

OPEN

# The Value of Cardiopulmonary Exercise Testing in Determining Severity in Patients with both Systolic Heart Failure and COPD

Cássia da Luz Goulart<sup>1</sup>, Polliana Batista dos Santos<sup>1</sup>, Flávia Rossi Caruso<sup>1</sup>, Guilherme Peixoto Tinoco Arêas<sup>1</sup>, Renan Shida Marinho<sup>1</sup>, Patricia de Faria Camargo<sup>1</sup>, Tiago da Silva Alexandre<sup>2</sup>, Claudio R. Oliveira<sup>1</sup>, Andréa Lúcia Gonçalves da Silva<sup>3</sup>, Audrey Borghi-Silva<sup>1\*</sup>, Renata Gonçalves Mendes<sup>1</sup> & Meliza Goi Roscani<sup>1</sup>

Our aim was to identify optimal cardiopulmonary exercise testing (CPET) threshold values that distinguish disease severity progression in patients with co-existing systolic heart failure (HF) and chronic obstructive pulmonary disease (COPD), and to evaluate the impact of the cut-off determined on the prognosis of hospitalizations. We evaluated 40 patients (30 men and 10 woman) with HF and COPD through pulmonary function testing, doppler echocardiography and maximal incremental CPET on a cycle ergometer. Several significant CPET threshold values were identified in detecting a forced expiratory volume in 1 second ( $FEV_1$ ) < 1.6 L: 1) oxygen uptake efficiency slope (OUES) < 1.3; and 2) circulatory power (CP) < 2383 mmHg.mlO<sub>2</sub>.kg<sup>-1</sup>. CPET significant threshold values in identifying a left ventricular ejection fraction (LVEF) < 39% were: 1) OUES: < 1.3; 2) CP < 2116 mmHg.mlO<sub>2</sub>.kg<sup>-1</sup>.min<sup>-1</sup> and minute ventilation/carbon dioxide production ( $\dot{V}_E/\dot{V}CO_2$ ) slope > 38. The 15 (38%) patients hospitalized during follow-up (8 ± 2 months). In the hospitalizations analysis, LVEF < 39% and  $FEV_1$  < 1.6, OUES < 1.3, CP < 2116 mmHg.mlO<sub>2</sub>.kg<sup>-1</sup>.min<sup>-1</sup> and  $\dot{V}_E/\dot{V}CO_2$  > 38 were a strong risk predictor for hospitalization (P ≤ 0.050). The CPET response effectively identified worsening disease severity in patients with a HF-COPD phenotype. LVEF,  $FEV_1$ , CP, OUES, and the  $\dot{V}_E/\dot{V}CO_2$  slope may be particularly useful in the clinical assessment and strong risk predictor for hospitalization.

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) coexist not because of their high individual prevalence, but because both share common etiological and pathophysiological factors, such as smoking and systemic inflammation<sup>1–3</sup>. COPD overlap syndrome in HF can reach up to 30%<sup>4</sup>. The prevalence of COPD in patients hospitalized for HF is 10%, and the risk of developing HF during hospitalization due to COPD decompensation is 4.5%<sup>5</sup>. These diseases also have relevant systemic components that affect widely the musculoskeletal system<sup>6–8</sup> in addition to the heart and lungs.

There is an increasing recognition that exercise intolerance in overlap of HF-COPD cases may be associated with increased ventilatory responses due to metabolic demand, resulting in ventilatory inefficiency<sup>9,10</sup>. This varies considerably in patients with HF-COPD with pulmonary involvement [Forced Expiratory Volume in the first second ( $FEV_1$ )] and cardiac [left ventricular ejection fraction (LVEF)]<sup>11–13</sup>. However, the structural and physiological determinants that support this great variability remain poorly understood. It is not clear the impact of  $FEV_1$  and LVEF on cardiorespiratory and metabolic variables within cardiopulmonary exercise testing (CPET) in HF-COPD patients.

CPET is the gold standard and established tool to assess functional capacity and to determine prognosis in HF and COPD patients<sup>14</sup>. In addition, variables such as peak oxygen uptake ( $\dot{V}O_2$ ), the product of peak ventilation ( $\dot{V}_E$ ) and carbon dioxide production ( $\dot{V}_E/\dot{V}CO_2$  slope)<sup>14,15</sup> are important cardiac prognostic indices<sup>13</sup>. Guazzi *et al.*

<sup>1</sup>Cardiopulmonary Physiotherapy Laboratory, Physiotherapy Department, Federal University of Sao Carlos, UFSCar, Rod Washington Luis, KM 235, Monjolinho, CEP: 13565-905, Sao Carlos, SP, Brazil. <sup>2</sup>Department of Gerontology, Federal University of São Carlos, São Carlos, Brazil. <sup>3</sup>Department of Physical Education and Health, University of Santa Cruz of Sul, Rio Grande do Sul, Brazil. \*email: [audrey@ufscar.br](mailto:audrey@ufscar.br)

(2013) showed that the peak of  $\dot{V}O_2 < 10$  mL/kg/min and  $\dot{V}_E/\dot{V}CO_2$  slope  $\geq 45$  were independent predictors of long-term mortality in HF and COPD<sup>14,15</sup>.  $O_2$  pulse, circulatory and ventilatory power (CP and VP, respectively) are related to predictors of mortality in all chronic heart failure patients<sup>16–18</sup>.

In addition, the studies that performed CPET focused on the variation between different populations presented as main objective the comparison with tests<sup>10–12,19,20</sup>. Thus, there is no information about the impact of HF-COPD on CPET variables, since these patients have marked ventilatory and cardiac limitations and, from a clinical point of view, established cut-off values for these patients based on the disease severity. It would be of utmost importance to determine during the performance of CPET, the clinical condition, diagnosis and best prescription of cut-off training for these patients.

Our aim was to identify optimal CPET threshold values that distinguish disease severity progression in patients with co-existing systolic HF and COPD. Our secondary aim was to evaluate the impact of the cut-off determined on the prognosis of hospitalizations of these patients. We hypothesize that CPET variables are important prognostic determinants for cardiorespiratory worsening in patients with  $FEV_1 < 1.6$  and  $LVEF < 39\%$ .

## Methods

**Study design.** This cross-sectional study was designed following the recommendations of the STROBE statement. All patients were recruited from the Cardiology and Pulmonology outpatient clinic of São Carlos. The study followed the Declaration of Helsinki and was approved by the local ethics committees (Federal University of Sao Carlos) (protocol number: 91088318.7.1001.5504). All volunteers signed a written informed consent statement prior to participation.

**Subjects.** 51 patients with clinical diagnosis of COPD by pulmonary function test [ $FEV_1$ /forced vital capacity (FVC) ratio of 0.7;  $FEV_1$  60% of predicted] without previous COPD exacerbation (3 months before the study) and clinical diagnosis of HF from a cardiologist with ejection fraction ( $< 50\%$  by echocardiogram), without cognitive impairment or comprehension deficiencies, older than 50 years of age and with HF class I, II or III according to the New York Heart Association Functional Classification (NYHA) were included in the study<sup>16</sup>.

Some HF-COPD patients were excluded from this study, as follows: patients with musculoskeletal disorders or neurological conditions affecting the locomotor system in a way that precluded them from protocol participation, patients recently hospitalized with clinical diagnoses of lung cancer, heavy alcohol drinkers, any patient with observed complex cardiac arrhythmias or electrocardiogram alterations, and patients with uncontrolled metabolic diseases, such as diabetes mellitus.

According to GOLD (2016)<sup>1</sup> the mean  $FEV_1$  value of COPD patients is 1.7 L. Thus, we emphasize that our results are based on the average of our study, which is similar to the recommended by GOLD for  $FEV_1 1.6 \pm 0.1$  L and  $LVEF < 39\%$ .

**Protocol.** All patients underwent an echocardiogram administered by a cardiologist, a pulmonary function exam performed by a pulmonologist, and a clinical assessment. Every patient completed the comprehensive evaluation process in two days: (1) clinical evaluation by a physician and a physical therapist, followed by lung function test and Doppler echocardiography; (2) CPET; (3) follow-up.

**Measurements.** *Doppler echocardiography.* Initially for the clinical and diagnostic stratification, the HF-COPD patients were submitted to a 2D-echocardiogram using an iE33 system (Philips, Andover, MA, USA) with a 2–5 MHz matrix transducer and tissue Doppler imaging software. Quantification of the cardiac chambers was performed according to the American Society of Echocardiography. In our study we only included patients with reduced  $LVEF (< 50\%)$ . Patients who presented preserved  $LVEF (> 50\%)$  or diastolic HF were excluded from study<sup>16</sup>.

*Pulmonary function.* The pulmonary function was assessed using a digital spirometer (Breeze<sup>®</sup>, Medgraphics, MGC Diagnostics Corporation, St. Paul, MN, EUA) that provided measures of the forced expiratory volume in the 1<sup>st</sup> second ( $FEV_1$ ) and the forced vital capacity (FVC), enabling the calculation of the  $FEV_1/FVC$  ratio. Spirometry was performed according to the recommendations of the American Thoracic Society/European Respiratory Society guidelines. The classification of severity of airflow limitation in COPD was assessed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, and patients were classified as moderate (GOLD II), severe (GOLD III), or very severe (GOLD IV)<sup>1</sup>.

*Cardiopulmonary exercise testing.* In accordance with the American College of Cardiology and American Heart Association Guidelines<sup>15</sup>, a physician and physical therapist supervised the CPETs and the subjects were asked to maintain routine medications on the day of testing. The test was performed on an electronically braked cycle ergometer (Corival Recumbent, Medical Graphics Corporation, St. Paul, Mo, USA) and respiratory gas analysis was measured breath-by-breath with Oxycon Mobile (Mijnhardt/Jäger, Würzburg, German).

The protocol consisted of the following: (I) 5-minute rest period while sitting on the cycle ergometer; (II) 1-minute exercise at free-wheel and 60 rotations per minute (rpm); (III) incremental phase with an increase of 5–10 W/min (ramp protocol); (IV) 1-minute of active recovery at free-wheel; and (V) 5-minute passive recovery resting in sitting position. A twelve-lead Electrocardiogram (ECG) was continuously monitored throughout the test (WinCardio, Micromed, Brasilia, Brazil). The test was finished when subjects were pedaling at their maximum possible effort level (physical exhaustion) and reported at least 2 of the following criteria: (I) age predicted maximal HR ( $220 - \text{age}$ ); (II) general/leg fatigue or dyspnea; (III) angina or electrocardiographic evidence of ischemia or malignance arrhythmia (ventricular tachyarrhythmia, ventricular fibrillation, bigeminism); or (IV) inability to maintain a pedaling rate of 60 rpm for 30 seconds.

Variables	HF-COPD (N = 40)
Male, n (%)	30 (75)
Woman, n (%)	10 (25)
Age (years)	66 ± 8
Weight (kg)	71 ± 23
LVEF (%)	39 ± 8
<b>Medications, n (%)</b>	
β-Blocker	40 (100)
B <sub>2</sub> -agonists	40 (100)
Diuretics	20 (50)
<b>Pulmonary Function</b>	
FEV <sub>1</sub> , L	1.6 ± 0.1
FVC, L	2.2 ± 1
FEV <sub>1</sub> /FVC, L	0.56 ± 0.1

**Table 1.** Clinical, echocardiogram and spirometry's characteristics in HF-COPD patients. Notes: \*Mean ± SD; HF: heart failure; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; FVC: Forced Vital Capacity; FEV<sub>1</sub>, Forced Expiratory Volume in the 1 second; FEV<sub>1</sub>/FVC = Forced Expiratory Volume in the 1 second /Forced Vital Capacity.

**Ventilatory and hemodynamic measurements during CPET.** During CPET the following parameters were measured: peak systolic and diastolic blood pressure (SBP and DBP) (mmHg), peak  $\dot{V}O_2$  (ml/kg/min),  $\dot{V}CO_2$  (ml/min),  $\dot{V}_E/\dot{V}CO_2$  slope<sup>21</sup>, workload (WR) (watts), HR peak (bpm) and  $\dot{V}O_2$  efficiency slope (OUES)<sup>22</sup>. O<sub>2</sub> pulse was calculated using the product of peak  $\dot{V}O_2$  and peak HR. CP was calculated using the product of peak  $\dot{V}O_2$  and peak SBP<sup>17</sup>. VP was obtained by dividing peak SBP by the  $\dot{V}_E/\dot{V}CO_2$  slope<sup>21</sup>.  $\dot{V}O_2$ /WR was determined by the relationship between maximal workload obtained and  $\dot{V}O_2$  peak<sup>23</sup>.

**Follow-up.** Patients were included and accompanied during 12 months by telephone calls to their home or family physician. The hospitalizations were determined when the patient was hospitalized for more than one day, our patients had the following hospitalizations: COPD exacerbations (type II and III) (n = 6), HF decompensation (n = 5) and myocardial revascularization (n = 4). COPD exacerbations are classified as: type II - increased medication and medical intervention; and type III - worsening of the clinical condition requiring hospitalization<sup>1</sup>.

**Statistical analysis.** The Shapiro-Wilk test was used to verify the data distribution. Descriptive data was shown as a mean, standard deviation and frequency. The parametric Student's t-test was used for normally distributed data. Pearson correlation analysis were performed to investigate the relationship between variables. All tests were made in Statistical Package for the Social Sciences (SPSS) and values were accepted as  $P \leq 0.05$ .

**ROC curve.** First, receiver operating characteristic (ROC) curve analyses selected the optimal threshold values to differentiate the severity of COPD considering FEV<sub>1</sub> (L) and the severity of HF considering LVEF (%). Cut-off points discriminated the precision of CPET variables: VP, CP, O<sub>2</sub> pulse, OUES,  $\dot{V}_E/\dot{V}CO_2$  slope and  $\dot{V}O_2$  peak in determining points of predictive cut-off in HF-COPD. The confidence interval (95% CI) was used to determine the ability of the clinical variables, with the lower limit being greater than 0.50. Subsequently, the cut-off points of the variables that obtained significant areas under the ROC curve were identified, with the respective values of sensitivity and specificity.

**Kaplan-meier.** We examined all hospitalization that occurred during the 12-months follow-up. Hospitalization curves were analyzed according to the Kaplan-Meier method to explore the impact of FEV<sub>1</sub> < 1.6 and LVEF < 39%, CP < 2338, VE/VCO<sub>2</sub> > 38 and OUES > 1.3. Differences between curves were evaluated using the log-rank test.

## Results

**General characteristics.** We initially included 51 HF-COPD patients, however due to our exclusion criteria, 11 patients did not participate in the study protocol: 1 was excluded for brain cancer, 7 did not agree to participate in the study, 1 due to aortic aneurysm, and 2 due to encephalic vascular accident. Therefore the protocol was carried out with 40 HF-COPD patients.

Table 1 presents the clinical, echocardiogram and spirometry's characteristics in HF-COPD patients, 40 adult men and 10 woman with beta blocker and beta-agonists use (Table 1).

During follow-up (10 ± 2 months), 15 patients were hospitalized (7 ± 2 months) and 25 were not hospitalized (10 ± 1 months). Table 2 expresses metabolic, ventilatory and hemodynamic variables of CPET in HF-COPD patients with hospitalizations [n = 15 (38%)] and non-hospitalizations [n = 40 (62%)]. We reported that the most hospitalized patients were those with FEV<sub>1</sub> < 1.6 L [11 (71%)] and presented reduced O<sub>2</sub> pulse when compared with non-hospitalized (p < 0.05).

We found significant correlations between: OUES vs LVEF (p = 0.018; r = 0.371) and FEV<sub>1</sub> vs  $\dot{V}O_2$ /WR (p < 0.001; r = -0.735), suggesting that the worse the airway obstruction and LVEF, the worse the behavior of these variables in CPET, thus compromising the performance of these HF-COPD patients.

Variables	HF-COPD (N = 40)	Hospitalizations (N = 15)	Non Hospitalizations (N = 25)	P value
FEV <sub>1</sub> (L)	1.6 ± 0.1	1.4 ± 0.6	1.7 ± 0.9	0.27
FEV <sub>1</sub> < 1.6				0.05
Yes	21 (52)	11 (71)	10 (40)	
No	19 (48)	4 (29)	15 (60)	
LVEF < 39%				0.46
Yes	19 (48)	9 (60)	12 (48)	
No	21 (52)	6 (40)	13 (52)	
LVEF (%)	39 ± 8	36 ± 8	41 ± 9	0.53
WR peak (W)	60 ± 20	56 ± 16	63 ± 23	0.40
$\dot{V}_E$ peak (L/min)	39 ± 8	28 ± 9	38 ± 20	0.08
$\dot{V}O_2$ peak (ml.kg <sup>-1</sup> .min <sup>-1</sup> )	12 ± 3	11 ± 3	12 ± 3	0.51
$\dot{V}_E/\dot{V}CO_2$ slope	38 ± 10	40 ± 10	35 ± 11	0.22
O <sub>2</sub> pulse (ml.bpm <sup>-1</sup> )	10 ± 5	8 ± 2	13 ± 8	0.01
VP (mmHg)	4 ± 1	4.9 ± 2	4.5 ± 1	0.20
CP (mmHg.mlO <sub>2</sub> .min <sup>-1</sup> )	2045 ± 727	1833 ± 708	2172 ± 722	0.15
OUES	1.3 ± 0.3	1.2 ± 0.4	1.3 ± 0.3	0.74
HR peak (bpm)	111 ± 24	114 ± 25	105 ± 20	0.24
SBP peak (mmHg)	165 ± 39	171 ± 40	162 ± 39	0.54
DBP peak (mmHg)	93 ± 26	105 ± 32	87 ± 19	0.03

**Table 2.** Metabolic, ventilatory and hemodynamic variables of CPET in HF-COPD patients. Notes: \*p < 0.05 = FEV<sub>1</sub> > 1.9 vs FEV<sub>1</sub> < 1.9; †p < 0.05 = LVEF < 39% vs FEV<sub>1</sub> < 1.9; ‡p < 0.05 = LVEF < 39% vs LVEF > 39%; HF: heart failure; COPD: chronic obstructive pulmonary disease; HR: heart rate; WR: work rate;  $\dot{V}O_2$ : oxygen uptake; RER: respiratory exchange ratio;  $\dot{V}_E$ : Minute ventilation;  $\dot{V}CO_2$ : carbon dioxide production;  $\dot{V}_E/\dot{V}CO_2$  slope: linear relation between minute ventilation and carbon dioxide production; OUES: Oxygen uptake efficiency slope; CP: circulatory power; VP: ventilatory power. HRR 1: Peak - Heart rate recovery in the first minute; SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

HF-COPD (N = 21)						
Variables	Cut-off	Sensitivity	Specificity	AUC [CI 95%]	Positive likelihood	Negative likelihood
CP (mmHg.mlO <sub>2</sub> .kg <sup>-1</sup> .min <sup>-1</sup> )	2383	70	53	0.700 [0.501–0.810]	1.39	0.60
OUES	1.3	66	61	0.682 [0.487–0.823]	1.74	0.53

**Table 3.** Cut-off values, sensitivity and specificity of hemodynamic response in CPET in HF-COPD with FEV<sub>1</sub> < 1.6 L. HF: heart failure; COPD: chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in the 1 second; CP: Circulatory power and OUES: Oxygen uptake efficiency slope.

**Cut-off points for FEV<sub>1</sub> < 1.6 and LVEF < 39%.** From this point of the study, our results will be divided by the mean found in our patients FEV<sub>1</sub> < 1.6 L [n = 21 (52%)] and LVEF < 39% [19 (n = 48%)], our aim in performing this stratification is to demonstrate the impact of diseases on CPET variables and may assist in clinical practice.

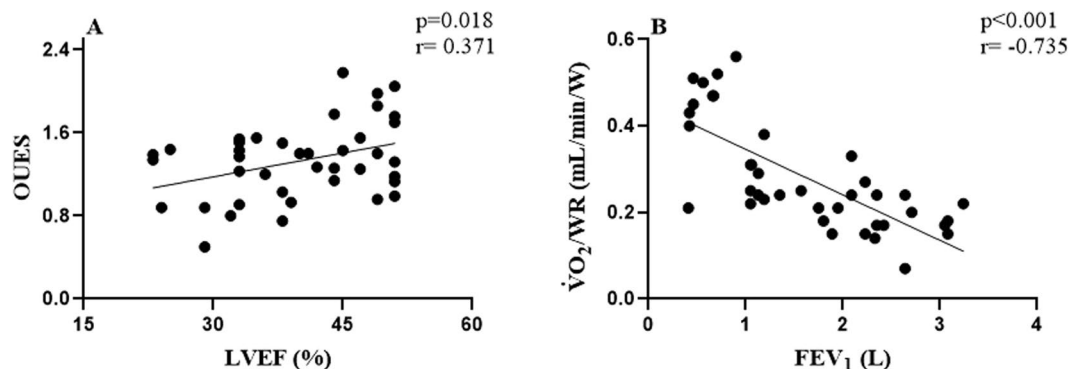
The cut-off points, the areas under the ROC curve and 95% CI, as well as the sensitivity and specificity of the clinical variables are shown in Table 3. According to the prediction, the best models of sensitivity and specificity are: OUES < 1.3 and CP < 2383 mmHg.mlO<sub>2</sub>.min<sup>-1</sup> identified as cut-off points for HF-COPD patients with FEV<sub>1</sub> < 1.6 L.

The cut-off points, the areas under the ROC curve and 95% CI, as well as the sensitivity and specificity of the clinical variables are shown in Table 4. According to the prediction, the best models of sensitivity and specificity are: OUES: < 1.3, CP < 2116 mmHg.mlO<sub>2</sub>.kg<sup>-1</sup>.min<sup>-1</sup> and  $\dot{V}_E/\dot{V}CO_2$  slope > 38 identified as cut-off points for HF-COPD patients with LVEF < 39% (Fig. 1).

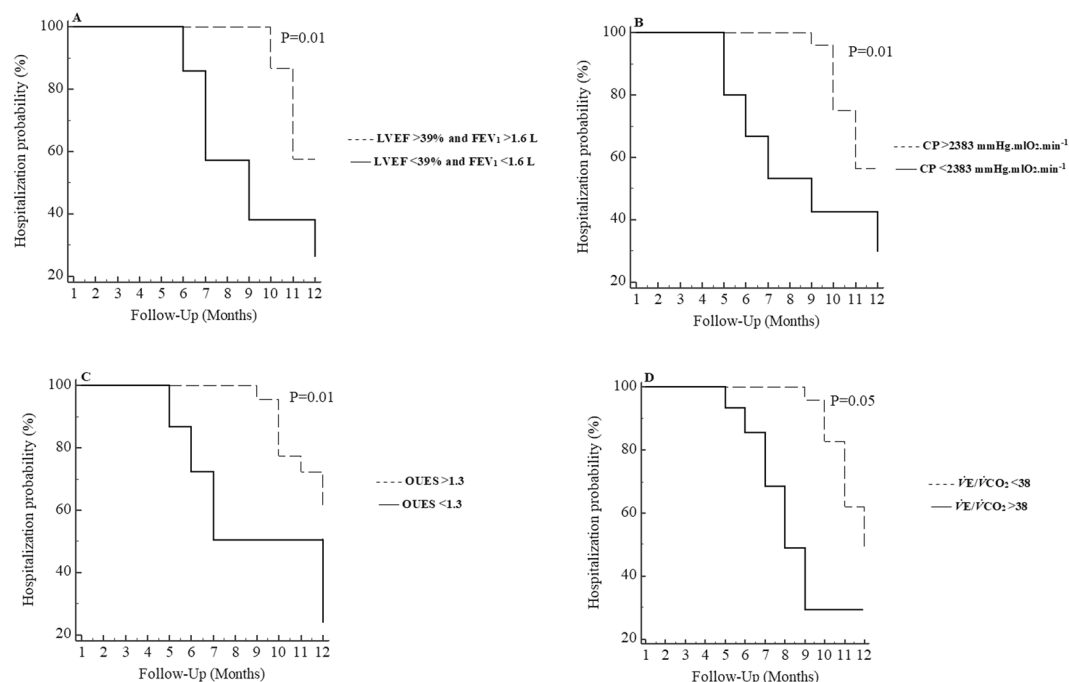
**Hospitalization analysis.** In the Kaplan-Meier analysis, when we associated patients with LVEF < 39% and FEV<sub>1</sub> < 1.6 [n = 14] with a higher probability of hospitalizations over a 12-month period. The hospitalization curve differed significantly in the log-rank test (p = 0.018). In the analysis for the CPET variables, we found that only  $\dot{V}_E/\dot{V}CO_2$  > 38, OUES < 1.3 and CP < 2383 mmHg.mlO<sub>2</sub>.min<sup>-1</sup> were prognostic indicators for hospitalization (P ≤ 0.05) in COPD-HF patients (Fig. 2).

HF-COPD (N = 19)						
Variables	Cut-off	Sensitivity	Specificity	AUC [CI 95%]	Positive likelihood	Negative likelihood
OUES	1.3	70	50	0.701 [0.523–0.862]	1.30	0.66
$\dot{V}E/\dot{V}CO_2$ slope	38	71	53	0.610 [0.520–0.788]	1.30	0.66
CP ( $ml \cdot kg^{-1} \cdot min^{-1} / W$ )	2116	70	60	0.762 [0.522–0.803]	1.59	0.56

**Table 4.** Cut-off values, sensitivity and specificity of hemodynamic response in CPET in HF-COPD with LVEF < 39%. HF: heart failure; COPD: chronic obstructive pulmonary disease;  $\dot{V}E/\dot{V}CO_2$  slope: Linear relation between minute ventilation and carbon dioxide production; CP: Circulatory power and OUES: Oxygen uptake efficiency slope.



**Figure 1.** Correlations between pulmonary and cardiac function with metabolic and cardiorespiratory variables in CPET in HF-COPD patients. (A) Left ventricular ejection fraction (LVEF) vs OUES; (B) Forced expiratory volume in the 1 second ( $FEV_1$ ) vs  $\dot{V}O_2/WR$ . Pearson correlation test ( $p < 0.05$ ),  $N = 40$ .



**Figure 2.** Kaplan-Meier curve for hospitalization according to presence of LVEF < 39% and  $FEV_1 < 1.6$ ,  $CP < 2383 \text{ mmHg} \cdot \text{mlO}_2 \cdot \text{min}^{-1}$ ,  $OUES < 1.3$  and  $\dot{V}E/\dot{V}CO_2 > 38$ . LVEF: Left ventricular ejection fraction;  $FEV_1$ : forced expiratory volume in the 1 second. (A) LVEF < 39% and  $FEV_1 < 1.6$   $n = 14$  and LVEF > 39% and  $FEV_1 > 1.6$   $n = 15$ ; (B)  $CP < 2383$   $n = 25$  and  $CP > 2383$   $n = 15$ ; (C)  $OUES < 1.3$   $n = 22$  and  $OUES > 1.3$   $n = 18$ ; (D)  $\dot{V}E/\dot{V}CO_2 > 38$   $n = 17$  and  $\dot{V}E/\dot{V}CO_2 < 38$   $n = 23$ .

## Discussion

This is the first study to identify relative cut-off scores to determine prognostic markers of cardiorespiratory worsening and hospitalization in patients through variables of CPET based on COPD and HF severity. The main findings of the present study were: I) Correlations suggest that worsening airway obstruction and LVEF, directly impact in aerobic function ( $\dot{V}O_2/WR$ ) and ventilatory equivalent oxygen (OUES); II) OUES < 1.3 and CP < 2383 mmHg.mlO<sub>2</sub>.kg<sup>-1</sup>.min<sup>-1</sup> were identified as cut-off points for HF-COPD patients with FEV<sub>1</sub> < 1.6L; III) OUES < 1.3, CP < 2116 mmHg.mlO<sub>2</sub>.min<sup>-1</sup> and  $\dot{V}_E/\dot{V}CO_2$  slope > 38 were identified as cut-off points for HF-COPD patients with LVEF < 39%; IV) In Kaplan-Meier analysis: LVEF < 39% and FEV<sub>1</sub> < 1.6,  $\dot{V}_E/\dot{V}CO_2$  > 38, OUES < 1.3 and CP < 2383 mmHg.mlO<sub>2</sub>.min<sup>-1</sup> were prognostic indicators for hospitalization in COPD-HF patients.

We found that airway obstruction and LVEF directly influence aerobic function and OUES. Our study corroborates with Hansen *et al.*<sup>24</sup>, who found a lower  $\dot{V}O_2/WR$  in cardiorespiratory disease and suggesting that cardiorespiratory limitation may decrease the load ratio, even with optimal exercise duration.

The main result of our study was to find predictive CPET values for worsening of cardiorespiratory capacity based on airway obstruction in patients with COPD and LVEF in patients with HF and prognostic indicators for hospitalization. We can highlight that through these cutoff points it will be possible to determine diagnosis, training prescriptions, as well as the general state of these patients. De Miguel *et al.*<sup>25</sup> highlighted that HF-COPD patients have a mixed pulmonary dysfunction. COPD is characterized by airway obstruction and emphysema. In HF, the enlargement of the heart, venous congestion, and interstitial fibrosis compresses the lungs, leading to a restrictive pulmonary disorder<sup>26</sup>. The coexistence of diseases may lead to further increases in disability and mortality, perhaps even impairing the CPET results since variables of the test are poorer in these patients<sup>17-27</sup>.

We emphasize the importance in determining other prognostic indices of cardiorespiratory worsening of CPET in these patients. Another cut-off values in our study were CP < 2383 mmHg.mlO<sub>2</sub>.min<sup>-1</sup> and CP < 2116 mmHg.mlO<sub>2</sub>.kg<sup>-1</sup>.min<sup>-1</sup> for FEV<sub>1</sub> < 1.6 and LVEF < 39% respectively, a new cardiac index recently studied, and an original result for this population. A previous study demonstrated that CP is a surrogate index of cardiac power, shown to have a better prognostic value than peak  $\dot{V}O_2$ ,  $\dot{V}O_2/HR$  and peak SBP in HF<sup>20,22,27</sup>. Physiologically, CP represents the volume of O<sub>2</sub> added to the mixed venous blood by the lungs and transferred to systemic arterial circulation, against a pressure gradient produced by the heart<sup>22</sup>. CP is related to the central and peripheral components of the cardiac work<sup>16,22</sup>. We emphasize that CP < 2383 mmHg.mlO<sub>2</sub>.min<sup>-1</sup> was a predictor of hospitalization in these patients.

In COPD, an emphysema burden has been associated with increased  $\dot{V}_E/\dot{V}CO_2$ , as a consequence of increased ventilatory drive and greater neuromechanical dissociation<sup>28,29</sup>. In HF, disease progression is associated with higher  $\dot{V}_E/\dot{V}CO_2$  because of an increased ventilatory drive leading to hypocapnia in highly variable combinations<sup>30,31</sup>. Aposto *et al.*<sup>20</sup>, found that increased  $\dot{V}_E$  of the linear  $\dot{V}_E/\dot{V}CO_2$  relationship during ramp-incremental exercise should raise the suspicion of coexistent COPD in patients with HF. The new result of our study is that the  $\dot{V}_E/\dot{V}CO_2$  slope > 38 for patients with LVEF < 39% that was identified as cut-off points and predictor of hospitalization for HF-COPD patients.

Lin *et al.*<sup>32</sup> found that HF patients with OUES < 1.3 had a higher risk of cardiac events. OUES is considered a method of evaluating cardiopulmonary endurance and it is easily determined when using the breath-by-breath respiratory analysis method<sup>32</sup>. Compared with the values already described in the literature, our result of OUES < 1.3 for patients with FEV<sub>1</sub> < 1.6 and LVEF < 39%, emphasizes that our study is the first to find a cut-off value for a HF-COPD population.

Thus, our results highlight the importance of identifying predictive values of disease severity-based exercise testing (COPD and HF), as well as the prognosis value of cardiopulmonary exercise testing to help healthcare professionals to identify potential patients for hospitalization. It is possible with cut-off values to obtain a response about the patient's general health, as we know that hospitalizations limit or even preclude rehabilitation and may aggravate the exercise intolerance of this population.

## Strength and Limitation of the Study

The main limitation in our study is the small number of COPD-HF coexistence, however, despite the high prevalence of COPD and HF, such coexistence has been poorly studied, especially considering the impact of disease severity on exercise capacity. In this sense, future studies should be conducted with a larger sample to confirm our findings<sup>33</sup>.

The strengths of our study include the novelty of finding cut-offs for new rates (CP, OUES and  $\dot{V}_E/\dot{V}CO_2$  slope) and predictors of hospitalization for HF-COPD patients with FEV<sub>1</sub> < 1.6L and LVEF 39%. Thus, this is the first study to investigate these indices in HF-COPD patients based on the severity of the diseases. We emphasize as a limitation the sample size, however it is known the difficulty in screening COPD-HF coexistence and that so far no follow-up studies and prognosis of hospitalizations in this population have been conducted, thus highlighting the importance of this work.

## Conclusion

In conclusion, heart failure with reduced left ventricular ejection fraction as well as the severity of COPD impacted negatively selected physiological responses obtained by CPET. CP, OUES and  $\dot{V}_E/\dot{V}CO_2$  slope provided to be useful in practice to clinical interpretation of cardiopulmonary responses during exercise and are a strong risk predictor for hospitalization in HF-COPD coexistence patients.

Received: 5 November 2019; Accepted: 20 January 2020;

Published online: 09 March 2020

## References

1. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Management and Prevention. Global Initiative for Chronic Obstructive Lung Disease; 2018. Available from: [http://www.goldcopd.it/materiale/2018/GOLD\\_Pocket\\_2018.pdf](http://www.goldcopd.it/materiale/2018/GOLD_Pocket_2018.pdf).
2. Beghé, B. *et al.* Echocardiography, spirometry, and systemic acute-phase inflammatory proteins in smokers with COPD or CHF: an observational study. *PLoS One*. **8**, 80166 (2013).
3. Sin, D. D. & Hogg, J. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc. Am. Thorac. Soc.* **2**, 8–11 (2005).
4. Griffo, R. *et al.* Italian survey on prevalence and disease management of chronic heart failure and chronic obstructive pulmonary disease comorbidity in ambulatory patients. SUSPIRIUM study rationale and design. *Monaldi Arch. Chest Dis.* **82**, 29–34 (2014).
5. Ni, H. *et al.* Managed care and outcomes of hospitalization among elderly patients with congestive heart failure. *Arch. Int. Med.* **158**, 1231–6 (1998).
6. Gosker, H. R. *et al.* Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest*. **5**, 1416–24 (2003).
7. Dumitru, L. *et al.* Disability in COPD and Chronic Heart Failure Is the Skeletal Muscle the Final Common Pathway? *Maedica*. **8**, 206–13 (2013).
8. Ukena, C. *et al.* The cardiopulmonary continuum systemic inflammation as ‘common soil’ of heart and lung disease. *Int. J. Cardiol.* **145**, 172–6 (2010).
9. Whipp, B. J. Control of the exercise hyperpnea: the unanswered question. *Adv. Exp. Med. Biol.* **605**, 16–21 (2008).
10. Sue, D. Y. Excess ventilation during exercise and prognosis in chronic heart failure. *Am. J. Respir. Crit. Care Med.* **183**, 1302–1310 (2011).
11. Arbex, F. F. *et al.* Exercise ventilation in COPD: influence of systolic heart failure. *COPD*. **13**, 693–699 (2016).
12. Alencar, M. C., Arbex, F. F., O'Donnell, D. E. & Neder, J. A. Does exercise ventilatory inefficiency predict poor outcome in heart failure patients with COPD? *J. Cardiopulm. Rehab Prev.* **13**, 416–424 (2016).
13. Rocha, A. *et al.* Physiological and sensory consequences of exercise oscillatory ventilation in heart failure-COPD. *J. Cardiopulm. Rehabil. Prev.* **224**, 447–453 (2016).
14. Guazzi, M. *et al.* Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation*. **126**, 2261–2274 (2012).
15. Fletcher, G. F. *et al.* American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. **20**, 873–934 (2013).
16. Mitja, L. *et al.* Definition and Classification of Heart Failure. *International Cardiovascular Forum Journal*. **10**, (2017).
17. Hulkkonen, J. *et al.* Determinants of exercise peak arterial blood pressure, circulatory power, and exercise cardiac power in a population based sample of Finnish male and female aged 30 to 47 years: the Cardiovascular Risk in Young Finns Study. *BMC Cardiovasc. Disord.* **14**, 35 (2014).
18. Corrà, U., Mezzani, A., Giordano, A., Bosimini, E. & Giannuzzi, P. Exercise hemodynamic variables rather than ventilatory efficiency indexes contribute to risk assessment in chronic heart failure patients treated with carvedilol. *Eur. Heart J.* **30**, 3000–6 (2009).
19. Mezzani, A. *et al.* Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *Eur. J. Cardiovasc. Prev. Rehab.* **16**, 249–267 (2009).
20. Apostolo, A. *et al.* Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. *Int. J. Cardiol.* **189**, 134–40 (2015).
21. Arena, R., Humphrey, R. & Peberdy, M. A. Prognostic ability of VE/VCO<sub>2</sub> slope calculations using different exercise test time intervals in subjects with heart failure. *Eur. J. Cardiovasc. Prev. Rehabil.* **6**, 463–8 (2003).
22. Baba, R. *et al.* Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J. Am. Coll. Cardiol.* **28**, 1567–1572 (1996).
23. Rocha, A. *et al.* Exercise intolerance in comorbid COPD and heart failure: the role of impaired aerobic function. *Eur Respir J.* **53** (2019).
24. Hansen, J. E. *et al.* Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. *Am. J. Cardiol.* **59**, 669–674 (1987).
25. De Miguel, D. J., Morgan, J. C. & Jimenez Garcia, R. The association between COPD and heart failure risk: a review. *Int. J. Chron. Obstruct Pulmon Dis.* **8**, 305–312 (2013).
26. Rutten, F. H., Cramer, M. J., Lammers, J. W., Grobbee, D. E. & Hoes, A. W. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur. J. Heart Fail.* **8**, 706–711 (2006).
27. Hawkins, N. M., Virani, S. & Ceconi, C. Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services. *Eur. Heart J.* **34**, 2795–2803 (2013).
28. Borghi-Silva, A. *et al.* Exercise ventilatory power in heart failure patients: functional phenotypes definition by combining cardiopulmonary exercise testing with stress echocardiography. *Int. J. Cardiol.* **76**, 1348–9 (2014).
29. Paoletti, P. *et al.* Cardiopulmonary exercise testing (CPET) in pulmonary emphysema. *Respir. Physiol. Neurobiol.* **179**, 167–173 (2011).
30. Davis, J., Whipp, B. & Wasserman, K. The relation of ventilation to metabolic rate during moderate exercise in man. *Eur. J. Appl. Physiol.* **44**, 97–108 (1980).
31. Teopompi, E. *et al.* Ventilatory response to carbon dioxide output in subjects with congestive heart failure and in patients with COPD with comparable exercise capacity. *Respir. Care.* **59**, 1034–1041 (2014).
32. Lin, Y. S. *et al.* Oxygen Uptake Efficiency Slope Predicts Major Cardiac Events in Patients With End-Stage Heart Failure. *Transpl. Proc.* **48**, 956–8 (2016).
33. Griffo, R. *et al.* Frequent coexistence of chronic heart failure and chronic obstructive pulmonary disease in respiratory and cardiac outpatients: Evidence from SUSPIRIUM, a multicentre Italian survey. *Eur. J. Prev. Cardiol.* **24**, 567–576 (2017).

## Acknowledgements

The authors would like to thank FAPESP (grant numbers 2018/03233–0 and 2015/26501–1) and Ministry of Education/CAPES-Brazil, for financial support.

## Author contributions

C.G., P.B.S., G.A., F.R.C. and A.B.S. conception or design; C.G., A.B.S., G.A., C.O., T.A., P.C., R.M., A.S., F.R.C. and A.B.S. acquisition, analysis, drafted, or interpretation of data of the manuscript; C.G., A.B.S., G.A., C.O., T.A., P.C., R.M., A.S. F.R.C. and A.B.S. final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

## Competing interests

The authors declare no competing interests.

## Additional information

**Correspondence** and requests for materials should be addressed to A.B.-S.

**Reprints and permissions information** is available at [www.nature.com/reprints](http://www.nature.com/reprints).

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2020