

# Subclinical cardiovascular changes in chronic obstructive pulmonary disease patients: Doppler ultrasound evaluation

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**Introduction** Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive poorly reversible airway obstruction. COPD is associated with chronic systemic inflammation, hypercoagulable status, platelet activation, and oxidative stress. These factors may result in subclinical cardiovascular diseases (CVD): for example, carotid atherosclerosis, peripheral arterial diseases, and coronary artery diseases.

**Aims** The aim of this case-control study was the detection of subclinical CVD in COPD patients.

**Settings and design** This was a case-control study.

**Materials and methods** A total of 62 COPD patients and 62 healthy volunteers were enrolled in the present study. All patients were subjected to full medical history and clinical examination, chest radiography, arterial blood gas analysis, laboratory assessment of C-reactive protein, complete blood count, lipid profile, spirometry, transthoracic echocardiography, carotid Doppler ultrasound, and measurement of ankle-brachial index. A comparison between COPD and control groups regarding different parameters was performed, and a comparison between different stages of COPD regarding different parameters was also performed.

**Results** The carotid intima-media thickness and carotid plaques were significantly higher, whereas the ankle-brachial

index was significantly lower in COPD patients compared with the control group, with no differences observed in different stages of COPD. Pulmonary hypertension and right ventricular dilatation were significantly common in COPD patients compared with the control group, and they were significantly increased with progressive stages of COPD. Pulmonary artery systolic pressure and carotid intima-media thickness showed a significant negative correlation with PaO<sub>2</sub>, but showed a significant positive correlation with PaCO<sub>2</sub>.

**Conclusion** COPD is a risk factor for subclinical CVD, mainly carotid artery atherosclerosis and peripheral arterial diseases. *Egypt J Broncho* 2015 9:140–145

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**Keywords:** arterial blood gases, carotid atherosclerosis, chronic obstructive pulmonary disease, peripheral arterial diseases

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by progressive and persistent air flow limitation with an enhanced inflammatory response to noxious gases both in the airways and the lungs. The disease severity is exaggerated by exacerbations and comorbidities [1]. The WHO predicts that COPD will become the third leading cause of death and the fifth leading cause of disability by 2020 [2]. Extrapulmonary manifestations of COPD include weight loss, nutritional abnormalities and skeletal mass dysfunction, cardiovascular diseases (CVD), osteoporosis, anxiety and depression, lung cancer, infections, metabolic syndrome, and diabetes [3]. Smoking, which is a risk factor for both COPD and CVD, leads to oxidative stress, which directly affects the endothelium, causing both humeral and cellular systemic inflammation and activation of coagulation factors, leading to cardiovascular complications [4]. Extrapulmonary manifestations are more common in patients with COPD than in smokers without COPD, which suggests that COPD may be an independent risk

factor for these manifestations [5]. The specific cellular mechanisms by which systemic inflammation plays a role in the pathogenesis of CVD are complex. However, some studies revealed the importance of systemic inflammation in plaque initiation, development, and rupture. The atherosclerotic process starts with injury to the vascular endothelium, which becomes more permeable by a variety of factors, including systemic inflammation and oxidative stress [6]. In addition to the role of proteases in the pathogenesis of COPD, extracellular proteases cause breakdown of the vascular endothelia, leading to vascular remodeling and development of atherosclerosis. Elastin degradation and disorders of elastic fibers increase with aging, resulting in atherosclerosis and nonvascular diseases, mainly emphysema [7].

## Objective

The aim of the present study was the detection of subclinical CVD in COPD patients.

## Materials and methods

The present case-control observational study was conducted in the Departments of Chest Diseases, Internal Medicine, and Radiology, Faculty of Medicine, Assiut University Hospital, where 62 patients with COPD and 62 healthy volunteers were included.

Written informed consents were obtained from all participants according to national Ethics Committee.

Individuals of both groups were subjected to the following:

- (1) Detailed history and physical examination.
- (2) Chest radiography.
- (3) Spirometry was performed using D 97723 (Zan 300, Oberthulba, Germany), and the predicted values for forced vital capacity (FVC), forced expiratory volume in 1 s ( $FEV_1$ ), and  $FEV_1/FVC$  were calculated. The diagnosis of COPD was based on the GOLD 2014 criteria, whereby  $FEV_1/FVC$  less than 70 and the subsequent staging of COPD patients into stages I, II, III, and IV based on postbronchodilator  $FEV_1\%$  was predicted.
- (4) An arterial blood gas sample was obtained at rest from the radial artery and analyzed using a blood gases analyzer (Rapid lab 850; CHIRON/Diagnostics, Halstead, UK; critical care systems), with calculation of  $PaO_2$ ,  $SaO_2$ , and  $PaCO_2$ .
- (5) Two-dimensional transthoracic Doppler echocardiography was performed for both groups using Philips invisor, 2002 (USA).
  - (a) Doppler echocardiography was performed according to the recommendation of the American Society of Echocardiography; M-mode and two-dimensional images as well as spectral-flow and color-flow Doppler recordings were obtained. Measurement of the right ventricular diameter and the pulmonary artery systolic pressure (PASP) were obtained from the measurement of the jet of the tricuspid regurgitation 'TR' plus 10. The left ventricular end-diastolic diameter, the left ventricular end-systolic diameter, the interventricular septal thickness, and the left ventricular posterior wall thickness were measured.
  - (b) The left ventricular ejection fraction (EF) was calculated with the Teichholz techniques. An EF less than 55% was considered as systolic dysfunction.
- (6) Carotid Doppler were conducted using a real-time ultrasound equipment capable of B-mode imaging, pulsed-wave duplex scanning, color Doppler flow imaging, and power Doppler imaging. Using ultrasound with high-frequency linear transducer

10.0 MHz (Aloka Echo Camera SSD-3500; Aloka Pro-sound; Japan ultrasound) the carotid intima-media thickness (CIMT) was considered abnormal if it is 1 mm or more. The extent, the location, and the characteristics of atherosclerotic plaques in the common carotid artery and the internal carotid artery were documented with gray-scale imaging [8].

- (7) Assessment of the ankle-brachial index (ABI) was performed using a bidirectional blood flow meter with a wave form display of 8 MHz and a precalibrated mercury sphygmomanometer. The ABI was calculated by dividing the higher of the two ankle systolic blood pressures in each leg by the higher of the two brachial systolic blood pressures. The ABI was calculated for each leg, and the lower value was the patient's overall ABI. An abnormal value in either leg indicates peripheral artery disease. Diagnostic criteria for the ABI were standardized as follows: most healthy adults have a value greater than 1.0; a value of less than 0.91 is consistent with significant peripheral artery disease and a value lower than 0.40 at rest generally indicates severe disease. A value between 0.91 and 0.99 is borderline abnormal and does not rule out peripheral artery disease. A value greater than 1.40 reflects noncompressibility of the leg arteries and is not diagnostic [9].
- (8) Laboratory evaluation including a complete blood count, C-reactive protein (CRP), and lipid profile including LDL, HDL, cholesterol, and triglyceride were measured.

### Exclusion criteria

- (1) Patients with known cardiac disease, for example, cardiomyopathy, valvular heart diseases, and coronary artery diseases.
- (2) Patients with hypertension and/or dyslipidemia.
- (3) Patients with respiratory disorders other than COPD.

### Statistical analysis

We used the SPSS statistical software, 16.00 (Lead Technologies Inc., Chicago, Illinois, USA) for statistical analyses. Different numeric variables were expressed as mean  $\pm$  SD; COPD patients and healthy control groups were compared regarding different parameters using the *t*-test. Also, different stages of COPD were compared with regard to CIMT, ABI, and echocardiographic parameters. Categorical variables were expressed as absolute numbers and percentages. Comparisons between two groups were analyzed by the independent-sample *t*-test for continuous variables and the  $\chi^2$ -test for discrete variables. A Spearman rank univariate correlation study was conducted for correlation between two continuous variables.

A *P*-value of less than 0.05 was considered to be statistically significant.

## Results

The mean age of our COPD patients was  $61.6 \pm 9.1$  years: 90.3% of them were male (Table 1). Regarding cardiovascular risk factors, COPD patients had significantly higher total cholesterol, LDL, triglyceride, and CRP levels. In contrast, there was an insignificant difference between both groups with regard to the smoking index and the hemoglobin level. Most of our COPD patients were classified as GOLD III (45.16%) and IV (32.26%), whereas none was classified as GOLD I. We observed that COPD patients had a higher CIMT and lower ABI in comparison with the control group. Carotid plaques were observed in 22.6% of the COPD patients; the control group had no carotid plaques (Table 2 and Fig. 1). The PASP was significantly higher in the COPD group; however, both segmental wall motion abnormalities (SWMA) and a dilated right side were observed only in COPD patients (25.8 and 45.2%, respectively), whereas it is not detected in the control group. The EF% was significantly lower in the COPD group than in the control group, but it was still within normal range in both studied groups (Table 2). By comparing different stages of COPD, we found no significant differences between the different stages regarding CIMT, the presence of plaques, and ABI. In contrast PASP and a dilated right side increased significantly with progressive staging of COPD (Table 3). Correlations between ABG parameters and cardiovascular parameters revealed significant negative correlations between  $\text{PaO}_2$  and each of PASP and CIMT, and significant positive correlations between  $\text{PaCO}_2$  and each of PASP and CIMT (Fig. 2).

## Discussion

In addition to pulmonary limitations that are frequently exaggerated by COPD exacerbations, comorbidities and systemic manifestations markedly affect the clinical course and the prognosis of COPD [10]. CVD is one

of these systemic manifestations frequently observed in COPD patients. Therefore, the evaluation of COPD patients for systemic manifestations, especially for CVD, is important. Possible explanations for the high cardiovascular morbidity and mortality observed in COPD patients are a high smoking prevalence, diet, and a sedentary lifestyle [10]. Even in the absence

**Table 1 Demographic and laboratory data of the studied groups**

Variables	COPD ( <i>n</i> = 62)	Control ( <i>n</i> = 62)	<i>P</i> -value
Age (mean $\pm$ SD)	61.6 $\pm$ 9.1	62.7 $\pm$ 4.5	0.367 (NS)
Sex [ <i>n</i> (%)]			
Males	56 (90.3)	52 (83.9)	0.422 (NS)
Females	6 (9.7)	10 (16.1)	
Smoking [ <i>n</i> (%)]			
Smoker	34 (45.8)	34 (45.8)	
Exsmoker	20 (32.3)	18 (29)	0.283 (NS)
Nonsmoker	8 (12.9)	10 (16)	
BMI (mean $\pm$ SD)	24.9 $\pm$ 5.7	23.8 $\pm$ 1.8	0.181 (NS)
Total cholesterol (mg/dl)	172 $\pm$ 42.8	95.1 $\pm$ 17	<0.001
LDL (mg/dl)	98.4 $\pm$ 30.9	78.9 $\pm$ 8.1	<0.001
HDL (mg/dl)	48.9 $\pm$ 14.4	50 $\pm$ 3.4	0.542 (NS)
TG (mg/dl)	114 $\pm$ 52.9	58.29 $\pm$ 13.6	<0.001
CRP (IU/l)	12.1 $\pm$ 13.8	2.2 $\pm$ 0.7	<0.001
Hemoglobin (g/dl)	13.6 $\pm$ 1.9	13.2 $\pm$ 1.5	0.201 (NS)
WBCs	8.2 $\pm$ 3.2	6.5 $\pm$ 1.7	<0.001

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; TG, triglyceride; WBCs, white blood cells.

**Table 2 Differences between COPD and control groups with regard to vascular changes**

Parameters	COPD ( <i>n</i> = 62)	Control ( <i>n</i> = 62)	<i>P</i> -value
ABI	1.05 $\pm$ 0.054	1.23 $\pm$ 0.27	0.001
CIMT	2.1 $\pm$ 0.40	0.65 $\pm$ 0.11	<0.001
Carotid plaques [ <i>n</i> (%)]	14 (22.6)	0 (0)	<0.001
PASP	46.74 $\pm$ 16.78	20.06 $\pm$ 3.36	<0.001
LVEF	66.26 $\pm$ 8.57	68.94 $\pm$ 4.45	0.130 (NS)
SWMA [ <i>n</i> (%)]	16 (25.8)	0 (0)	<0.001
Dilated right side of the heart [ <i>n</i> (%)]	28 (45.2)	0 (0)	<0.001

ABI, ankle-brachial index; CIMT, carotid intima-media thickness; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NS, nonsignificant; PASP, pulmonary artery systolic pressure; SWMA, segmental wall motion abnormalities.

**Table 3 Comparison between different stages of COPD with regard to vascular changes**

Parameters	GOLD II	GOLD III	GOLD IV	<i>P</i> -value
ABI	1.05 $\pm$ 0.043	1.05 $\pm$ 0.06	1.06 $\pm$ 0.054	0.904 (NS)
CIMT	2.09 $\pm$ 0.48	2.03 $\pm$ 0.37	2.21 $\pm$ 0.36	0.563 (NS)
Carotid plaques [ <i>n</i> (%)]	0 (0)	8 (28.6)	6 (30.0)	0.071 (NS)
PASP	29.86 $\pm$ 5.90	46.00 $\pm$ 10.45	59.60 $\pm$ 18.74	<0.001
LVEF	69.30 $\pm$ 3.56	66.29 $\pm$ 9.72	61.86 $\pm$ 10.25	0.216 (NS)
SWMA [ <i>n</i> (%)]	2 (14.2)	6 (21.4)	8 (40)	0.089 (NS)
Dilated right side of the heart [ <i>n</i> (%)]	0 (0)	16 (57.1)	12 (60.0)	0.001

ABI, ankle-brachial index; CIMT, carotid intima-media thickness; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NS, nonsignificant; PASP, pulmonary artery systolic pressure; SWMA, segmental wall motion abnormalities.

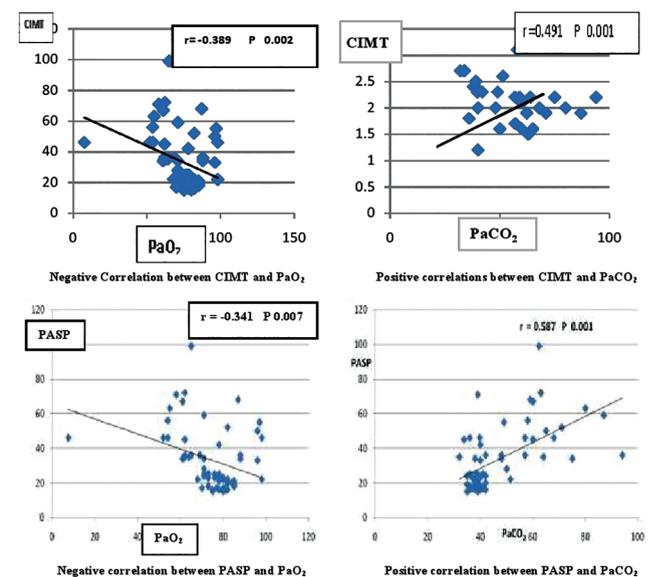
Fig. 1



Gray-scale assessment of CIMT demonstrating the increased thickening of the wall with the presence of a carotid plaque (white arrow). CIMT, carotid intima-media thickness.

of these factors,  $FEV_1$  was reported to be correlated with cardiovascular risk in these patients [10]. Other studies demonstrated that oxidative stress and chronic hypoxia in COPD patients may contribute to the development of CVD, but the most obvious factor is thought to be the systemic inflammation [11]. Airway inflammation may induce systemic inflammation, particularly CRP production, which is also associated with the progression of atherosclerosis [12,13]. In this study, COPD patients had significantly increased total cholesterol, total triglyceride, and LDL levels than controls. These factors play an important role in the cardiovascular dysfunction observed in those patients. Moreover, the CRP level in our patients was significantly increased compared with the control group, which acts as a serious novel cardiovascular risk factor and an inflammatory marker. Gan *et al.* [14] demonstrated that levels of systemic inflammatory markers, including the blood leukocyte count, CRP, interleukin-6, and fibrinogen, were elevated in patients with COPD compared with healthy controls, which agreed with our findings. In the present study, we tried to assess some subclinical cardiovascular changes in patients with COPD. Regarding vascular changes, we observed a higher CIMT, a lower ABI, and an increased frequency of carotid plaques in the COPD group compared with the control group. This was in agreement with the results of Ozgen Alpaydin *et al.* [10] who reported that the COPD group had a statistically thicker carotid IM compared with controls ( $P < 0.001$ ). These changes were present in all stages of COPD with no significant differences observed between them. Kim *et al.* [15] agreed with our results: they observed that newly diagnosed, untreated patients with COPD had a significant increase in the CIMT compared with healthy individuals matched for age, sex, BMI, the smoking status, and the smoking

Fig. 2



Correlations between arterial blood gas parameters and cardiovascular abnormalities in COPD patients. COPD, chronic obstructive pulmonary disease.

amount; meanwhile, they disagreed with our results in that they found that the CIMT was significantly correlated with a decrease in lung function, but Pobeha *et al.* [16], while studying the carotid IMT in COPD, reported that the average IMT was  $0.85 \pm 0.22$ , with no significant difference from stage II to stage IV of the disease; this result supported our findings. Also, Barr *et al.* [17] reported that the obstructive pattern of spirometry and emphysema was associated with subclinical atherosclerosis in the carotid arteries and peripheral circulation in terms of an increased CIMT and a decreased ABI. In another study, Pecci *et al.* [18] observed that asymptomatic peripheral arterial diseases (PAD) highly prevalent in COPD and abnormal ABI were associated with severe COPD. In agreement with our study, Matsuoka *et al.* [19] observed that the prevalence of subclinical PAD in COPD patients was higher than that in healthy control smokers and the ABI in COPD patients was lower than in healthy smokers. They also stated that hypoxia in advanced stages of COPD and the resulting inflammation may play role in the pathogenesis of subclinical atherosclerosis. Our study revealed that cardiac abnormalities are more common in COPD than in the control group and this is in agreement with Freixa *et al.* [20] as they found that significant cardiac alterations were present in 64% of the COPD patients. The most common were right ventricle enlargement (30%) and pulmonary hypertension (19%). Left ventricle enlargement was present in 6%, left ventricle systolic dysfunction in 13%, left ventricle diastolic impairment in 12%, and left atrial dilatation in 29% of the cases. We observed

that PASP and right ventricular dilatation increased significantly with progressive staging of COPD. We considered that these changes may occur as a logical consequence of the disease, wherein increasing severity of hypoxemia and hypercapnea with disease progression leads to pulmonary vascular remodeling. Inconsistent with this study, Gupta *et al.* [21] found that the prevalence of pulmonary hypertension has a linear relationship with the grade and the severity of COPD, and echocardiography helps in the early detection of cardiac complications in COPD cases, giving time for early interventions. Sultan *et al.* [22] also recorded that the incidence of pulmonary hypertension, right ventricular enlargement, tricuspid regurgitation, and right atrial enlargement increased with the duration and the severity of COPD. The present study revealed that the LV systolic function was preserved in different grades of the studied COPD patients despite the presence of SWMA in about one third of them. Similar results were obtained by Vonk-Noordegraaf *et al.* [23] who stated that in the absence of problems primarily leading to left ventricular systolic function impairment such as ischemic heart disease, systemic arterial hypertension etc., derangement of systolic function in the course of COPD is rarely found. However, some investigators suggest that even with the presence of a normal EF and a normal left ventricular shortening fraction, subclinical systolic dysfunction is frequently present in COPD patients [24]. The higher prevalence of SWMA in our patient group (25.8%) may be due to the high prevalence of GOLD III, IV and consequently hypoxemia and hypercapnia. This result matched with that of Mapel *et al.* [25], who stated that the prevalence of coronary artery disease was 33.6%, which was significantly higher than the 27.1% prevalence seen in a matched cohort without COPD. We found a negative correlation between PaO<sub>2</sub> and each of CIMT and PASP, and a positive correlation between them and PaCO<sub>2</sub>. There was an association between the presence of low-grade systemic inflammation in COPD and atherosclerotic CVD. These systemic inflammations in COPD play a role in the pathogenesis of ischemic heart disease and atherosclerosis. Moreover, atherosclerotic plaques show low-grade inflammation, with increased numbers of macrophages and interferon- $\gamma$ -secreting Th1 lymphocytes [26]. We suggest that hypoxemia and hypercapnea in COPD result in systemic inflammation, and consequently, in the development of atherosclerosis and increased CIMT. Also, Chhabra [27] stated that hypoxemia not only promotes vasoconstriction, but also contributes to the process of vascular remodeling as hypoxia inhibits the expression of voltage-gated potassium channels, resulting in membrane depolarization and stimulation of smooth muscle cell proliferation. Rodriguez-Roisin and MacNee [28] reported that hypoxia is a potent

pulmonary vasoconstrictor in normal individuals and they documented that many studies have shown a negative correlation between oxygen saturation and pulmonary artery pressure in patients with COPD. A positive correlation has also been shown between PaCO<sub>2</sub> and the pulmonary artery pressure [22]. In contrast, the presence of vascular changes in COPD patients without hypoxemia (stage II) suggest that factors other than hypoxemia and hypercapnea such as smoking, oxidative stress, and systemic inflammation may be responsible for the development of vascular changes in these patients.

## Conclusion and recommendations

This study found that COPD is a risk factor for many subclinical cardiovascular changes, mainly carotid artery atherosclerosis and PAD. Intervention studies attempting to reduce systemic inflammation and to improve platelet function and endothelial function and large-vessel stiffness in COPD patients are required. In addition, large prospective intervention studies with antiplatelet agents and statins would be beneficial.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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