# Association between left ventricular dysfunction and severity of chronic obstructive pulmonary disease

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**OBJECTIVES:** The prevalence of electrocardiographic and echocardiographic abnormalities in chronic obstructive pulmonary disease according to disease severity has not yet been established. The aim of this study was to assess the prevalence of electrocardiographic and echocardiographic abnormalities in chronic obstructive pulmonary disease patients according to disease severity.

**METHODS:** The study included 25 mild/moderate chronic obstructive pulmonary disease patients and 25 severe/very severe chronic obstructive pulmonary disease patients. All participants underwent clinical evaluation, spirometry and electrocardiography/echocardiography.

**RESULTS:** Electrocardiography and echocardiography showed Q-wave alterations and segmental contractility in five (10%) patients. The most frequent echocardiographic finding was mild left diastolic dysfunction (88%), independent of chronic obstructive pulmonary disease stage. The proportion of right ventricular overload ($p < 0.05$) and blockage of the anterosuperior division of the left bundle branch were higher in patients with greater obstruction. In an echocardiographic analysis, mild/moderate chronic obstructive pulmonary disease patients showed more abnormalities in segmental contractility ($p < 0.05$), whereas severe/very severe chronic obstructive pulmonary disease patients showed a higher prevalence of right ventricular overload ($p < 0.05$), increased right cardiac chamber ($p < 0.05$) and higher values of E-wave deceleration time ($p < 0.05$). Age, sex, systemic arterial hypertension, C-reactive protein and disease were included as independent variables in a multiple linear regression; only disease severity was predictive of the E-wave deceleration time [$r^2 = 0.26$, $p = 0.01$].

**CONCLUSION:** Chronic obstructive pulmonary disease patients have a high prevalence of left ventricular diastolic dysfunction, which is associated with disease severity. Because of this association, it is important to exclude decompensated heart failure during chronic obstructive pulmonary disease exacerbation.

**KEYWORDS:** Chronic Obstructive Pulmonary Disease; Electrocardiography; Echocardiography; GOLD; Spirometry.

## ■ INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and a range of pathological changes in the lungs. In addition, COPD presents significant extra-pulmonary effects and is associated with important comorbidities that may contribute to the disease severity. Chronic airflow limitation is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, particularly cigarette smoke (1). The main causes of morbidity and mortality among COPD patients are cardiovascular disease (CVD) and lung cancer (2–4).

CVD is the leading cause of death worldwide (5), and smoking is the main modifiable risk factor related to CVD (6,7). Among COPD patients, CVD is responsible for approximately 50% of all hospitalizations and 20% of all deaths (8). However, population-based studies have suggested that regardless of smoking status, age or sex, a COPD diagnosis increases the risk of cardiovascular morbidity and mortality by approximately two fold (9). In summary, COPD patients appear to face a greater risk of dying from or being diagnosed with CVD.

Anthonisen et al. and Sin et al. have already assessed the association among COPD, CVD and increased serum concentrations of inflammatory markers (2,9). Inflammation is considered to be one of the systemic manifestations of COPD and provides an alternative hypothesis to explain the relationship between airflow limitation and cardiovascular risk (4,9). However, the prevalence of electrocardiographic and echocardiographic abnormalities in COPD according to disease severity has not yet been established. Therefore, the present study aimed to assess the prevalence of electrocardiographic and echocardiographic abnormalities in mild/moderate and severe/very severe COPD patients.

## ■ METHODS

The participants were informed of the proposed study procedures and provided written informed consent. All procedures were approved by the Committee for Research Ethics of the University Hospital at Botucatu Medical School.

We used the Fisher and Belle formula (10) to estimate the sample size. The prevalence of cardiovascular hospitalization or mortality in COPD patients is approximately 15% (11), with a 95% confidence interval (CI) and a 10% sample error. The result was a sample size of 49 patients.

Sixty-two consecutive COPD patients recruited from the Pulmonary Outpatient Clinic of the university hospital were evaluated. Patients aged $\geq$ 40 years with $\geq$10 pack-year smoking histories were included. The exclusion criteria included a primary diagnosis of other respiratory diseases [e.g., asthma, restrictive disorders (tuberculosis sequelae or interstitial fibrosis], sleep apnea/hypopnea syndrome or lung cancer. In addition, a primary diagnosis of unstable angina, congestive heart failure (New York Heart Association class III or IV) or other chronic diseases, such as uncontrolled diabetes mellitus, kidney or liver failure and cancer, also constituted grounds for exclusion. The patients were assessed on three different days of the same week by clinical evaluations, spirometry and electrocardiogram/echocardiogram tests. The COPD diagnosis was confirmed according to the guidelines established in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (1,12): a post-bronchodilator $FEV_1$/forced vital capacity (FVC) ratio <0.70 and an increase <15% or 200 mL in $FEV_1$ after inhalation of a ß2 agonist. COPD severity was categorized according to the GOLD stages, considering the $FEV_1$ (% predicted) and arterial blood gas values (1).

### Measurements

Spirometry was performed using the KOKO spirometer (Ferrari KOKO, Louisville, CO 80027, USA) before and 15 minutes after the inhalation of 400 mcg of salbutamol according to the criteria set by the American Thoracic Society (13). $FEV_1$ values are expressed in liters and as percentages of FVC or percentages of reference values (14). Pulse oximetry ($SpO_2$) was assessed using an Onyx oximeter (Model 9500 Oximeter, Nonin Medical Inc., Minneapolis, MN, USA) while the patients were breathing room air. Body weight and height were measured by anthropometric mechanical scale (Filizola, mod-MIC2/B-A, São Paulo, SP, Brazil). Body mass index [BMI] was calculated using the following formula: BMI = weight [kg]/height [m$^2$]. The BMI/airflow obstruction/dyspnea/exercise capacity (BODE) index was calculated using the model described by Celli et al. (15) The BODE scores

were categorized as class 1 (score 0 to 2), class 2 (score 3 to 4), class 3 (score 5 to 6) and class 4 (score 7 to 10) (15). According to the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, systemic hypertension was defined as a systolic blood pressure > 140 mmHg and/or a diastolic blood pressure >90 mmHg (16). Fasting peripheral blood was collected, and the plasma was stored at $-80°C$ until analysis. CRP was assessed in duplicate by high-sensitivity particle-enhanced immunonephelometry (CardioPhase, Dade Behring Marburg GmbH, Deerfield, Illinois, USA) with a lower detection limit of 0.007 mg/L.

### Electrocardiogram (EKG)

EKGs were performed on all of the patients. A Micromed® device (Micromed Biotechnology LTDA, Wincardio, Brasília, DF, Brazil) was used with 12 simultaneous leads (DI, DII, DIII, V1, V2, V3, V4, V5, V6, aVR, aVL and aVF) and digital filters to eliminate the baseline fluctuation and interference (Wincardio 5.0.4.12, Firebird editing software). The diagnosis of EKG alteration was based on the criteria used in the literature (17). The same examiner performed all tests.

### Echocardiographic analysis

The echocardiograph device was an Envisor C model (Philips Medical Systems, Andover, Massachusetts, USA) equipped with a 2.0–4.0 MHz probe capable of capturing second harmonic, tissue, pulsed, continuous and color Doppler traces, as well as one- and two-dimensional mode images. With participants positioned in left lateral decubitus and monitored using an electrocardiographic lead, the following echocardiographic cuts were performed: short parasternal axis to measure ventricles, aorta and left atrium and apical two, four and five chambers to evaluate cavities and systolic and diastolic functions of ventricles. All of the measurements were performed in accordance with the American Society of Echocardiography/European Association of Echocardiography (18) recommendations. An average of three measurements was calculated for each variable. Two operators assessed all echocardiograms; however, an individual patient's echocardiograms were assessed by the same operator. The intra-observer and inter-observer variabilities were < 3% and 5%, respectively.

The left ventricular (LV) mass (LVM) was calculated according to the following formula: $LVM = 0.8 \times \{1.04 \times [(LVDD+IVSDT+PWDT)^3 - LVDD^3]\} + 0.6$, where LVDD, IVS and PWDT represent the LV diastolic diameter, interventricular septum and posterior wall thickness, respectively. The left ventricular systolic function was evaluated by measuring the ejection fraction (EF) according to the Teichholz method. The LV diastolic function was evaluated by measuring the early (E wave) and late (A wave) diastolic mitral inflow velocities, their ratio, the E wave deceleration time (EDT) and the isovolumic relaxation time (IVRT).

### Statistical analyses

The mean $\pm$ SD or the median interquartile range (25–75%) was used to present the results according to the data distribution. The patients were divided into two groups based on disease severity (COPD I/II and COPD III/IV) (1). When comparing the two study groups, an unpaired t-test was used for continuous variables, and the Mann-Whitney

U-test was used for ordinal variables. The Chi-squared test or Fisher's exact test was used to evaluate the qualitative variables. For multiple linear regressions, non-collinear clinically relevant variables were selected. The included categorical variables were sex (female = 0, male = 1), systemic arterial hypertension (absence = 0, presence = 1) and disease severity (COPD I/II = 0 and COPD III/IV = 1). The continuous variables were age and CRP. Mild left ventricular diastolic dysfunction was considered when the E/A ratio was <1, according to the literature.

All of the data were analyzed using the software SigmaStat 3.2 (SPSS Inc., Chicago, Illinois, USA). Statistical significance was defined as $p<0.05$.

### ■ RESULTS

Of the 62 patients initially evaluated, 12 were excluded from the final analyses, including 6 because of a primary diagnosis of another respiratory disease, 1 because of prostate cancer and 5 who did not complete the study protocol. Thus, 50 patients were included in the final analysis of the results. Table 1 shows the characteristics of all 50 COPD patients and also of the two groups according to the COPD severity. Age and sex did not differ statistically between the groups. As expected, the patients with severe/very severe obstruction showed lower values of spirometric variables and pulse oximetry and higher values of the BODE index (Table 1).

In five (10%) patients, the electrocardiographic and echocardiographs presented alterations of the Q wave and segmental contractility, respectively. Two patients (8%) had mild/moderate disease, and three (12%) had severe/very severe disease. All of these patients had received a previous diagnosis of coronary artery disease, as documented in their medical records. The most frequent echocardiographic finding was mild left diastolic dysfunction, which was observed in 44 patients independently of their COPD stages. In addition, left atrium enlargement was diagnosed in 46% of the patients in our sample.

In the current study, differences between the electrocardiographic and echocardiographic findings were verified. Fifty-two percent of patients showed normal or near-normal EKGs, whereas only 2% had normal echocardiograms. The most common electrocardiographic findings are shown in Table 2. The proportions of right ventricular overload ($p<0.05$) and anterosuperior division block of the left bundle branch were higher in patients with severe/very severe COPD relative to mild/moderate COPD patients. The proportions of the other electrocardiographic findings were similar between the groups (Table 2).

In the echocardiographic analyses, the mild/moderate COPD patients presented with more abnormalities in segmental contractility ($p<0.05$), whereas the severe/very severe COPD patients displayed a higher prevalence of right ventricular overload ($p<0.05$) and increased right cardiac chamber ($p<0.05$). The other morphological variables did not show any statistically significant differences between the groups (Table 3).

Table 4 shows the systolic and diastolic function of the studied patients, as evaluated by Doppler echocardiography. Patients with severe/very severe obstruction presented higher values of E-wave deceleration time (EDT) ($p<0.05$) than mild/moderate COPD patients. The other variables did not differ statistically.

Age, sex, systemic arterial hypertension, C-reactive protein and disease severity (COPD I/II and COPD III/IV) were included as independent variables in the multiple linear regression to identify the factors associated with EDT. Only disease severity showed an association with EDT [$r^2 = 0.26$, $p = 0.01$] (Table 5).

### ■ DISCUSSION

The main finding of this study was the high prevalence of mild left diastolic dysfunction in COPD patients, which was associated with increased disease severity. Only 10% of our patients displayed segmental left ventricular wall motion abnormalities, whereas, as expected, electro- and echocardiographic signs of enlargement of the right chambers were more pronounced in severe/very severe COPD patients.

Ventilation/perfusion mismatch resulting from progressive airflow limitation and emphysema is the key driver of hypoxia in COPD patients. Hypoxia is associated with COPD severity and leads to pulmonary vasoconstriction and right cardiac chamber enlargement, also known as cor pulmonale. Thus, cor pulmonale is associated with COPD severity. Schena et al. evaluated patients with cor pulmonale and pulmonary arterial hypertension secondary to COPD and found increases in the right ventricular systolic and diastolic diameters, without left ventricular alteration (19). However, associations were not observed between echocar-

**Table 1 -** Demographic and spirometric variables of 50 COPD patients according to the GOLD classification.

| Variables | Total Group (n = 50) | COPD I/II (n = 25) | COPD III/IV (n = 25) |
|---|---|---|---|
| Sex M/F (N) | 31/19 | 17/8 | 14/11 |
| Age (years) | 67 ± 9 | 65 ± 8 | 69 ± 9 |
| FVC (L) | 2.5 ± 0.9 | 3.2 ± 0.8 | 1.9 ± 0.5* |
| FVC (%) | 81.3 ± 24.6 | 98.4 ± 19.4 | 64.3 ± 16.2* |
| FEV$_1$ (L) | 1.3 (0.8–1.7) | 1.7 (1.4–2.2) | 0.8 (0.6–1.0)* |
| FEV$_1$ (%) | 56.8 ± 23.6 | 73.2 ± 15.6 | 40.4 ± 18.4* |
| SpO$_2$ (%) | 93.0 ± 4.2 | 94.8 ± 2.4 | 91.3 ± 4.9* |
| BODE index | 2.9 ± 4.2 | 1.5 ± 1.3 | 4.3 ± 1.6* |

Data are reported as the means $\pm$ SD or as median interquartile range (25–75%). M/F = male/female; FVC = forced vital capacity (% of predicted); FEV$_1$ = forced expiratory volume in the first second (% of predicted); SpO$_2$ = pulse oximetry; BODE index: **B**ody mass index, **O**bstruction, **D**yspnea, **E**xercise. GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD I/II: mild/moderate; COPD III/IV: severe/very severe. *$p<0.05$, COPD I/II compared to COPD III/IV (unpaired t-test or Mann-Whitney U-test and Chi-squared test).

**Table 2 -** Electrocardiographic study of the 50 patients according to COPD severity.

| Variables | COPD I/II (n = 25) | COPD III/IV (n = 25) |
|---|---|---|
| Normal electrocardiogram (%) | 26 (52) | 26 (52) |
| Left ventricular hypertrophy (%) | 4 (8) | 2 (4) |
| Right ventricular hypertrophy (%) | 0 (0) | 4 (8)* |
| Left atrium enlargement (%) | 4 (8) | 2 (4) |
| Right atrium enlargement (%) | 0 (0) | 2 (4) |
| Q waves (%) | 2 (4) | 2 (4) |
| Right bundle branch block (%) | 2 (4) | 0 (0) |
| Block of the anterosuperior division of the left bundle branch (%) | 0 (0) | 6 (12)* |
| Sinus tachycardia (%) | 0 (0) | 2 (4) |

COPD I/II: mild/moderate; COPD III/IV: severe/very severe. *$p<0.05$, COPD I/II compared to COPD III/IV (Chi-squared test or Fisher's exact test).

**Table 3 -** Morphological echocardiographic evaluation of the 50 patients according to COPD severity.

| Variables | COPD I/II (n = 25) | COPD III/IV (n = 25) |
|---|---|---|
| Normal echocardiogram (%) | 0 (0) | 2 (4) |
| Left atrial enlargement (%) | 20 (40) | 26 (52) |
| Dilatation of the aortic root (%) | 6 (12) | 0 (0)* |
| Enlargement of the right cardiac chambers (%) | 2 (4) | 10 (20)* |
| Alterations in segment contractility | 4 (8) | 0 (0)* |

Data are reported as percentages. COPD I/II: mild/moderate; COPD III/IV: severe/very severe. *$p<0.05$, COPD I/II compared to COPD III/IV (Chi-squared test or Fisher's exact test).

diographic variables and functional respiratory parameters (19). In the present study, as expected, the prevalence of right ventricular hypertrophy and right cardiac chamber enlargement was higher in patients with severe/very severe COPD than in those with mild/moderate obstructions.

Although cor pulmonale is a well-known echocardiographic alteration in COPD patients, few studies have evaluated left ventricular diastolic function in the context of this disease (20–23). In agreement with our results, Boussuges et al. found a high prevalence of left ventricular diastolic dysfunction in COPD patients relative to control subjects (76% *vs.* 35%) (20). Although the frequency of diastolic dysfunction was not as high as in our study (88%), Rutten et al. and Funk et al. also reported a prevalence >50%. (21,22). In addition, a recent study showed evidence of diastolic dysfunction in 47.5% (24) of COPD patients. However, Freixa et al. found a lower frequency of this echocardiographic alteration (12%) in COPD patients in their first hospital admission (25).

Left diastolic dysfunction can be asymptomatic or associated with classical heart failure symptoms (diastolic heart failure). The incidence of diastolic heart failure increases with age and is more common in older women. Hypertension and cardiac ischemia are the most common causes of diastolic heart failure. Other risk factors are obesity and diabetes mellitus (25). Note that 40% of our patients had systemic arterial hypertension, whereas 10% had received a previous diagnosis of ischemic heart disease. In the current study, the prevalence of ischemic heart disease was lower than that in previous studies (26,27). Brekke et al. observed that 27.7% of patients who were hospitalized because of COPD exacerbation showed electrocardiographic signs of myocardial

**Table 4 -** Echocardiographic variables of systolic and diastolic function of the 50 patients according to COPD severity.

| Variables | COPD I/II (n = 25) | COPD III/IV (n = 25) |
|---|---|---|
| EF (Teichholz) | 69.0 (67.0–71.2) | 70.5 (69.5–73.0) |
| E/A | 0.7 (0.6–0.8) | 0.7 (0.6–0.8) |
| EDT (ms) | 234.7 ± 57.2 | 283.8 ± 51.6* |
| IVRT (MS) | 112.0 (112.0–116.0) | 112.0 (105.0–112.0) |

Data are reported as the means ± SD or as median interquartile range (25–75%). COPD I/II: mild/moderate; COPD III/IV: severe/very severe. EF: ejection fraction; E wave: peak velocity of early ventricular filling; A wave: peak velocity of transmitral flow during atrial contraction; EDT: E-wave deceleration time; IVRT: isovolumetric relaxation time. *$p<0.05$, COPD I/II compared to COPD III/IV (unpaired t-test or Mann-Whitney U-test).

**Table 5 -** Multiple linear regression to evaluate the predictors of E-wave deceleration time ($r^2 = 0.26$).

| Variables | Coefficient | Standard Error | *p*-value |
|---|---|---|---|
| Age (years) | −0.332 | 1.068 | 0.75 |
| Sex | −27.332 | 18.658 | 0.15 |
| SAH (mmHg) | −18.717 | 19.863 | 0.35 |
| CRP (mg/L) | −0.548 | 2.350 | 0.81 |
| Disease severity | 51.314 | 18.672 | 0.01 |

SAH: systemic arterial hypertension; CRP: C-reactive protein; disease severity: COPD I/II (0), COPD III/IV (1).

infarction; 30% of these patients had no previous diagnosis (27). The higher prevalence of ischemia in these studies may be have resulted from differences in study design, sample characteristics and methods used for CVD diagnosis. For example, in a study by Brekke et al., an electrocardiographic score was used, which was contrary to Thurnheer et al., who employed coronarography (27,26). In the present study, the prevalence of ischemic changes may have been underestimated because no additional specific investigation, beyond electrocardiography and echocardiography, was performed on patients with no previous diagnoses of ischemic heart disease.

Recent studies have revealed that diastolic heart failure is associated with high morbidity and mortality. Patients with diastolic heart failure have mortality rates of 29% one year after the diagnosis and 65% after five years (28). Abusaid et al. evaluated patients who were hospitalized for exacerbation of COPD associated with diastolic dysfunction, and showed that left diastolic dysfunction increased the risk of hospitalization for exacerbation (29). These data reinforce the importance of left ventricular diastolic evaluation in COPD patients.

Note that EDT was increased in patients with severe/very severe obstruction relative to those with mild or moderate obstruction. Although nearly all of the patients presented with mild diastolic dysfunction, the higher EDT values in severe/very severe COPD suggest that disease severity was associated with decreased diastolic function. Disease severity predicts EDT even after adjusting for age, sex, systemic arterial hypertension and CRP. One explanation for this association between disease severity and diastolic function could be systemic inflammation. Inflammation is considered to be one of the systemic manifestations of COPD and provides an alternative hypothesis for explaining the relationship between airflow limitation and atherosclerotic plaque formation, which are two factors that are also associated with myocardial ischemia and left ventricular diastolic dysfunction. Furthermore, the presence of cor pulmonale secondary to pulmonary hypertension can lead to interventricular septum deviation toward the left ventricle, which alters left ventricular geometry and delays filling (31). This mechanism could also explain why disease severity was associated with worse diastolic function. In addition, because of the association between left ventricular diastolic dysfunction and COPD severity, it is also important to exclude decompensated heart failure during COPD exacerbation.

We should consider the major limitations of the present work, e.g., its small sample size and the recruitment of all patients from a single medical center. In addition, tissue Doppler imaging was not performed for evaluation of diastolic function. Further studies are needed to elucidate

the specific mechanisms associated with COPD severity and left ventricular diastolic dysfunction.

In conclusion, the electro- and echocardiographic signs of right chamber enlargement are more pronounced in severe/very severe COPD patients. In addition, COPD patients have a high prevalence of left ventricular diastolic dysfunction, which is associated with disease severity. Thus, because of this association, it is important to exclude decompensated heart failure during COPD exacerbation.

## Scientific knowledge of the subject

Chronic obstructive pulmonary disease (COPD) patients have a high prevalence of left ventricular diastolic dysfunction according to disease severity.

## What this study adds to the field

COPD patients have a high prevalence of electrocardiographic and echocardiographic abnormalities regardless of disease severity.

COPD patients have a high prevalence of left ventricular diastolic dysfunction, which is associated with disease severity. Because of this association, it is important to exclude decompensated heart failure during COPD exacerbation.

## ■ AUTHOR CONTRIBUTIONS

Caram LM, Minicucci MF and Godoy I conceived the study. Caram LM, Minicucci MF, Tanni SE and Ferrari R performed the statistical analysis. Caram LM, Minicucci MF, Tanni SE and Godoy I analyzed the data and drafted the manuscript. Caram LM, Ferrari R, Naves CR, Coelho LS and Zanatti SG contributed to the data collection. All of the authors contributed to the writing of the manuscript, read and approved its final version.

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