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

Maria Angélica Pires Ferreira (mpiferreira@hcpa.edu.br)  
Hospital de Clinicas de Porto Alegre  https://orcid.org/0000-0003-0961-524X

Leila Beltrami Moreira  
UFRGS Universidade Federal do rio Grande Do Sul

Felipe Soares Torres  
UFRGS: Universidade Federal do Rio Grande do Sul

Marli Maria Knorst  
Universidade Federal do Rio Grande do Sul

Research

Keywords: chronic obstructive pulmonary disease, smoking, atherosclerosis, cardiovascular disease, coronary-artery calcium score, ankle-brachial index

DOI: https://doi.org/10.21203/rs.3.rs-91443/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
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 > 75th 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 ± 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:

\[
\text{Right ABI} = \frac{\text{SBP}_{\text{right}}}{\text{SBP}_{b}}, \quad \text{where SBP}_{\text{right}} = \text{right ankle systolic BP and SBP}_{b} = \text{highest systolic BP in the arms;}
\]

\[
\text{Left ABI} = \frac{\text{SBP}_{\text{left}}}{\text{SBP}_{b}}, \quad \text{where SBP}_{\text{left}} = \text{left ankle systolic blood pressure and SBP}_{b} = \text{highest systolic BP in the arms.}
\]

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 (FEV$_1$ %) 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 (Rₚ) 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
Demographic characteristics and smoking load

|                      | TOTAL | GROUP 1 | GROUP 2 | P value |
|----------------------|-------|---------|---------|---------|
|                      | n=87  | n=49    | n=38    |         |
| 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   |

Pulmonary function

|                      |     |         |         |         |
|----------------------|-----|---------|---------|---------|
| 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 |
| FEV₁ (L)             | 1.76 ± 0.85 | 1.24 ± 0.61 | 2.44 ± 0.62** | <0.0001 |
| FEV₁%                | 65.9 ± 28.3 | 45.8 ± 17.24 | 91.7 ± 15.9** | <0.0001 |
| FEV₁/FVC             | 0.63 ± 0.17 | 0.50 ± 0.10 | 0.79 ± 0.06** | <0.0001 |
| PaCO₂ (mmHg)         | 41.3±6.1 | 42.9 ±6.4 | 37.9 ±3.4 | 0.006 |
| PaO₂ (mmHg)          | 73.8±18.0 | 68.4 ±15.4 | 85.0 ±18.8 | 0.002 |

Anthropometric and laboratory measurements

|                      |     |         |         |         |
|----------------------|-----|---------|---------|---------|
| Waist circumference (cm) | 90 ± 13.7 | 90.3 ± 13.7 | 89.6 ± 14.0 | NS      |
| BMI (Kg/m²)           | 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 ± | 0.004   |
| HDL cholesterol (mg/dL) | 48.3 ± 13.4 | 51.5 ± 44.3 ± ** | 0.011   |
|                     | Group 1 | Group 2 | Group 3 |     |
|---------------------|---------|---------|---------|-----|
| 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  |

**Medication use**

|                     | Group 1 | Group 2 | Group 3 |     |
|---------------------|---------|---------|---------|-----|
| 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 |

**Framingham Risk Score**

|                     | Group 1 | Group 2 | Group 3 |     |
|---------------------|---------|---------|---------|-----|
| 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 ≥ 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     | Group 1     | Group 2     | P       |
|---------------------------|-----------|-------------|-------------|---------|
|                           | n = 87    | n = 49      | n = 38      |         |
| Median CCS, AU (IQR)      | 11 (0–175.0) | 19 (0–188.5) | 0 (0–113)  | NS      |
| CCS > P<sub>75</sub>, 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 > P<sub>75</sub>. 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<sub>s</sub>).

|         | FEV<sub>1</sub> | Smoking Index | CRP     | Framingham Risk Score |
|---------|-----------------|---------------|---------|-----------------------|
| CCS     | -0.0148;        | 0.223;        | 0.136;  | 0.303; p = 0.004      |
|         | p = 0.171       | p = 0.038     | p = 0.265 |                       |
| ABI     | 0.09;           | 0.280;        | 0.136;  | -0.231;               |
|         | p = 0.395       | p = 0.01      | p = 0.265 | p = 0.016             |

FEV<sub>1</sub>, 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<sub>s</sub> = 0.291, p = 0.015) and inversely with FEV1% (r<sub>s</sub> = − 0.419; p < 0.001). Similarly, the FEV<sub>1</sub>/FVC ratio correlated inversely with CRP (r<sub>s</sub> = − 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 FEV$_1$ % 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 FEV$_1$ %, 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 pulmonary disease

CVD – Cardiovascular disease

CRP – C-reactive protein

CT – Computerized tomography

DLco – Diffusion capacity of lungs for carbon 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
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.

Funding

This study was funded by the Brazilian National Council on Scientific and Technological Development (CNPq) and by the Coordination for the Improvement of Higher Education Personnel (CAPES).

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.

Acknowledgements

The authors acknowledge the valuable contributions of the students Fernanda Mossatte (Nursing School-UFRGS) and Mariana Hoffmeister (Medicine School-UFRGS).

References

1. Diaz-Guzman E, Mannino DM. Epidemiology and prevalence of chronic obstructive pulmonary disease. Clin Chest Med. 2014;35(1):7–16.
2. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med. 2002;166(3):333–9.
3. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. Eur Respir J. 2006;28(6):1245–57.
4. Maclay JD, McAllister DA, Macnee W. Cardiovascular risk in chronic obstructive pulmonary disease. Respirology. 2007;12(5):634–41.
5. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ. 1996;313(7059):711–5.
6. Faxon DP, Fuster V, Libby P, Beckman JA, Hiatt WR, Thompson RW, et al. Atherosclerotic Vascular Disease Conference: Writing Group III: pathophysiology. Circulation. 2004;109(21):2617-25.
7. Castagna O, Boussuges A, Nussbaum E, Marqueste L, Brisswalter J. Peripheral arterial disease: an underestimated aetiology of exercise intolerance in chronic obstructive pulmonary disease patients. Eur J Cardiovasc Prev Rehabil. 2008;15(3):270–7.
8. Rasmussen T, Øbøer L, Pedersen JH, Dirksen A, Thomsen LH, Stender S, et al. Relationship between chronic obstructive pulmonary disease and subclinical coronary artery disease in long-term smokers. Eur Heart J Cardiovasc Imaging. 2013;14(12):1159–66.
9. Dransfield MT, Huang F, Nath H, Singh SP, Bailey WC, Washko GR. CT emphysema predicts thoracic aortic calcification in smokers with and without COPD. COPD. 2010;7(6):404–10.
10. McAllister DA, MacNee W, Duprez D, Hoffman EA, Vogel-Claussen J, Criqui MH, et al. Pulmonary function is associated with distal aortic calcium. not proximal aortic distensibility. MESA lung study. COPD. 2011;8(2):71–8.
11. Zureik M, Kauffmann F, Touboul PJ, Courbon D, Ducimetière P. Association between peak expiratory flow and the development of carotid atherosclerotic plaques. Arch Intern Med. 2001;161(13):1669–76.
12. Stone IS, Barnes NC, Petersen SE. Chronic obstructive pulmonary disease: a modifiable risk factor for cardiovascular disease? Heart. 2012;98(14):1055–62.

13. Kim SJ, Yoon DW, Lee EJ, Hur GY, Jung KH, Lee SY, et al. Carotid atherosclerosis in patients with untreated chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2011;15(9):1265–70.

14. 2018 Global Strategy for Prevention, Diagnosis and Management of COPD. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf.

15. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486–97.

16. World Health Organization Consultation of Obesity. Obesity: Preventing and Managing the Global Epidemic. Geneva. Switzerland: Division of Non-communicable Diseases. Programme of Nutrition. Family and Reproductive Health. WHO [Internet]. 1998 2000.updated 2004. Available from: http://apps.who.int/iris/bitstream/10665/42330/1/WHO_TRS_894.pdf?ua=1.

17. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement from the American Heart Association. Circulation. 2012;126(24):2890–909.

18. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation. 1993;88(3):837–45.

19. Tendera M, Aboyans V, Bartelink ML, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases. Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2851–906.

20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.

21. Pereira CAC, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. Jornal Brasileiro de Pneumologia. 2007;33:397–406. Available from http://www.scielo.br/pdf/jbpneu/v33n4/en_v33n4a08.pdf.

22. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte MJr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827–32.

23. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of Coronary Artery Calcium by Race, Gender, and Age: Results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006;113(1):30–7.
24. Budoff MJ, Nasir K, McClelland RL, Detrano R, Wong N, Blumenthal RS, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2009;53(4):345–52.

25. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004;291(2):210–5.

26. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300(2):197–208.

27. Price JF, Stewart MC, Douglas AF, Murray GD, Fowkes GF. Frequency of a low ankle brachial index in the general population by age, sex and deprivation: cross-sectional survey of 28,980 men and women. Eur J Cardiovasc Prev Rehabil. 2008;15(3):370–5.

28. Dachun X, Jue L, Liling Z, Yawei X, Dayi H, Pagoto SL, et al. Sensitivity and specificity of the ankle-brachial index to diagnose peripheral artery disease: a structured review. Vasc Med. 2010;15(5):361–9.

29. Xu D, Zou L, Xing Y, Hou L, Wei Y, Zhang J, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. Can J Cardiol. 2013;29(4):492–8.

30. Frantz S, Nihlén U, Dencker M, Engström G, Löfdahl CG, Wollmer P. Atherosclerotic plaques in the internal carotid artery and associations with lung function assessed by different methods. Clin Physiol Funct Imaging. 2012;32(2):120–5.

31. Sverzellati N, Cademartiri F, Bravi F, Martini C, Gira FA, Maffei E, et al. Relationship and prognostic value of modified coronary artery calcium score, FEV1, and emphysema in lung cancer screening population: the MILD trial. Radiology. 2012;262(2):460–7.

32. Romme EA, McAllister DA, Murchison JT, Van Beek EJ, Petrides GS, Price CO, et al. Associations between COPD related manifestations: a cross-sectional study. Respir Res [Internet]. 2013 PMC3840707]; 14(1):[129 p.]. Available from: http://respiratory-research.com/content/14/1/129.

33. Williams MC, Murchison JT, Edwards LD, Agustí A, Bakke P, Calverley PM, et al. Coronary artery calcification is increased in patients with COPD and associated with increased morbidity and mortality [Epub ahead of print]. Thorax [Internet]. 2014 Jan 2014. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24473329.

34. Ambrosino P, Lupoli R, Cafaro G, Iervolino S, Carone M, Pappone N, Di Minno MND. Subclinical carotid atherosclerosis in patients with chronic obstructive pulmonary disease: a meta-analysis of literature studies. Ann Med. 2017;49(6):513–24.

35. Gotsman I, Stabholz A, Planer D, Pugatsch T, Lapidus L, Novikov Y, et al. Serum cytokine tumor necrosis factor-alpha and interleukin-6 associated with the severity of coronary artery disease: indicators of an active inflammatory burden? Isr Med Assoc J. 2008;10(7):494–8.

36. Fimognari FL, Scarlata S, Conte ME, Incalzi RA. Mechanisms of atherothrombosis in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2008;3(1):89–96.
37. Fimognari FL, Scarlata S, Antonelli-Incalzi R. Why are people with "poor lung function" at increased atherothrombotic risk? A critical review with potential therapeutic indications. Curr Vasc Pharmacol. 2010;8(4):573–86.

38. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59(7):574–80.

39. Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM. Raised CRP levels mark metabolic and functional impairment in advanced COPD. Thorax. 2006;61(1):17–22.

40. Karadag F, Karul A, Cildag O, Yilmaz M, Ozcan H. Biomarkers of systemic inflammation in stable and exacerbation phases of COPD. Lung. 2008;186:403–9.

41. Hamirani YS, Pandey S, Rivera JJ, Ndumele C, Budoff MJ, Blumenthal RS, et al. Markers of inflammation and coronary artery calcification: a systematic review. Atherosclerosis. 2008;201(1):1–7.

42. Andell P, Koul S, Martinsson A, Sundström J, Jernberg T, Smith JG, et al. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. Open Heart [Internet]. 2014; 1(1). Available from: http://openheart.bmj.com/content/1/1/e000002.abstract.