Original Investigation

Eurasian J Pulmonol 2016; 18: 165-71

Atherosclerosis is Associated Comorbidity in Patients with Chronic Obstructive Pulmonary Disease: Ultrasound Assessment of Carotid Intima Media Thickness

Manal R. Hafez[1], Eman Sobh[1], Omaima I. Abo-Elkheir[2], Lobna K. Sakr[3]

[1]Department of Chest Diseases, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt
[2]Department of Community and Occupational Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt
[3]Department of Radiodiagnosis, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt

Abstract

Objective: To assess atherosclerotic comorbidity in chronic obstructive pulmonary disease (COPD) patients and its relationship to COPD severity, hypoxemia, and hypercapnia.

Methods: A hospital-based observational case-control study was conducted on 86 male COPD patients, and 86 age-matched healthy subjects (non-COPD group). Carotid intima-media thickness (CIMT) was assessed by Doppler ultrasound; in addition, spirometry and arterial blood gas tests were done.

Results: CIMT was significantly increased in the COPD group compared to the non-COPD group (0.84±0.15 vs. 0.63±0.076, p<0.001). When the CIMT value of ≥0.8 mm was defined as a cutoff value for a thickened CIMT complex, 64% of COPD patients versus 8.1% of non-COPD subjects had a thickened CIMT. COPD patients with a thickened CIMT were older and had a higher $PaCO_2$, lower FEV_1%, FVC, and FEF_{25-75}% compared to COPD patients with a normal CIMT. Thickened CIMT in COPD patients was significantly associated with hypoxemia (p=0.008, OR=8.2), hypercapnia (p=0.04, OR=6.2), and airflow limitation (p=0.11, OR=2.1). There was no significant difference in CIMT in relation to COPD severity (p=0.83).

Conclusion: Atherosclerosis is prevalent in COPD patients, even in the early stages of the disease. Hypoxemia, hypercapnia, and airflow limitation are risk factors of atherosclerosis in COPD patients.

Keywords: Arterial stiffness in COPD, atherosclerosis, cardiovascular risk in COPD, carotid intima media thickness, COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is considered a systemic disease with various co-morbidities (1). It is well established that cardiovascular diseases (CVDs) contribute significantly to both morbidity and mortality in COPD (2). In addition, there is increasing evidence that COPD is an independent risk factor for cerebrovascular ischemic stroke and that the risk increases with severity of airflow limitation (3).

Preclinical carotid atherosclerosis, characterized by increased intima-media thickness (IMT), is an indicator of atherosclerosis burden and a CVD risk (4). It reflects the atherosclerotic involvement of the vascular structure, thereby indicating coronary artery disease, cerebrovascular disease, and peripheral arterial disease (5). Carotid atherosclerosis strongly correlates with coronary atherosclerosis (6).

The mechanism for the association of COPD with increased carotid wall IMT is not well known (7, 8). It has been postulated that COPD is a disease of accelerated aging (9, 10). Mechanisms related to accelerate aging and cellular senescence are also considered to be involved in the pathogenesis of atherosclerosis (11). Evidence of the accelerated aging process in both COPD and atherosclerosis was confirmed by shortened leukocyte telomere lengths (10, 12), which may provide a mechanistic link between COPD and vascular dysfunction (2). Additionally, low-grade systemic inflammation (8),

Received Date: 18.08.2016
Accepted Date: 19.10.2016

DOI: 10.5152/ejp.2016.63626

Corresponding Author
Eman Sobh
E-mail: emansobh2012@gmail.com

• Available online at www.eurasianjpulmonol.com

high smoking prevalence, a sedentary lifestyle, low forced expiratory volume in first second (FEV_1) (13), platelet activation, hypercoagulability, and oxidative stress are possible important contributors (7, 14). Patients with COPD are subjected to hypoxia, either sustained or intermittent, during exercise or exacerbations. Chronic intermittent hypoxia is associated with hyperlipidemia, atherosclerosis, and a high cardiovascular risk; and the severity of atherosclerosis correlates with the severity of hypoxia (15). Moreover, abnormalities of the arterial wall extracellular matrix as a result of elastin degradation in the lungs (resulting in emphysema), and in the vasculature (resulting in atherosclerosis) (16) could be a possible mechanism. Among these factors, systemic inflammation was thought to be the most obvious risk factor (13).

There is increasing evidence that non-invasive imaging modalities, such as ultrasonography, may be able to detect subclinical atherosclerotic lesions (17). Carotid intima-media thickness (CIMT) measured by carotid Doppler ultrasound is an effective, reliable, and validated method for evaluating carotid atherosclerosis (18). Measurement of the CIMT by ultrasound can detect thickening of the artery wall during the initial phases of atherosclerosis before the lumens become compromised (19).

Increased IMT was connected to increased cardiovascular morbidity in patients with COPD (4). However, the clinical relevance of these observations remains unknown in patients with COPD (17). Accordingly, the aim of this study was to assess atherosclerotic comorbidity in COPD patients and its relation to COPD severity, hypoxemia, and hypercapnia.

METHODS

Study Design

This was a hospital-based observational case-control study conducted from December 2014 to January 2016.

Sample and Place of Study

The study was conducted on 172 participants [86 COPD patients and 86 non-COPD subjects (controls)]. It was carried out at the Chest Diseases Department, Al-Zahraa University Hospital, Cairo, Egypt.

Selection of Subjects

1. **COPD group:** The diagnosis and staging of COPD were based on the GOLD, 2014 criteria (post-bronchodilator $FEV_1/FVC<0.7$) and an increase in $FEV_1<200$ mL, or <12% of the baseline value 20 minutes after 200 µg puffs of inhaled Salbutamol (given via a metered-dose inhaler at the time of diagnosis) (20).
2. **Non-COPD group:** An equal number of age and sex-matched healthy volunteers with spirometric indices and arterial blood gases (ABG) parameters within the normal range and no history of chronic chest diseases.

Exclusion Criteria

Subjects with systemic hypertension, diabetes mellitus, atherosclerosis, dyslipidemia, known CVD/cerebrovascular diseases, or history of lipid lowering drugs intake were excluded from the study.

Age, smoking frequency (pack/year), and body mass index (BMI) were recorded; and all participants were subjected to the following:

1. **Spirometry:** Spirometry was carried out on a MEDISOFT-HYPER-AIR compact + flow meter pulmonary function testing device (Medisoft, Sorinnes, Belgium). The test procedure was explained in full detail. Short-acting β2 agonist, long-acting β2-agonists, and sustained-release theophylline, were withheld before the test for 6, 12, and 24 hours, respectively. Heavy meals, exercise, and smoking were avoided 6 hours before the test. FEV_1%, forced vital capacity (FVC%), FEV_1/FVC ratio, and forced expiratory flow rate 25%–75% ($FEF_{25–75}$%) were measured. Spirometric indices were calculated using the best of 3 technically acceptable performances in accordance with the recommendations of the European Respiratory Society (21).
2. **Arterial blood gases:** ABG analysis was done after a 15-minute resting period in ambient room air using a Rapid Lab 248 blood (Siemens Medical Solutions, Malvern, PA, US) gases analyzer; PaO_2 mmHg, and $PaCO_2$ mmHg were recorded.
3. **Measurements of CIMT:** Carotid artery intima-media thickness was measured using ultrasound by well-trained investigators (two pulmonologists and a radiologist).

Estimation of the inter-rater reliability of measurements from the three investigators was performed. Data from ultrasound imaging of IMT, one reading per investigator, were recorded for 20 participants as a pilot test. The inter-rater (inter-observer) reliability of the measurements among the three investigators was assessed by calculating the Intraclass Correlation Coefficient (ICC) (22). Our estimated ICC was 0.882, with a 95% Confidence Interval (CI) (0.78, 0.94), which was considered excellent (23). Accordingly, we have evidence to support the reliability of measurements between the three investigators. The measurements of the pilot test were not included in the sample of this study.

Intima-media thickness was measured by ultrasonography using the longitudinal axis of both common carotid arteries (CCA) while the patient lying in the supine position with neck rotated to the opposite side of examination. The exams were performed using a B-mode ultrasound with a Sonoscape A8 (Medical Systems, Shenzhen, China), using a 10–12 MHz linear transducer. Optimal B-mode settings of gain, depth of placement, and compression were individually adjusted for each vessel to enhance arterial wall structures and image quality, in accordance with IMT measurement protocols (24). The normal thickness of the intima-media complex measured in the B-mode [from the lumen-intima interface (the first hyperechoic line) to the media-adventitia interface (the second hyperechoic line)] was 0.5–0.6 mm and increased somewhat with age (Figure 1) (25). Bilateral carotid arteries were evaluated and CCA-IMT was measured. At least three IMT measurements were obtained for each near and far wall. Mean CIMT values from the far walls of both the right and left CCAs (mean-mean) were reported (26, 27). CIMT values ≥0.8 mm were defined as the cut-off value for a thickened CIM complex (Figure 2) (8).

Ethical Considerations

This study was approved by the ethical review committee of the Faculty of Medicine for Girls Al-Azhar University, Cairo, Egypt. Participation was voluntary; an informed consent was obtained from each study participant. Each participant had the right to refuse participation or withdraw from the study at any point without giving any reasons and without affecting their rights of medical care. Also, data were anonymous and coded to assure confidentiality of participants.

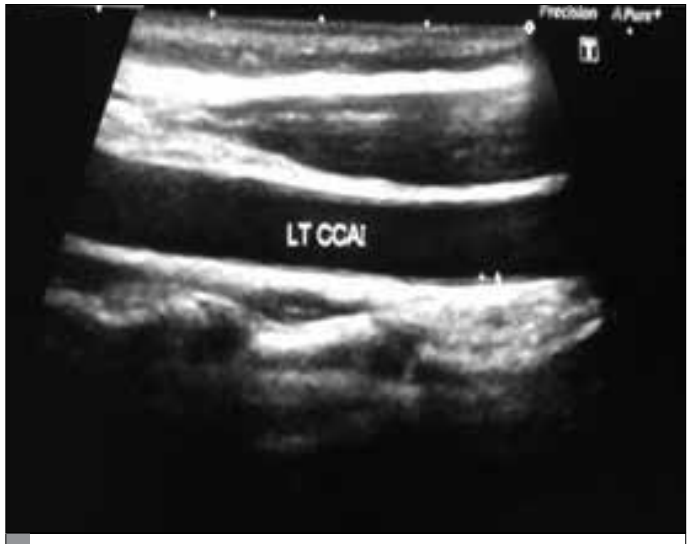

Figure 1. Normal CIMT. Normal carotid intima media thickness (0.6 mm)
LT CCA: Left common carotid artery; CIMT: carotid intima-media thickness

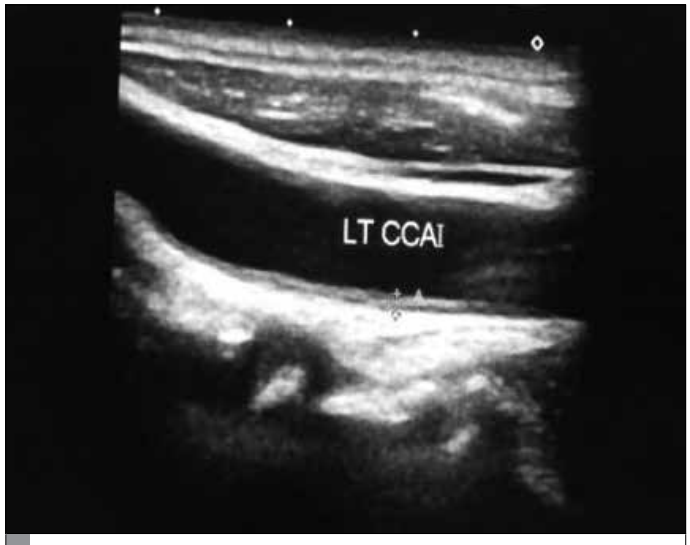

Figure 2. Thickened CIMT. Increased carotid intima media thickness (1.4 mm)
LT CCA: Left common carotid artery; CIMT: carotid intima-media thickness

Table 1. Comparison between COPD group and non-COPD group regarding personal characteristics, spirometric indices, and carotid artery intima-media thickness

Groups Items	COPD group No.= 86	Non–COPD group No.= 86	Sig. test p
Carotid IM thickness			
Normal	31 (36.0%)	79 (91.9%)	χ^2 =58.1
Thickened (≥0.8mm)	55 (64.0%)	7 (8.1%)	p<0.001*
CIMT/mm			
Mean ± SD	0.84±0.15	0.63±0.076	t-test=11.0 p<0.001*
Age/year			
Mean ± SD	61.9±9.2	60.3±8.9	t-test=1.2 p=0.23
BMI/kg/m^2			
Mean ± SD	28.5±5.11	29.1±3.1	t-test=0.88 p=0.38
Smoking status			
Non smoker	6 (7.0%)	57 (66.3%)	χ^2 = 65.1
Smoker	80 (93.0%)	29 (33.7%)	p<0.001*
Smoking (pack/year)			
Mean ± SD	40.0 ± 5.5	25.4 ± 9.6	t-test=11.7 p<0.001*
FEV_1/FVC			
Mean ± SD	58.2±13.72	83.5±10.3	t-test=13.6 p<0.001*
FEV_1%			
Mean ± SD	46.3±19.19	92.6±15.9	t-test=17.4 p<0.001*
FVC%			
Mean ± SD	61.5±19.2	94.3±10.9	t-test=13.7 p<0.001*
FEF_{25-75}%			
Mean ± SD	34.2±17.8	71.4±7.4	t-test=17.9 p<0.001*

* Significant p-value
BMI: Body Mass Index; CIMT: carotid intima-media thickness; COPD; chronic obstructive pulmonary disease; FEF_{25-75}%: forced expiratory flow rate 25%–75%; FEV_1: forced expiratory volume in first second; FVC: forced vital capacity; SD: standard deviation

Statistical Analysis

Data was statistically analyzed by the Statistical Package for Social Science (SPSS) program version 17.0 (SPSS Inc.; Chicago, USA). Descriptive analysis was done for each item and the results were expressed as mean ± SD for quantitative continuous variables, and as percentages for qualitative (categorical and nominal) variables. The studied COPD cases were categorized into two groups based on their CIMT. Comparisons to assess the difference between the groups used the Chi-square (X^2) test for qualitative data and the Student's t-test for quantitative data (the Shapiro-Wilk test was used for testing normality of the studied variables). The odds ratio was calculated to measure the association between the risk factors and the outcome. Multivariate logistic regression analysis was used to identify the most relevant risk factors affecting thickness of the carotid intima among patients with COPD. The strength of relevance between the risk factors and the outcome was determined according to the value of the Beta coefficient (B), and significance according to the Wald Chi-square test; also, the Odds ratio (OR) was calculated. Analysis of inter-observer reliability was made with the ICC and CI of 95%. Agreement levels were classified as poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), and excellent (>0.80) (23). Statistical significance was considered at a p-value <0.05 (with a confidence limit at 95%). Results are presented in tables and figures.

RESULTS

Table 1 shows that the smoking frequency (pack/year) was significantly higher (p=0.001), while spirometric-indices were significantly lower in the COPD group than the non-COPD group. CIMT was signifi-

Table 2. Comparison between COPD with normal CIMT and COPD with thickened CIMT group in regards to personal characteristics, spirometric indices and carotid thickness

Groups Items	COPD with Normal CIMT No.= 31	COPD with Thickened CIMT No.= 55	Sig. test p
CIMT Mean ± SD	0.67±0.05	0.94±0.09	t-test=13.4 p<0.001*
Age/years Mean ± SD	58.1±7.6	63.3±10.6	t=2.4 p=0.02*
BMI kg/m^2 Mean ± SD	27.9±4.6	28.9±5.4	t=0.79 p=0.37
Smoking status Non smoker Smoker	2 (6.5%) 29 (93.5%)	4 (7.3%) 51 (92.7%)	χ^2 =0.02 p=0.88 OR=0.87 (0.152 - 5.1)
Smoking (pack/year) Mean ± SD	41.1±31.3	39.4±21.6	t-test=0.26 p=0.78
COPD duration/ years Mean ± SD	11.7±8.1	13.3±8.7	t-test=0.82 p=0.41
Hypoxemia No Yes	10 (32.3%) 21 (67.7%)	3 (5.5%) 52 (94.5%)	χ^2 =11.1 p=0.001* OR=8.2 (2.1- 33.0)
PaO_2 mmHg Mean ± SD	75.8±8.7	64.9±11.2	t=4.7 p<0.001*
Hypercapnia No Yes	28 (90.3%) 3 (9.7%)	33 (60.0%) 22 (40.0%)	χ^2 =8.8 p=0.003* OR=6.2 (1.68 – 22.9)
$PaCO_2$ mmHg Mean ± SD	39.9±6.8	44.4±10.7	t-test=2.1 p=0.04*
COPD Severity Mild - moderate Severe -very severe	15 (48.4%) 16 (51.6%)	17 (30.9%) 38 (69.1%)	χ^2 =2.6 p=0.11 OR=2.1 (0.846 - 5.19)
FEV_1% Mean ± SD	53.4±17.4	42.4±19.2	t-test=2.6 p=0.01*
FEV_1/FVC Mean ± SD	57.5±13.8	58.6±13.8	t-test=0.37 p=0.7
FVC% Mean ± SD	73.8±18.8	54.5±15.6	t-test=5.1 p<0.001*
FEF_{25-75}% Mean ± SD	39.9±21.8	31.0±14.4	t-test=2.3 p=0.02*

* Significant p-value
BMI: Body Mass Index; CIMT: carotid intima-media thickness; COPD: chronic obstructive pulmonary disease; FEF_{25-75}%: forced expiratory flow rate 25%–75%; FEV_1: forced expiratory volume in first second; FVC: forced vital capacity; mmHg: millimeter mercury $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial oxygen pressure; SD: standard deviation

Table 3. Comparison of CIMT in COPD patients according to hypoxemia, hypercapnia, and COPD severity

Items	CIMT Mean ± SD	Sig. test p
Hypoxemia		
No (No.=13)	0.74±0.17	t-test=2.7
Yes (No.=73)	0.86±0.14	p=0.008*
Hypercapnia		
No (No.=61)	0.82±0.15	t-test=2.0
Yes (No. =25)	0.89±0.13	p=0.04*
COPD Severity		
Mild - moderate (No.=32)	0.83.±0.15	t-test=0.042
Severe - very severe (No.=54)	0.84±0.16	p=0.83

*Significant p-value
CIMT: carotid intima-media thickness; COPD: chronic obstructive pulmonary disease; SD: standard deviation

cantly increased in the COPD group compared to the control group (p<0.001). Additionally, 64% of COPD patients and 8.1% of non-COPD controls had a thickened CIM (p<0.001). Table 2 shows that age and $PaCO_2$ were significantly higher while PaO_2, FEV_1%, FVC, and FEF_{25-75}% were significantly lower in COPD patients with a thickened CIMT compared to COPD patients with a normal CIMT. There was no significant difference between both groups regarding BMI, smoking history (OR<1), smoking frequency (pack/year), and airflow limitation (OR=2.195. %CI 0.846–5.19). Thickened CIMT in COPD patients was significantly associated with hypoxemia (OR=8.2, 95% CI, 2.1–33.0) and hypercapnia (OR=6.2, 95% CI, 1.68–22.9). These findings indicate that COPD patients with hypoxemia had an 8-fold increased risk for developing atherosclerosis while COPD patients with hypercapnia had a 6-fold increased risk of developing atherosclerosis. Table 3 shows that CIMT was significantly increased in COPD patients with hypoxemia compared to COPD patients without hypoxemia (p=0.008), and in COPD patients with hypercapnia compared to COPD patients without hypercapnia (p=0.04). No significant difference in CIMT was found among different stages of COPD severity (p=0.83). The Table 4 multivariate logistic regression analysis revealed that the most significant risk factors relevant to the thickened carotid intima among patients with COPD were age (B=0.139) followed by PaO_2 (B=−0.1). Both $PaCO_2$ and FEV_1% (B=0.056 and −0.016, respectively) were insignificantly relevant to a thickened CIMT. Moreover, smoking frequency (pack/year) was not relevant to a thickened carotid intima (B=0.000).

DISCUSSION

There is increasing awareness that the inflammatory state associated with COPD is not confined to the lungs, but also involves the whole circulation system and can affect extra-pulmonary organs (28). These comorbidities account for more than 50% of COPD-related health costs (29). Thus, it is important to evaluate COPD patients for these comorbidities.

In the current study, 64% of COPD patients (versus 8.1% of healthy controls) had a thickened CIMT. In the same context, other investigators reported a higher prevalence of thickened CIMT in patients with COPD than the control group (8, 17, 30, 31), Furthermore, Chindhi

Table 4. Multivariate logistic regression of risk factors for carotid intima thickening among patients with COPD

Independent variables	Beta coefficient (B)	S.E.	Wald test	p	Exp (B)	95% C.I. for EXP(B)	
						Lower	Upper
Age/years	0.139	0.042	10.852	0.001*	1.149	1.058	1.249
PaO_2 mmHg	- 0.100	0.031	10.166	0.001*	0.905	0.851	0.962
$PaCO_2$ mmHg	0.056	0.053	1.099	0.294	1.057	0.953	1.173
FEV_1%	-0.016	0.021	0.632	0.427	0.984	0.945	1.024
Smoking (pack/year)	0.000	0.001	1.860	0.173	0.999	0.998	1.000
Constant	-1.663	4.810	0.119	0.730	0.190		

*Significant p-value
C.I.: confidence interval; FEV_1: Forced expiratory volume in first second; mmHg: millimeter mercury; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial oxygen pressure; S.E.: standard error

et al. (32) documented that the prevalence of carotid plaque formation was significantly higher among COPD patients compared to the controls. Additionally, CIMT was found to be significantly higher among our study COPD patients than the controls (0.85±0.18 mm vs. 0.63±0.076 mm, p<0.001). These results coincide with the results of other studies in the literature (4, 17, 33-39).

Although, smoking is a well-known risk factor for atherosclerosis; results of this study revealed that smoking was not relevant to an increased CIMT among the studied COPD patients both by logistic regression analysis and by estimation of risk (OR<1) (Table 2, 4). Similar results were reported by other investigators (38); they found that smoking frequency (pack/year) did not differ between COPD patients with normal CIMT and those with a thickened CIMT. Two other studies reported that CIMT was significantly increased: in smoker COPD patients compared to the smoker control group (37) and in smokers with airflow limitation compared to smokers in the control group and never-smokers in the control group (40). This might be an indication of the influence of other factors leading to intimal thickening other than smoking.

This study demonstrated that FEV_1% was significantly lower in COPD patients with a thickened CIMT compared to those with a normal CIMT; however, CIMT did not differ significantly between the mild-to-moderate and severe-to-very severe COPD patients. These findings indicate that atherosclerosis initiated in the early stages of COPD and it also suggests that airflow limitation is associated with atherosclerosis. These results are supported by many studies that reported significantly higher CIMT in COPD patients with a lower FEV_1 (41–45), and it was not significant between different COPD stages (8, 32). In addition, van Gestel et al. (17) documented that moderate-to-severe COPD was independently associated with increased CIMT, regardless of the smoking status. In the same context, Anthonisen et al. (46) reported that, for every 10% decrease in FEV_1, there was a 20% increase in non-fatal coronary events and 28% increase in fatal coronary events among patients with mild-to-moderate COPD. However, other investigators reported that FEV_1% was not significantly different between COPD patients with normal CIMT and those with a thickened CIMT (38).

Our data demonstrated that PaO_2 was significantly lower, while $PaCO_2$ was significantly higher, in COPD patients with a thickened CIMT compared those with a normal CIMT. These results suggest that COPD-related hypoxemia and/or hypercapnia are relevant factors for atherosclerosis. Hypoxemia could lead to atherosclerosis through increasing systemic inflammation, oxidative stress, upregulating cell adhesion molecules, inducing hemodynamic stress, and increased foam cell production (15, 47, 48). The same results were recorded by Ozbay et al. (36); they found that oxygen saturation was decreased in COPD patients with a thickened CIMT and reported that both intermittent and continuous hypoxemia resulted in remarkable alterations in CIMT.

In this study, logistic regression analysis demonstrated that age was a significant risk factor for a thickened intima and this might be explained by degenerative changes that occur with increasing age, including thickening of the vascular intima. This result is concordant with previous work that documents accelerated atherosclerosis of the arterial walls with age and various comorbid risk factors (9).

The limitation of this study was that the distributions of the groups according to smoking status and COPD stages were relatively heterogeneous.

CONCLUSION

Atherosclerosis was prevalent in about two-thirds (64%) of COPD patients. A thickened CIMT was detected in the early stages of COPD patients and an insignificant difference was found between the mild-moderate to severe-very severe COPD patients. Factors contributing to atherosclerosis in COPD patients included: age, hypoxemia, hypercapnia, and COPD severity. Smoking status as not a contributing factor. Screening for atherosclerosis in COPD patients is recommended for starting early and proper management. Furthermore, interventional studies targeting atherosclerosis as well as studies to evaluate the effects of early oxygen therapy on CIMT in COPD patients are recommended.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Al-Azhar University, Cairo, Egypt.

Informed Consent: Written and verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.R.H., E.S., O.I.A., L.K.S.; Design - M.R.H., E.S., O.I.A., L.K.S.; Supervision - M.R.H., E.S., O.I.A., L.K.S.; Resources - M.R.H., E.S., O.I.A., L.K.S.; Materials - M.R.H., E.S., O.I.A., L.K.S.; Data Collection and/or Pro-

cessing - M.R.H., E.S., O.I.A., L.K.S.; Analysis and/or Interpretation - M.R.H., E.S., O.I.A., L.K.S.; Literature Search - M.R.H., E.S., O.I.A., L.K.S.; Writing Manuscript - M.R.H., E.S., O.I.A., L.K.S.; Critical Review - M.R.H., E.S., O.I.A., L.K.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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