dot{V}_{O_2} \geq 16$  mL/kg/min, respectively. The positive intercept in the linear  $\dot{V}_E/\dot{V}_{CO_2}$  relationship is considered by Whipp<sup>26</sup> to be a dependent parameter that is secondary to a mechanistic coupling of  $\dot{V}_E$  to changes in dead-space-to-tidal-volume ratio ( $V_D/V_T$ ) during exercise. According to Whipp's law, a significant intercept can result from a decrease in  $V_D/V_T$  with increasing exercise  $\dot{V}_E$  and, in this case, from an increasing mechanical constraint with in-

creasing exercise  $\dot{V}_E$  to conserve the work of breathing.<sup>7</sup> It is of note that, in our subjects with COPD, the  $\dot{V}_E/\dot{V}_{CO_2}$  intercept was inversely related to the corresponding FEV<sub>1</sub>/VC.

In this study, peak  $P_{ETCO_2}$ , considered to be an estimate of  $P_{aCO_2}$ ,<sup>27</sup> when compared with the corresponding unloaded  $P_{ETCO_2}$  was significantly different in subjects with congestive heart failure compared with subjects with COPD regardless of the reduction in exercise capacity. These values were, on average, near zero in subjects with congestive heart failure and 7 mm Hg in subjects with COPD. In patients with congestive heart failure, augmented hyperpnoea may occur and may reflect neural compensation for the increased pulmonary ventilation/perfusion mismatching during exercise, which increases the apparent metabolic CO<sub>2</sub> load as perceived by the central respiratory controller.<sup>7</sup> These patients may also experience exercise-induced hyperventilation, which is due mainly to early onset of systemic lactic acidosis<sup>9</sup> and/or to overactive reflexes from metaboreceptors, baroreceptors, and chemoreceptors, as part of a deranged cardiorespiratory reflex,<sup>28</sup> although none of these reflexes have lasting effects on ventilatory control.<sup>7</sup> In subjects with COPD, the increase in  $V_D/V_T$  caused by gas exchange abnormalities resulting from deformed acini does not necessarily result in hypercapnia, which can occur, however, with excessive mechanical constraints.<sup>7</sup>

A limitation to our noninvasive study is the use of  $P_{ETCO_2}$  as an estimate of  $P_{aCO_2}$ .  $P_{ETCO_2}$  has the potential of underestimating  $P_{aCO_2}$ , in particular in patients with lung disease.<sup>27</sup> Notably, our finding of a significantly lower resting  $P_{ETCO_2}$  in subjects with COPD compared with subjects with congestive heart failure might be due to the fact that  $P_{ETCO_2}$  could underestimate, to a greater extent, the corresponding  $P_{aCO_2}$  in subjects with COPD. In addition, our finding of a significantly lower resting  $P_{ETCO_2}$  in congestive heart failure subjects with lower peak  $\dot{V}_{O_2}$  could be explained by the increase in  $P_{aCO_2}$ - $P_{ETCO_2}$  gradient due to an increase in  $V_D/V_T$ , as reported in congestive heart failure subjects<sup>29</sup> and in animal models.<sup>30</sup> Therefore, on the basis of our results, we can only infer, but not establish, the mechanisms underlying the ventilatory response to  $\dot{V}_{CO_2}$  of subjects during exercise. Thus, an additional study with  $P_{aCO_2}$  measurements is needed.

In summary, we have demonstrated that the ventilatory response to  $\dot{V}_{CO_2}$  during progressive exercise is significantly different in subjects with congestive heart failure and those with COPD in terms of the slope of the  $\dot{V}_E/\dot{V}_{CO_2}$  linear relationship with a moderate-to-severe reduction in exercise capacity, and in terms of the intercept of the  $\dot{V}_E/\dot{V}_{CO_2}$  linear relationship, regardless of the exercise capacity. Notably, we found that the intercepts were positive in 93% of subjects with COPD and in 61% of subjects with congestive heart failure and that, in subjects with

peak  $\dot{V}_{O_2} < 16$  mL/kg/min, a  $\dot{V}_E/\dot{V}_{CO_2}$  intercept of 2.14 L/min can highly discriminate between subjects with COPD and those with congestive heart failure.

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