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Interrelationship between Emphysema and Left Ventricular Diastolic Dysfunction: our experience in the Hospital Privado Centro Médico de Córdoba

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Abstract

Introduction: The hemodynamic consequences of hyperinflation and emphysema are produced by cardiac compression due to high intrathoracic pressures, which could produce subclinical left ventricular diastolic dysfunction. Our purpose is to correlate the percentage of emphysema with lung function parameters and cardiac chamber sizes, the global ventricular systolic function and the left ventricular diastolic function, in cases of chronic obstructive pulmonary disease.

Materials and Methods: The participants were patients with moderate and severe chronic obstructive pulmonary disease treated in the Pulmonology Service of the Hospital Privado Centro Médico de Córdoba from January 1st to October 13th, 2014. We quantified the volume and percentage of emphysema by high resolution computed tomography and carried out a spirometry, a Six Minute Walk Test, measurement of pulmonary volumes and color Doppler echocardiography.

Results: We found a significant negative correlation between the percentage of emphysema and the percentage of the post-bronchodilator FEV_1 theoretical value ($p = 0.005$) and the post-bronchodilator FEV_1/FVC (Forced Expiratory Volume in First Second/Forced Vital Capacity) quotient ($p = 0.004$), and, also, between the post-bronchodilator FEV_1/FVC quotient and the emphysema volume in cm^3 ($p = 0.000$). Out of a sub-group of 20 patients, seven patients (35%) were diagnosed with grade I left ventricular diastolic dysfunction. We found negative, but not significant correlations between the percentage of emphysema and global ventricular systolic function and cardiac chamber sizes.

Conclusions: We should emphasize the usefulness of the echocardiography in reducing sub-diagnoses of left ventricular diastolic dysfunction. We should also stress on the importance hyperinflation and emphysema would have in the impairment of the left ventricular diastolic filling pattern and in the decrease in cardiac chamber sizes, with a decrease in exercise tolerance.

Key words: emphysema; left ventricular diastolic dysfunction

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation, which can be attributed to alveolar and/or airflow anomalies, usually caused by significant exposure to harmful particles or gases[1].

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While airflow obstruction detected by spirometry is essential for the diagnosis of COPD, there are morphological changes that could be determined by means of a quantitative and volumetric evaluation of emphysema through axial High Resolution Computed Tomography (HRCT) imaging. This study technique represents significant progress for research, since it eliminates inter- and intra-observer variations[2], and has been used to define COPD phenotypes[3]. Several studies evaluated the relationship between the percentage of emphysema determined by axial HRCT and lung function results in COPD patients[4-11]. According to the meta-analysis of Xie X et al[12], measurements of emphysema and the peripheral airways are significantly related to airflow obstruction in COPD. Hyperinflation best correlates with variables that have the strongest impact on the patient, such as dyspnea, quality of life and exercise tolerance; and has been reported as predictor of mortality in COPD[13].

Cardiovascular effects of COPD, known and well-proven for some time now, have only been studied in patients with severe and very severe conditions[14]. The repercussion of hyperinflation on the cardiovascular level is more complex and less known and identified than respiratory disorders. The hemodynamic consequences are produced by cardiac compression as a consequence of an increase in intrathoracic pressure and passive compression of alveolar vessels with an increase in pulmonary vascular resistance, and reduction of ventricular preload, of the systolic volume and of left ventricular (LV) end-diastolic volume[15]. Jörgensen K. et al[16] found that in patients with COPD and severe emphysema, the dimensions of both ventricles were small, with reduced intrathoracic blood volume and impairment of the LV filling process (reduced preload by pulmonary hyperinflation).

To sum up, in COPD patients, emphysema with lung hyperinflation could be the cause of subclinical left ventricular diastolic dysfunction (LVDD), with increased limitation of the capacity to exercise.

In this study we analyze a selected group of patients with moderate and severe COPD who were treated in the Pulmonology Service of the Hospital Privado Centro Médico de Córdoba. Our purposes are: to establish correlations between the percentage of emphysema and lung function parameters (severity of the obstruction, tolerance to exercise and hyperinflation); between the percentage of emphysema and cardiac chamber sizes, the global ventricular systolic function and the LV diastolic function; between lung function parameters and cardiac chamber sizes, the global ventricular systolic function and the LV diastolic function.

Materials and Methods

Patients and Data Collection. Descriptive, analytical, observational, prospective study evaluating patients diagnosed with COPD treated in the Pulmonology Service of the Hospital Privado Centro Médico de Córdoba, from January 1st to October 31st, 2014. We took into account the GOLD (Global Initiative for Chronic Obstructive Pulmonary Disease) definition of COPD, including the clinical diagnosis and spirometric criterion: *"the relationship between the post-bronchodilator forced expiratory volume in first second (FEV_1)/Forced Vital Capacity (FVC) < 0.7"*[17]. *Inclusion criteria:* Patients age ≥ 40 years; moderate and severe COPD (post-bronchodilator [PBD] FEV_1 ≥ 30 and ≤ 79% of its theoretical value), according to the Gold Guide[17]; present or past history of smoking, with an annual smoking load of ≥ 10 packs per year; signing of informed consent; the possibility to carry out all the procedures of the study. *Exclusion Criteria:* mild and very severe COPD (PBD FEV_1 ≥ 80% and < 30% of its theoretical value), according to the GOLD Guide[17]; other concomitant pulmonary diseases: interstitial diseases, cystic fibrosis, asthma, allergic bronchopulmonary aspergillosis (ABPA), etc.; lung function studies with technical deficiencies; weight > 120 kg (because it is impossible to perform the HRCT). We excluded from the study the echocardiographies with poor or suboptimal acoustic window, or those showing regional motility abnormalities, reduced ejection fraction, valvuloplasty and rhythm disorders.

Procedures. *Demographic data:* age and sex; Body Mass Index (BMI); smoking (active smoker, ex-smoker) and smoking load (packs-year); symptoms evaluated by the CAT (COPD Assessment Test)[17]

questionnaire, degree of dyspnea evaluated by the modified questionnaire of the *Medical Research Council* (mMRC)[17]. *Lung function:* we used Ultima PF&PFX System Medical Graphics Corporation 2009 equipment, and performed the following: 1) Pre- and post-bronchodilator spirometry according to the criteria of the American Thoracic Society/European Respiratory Society (ATS/ ERS)[18] with determination of PBD FEV_1 and its relationship with FVC; 2) Lung volumes by means of the nitrogen washout technique according to the ATS/ERS[20] criteria, evaluating the IC/TLC (Inspiratory Capacity/ Total Lung Capacity) relationship, taking into account that a IC/TLC relationship ≤ 25% is a marker of hyperinflation and mortality in COPD[13]; 3) Six-Minute Walk Test (6MWT) according to the ATS/ ERS criteria[19] with an evaluation of tolerance to exercise for the distance traveled, expressed in meters. *HRCT of the chest* We used Toshiba Activion 16 equipment, detectors with 0.1 mm thick sections. By means of non-contrast HRCT with volumetric reconstruction we determined, in each lung, the index of emphysema that makes reference to the pulmonary emphysema volume percent, defined by the total of voxels with attenuation value between -950 and -850 Hounsfield Units (HUs) in relation to the total lung volume[2]. *Echocardiography*: We used GE Vivid 7 equipment, following the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACI)[21, 22]. All the studies were conducted by the same operator (cardiologist), who did not have the data regarding the COPD severity and/or the percentage of emphysema of the participants. The study only included measurements with a satisfactory quality of image; and excluded patients with associated comorbidities such as ischemic cardiopathy, arrhythmia, severe valvulopathies, etc. We gathered information relating to: a) Body surface area (m^2), b) Dimensions of cardiac cavities, c) Global ventricular systolic function, d) Left ventricular diastolic function.

We defined the LVDD as heart failure with normal ejection fraction of the left ventricle[22]. Various levels of diastolic function disorders can be recognized, according to the left ventricular relaxation state and filling pressures[23]. Level I: incomplete or slow relaxation with normal or high filling pressures; Level II: pseudonormalized pattern (with reduced relaxation and increased filling pressures); Level III: reversible restrictive, where the changes described in the previous level are accentuated; Level IV: reversible restrictive. We followed the 2009 ASE recommendations[22] for the diagnosis of LVDD and its degrees of severity.

Ethical Considerations. All the patients signed an informed consent. The information provided by the patients and data gathered from their respective clinical records is kept confidential by study researchers.

Statistical Analysis. We used Infostat and PASW version 18.0 of the SPSS Company as statistical software. We applied the Bivariate Correlations Test at a 0.05 significance level and selected the Spearman coefficient reading. For the comparison by gender (male and female), we used a T test of independent samples for continuous numerical variables. A value of $p < 0.05$ was considered as significant.

Results

56 patients were analyzed. **Table 1** describes the general characteristics of the sample. In **Table 2** we can see that out of the analyzed variables, only age (women were younger, $p = 0.028$), the PBD FEV_1/ FVC relationship (men showed greater obstruction, $p = 0.01$) and emphysema volume (higher in men, $p = 0.002$) showed statistically significant differences between men and women.

TABLE 1. General Characteristics of the Sample
(Data expressed in absolute value (n), percentage (%) and mean value ± SD)

		n 56
Patients Gender Male Female	 55% 45%	 n 31 n 25
Smoking Active smoker Ex-smoker	 27% 73%	 n 15 n 41
COPD Active smoker Ex-smoker	 70% 30%	 n 39 n 17
Age	67.75 ± 8.11	
BMI* (kg/m^2)	27.63 ± 4.53	
Packs/year	55.34 ± 40.60	
PBD FEV$_1$ %**	56.61 ± 8.95	
CAT$^{\alpha}$α	10.96 ± 6.13	
mMRC$^{\rho}$α	1.38 ± 0.86	
6MWT$^{\pi}$	478.82 ± 122.25	
IC/TLC^{f}α	0.33 ± 0.11	
Volume of emphysema (cm^3)	2624.58 ± 1274.43	
Percentage of emphysema	45.96 ± 17.23	

*BMI: Body Mass Index; $^{\alpha}$CAT: COPD Assessment Test; ^{f}IC/TLC: Inspiratory Capacity/Total Lung Capacity relationship; $^{\rho}$mMRC: Modified Dyspnea Scale of the Medical Research Council; $^{\pi}$6MWT: 6-Minute Walk Test; **PBD FEV1 %: percentage of Post-Bronchodilator Forced Expiratory Volume in first second

TABLE 2. General Characteristics of the Sample Regarding the Gender
(Data expressed in absolute value (n), and mean value ± SD)

	Men (n 31)	Women (n 25)	p
Age	69.87 ± 7.78	65.12 ± 7.88	**0.028**
BMI* (kg/m^2)	28.29 ± 4.97	26.80 ± 3.85	0.224
Packs/year	63.52 ± 45.95	45.20 ± 30.74	0.094
PBD FEV$_1$ %**	57.55 ± 14.29	58.12 ± 12.23	0.875
PBD FEV$_1$/ FVC$^{\phi}$	53.97 ± 9.72	59.88 ±6.72	**0.01**
CAT$^{\alpha}$	11.39 ± 6.19	10.44 ± 6.15	0.570
mMRC$^{\rho}$	1.39 ± 0.80	1.36 ± 0.95	0.908
6MWT$^{\pi}$	494.35 ± 124.68	459.56 ± 118.83	0.294
IC/TLC^{f}	0.35 ± 0.11	0.31 ± 0.11	0.216
Volume of emphysema (cm^3)	3066.48 ± 1376.52	2076.62 ± 888.02	**0.002**
Percentage of emphysema	46.51 ± 18.47	45.28 ± 15.91	0.794

*BMI: Body Mass Index; $^{\alpha}$CAT: COPD Assessment Test; ^{f}IC/TLC: Inspiratory Capacity/Total Lung Capacity relationship; $^{\rho}$mMRC: Modified Dyspnea Scale of the Medical Research Council; $^{\pi}$6MWT: 6-Minute Walk Test; **PBD FEV1 %: percentage of Post-Bronchodilator Forced Expiratory Volume in first second $^{\phi}$PBD FEV1/ FVC: Post-Bronchodilator Forced Expiratory Volume in first second/Forced Vital Capacity relationship

Emphysema and lung function

The highest percentage of emphysema was significantly correlated with greater airflow obstruction, determined by FEV_1 reduction and the FEV_1/FVC relationship (negative correlation): FEV_1 with a correlation coefficient (CC) of 0.372 (p = 0.005) **(Figure 1)** and FEV_1/FVC with a CC of 0.383 (p= 0.004) **(Figure 2).** Also the greatest volume of emphysema in cm^3 was correlated with a reduced FEV_1/FVC relationship, and a CC of 0.481 (p = 0.000) **(Figure 3).**

We found that the highest percentage of emphysema was associated with a decrease in the distance traveled at the Six Minute Walk Test (6MWT) and a reduced IC/TLC relationship, though such correlations weren't significant (CC of 0.039; p = 0.774 and CC of 0.216; p = 0.110, respectively). There was a positive (direct) but not significant correlation between the degree of dyspnea (mMRC) and the percentage of emphysema (CC of 0.087; p = 0.522).

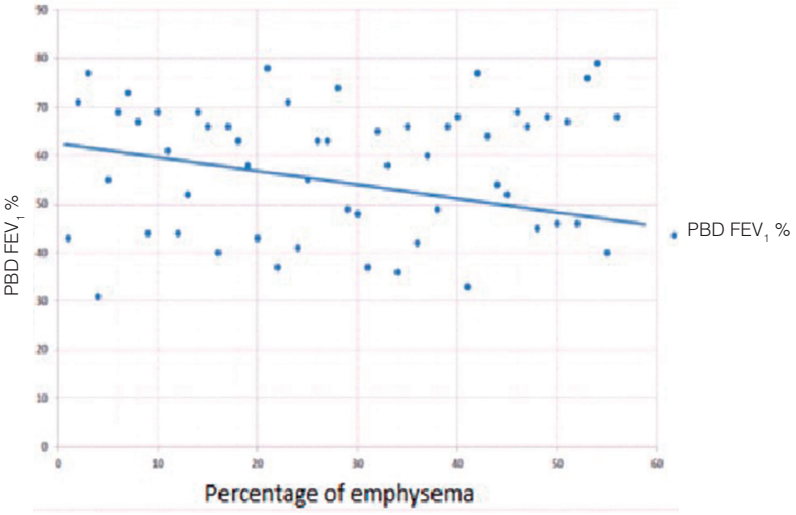

Figure 1. Relationship between percentage of emphysema and PBD FEV_1 % of the theoretical value. p = 0.005 (Spearman correlation)

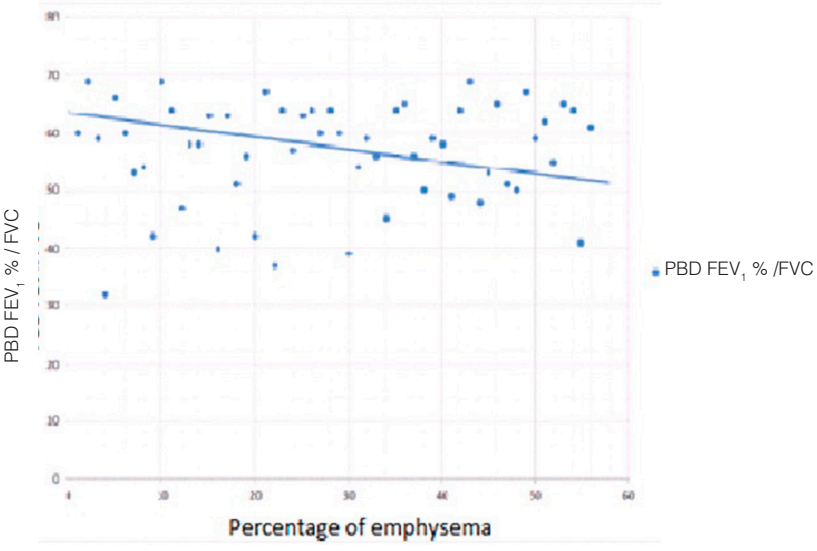

Figure 2. Relationship between percentage of emphysema and PBD FEV1 p = 0.0004 (Spearman correlation)

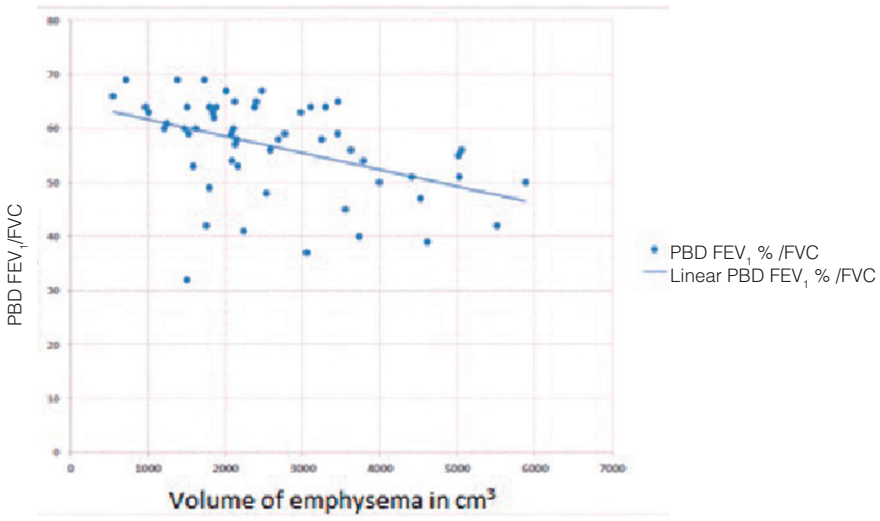

Figure 3. Relationship between volume of emphysema and PBD FEV_1. p = 0.000 (Spearman correlation)

Emphysema with cardiac structure and function variables

Basing on the quality of the echocardiographic study and the presence of cardiopathies, and with the purpose of taking measurements and making a reliable diagnosis of LVDD, we excluded 36/56 participants **(Figure 4)**.

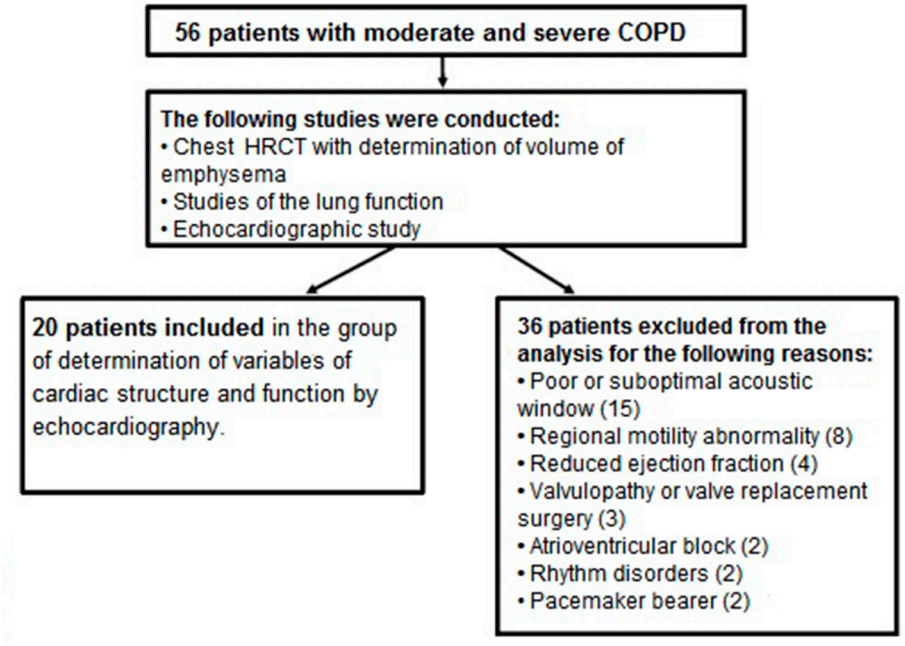

Figure 4. Diagrama of patient distribution in the study sample regarding the echocardiographic evaluation.

The group of the remaining 20 participants had technically acceptable echocardiographies to measure diastolic dysfunction parameters; 7/20 (35%) showed Grade I LVDD diagnosis. **Table 3** describes the analyzed echocardiographic characteristics. We observed that the increase in the percentage of emphysema was correlated with decreased cardiac chamber sizes and a decreased global ventricular systolic function (negative correlation), though such correlations weren't significant; **Table 4** describes these correlations with their correlation coefficient (CC) and corresponding p values.

TABLE 3. Size of Cardiac Chambers, Global Ventricular Systolic Function and Left Ventricular Diastolic Function (n 20)
(Data expressed in mean value ± SD)

LV end-D diameter (mm)	46.25 ± 4.64
LV end-D volume (ml)	71.05 ± 19.87
LV end-S diameter	30.60 ± 4.27
LV end-S volume (ml)	29.90 ± 10.80
Indexed LA (ml/m^2)	25.55 ± 6.57
LV end-D volume (ml/m^2)	39.20 ± 10.07
LV end-D diameter (mm/m^2)	25.72 ± 2.62
LV end-S volume (ml/m^2)	16.41 ± 5.49
LV end-S diameter (mm/m^2)	16.94 ± 1.72
Heart rate volume (ml)	72.70 ± 26.69
HRV (ml/m^2)	39.80 ± 12.41
Cardiac output (L/min)	5.12 ± 1.39
Cardiac index (L/min/m^2)	2.83 ± 0.66
IVRT (milliseconds)	96.56 ± 20.02
Deceler E (milliseconds)	233.80 ± 44.26
E/A (mts/sec)	0.82 ± 0.16
E' (mts/sec)	0.11 ± 0.02

A: wave velocity of late diastolic filling; D: diastolic; Deceler E: E wave deceleration time; E: wave velocity of early diastolic filling; E': E-wave velocity in mitral annulus; HRV: indexed heart rate volume; IVRT: Isovolumetric Relaxation Time; LA: left atrium; LV: left ventricle; S: systolic

TABLE 4. Correlation between Emphysema and Global Ventricular Systolic Function. Correlation between Emphysema and Size of Cardiac Chambers

Global Ventricular Systolic Function	Size of Cardiac Chambers
Heart rate volume (ml): CC of - 0.361 (p = 0.118)	LA volume in ml/m^2: CC of - 0.381 (p = 0.097)
Indexed heart rate volume (ml/m^2): CC of - 0.324 (p = 0.164	LV end-D volume (ml): CC of - 0.434 (p = 0.056)
Cardiac output (l/min): CC of - 0.413 (p = 0.070	LV end-S volume (ml): CC of - 0.259 (p = 0.270)
Cardiac index (l/min/m^2): CC of - 0.248 (p = 0.291)	LV end-S diameter (mm): CC of - 0.026 (p = 0.913)
	LV end-D diameter (mm): CC of - 0.105 (p = 0.661)

CC: correlation coefficient. LA: left atrium. LV: left ventricle

Lung function with cardiac structure and function variables

We observed a correlation between the decrease in lung function (lower FEV1, PBD FEV1/FVC, 6MWT and IC/TLC) and decreased cardiac chamber sizes, the reduced global ventricular systolic function and the impairment of LV relaxation and filling. Such correlations weren't significant. They are described in **Table 5** with their CCs and corresponding p values.

TABLE 5. Positive (direct) Correlations between Lung Function Variables, Size of Cardiac Chambers and Left Ventricular Diastolic Function and Global Systolic Function

Size of cardiac chambers	LV diastolic function	Función sistólica global
PBD FEV_1 % of theoretical value		
LA volume (ml): CC of 0.153 (p = 0.521)	E' (mts/sec): CC of 0.207 (p = 0.380)	
LV end-diastolic diameter (mm): CC of 0.033 (p = 0.890)	Deceler E (millisec): CC of 0.002 (p = 0.992)	
6 MWT (mts)		
LV end-systolic volume (ml): CC of 0.108 (p = 0.649)	E' (mts/sec): CC of 0.041 (p = 0.863)	
LV end-diastolic volume (ml): CC of 0.103 (p = 0.665)	Deceler E (millisec): CC of 0.010 (p = 0.967)	
LV end-systolic diameter (mm): CC of 0.090 (p = 0.706		
LV end-diastolic diameter (mm): CC of 0.092 (p = 0.700)		
IC/TLC		
LA volume (ml): CC of 0.351 (p = 0.129	E/A relationship (mts/sec): CC of 0.117 (p = 0.623)	
LV end-systolic diameter (mm): CC of 0.301 (p = 0.197)	E' (mts/sec): CC of 0.076 (p = 0.751)	
LV end-diastolic diameter (mm): CC of 0.177 (p = 0.456		
PBD FEV_1/FVC		
LA volume (ml): CC of 0.393 (p = 0.086)		Cardiac output (L/min): CC of 0.007 (p = 0.976)
LV end-systolic volume (ml): CC of 0.079 (p = 0.741)		Cardiac index (L/min/m^2): CC of 0.066 (p = 0.783)
LV end-diastolic volume (ml): CC of 0.064 (p = 0.789)		

A: wave velocity of late diastolic filling; CC: correlation coefficient; Deceler E: E wave deceleration time; E: wave velocity of early diastolic filling; E': E-wave velocity in mitral annulus; LA: left atrium; LV: left ventricle

Discussion

In this study, we observed that in COPD patients, the emphysema determined by tomography was more severe in men than in women, just like the study of M. Dransfield et al.[29] This gender discrepancy in the radiologic expression could represent an important difference in the physiopathology of the airway obstruction and, to some degree, these findings would explain the different presentation and natural history of COPD[29]. Unlike the study of Torres et al[30], in this study men showed greater airway obstruction, with a reduced PBD FEV_1/FVC relationship, and there weren't significant gender differences regarding the distance traveled in the 6-Minute Walk Test, the degree of dyspnea, the smoking load and BMI. In our study, just like in the consulted literature[4-5, 9-12, 24-26], we found that a higher percentage of emphysema was significantly associated with a higher degree of airway obstruction, determined by a reduced FEV_1 and a reduced FEV_1/FVC relationship (negative correlation). Unlike some of these studies[24-26], there was also a negative yet not significant correlation between the percentage of emphysema and the IC/TLC relationship, probably due to the reduced number of participants in our sample. Unlike the study of Chierakul N. et al[5], in our study we found that the higher percentage of emphysema was correlated (not significantly) with a shorter distance covered in the 6MWT and with a higher degree of dyspnea determined by the mMRC questionnaire.

In a study based on the population including patients without clinical cardiovascular disease and with preserved ejection fraction, Graham Barr R. et al[14] found that a more severe pulmonary emphysema determined by HRCT was associated with a lower left ventricular end-diastolic volume and reduced systolic volume and cardiac output. In our study we also found a negative but not significant correlation between a higher percentage of emphysema and a reduced global ventricular systolic function (systolic volume, cardiac output and index) and decreased cardiac chamber sizes (left atrial volume and LV end-diastolic and end-systolic diameter and volume).

The study of Watz H. et al[27] of 138 patients with mild to severe COPD revealed that hyperinflation (defined by IC/TLC ≤ 0.25 relationship) shows a substantial relationship with cardiac chamber sizes. These authors noted that patients with hyperinflation showed impaired LV diastolic filling pattern in the echocardiography, and that LV diastolic dysfunction had an independent effect on tolerance to exercise in COPD patients. Just like in that study, we found positive correlations between lung function (reduced IC/TLC relationship, lower PBD FEV_1 % of the theoretical value and shorter 6MWT distance) and the decrease in cardiac chamber sizes (left atrial volume and LV end-diastolic diameter) and the decreased LV diastolic filling (Deceleration E/E/A relationship), but in our study, these correlations weren't significant.

The correlations of lung function and emphysema with cardiac structure and function weren't significant in this study, and this could be attributed to the reduced number of participants included in our sample.

Grade I LVDD was diagnosed in 7 patients (35%) out of the group of 20 patients with technically acceptable echocardiographies. We can't establish its real prevalence due to the reduced number of patients included in the determination of cardiac variables through echocardiography, but the prevalence of heart failure in COPD patients reported in the references was approximately 20%, and half of these cases would correspond to diastolic heart failure with preserved ejection fraction[28].

The most important limitation of the present study is the reduced number of participants included in the determination of cardiac variables. Although the echocardiography is the most common noninvasive procedure for quantifying cardiac chamber sizes and evaluating their function[21], generally it is difficult to use in COPD patients due to a suboptimal acoustic window.

Conclusions

We found a significant correlation between the percentage of emphysema and airflow obstruction, thus the HRCT would provide a quantitative morphologic method that could contribute to the definition

of phenotypes in patients with moderate and severe COPD for the customized management of the treatment.

We detected that the increase in the percentage of emphysema was correlated with a decrease in cardiac chamber sizes and a reduced global ventricular systolic function. We also objectively showed a correlation between the reduced lung function and the decrease in cardiac chamber sizes, a reduced global ventricular systolic function and impaired left ventricular relaxation and filling; but such correlations weren't significant probably due to the reduced number of patients included in our sample.

The important cardiovascular impact of hyperinflation associated with emphysema could be attributed to the impairment of the left ventricular diastolic filling pattern and to a decrease in cardiac chamber sizes with lower tolerance to exercise.

We want to emphasize the usefulness of the echocardiography to reduce the sub-diagnosis of LVDD, reported in one third of the participants of our study.

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