Original Article

Bronchiectasis associated with severe COPD: Clinical, functional, microbiological and tomographic features

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ABSTRACT

Background: Bronchiectasis is frequently identified in patients with COPD, especially in severe patients, but the relevance of this finding remains unclear. We aimed to investigate the factors that would increase the chance of having bronchiectasis in patients with severe COPD. **Methods:** This is an analytical, observational, cross-sectional study. Patients with severe COPD with (BC group) and without bronchiectasis (NBC group) were clinically evaluated and performed spirometry, 6-minute walk test (6MWT), volumetric capnography (VCap) and high resolution computed tomography (CT). CT was scored for the findings, and multiple linear regression was performed to identify variables related to the score's severity and logistic regression in order to identify factors that could be associated with the presence of bronchiectasis. **Results:** There was no significant difference between BC and NBC groups regarding clinical variables, except in the smoking load, which was lower in the BC group. In functional evaluation, NBC patients walked shorter distances in 6MWT ($P < 0.005$). In the BC group the distribution of CT findings was mostly bilateral and in lower lobes. Using the multiple linear regression analysis within the BC group, we found that the higher the bronchiectasis score, the higher ΔSpO2 during the 6MWT and the lower the FVC. The chance of having bronchiectasis was 4.78 times higher in the presence of positive isolates (sputum) (CI 1.35-16.865; $P = 0.023$). The higher the distance covered (6MWT) and Slp3 (VCap), (OR 1.01, CI 1.004; 1.0202, $P = 0.0036$; OR 1.04, CI 1.003; 1.077; $P = 0.036$), the greater are likelihood of bronchiectasis. **Conclusions:** In patients with COPD and bronchiectasis, higher CT scores were associated with worse lung function and a greater drop in oxygenation during exercise.

KEY WORDS: 6-minute walk test, bronchiectasis, chronic obstructive pulmonary disease, computed tomography, respiratory function tests, volumetric capnography

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) remains one of the leading causes of morbidity and mortality around the world.[1] COPD is characterized by persistent respiratory symptoms and airflow limitation that result from the airway and/or alveolar abnormalities. The heterogeneity of COPD derives from multiple risk factors, individual susceptibility and a range of clinical features and systemic effects that vary according to the type and predominance of pathological and structural abnormalities present in the patient.[2]

High-resolution computed tomography (HRCT) of the thorax has been increasingly used in the assessment of patients with COPD, and it allows for identifying even mild small airway disease, bronchiectasis and emphysema.

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HRCT is also a useful tool for phenotyping patients as having airway disease or emphysema.[3,4] Bronchiectasis is frequently found in patients with COPD,[5-9] and although it may be present in COPD patients of various stages of severity, the worse the lung function, the greater the likelihood of finding bronchiectasis.[6]

In the GOLD document, bronchiectasis is considered a comorbidity of COPD.[1] Comorbidity is a term that refers to diseases that coexist in an individual, with no known relationship between them, either as a causal factor or related to the progression of diseases. One important aspect is that both conditions (COPD and bronchiectasis) share clinical symptoms (chronic cough) and some pathophysiological events, such as increased susceptibility to exacerbations, the persistence of potentially pathogenic microorganisms in the airways and incompletely reversible airflow obstruction.[10-13]

In addition to being frequent in more functionally severe COPD patients, bronchiectasis is associated with longer exacerbations[9] and increased mortality.[7] Besides its association with meaningful clinical outcomes, the presence of bronchiectasis in COPD patients is associated with increased bronchial inflammation, frequent colonization of the airway by potential pathogenic microorganisms (PPMs) and severe airflow obstruction.[7,9]

Although there have been advances in understanding the clinical and prognostic importance of bronchiectasis in the evolution of patients with COPD, there are some gaps in understanding the relationship between these two conditions. Therefore, we hypothesize that by expanding the understanding of other functional aspects of patients with this association – such as performance in field tests (6-minute walk test) and other functional tests [such as volumetric capnography (VCap)] – we can contribute to the understanding of clinical heterogeneity and the function of COPD. It is important to mention that capnography can show different patterns according to COPD tomographic phenotypes.[4]

Our study aimed to compare clinical, functional, and tomographic characteristics of severe COPD patients with and without bronchiectasis, and to check for associations of factors that would increase the chance of having bronchiectasis.

METHODS

This is an analytical, observational, cross-sectional study with patients followed at the outpatient clinics of the Pulmonology Division of the University Hospital, Campinas, São Paulo, Brazil. The study was submitted to and approved by the Research Ethics Committee of the Faculty of Medical Sciences under approval (No. 768/2010, amendment on 22/11/2011). All patients participating in the study signed the informed consent form.

Patients diagnosed with COPD according to the guidelines[1] were recruited between 2011 and 2018. Those with severe obstructive defect (post-bronchodilator Forced Expiratory Volume in one second (FEV_1) below 50% of predicted value and former smokers (over 10 pack-years) were included. Participants who were not able to perform the proposed tests, as well as those diagnosed with asthma or bronchiectasis of other causes (other pulmonary diseases or immunological deficiencies), were not included. In our institution, patients who show bronchiectasis on HRCT are usually tested for these aforementioned aetiologies. The results presented here are part of a Ph.D. thesis by Doria, SMS.[14]

Patients were seen during these three visits. At the first visit, each patient had a clinical evaluation: symptoms severity, physical examination, and dyspnea score using the modified MRC scale.[15] By reviewing medical files data on the frequency of exacerbations during the last year before inclusion, medicines in use at the time of inclusion in the study and comorbidities were collected. Exacerbations were defined as (1) worsening of baseline symptoms such as dyspnea, cough, and sputum, which had led to a short-term change in therapy, such as the addition of oral corticosteroids or antibiotics, (2) the need for unscheduled clinic visit at the emergency room due to increasing of baseline symptoms, or (3) the evidence of hospitalization caused by worsening of oxygenation or respiratory symptoms.

At the second visit, after assuring that patients were clinically stable, sputum samples were collected for microbiological culture, and functional tests were performed: (1) spirometry (Easy One World spirometer®) was performed according to the American Thoracic Society Guidelines[16] and reference values for the Brazilian population were used.[17,18] (2) The 6MWT was performed under the supervision of the same technician, according to the American Thoracic Society guidelines[19]; the walked distance was compared with predicted values,[20,21] peripheral oxygen saturation (SpO_2), Borg dyspnea scale and vital signs were evaluated at rest and in the 6th min. Desaturation (ΔSpO_2) was calculated as the difference between the final and the initial SpO_2. (3) VCap was performed using CO_2SMO Plus (Dixtal/Novametrix Inorporation, Wallingford, CT, USA) oxi-capnograph equipment; with the patient seated, and after 5- to 10-min rest, the test began with spontaneous breathing for 1 min; after that, data were collected using the APlus® software over the next 4 to 5 min. At the end of data collection, an offline sequence of respiratory cycles of patients was selected in a variation of <15% of end-expiratory volume and <5% of $ETCO_2$ (partial pressure of carbon dioxide at end-tidal). Respiratory cycles that presented zero slope values for phases 2 and 3 were excluded; a mean value was determined for each breathing pattern. Among the collected variables, the phase 2 and 3 slopes (Slp2 and Slp3) of the VCap and the $ETCO_2$ were analyzed.

At the third visit, HRCT with inspiratory and expiratory scans was performed on a 64-channel multidetector tomography device, Toshiba®, with 0.5 mm-thick volumetric acquisitions and 1 mm-thick reconstruction, using a high spatial resolution algorithm. The exams were performed with maximum inspiration and maximum expiration. All CT scans were performed with patients who were clinically stable, and with a time interval of no more than 60 days from the patient's inclusion in the study. The procedures of the second and third visits were performed as long as the patient was clinically stable, without worsening of baseline symptoms or diagnosis of exacerbation in the previous 4 weeks. The exams were rescheduled if the patient reported a recent worsening of symptoms or respiratory infection in the last 4 weeks.

All exams were read by a single professional, a senior professor (MCP) with experience in reading CT scans, using a standardized form used in a previous study.[4] Bronchiectasis, bronchial wall thickening, air trapping (expiratory scan), tree-in-bud sign, mucus impaction, bullae and emphysema were identified and the severity of these findings was scored in each of the six pulmonary lobes. After the analysis of the CT scans, the patients were classified into two groups: those who had bronchiectasis in at least two pulmonary lobes (BC group) and those without bronchiectasis or with just one affected lobe (NBC group). Follow the flow-chart which describes the recruitment of the patients [Figure 1].

Statistical analysis

Continuous variables are displayed as mean ± sd or median (min – max range). We used the Chi-square test or Fisher's exact test as appropriate. The Mann–Whitney test was used to compare numerical values between two groups.

Logistic regression analysis was performed in order to identify factors that may be associated with the presence of bronchiectasis. Factors that were included in the analysis were age, sex, tobacco load, symptoms, Charlson index, body mass index (BMI), exacerbation rate in 12 months, presence of potentially pathogenic microorganisms (PPM) in sputum sample, Forced Vital Capacity (FVC), FEV_1,

walked distance in 6MWT, $ETCO_2$, Slp2 and Slp3. All CT scans were scored for the findings, and multiple linear regression analysis was performed within the BC group to identify variables related to the severity of the score of bronchiectasis.

A value of $P < 0.05$ was adopted as the level of significance. The software package was The SAS System for Windows (Statistical Analysis System), version 9.4. SAS Institute Inc. 2002-2008. Cary., NC, USA.

RESULTS

Based on medical records, we considered 300 patients with COPD for inclusion. According to the inclusion criteria, 150 patients were included, but 62 did not complete all proposed tests (12 patients withdrew from participating, 34 did not attend the scheduled visits, and 6 participants died) so only 98 patients were fully evaluated. They were functionally severe patients (51 GOLD III and 47 GOLD IV) with mean FEV_1 of 1.1 L. The mean age was 64.6 years, 63% were men, and the median tobacco load was 43.9 pack-year. The main comorbidity was systemic arterial hypertension (54%). The majority of patients were using double therapy with long-acting bronchodilators, and all of them used inhaled corticosteroids. Four participants were taking macrolides due to frequent exacerbations. In the 6MWT, the mean distance was 365.5 m, and in Vcap, the mean Slp3 was 34.6 mmHg/L.

Bronchiectasis was identified in HRCT in 28 patients and in 24 (24.5%) of them this finding was present in at least two lobes. This group was named the BC group, and the other group was called the NBC group (N = 74). The clinical and microbiological data of patients of BC and NBC groups can be seen in Table 1.

There was no significant difference between groups regarding age, sex, home oxygen therapy, severity of dyspnea, exacerbation annual rate and symptoms. There was a significant difference between groups regarding smoking load and the BODE index,[22] which were higher

Figure 1: Flow-chart of recruitment of the patients

in the group without bronchiectasis. Also, systemic arterial hypertension was less frequent in the BC group.

A significant difference between groups was found in 6MWT: BC patients walked more than NBC ones (409 m versus 351 m, respectively; *P* = 0.014). Most patients in both the groups showed ΔSpO_2 of at least four points. There were no differences between the groups concerning spirometric and capnographic variables. Functional characteristics of BC and NBC patients are shown in Table 2.

A sputum sample was collected in 74 patients (75.5%) and there were positive isolates in 52.5% of patients in the BC group and in 30.2% of the NBC group (*P* = 0.074). *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Haemophilus influenzae* were the most frequently identified microorganisms [Table 3].

In addition to the finding of bronchiectasis on HRCT in a quarter of the patients, peribronchial thickening and emphysema were very frequent findings, both found in 73.5% of the individuals. CT findings for each group are shown in Table 4. Patients in the BC group more often showed signs of airway involvement, such as air trapping and peribronchial thickening.

HRCT findings of the BC group are shown in Table 5. It is worth noting that in 91.7% bronchiectasis presented bilaterally, and in 87.5%, the lower lobes were involved. Bronchial wall thickening was present at 91.7% within the BC group. Moderate and severe airway dilation was observed in 37.5% of cases and 65% had air trapping. Emphysema was observed in 62.5% of cases.

To assess factors related to the presence of bronchiectasis, logistic regression analysis was used, and the criterion for selection was stepwise. The chance of having bronchiectasis was 4.78 times higher in the presence of PPM in sputum culture (CI 1.35-16.865; *P* = 0.023). In addition, the higher the distance covered in 6MWT (OR 1.01, CI 1.004; 1.0202, *P* = 0.0036) and the Slp3 value of the VCap (OR 1.04, CI 1.003; 1.077; *P* = 0.036), the greater the likelihood of bronchiectasis.

Within the BC group, the linear correlation analysis showed correlations with lung function and 6MWT, with worse values in both tests correlating with higher bronchiectasis scores. Data are shown in Table 6. Using the multiple linear regression analysis, it was possible to identify the variables related to the severity score of bronchiectasis within the BC group. The R^2 model was used to identify how much of the dependent variable

Table 1: Clinical, microbiological and quality of life data of COPD patients with or without bronchiectasis (BC x NBC

Variable	BC group (*n*=24)	NBC group (*n*=74)	*P*
Male/female, *n* (%)	15/9 (63%/37%)	47/27 64%/36%	0.929
Age, years	64.2±9.8	64.7±7.8	0.482
Tobacco load (pack/years)	42.8±42.7 23.8 (10-140) *	55.2±39.2 47.5 (10-208) *	0.038
BMI, Kg/m²	26.3±5.8	27.2±6.5	0.594
Symptoms and comorbidities			
Daily cough, *n* (%)	10 (41.7%)	31 (41.9%)	0.985
Daily sputum production, *n* (%)	7 (29.2%)	24 (32.4%)	0.765
Charlson comorbidity index- age	1.9±1.0	2.1±0.8	0.427
Systemic arterial hypertension, *n* (%)	8 (33.3%)	45 (60.8%)	0.019
Exacerbation (last year)	0.87±0.7	0.87±0.52	0.394
Therapy			
Long-acting beta agonists, *n* (%)	24 (100%)	74 (100%)	-
Long-lasting muscarinic antagonists, *n* (%)	23 (95.8%)	69 (93.2%)	1.000
Inhaled corticoids, *n* (%)	24 (100%)	74 (100%)	-
Macrolides, *n* (%)	3 (12.5%)	1 (1.4%)	0.044
Home oxygen therapy, *n* (%)	6 (25%)	25 (33.8%)	0.421
Sputum culture	(*n*=21)#	(*n*=53)#	0.074
PPM +, *n* (%)	11 (52.4%)	16 (30.2%)	
C-reactive protein (IU/mL)	(*n*=13)# 9.5±13.9	(*n*=25)# 11.0±16.3	0.735
GOLD 3 (*n*, %)	14 (58%)	37 (50%)	0.477
GOLD 4 (*n*,%)	10 (42%)	37 (50%)	
BODE index	3.7±1.5	4.5±1.5	0.029
MRC (range 1-4)	2.0±0.8	2.4±1.0	0.087

Values expressed as mean±standard deviation, unless (*), then expressed as median (minimum-maximum). #Values with reduced *n*. BMI: body mass index; PPM: potentially pathogenic micro-organism; BODE: body-mass index, airflow obstruction, dyspnea and exercise capacity index

Table 2: Functional data of COPD patients with or without bronchiectasis (BC x NBC)

Variable	BC group (*n*=24)	NBC group (*n*=74)	*P*
SpO_2 (%), room air	93.1±3.1	92.6±3.8	0.756
Lung function			
Post-BD FEV_1, % predicted	41.3±10.3	39.6±13.1	0.392
Post- BD FVC, % predicted	57.7±11.7	55.8±13.0	0.399
Post-BD $FEF_{25-75\%}$, % predicted	22.1±8.3	23.5±13.9	0.694
FEV_1 increase in FEV_1 after BD ≥10%, *n* (%)	6 (25%)	27 (36.5%)	0.301
6MWT			
6MWD, m	408.9±86.8%	351.5±87%	0.014
6MWD, % predicted[22]	84.4±20.6%	72.7±16.1%	0.019
6MWD, % predicted[23]	75.5±15.5%	64.7±15.3%	0.007
Δ SpO_2≥4%, *n* (%)	# (*n*=21) 11 (52.4%)	#(*n*=60) 36 (60%)	0.543
VCap			
$ETCO_2$ (mmHg)	36.2±5.5	35.1±6.9	0.445
Slp3 (mmHg/L)	38.5±17.7 * 32.9 (9.0-81.3)	33.4±18.2 * 29.4 (7.6-116.3)	0.091
Slp2 (mmHg/L)	253.2±121.5	252.3±119.1	0.924
$Slp3/ETCO_2$	1.1±0.4	0.9±0.5	0.128

Values expressed as mean±standard deviation, unless (*), then expressed as median (minimum-maximum). #Values with reduced *n*. SpO_2, peripheral oxygen saturation; FVC, forced vital capacity; BD, bronchodilator; FEV_1, forced expiratory volume per second; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% of FVC; 6MWD, 6-minute walked distance; Δ SpO_2, final SpO_2- initial SpO_2; $ETCO_2$, partial pressure of carbon dioxide at end-tidal; Slp2, slope of phase 2; Slp3, slope of phase 3.

Table 3: Microbiological characteristics of COPD patients with or without bronchiectasis (BC x NBC)

	BC group (*n*=21)#	NBC group (*n*=53)#	*P*
PPM +, *n* (%)	11 (52.4%)	16 (30.2%)	0.074
Pseudomonas (all)	3 (14.3%)	3 (5.7%)	
Staphylococcus aureus, n (%)	4 (19.0%)	5 (9.4%)	-
Haemophylus influenzae, n (%)	2 (9.5%)	3 (5.7%)	-
Streptococcus pneumoniae, n (%)	-	3 (5.7%)	-
Stenotrophomonas maltophilia, n (%)	1 (4.8%)	1 (1.9%)	-
Staphylococcus sp, n (%)	1 (4.8%)	-	-
Branhamella catarralis, n (%)	-	1 (1.9%)	-

#Reduced number of patients who collected sputum for microbiological analysis

Table 4: CT scoring of COPD patients with or without bronchiectasis (BC x NBC)

Computed Tomography scores	BC group (*n*=24)	NBC group (*n*=74)	*P*
Total score (0-77)	17.50±9.24	6.38±3.60	<0.0001
Bronchiectasis (extension + dilatation) (range 0-30)	7.75±5.77	0.14±0.51	-
Peribronchial thickening, *n* (%) (range 0-18)	22 (91.7%) 3.75±2.09	50 (67.6%) 1.78±1.73	<0.0001
Tree-in-bud/Mucoid plug, *n* (%) (range 0-6)	6 (25%) 0.67±1.93	4 (5.4%) 0.15±0.73	0.0739
Air trapping#, *n* (%) (range 0-6)	13 (65%) 2.40±2.37	16 (21.6%) 0.93±1.56	0.0105
Bullae, *n* (%)	3 (12.5%)	14 (18.9%)	0.455
Emphysema, *n* (%) (range 0-6)	15 (62.5%) 4.1±1.8	57 (77%) 4.1±1.9	0.258

Values expressed as mean±standard deviation. #Air trapping was evaluated only in patients with expiratory scan (*n*=20)

Table 5: Distribution and severity of CT findings in BC group (*n*=24)

CT findings	*n* (%)
Distribution	
Upper lobes	11 (45.8%)
Lower lobes	21 (87.5%)
Unilateral	2 (8.3%)
Bilateral	22 (91.7%)
Peribronchial thickening	
Light	22 (91.7%)
Moderate	2 (8.3%)
Dilation severity	
Light	21 (87.5%)
Moderate	7 (29.2%)
Severe	2 (8.3%)
Small airway findings	
Air trapping *	13 (65%)
Tree in bud	2 (8.3%)
Mucoid plug	4 (16.7%)
Other findings	
Bullae	3 (12.5%)
Emphysema	15 (62.5%)

*Air trapping was evaluated only in patients with expiratory scan (*n*=20)

can be explained by the variation of the independent variables that remained in the model, and we found that the higher the bronchiectasis score, the higher ΔSpO_2 during the 6MWT and the lower the FVC (% predicted post-bronchodilatator).

DISCUSSION

In this study, bronchiectasis was identified in 24.5% of the patients analyzed. Patients with bronchiectasis had a lower smoking load, and there was no significant difference in the other evaluated clinical parameters. Bronchiectasis has been identified in individuals with COPD with frequencies ranging from 18.8% to 57.6%,[4,6-9,23-28] and seems to be more frequent in more severe patients.[6-9,29]

In our study, we chose to include in the BC group patients in whom bronchiectasis had been identified in at least two lung lobes. It can be argued that the definition used was somewhat arbitrary, which could lead to a situation of underdiagnosis of bronchiectasis in the population studied. This option was made taking into account the fact that both peribronchial thickening and bronchial dilation, diagnosed by the increase in the bronchoarterial ratio – may occur without clinical significance in the elderly, asymptomatic people and even healthy subjects.[30-32] In addition, bronchial changes are frequent and expected within the clinical spectrum of COPD, and are therefore often observed when performing a CT scan. In view of these considerations, we chose to consider bronchiectasis when visible in at least two lobes as a way to reduce the chance of an occasional finding and without clinical significance.

Regarding demographic aspects, we found no differences between the BC and NBC groups. The predominance of males in the study agrees with the literature and may simply reflect the prevalence of COPD, still more common in men.[33,34] The mean age was 64.6 years and there was no difference between the groups.

Patients in the BC group had a lower tobacco load, and it is in fact an interesting and unusual finding. We identified another study with a similar finding,[28] although others did not find such a difference.[23] Further studies are needed to confirm the relevance of this finding.

The mean annual rate of exacerbations in the year before inclusion was 0.87 in both groups. Several studies[6,7,23,26] and two meta-analyses[35,36] reinforced the association between exacerbations and the presence of bronchiectasis. Furthermore, the presence of bronchiectasis in COPD is associated with more hospitalizations due to exacerbations[6,7,36] and higher mortality.[7,28,36] However, there are some studies that did not find an increase in exacerbations in patients with bronchiectasis.[9,29]

Positive PPM was more frequent in the BC group (52.4 vs. 30.2%), but it was not statistically significantly different (*P* = 0.074). Interestingly, the presence of positive PPM in the sputum increased the chance of having bronchiectasis in our patients. Indeed, several studies have shown that patients with COPD and bronchiectasis are more predisposed to having PPM

Table 6: Linear correlation coefficient between bronchiectasis score and variables of interest

	Post-BD FVC, % predicted	Post-BD FEV₁, % predicted	6MWD	SpO₂	Number of exacerbation
Bronchiectasis score					
r	−0.483	−0.462	0.146	−0.454	0.060
P	0.017	0.023	0.496	0.039	0.781
	ETCO₂	Slp2	Slp3	Fall SpO₂	
r	0.163	−0.168	0.268	0.482	
P	0.447	0.432	0.205	0.027	

SpO₂, peripheral oxygen saturation; FVC, forced vital capacity; BD, bronchodilator; FEV₁, forced expiratory volume per second; 6MWD, 6-minute walked distance; ETCO₂, partial pressure of carbon dioxide at end-tidal; Slp2, slope of phase 2; Slp3, slope of phase 3

in airway secretions.[6,8,9,27,35-37] Martinez-Garcia *et al*.[6] demonstrated that the persistence of PPM in sputum and hospitalization for exacerbation in the previous year were predictors of bronchiectasis in patients with COPD, and Gallego *et al*.[27] and Patel *et al*.[9] demonstrated that the extension of bronchiectasis is associated with an increased risk of isolation of PPM.

More patients in the BC group (87.5%) than in the NBC group (71.6%) collected sputum samples for microbiological culture. In the BC group, *Pseudomonas aeruginosa* was found in 14.3% of collected samples versus 5.7% in the NBC group. There are several studies with patients with bronchiectasis and COPD in which *Pseudomonas aeruginosa* was the most frequently found bacterium in airway secretions.[8,27,37] Perhaps the low number of collected samples in this study affected the result found, which was in disagreement with those authors.

Some studies have shown that patients with COPD and bronchiectasis with chronic infection of the airways have increased levels of inflammatory markers in the sputum,[6,9,38] which reinforces the association of PPM and chronic inflammation and progression of airway injury. In our study, we did not have the methodology for measuring inflammatory molecules in sputum. Despite this limitation, it is important to emphasize that the finding of peribronchial thickening, which results from chronic airway inflammation, was a very frequently found in our study. Similar finding were described by other authors,[6,37] which highlights the potential clinical relevance of identifying this structural abnormality.

Lung function and 6MWT

There is robust evidence of the association between lung function and the presence of bronchiectasis, wherein lower FEV₁ values are associated with the presence of bronchiectasis.[8,23,26] Comparing BC and NBC groups, there was no difference in spirometric values, and this can be explained by the fact that this was a homogenous severe sample of patients, with a mean FEV₁ of 1.1 L, which corresponded to 40% of the predicted value. Patel

et al.[9] studying a group of patients with a spirometric profile similar to ours also found no relationship between the severity of bronchiectasis and FEV₁ measurements. It is important to note that within the BC group, multiple regression analysis showed an association between the severity of the bronchiectasis score and lung function, in which the higher the CT scores, the lower the FVC and the FEV₁.

6MWT is a useful tool to access functional capacity in patients with COPD. We found that the walked distance was significantly lower in NBC compared with the BC group. COPD is a very heterogeneous disease, and as it is a condition defined only by FEV1, many clinical forms and phenotypes can be included under the heading. It is possible that by identifying patients with bronchiectasis within a sample of patients with severe COPD, we have separated these individuals from others in which there is no predominance of airway disease, but rather emphysema. Patients with emphysema phenotype walked shorter distances on the 6MWT compared with those with airway disease phenotype,[4] and this finding may be due to the greater mechanical disadvantage and dynamic hyperinflation of these individuals, which would greatly compromise their performance during exercise.

Another interesting finding is that oxygen desaturation during 6MWT occurred frequently in our patients. This is an early sign of low ventilation/perfusion ratios, a frequent finding in airway diseases.[39,40] Patel *et al*.[9] found a correlation between the bronchiectasis score and bacterial load with PaO₂. The authors suggest that hypoxemia could contribute to bronchial colonization, which would enhance the structural damage in the airways of patients with COPD. Indeed among the patients in the BC group, those with the highest scores desaturated the most on the 6MWT.

Volumetric capnography

We found higher values of Slp3 than those usually seen in normal subjects,[41,42] and similar to other studies that analysed VCap in patients with COPD.[4,41]

The phase 3 slope (Slp3) of the VCap represents the elimination of CO₂ from most alveoli. In normal individuals, Slp 3 is basically a plateau, with a slight upward slope and low values.[4] Elevation of Slp3 occurs in situations that lead to heterogeneous air distribution in distal air spaces and consequent reduction of contact between the new air that arrives at each inspiration with the air of the functional residual capacity. Thus, higher values of Slp3/EtCO₂ suggest the existence of structural damage in the lung periphery and greater heterogeneity in ventilation distribution.[41,43,44]

Airway diseases cause an increase in Slp3 compared to normal individuals,[41,43-46] and even considering patients with severe COPD, those with greater airway compromise (and less emphysema) have higher

Slp3.[4] In more emphysematous patients, especially in the centrilobular type, the impairment of ventilation has a heterogeneous and diffuse distribution, but it involves focal areas. In COPD with greater involvement of the airways, areas with reduced ventilation resulting from the subocclusion of terminal bronchioles also have a heterogeneous distribution, but they are more extensive and involve the entire region located downstream. Corroborating this association, we found that the higher the Slp3 value of the VCap, the greater the likelihood of bronchiectasis in our patients with COPD.

Tomographic findings

Among the spectrum of tomographic findings in the BC group, we highlight the bronchial wall thickening, which has been seen here in 91.7% of patients. Both dilation and thickening of the bronchial wall were generally mild, with bilateral distribution, preferentially involving the lower lobes (87.5%). The preferential involvement of the lower lobes has been described by several other authors.[6-9,29]

Air trapping was seen in 65% of patients in the BC group. In one of the few studies that evaluated air trapping in patients with COPD and bronchiectasis by quantitative tomography analysis, Bak *et al*.[29] reported a correlation between the severity of air trapping and the severity of bronchiectasis. It is known that air trapping is associated with higher mortality in patients with COPD,[47] which makes this finding even more relevant.

Emphysema was found in 62.5% of the BC group and in 77% of the NBC group. This data highlight how frequently the two main patterns of structural injury coexist in the individual with COPD. In addition, it reinforces how the definition of the disease only by FEV_1 is poor, placing under the same name as heterogeneous patients, with a wide range of structural injuries and functional repercussions.

Study limitations

One of the limitations of the study was the large number of patients lost due to difficulties in coming to the hospital for exams or even due to death (in a small number of cases). It is possible that the severity of the patients (one-third of them used home oxygen therapy) and the transport difficulties inherent to the population treated at a large public university hospital explain this high dropout rate.

Although all patients underwent HRCT, 35% had no expiratory scan, so it was not possible to assess air trapping in these patients. Another limitation of the study is that the findings refer to a sample of patients with severe COPD (GOLD III-IV), so the results cannot be extrapolated to other levels of severity of the disease.

Final comments

Bronchiectasis was found in 24.5% of patients with severe COPD, and among these patients, the more severe the structural lesion (the higher the bronchiectasis score), the worse the lung function and the greater the drop in oxygenation during exercise. Investigating the factors associated with bronchiectasis in COPD, we found that the chance of having bronchiectasis was 4.8 times higher in the presence of positive sputum culture. In addition, the higher the distance covered in 6MWT and the Slp3 value of the VCap, the greater the likelihood of bronchiectasis.

The great heterogeneity of structural and functional findings found in these individuals with severe COPD reinforces the need for evaluating these patients with multiple tools, in order to personalize the clinical and functional diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

There are no conflicts of interest.

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