











Comparing cardiac function and structure and their relationship with exercise capacity between patients with stable COPD and recent acute exacerbation: a cross-sectional study

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ABSTRACT

Objective: Patients with COPD are prone to cardiac remodeling; however, little is known about cardiac function in patients recovering from an acute exacerbation of COPD (AECOPD) and its association with exercise capacity. The aim of this study was to evaluate the cardiac function and structure and to compare their relationship with exercise capacity in patients with a recent AECOPD and patients with clinically stable COPD. **Methods:** This was a cross-sectional study including 40 COPD patients equally divided into two groups: recent AECOPD group (AEG) and clinically stable COPD group (STG). Echocardiography was performed to assess cardiac function and chamber structure. The six-minute walk distance (6MWD) and the Duke Activity Status Index (estimated Vo_2) were used in order to assess exercise capacity. **Results:** No significant differences in cardiac function and structure were found between the groups. The 6MWD was associated with early/late diastolic mitral filling velocity ratio ($r = 0.50$; $p < 0.01$), left ventricular posterior wall thickness ($r = -0.33$; $p = 0.03$), and right atrium volume index ($r = -0.34$; $p = 0.04$), whereas Vo_2 was associated with right atrium volume index ($r = -0.40$; $p = 0.02$). **Conclusions:** Regardless of the clinical condition (recent AECOPD vs. stable COPD), the cardiac function and structure were similar between the groups, and exercise capacity (determined by the 6MWD and Vo_2) was associated with cardiac features.

Keywords: Pulmonary disease, chronic obstructive; Echocardiography; Walk test; Pulmonary medicine.

INTRODUCTION

COPD is already the third leading cause of death worldwide, causing 3.23 million deaths in 2019.⁽¹⁾ Acute exacerbation of COPD (AECOPD) is a common event in the clinical course of the disease, imposing a general increase in physiological stress toward a homeostatic imbalance,⁽²⁾ and has been associated with an increased risk of cardiovascular events.⁽³⁾ In a recent study⁽³⁾ with a cohort of 16,485 COPD patients, the greatest risk was demonstrated especially within the first 30 days after the exacerbation; high concentrations of circulating proinflammatory biomarkers, which can be slow to return to baseline levels, are one of the plausible explanations.

Echocardiography findings have also demonstrated that lung hyperinflation affects pulmonary hemodynamics and, consequently, cardiac function.^(4,5) In a study of hospitalized patients with AECOPD, evidence of pulmonary arterial hypertension was found in all patients evaluated, and there was evidence of right ventricle (RV) enlargement and decline in RV systolic function.⁽⁶⁾ In a previous study in which COPD patients were evaluated at least three months after hospital discharge from their first admission for an exacerbation, cardiac alterations were found in 64% of the patients (left and right cardiac disorders in 27% and 48%, respectively), and the

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most common abnormalities were RV enlargement (in 30%) and pulmonary hypertension (in 19%).⁽⁷⁾ The authors showed that echocardiographic abnormalities were unrelated to COPD severity and that they were highly prevalent in patients with moderate-to-severe COPD, even among those with unknown cardiac disease or cardiovascular risk factors other than smoking.

Previous studies^(8,9) have shown that an AECOPD has a negative impact on physical activity, and although there is improvement after hospital discharge, it still remains low in relation to clinically stable patients. This decrease in physical activity levels found in patients with an AECOPD increases the risk of a new hospital admission and has a negative impact on the emergence and advance of comorbidities.⁽¹⁰⁾

In this context, regardless of the clinical status, there is evidence of impaired cardiac function and structure in COPD patients^(6,7); however, to the best of our knowledge, no studies investigated the period shortly after an AECOPD and its possible relationship with exercise capacity. These results can support rehabilitation and health care strategies for COPD patients at different stages of the disease. Therefore, the aim of this study was to evaluate both cardiac function and structure and to compare their relationship with exercise capacity in patients with clinically stable COPD and patients with a recent AECOPD. We hypothesized that patients recovering from an AECOPD would have a similar cardiac structure but worse cardiac function when compared with patients with clinically stable COPD. Furthermore, we hypothesized that cardiac function and structure would be significantly associated with exercise capacity.

METHODS

Study design and population

This was a cross-sectional study including 40 patients diagnosed with COPD⁽²⁾ and ≥ 40 years of age regardless of the sex. Patients were evaluated between February of 2016 and March of 2020 and allocated into two groups: recent AECOPD group (AEG) and clinically stable COPD group (STG). Groups were matched in terms of age and sex. No patients were allocated into the two groups at any time.

The AEG comprised recently hospitalized patients who received standard pharmacological therapy during hospitalization⁽²⁾ without requiring ICU admission or mechanical ventilation; these patients were screened at the University Hospital of the Federal University of São Carlos, located in the city of São Carlos, Brazil. The STG consisted of patients with no exacerbation episodes for at least three months who were selected at the *Ambulatório de Pneumologia do Centro de Especialidades Médicas* (Pulmonology Outpatient Clinic of the Center of Medical Specialties) in the city of São Carlos, at the *Unidade Saúde Escola* (Health School Unit), or from the *Laboratório de Fisioterapia Cardiopulmonar* (Laboratory of Cardiopulmonary

Physiotherapy) database, the latter two being part of the Federal University of São Carlos.

The exclusion criteria were as follows: being heavy alcohol drinkers; having uncontrolled hypertension, uncontrolled diabetes mellitus, concomitant respiratory diseases, unstable angina, recent cardiac events (within the last six months), reduced left ventricular (LV) ejection fraction ($< 50\%$), heart valve disease, cardiac pacemaker, cardiac arrhythmias, chronic kidney disease, cancer, neurological conditions, or orthopedic conditions; participating in a regular exercise program within the last six months; and being unable to perform experimental procedures.

This study is in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee at the Federal University of São Carlos (no. 46431415.0.0000.5504; approval no. 2015/1220983). All patients gave written informed consent.

Experimental procedures

Assessments were performed on two separate days with an interval of 24-48 h between them. On the first day, patients underwent an initial evaluation comprising anamnesis, physical examination, electrocardiogram, modified Medical Research Council dyspnea scale,⁽¹¹⁾ COPD Assessment Test (CAT),⁽¹²⁾ Saint George's Respiratory Questionnaire (SGRQ),⁽¹³⁾ Duke Activity Status Index (DASI),^(14,15) and pulmonary function test. On the second day, patients underwent transthoracic echocardiography and the six-minute walk test (6MWT). For the AEG, the first assessment was preferably carried out 30 days after hospital admission due to the AECOPD, and a period of up to three days later was tolerated. All procedures were carried out in the afternoon, and the patients were instructed to abstain from caffeinated and alcoholic beverages or any other stimulants the night before and on the day of evaluation, as well as not to perform activities requiring moderate-to-heavy physical exertion the day before the application of the procedures.

Pulmonary function test

The pulmonary function test was performed using a calibrated spirometer (CPFS/S; Medical Graphics, Saint Paul, MN, USA). The parameters (FVC, FEV₁ and FEV₁/FVC ratio) were obtained 20 min after inhaling albuterol sulfate (400 μg).⁽¹⁶⁾ The results were compared with the predicted values,⁽¹⁷⁾ and COPD was confirmed when FEV₁/FVC < 0.7 ⁽²⁾; all of the patients were classified by severity of airflow limitation in accordance with the GOLD.⁽²⁾

Transthoracic echocardiography

To assess cardiac function and structure, transthoracic echocardiography was performed by a cardiologist, using an ultrasound device—a 3-MHz mechanical sector transducer—(HD11 XE; Phillips, Bothell, WA, USA) following the manufacturer recommendations.⁽¹⁸⁾

The aortic root diameter, left atrium (LA) diameter, LV end-diastolic diameter, LV end-systolic diameter,

interventricular septum (IVS) thickness, LV posterior wall thickness, and RV diameter were measured. The LA volume and right atrium (RA) volume were obtained and indexed by the body-surface area (LA volume index and RA volume index).⁽¹⁹⁾ The LV mass index was calculated using the following formula⁽²⁰⁾:

$$\text{LV mass index} = 0.8 \times \{1.04 \times [(\text{IVS thickness} + \text{LV end-diastolic diameter} + \text{LV posterior wall thickness})^3 - (\text{LV end-diastolic diameter})^3]\} + 0.6 / \text{body surface area}$$

Data were presented in absolute values, and reference values were presented for comparison purposes.^(21,22)

Tissue Doppler imaging was performed, and LV and RV functions were assessed; early diastolic mitral or tricuspid filling velocity (E wave) and late diastolic mitral or tricuspid filling velocity (A wave) were measured, and the E/A ratios were calculated. In addition, the S wave (atrial relaxation wave) and early diastolic mitral or tricuspid annular velocity (E' wave) were obtained; then, the ratios between the mitral and tricuspid E and E' velocities (E/E' ratios) were calculated. The LV ejection fraction was calculated using the Teichholz method. Data were presented in absolute values, and reference values were presented for comparison purposes.^(18,21)

Exercise capacity—DASI and 6MWT

Exercise capacity was evaluated by the six-minute walk distance (6MWD) and by the estimated Vo_2 derived from the DASI questionnaire ($\text{Vo}_2 = 0.43 \times \text{DASI score} + 9.6$).⁽¹⁵⁾

The 6MWT was performed following international recommendations.⁽²³⁾ Dyspnea and lower limb fatigue were assessed by the 0-10 Borg scale.⁽²⁴⁾ HR was monitored with an HR monitor (Polar, Kempele, Finland), and SpO_2 was measured by pulse oximetry (UT-100 MR; Rossmax Inc. Ltd., Shanghai, China) at rest, at every minute, at peak, and 1 min after recovery. Blood pressure was measured at rest and at peak with a sphygmomanometer (BD, São Paulo, Brazil).

The 6MWD was presented in meters and in % of the predicted values.⁽²⁵⁾ The criteria for test termination were as follows: chest pain, intolerable dyspnea, leg cramps, excessive diaphoresis, pale or ashen appearance, HR > 85% of maximum HR (220 – age for men; 210 – age for women), or $\text{SpO}_2 < 85\%$ (oxygen was administered in these cases).⁽²³⁾

Statistical analysis

Using the G*Power software package, version 3.1.9.2 (Kiel, Germany), the sample size was calculated based on pilot studies using the association between the mitral E/A ratio and the 6MWD (10 patients in each group). To reach statistical significance ($p < 0.05$) at a power of 80%, a minimum sample of 16 patients (8 in each group) was required. Due to the fact that this study is part of a more extensive one, we chose

to include a larger sample ($n = 40$) than necessary, thus making the results more robust.

For all statistical analysis, the SigmaPlot, version 11.0, was used (Systat Software, San Jose, CA, USA). The Shapiro-Wilk test was used in order to investigate data distribution. Continuous quantitative variables were expressed as means \pm standard deviations or medians (interquartile ranges), whereas discrete quantitative variables were expressed as absolute and relative frequencies. To compare continuous quantitative variables between the groups, the unpaired Student's t-test was used, whereas to compare discrete quantitative variables, the Fisher's exact test was used. The Pearson's correlation analysis was applied to assess the association of cardiac function and structure with exercise capacity. A value of $p < 0.05$ was considered significant.

RESULTS

We observed a prevalence of male patients in both groups. The AEG had lower values in weight, diastolic blood pressure, CAT scores, DASI scores, estimated Vo_2 , FVC (in % of predicted values), and FEV_1 (in absolute and in % of predicted values), and it had higher values in SGRQ scores (symptoms, activity, and total score) when compared with the STG. The number of patients with mild disease, in accordance with the GOLD classification, and of those receiving short-acting β -agonists or long-acting β -agonists was higher in the STG in comparison with the AEG. Regarding the 6MWT, both groups presented low values of 6MWD (in % of predicted); however, the AEG had a lower 6MWD mean both in absolute and in % of predicted values when compared with the STG (Table 1).

Echocardiographic data for both groups are shown in Table 2. No significant differences were observed in the values obtained in terms of cardiac function and structure between the groups.

By means of the relationship of cardiac function and structure with exercise capacity, we found a positive correlation between the mitral E/A ratio and the 6MWD ($r = 0.50$; $p < 0.01$) and negative correlations between the LV posterior wall thickness and 6MWD ($r = -0.33$; $p = 0.03$), between RA volume index and 6MWD ($r = -0.34$; $p = 0.04$), and between RA volume index and estimated Vo_2 ($r = -0.40$; $p = 0.02$; Figure 1).

DISCUSSION

The present study evaluated the cardiac function and structure and compared their relationship with exercise capacity in two groups of patients in different clinical phases of COPD: those who were recently recovering from a recent AECOPD and those who were clinically stable. Our findings demonstrated that the cardiac function and structure were similar in patients recovering from an AECOPD (30 days after the exacerbation) and in those who had been clinically stable (for at least three months). Additionally, a positive association

Table 1. Characteristics of the patients studied (N = 40).^a

Characteristic	Total	Group		p
		AEG n = 20	STG n = 20	
Age, years	67.6 ± 8.7	68.9 ± 8.3	66.4 ± 9.3	0.38
Male sex	22 (55)	11 (55)	11 (55)	1.00
Anthropometry				
Weight, kg	66.9 ± 18.2	60.0 ± 12.1	73.7 ± 20.8*	0.01
Height, m	1.61 ± 0.09	1.60 ± 0.10	1.61 ± 0.08	0.55
BMI, kg/m ²	25.7 ± 7.2	23.5 ± 4.6	27.9 ± 8.8	0.05
Clinical data				
HR, bpm	78.5 ± 14.0	82.4 ± 16.9	74.6 ± 9.2	0.07
Systolic BP, mmHg	120.7 ± 15.3	119.8 ± 17.3	121.7 ± 13.4	0.69
Diastolic BP, mmHg	76.8 ± 10.0	73.1 ± 10.0	80.4 ± 8.7*	0.01
SpO ₂ , %	93.1 ± 3.9	92.9 ± 4.0	93.3 ± 3.8	0.68
Supplemental oxygen	3 (7.5)	3 (15.0)	0 (0.0)	0.23
Risk factors				
Hypertension	22 (55)	12 (60)	10 (50)	0.75
Diabetes mellitus	3 (8)	2 (10)	1 (5)	1.00
Myocardial infarction	1 (2.5)	1 (5.0)	0 (0.0)	1.00
Current smokers	14 (35)	8 (40)	6 (30)	0.74
Former smokers	26 (65)	12 (60)	14 (70)	0.74
Smoking history, pack-years	60.4 ± 61.2	56.1 ± 47.3	64.4 ± 73.2	0.67
mMRC score	2 [1-2]	2 [1-3]	1 [1-2]	0.14
CAT score	15.4 ± 8.5	18.5 ± 6.9	12.65 ± 8.9*	0.03
SGRQ score				
Symptoms domain	41.0 ± 22.4	54.3 ± 20.4	31.1 ± 18.6*	< 0.01
Activity domain	61.4 ± 25.8	73.1 ± 19.1	52.6 ± 27.1*	0.01
Psychosocial impact domain	35.2 ± 20.2	38.8 ± 20.9	32.4 ± 19.7	0.36
Total	44.2 ± 18.4	51.8 ± 14.1	38.4 ± 19.4*	0.03
DASI				
Estimated Vo _{2max} , mL · kg ⁻¹ · in ⁻¹	21.8 ± 5.8	19.4 ± 4.9	24.1 ± 5.7*	< 0.01
DASI score	28.3 ± 13.4	22.9 ± 11.5	33.7 ± 13.2*	< 0.01
Pulmonary function				
FVC, % of predicted	84.0 ± 25.0	70.0 ± 20.1	95.7 ± 22.9*	< 0.01
FEV ₁ , L	1.3 ± 0.6	1.0 ± 0.3	1.5 ± 0.7*	0.01
FEV ₁ , % of predicted	53.6 ± 20.5	43.8 ± 11.8	63.8 ± 22.9*	< 0.01
FEV ₁ /FVC	50.6 ± 15.0	48.2 ± 16.6	53.0 ± 12.9	0.32
GOLD 1	6 (15)	0 (0)	6 (30)*	0.02
GOLD 2	12 (30)	5 (25)	7 (35)	0.73
GOLD 3	20 (50)	13 (65)	7 (35)	0.11
GOLD 4	2 (5)	2 (10)	0 (0)	0.48
Medications				
Inhaled corticosteroid	4 (10)	4 (20)	0 (0)	0.10
SAMA	2 (5)	2 (10)	0 (0)	0.48
LAMA	6 (15)	4 (20)	2 (10)	0.66
SABA	17 (42.5)	4 (20)	13 (65)*	< 0.01
LABA	8 (20)	1 (5)	7 (35)*	0.04
Beta-blocker	2 (5)	0 (0)	2 (10)	0.48
Calcium channel blocker	1 (2.5)	1 (5)	0 (0)	1.0
ACE inhibitor	3 (7.5)	2 (10)	1 (5)	1.0
Diuretic	3 (7.5)	3 (15)	0 (0)	0.23
Hypoglycemic agent	3 (7.5)	2 (10)	1 (5)	1.0
6MWD, m	357.0 ± 121.5	305.2 ± 109.9	408.7 ± 112.1*	< 0.01
6MWD, % predicted	67.2 ± 22.6	57.9 ± 20.9	76.5 ± 20.7*	< 0.01

AEG: recent acute exacerbation of COPD group; STG: clinically stable COPD group; BP: blood pressure; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test; SGRQ: Saint George's Respiratory Questionnaire; DASI: Duke Activity Status Index; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting β-agonist; LABA: long-acting β-agonist; ACE: angiotensin converting enzyme; and 6MWD: six-minute walk distance. ^aValues expressed as n (%), mean ± SD, or median [IQR]. *Unpaired Student's t-test and Fisher's exact test.

Table 2. Echocardiographic data of the patients studied (N = 40).^a

Variable	Reference values	Total	Group		p*
			AEG n = 20	STG n = 20	
Structure					
Aortic root diameter, mm	22-36	33.1 ± 5.5	32.9 ± 6.2	33.4 ± 4.9	0.75
LA diameter, mm	F: 27-38 M: 30-40	36.6 ± 8.4	35.3 ± 7.0	37.9 ± 9.6	0.33
LV end-diastolic diameter, mm	F: 37.8-52.2 M: 42.0-58.4	45.3 ± 6.3	44.8 ± 5.6	45.9 ± 7.0	0.56
LV end-systolic diameter, mm	F: 21.6-34.8 M: 25.0-39.8	29.0 ± 5.8	28.2 ± 6.8	29.8 ± 4.6	0.37
IVS thickness, mm	F: 6-9 mm M: 6-10 mm	10.3 ± 2.0	10.7 ± 2.3	11.9 ± 8.0	0.52
LV mass index, g/m ²	F: 44-88 M: 50-102	103.5 ± 41.7	104.1 ± 39.2	102.9 ± 45.3	0.92
LV posterior wall thickness, mm	F: 6-9 mm M: 6-10 mm	11.3 ± 5.9	10.6 ± 2.2	10.1 ± 1.7	0.50
RV diameter, mm	25-41 mm	33.7 ± 7.2	35.6 ± 7.7	31.6 ± 6.2	0.09
LA volume index, mL/m ²	16-34	20.3 ± 7.7	21.2 ± 9.9	19.6 ± 5.3	0.56
RA volume index, mL/m ²	F: 21 ± 6 M: 25 ± 7	16.5 ± 5.3	18.2 ± 6.3	15.3 ± 4.1	0.11
LV function					
LV ejection fraction, %	≥ 50	67.4 ± 8.2	67.9 ± 9.3	66.9 ± 6.8	0.74
Mitral S wave, cm/s	≥ 8.2 ± 1.3	9.0 ± 2.3	8.9 ± 2.3	9.2 ± 2.3	0.75
Mitral E/A ratio	≥ 0.8 to ≤ 2.0	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.30
Mitral E/E' ratio	< 14	7.5 ± 2.8	7.6 ± 2.6	7.4 ± 3.1	0.82
RV function					
Tricuspid S wave, cm/s	≥ 9.5	13.7 ± 4.6	14.0 ± 6.1	13.4 ± 2.9	0.70
Tricuspid E/A ratio	≥ 0.8 to ≤ 2.0	1.0 ± 0.4	1.0 ± 0.5	0.9 ± 0.3	0.43
Tricuspid E/E' ratio	≤ 6	4.0 ± 1.9	4.3 ± 2.3	3.7 ± 1.5	0.41

AEG: recent acute exacerbation of COPD group; STG: clinically stable COPD group; LA: left atrium; F: female; M: male; LV: left ventricular; IVS: interventricular septum; RV: right ventricle; RA: right atrium; S wave: atrial relaxation wave; E/A: early diastolic mitral or tricuspid filling velocity/late diastolic mitral or tricuspid filling velocity; E/E': early diastolic mitral or tricuspid filling velocity/early diastolic mitral or tricuspid annular velocity. ^aValues expressed as mean ± SD. *Unpaired Student's t-test.

between the mitral E/A ratio and the 6MWD was demonstrated, as were negative associations between LV posterior wall thickness and 6MWD, between RA volume index and 6MWD, and between RA volume index and estimated \dot{V}_{O_2} .

The use of transthoracic echocardiography, which is a noninvasive and relatively inexpensive imaging technique, in the evaluation of COPD patients may help reveal more specific information about the right side of the heart, the presence of pulmonary arterial hypertension,⁽²⁶⁾ changes in LV geometry,⁽²⁷⁾ and, consequently, the cardiac function. These findings will contribute to the foundation of future interventional proposals, such as cardiopulmonary rehabilitation aimed at these different clinical phases of COPD. Furthermore, we were unaware of any study evaluating cardiac function and structure and their relationship with exercise capacity by comparing patients recently recovering from a recent AECOPD with clinically stable COPD patients, which made our findings extremely relevant, because this is an important subject for clinical practice in order to increase cardiovascular health care and attention in patients with pulmonary disease.

Although cardiac abnormalities are often associated with RV dysfunction due to underlying pulmonary hypertension in COPD patients,⁽²⁶⁾ the LV can also be impaired.⁽²⁸⁾ According to a recent study⁽²⁸⁾ that evaluated patients with clinically stable COPD, those with concentric LV hypertrophy were associated with an increase in the LA volume index, which represents an increase in the LV filling pressure as a consequence of diastolic dysfunction. Regarding cardiac damage due to AECOPD, one study⁽²⁹⁾ showed that this leads to pulmonary arterial hypertension, which negatively affects the RV, although the patients had no overt clinical RV failure. Pulmonary arterial hypertension stimulates RV hypertrophy in a compensatory attempt to maintain cardiac output; however, there may be an eventual maladaptive remodeling causing RV dilation in some patients.⁽³⁰⁾ Although we found no significant difference between the groups regarding the RV basal diameter (AEG: 35.6 mm vs. STG: 31.6 mm; $p = 0.09$), the AEG presented a higher mean value even after the 30-day period after the exacerbation. RV diameter is an extremely important parameter because it is able to identify patients with high-risk lung disease and

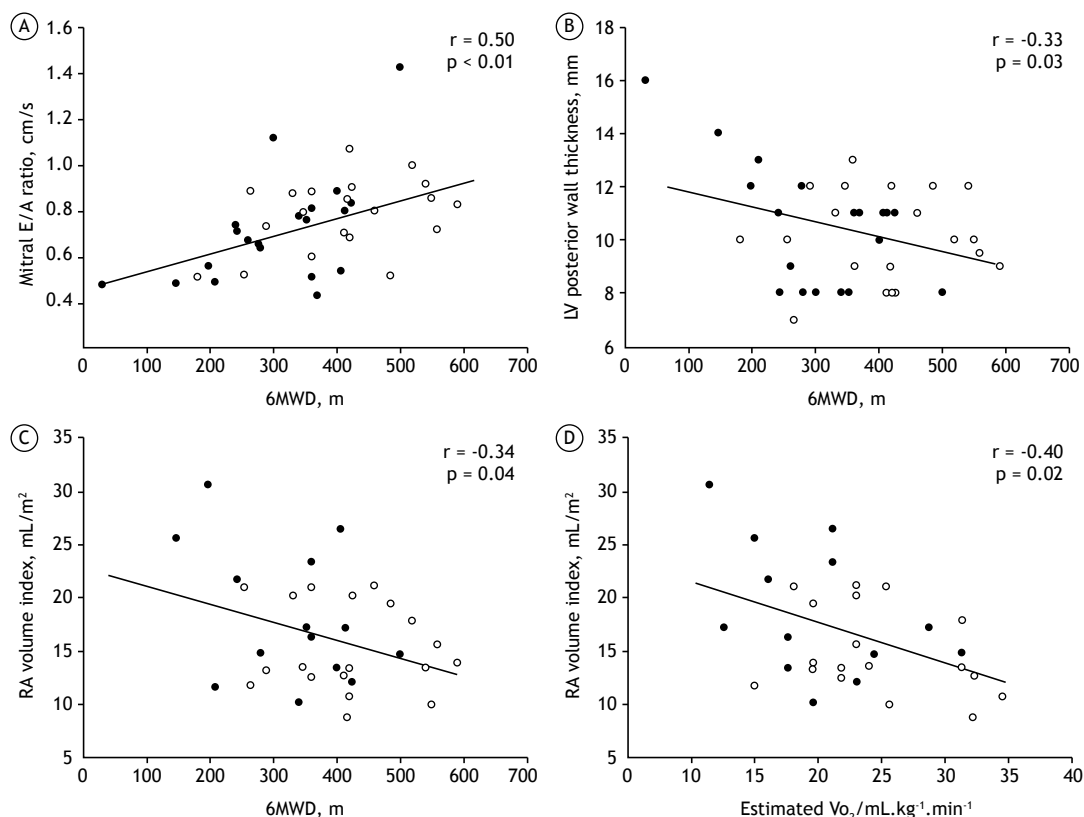


Figure 1. Correlations* between the group of patients with a recent acute exacerbation of COPD (●) and the group of patients with clinically stable COPD (○). In A, mitral E/A (early diastolic mitral filling velocity/late diastolic mitral filling velocity) ratio vs. the six-minute walk distance (6MWD). In B, left ventricular (LV) posterior wall thickness vs. 6MWD. In C, right atrium (RA) volume index (RA volume/body surface area) vs. 6MWD. In D, RA volume index vs. estimated Vo₂ estimated from the Duke Activity Status Index. *Pearson's correlation coefficient.

provides incremental prognostic information beyond that provided by clinical data.⁽³¹⁾

Our hypothesis was formulated because AECOPD imposes a general increase in physiological stress marked by increased airway resistance (due to bronchospasm, mucosal edema, and hypersecretion), which leads to an increase in end-expiratory lung volume above normal and, consequently, to dynamic lung hyperinflation.⁽³²⁾ As a result, cardiovascular effects can be observed, such as cardiac compression, intrathoracic hypovolemia, and reduced venous return due to the recruitment of abdominal expiratory muscles, impeding the normal increase in cardiac output during exercise.⁽³³⁾ A previous study⁽³⁴⁾ showed that LV and RV performance is impaired in patients with very severe COPD because of a small LV end-diastolic diameter and, consequently, a decreased biventricular preload, which was attributed to the intrathoracic hypovolemia caused by hyperinflated lungs. These findings led us to hypothesize that patients recovering from an AECOPD would have worse cardiac function when compared with patients in a stable clinical condition. However, no significant differences were found in cardiac function and structure between the patients who were recovering from a recent AECOPD and those who were clinically stable. One possible explanation for our findings may

be the fact that the hospitalized patients did not have respiratory failure that was significant enough to require invasive ventilatory support, causing little or no change in cardiac function. Therefore, the counterpoint is part of our hypothesis—that patients recovering from an AECOPD would have worse cardiac function when compared with stable patients. Furthermore, the cardiac changes mentioned in a previous study⁽⁶⁾ of COPD patients during the hospital phase could possibly have been transitory, and the period of 30 days after the exacerbation in our study may have been enough for these findings to normalize. On the other hand, another study⁽⁷⁾ that evaluated patients at least three months after hospital discharge from their due to the first admission for a COPD exacerbation revealed a high prevalence of both left and right echocardiographic abnormalities, even after excluding those with cardiovascular risk factors, and this prevalence was unrelated to COPD severity.

Our results clearly showed that, regardless of the clinical condition, COPD patients in general present with an impairment in the LV structure, as observed by the high values of IVS thickness (AEG: 10.7 mm vs. STG: 11.9 mm; $p = 0.52$), LV mass index (AEG: 104.1 g/m² vs. STG: 102.9 g/m²; $p = 0.92$), and LV posterior wall thickness (AEG: 10.6 mm vs. STG: 10.1 mm; $p =$

0.50) in comparison with the predicted values.⁽¹⁸⁾ We also observed a reduced value for the mitral E/A ratio in the AEG (i.e., 0.7) in comparison with the reference values (≥ 0.8), indicating an incipient/initial alteration in diastolic function.⁽²¹⁾

A particularly relevant finding of our study was the association of cardiac structure and ventricular function with exercise capacity regardless of whether the patients were recovering from an exacerbation or were clinically stable; regarding the cardiac structure, negative associations between LV posterior wall thickness and 6MWD, between RA volume index and 6MWD, and between RA volume index and estimated Vo_2 were found. The LV posterior wall thickness is a determinant factor of the stiffness and of the diastolic pressure of the LV, directly influencing ventricular relaxation⁽³⁵⁾; the RA volume index is an independent predictor of morbidity and can serve as a quantitative marker of RV dysfunction.⁽³⁶⁾ Thus, our results suggest that ventricular stiffness and increased filling pressure in both ventricular chambers may negatively influence exercise capacity, which was assessed by the 6MWD and Vo_2 (estimated from the DASI score).

We also observed a positive association between the mitral E/A ratio and the 6MWD; this result might indicate the possible influence of LV diastolic dysfunction on exercise capacity since a low mitral E/A ratio is indicative of impaired LV relaxation. Reduced exercise capacity in diastolic dysfunction results from a number of pathophysiological alterations, such as slow myocardial relaxation, reduced myocardial distensibility, elevated filling pressures, and reduced ventricular suction forces. These alterations limit the increase in ventricular diastolic filling and cardiac output during exercise, leading to pulmonary congestion.⁽³⁷⁾

Our results regarding the perception of dyspnea (modified Medical Research Council scale score) showed that the two groups were similar. On the other hand, the AEG had worse health status (CAT score and SGRQ symptoms, activity, and total scores) and worse estimated exercise capacity (DASI score and estimated Vo_2) when compared with the STG, corroborating a previous study.⁽⁸⁾ With respect to CAT, both groups were classified as moderate (a score of 10-20 points) according to the impact of COPD on the patient's life⁽¹²⁾; however, the AEG presented a significant difference in the lowest score (5.85; $p = 0.03$) in comparison with the STG. Our results showed that even 30 days after an AECOPD, health status and exercise capacity continued to be affected.

As for exercise capacity, we also observed that patients who had recently recovered from an AECOPD had worse 6MWD when compared with clinically stable patients, even 30 days after hospital discharge. A recent study⁽³⁸⁾ showed that performance on the 6MWT is able to predict exacerbations in COPD patients over two years, and patients with a 6MWD $\leq 80\%$ of the predicted value have more than twice the chance of having an exacerbation within two years when compared with those whose exercise capacity was preserved.

Our results showed that both groups had a 6MWD $< 80\%$ of the predicted, but the AEG presented a value of 18.6%, which was significantly lower in relation to that of the STG ($p < 0.01$), representing an absolute difference of 103.5 m. ($p < 0.01$). Thus, our results showed that a recent AECOPD further affected the reduction in exercise capacity, showing a minimal clinically important difference between the groups (estimated at 26 ± 2 m for COPD patients).⁽³⁹⁾ At the same time, another possible factor influencing these findings is the severity of COPD, as the AEG had the lowest FEV_1 (in absolute and in % of predicted values) when compared with the STG, a condition that has already been reported in a previous study⁽⁴⁰⁾ in which a positive association between the severity of COPD and the 6MWD was demonstrated.

Regarding future prospects, our findings contribute to future studies that address other aspects of cardiac comorbidity and the effects of rehabilitation on cardiac function outcomes. Further studies should investigate COPD patients with a recent, more severe exacerbation (e.g., ICU admission and use of mechanical ventilation), in whom a greater ventilatory impact, such as increased ventilatory work and air trapping, might have a more deleterious effect on cardiac function, cardiac structure, and exercise capacity.

Some limitations of our study should be considered. The study had a cross-sectional design, making firm conclusions about causality to be impossible. In addition, groups were initially matched for age and gender, but not for severity of the disease. Another limitation was that it was not possible to determine the presence of air trapping or lung hyperinflation in the patients. Finally, echocardiographic assessments were not performed prior to the exacerbation episode, and therefore we had no information on the cardiac chamber structure and LV/RV functions prior to the AECOPD in order to understand the real impact of their worsening on the clinical condition of patients.

In conclusion, our results demonstrated that, regardless of the clinical condition, patients with clinically stable COPD and those with a recent AECOPD had similar cardiac function and structure, and that cardiac characteristics, that is, mitral E/A ratio, LV posterior wall thickness, and RA volume index, were associated with exercise capacity (determined by the 6MWD and estimated Vo_2). Although the follow-up of those patients was not the focus of the current study, we suggest that future studies should consider using a longitudinal design, since this would also be very interesting.

AUTHOR CONTRIBUTIONS

MBCMP, VCS, and RGM: study design and planning; interpretation of evidence; drafting the preliminary version; and revision and approval of the final version. ADH: data collection and cataloging; interpretation of evidence; drafting the preliminary version; and revision and approval of the final version. EZK and NSS: data collection and cataloging; drafting the preliminary

version; and revision and approval of the final version. MGR and ABS: drafting the preliminary version; and revision and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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