Is Chronic Obstructive Pulmonary Disease An Independent Risk Factor For Coronary and Peripheral Atherosclerosis In Heavy Smokers?

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Abstract

BACKGROUND

There is a high prevalence of cardiovascular disease (CVD) and atherosclerosis in people with chronic obstructive pulmonary disease (COPD); sharing of risk factors could not be the only cause of the association.

OBJECTIVES

To verify whether coronary atherosclerosis and peripheral vascular disease are independently associated with COPD in heavy smokers. We also investigated whether inflammation and poor lung function were related with atherosclerosis findings.

METHODS

Heavy smokers (≥ 20 pack-years) with COPD (group 1) or normal spirometry (group 2) were recruited. Clinical, laboratory, and anthropometric data were obtained. Main interest variables were prevalence of CCS > 75 th percentile (P75), and rates of ABI $< 0,9$ by Doppler ultrasound. CVD risk was calculated using the Framingham risk score. Serum C-reactive protein (CRP) was measured, and lung function was assessed by spirometry. Differences between groups were compared using parametric and nonparametric tests as adequate.

RESULTS

Were included 87 patients, 49 with COPD (group 1). The mean $\pm$ SD age was 57.2 ± 6.0 years (58.7 ± 5.1 in group 1, 55.2 ± 6.6 in group 2, $p=0.006$). The mean FEV 1 % was 45.8 ± 17.24 vs. 91.7 ± 15.9 in groups 1 and 2, respectively; $p<0.05$. The mean smoking index was 48.6 ± 25.4 , higher in the COPD group ($p=0.037$). Stratification by Framingham score yielded a similar distribution in both groups. The frequency of patients with CCS $> P75$ was 55% vs. 66% in groups 1 and 2, respectively ($p=0.823$); ABI < 0.9 occurred in 6,3% vs 2,6%, respectively ($p=0.555$). CCS and ABI were not associated to FEV 1 %. CRP was inversely associated with VEF 1 ($r s= -0.419$; $p<0.001$), but unrelated to CCS ($r s= 0.136$; $p=0.265$) and ABI ($r s= -0.51$; $p=0.677$).

CONCLUSIONS

The studied coronary and peripheral atherosclerosis markers were similar between heavy smokers with COPD and those with normal spirometry. Nor serum CRP neither poor lung function related to CCS or ABI. Our results suggest absence of a independent association between COPD and atherosclerosis.

Background

Once considered a lung-limited disease originating mainly from smoking, chronic obstructive pulmonary disease (COPD) is now seen as a disease with systemic repercussions and multifactorial etiology, incorporating genetic and environmental influences (1).

Cardiovascular comorbidities are frequent in individuals with COPD, and are responsible for about 30–50% of deaths in this population (2–4). Epidemiological studies have suggested impaired pulmonary function as a predictor of general and cardiovascular mortality, especially in men (5), and have shown an association between COPD and clinical or subclinical atherosclerosis, regardless of conventional risk factors (6–13).

The primary objective of the present study was to verify whether coronary atherosclerosis and peripheral vascular disease are independently associated with COPD. In order to test this hypothesis, we compared the distribution of the variables in study in two groups of heavy smokers with similar CVD risk profile, being one group of individuals with COPD diagnosis and another with normal lung function. The secondary objective was to test for association of the evaluated atherosclerosis markers with systemic inflammation and pulmonary function in heavy smokers.

Methods

Patients

Individuals of both sexes, aged 45–70 years, with a smoking history equal to or greater than 20 pack-years and a diagnosis of COPD (group 1) or absence of respiratory symptoms and normal spirometry (group 2), in stable clinical condition, were recruited. All patients were selected consecutively from the outpatient COPD and smoking clinics of the Pulmonology Department of Hospital de Clínicas de Porto Alegre (HCPA), Brazil. For the definition of COPD, clinical (chronic respiratory symptoms and smoking) and functional criteria (FEV_1 /Forced Vital Capacity (FVC) ratio < 0.7) were used, according to the international Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines (14). Patients with clinically relevant pulmonary or systemic comorbidities (structural pulmonary or chest-wall alterations; history of lung transplantation, lung resection, or thoracic radiotherapy; metastatic malignancy; alpha-1 antitrypsin deficiency; myocardial revascularization or coronary angioplasty; lower-limb revascularization; atrial fibrillation; decompensated heart failure; collagen diseases; human immunodeficiency virus infection; chronic hepatitis; chronic renal failure with creatinine over 1.5 mg/dL; and cirrhosis of the liver), as well as those on regular corticosteroid therapy at doses over 30 mg/day, were excluded. Patients with mechanical heart valves or implantable cardiac devices that might interfere with image acquisition were also excluded. The study was approved by the institutional Research Ethics Committee from HCPA. All patients provided written informed consent prior to inclusion in the study.

Design

prospective, cross sectional, controlled study

Clinical data and cardiovascular risk profile

Clinical data were collected through interviews and analysis of medical records, using a standardized protocol. A standardized cardiovascular risk assessment questionnaire was applied; risk stratification was performed according to the Framingham Risk Score.(15)

Anthropometry, blood pressure (BP), and ankle–brachial index (ABI). Anthropometric data (weight, height and waist circumference) were measured as recommended by the World Health Organization (16). BP and ABI were measured according to American Heart Association guidelines (17). BP measurement was performed on the right arm (over the antecubital fossa) with an aneroid sphygmomanometer and stethoscope. For ABI calculation, systolic blood pressure was measured in the upper limbs (brachial artery) and lower limbs (posterior tibial artery and dorsal foot artery) by means of a sphygmomanometer and handheld 10-MHz Doppler device (Medmega Indústria de Equipamentos Médicos Ltda., Brazil). ABI was calculated for each side by the following formula:

Right ABI=(SBP_{t_{right}} /SBPb), where SBP_{t_{right}}=right ankle systolic BP and SBPb = highest systolic BP in the arms;

Left ABI= (SBP_{t_{left}} / SBPb), where SBP_{t_{left}}=left ankle systolic blood pressure and SBPb = highest systolic BP in the arms.

The lowest-value ABI between the two sides was recorded as the final index. ABI was considered indicative of peripheral arterial occlusive disease if < 0.9. (18–19)

Spirometry. Spirometry with bronchodilator test was performed at the Pulmonary Function Unit of the hospital Pulmonology Service, following American Thoracic Society recommendations and using reference values for the Brazilian population (20–21). The spirometric classification of the GOLD guideline (14) was used to classify as GOLD 1, 2, 3, and 4 those with a forced expiratory volume in the first second as percentage of predicted for age and height (FEV₁ %) in the following ranges, respectively: >80% of predicted, 50–80% of predicted, 30–50% of predicted, and ≤ 30% of predicted.

Coronary calcium score (CCS). All participants underwent non-contrast coronary computed tomography in a 64-row computed tomography (CT) scanner (Aquilion 64, Toshiba Medical Systems Corporation, Ōtawara, Japan). Electrocardiographic monitoring was performed to synchronize image acquisition with the diastolic phase. Axial slices of the chest were obtained, covering the entire cardiac area, with a slice thickness of 3.0 mm and a field of view of 200–220 mm. Image acquisition occurred during an average inspiratory pause of 15 seconds, as per a previously validated protocol (22). Coronary artery calcification was defined as an image of two contiguous pixels with an attenuation coefficient > 130 Hounsfield units (HU). The CCS was calculated by the Agatston method, multiplying the calcification area in square millimeters by a factor of 1, 2, 3, or 4, depending on the attenuation coefficients determined within the calcium pixels: Factor 1 was used for coefficients between 130 and 199 HU; factor 2, if 200–299 HU; factor 3, if 300–399 HU; and factor 4, for coefficients > 400 HU. The CCS was the sum of all the scores

obtained from all coronary arteries, in all CT sections, and was expressed in Agastston units (AU). The images were transferred to a dedicated workstation, where the CCS was calculated using specific software (Vitrea™, Vital Images Inc., MN, USA). (22) All scans were interpreted by the same radiologist, who was blinded to clinical condition and group allocation. To adjust the CCS values, each individual had their percentile determined according to predicted values for their age group, gender, and race/ethnicity, as reported in the Multi-Ethnic Study of Atherosclerosis (MESA). (23)

Laboratory data. High-sensitivity serum C-reactive protein (CRP), fasting blood glucose, total cholesterol, high density lipoprotein (HDL), and low density lipoprotein (LDL) measurements were obtained. When available, results of outpatient tests performed up to 3 months prior to study inclusion were accepted.

Statistical analysis. The variables were described as mean and standard deviation or as median and interquartile range, according to the type of distribution. Comparisons between groups were performed using Student’s *t*-test for independent samples for variables with normal distribution or the Mann–Whitney *U* test otherwise. Pearson’s correlation test (*R*) was used for normal distribution variables, and Spearman correlation test (*R_s*) for non-parametric variables. Chi-square or Fisher’s exact tests were used to compare distribution of categorical variables between groups. Multivariate analysis was planned with the aim of identifying an independent association of potential confounding factors identified in the univariate analysis. The estimated sample size was 68 individuals (34 in each group), considering an absolute difference of 25% in the frequency of patients with CCS > P75 for age between the two groups (25% in the group with normal spirometry and 50% in the group with COPD), and a statistical power of 80%. P-values of less than 5% (*p* < 0.05) were considered statistically significant. Statistical analysis was performed in the PASW Statistics 18.0 software package (IBM Corp, New York, NY, USA).

Results

A total of 87 individuals completed the research protocol (49 in group 1 and 38 in group 2), and were included in the analysis. The mean ± SD age was 57.2 ± 6.0 years, and most were women (63.7%). Regarding the spirometric classification of COPD, 2 (4.0%), 12 (24.4%), 26 (53.0%), and 9 (18.3%) individuals were classified as GOLD 1, 2, 3, and 4, respectively. Other anthropometric, clinical and laboratory data are described in Table 1.

Table 1. Sample characterization

<i>Demographic characteristics and smoking load</i>	TOTAL n=87	GROUP 1 n=49	GROUP 2 n=38	P value
Age (years)	57.2 ± 6.0	58.7 ± 5.1	55.2 ± 6.6**	0.006
Male, n (%)	29 (33.3)	19 (38.8)	10 (26.3)	NS
White, n (%)	68 (78.2)	36 (73.5)	32 (84.2)	NS
Smoking index (pack-years)	48.6± 25.4	53.6± 26.8	42.2 ± 22.1**	0.037
Current smokers (%)	44 (50.6)	18 (36.7)	28 (73.7)**	0.001
<i>Pulmonary function</i>				
FVC (L)	2.7 ± 0.85	2.41 ± 0.82	3.08 ± 0.75**	<0.0001
FVC%	81.4 ± 18.2	72.9 ± 16.83	92.4 ± 13.77**	<0.0001
FEV ₁ (L)	1.76 ± 0.85	1.24 ± 0.61	2.44 ± 0.62**	<0.0001
FEV ₁ %	65.9 ± 28.3	45.8 ± 17.24	91.7 ± 15.9**	<0.0001
FEV ₁ /FVC	0.63 ± 0.17	0.50 ± 0.10	0.79 ± 0.06**	<0.0001
PaCO ₂ (mmHg)	41.3±6.1	42.9 ±6.4	37.9 ± 3.4	0.006
PaO ₂ (mmHg)	73.8±18.0	68.4 ± 15.4	85.0 ± 18.8	0.002
<i>Anthropometric and laboratory measurements</i>				
Waist circumference (cm)	90 ± 13.7	90.3 ± 13.7	89.6 ± 14.0	NS
BMI (Kg/m ²)	26.6 ± 5.34	25.5 ±	28.1 ±	0.021
Systolic blood pressure (mmHg)	131.8 ± 17.0	133.1 ±15.4	130.1 ±19.1	NS
Diastolic blood pressure (mmHg)	87 ± 13.9	87.4 ± 10.2	86.3 ± 17.7	NS
Fasting blood glucose (mg/dL)	108.9 ± 34.8	101.4 ±	118.0 ±	0.04
Total cholesterol (mg/dL)	208.3 ± 42.1	210.4 ±	205.7 ±	NS
HDL cholesterol (mg/dL)	48.3 ± 13.4	51.5 ±	44.3 ± **	0.011

LDL cholesterol (mg/dL)	125.2 ± 39.2	129.5 ± 38.5	120.3 ± 40.0	NS
Triglycerides (mg/dL)	168.6 ± 119.6	139.3 ± 84.7	204.0 ± 144.9	0.019
Diabetes mellitus [‡] , n (%)	18 (21)	8 (16)	10 (26)	NS
Hypertension [£] , n (%)	47 (54)	28 (57)	19 (50)	NS
<i>Medication use</i>				
Statins, n (%)	23 (26)	10 (20)	13 (34)	NS
Beta-blockers, n (%)	10 (11)	4 (8)	6 (16)	NS
Diuretics, n (%)	24 (28)	14 (29)	10 (26)	NS
ACE inhibitors/angiotensin II receptor antagonists, n (%)	26 (30)	16 (33)	10 (26)**	NS
Inhaled corticosteroids, n (%)	38 (44)	35 (71)	3 (8)**	<0.001
<i>Framingham Risk Score</i>				0.326
Low (<10%), n (%)	14 (16)	10 (20)	4 (10)	
Intermediate (10-20%), n (%)	36 (41)	21 (43)	15 (39)	
High (>20%), n (%)	37 (42)	18 (37)	19 (50)	

Group 1: Smokers with COPD; Group 2: Smokers with normal spirometry findings. Continuous variables presented as mean ± standard deviation or median (interquartile range) as appropriate; categorical variables presented as absolute and relative frequencies. BMI, body mass index; FEV₁, forced expiratory volume in the first second; FEV₁%, FEV₁ as percentage of predicted value; FVC, forced vital capacity; FVC%, FVC as percentage of predicted; HDL, high-density lipoprotein; LDL, low-density lipoprotein

[#]According to Framingham risk score. [‡]Defined by treatment with oral antidiabetics or insulin, or fasting blood glucose higher than 126 mg/dL, or 2-h postchallenge blood glucose higher than 200 mg/dL;

[£]Patient-reported and/or defined by intake of antihypertensive medications; NS: Non-significant ($p \geq 0.05$).

CCS measurements exceeding the 75th percentile of the MESA study for age, sex, and race/ethnicity were observed in 59.8% of the sample. Abnormal ABI (≤ 0.9 or > 13) was found in 13 patients (15.1%); 4 patients (4.7%) had an ABI lower than 0.9, indicative of peripheral arterial disease. When comparing the groups with and without COPD, no statistically significant difference was observed in absolute CCS values ($p = 0.170$), prevalence of ABI < 9.0 ($p = 0.555$), or abnormal ABI ($p = 0.877$). Table 2 shows the results related to the outcomes of interest stratified by group.

Table 2
Coronary calcium score, ankle–brachial index, and C-reactive protein levels in heavy smokers with and without COPD

Variable	Total n = 87	Group 1 n = 49	Group 2 n = 38	P
Median CCS, AU (IQR)	11 (0–175.0)	19 (0–188.5)	0 (0–113)	NS
CCS > P ₇₅ , n (%)	52 (60)	27 (55)	25 (66)	NS
Median ABI (IQR)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.1–1.2)	NS
ABI < 0.9, n (%)	4 (4.7)	3 (6.3)	1 (2.6)	NS
Median CRP, mg/dL (IQR)	4.0 (3.0–12.8)	5.3 (4.0–19.6)	3.0 (3.0–12.0)	0.01
Group 1: Heavy smokers with COPD; Group 2: Heavy smokers with normal spirometry. AU, Agatston units; CCS, coronary calcium score; ABI, ankle-brachial index; CRP, high-sensitivity C-reactive protein; NS, p ≥ 0.05.				

On multivariate analysis, including sex, age, smoking index, and BMI, there was no association between COPD and CCS > P₇₅. The only predictor of coronary atherosclerosis identified in the samples was female gender (PR = 1.19; p = 0.020); a borderline association with age (p = 0.055) was observed.

There was no statistically significant difference between the two groups in CVD risk distribution. Framingham score presented a positive and statistically significant correlation with CCS values, and an inverse correlation with ABI (Table 3).

Table 3
Coefficients of correlation between atherosclerosis outcomes and variables associated with airway obstruction, smoking, systemic inflammation and cardiovascular risk (r_s).

	FEV ₁	Smoking Index	CRP	Framingham Risk Score
CCS	-0.0148; p = 0.171	0.223; p = 0.038	0.136; p = 0.265	0.303; p = 0.004
ABI	0.09; p = 0.395	0.280; p = 0.01	0.136; p = 0.265	-0.231; p = 0.016
FEV ₁ , forced expiratory volume in the first second; CCS, coronary calcium score; CRP, C-reactive protein; ABI, ankle–brachial index.				

Serum CRP was significantly higher in the COPD group; in fact, serum CRP correlated positively with smoking load ($r_s=0.291$, p = 0.015) and inversely with FEV₁% ($r_s = - 0.419$; p < 0.001). Similarly, the FEV₁/FVC ratio correlated inversely with CRP ($r_s = - 0.328$; p = 0.006). nor CCS or ABI were significantly related to CRP levels (Table 3).

Discussion

The study sample consisted of heavy smokers, over age 50, mostly women, and with a predominantly moderate to high cardiovascular risk profile. Coronary calcifications were highly prevalent, and more than half of the sample had evidence of coronary atherosclerosis (identified by CCS values exceeding the 75th percentile of the MESA study). However, although smoking is an established risk factor for peripheral arterial disease, relatively few individuals had abnormal ABI values.

In contrast to what was suggested by previous studies, such as Rasmussen *et al.* (8), the presence of COPD was not associated with a higher prevalence of atherosclerosis outcomes. The systemic inflammation marker used (serum CRP) showed a weak correlation with pulmonary function, but not with atherosclerosis markers.

The parameters used for comparison of CCS between groups (≥ 400 AU in absolute terms, or $> P75$ in relative terms) are indicators of severe atherosclerotic impairment in the case of absolute values, whereas CCS by the MESA already contemplates factors predictive of CCS (age, gender, race) (23–25). Comparison of their distribution in relation to the predicted values for age, gender, and race/ethnicity, defined for each individual, rather than comparing the distribution of absolute CCS values between the groups, also enhances the quality of our analysis. In the absence of predicted values for both sexes in the Brazilian population, data for the U.S. population were used instead. The MESA study was chosen because its data are widely used, and are considered compatible from the epidemiological point of view.

ABI measurement is easy to perform, inexpensive, and values ≤ 0.9 have good accuracy for detecting peripheral arterial disease (17). Values below this threshold were relatively uncommon in both groups, and were weakly associated with smoking load and cardiovascular risk profile. This finding could be explained by the variable sensitivity of the method, which seems to be lower in older adults and patients with diabetes (26–29).

Several studies have reported similar results to ours, including Frantz *et al.* (30), Sverzellati *et al.* (31), Romme *et al.* (32), and Williams *et al.* (33). In the study by Frantz *et al.* (30), 450 smokers, former smokers, and non-smokers who had participated in research on respiratory symptoms underwent carotid ultrasonography to identify atherosclerotic plaques. Individuals with atherosclerotic plaques had lower diffusing capacity of lungs for carbon monoxide (DLco) and higher pulmonary residual volume than individuals without plaques. However, FEV1% and COPD diagnosis were not independently correlated with markers of coronary atherosclerosis. Sverzellati *et al.* (31) evaluated CCS and pulmonary attenuation by CT in a cohort of 1159 heavy smokers who had participated in a screening study for lung cancer. In this study, CCS was not significantly associated with pulmonary emphysema or FEV1%. Likewise, there was no association between CCS and smoking load. This study had a number of limitations, including the measurement of FEV₁ without bronchodilators, the use of relatively thick CT slices (5 mm) to calculate the CCS, and the lack of data referring to cardiovascular risk factors. Despite the smaller sample, the present study avoided these limitations; even so, no association of COPD with CCS was

observed. Romme *et al.* (32) studied 119 individuals with COPD in order to evaluate the relationship between COPD, atherosclerosis, and osteoporosis. In their study, CCS did not correlate with FEV₁% or with the extent of emphysema on CT.

Williams *et al.* (33) evaluated the CCS in a historical cohort of 942 individuals, 672 of whom had COPD. Their objective was to evaluate the association of coronary calcification with airway obstruction severity, functional capacity, and clinical outcomes in patients with COPD. The median of CCS values was significantly higher in individuals with COPD than in smokers without COPD and non-smokers (128 AU, 75 UA, and 0 AU, respectively; $p < 0.001$). Individuals with COPD also presented CCS values in higher percentiles (based on the MESA study) compared to smokers without COPD and non-smokers. However, the CCS was associated with smoking load, but not with FEV₁%, as observed in our study. This disagreement may be explained by differences in sample characteristics such as age and gender. One possible limitation is the fact that the results were not adjusted for known cardiovascular risk factors, such as hypertension. Although this condition was more prevalent in the COPD group, the Framingham Cardiovascular Risk score (15), which takes into account systolic BP, was similar between groups. A 2017 systematic review (34) showed an association between subclinical carotid atherosclerosis and COPD. In this review, which included 20 studies (2082 individuals with COPD and 4844 controls), common carotid artery intima-media thickness (CCA-IMT) and carotid plaques were used as surrogate markers of subclinical atherosclerosis and predictors of cardiovascular events. Patients with COPD had significantly higher CCA-IMT values (mean difference 0.201 mm; 95% CI: 0.142, 0.260; $p < 0.001$), and a higher prevalence of carotid plaque (OR 2.503; 95%CI: 1.333–2.175; $p < 0.0001$). The severity of COPD was associated with the difference in risk of carotid plaque. Other covariates, including baseline smoking status and cardiovascular risk profile, were not associated with the risk difference. Potential limitations of this meta-analysis, however, include significant heterogeneity across studies and the consideration of baseline smoking status rather than smoking load itself (pack-years) in the meta-regression models.

In one cross-sectional study (8), long-standing smokers who participated in the Danish Lung Cancer Screening Trial ($n = 1535$) were classified into CCS bands according to Agatston score and into levels of airflow obstruction according to GOLD consensus criteria (14). Multivariate analysis including age, male gender, hypercholesterolemia, hypertension, and active smoking showed an independent correlation between COPD and coronary calcification; the risk for calcification in the coronary arteries was higher among individuals with severe obstruction in relation to those without COPD (OR 1.32; 95%CI 1.05–1.67).

In the present study, the hypothesis of association between systemic inflammation and atherosclerosis in smokers was also evaluated. The rationale for this hypothesis is the fact that atherosclerosis and COPD are diseases with a known inflammatory substrate, and that the systemic inflammation observed in COPD contributes to the progression of atherosclerosis (35–38). We observed that increased CRP levels correlated with airflow limitation, which is congruent with literature data (38–40). However, there was no association between serum CRP levels and the evaluated atherosclerosis outcomes. This finding is consistent with the results of a systematic review conducted by Hamirani *et al.* (41), which investigated the association between inflammatory markers and coronary atherosclerosis, assessed tomographically

by calcium score. This review included 12 studies evaluating the association of levels of a series of markers (CRP, fibrinogen, metalloproteinase 9, monocyte chemotactic protein, resistin, lipoprotein-associated phospholipase A2, interleukin 6, tumor necrosis factor alpha, and fibroblast transforming growth factor-beta) with atherosclerosis. In most studies, there was a weak correlation between inflammatory markers and coronary calcification. The association was more often found in women; however, it disappeared after adjusting for traditional risk factors such as weight and body mass index. The authors concluded that there was no conclusive evidence of association between molecular markers of inflammation and coronary calcification.

We observed a higher frequency of statin use by smokers without COPD in relation to those with the disease, although the difference was not statistically significant and both groups had similar cardiovascular risk. This finding is likely to relate to recent evidence that individuals with COPD receive fewer interventions with a high degree of recommendation for the prevention and treatment of cardiovascular disease than individuals without COPD (42).

As explained above, studies evaluating the association between COPD and cardiovascular disease have been fraught with methodological issues, including inaccurate definitions of COPD and lack of adjustment for potential confounding factors, such as the presence of comorbidities, smoking load, and cardiovascular risk profile (36, 37). Unlike many studies investigating the association between atherosclerosis and COPD, ours was prospectively designed, and clinical and functional criteria were used to define COPD. The exclusion of patients with pulmonary and systemic comorbidities that could act as confounding factors aimed to reduce the potential for biases. Although both groups were characterized by a history of heavy smoking, tobacco exposure was significantly higher among patients with COPD, as demonstrated by the smoking index. Another strength of the study is that both groups had similar cardiovascular risk profiles, which could help elucidate the potential independent effect of COPD on the development of atherosclerosis.

Limitations of our study include the lack of the statistical power to demonstrate a smaller difference than initially estimated in CCS measures, as well as the cross-sectional design, which cannot demonstrate causality. Actually, CCS > P75 was numerically more frequent in smokers with COPD; in fact, it's possible that the absence of statistically significant difference was due to a small sample. However, our findings do not support a difference of great magnitude between the groups in terms of coronary or peripheral atherosclerosis. If any such difference exists, it may be of questionable clinical relevance. The predominance of female participants may reduce the generalizability of our data to both sexes.

Conclusion

Results are compatible with the absence of an strong independent association between COPD and parameters of coronary and peripheral atherosclerosis in heavy smokers. These findings corroborate the idea that smoking cessation, as long as the control of other cardiovascular risk factors, play a central role

in the prevention of atherosclerotic disease in smokers with COPD, as they do in patients without the disease.

Abbreviations

ABI – Ankle-brachial index

ACE – Angiotensin conversion enzyme

AU – Agatston units

BMI – Body mass index

BP – Blood pressure

CAPES - Coordination for the Improvement of Higher Education Personnel

CCA-IMT – Common carotid artery intima-media thickness

CCS – Coronary calcium score

CI – Confidence interval

CNPq - Brazilian National Council on Scientific and Technological Development

COPD – Chronic obstructive pulmonar disease

CVD – Cardiovascular disease

CRP – C-reactive protein

CT – Computerized tomography

DLco – Diffusion capacity of lungs for carbono monoxide

FEV1 – Forced expiratory volume in one second

FEV1 % - Forced expiratory volume in one second as percent of predicted

FVC – Forced vital capacity

FVC % - Forced vital capacity as percent of predicted

HCPA - Hospital de Clínicas de Porto Alegre

HU – Hounsfield units

HDL – high-density lipoprotein

LDL – low-density lipoprotein

MESA – Multi Ethnic Study of Atherosclerosis

NS- Non statistically significant

OR – Odds ratio

PaO₂ – Arterial partial pressure of oxygen

PaCO₂ - Arterial partial pressure of carbon monoxide

R_s – Spearman correlation

SBP – Systolic blood pressure

SBP_b – Highest systolic blood pressure in arms

UFRGS – Federal University of Rio Grande do Sul

Declarations

Ethical approval and consent to participate

The study was approved by the institutional research ethics committee at Hospital de Clínicas de Porto Alegre. All patients provided written informed consent (standardized form provided by the local research ethics committee) prior to inclusion in the study.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author on reasonable request.

Competing interests

The authors have no competing interests to declare.

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Authors' contributions

MAPF designed the study, supervised the data acquisition, analyzed and interpreted the data, and wrote the manuscript. MMK and LBM participated of the study conception, interpreted the data and reviewed the manuscript; FST conducted and interpreted all the coronary tomography exams, participated on the analysis of CCS data and reviewed the manuscript. All the authors read and approved the final version.

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