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Original Article

Pulmonary function test and carotid intima-media thickness in chronic obstructive pulmonary disease

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Abstract

Background: Studies have shown that carotid intima-media thickness (CIMT) is an indicator of cardiovascular events and mortality and its increase has correlation with severe airflow obstruction in patients with COPD. The aim of this study was to investigate the association between pulmonary function and CIMT in COPD patients.

Methods: This study was performed on two groups of patients with and without COPD (cases & controls) who were referred to pulmonary clinics. Demographic, clinical, and laboratory tests were recorded in questionnaire. Spirometry was performed in cases and FVC, FEV1, and FEV1/FVC were measured. CIMT was determined via ultrasound.

Results: Our results indicated that right carotid IMT was 0.51±0.112 mm and 0.65±0.131 mm in the control and case groups, respectively (p< 0.001). Left CIMT was 0.48±0.089 mm and 0.68±0.113 mm in the control and case groups, respectively (p< 0.001). FEV1 and FEV1/FVC had an inverse and significant correlation with IMT of the carotid (both right and left carotid).

Conclusion: The results indicated an inverse association between carotid IMT and lung function test in COPD patients.

Keywords: Pulmonary Disease, Chronic Obstructive, Carotid Intima-Media Thickness, Forced Expiratory Volume.

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It has been shown that in patients with COPD, increase in CIMT has correlation with the severity of airflow obstruction (1). The relation between reduced lung function with increased IMT of the common carotid artery is proven by various studies (2). Hypoxia, systemic inflammation, and endothelial dysfunction may contribute in increased CIMT in COPD patients (1). According to reports, a decrease in forced expiratory volume in 1 second (FEV1) is in line with an increase in cardiovascular risk (3). So, every 10% reduction in lung function measured by FEV1 led to a 30% increase in cardiovascular mortality (2). Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory and irreversible disease that is recognized as one of the main causes of mortality and morbidity in adults worldwide (1). This disease is characterized by progressive airflow limitation and is the result of an abnormal inflammatory response to harmful particles and gases (3). Although this is a respiratory system disease, it is multi-system in nature and is associated with malnutrition, diabetes, musculoskeletal abnormalities and cardiovascular diseases (4). Systemic inflammation caused by airway inflammation is also associated with the progression of atherosclerosis (4). Various studies have shown the importance of subclinical atherosclerosis in COPD, and based on the evidence presented in these studies, COPD patients should be monitored more carefully for the risk of cardiovascular disease (5, 6). In patients with COPD, increased CIMT indicates increased overall and cardiovascular mortality, making CIMT a reliable biomarker for morbidity and mortality in these patients (7, 8).

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In a study in China on 1625 patients, CIMT was measured and COPD patients were determined. According to the results of this study, the average thickness of CIM was higher in patients with COPD than in patients without COPD. Also, in this study, it was shown that the CIMT increases with a decrease in FEV1, so that the highest CIMT was observed in patients with low FEV1. This study stated that lung functional status can be independently related to carotid atherosclerosis (9). In another study that was conducted with the aim of investigating subclinical cardiovascular changes in COPD patients in Egypt, the CIMT was significantly higher in COPD patients than in healthy subjects. This study concluded that COPD can be a risk factor for cardiovascular disease (10).

Considering that COPD is a systemic disease and can cause inflammatory conditions in the body, including metabolic syndrome and vascular involvement, our goal in implementing this project was to see if there is a relationship between the severity of the disease and vascular involvement. The importance of carrying out the research is that the involvement of right and left common and internal carotid arteries can ultimately lead to vascular events such as ischemic strokes and can also be a predictor of stenosis in other vessels, and in COPD patients, with knowing this, we can start prophylaxis measures. Hence, the aim of this study was to investigate the relationship between lung function and CIMT in patients with COPD.

Methods

Study design and measurements: This case-control study was conducted on patients with COPD who referred to the lung clinic of 2 reference hospitals in Mashhad in 2021. Patients in the age range of 45 to 80 years, whose diagnosis of COPD was proven based on symptoms and history and lung function tests, were included in the study as the case group. The diagnosis of COPD was confirmed according to spirometry and that all were treated with inhalation sprays. The control group was people who matched the patients in terms of age, and body mass index (BMI) without COPD. Two groups were matched in terms of age, BMI, and positive history of COPD in the family. Patients with a history of high blood pressure, diabetes, dyslipidemia, cardiovascular disease, exacerbation of COPD, and other lung diseases were excluded from the study. An informed consent form was obtained from all patients participating in the study. A questionnaire containing demographic, clinical, smoking and laboratory test information was completed for each participant. For both groups, chest radiography was performed, and for patients in the case group, spirometry was performed with the chest-desktop-spirometry. In this test, FVC, FEV1 and FEV1/FVC were measured. The radiologist measured the IMT of the right and left common and internal carotid arteries using a Medison X8 sonography device with a 10 MHz surface probe. The results of carotid sonography were statistically analyzed in relation to the underlying disease criteria in 2 groups. The normal range of IMT cut off value is equal to 1.5 mm while cut off values higher than 1 mm are considered in increased risk.

This project was ethically approved by the Ethics Committee of Mashhad University of Medical Sciences with code: IR.MUMS.REC.1393.183.

Sample size: The sampling method was non-probability based on purpose. Considering that the minimum amount of intima thickness change that has clinical value is assumed to be 0.1 mm with a standard deviation of 0.1 mm, the required sample size in each of the two study groups was at least 23 people, and for more certainty in this study, at least 30 patients were included in each group. In this calculation, alpha was 0.05 and the power of the test was 0.90.

Data management and statistical analysis: SPSS Version 24 was used to analyze data. To describe quantitative data, indicators such as mean, standard deviation, minimum and maximum were used. Also, the description of qualitative data was based on frequency and frequency percentage. The chi-square test was used to compare the qualitative data, and the independent t-test was used to compare the quantitative data between the two groups if the data were normally distributed, and otherwise, the equivalent non-parametric test (Mann-Whitney) was used. To check the relationship between two quantitative variables, the normality of the data was checked first, and if it was normal, Pearson's test was used, and otherwise, the parametric equivalent test (Spearman) was used.

Results

Demographic information: A total of 59 (30 cases and 29 controls) people were included in the study. In the control group, 75.9% of people were males, which was 83.3% in the case group. According to the Pearson chi-square test, the observed difference between the two groups in terms of gender was not significant (P=0.476). The average age of the control group was 49.1±3.10 years and in the range of 45-57 years. The average age of people in the case group was 50.5±3.46 years and in the range of 45-58 years. Statistical comparison by independent sample t-test showed that the difference between the two groups in terms of age was not significant (P=0.100). None of the people in the control group had a history of smoking. While 25 (83.3%) people of the case group had a history of smoking.

Anthropometric and laboratory findings: In the examination of the study subjects in terms of height, weight and BMI variables, the two groups did not have any significant difference in terms of height; but the difference in terms of weight and BMI between the two groups was significant. Laboratory studies showed that the level of each parameter of cholesterol, LDL and triglyceride was significantly higher in the case group than in the control group. The detailed results related to anthropometric variables and laboratory findings are presented in table 1.

Table 1. Comparison of the mean and standard deviation of anthropometric indices and laboratory findings between two groups of cases and controls

Variables		Case	Control	Statistical Comparison *
Anthropometric indices	Height (cm)	168.7±4.93	170.8±4.11	P= 0.356
	Weight (kg)	72.7±3.53	77.5±5.51	P= 0.004
	BMI (Kg/m²)	25.2±5.14	26.2±8.36	P= 0.032
laboratory findings	Fasting blood sugar (mg/dl)	95.8±3.40	93.7±2.44	P= 0.308
	Cholesterol(mg/dl)	199.36±3.71	138.26±8.85	p< 0.001
	LDL**(mg/dl)	144.19±3.29	94.20±5.80	p< 0.001
	HDL***(mg/dl)	35.5±3.24	36.4±7.87	P= 0.296
	Triglyceride (mg/dl)	167.27±3.21	145.29±5.62	P= 0.005

* Independent sample t-test, **LDL: low-density lipoprotein, ***HDL: High-density lipoprotein

Pulmonary function test results: Table 2 shows the status of pulmonary function test criteria in patients of the case group. In these people, the average FEV1 was 59.9±10.10, the average FVC was 89.3±3.73, and the average FEV1/FVC was 66.9±10.67.

Table 2. The results of pulmonary function test criteria in the case group

	N	Mean	Std	Min	Max
FEV1* (%)	30	59.9	10.10	28.2	78
FVC** (%)	30	89.3	3.73	84.8	97.5
FEV1/FVC	30	66.9	10.67	33.1	91.7

*FEV1: Forced expiratory volume in 1 second, **FVC: Forced vital capacity

Ultrasound findings: The IMT of right and left carotid was investigated in two groups, the results are shown in figure 1. As it is clear, CIMT was significantly higher in both sides, in the case group compared to the control group. Right CIMT was 0.51±0.112 mm and 0.65±0.131 mm in the control and case groups, respectively (p< 0.001 using independent sample t-test). Left CIMT was 0.48±0.089 mm and 0.68±0.113 mm in the control and case groups, respectively (p< 0.001 using Mann-Whitney t-test).

Correlation between lung function tests and carotid intima media thickness: The findings related to the study of the correlation between the variables obtained from the lung function test and the IMT of the right and left carotid are presented in table 3. Accordingly, there was a significant and inverse relationship between FEV1 and left CIMT, as well as between FEV1 and right CIMT. Likewise, an inverse and significant relationship was observed between FEV1/FVC and left CIMT, as well as between FEV1/FVC and right CIMT.

Table 3. Correlation between variables obtained from lung function test and intima media thickness of right and left carotid

		Right CIMT	Left CIMT
FEV1	Correlation coefficient	-0.378	-0.566
	Significance	P=0.04	P=0.001
FVC	Correlation coefficient	0.006	-0.303
	Significance	P=0.975	P=0.103
FEV1/FVC	Correlation coefficient	-0.404	-0.532
	Significance	P=0.027	P=0.002

*FEV1: Forced expiratory volume in 1 second, **FVC: Forced vital capacity

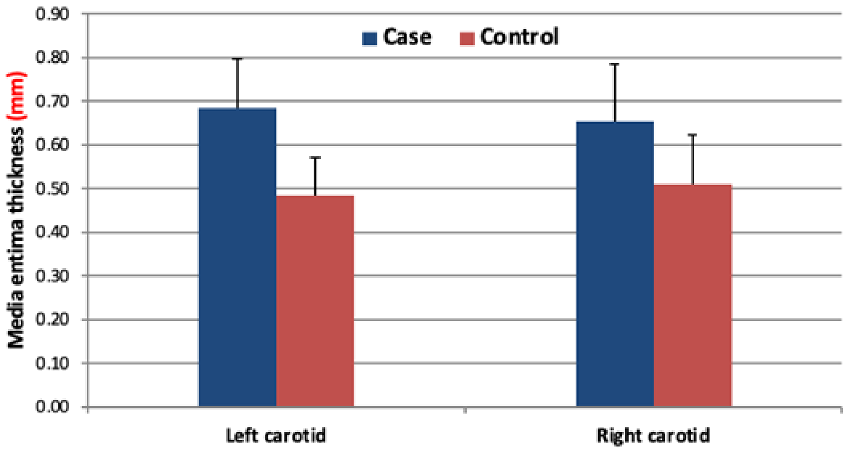

Figure 1. Comparison of the right and left carotid intima media thickness in two studied groups

Discussion

The results of this study showed that the differences between the case group and the control group were not significant in terms of age and gender, indicating appropriate sampling and no bias in the selection of the statistical population in the study. Considering that the risk of cardiovascular disease increases with age and that carotid intima media thickness increases with age in normal subjects (11, 12), the study population in this study was age-matched to avoid bias. According to the existing studies, the average thickness of the carotid intima media in men and women is significantly different (12). For this reason, with respect to the comparison of the mean carotid intima media thickness between cases and controls in the present study, the similarity of the two groups in terms of gender was important. Other findings of this study showed that the two groups differed significantly in weight and BMI. In previous studies, it has been demonstrated that CIMT can be used to diagnose preclinical atherosclerosis (13, 14). Considering that high BMI can be considered as a risk factor for atherosclerosis, it seems likely that high BMI also affects CIMT. On the other hand, previous studies also showed that carotid intima media thickness was higher in people with higher BMI (15-17). Of course, the study by Freedman et al., showed that CIMT only changed in patients with BMI over 30 and in other ranges, BMI did not affect CIMT (16). In the following, it was shown that no one in the control group had a history of smoking; While 25 cases (83.3%) had a history of smoking. Considering that the patients in the case group had COPD and that one of the most important risk factors for COPD is smoking, it seems that this difference between the two groups is reasonable.

In the present study, cholesterol, LDL, and triglyceride levels were significantly higher in the case group than in the control group. In the study by Niranjan et al., to study the lipid composition of COPD patients and compare it with the control group, it was found that HDL, triglyceride and cholesterol concentrations in both groups were not significantly different, while LDL levels in COPD patients were significantly higher than in the control group (18). In explaining this difference, it can be said that smoking (more common in COPD patients) may affect lipid composition through proven mechanisms. When consumed, nicotine stimulates the adrenal medulla and immediately increases fatty acid levels by 30% (19). However, there is still much controversy regarding changes in the lipid profile of COPD patients. For example, in the study by Nallawar et al., it was found that fat composition in COPD patients was not significantly different from that in the control group (20).

Examination of functional tests in patients in the case group showed that in these patients, the mean FEV1 was 59.9±10.10, the mean FVC was 89.3±3.73, and the mean FEV1/FVC is 66.9±10.67. It was found that FEV1/FVC below 70% may indicate obstructive disease in a person (21). As mentioned, this average rate in treated patients in this study remained below 70%. Based on FEV1, COPD patients are divided into three categories: mild (FEV1 above 70%), moderate (FEV1 between 50 and 69%) and severe (FEV1 below 50%) (22). In this study, the average FEV1 was 59.9±10.10 and most patients were in the average category. Comparison of ultrasound results in this study showed that the intima-media thickness of the carotid arteries (right carotid artery and left carotid artery) in the disease group was significantly higher than the control group ($p < 0.001$). Furthermore, the correlation between variables obtained from pulmonary function tests and right and left carotid intima media thickness in patients in the case group showed that FEV1 and FEV1/FVC had an inverse relationship with CIMT (both right carotid and left carotid). These results have been tested and confirmed in other studies such as that of Pan et al. (9), Chindhi et al. (23), and Ma et al. (24). In these studies, it was found that there was a significant and inverse relationship between carotid intima media thickness and pulmonary function, and in these studies, it was also found that CIMT in COPD patients was higher than CIMT in none-COPD patients.

Different mechanisms have been mentioned for this. One of these mechanisms states that lung inflammation as a result of COPD may lead to systemic inflammation by increasing leukocytes, platelets, cytokines and acute phase proteins in the bloodstream. These mediators activate the vascular endothelium and lead to endothelial dysfunction. Endothelial dysfunction causes a decrease in vasodilation (through a decrease in nitric oxide and an increase in endothelin), an increase in vascular permeability, and an increase in the absorption of LDL in the vessel wall, and as a result, the thickness of the intima-media of the vessels increases and also provides the basis for the creation of atherosclerotic plaques (25). Also, the reduction of lung function leads to chronic hypoxia of the arterial wall. The hypoxia of the vessel wall stimulates the activation of a cascade of growth factors and cytokines, causing changes such as increased activation and migration of macrophages, increased vascular permeability and increased platelet adhesion. These changes, together with hypoxia, lead to an increase in the growth and division of intima cells and the vascular wall in general, and increase the thickness of the intima-media of the vessels (26).

Results similar to our study are also seen in some new studies. The association between lung function and CIMT was studied in a Japanese population by Takase et al. (2023), Lung function was measured using FEV1and FVC was determined using spirometry. This study showed lower FEV 1 and FVC were associated with higher CIMT in both men and women ($p <0.001$) (27). The results of this study showed that the CIMT (both right and left carotid) in people with COPD was significantly higher than healthy people. Also, the correlation between the variables obtained from the lung function test and the thickness of the right and left carotid intima media in the patients of the case group showed that FEV1 and FEV1/FVC have an inverse significant relationship with the thickness of the carotid intima media (both right carotid and left carotid).

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Authors' contribution: SH.S, and S.H, Data Collection and/or Processing SH.S, and M.N, Analysis or Interpretation: S.H, Writing: SH.S, and M.N.

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