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ORIGINAL RESEARCH

Eccentric Left Ventricular Hypertrophy and Left and Right Cardiac Function in Chronic Heart Failure with or without Coexisting COPD: Impact on Exercise Performance

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Aim: Our aim was to assess: 1) the impact of the eccentric left ventricular hypertrophy (ELVH) on exercise performance in patients diagnosed with chronic heart failure (CHF) alone and in patients with co-existing CHF and chronic obstructive pulmonary disease (COPD) and 2) the relationship between left and right cardiac function measurements obtained by doppler echocardiography, clinical characteristics and primary measures of cardiorespiratory fitness.

Methods: The current study included 46 patients (CHF:23 and CHF+COPD:23) that performed advanced pulmonary function tests, echocardiography and symptom-limited, incremental cardiopulmonary exercise testing (CPET) on a cycle ergometer.

Results: Patients with CHF+COPD demonstrated a lower work rate, peak oxygen uptake (VO_2), oxygen pulse, rate pressure product (RPP), circulatory power (CP) and ventilatory power (VP) compared to those only diagnosed with CHF. In addition, significant correlations were observed between VP and relative wall thickness (r: 0.45 p: 0.03),V_E/VCO_2 intercept and Mitral E/e' ratio (r: 0.70 p: 0.003) in the CHF group. Significant correlations were found between indexed left ventricle mass and RPP (r: −0.47; p: 0.02) and relative VO_2 and right ventricle diameter (r: −0.62; p: 0.001) in the CHF+COPD group.

Conclusion: Compared to a diagnosis of CHF alone, a combined diagnosis of CHF+COPD induced further impairments in cardiorespiratory fitness. Moreover, echocardiographic measures of cardiac function are related to cardiopulmonary exercise performance and therefore appear to be an important therapeutic target when attempting to improve exercise performance and functional capacity.

Keywords: heart failure, chronic obstructive pulmonary disease, eccentric hypertrophy, ventricular dysfunction, cardiopulmonary exercise testing, echocardiography

Introduction

Chronic heart failure (CHF) is defined as an inability of the heart to maintain systemic perfusion at a rate compatible with the needs of a body without the need for high filling pressures and is the result of common triggers of disease, including hypertension, myocardial infarction or ischemia associated with coronary artery disease, dilated cardiomyopathies, diabetic cardiomyopathy, and others.[1–4] The initial phase of this process is marked by adaptative mechanisms that lead to left ventricle (LV) hypertrophy.[5–7] However, maintaining this stimulus leads to the

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development of a unique pattern of geometry, which is characterized as an eccentric left ventricular remodeling resulting from volume overload.[8] LV hypertrophy is characterized by an increase of chamber diameter, but a normal relationship between wall thickness and LV radius. Eccentric left ventricle hypertrophy (ELVH) is associated with increased death of cardiomyocytes and fibrotic remodeling that culminates in reduced diastolic and systolic cardiac function as well as increased risk for a higher cardiovascular morbidity and mortality.[9]

Chronic obstructive pulmonary disease (COPD) is a chronic condition characterized by progressive airflow limitation that is not fully reversible, airways inflammation, and a host of systemic effects that contribute to a poor prognosis.[10] The prevalence of COPD GOLD stages II–IV is approximately 5–10% of the adult population and epidemiologic studies show that it is currently the third leading cause of death in the world, producing a significant economic burden, with a high hospitalization rate, absence from work, and disability.[11,12]

Both COPD and CHF are highly prevalent worldwide.[13,14] In addition, CHF+COPD frequently coexists in combination, characterized as an overlap syndrome that increases both morbidity and mortality.[15] Both conditions share common etiologies (eg, chronic tobacco use, systemic inflammation, etc.), have significant systemic effects (eg, dyspnea, fatigue, exercise intolerance and impaired functional capacity) and a chronic progressive evolution.[11,16] The prevalence of CHF+COPD coexistence is estimated to be ≈25% among adults smoking is considered the common risk factor for both diseases, and both increased systemic inflammation and hyperoxidative stress are common.[16,17]

Interestingly, differences in cardiac function and geometry patterns could influence cardiorespiratory responses to exercise, in this context, cardiopulmonary exercise testing (CPET) allows for the most refined assessment of cardiorespiratory fitness.[18,19] In addition, CPET allows for the comprehensive assessment of physiological responses to physical exertion and identify the impact of pathophysiologic processes that are not always readily apparent at rest.[20] In addition to quantifying exercise capacity [ie, peak oxygen uptake (VO_2)], the minute ventilation/carbon dioxide production (V_E/VCO_2) slope and ventilatory power (VP = systolic blood pressure/V_E/VCO_2 slope) have emerged as important physiologic markers of cardiovascular events in both CHF and COPD.[21] However, resting variables obtained by doppler echocardiography could help to understand the relationship between the structure and cardiac function at rest and their relationship to primary markers of cardiorespiratory fitness obtained through CPET.[22]

In the present study, we hypothesized that CHF+COPD would further deteriorate cardiorespiratory fitness compared to patients diagnosed with CHF in isolation. We additionally hypothesized that there are relationships between measures of cardiac function obtained by doppler echocardiography, clinical characteristics and primary CPET measures of cardiorespiratory fitness.

Methods

Study Design and Subjects

This cross-sectional study followed recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[23] Two-hundred and twenty-two patients were screened from 3 cardiology and pneumology outpatient clinics at our University, from 01 June 2017 to 30 August 2019. All patients who attended during this period with the diagnosis of CHF with reduced or borderline ejection fraction (EF) and/or COPD were contacted by phone and was asked questions regarding diagnosis, clinical conditions, disease stability, drug optimization, and functional mobility. For all patients, eligibility criteria were: 1) age range of 40–85 years; 2) clinically stable for at least 3 months (no worsening of symptoms, exacerbation or decompensation of diseases; 3) no change in dose or change in medication for at least 3 months; 4) no hospitalizations for any cause for at least 3 months; and 5) absence of any condition that may affect exercise performance (ie, anemia, neuromuscular disorders, or malignancies). Exclusion criteria included: 1) long-term O_2 therapy; 2) musculoskeletal disease that would impact exercise performance (eg, osteoarthritis, osteonecrosis, trauma, etc.); and 3) peripheral arterial disease associated with claudication. Moreover, CHF or COPD exacerbation or hospitalization during the study was a criterion for study drop-out. All patients who met the eligibility criteria were invited for an initial assessment and tests to confirm the diagnosis of one (CHF) or both (CHF+COPD) diseases being assessed in the current study.

Disease treatment was optimized before study entry and patients underwent CPET only after an agreement had been reached between pneumologists and cardiologists regarding disease stability. As shown in Figure 1, 46 patients with a confirmed reduced or borderline ejection

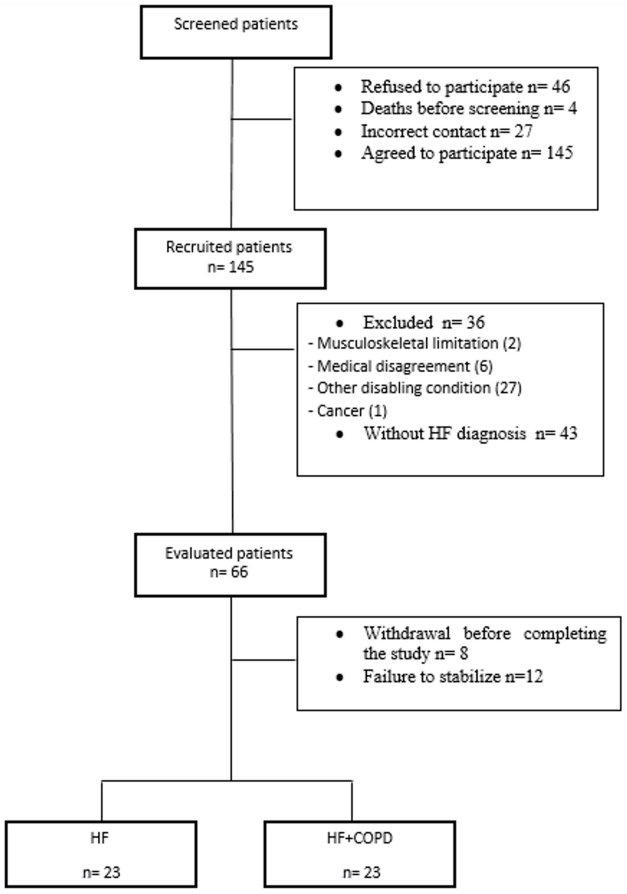

Figure 1 Study flow chart (screened patients n=222).

fraction of left ventricle by echocardiography in combination with symptoms consistent with heart failure were included. Twenty-three of these patients also had a coexisting diagnosis of COPD. The Study followed the resolution no. 466 of the National Health Council (current guideline in Brazil) and The Declaration of Helsinki and was approved by the Ethics and Research Committee of the Federal University of São Carlos, São Paulo, Brazil (CAAE nº 91088318.7.1001.5504). All participants were informed about the objectives, experimental procedures and potential risks involved in this study and gave written informed consent statement prior to participation.

Cardiac and Lung Function Assessments

All patients underwent a transthoracic two-dimensional and Doppler echocardiographic examination at baseline (HD11 XE, Philips, Amsterdam, Netherlands) to confirm the CHF diagnosis, stratify the degree of systolic dysfunction and obtain the necessary measures for the left and right cardiac function and calculation of eccentric hypertrophy. For inclusion in the study, the left ventricular ejection fraction had to be ≤50%.[24] Eccentric hypertrophy of the left ventricle was calculated using the values of relative wall thickness (RWT) at end-diastole and LV mass indexed for body surface area. A cut-off value adopted to classify an eccentric hypertrophy geometric pattern was RWT ≤ 42 and LV mass greater than or equal to 115 g/m^2 for men and greater than or equal to 95 g/m^2 for women.[25,26] Advanced pulmonary function assessment (Masterscreen Body, Mijnhardt/Jäger, Würzburg, German) was performed to obtain dynamic and static lung volumes and capacities pre- and post-bronchodilator therapy. The GOLD criteria [post-bronchodilator forced expiratory volume in the 1 second (VEF_1)/forced vital capacity (FVC) ratio <0.70] was used to confirm a COPD diagnosis.[27]

Cardiopulmonary Exercise Testing

All patients underwent a symptom-limited incremental CPET on an electronically braked cycle ergometer (Corival Recumbent, Lode, Groningen, Netherlands) using the Oxycon Mobile System (Mijnhardt/Jäger, Würzburg, German). The exercise protocol started with an initial 5 min of rest, followed by unloaded cycling for 1 min with a subsequent increment of 5–10 watts each minute (ramp protocol). Patients were instructed to pedal at the speed of 60 rotation per minute and the work rate (WR) increment was individually selected according to reported exercise tolerance. Breath-by-breath VO_2 (L/min), VCO_2 (L/min), and V_E (L/min) were recorded. The CPET variables were reported as 20-second averaged data. During the exercise test, heart rate (HR) twelve-lead electrocardiogram (ECG), blood pressure, and arterial oxygen saturation were monitored. Arterial oxygen saturation was measured non-invasively by pulse oximetry (SpO_2, %). Breathlessness and leg effort scores were rated according to the 10-point Borg category ratio.[28] Established exercise test termination criteria were followed and included Angina (score above 2 on a scale of 0–10), life-threatening arrhythmias, electrocardiographic evidence of ischemia, a drop in systolic blood pressure, or arterial oxygen saturation ≤84% were considered to interrupt the test.[29] Key CPET variables were calculated for all patients as previously described. The V_E/VCO_2 slope was obtained through linear regression analysis.[30] Additionally, the linear relationship between oxygen uptake and the log transformation of V_E (OUES) was calculated using the following equation: VO_2= a log V_E+ b, with the constant "a" referring to the rate of increase of VO_2.[31] Circulatory

power (CP) was obtained through the product of peak VO_2 and peak systolic blood pressure and Ventilatory Power (VP) was calculated by dividing peak systolic blood pressure by the V_E/VCO_2 slope.[32,33]

Statistical Analysis

A sample calculation was performed (GPower 3.1-Universidade de Kiel, Kiel, Alemanha) using the peak VO_2 obtained in pilot studies previously performed in our laboratory with individuals who were diagnosed with CHF. From this sample calculation, 52 subjects, 26 for each group, were needed to reach sufficient statistical power (1-β err prob) of 0.80. The Shapiro–Wilk test was used to verify the data distribution. Descriptive variables were expressed as mean ± standard deviation (when normal distribution) or median and interquartile (when non-normal distribution). Categorical variables are expressed as frequencies and percentages and compared using the chi-square test. The unpaired *t*-test was used to compare anthropometric measures, cardiac and pulmonary function measures and CPET measures. Relationships between measures of cardiac function and other measures collected in the current study were assessed by the Pearson Correlation coefficient (variables with non-normal distribution were log-transformed to reduce non-uniformity of error) for CHF and CHF+COPD groups separately. A p-value <0.05 was considered as statistically significant for all tests. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 20.0 (IBM, Armonk, New York).

Results

Clinical and Resting Characteristics

The characteristics of the patients are reported in Table 1. Groups were homogeneous in relation to clinical characteristics, anthropometric data and the presence of comorbidities. Most patients in both groups were male while patients in the CHF+COPD group were older. In relation to the left cardiac function, differences were found only in the Mitral e'. There were no between-group differences with respect to systolic dysfunction assessed by EF, LV mass and relative LV wall thickness. In relation to the right cardiac function, differences were found between right ventricle diameter (RVD). Interestingly, the CHF group obtained higher values; however, both groups were within the established normal value range for this variable (<42mm).[34] The Tricuspid E/A ratio and Tricuspid E/e' ratio was different between groups. The Tricuspid E/A in both groups suggests the presence of impaired RV relaxation. As expected, CHF+COPD patients showed evidence of an obstructive ventilatory disorder. The frequency of patients in stage 2 according to the GOLD guidelines was greater in CHF+COPD group. CHF patients showed preserved spirometry but similar static lung volumes when compared to the CHF+COPD group; differences between-group were found only in Total lung capacity (TLC) and lung diffusing factor for carbon monoxide (DLCO). In relation to medications, patients in the CHF group used diuretics with greater frequency compared to the CHF +COPD group.

Metabolic, Cardiovascular and Ventilatory Responses to Exercise

Table 2 lists the CPET responses in both groups and the comparison between them. WR and absolute peak VO_2 were significantly lower in CHF+COPD when compared to CHF ($p<0.05$). As expected from pharmacological β-blocking use, both groups similarly presented with lower peak HR. Systolic and diastolic blood pressure was higher in the CHF group when compared to the CHF+COPD group ($p<0.05$). The CHF+COPD group demonstrated a significantly lower peak O_2 pulse and rate-pressure product (RPP) compared to the CHF+COPD. In addition, a significant difference in CP was found, again being significantly lower in the CHF+COPD group ($p<0.05$).

Similar ventilatory responses were found between groups; however, minute-ventilation was higher in the CHF group. The V_E/MVV ratio was 0.49 ± 0.16 and 0.53 ± 0.17 in the CHF and CHF+COPD, respectively, and both groups presented with a higher V_E/VCO_2 slope. A low OUES was also observed in both groups. Ventilatory power was significantly higher in the CHF +COPD group when compared with CHF group ($p<0.05$). No significant difference was found in peak SpO_2 between groups; however, dyspnea and leg fatigue were higher in CHF+COPD group ($p<0.05$). In both groups, the main reason for test termination was dyspnea.

Relationships Between Measures of Left Function, Right Function, ELVH Pattern, Clinical Characteristics and Exercise Responses

We found associations between key components of left and right cardiac function and CPET variables. For the

Table 1 Anthropometric and Clinical Characteristics of Studied Subjects

Variables	CHF (n= 23)	CHF+COPD (n= 23)	p
Age, years	60 ± 9	68 ± 6	0.002
Gender, M/F (n)	18/5	23/0	0.03
Height, cm	169 ± 7	168 ± 7	0.46
Weight, kg	79 ± 15	74 ± 15	0.12
BMI, kg/m^2	27 ± 5	27 ± 7	0.92
Cardiac function			
Indexed LA volume, mL/m^2	39 ± 22	33 ± 15	0.37
Indexed RA volume, mL/m^2	35 ± 19	30 ± 19	0.57
Left ventricle measures			
Ejection Fraction, %	40 ± 5	38 ± 7	0.27
Dysfunction classification of LV, Mild/Moderate/Severe	13/9/1	8/12/3	0.27
Indexed LV mass, gm/m^2	138 (120–153)	143 (124–179)	0.40
Relative LV wall thickness	0.35 (0.28–0.39)	0.35 (0.31–0.37)	0.74
LVEDD, mm	62 ± 9	62 ± 6	0.91
LVESD, mm	45 ± 16	52 ± 8	0.16
Mitral E wave, cm/sec	65 ± 28	68 ± 23	0.78
Mitral A wave, cm/sec	61 ± 23	76 ± 24	0.14
Mitral e' wave, cm/sec	8.9 ± 2	7.1 ± 2	0.04
Mitral a' wave, cm/sec	9.5 ± 2	9.5 ± 3	0.97
Mitral S wave, cm/sec	7.4 ± 1	7.7 ± 2	0.71
E/A ratio. cm/sec	1.0 ± 0.3	0.9 ± 0.6	0.76
E/e' ratio. cm/sec	8.6 ± 3	10.3 ± 4	0.30
Right ventricle measures			
RVD, mm	37 ± 4	30 ± 7	0.005
Tricuspid E wave, cm/sec	47 ± 11	41 ± 11	0.24
Tricuspid A wave, cm/sec	41 ± 13	47 ± 6	0.31
Tricuspid e' wave, cm/sec	11 ± 3	11 ± 2	0.99
Tricuspid a' wave, cm/sec	12 ± 5	13 ± 2	0.54
Tricuspid S wave, cm/sec	11 ± 2	11 ± 2	0.71
E/A ratio. cm/sec	1.3 ± 0.6	0.8 ± 0.2	0.03
E/e' ratio. cm/sec	4.6 ± 1.0	3.4 ± 0.8	0.04
Pulmonary function			
FEV_1, L/s	2.7 ± 0.7	2.0 ± 0.5	<0.001
FEV_1, %	79 ± 21	65 ± 17	0.01
FVC, L/s	3.5 ± 0.9	3.3 ± 0.7	0.50
FVC, %	85 ± 12	84 ± 19	0.71
FEV_1/FVC, L/s	0.78 ± 0.04	0.58± 0.11	<0.001
GOLD Stage, I/II/III/IV	–	8/11/4/0	–
MVV, L	103 ± 27	76 ± 21	0.001
RV, L/s	2.4 ± 0.7	3.0 ± 0.9	0.04
RV, $\%_{pred}$	109± 38	136 ± 44	0.08
TLC, L/s	4.5 ± 1.4	5.8 ± 1.1	0.004
TLC, $\%_{pred}$	74 ± 21	93 ± 23	0.01
RV/TLC, %	0.51 ± 0.13	0.51 ± 0.10	0.83
IC, L/s	1.8 ± 0.6	2.2 ± 1.1	0.14
IC, $\%_{pred}$	63 ± 28	63 ± 26	0.98
DLCO	20 ± 4	14 ± 5	0.002
DLCO, %	78 ± 12	52 ± 12	<0.001

(*Continued*)

Table 1 (Continued).

Variables	CHF (n= 23)	CHF+COPD (n= 23)	p
Functional classification			
NYHA functional class, I/II/II/IV	9/10/4/0	9/9/5/0	0.72
mMRC dyspnoea score, 0/I/II/III/IV	–	2/8/7/2/4	–
Medications			
LABA, n (%)	0 (0)	8(34)	–
SABA, n (%)	0 (0)	3(13)	–
LAMA, n (%)	0 (0)	10(43)	–
Beta-blockers, n (%)	22 (96)	22 (96)	0.31
ACE inhibitors, n (%)	9 (39)	16 (69)	0.07
Diuretics, n (%)	22 (96)	11 (47)	<0.001
Comorbidities			
Hypertension, n (%)	18 (78)	20 (86)	0.13
DM, n (%)	9 (39)	10 (43)	0.86
CI, n (%)	3 (13)	4 (17)	0.72
Dyslipidemia, n (%)	10 (43)	14 (60)	0.30
Others, n (%)	17 (73)	13 (56)	0.14

Note: Used Unpaired Student's *t* test for continuous variables and used chi-square test for categorical variables.
Abbreviations: CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; M, male; F, female; BMI, body mass index; LA, left atrium; RA, right atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RVD, right ventricle diameter; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity; MVV, maximal voluntary ventilation; RV, residual volume; TLC, total lung capacity; IC, inspiratory capacity; DLCO, diffusion capacity carbon monoxide; NYHA, New York Heart Association; mMRC, modified Medical Research Council scale; LABA, long-acting β2 adrenoceptor agonist; SABA, short-acting beta-agonists; LAMA, long-acting muscarinic antagonists; ACE, angiotensin converting enzyme; DM, diabetes mellitus; CI, coronary insufficiency.

CHF group (Figure 2), significant correlations were observed between VP and RWT (r: 0.45 p: 0.03) and V_E/VCO_2 intercept and Mitral E/e' ratio (r: 0.70 p: 0.003). In the CHF+COPD group (Figure 3), significant correlations were found between Indexed LV mass and RPP (r: −0.47; p: 0.02) and relative VO_2 and RVD (r: −0.62; p: 0.001).

Discussion

This is the first study that investigated the exercise responses of CHF patients with confirmed eccentric left ventricular hypertrophy and, in a group, the coexistence of COPD. The main original findings of the present investigation is that CHF+COPD led to a significantly poorer CPET response, including a lower work rate, peak VO_2, O_2 pulse, RPP, CP, and VP. In addition, we found correlations between VP and RWT and V_E/VCO_2 intercept and Mitral E/e' ratio, in the CHF group. In contrast, we found the CHF+COPD group presented with correlations between Indexed LV mass and RPP, relative VO_2 and RVD. These distinct correlations between groups indicate cardiac function and pattern of remodelling differently impacts the exercise response when CHF is present on isolation in comparison to the coexistence of CHF +COPD patients.

In relation to clinical and anthropometric variables, we can see that the groups were homogeneous; however, the CHF+COPD group was older than the CHF group and comprised of male subjects exclusively. Factors that can influence the VO_2 and maximal WR are age, sex, weight and height. In the Brazilian population, age had an important role in the decline of VO_2 peak and WR. Moreover, a greater reduction in males with aging may have influenced the differences found between groups with respect to VO_2 peak, maximal predicted VO_2, WR and predicted WR.[35] However, compared to the clinical condition, association of other comorbidities and level of physical activity, we believe age and sex were not the main influencing factors for the significant limitations observed in exercise capacity (see study limitations section)

According to Weber rating, in both groups peak VO_2 presented with a compatible worse prognosis.[36] Eccentric hypertrophy and higher left ventricular end diastolic diameter in both groups was indicative of advanced CHF.[37] Given the influence of cardiac output on aerobic capacity, eccentric hypertrophy remodeling and associated reduced

Table 2 Comparison Between Group Responses to Incremental CPET

Variables	CHF (n=23)	CHF+COPD (n=23)	p
Work rate, Watts	86 ± 30	57 ± 18	<0.001
Work rate $_{predicted,}$ Watts	130±29	109±23	0.01
Work rate $_{\% \text{ of predicted,}}$ %	66±20	54±18	0.05
Metabolic responses			
$VO_{2\ predicted,}$ mL.min	1907 ± 423	1603 ± 299	0.008
$VO_{2\ peak,}$ mL.min	1109 ± 349	847 ± 307	0.01
$VO_{2\% \text{ of predicted,}}$ %	57 ± 12	53 ±18	0.43
$VO_{2\ peak,}$ $mL.kg^{-1}.min^{-1}$	13.3 (11.0–15.4)	13.7 (10.9–14.7)	0.32
VO_2/WR, mL.min.W	13 ± 3	15 ± 4	0.16
VCO_2, mL.min	1232 ± 439	792 ± 348	0.003
RER $_{peak}$	1.09 ± 0.11	1.05 ± 0.09	0.19
Cardiovascular responses			
HR $_{rest}$, bpm	73 ± 10	91 ± 6	<0.001
HR $_{maximal,}$ bpm	159 ± 9	152 ± 6	0.002
HR $_{peak}$, bpm	121 ± 18	112 ± 25	0.17
HR $_{\% \text{ of maximal}}$	76 ± 11	74 ± 17	0.63
HR $_{rec}$, bpm	107±21	106 ±22	0.90
Δ $HR_{rec,}$ bpm	26± 20	23 ± 17	0.68
SBP_{rest}, mmHg	122 ± 13	116 ± 20	0.24
DBP_{rest}, mmHg	81 ± 8	76 ± 11	0.11
SBP_{peak}, mmHg	200 ± 31	168 ± 46	0.008
DBP_{peak}, mmHg	112 ± 15	97 ± 25	0.01
Peak O_2 pulse, mL/beat	10 ± 3	5 ± 2	<0.001
RPP, bpm.mmHg	24,516± 5887	19,391 ± 8157	0.01
CP, mmHg.mL.kg^{-1} min^{-1}	2730 ± 768	2051 ± 735	0.004
Ventilatory responses			
V_E, L.min	50 ± 17	39 ± 16	0.03
V_E/MVV, L.min	0.49 ± 0.16	0.53 ± 17	0.45
V_E/VCO_2 slope	37 ± 6	38 ± 15	0.68
V_E/VCO_2 intercept, L/minute	1.2 ± 1	2.2 ± 3	0.35
OUES	1.39 ± 0.3	1.21 ± 0.5	0.20
VP, mmHg	5.6 (4.9–6.1)	3.7 (3.1–5.8)	0.005
Gas exchange responses			
SaO_{2rest}, %	95 ± 1	95 ± 2	0.23
SaO_{2peak}, %	94 ± 3	94 ± 2	0.63
Perception of symptoms			
Peak dyspnea score, 0–10	4 ± 3	7 ± 2	0.01
Peak leg effort score, 0–10	3 ± 2	6 ± 3	0.01

Note: Used unpaired Student's *t* test.

Abbreviations: CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; VO_2, oxygen uptake; VCO_2, carbon dioxide output; RER, respiratory exchange ratio; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPP, rate-pressure product; CP, circulatory power; VE, ventilation; MVV, maximal voluntary ventilation; V_E/VCO_2 slope, linear relation between minute ventilation and carbon dioxide output; OUES, linear relationship between oxygen uptake and minute ventilation; VP, ventilatory power; SaO_2, peripheral saturation of O_2.

LV function certainly contributes to an impaired CPET response, as observed in the present study.[38] In addition, the heart's incapacity to deliver O_2 may also arise from secondary complications, such as vascular or pulmonary complications. Another important factor that may have contributed to worsening peak VO_2 values in patients in the current study is potential hyperinflation that raises intrathoracic pressure, which is associated with reduced

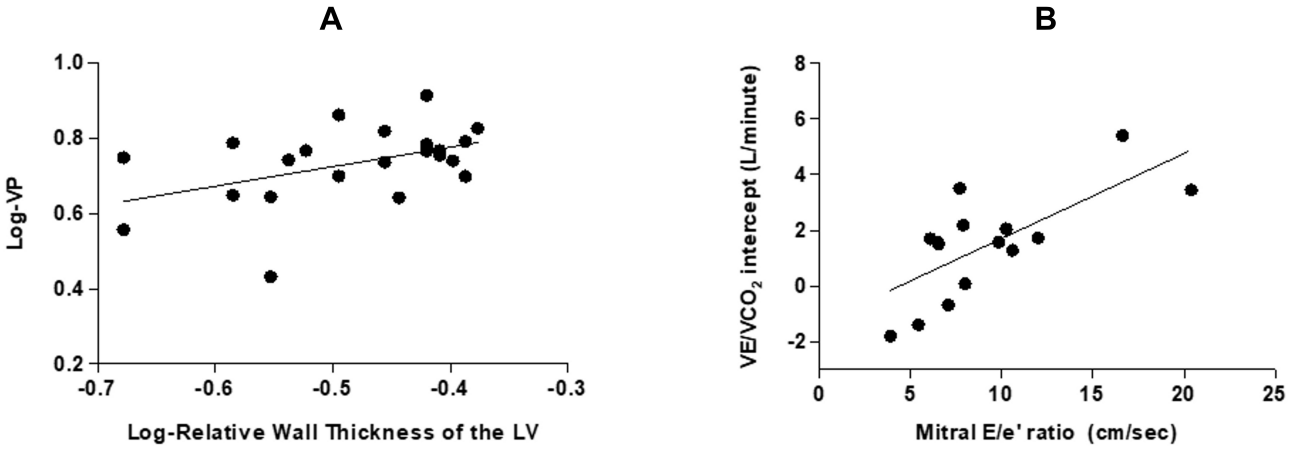

Figure 2 Correlation between cardiac function and CPET responses in CHF group; Used Pearson correlation coefficient. LV, left ventricle; In (**A**) relationship between log-ventilatory power and log-relative wall thickness (r: 0.45 p: 0.03); (**B**) relationship between V_E/VCO_2 intercept and Mitral E/e' ratio (r: 0.70 p: 0.003).

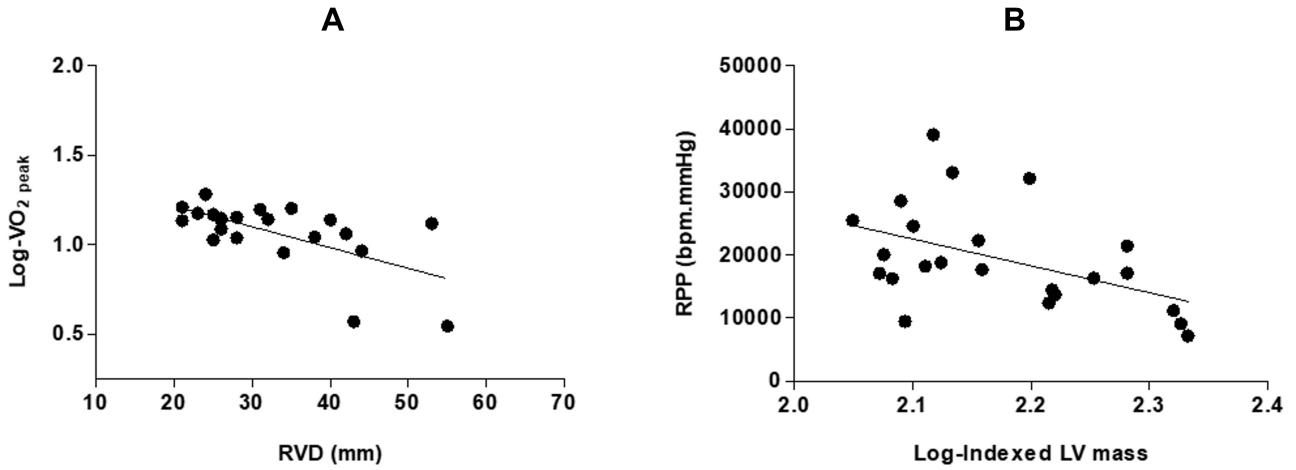

Figure 3 Correlation between cardiac function and CPET responses in CHF+COPD group; Used Pearson correlation coefficient. LV, left ventricle; In (**A**) log-relative VO_2 and right ventricle diameter (r: −0.47; p: 0.02); (**B**) log-indexed LV mass and rate pressure product (r: −0.62; p: 0.001).

left ventricular end-diastolic volume, stroke volume and cardiac output.[39] The CHF+COPD group obtained worse values of absolute peak VO_2, which is also potentially associated with a reduced pulmonary diffusing capacity, as indicated by the DLCO response. COPD leads to pulmonary alveolar and vascular destruction, promoting to increased inefficiency between ventilation - perfusion, thus decreasing lung diffusion capacity.[40]

In one study with 644 patients followed for 48 months, Myers et al determined cut-off points for risk stratification through peak VO_2, showing that patients that reach a cut-off between 10 and 18 $mL.kg.min^{-1}$ have a worse diagnosis.[41] In our study, both groups presented average values of peak VO_2 below 18 $mL.kg^{-1}.min^{-1}$, reflecting a worse prognosis. Hemodynamic abnormalities arise in patients with CHF+COPD, due to increased intrathoracic pressure resulting from hyperinflation leading to a reduced gradient for venous return. Moreover, an increase in right ventricular afterload may occur due to pulmonary vasoconstriction caused by hypoxemia and posteriorly hypercapnia.[42,43] Patients in the group CHF+COPD presented with worse values when compared to the CHF group in the variables that reflect hemodynamic function. Peak RPP and O_2 pulse were significantly lower in individuals with overlap, showing poor cardiac function. Both variables are heavily dependent on VO_2 and stroke volume, while arteriovenous O_2 difference does not change significantly. The association of the two conditions (CHF leading to direct changes in the myocardial structure and the change in lung volumes resulting from COPD

directly affecting the ventricular diastolic function) leads to a greater impairment of systolic volume and function, thus changing the volume of blood ejected and consequently the supply of systemic O_2.[39,44]

For CP, Goulart et al recently suggested cut-off values for predicting adverse events in patients with CHF+COPD, being that individuals with values lower than 2383 mmHg. mL/kg^{-1} min^{-1}, are more likely to be hospitalized.[45] Patients with CHF+COPD, in the current study, presented with average values below this threshold; 65% of the CHF +COPD patients were below the cut-off values whereas, in the CHF group, only 40% of the patients were below the threshold. This reflects worse central and peripheral cardiac function, representing the relationship between the blood flow generated by the heart and peripheral perfusion pressure.[46] In patients with CHF+COPD, the presence of low cardiac output due to negative cardiopulmonary interactions associated with impaired central hemodynamics and abnormalities in peripheral vascular control and sympathetic overexcitation may also contribute to a decreased CP.[47]

Patients with overlap syndrome present with impaired exercise capacity due to an increased ventilatory response to metabolic demand.[48] The physiological determinants are already widely studied - the dynamic hyperinflation, inspiratory constraints and lower tidal volume contribute to ventilatory inefficiency.[49,50] Interestingly, with respect to ventilatory inefficiency, both groups showed similar responses, except for VP, which was reduced in the CHF-COPD group. Similar responses between groups are possible because patients with advanced CHF have lower changes in lung volume compared to variations in transpulmonary pressure and other factors such as: 1) accumulation of extravascular water in the lung; 2) pulmonary congestion; 3) septal thickening; 4) pulmonary compression due to heart enlargement; and; 5) in some patients, weakness of the inspiratory musculature leading to increased dead-space, low tidal volume, increased ventilation, hypocapnia and inefficient gas exchange.[51–53] Another important factor that may have contributed to similar ventilatory responses between groups is the fact that the CHF+COPD group was mostly comprised of individuals in GOLD I–II stages, indicative of less severe ventilatory limitations (as observed in the variables V_E /MMV, V_E/VCO_2 slope, V_E/VCO_2 intercept and OUES). As such, exercise limitations may have been more reliant on cardiovascular and skeletal muscle dysfunction. The VP in our study was less in the CHF+COPD group as expected in this population. This variable reflects peak cardiac output, alveolar perfusion, peripheral perfusion, and skeletal muscle chemo- and afferent-reflexes, which in the presence of COPD in moderate-to-very severe stages is more impaired. There are currently no established threshold values for patients with CHF+COPD; however, CHF patients with values below 3.5 mmHg indicate a worse prognosis. In our study, only 4% of our sample of patients with CHF were below this value, whereas in the CHF+COPD group, 30% of the individuals had a VP less than 3.5.[33]

Systemic cardiocirculatory maladjustments were apparent in both groups, with CHF+COPD patients demonstrating a more prominent phenotype. Muscle weakness is the most common systemic effect, in which is a result of the chronic processes in both conditions where there is an imbalance between the synthesis and degradation of muscle protein leading to sarcopenia and subsequent cachexia. These peripheral impairments produce loss of muscle strength and endurance that directly impacts in respiratory function, exercise intolerance, health status and mortality.[54–56] Our patients with CHF+COPD presented with a worse perception of symptoms, being that dyspnea and fatigue were the main causes for test termination.

Eccentric left ventricular hypertrophy is an adaptation that involves a complex process of modifications in cardiac structure, signaling, transcriptional, electrophysiological, metabolic, and functional events within the growing cardiac cell.[57] The hypertrophic growth of the myocardium is a compensatory mechanism that helps maintain cardiac contractility; however, some authors believe that this adaptation leads to an increase in mortality due to cardiovascular causes.[58] We found that left and right cardiac function and eccentric left ventricular hypertrophy appear influence exercise responses differently, depending on whether or not a patient with CHF has coexisting COPD. For the CHF cohort, our results indicate that global cardiac function has an effect on exercise responses. However, in the CHF+COPD group, the exercises responses are influenced by cardiac function differently.

In CHF group, we observed that RWT positively influenced VP. A lower RWT associated with an increase in LV mass suggests greater CHF severity. In these patients, reduced RWT associated with increased LV mass results in loss of myocardial contractility, so the heart is unable to maintain its normal pumping function, thereby decreasing cardiac output.[37] During high-intensity exercise, reduced cardiac function can lead to pulmonary congestion, which,

associated with higher pulmonary arterial pressure and pulmonary vascular resistance, increases ventilation-perfusion mismatch, producing ventilatory inefficiency and contributing to low values of PV.[59] We found a strong correlation between the V_E/VCO_2 intercept and Mitral E/e' ratio in the CHF group. These variables, respectively, reflect the V_E versus VCO_2 relationship (representing one index of ventilatory efficiency during exercise) and LV filling pressures. Individuals with increased filling pressures may present with changes in LV relaxation and diastolic dysfunction, which can lead to changes in pulmonary capillary wedge pressure compromising the ventilation at the beginning of the exercise.[50,60]

For CHF+COPD group, we found one important correlation between RVD and relative VO_2. The increased RV diameter suggests dilation, which is the first indicator of increased pulmonary resistance. An increased pulmonary vascular resistance leads to pulmonary hypertension and consequent impairment of systemic oxygen supply.[61] Burgess et al conducted a study with 87 COPD patients, with the aim of verifying whether echocardiographic markers of RV function could determine prognosis. Findings indicated that RV dimensions, RV area, and Doppler indices were all strongly associated with survival.[62,63] For individuals with CHF+COPD, a higher LV mass may negatively influence RPP because when maladaptive eccentric left ventricular hypertrophy occurs, myocardial oxygen uptake increases, leading to the exhaustion of coronary blood flow reserve. In this context, changes in coronary microcirculation may lead to a loss of myocytes and myocardial fibrosis in addition to myocardial perfusion impairment.[64–66]

Study Limitations

The main limitation in our study is the sample size in both groups; however, we managed to reach 88% of the a priori sample calculation. However, it is important to consider that in the present study, all patients presented with similar conditions of CHF, including reduced or borderline EF and left ventricular shape and cardiac geometry (ie, eccentric hypertrophy), which contrasts other published studies that did not consider these measures to assess patients with CHF+COPD. In addition, we consider it important to note that our findings are limited to men with CHF +COPD. However, in order to mitigate this bias, knowing that some variables could be influenced by sex, we performed a Spearman Correlation coefficient analysis and found no correlation with the variables analyzed (WR, absolute VO_2, RPP, O_2 pulse, CP, VP). Another important factor that is known to influence variables is age that was different between groups; however, we performed a linear regression analysis to verify the influence of age on CPET variables that differed. We verified that age had a weak but significant influence on absolute VO_2 (R^2:0.16 p: 0.006) and O_2 pulse (R^2:0.15 p: 0.006).

In conclusion, the coexistence of CHF+COPD induced marked impairment of exercise capacity as well as ventilatory and circulatory inefficiency, all negatively impacting functional capacity, exertional symptoms and quality of life. Moreover, given our findings related to cardiac function and geometry and exercise responses, left and right cardiac function, LV mass and RWT measured at rest may provide important information to guide treatment decisions for these patients with the goal of improving exercise performance and functional capacity.

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Authorship Contribution Statement

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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