Association between carotid intima-media thickness and presence of coronary artery disease in chronic obstructive pulmonary disease patients

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Abstract

Objective: Chronic obstructive pulmonary disease (COPD) is a risk factor for cardiovascular disease (CVD). Carotid intima-media thickness (CIMT) is the sign of subclinical atherosclerosis. Therefore, the aim of this study was to evaluate whether CIMT measurement is related with significant coronary artery disease (CAD) in patients with COPD, similar to those without COPD.

Methods: One hundred and eight patients with previously diagnosed COPD and 78 patients without COPD who underwent coronary angiography (CAG) were enrolled in this prospective cross-sectional study. Carotid artery ultrasonography was performed on all patients after coronary angiography by another operator who was blind to the CAG results. The patients were divided into four subgroups as follows: group 1: COPD (–) and CAD (–); group 2: COPD (–) and CAD (+); group 3: COPD (+) and CAD (+); and group 4: COPD (+) and CAD (–). Patients with previous coronary revascularization, carotid artery disease, and lung disease other than COPD were not enrolled in this study. The student's t-test, chi-square analysis, multiple logistic regression analysis, and receiver operating characteristic (ROC) curve were used for statistical analysis.

Results: CIMT was found to be highest in patients with both significant CAD and COPD (group 3) ($p<0.05$). Among the 108 COPD patients, the odds ratio associated with the CIMT >1.25 mm to predict CAD was 12.4. The area under the ROC curve for a cut-off value of 1.25 mm for CIMT to predict CAD in COPD patients was calculated as 0.913, with a sensitivity of 89.7% and specificity of 86.7%.

Conclusion: CIMT has a predictive value for the presence of CAD in patients with COPD. Further studies are needed to validate our results.
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Keywords: chronic obstructive pulmonary disease, coronary artery disease, carotid intima-media thickness

Introduction

Chronic obstructive pulmonary disease (COPD) is an irreversible disease that occurs as a result of an abnormal inflammatory response of the lungs and is characterized by a progressive obstruction of airflow (1). It is one of the most frequent causes of mortality and morbidity in adults (2, 3). Because COPD is an independent risk factor for cardiovascular diseases, a large portion of deaths in patients with COPD is associated with cardiovascular diseases (4–8). Although the relationship between COPD and cardiovascular disease has been shown, the diagnosis of coronary artery disease (CAD) with non-invasive tests displays some difficulties in COPD patients because of suboptimal echocardiographic imaging or inadequate duration of exercise because of COPD-related dyspnea.

One of the most widely used, simple, non-invasive atherosclerosis imaging methods is the carotid intima-media thickness (CIMT) measurement. CIMT is an indicator of atherosclerosis, and studies have shown that it is an indicator of cardiovascular events and mortality (9–12). It has also been found to be associated with CAD, coronary atherosclerotic load, endothelial dysfunction, and mitral annular calcification, which has a value in the prediction of atherosclerosis and arrhythmias (13–19).

Previous studies have demonstrated that CIMT increased and correlated with the severity of airflow obstruction in patients with COPD (20–22). Moreover, increased CIMT in patients with COPD has been found to be associated with deaths from cardiovascular diseases (23). Various hypotheses have been discussed to explain the association between COPD and increased CIMT. It has been

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speculated that increased CIMT occurring in COPD may be due to hypoxia, systemic inflammation, and endothelial dysfunction rather than traditional lipid-driven atherosclerosis of coronary arteries (22). The literature concerning the relationship between the lung function, CIMT, atherosclerosis of coronary or peripheral arteries, and the underlying mechanisms is quite limited. Furthermore, there is no study investigating the particular relationship between CIMT and presence of significant CAD in COPD patients. In this study, we aimed to investigate whether the CIMT measurement can be used in predicting significant CAD in patients with COPD, similar to those without COPD.

Methods

Study design and patient selection

This is a prospective cross-sectional study including 108 patients with COPD and 78 patients without COPD. In total, 121 patients with previously diagnosed COPD and 83 patients without COPD who applied to the cardiology outpatient clinic between February 2013 and February 2014 were enrolled in the study consecutively. The exclusion criteria were as follows: chronic lung disease other than COPD, previous coronary revascularization and carotid artery surgery, cerebrovascular disease, acute coronary syndrome, severe valvular heart disease, atrial fibrillation, history of malignancy or inflammatory disease, hepatic or renal insufficiency and receiving anticoagulation, and antiplatelet or statin treatment. Thirteen patients with COPD and five patients without COPD were excluded because of refusal of coronary angiography or lack of carotid ultrasound results. Thus, the final number of patients included in our analysis became 108 patients with COPD and 78 patients without COPD. All patients underwent coronary angiography because of suspicion of CAD based on their symptoms or diagnostic tests. History of diabetes mellitus, hypertension, dyslipidemia, smoking status, and echocardiographic and laboratory measurements were recorded. Repeated systemic blood pressure measurements exceeding 140/90 mm Hg or treatment with antihypertensive drugs for a known diagnosis was defined as hypertension. Diabetes mellitus was diagnosed by fasting blood glucose ≥126 mg/dL, blood glucose >200 mg/dL at any time, or a history of diabetes mellitus, including those treated with diet modifications, oral medications, or insulin. Hypercholesterolemia was defined as a baseline cholesterol level >200 mg/dL and/or a low-density lipoprotein cholesterol level >130 mg/dL or previously diagnosed and treated hypercholesterolemia. Patients who reported smoking regularly in the previous 6 months were defined as a current smoker. This study protocol was approved by the Local Ethics Committee, and written informed consents were obtained from all patients.

COPD

A respiratory function test was administered in accordance with the American Thoracic Society guideline criteria to all patients who were included in the study using a spirometer (Jeager, Würzburg, Germany) (24). During the bronchodilatation test, 15 min following the inhalation of four puffs of salbutamol (400 µg) through a drip chamber, the FEV1/FVC (%), FEV1 (%, lt), and FVC (%, lt) values were measured. The post-bronchodilatation FEV1/FVC was found to be <70% in all patients diagnosed with COPD and FEV1/FVC >70% in all patients without COPD. Patients with COPD had to be clinically stable for at least 4 weeks prior to entry to be enrolled. COPD was evaluated and excluded by a pulmonary specialist in the non-COPD cohort. FEV1 was used as the main measurement of the severity of the air flow limitation for this study. COPD grade was determined according to the GOLD classification as FEV1 ≥80%, grade 1; 80%> FEV1 ≥50%, grade 2; 50%> FEV1 ≥30%, grade 3; and 30%< FEV1, grade 4. There was no need for hospitalization or therapy modification in the last 3 months in patients with COPD.

CIMT

The carotid artery B-Mode ultrasonography examinations were performed with a Vivid 7 Pro ultrasonography device (Vingmed System Seven GE ultrasound, Horten, Norway) using a 5–12 MHz linear array transducer. All ultrasonography examinations were performed by the same operator who was blind to the results of the coronary angiography results. The images obtained during the ultrasonographic imaging were recorded electronically and then evaluated.

The carotid artery imaging was performed while the patient was lying in a supine position, lifting his neck at an angle of approximately 20° to the front. The far walls of the right and left common carotid arteries were evaluated. The intima-media thickness was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. CIMT measurements were performed from the longitudinal plane during the B-Mode examination. The averages of the CIMT values obtained from the far walls of the right and left common carotid arteries were calculated. The correlation coefficient for the intra-observer reliability was 0.93 ($p<0.001$).

Coronary angiography

All coronary angiography procedures were performed through the femoral artery using the standard Judkins method. A Siemens coronary angiography device (Artis Zee, Munich, Germany) was used for cineangiography. All the coronary angiograms were recorded on compact discs in DICOM format. Baseline diagnostic angiograms of the patients were assessed independently by two experienced interventional cardiologists who were blind to the carotid artery ultrasonography results. Epicardial coronary vessel stenosis being ≥50% was considered as significant CAD. The κ statistics for intra- and inter-observer variability were 0.95 and 0.86, respectively.

The patients were divided into two groups according to the presence of COPD [COPD (+); and COPD (–)]. Also, the patients were divided into four subgroups as follows:

- group 1: COPD (–) and CAD (–)
- group 2: COPD (–) and CAD (+)
- group 3: COPD (+) and CAD (+)
- group 4: COPD (+) and CAD (–)

Table 1. Patient characteristics

Variables	Patients without COPD (n=78)	Patients with COPD (n=108)	*P*
Age, years	65.6±8.9	66.4±8.8	0.543
Male, n (%)	61 (78.2)	81 (75.0)	0.72
Body mass index, kg/m^2	26.3±3.2	27.5±3.9	0.176
Any smoking history, n (%)	58 (74.3)	89 (82.4)	0.216
Systolic blood pressure, mm Hg	132.5±14.0	131.5±16.2	0.675
Diastolic blood pressure, mm Hg	86.0±7.6	85.2±8.0	0.290
Diabetes mellitus, n (%)	30 (38)	47 (44)	0.35
Total cholesterol, mg/dL	190.1±37.1	194.3±39.0	0.426
Low-density lipoprotein, mg/dL	117.1±26.3	116.6±30.2	0.657
FEV1, % predicted	83±3	66±11	**<0.001**
LVEF, %	57.3±10.3	55.8±11.9	0.193
PASP, mm Hg	24.0±1.1	42.8±9.1	**<0.001**
CIMT, mm	1.24±0.28	1.40±0.34	**<0.001**
Hemoglobin, g/L	13.07±1.35	14.5±1.33	**<0.001**
Hemotocrit, %	40.1±5.4	43.2±4.1	**<0.001**
White blood cell, 10^3/μL±SD	5.24±1.8	7.2±2.1	**<0.001**
Neutrophil-to-lymphocyte ratio, n (%)	1.75±0.97	2.15±1.35	0.025
β_2 agonist, %	–	79 (73%)	–
Anticholinergic agents, %	–	60 (56%)	–
Steroids, %	–	61 (57%)	–

CIMT - carotid intima media thickness; FEV1 - forced expiration volume in first second; LVEF - left ventricular ejection fraction; PASP - pulmonary artery systolic pressure;
To compare continuous variables, student's t-test was used; to compare categorical variables, chi- square analysis was used

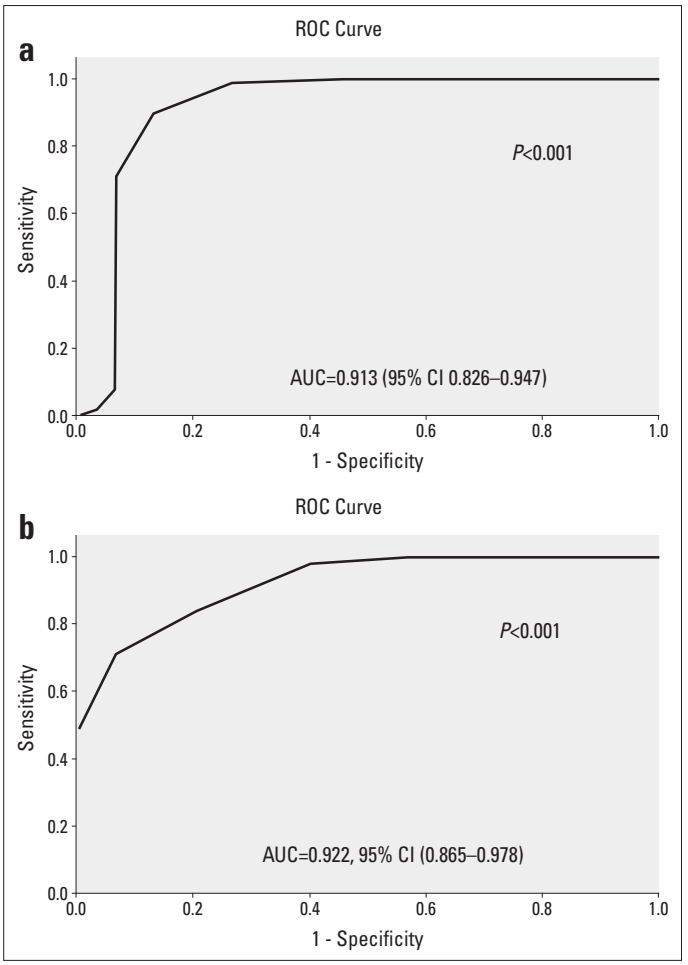

Figure 1. (a) The receiver operating characteristic curve for carotid intima-media thickness (CIMT) to predict coronary artery disease in patients with chronic obstructive pulmonary disease. (b) The receiver operating characteristic curve for carotid intima-media thickness (CIMT) to predict coronary artery disease in patients without chronic obstructive pulmonary disease

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate normal distribution. Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were defined as numbers and percentages. Student's t-test or one-way analysis of variance (ANOVA) was used to compare continuous variables. Differences in the distribution of categorical variables were assessed using chi-square analysis. In this study, for all possible multiple comparisons, the Bonferroni multiple comparison test was applied for controlling type I error. The forward elimination method was used to determine prognostic variables using default values. According to the Bonferroni multiple comparison test, a p value less than 0.025 was considered as statistically significant. The best predictors of the presence of significant CAD were evaluated by multiple logistic regression forward LR procedure. Any variable whose univariable test had a p value <0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Adjusted odds ratios and 95% confidence intervals (CIs) were also calculated. The receiver operating characteristic (ROC) was used to demonstrate the CIMT cut-off value for predicting the presence of significant CAD. The results were considered significant when the p value was <0.05. The Statistical Package for the Social Sciences (SPSS) version 20 was used for the analysis. The sample power was measured using the Power and Sample Size Calculations program version 3.1.2, and it was 0.88.

Results

Out of the 186 patients included in the study, 142 (76.3%) were males, 108 (58.0%) had COPD, and the mean age of the patients was 66.1±9.1 years. When patients with and without COPD were compared, there was no difference between the two groups in terms of age, gender, smoking status, systolic and diastolic blood pressures, presence of diabetes mellitus, and total cholesterol and LDL values (Table 1). As expected, FEV1 values were lower in patients with COPD than in those without COPD (66±11 vs. 83±3, p<0.001). CIMT was significantly higher in patients with

COPD than in those without COPD (1.40±0.34 mm vs. 1.24±0.28 mm, p<0.001). When the 108 patients with COPD were divided into two groups according to the presence of CAD, CIMT was found to be increased in patients with CAD compared with those without CAD (1.51±0.26 mm vs. 1.24±0.29 mm, p<0.001).

The areas under the ROC curve for a cut-off value of 1.25 mm for CIMT to predict the presence of CAD were 0.913 (95% CI 0.826–0.947) (Fig. 1a) and 0.922 (95% CI 0.865–0.978) (Fig. 1b) in patients with and without COPD, respectively. In patients with COPD, the cut-off value of 1.25 mm for CIMT presented a sensitivity of 89.7% and specificity of 86.7%, and CIMT >1.25 mm had a negative predicted value of 76.5%. In multiple logistic regression analyses adjusted for traditional cardiovascular risk factors, the CIMT >1.25 mm was associated with a 12-fold increase in the risk of having significant CAD in patients with COPD (odds ratio 12.40, 95% CI 2.93–172.54, p<0.001) (Table 2). The odds ratio associated with CIMT >1.25 mm for the prediction of the presence of significant CAD was 21.34 (95% CI 4.29–195.84, p<0.001) in patients without COPD.

All the patients were divided into four subgroups according to the presence of COPD and/or CAD. There were 30 patients without COPD and without significant CAD (group 1), 48 patients with significant CAD and without COPD (group 2), 78 patients with COPD and significant CAD (group 3), and 30 patients with COPD and without significant CAD (group 4). The baseline characteristics and variables of the four groups are shown in Table 3. There was no difference between the four groups in terms of age, gender, body mass index, blood pressure, presence of diabetes mellitus, total cholesterol, and medication. The number of patients with any history of smoking was higher in groups 2, 3, and 4 than in group 1 (p<0.05). The CIMT values of the groups were found to be 1.0±0.1 mm, 1.39±0.24 mm, 1.51±0.26 mm, and 1.24±0.29 mm, respectively (Fig. 2). CIMT was found to be the highest in group 3, and this difference was statistically significant when compared to the other three groups (p<0.05). There was a significant increase in CIMT in group 2 compared with group 1 and group 4 (p<0.05). A comparison of group 1 and group 4 concerning CIMT did not show a significant difference (p=0.144).

FEV1 was lower in COPD patients with CAD than in COPD patients without CAD (64.7±11 vs. 72.0±10, p<0.05). In the subgroup analysis according to FEV1 in patients with COPD, there were 72 GOLD grade 1–2 and 36 GOLD grade 3–4 COPD patients. The CIMT was higher in the grade 3–4 COPD patients than in the grade 1–2 COPD patients (1.70±0.31 vs. 1.26±0.24, p<0.001, respectively).

Table 2. Independent predictors of the presence of significant coronary artery disease in patients with COPD

Variable	Multivariate analysis	
	Odds ratio, 95% CI	*P*
Age, years	1.13 (1.00–1.32)	**0.042**
Gender	0.91 (0.76–1.12)	0.090
Smoking	0.96 (0.11–2.03)	0.964
Systolic blood pressure	0.97 (0.86–1.02)	0.131
Diastolic blood pressure	1.05 (0.91–1.22)	0.473
Diabetes mellitus	6.66 (1.12–10.07)	0.064
Low-density lipoprotein cholesterol	1.00 (0.98–1.03)	0.588
Left ventricular ejection fraction	1.15 (1.03–1.28)	**0.010**
Pulmonary artery systolic pressure	1.16 (1.01–1.32)	**0.031**
Hemoglobin	0.75 (0.38–1.45)	0.390
White blood cell	0.78 (0.52–1.16)	0.222
Carotid intima-media thickness	12.40 (2.93–172.54)	**<0.001**
Body mass index	0.92 (0.76–1.23)	0.426
Evaluated by multiple logistic regression analysis		

Discussion

In our study, we investigated whether CIMT has any role in predicting angiographically significant CAD in patients with COPD. We found that the CIMT increased more in patients with COPD than in patients without the diagnosis of COPD, and such an increase was higher in patients with both COPD and CAD than in patients with CAD or COPD only. We also demonstrated that CIMT >1.25 mm was a risk factor for CAD in COPD, and patients with COPD who had CIMT >1.25 mm had a 12-fold increased risk of having CAD.

Atherosclerosis is a diffuse disease where there may be an involvement in cerebrovascular and peripheral arteries, but coronary arteries are generally of primary concern. CIMT is recognized as a marker of atherosclerosis. In the present study, we observed that patients with increased CIMT had an increased risk of having angiographically significant CAD. A population-based study of 15.792 subjects established the association of CIMT with incident coronary heart disease (25). In a study by O'Leary et al. (26), it was found that increased CIMT was associated with an increased risk of new myocardial infarction in subjects without clinical cardiovascular disease. Nambi et al. (9) stated that the measurement of intima-media thickness of common carotid arteries in concert with plaque information improved coronary heart disease risk prediction. Amato et al. (14) demonstrated that CIMT was correlated with both angiographic and intravascular ultrasonographic findings of coronary atherosclerosis. It has been found that CIMT is an independent predictor of coronary atherosclerosis load in symptomatic intermediate risk patients (15). Zuo et al. (27) have shown that CIMT is associated with the severity of CAD.

The relationship between COPD and atherosclerosis has not been clearly understood. It has been argued in previous studies that the mechanisms such as inflammation, hypoxia, and endothelial dysfunction, which are present in COPD, may cause the rapid advancement of atherosclerosis; such aggregated atherosclerosis may lead to cardiac deaths due to an increased

Table 3. Patient characteristics

Variable	Group 1 (n=30)	Group 2 (n=48)	Group 3 (n=78)	Group 4 (n=30)	*P*
Age, years	67.7±9.9	64.2±8.1	66.6±9.4	66.0±7.1	0.35
Male, n (%)	23 (76.7)	38 (79.2)	58 (74.4)	23 (76.7)	0.82
BMI, kg/m^2	26.5±2.7	26.9±3.9	27.5±4.0	27.2±3.6	0.56
Any smoking history, n (%)	16 (53.3)	42 (87.5)$^{\alpha}$	67 (85.9)$^{\alpha}$	22 (73.3)$^{\alpha}$	**0.01**
Current smokers, n (%)	11 (36.6)	34 (70.8)	45 (57.6)	16 (53.3)	
Ex-smokers, n (%)	5 (16.6)	7 (14.5)	22 (28.2)	6 (20.0)	
Systolic blood pressure, mm Hg	134±13	131±15	130±16	133±16	0.75
Diastolic blood pressure, mm Hg	89.0±7.2	85.2±7.5	85.0±8.8	86.6±8.7	0.15
Diabetes mellitus, n (%)	15.0 (50.0)	15 (31.2)	34 (43.6)	14 (46.6)	0.21
Tchol, mg/dL	182±28	195±41	195±38	193±44	0.42
LDL, mg/dL	112±29	117±30$^{\alpha}$	116±29$^{\alpha}$	114.6±31.4	0.87
FEV1, % predicted	85.8±2.6	81.6±3.0	64.7±11.4$^{\alpha\beta\in}$	72.0±10.4$^{\alpha\beta}$	**<0.001**
LVEF, %	59.8±8.8	55.8±10.9$^{\in}$	52.7±10.7$^{\alpha\in}$	61.3±7.7	**<0.001**
sPAB, mm Hg	22±4	20±3	44±8$^{\alpha\beta\in}$	36.9±6.8$^{\alpha\beta}$	**<0.001**
CIMT, mm	1.0±0.10	1.39±0.24$^{\alpha\in}$	1.51±0.26$^{\alpha\beta\in}$	1.24±0.29$^{\alpha}$	**<0.001**
Hamoglobin, g/L	13.0±1.0	14.1±1.3$^{\alpha}$	14.5±1.3$^{\alpha}$	14.8±1.26$^{\alpha\beta}$	**<0.001**
Hematocrit, %	37.5±7.0	41.72±3.4$^{\alpha}$	43.2±4.0$^{\alpha}$	43.21±4.5$^{\alpha}$	**<0.001**
White blood cell, 10^3/µL	4.3±0.8	5.7±2.03$^{\alpha}$	7.1±2.16$^{\alpha\beta}$	7.5±2.11$^{\alpha\beta}$	**0.005**
NLR	1.40±0.39	1.92±1.17$^{\alpha}$	2.21±1.49$^{\alpha}$	2.01±0.89$^{\alpha}$	**0.036**
β_2 agonist, n %	–	–	70 (89)$^{\in}$	13 (45)	–
Anticholinergic agents, n %	–	–	44 (56)	17 (56)	–
Steroids, n %	–	–	53 (67)$^{\in}$	12 (39)	–
ACEI-ARB, n (%)	5 (16.7)	11 (22.9)	25 (32.1)	6 (20.0)	0.426
Beta-blockers, n (%)	3 (10.0)	5 (10.4)	8 (10.3)	3 (10.0)	0.871
Oral antidiabetics, n (%)	12(40.0)	14 (29.1)	30 (38.5)	12 (40.0)	0.102
Significant coronary artery disease, n (%)					
Left main coronary artery	–	2 (4.1)	7 (8.9)$^{\beta}$	–	
Left anterior descending artery	–	22 (45.8)	34 (43.5)	–	
Circumflex artery	–	10 (20.8)	18 (23)	–	
Right coronary artery	–	14 (29.1)	19 (24.3)	–	

BBMI - body mass index; CABG - coronary artery bypass graft; CIMT - carotid intima-media thickness; FEV1 - forced expiration volume in one second; LDL - low-density lipoprotein; LVEF - left ventricular ejection fraction; NLR - neutrophilia-to-lymphocyte ratio; sPAB - pulmonary artery systolic pressure; Tchol - total cholesterol; α - compared to group 1 <0.05; β - compared to group 2 <0.05; Ω - compared to group 3 <0.05; $\in$- compared to group 4 <0.05. To compare continuous variables, one-way ANOVA test was used; to compare categorical variables, chi-square analysis was used

frequency of cardiovascular events in patients with COPD (5, 28–32). Previous studies demonstrated the association between COPD and reduced lung functions with subclinical atherosclerosis. Iwamoto et al. (20) reported that smokers with an airflow limitation had exaggerated subclinical atherosclerosis, and FEV1 was independently associated with IMT. Also, in the ARIC Study and MESA Lung Study, low FEV1 was found to be associated with increased CIMT (21, 22). Lahousse et al. (33) showed that patients with COPD had a twofold increased risk of having carotid wall thickening compared with subjects with normal lung function. Alpaydın et al. (34) also found increased CIMT in patients with COPD compared with normal subjects. Similar to previous studies, we also found a higher CIMT in patients with COPD in our study.

In both the 2010 ACCF/AHA guideline for the assessment of cardiovascular risk in asymptomatic adults and 2013 ESC guidelines on the management of stable CAD, the measurement of

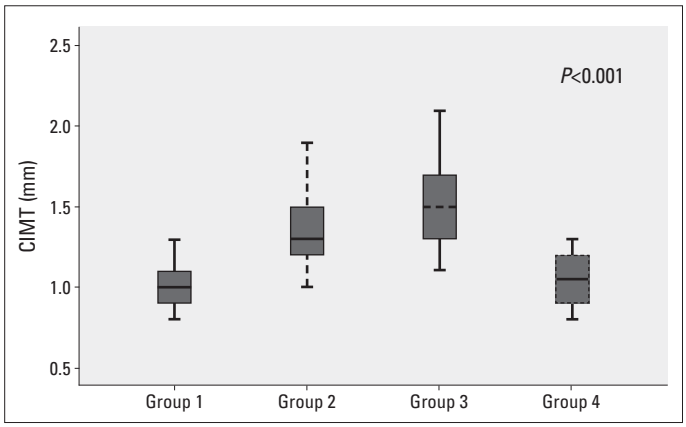

Figure 2. Carotid intima-media thickness (CIMT) values stratified by coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD), group 1: no CAD, no COPD; group 2: only CAD; group 3: CAD and COPD coexist; group 4: only COPD. To compare CIMT, one-way ANOVA was used

CIMT is suggested to be class IIa because it will assist in both risk stratification and diagnosis of CAD (35, 36). In the present study, we found that CIMT was an independent predictor of CAD, as detected by angiography in patients with COPD. The cut-off value of 1.25 mm for CIMT in patients with COPD has been observed to have a high sensitivity and specificity in predicting CAD (89.7% and 86.7%, respectively). CIMT >1.25 mm had a negative predictive value of 76.5%. There is a need for simple, non-invasive, and safe methods to diagnose CAD or to assess cardiovascular risk and decide risk reduction treatment in patients with COPD who have an increased risk of cardiovascular mortality. The cut-off value in our study has an acceptable sensitivity and negative predictive value. These findings may favor the measurement of CIMT as a complementary testing to decide invasive coronary angiography or risk stratifying in COPD patients.

Study limitations

Our study has some limitations. One of the main limitations of this study is the small sample size. Further large-scale studies will be required to validate our results. The other main limitation is that we have included patients suspected to have CAD. Because these patients have a relatively higher risk than the general population, it is not clear whether our results can be applied to the general COPD population. The lack of carotid plaque information is another possible limitation.

Conclusion

In conclusion, our study demonstrates, for the first time, to the best of our knowledge, that the increased CIMT is associated with the presence of angiographically significant CAD in patients with COPD. Non-invasive testing provided information on the presence of significant CAD in patients with COPD. Measurement of CIMT in addition to the standard diagnostic tests may add incremental value to the diagnosis and management of CAD in patients with COPD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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