Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH Open Access

Pulmonary emphysema and atherosclerosis: association or syndrome?

Atef W. Elrefai[1], Mohammad Mossaad Alsayyad[2] and Elsayed Mohamed Abd El-Hamid Hassan Dawood[3*]

Abstract

Background: Atherosclerosis is an inflammatory reaction of the vessel wall. Emphysema may induce systemic inflammation, part of which may be the development or progression of atherosclerosis. So, the relationship between emphysema and atherosclerosis, whether both are due to the same causative agent and pathogenesis or emphysema led to atherosclerosis, is still not clearly understood. So, the aim of this work is to study the relationship between carotid atherosclerosis versus pulmonary emphysema extent and airflow obstruction.

Results: Cigarette smoking index was higher in patients than controls. According to FEV1%, patients were classified into: GOLD 1 (mild): FEV1 ≥ 80% predicted, GOLD 2 (moderate): 50% ≤ FEV1 < 80% predicted, GOLD 3 (severe):30% ≤ FEV1 < 50% predicted, and GOLD 4 (very severe): FEV1 < 30% predicted. There was a significant difference between the studied groups as regard to ABG parameters. Emphysema score showed a positive correlation with thrombus size, plaque size, and stenosis percent. Approximately 2/3 of patients had atherosclerotic changes and the other 1/3 had increased IMT. GOLD staging, also, correlated with thrombus size and stenosis percent. So, there was a strong positive correlation between both emphysema score and GOLD staging and carotid atherosclerosis.

Conclusion: The relationship between emphysema and atherosclerosis is suggested to be the chronic inflammatory reaction (against the same risk factor) based on the positive correlation between carotid atherosclerosis versus emphysema score and GOLD staging. The inherence of emphysema and atherosclerosis may be considered a syndrome. If so, targeting the same pathogenic mechanism will be valuable for their control.

Keywords: Pulmonary emphysema, Emphysema, Carotid atherosclerosis

Background

Emphysema is a chronic inflammatory response due to cigarette smoke and other noxious particles with subsequent progressive airflow limitation ending in gas trapping [1]. On one side, COPD in most patients is associated with chronic diseases that share with the COPD the same risk factors like smoking, aging, and inactivity; these chronic diseases affect the morbidity and mortality of COPD [2]. COPD as a chronic inflammatory disease and through inflammatory mediators in the circulation may lead to the development or deterioration of other comorbidities like ischemic heart disease, metabolic syndrome, etc. [1].

The pathogenesis of the pulmonary emphysema had been suggested to be due to the increased elastolytic activity of neutrophil proteinases [3], oxidative stress that increases with cell senescence [4], the cellular and molecular factors, alveolar cell apoptosis, autoimmune, and genetic factors [5]. In addition, matrix metalloproteinases unbalance with their tissue inhibitors was suggested to contribute to the cerebrovascular damage in COPD [6]. Also, the systemic inflammation and endothelial dysfunction, according

* Correspondence: sayeddawood71@yahoo.com
[3]Radiology Department, Al-Azhar University, Faculty of Medicine, New Damietta, Egypt
Full list of author information is available at the end of the article

Table 1 Patient characteristics of studied populations

Variables		COPD	Control	*p* value
Age		64.2 ± 5.6	64.37 ± 5.1	0.86(ns)
Sex	**Male**	68(85.0%)	27(67.5%)	0.26(ns)
	Female	12(15.0%)	13(32.5%)	
Packs/year		24.35 ± 14.64	14.75 ± 15.13	0.001*

*Denoting the value is significant

to several studies, are incriminated in the development of the pulmonary and extrapulmonary vascular changes in COPD [7–15].

This systemic inflammation with endothelial dysfunction, also, promote the systemic vascular alteration in atherosclerosis [15–19], elevating the suggestion of the relation between atherosclerosis and COPD as regards to the same pathogenesis, particularly after the conclusion of many studies that atherosclerosis is predominantly an inflammatory reaction of the vessel wall [20].

The risk stratification of cardiovascular morbidity and mortality in COPD lacks established biomarkers, besides the normal lipid profile in most patients [21]. Hence, using common carotid artery ultrasonography being able to measure intima-media thickness (IMT) and to detect early atherosclerotic lesions, is a useful tool for risk-stratification [22, 23]. The carotid intima-media thickness (CIMT) measurement by ultrasonography is not only an indicator of atherosclerosis but also an indicator of cardiovascular (CV) events and mortality [24–27]. Besides that, there is a correlation between CIMT increase and airflow obstruction severity in COPD [28–30]. Explanation of the increase of CIMT in COPD is claimed to be due to systemic inflammation, endothelial dysfunction, hypoxia [30], a sedentary lifestyle, high smoking prevalence [31], hypercoagulability, platelet activation, and oxidative stress [32–34] rather than lipid-driven atherosclerosis [35]. Moreover, elastin degradation in the extracellular matrix of the arterial wall results in emphysema in the lungs and atherosclerosis in the vasculature [34, 36].

So, if both conditions (emphysema and atherosclerosis) have the same pathogenesis, the different stages of both could coincide. If this is proved, the relationship between them may be considered inherent more than just association.

Purpose

To study the relationship between carotid atherosclerosis and pulmonary emphysema extent and airflow obstruction.

Methods

3.1. Study design

This study was conducted on 80 patients with emphysema and 40 controls, conducted at the Chest Department, in the period from November 2016 to November 2017. The diagnosis of COPD was based on GOLD criteria [1]. All included subjects were submitted to the following: (1) full history taking: with special attention to the main complaint, age, sex, smoking status, duration of disease, risk factors (occupation, pollution, resident area, diabetes mellitus, dyslipidemia, etc.); (2) clinical examination; (3) HRCT of the chest reported by two observers; (4) ABG: PH, partial arterial oxygen tension (PaO2), partial arterial carbon dioxide tension (PaCO2), and arterial oxygen saturation (SaO2) were measured in the arterial blood sample at room air after 20 min from performing the HRCT; (5) spirometric tests: all subjects underwent spirometry with

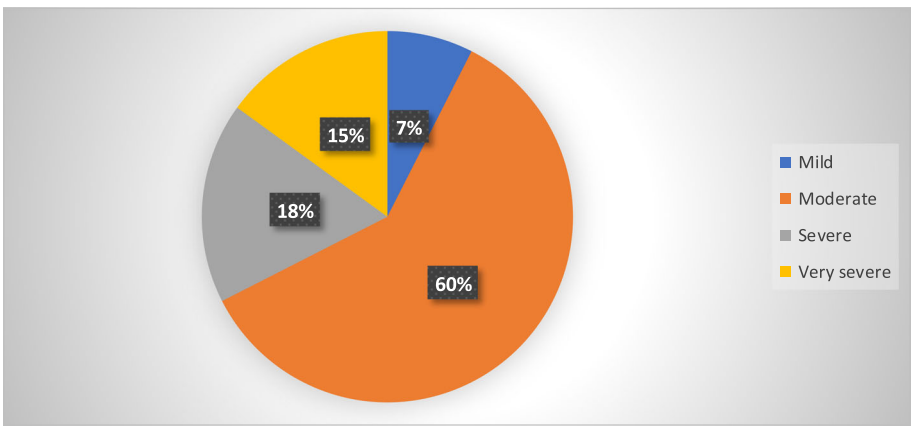


Fig. 1 GOLD classification

Table 2 Correlation between emphysema score and carotid duplex

Carotid duplex	Emphysema score	
	R	*P*
Right thrombus size	.839**	.000
Right plaque size	.870**	.000
Right stenosis percent	.878**	.000
Left thrombus size	.861**	.000
Left plaque size	.305**	.006
left stenosis percent	.938**	.000

*Denoting the value is significant

special measurement of; forced vital capacity (FVC), forced expiratory volume in 1 second% predicted (FEV1%), and FEV1/FVC ratio; (6) carotid duplex; control group consisted of age and sex-matched volunteers with no history of chronic chest diseases; in addition, lipid profile, fasting and postprandial BS, liver, kidney functions were done.

3.2. Exclusion criteria

The presence of systemic hypertension, diabetes mellitus, known cardio/cerebrovascular diseases, dyslipidemia, or history of lipid-lowering drug intake excluded the subject from the study.

Study protocol

A. Spirometry studies: were performed via ZAN MEBGERAEE GMBH D-97223 Oberthulba, Schlimpfhoferstr, Messgeraete GmbH Germany, Spirometry, according to the American Thoracic Society/European Respiratory Society standards [37]. According to GOLD, spirometry was required to diagnose emphysema and FEV1/FVC ratio < 0.70 confirmed persistent airflow limitation presence. Then, the severity of airflow limitation was classified on basis of a post-bronchodilator FEV 1[1].
B. Carotid Doppler U/S: was performed with a 7.5 MHZ superficial linear array transducer of (TOSHIBA, Xario 200, TOSHIBA Medical System, Japan) in axial and longitudinal section in B mode, by a single experienced operator. The images obtained during the ultrasonographic imaging were recorded electronically and then evaluated. 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. The averages of the CIMT values obtained from the far walls of the right and left common carotid arteries were calculated. Measurements were taken at least 10 mm

Table 3 Lipid profile and blood sugar among studied groups

Variables	COPD	Control	*p* value
Cholesterol	164.00 ± 22.23	160.90 ± 24.24	0.48(ns)
TG	81.23 ± 17.46	84.55 ± 15.56	0.31(ns)
Fasting BS	104.06 ± 4.07	104.97 ± 7.38	0.38(ns)
Postprandial BS	132.22 ± 4.59	128.15 ± 19.28	0.08(ns)

Table 4 Intraclass absolute agreement between two observers for emphysema score

	Intraclass correlation coefficient (ICC)	95% Confidence interval(CI)		*p* value
		Lower bound	Upper bound	
Single measures	.997b	.996	.998	<0.001*
Average MEASURES	.999c	.998	.999	<0.001*

*Denoting the value is significant

Table 5 Atherosclerotic plaques in studied groups

		COPD		Control		*p* value
		n	%	*N*	%	
Right surface	No plaque	25	31.3%	40	100.0%	<0.001*
	Smooth	16	20.0%	0	.0%	
	Irregular	31	38.8%	0	.0%	
	Ulcer	8	10.0%	0	.0%	
Right hemogoniecity	No plaque	25	31.3%	40	100.0%	<0.001*
	Homogeneous	23	28.8%	0	.0%	
	Heterogeneous	32	40.0%	0	.0%	
Right calcification	No plaque	25	31.3%	40	100.0%	<0.001*
	Soft	13	16.3%	0	.0%	
	Calcified	42	52.5%	0	.0%	
Left surface	No plaque	23	28.8%	40	100.0%	<0.001*
	Smooth	18	22.5%	0	.0%	
	Irregular	31	38.8%	0	.0%	
	Ulcer	8	10.0%	0	.0%	
Left hemogoniecity	NO plaque	23	28.8%	40	100.0%	<0.001*
	Homogeneous	16	20.0%	0	.0%	
	Heterogeneous	41	51.3%	0	.0%	
Left calcification	No plaque	23	28.8%	40	100.0%	<0.001*
	Soft	15	18.8%	0	.0%	
	Calcified	42	52.5%	0	.0%	

*Denoting the value is significant

proximal to the carotid bifurcation, in the near and far wall of the left and right common carotid arteries. Repeated measurements were performed along with a minimum of 10 mm length. Four measurements were taken from both the left and right common carotid arteries (two in the near and two in the far wall). The maximal measurement from these eight measurements was used for analysis, according to the 'Mannheim Carotid Intima-Media Thickness Consensus' [38]. A thickening ≥1.5 mm was categorized as an atheromatous plaque [39].

C. HRCT: examination was carried out with (TOSHIBA, Aquilion prime, 80 dual MDCT system, Japan) Examination was performed with the subject in the supine position at the end-inspiratory state. A total of 0.5-mm thick slices at 10-mm intervals (120 kVp, 250 mA, 1-s scanning time) were obtained from the diaphragm to the lung apex. A high-frequency reconstruction algorithm was used. Images format with window setting 1200/[a]500 Hounsfield units.

D. Visual analysis: radiologist and pulmonologist blindly and independently evaluated CT slices of subjects using the extent of emphysema. The evaluation was performed slice-by-slice, both lung fields together, and results were later combined as the total scores of each subject [40]. Emphysema was defined as hypovascular areas of pulmonary parenchyma not associated with a fissure, usually lacking a well-defined wall. Changes were decreased attenuation, few or no vessels, and bullae with a well- or ill-defined wall. The scale used was: 0 = normal; 1 = emphysema in 25% of the slice; 2 = emphysema in 25–50% of the slice; 3 = emphysema in 50–75% of the slice; and 4 = emphysema in >75% of the slice; as the maximum score in each slice was 4 and 10 slices were imaged per patient, the maximum possible score was 40 [41].

Statistical methodology

Data entry and analysis were done using SPSS version 17, data were presented as mean, SD, Median, No., and percentage, Cochran Armitage chi-square test was used to compare qualitative data between the two groups of patients, independent samples *T* test was

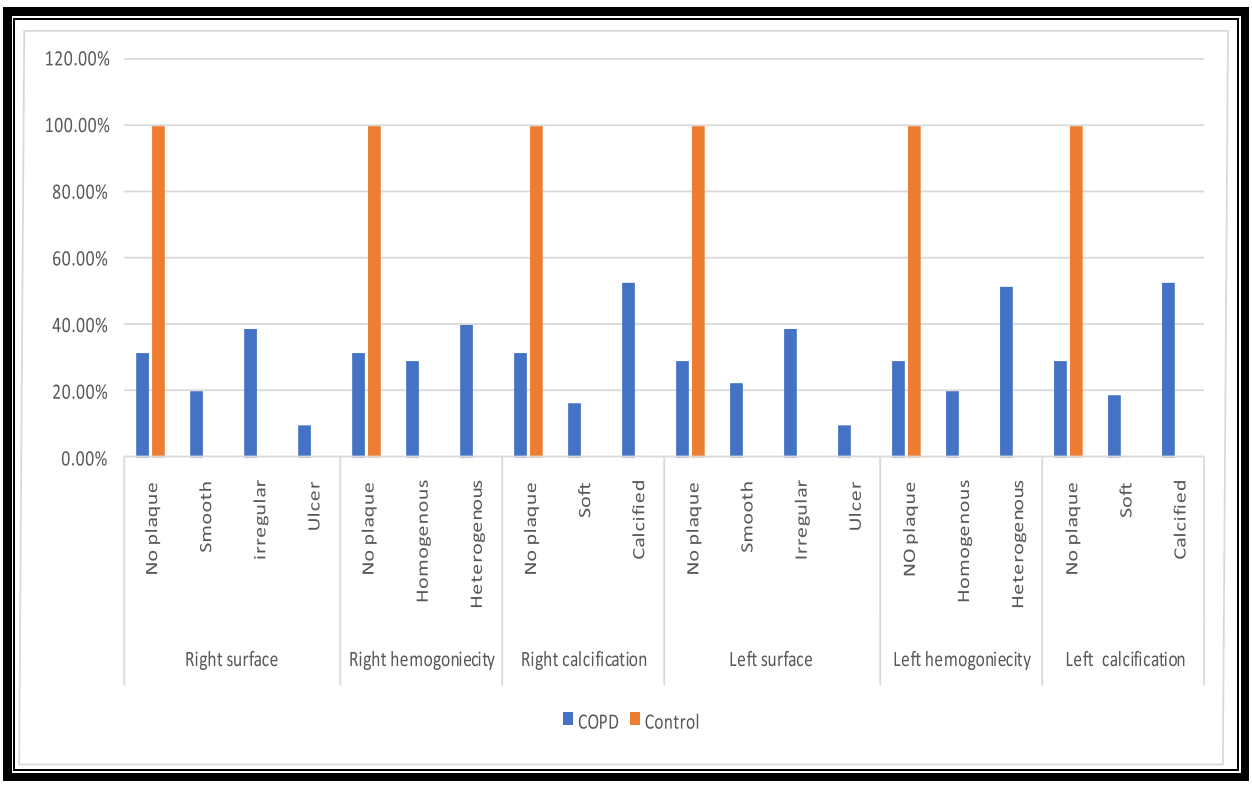
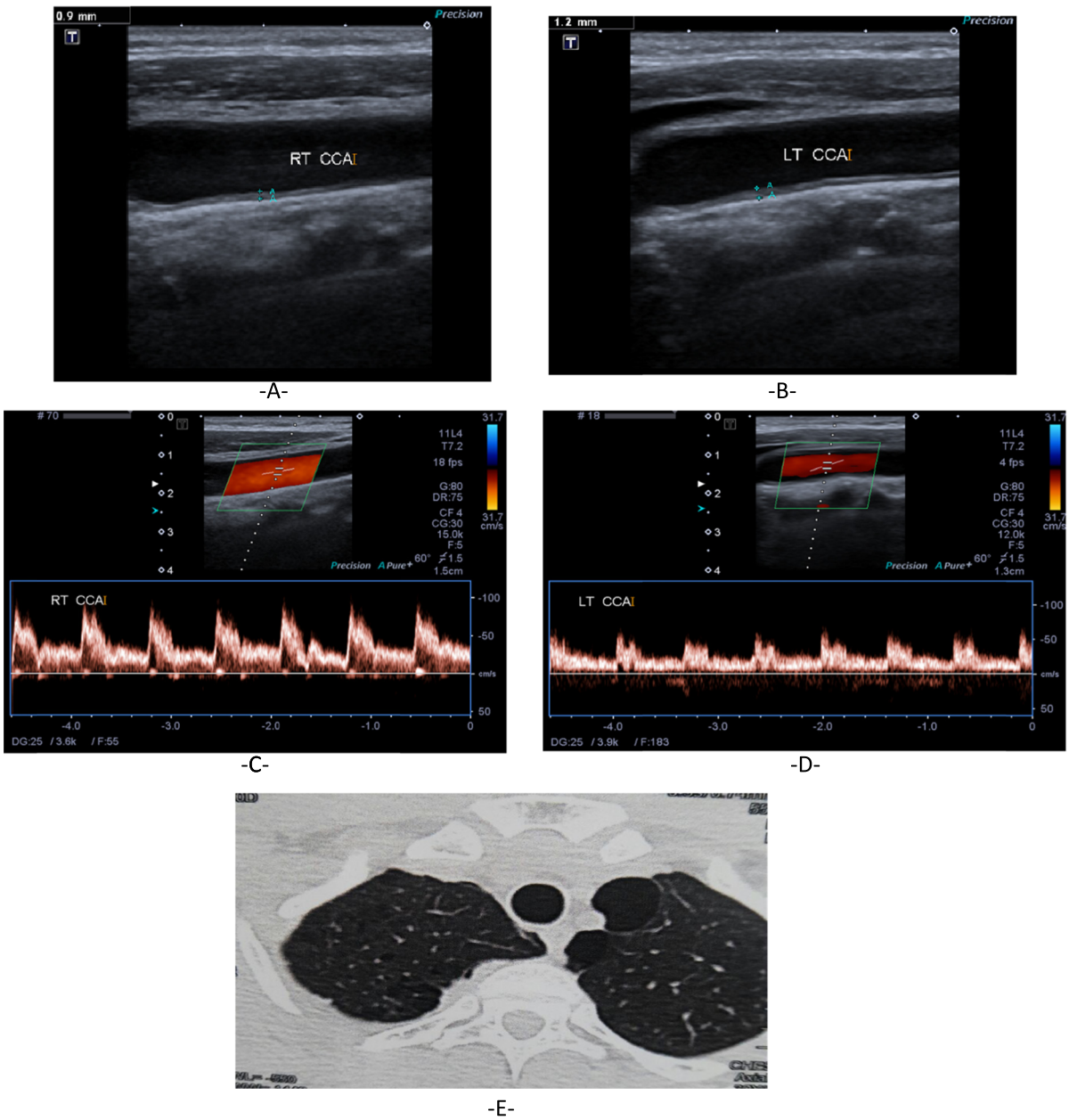


Fig. 2 Atherosclerotic plaques in studied groups



- Mild atherosclerotic changes affect the carotid arteries;
  - A- B-mode US of RT CCA shows diffuse increase intima media thickness, (IMT of RT CCA = 0.9 mm), without significant atheromatous plaques.
  - B- B-mode US of LT CCA shows diffuse increase intima media thickness,(IMT of LT CCA = 1.2 mm), without significant atheromatous plaques.
  - C- Color duplex US of RT CCA shows normal waveform.
  - D- Color duplex US of LT CCA shows normal waveform.
  - E- Axial HRCT cuts in lung window shows sever emphysematous changes and multiple emphysematous bullae.

Fig. 3 A case of severe emphysematous changes and mild carotid arteries atherosclerotic changes. Mild atherosclerotic changes affect the carotid arteries

used to compare means of both groups, paired samples *T* test was used to compare means before and after the procedure (CA or PCI) in the same group. *P* value is considered significant when it is <0.05; Regression analysis was done and or was calculated for independent risk factors, all results were presented in the form of tables and figures.

Results

In the present study, there was no significant difference between studied groups as regards to patient age and sex. However, there was a statistically significant difference between studied groups as regards to cigarette smoking index (Table 1).

Patients were classified into GOLD 1 (mild): FEV1 ≥ 80% predicted (*n.* = 6 [7.5%])/GOLD 2 (moderate): 50% ≤ FEV1 < 80% predicted (*n.* = 48 [60%])/GOLD 3 (severe): 30% ≤ FEV1 < 50% predicted (*n.* = 14 [17.5%]) /GOLD 4 (very severe): FEV1 < 30% predicted (*n.* = 12 [15%]). There was a statistically significant difference between studied groups as regards to SaO2, PH, PaO2, and PaCO2 (Fig. 1) (Table 2).

There was a statistically significant difference between studied groups as regard to FEV1%, FEV1/FVC, SaO2, PH, PaO2, and PaCO2 (Table 3). However, there was no significant difference between studied groups as regard to cholesterol, TG, fasting, and postprandial BS (Table 4).

In our work, the Intraclass Correlation Coefficient (ICC) for absolute agreement between two observers showed a high statistically significant absolute agreement between two observers in the reading of the emphysema score. Our estimated ICC was 0.999, with a 95% confidence interval (CI) (0.998, 0.999), and this was considered excellent.

In the present work, there was a highly positive correlation between emphysema score from one side and each of thrombus size (r = .839 on the right side and r = .861 on the left), plaque size (r = .870 right and r = .305 left) and stenosis percent (r = .878 right and r = .938 left) on both sides (Table 2).

In the studied groups, there was a statistically significant difference between COPD patients and controls as regards to atherosclerotic changes in the right and left carotid U/S findings. The incidence of carotid atherosclerotic plaques reached 68.8% on the right side and 71.3% on the left side, over that, the rest of patients without plaques showed an increase in IMT. The plaques were with smooth surface in 20%, irregular surface in 38.8%, ulcer in 10%, and homogeneous in 28.8%, heterogeneous in 40%, soft in 16.3% and calcific in 52.5% on the right side, and with smooth surface in 22.5%, irregular surface in 38.8%, ulcer in 10%, and homogeneous in 20%, heterogeneous in 51.3%, soft in 18.8%, and calcific in 52.5% on the left side (Table 5), (Fig. 2).

There were positive correlations between GOLD staging from one side and each of right thrombus size (r = .423), right plaque size (r = .451), right stenosis percent (r = .516), and left thrombus size (r = .440).

Discussion

In our work, the ICC for absolute agreement between two observers in reading emphysema score in chest HRCT showed high statistical significance (0.999, p < 0.001).

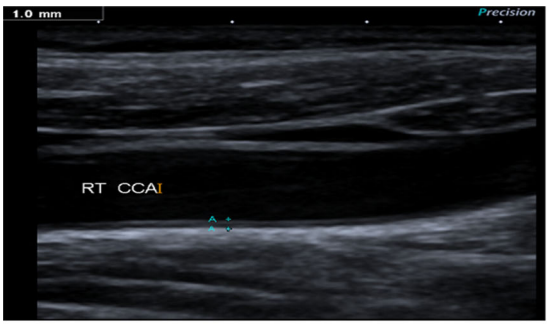
The use of B-mode ultrasound and carotid duplex can identify and quantify atherosclerosis and predict the risk for cardiovascular disease (CVD) and stroke in COPD patients [42].

Our study revealed a high incidence of carotid atherosclerotic plaques among about 70% of emphysema patients (68.8% on the right and 71.3% on the left side), while the rest of patients showed an increase in the IMT as an indicator of subclinical atherosclerosis. In addition, carotid atherosclerosis correlated well with emphysema CT score and more than its correlation with GOLD staging. This denotes the intimate association between atherosclerosis and emphysema with the slight prevalence of atherosclerotic changes in the left side. Of note that, cholesterol and TG levels in these patients were in the normal range.

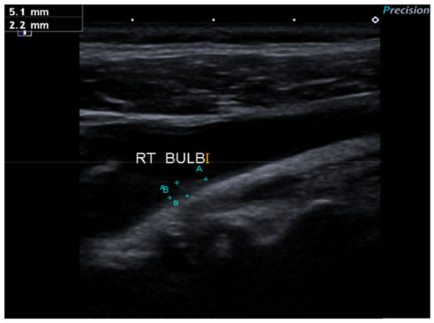
In agreement with our study, Hafez et al. [34] found atherosclerosis prevalence in COPD patients reaching about 64% (approximately two-thirds of COPD patients had atherosclerosis). Also, in agreement with the present study, the emphysema extent and airflow obstruction had been reported to correlate with atherosclerosis [7–11, 43].

FEV1 is considered a clinical indicator commonly used to evaluate the COPD severity [44], and GOLD classification of COPD depends mainly on FEV1. Our study showed a positive correlation between GOLD staging and carotid atherosclerosis.

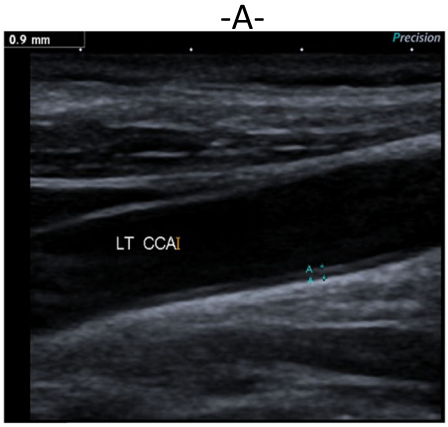
Barr et al. [35] reported the decrease in FEV1 to be an independent risk factor for carotid atherosclerosis and emphysema. Similarly, Alpaydin et al. [45], after adjusting their study for smoking, TG and cholesterol levels, hypertension, and fasting plasma glucose, had found IMT to be higher in COPD versus controls, and they suggested other mechanisms than smoking to be responsible for the association between COPD and IMT. So, airflow limitation and hypoxia are suggested to be responsible for the association between emphysema and carotid atherosclerosis. In a study by van Gestel et al., [23] they found moderate to severe COPD, independently and irrespective of associating comorbidities and smoking status, to be associated



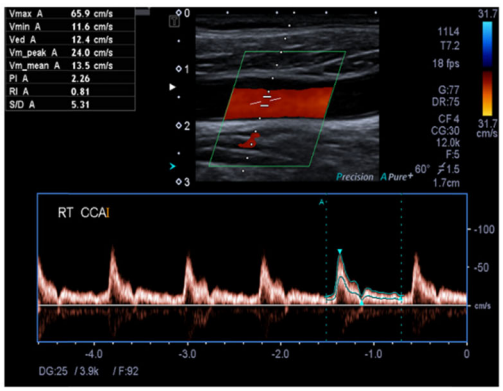
-A-



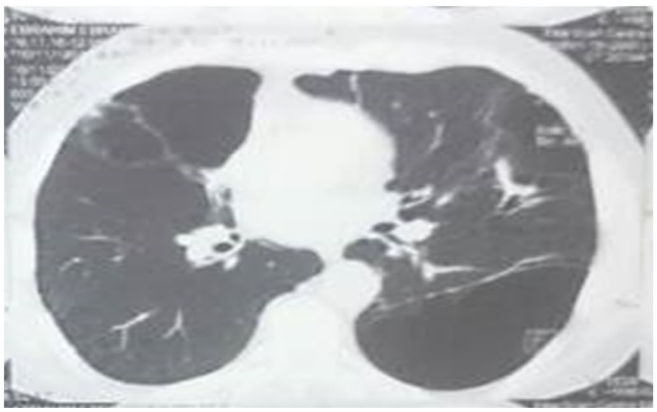
-B-



-C-



-D-



-E-

- Mild atherosclerotic changes affect the carotid arteries;

A- B-mode US of RT CCA shows diffuse increase intima media thickness, (IMT of RT CCA = 1mm).

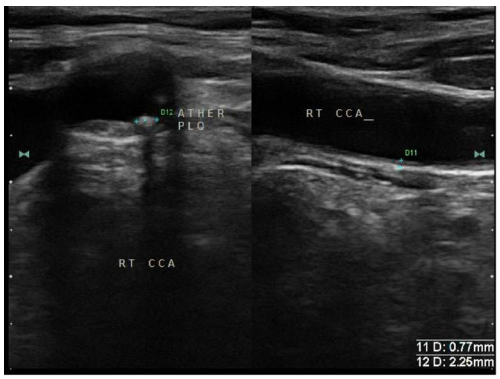
B- B-mode US of RT CCA shows Soft non calcified atheromatous plaque is noted involve the bulb of RT CCA measure about 5.1 X 2.2 mm.

C- B-mode US of LT CCA shows diffuse increase intima media thickness,(IMT of LT CCA = 0.9 mm), without significant atheromatous plaques.

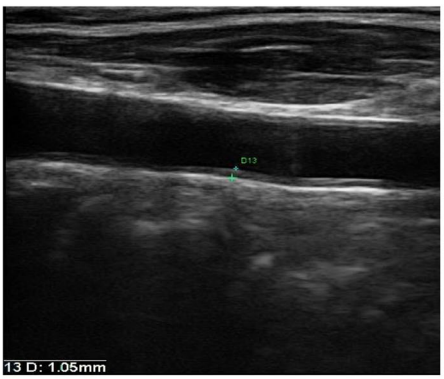
D- Color duplex US of RT CCA shows normal waveform.

E- Axial HRCT cuts in lung window shows sever emphysematous changes and multiple emphysematous bullae

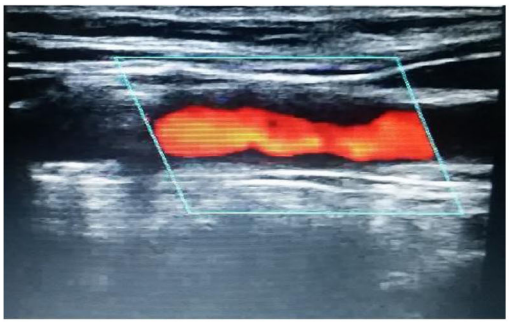
Fig. 4 A case of severe emphysematous changes and mild carotid arteries atherosclerotic changes



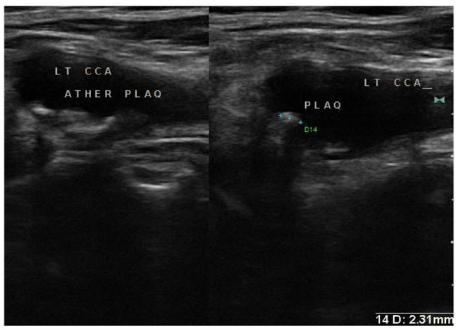
-A-



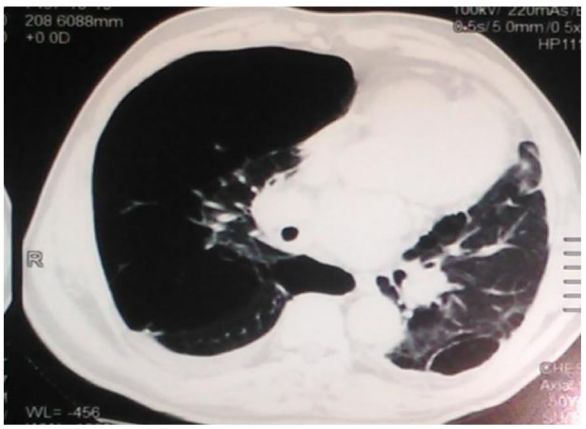
-B-



-C-



-D-



-E-

- Moderate atherosclerotic changes affect the carotid arteries;

A- B-mode US of RT CCA shows diffuse increase intima media thickness, (IMT of RT CCA = 0.8mm), with soft & calcified atheromatous plaques are noted involve RT carotid bulb.

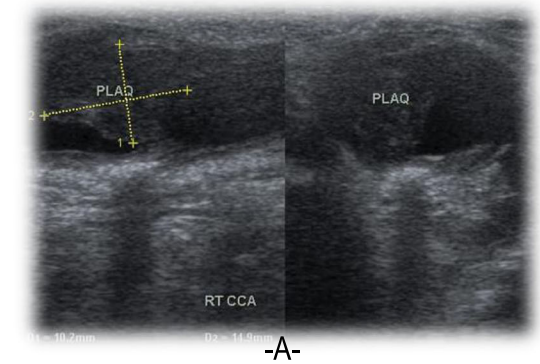
B- B-mode US of LT CCA shows diffuse increase intima media thickness,(IMT of LT CCA = 1 mm).

C- B-mode US of LT CCA shows calcified atheromatous plaques are noted through the LT carotid bulb, the largest is noted at the LT carotid bulb measure about 2.3 mm.

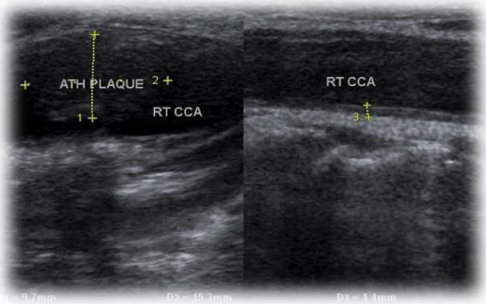
D- Colourdoppler US shows irregular outline of the common carotid artery secondary to atherosclerotic changes.

E- Axial HRCT cuts in lung window shows sever emphysematous changes and multiple emphysematous bullae

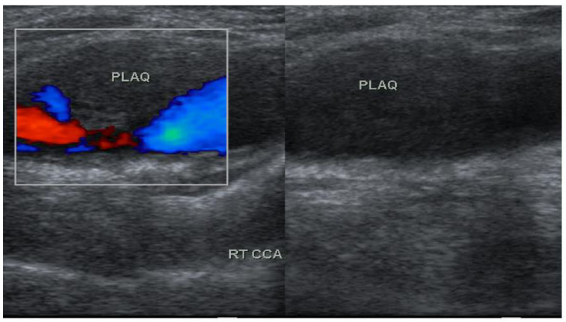
Fig. 5 A case of severe emphysematous changes and moderate carotid arteries atherosclerotic changes



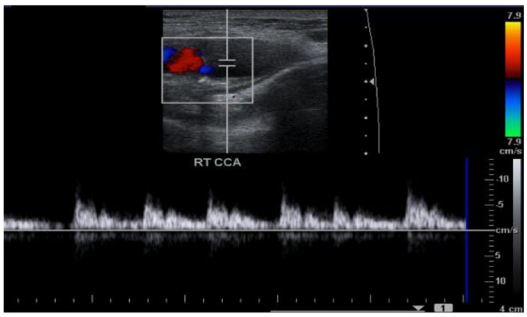
-A-



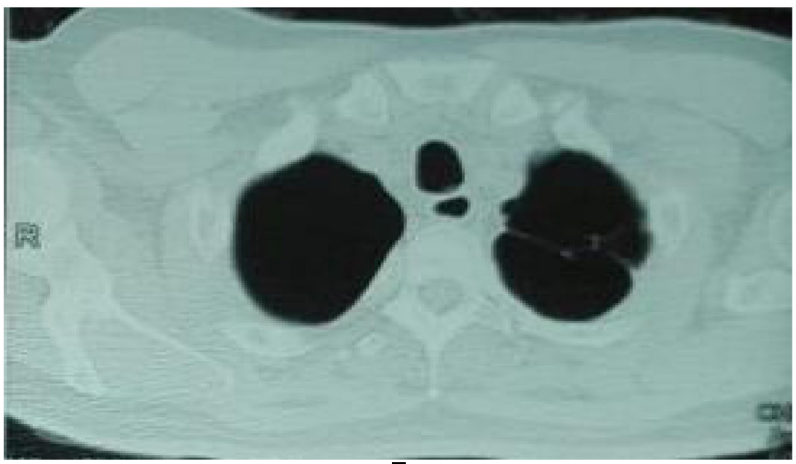
-B-



-C-



- D-



-E-

Advanced atherosclerotic changes affect the carotid arteries;

A- B mode US of RT CCA shows soft atheromatous plaque involve RT carotid bulb with sever lumina stenosis,

B- B mode US of RT CCA shows diffuse increase intima media thickness with irregular outline, and soft atheromatous plaque.

C- & D:colourdoppler US shows luminal colour filling defect by atheromatous plaque with sever luminal stenosis.

E-Axial HRCT cuts in lung window shows sever emphysematous changes and multiple emphysematous bullae.

Fig. 6 (See legend on next page.)

(See figure on previous page.)
Fig. 6 A case of severe emphysematous changes and advanced carotid arteries atherosclerotic changes. Advanced atherosclerotic changes affect the carotid arteries; **a** B mode US of RT CCA shows soft atheromatous plaque involve RT carotid bulb with sever lumina stenosis, **b** B mode US of RT CCA shows diffuse increase intima-media thickness with an irregular outline, and soft atheromatous plaque. **c** and **d**: colour doppler US shows luminal colour filling defect by an atheromatous plaque with severe luminal stenosis. **e** Axial HRCT cuts in the lung window show severe emphysematous changes and multiple emphysematous bullae

with increased IMT of the common carotid artery. In addition, Kim et al. [46] noticed IMT to be significantly correlated with FEV1, FEV1/FVC, and FVC, and suggested a bi-directional effect of COPD on CVS and vice versa. In a study by Köseoğlu et al.,[47] CIMT >1.25 mm was found to carry a 12-fold increased risk in COPD to have CAD (Figs. 3, 4, 5, and 6).

Hypoxemia and/or hypercapnia were considered relevant factors for atherosclerosis by Hafez et al. [34], on the basis of the significant decrease of PaO2 and significant increase of PaCO2 in COPD patients with increased CIMT versus those showing a normal CIMT. Systemic inflammation, oxidative stress, increased foam cell production, induction of hemodynamic stress, and upregulation of cell adhesion molecules are the possible mechanisms through which hypoxemia could lead to atherosclerosis [48–50].

In contrast to our study, Schroeder et al. [51] did not find an association between FEV1% and carotid plaque. In addition, Matsuoka et al. [15] did not find FEV1 to be significantly correlated with the severity of aortic calcification, but they explained that by the difference in the evaluation techniques and the difference in the pathological processes involved in different stages of atherosclerosis. However, Iwamoto et al. [11] reported a significant correlation between FEV1% and IMT. This may mean that airflow limitation initiates the increase in IMT, then the systemic inflammation induces atherosclerosis progression. Furthermore, atherosclerosis may be related to COPD phenotypes [15].

In a study by Pike et al .[52], they found that lung abnormalities may be directly related to carotid atherosclerosis in absence of airflow limitation in never- and ex-smokers. They suggested that subclinical airways disease may be present in never- and ex-smokers with increased IMT mediated by factors other than smoking. The relation of the extent of emphysema to arterial stiffness [8], and to endothelial dysfunction [7], besides the relation of endothelial dysfunction to systemic inflammation, both supported the conclusion of Matsuoka et al. [15] that emphysema and vascular alteration may be related by endothelial dysfunction and systemic inflammation.

Hypercholesterolemia is considered one of the main triggers of atherosclerosis [53]. So, the normal lipid profile in emphysema patients with atherosclerosis indicates the responsibility of other factors for this association. Atherosclerotic plaque in COPD patients has criteria that make them more easy to rupture [52], hence, the evaluation of carotid plaque composition/texture will be beneficial.

Our study results support the idea of complex heterogeneous lung and vascular disease in the context of an explanation of the relationship between emphysema and atherosclerosis, which also, was supported by other studies; Dransfield et al. [54], Chae et al. [55] showed the relationship between emphysema and each of carotid atherosclerosis, scores of calcification in the aorta, coronary arteries. Pike et al. [56] showed the significant relationship between upper-lobe emphysema and internal carotid IMT. In addition, [6] suggested the contribution of the imbalance of matrix metalloproteinases and their tissue inhibitors in the cerebrovascular damage in COPD [34, 36].

Emphysema & Cancer Action Project study [7] incorporated thoracic CT for the evaluation of the brachial artery flow-mediated dilation in the ex-smokers group with early COPD and showed that reduced FEV1 and greater emphysema indices were associated with attenuation of flow-mediated dilatation giving the conclusion that both lung function and structure influence vascular endothelial function [56].

Conclusion

Atherosclerotic plaques were prevalent in about two-thirds (70%) of emphysema patients and the rest of the patient showed subclinical atherosclerosis. The positive correlation between the carotid atherosclerosis and emphysema CT score was more than with GOLD staging. So, this inherence between pulmonary emphysema and atherosclerosis may not be just an association, it may be a syndrome. Thus, the staging of each of them can be guided from the other, and therapies targeted against the same pathogenesis can benefit both conditions. So, we recommend that management plan for emphysema should include the carotid US for early detection and treatment of atherosclerosis.

Abbreviations

HRCT: High-resolution computed tomography; BS: Blood sugar; ABG: Arterial blood gas; GOLD: Global initiative for chronic Obstructive Lung Disease;

COPD: Chronic obstructive pulmonary disease; CIMT: Carotid Intima-Media Thickness; CVD: Cardiovascular disease; PaO2: Partial arterial oxygen tension; PaCO2: Partial arterial carbon dioxide tension; SaO2: Arterial oxygen saturation; ICC: Intraclass correlation coefficient; CI: Confidence interval; TG: Triglycerides; U/S: Ultrasonography; CAD: Coronary artery disease; FVC: Forced vital capacity

Acknowledgement
The authors thank all the study participants for their patience and support.

Authors' contributions
AW suggest idea of the work, planning & design the work, clinical evaluation of the cases, observe HRCT studies, evaluation of pulmonary function tests, reviewing literature, Data collection and analysis, share in statistical analysis, write and revise the manuscript, share in preparation of the tables, share in preparation of the figures. MM discus the idea of the work, planning & design the work, clinical evaluation of the cases, reviewing literature, Data collection and analysis, share in statistical analysis, write and revise the manuscript, share in preparation of the tables, share in preparation of the figures. EM discus the idea of the work, planning & design the work, reviewing literature, Data collection and analysis, share in statistical analysis, write and revise the manuscript, share in preparation of the tables, share in preparation of the figures, revise figures, operate, interpretate & reporting carotid duplex ultrasound study, interpretate & reporting HRCT of the chest, publish the work in the journal. All authors read and approved the final manuscript.

Funding
This study had no funding from any resource.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest
The authors declare that they have no competing interests.

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of the Faculty of Medicine at Al-Azhar University (New Damietta), in Egypt, on 25 october 2016, reference number of approval: ADIMIRB 136/12.
Informed consent obtained from study participants was written and assigned by participants. If the patient was less than 16 years old or unconscious at the time of the study, written informed consent for their participation was given by their parent or legal guardian.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian.

Author details
[1]Chest Diseases Department, Al-Azhar University, New Damietta, Egypt. [2]Internal Medicine Department, Al-Azhar University, New Damietta, Egypt. [3]Radiology Department, Al-Azhar University, Faculty of Medicine, New Damietta, Egypt.

Received: 28 August 2020 Accepted: 14 September 2020
Published online: 20 October 2020

References

1. GOLD. Global Initiative for Chronic Obstructive Lung Disease; global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; (2018)
2. Miller J, Edwards LD, Agusti A et al (2013) Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med 107(9):1376–1384
3. Rufino R (2006) Lapa e Silva JR. cellular and biochemical bases of chronic obstructive pulmonary disease. J Bras Pneumol 32(3):241–248
4. Junqueira VB, Barros SB, Chan SS, Rodrigues L, Giavarotti L, Abud RL et al (2004) Aging and oxidative stress. Mol Asp Med 25(1-2):5–16
5. Petta AD (2010) Pathogenesis of pulmonary emphysema. Cellular Molecular Events Einstein 8(2 Pt 1):248–251
6. Zakharchuk N, Nevzorova V, Brodskaya T, Gonchar E (2018) Chronic obstructive pulmonary disease and cardiovascular comorbidity. J Lung PulmRespir Res 5(1):00153
7. Barr RG, Mesia-Vela S, Austin JH et al (2007) Impaired flow-mediated dilation is associated with low pulmonary function and emphysema in ex-smokers: the emphysema and cancer action project (EMCAP) study. Am J RespirCrit Care Med 176:1200–1207
8. McAllister DA, Maclay JD, Mills NL et al (2007) Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 176:1208–1214
9. Mills NL, Miller JJ, Anand A et al (2008) Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax 63:306–311
10. Eickhoff P, Valipour A, Kiss D et al (2008) Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. Am J RespirCrit Care Med 178:1211–1218
11. Iwamoto H, Yokoyama A, Kitahara Y et al (2009) Airflow limitation in smokers is associated with subclinical atherosclerosis. Am J RespirCrit Care Med 179:35–40
12. Kasahara Y, Tuder RM, Taraseviciene-Stewart L et al (2000) Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. J Clin Invest 106: 1311–1319
13. Santos S, Peinado VI, Ramirez J et al (2003) Enhanced expression of vascular endothelial growth factor in pulmonary arteries of smokers and patients with moderate chronic obstructive pulmonary disease. Am J RespirCrit Care Med 167:1250–1256
14. Peinado VI, Barbera´ JA, Abate P, et al. (1999) Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J RespirCrit Care Med 159:1605–1611
15. Matsuoka S, Yamashiro T, Diaz A, et. al. The relationship between small pulmonary vascular alteration and aortic atherosclerosis in chronic obstructive pulmonary disease: quantitative CT Analysis. Academic Radiology, (2011): Vol 18, No 1.
16. Ross R (1999) Atherosclerosis—an inflammatory disease. N Engl J Med 340: 115–126
17. Bonetti PO, Lerman LO, Lerman A (2003) Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 23:168–175
18. Anderson TJ, Uehata A, Gerhard MD et al (1995) Close relation of endothelial function in the human coronary and peripheral circulations. J Am CollCardiol 26:1235–1241
19. Neunteufl T, Katzenschlager R, Hassan A et al (1997) Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. Atherosclerosis 129:111–118
20. Al Qahtany FH, Al Shali HA, Bayamin AA et al (2018) Atherosclerosis: pathophysiology and management. Egyptian J Hospital Med 70:82–87
21. Sin DD, Man SF (2003) Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 107:1514e9
22. de Groot E, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart JC et al (2004 Jun 15) Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. Circulation 109:III33e8
23. Yvette RBM, van Gestel W-JF et al (2010) Association of COPD with carotid wall intima-media thickness in vascular surgery patients. Respir Med 104: 712–716
24. Lee HY, Oh BH (2010) Aging and arterial stiffness. Circulation 74:2257–2262
25. Galal-Eldin M, Ahmad E, Hafez M, Sobh E, Alrayes M (2015) Telomere length in chronic obstructive pulmonary disease. Egypt J Bronchol 9:20
26. Minamino T, Miyauchi H, Yoshida T, Ishida Y, Yoshida H, Komuro I (2002) Endothelial cell senescence in human atherosclerosis role of telomere in endothelial dysfunction. Circulation 105:1541–1544
27. Benetos A, Okuda K, Lajemi M, Kimura M, Thomas F, Skurnick J et al (2001) Telomere length as an indicator of biological aging the gender effect and relation with pulse pressure and pulse wave velocity. Hypertension 37:381–385
28. GOLD. Global Strategy of Diagnosis, Management and Prevention of COPD; 2014. Available from: URL: http:/ www.goldcopd.org.
29. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R et al (2005) General considerations for lung function testing. EurRespir J 26:153–161

30. Rankin G, Stokes M (1998) Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. ClinRehabil 12:187–199
31. Maclay JD, Mcallister DA, Macnee W (2007) Cardiovascular risk in chronic obstructive pulmonary disease. Respirology 12:634–641
32. Fimognari FL, Scarlata S, Conte ME, Incalzi RA, Fimognari FL, Scarlata S et al (2008) Mechanisms of atherothrombosis in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 3:89
33. Invernizzi G (2011) Persistence of systemic inflammation in COPD in spite of smoking cessation. MultidiscipRespir Med 6:210–211
34. Hafez MR, Sobh E, Abo-Elkheir OI, Sakr LK (2016) Atherosclerosis is associated comorbidity in patients with chronic obstructive pulmonary disease: ultrasound assessment of carotid intima media thickness. Eurasian J Pulmonol 18:165–171
35. Barr RG, Ahmed FS, Carr JJ, Hoffman EA, Jiang R, Kawut SM et al (2012) Subclinical atherosclerosis, airflow obstruction and emphysema: the MESA lung study. EurRespir J 39:846–854
36. Maclay JD, McAllister DA, Mills NL, Paterson FP, Ludlam CA, Drost EM et al (2009) Vascular dysfunction in chronic obstructive pulmonary disease. Am J RespirCrit Care Med 180:513–520
37. Brusasco V, Crapo R, Viegi G (2005) Series "ATS/ERS task force: standardization of lung function testing". EurRespir J 26:319–338
38. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004e2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovascular Dis 2007;23: 75e80.
39. MonteiroJúnior FC, Mandarino NR, Santos EM, et. al. Correlation between serum 25-hydroxyvitamin D levels and carotid intima-media thickness in a Brazilian population descended from African slaves. Braz J Med Biol Res (2018); 51(4): e7185.
40. Sanders C, Bailey WC (1988) Detection of emphysema with computed tomography correlation with pulmonary function tests and chest radiography. Investig Radiol 23:262
41. Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E et al (2010) CT scan findings of emphysema predict mortality in COPD. Chest 138(3):635–640
42. Doneen AL, Bale BF. Carotid intima-media thickness testing as an asymptomatic cardiovascular disease identifie and method for making therapeutic decisions. Postgraduate Medicine, Volume 125, Issue 2, March 2013,03:2645
43. Sabit R, Bolton CE, Edwards PH et al (2007) Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. Am J RespirCrit Care Med 175:1259–1265
44. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS, GOLD Scientific Committee (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization global initiative for chronic obstructive lung disease (GOLD): workshop summary. Respir Care 46(8):798–825
45. Alpaydin AO, Arslan IK, Serter S et al (2013) Metabolic syndrome and carotid intima-media thickness in chronic obstructive pulmonary disease. Multidiscip Respir Med 8:61
46. Kim SJ, Yoon DW, Lee EJ, et. al. Carotid atherosclerosis in patients with untreated chronic obstructive pulmonary disease. Int J Tuberc Lung Dis (2011);15(9):1265–1270.
47. Köseoğlu C, özgeKurmuş, GöktuğErtem A, et. al. Association between carotid intima-media thickness and presence of coronary artery disease in chronic obstructive pulmonary disease patients. Anatol J Cardiol 2016; 16: 601-607.
48. Savransky V, Nanayakkara A, Li J, Bevans S, Smith PL, Rodriguez A et al (2007) Chronic intermittent hypoxia induces atherosclerosis. Am J RespirCrit Care Med 175:1290–1297
49. Lattimore JD, Wilcox I, Nakhla S, Langenfeld M, Jessup W, Celermajer DS (2005) Repetitive hypoxia increases lipid loading in human macrophages-a potentially atherogenic effect. Atherosclerosis 179:255–259
50. Chen L, Einbinder E, Zhang Q, Hasday J, Balke CW, Scharf SM (2005) Oxidative stress and left ventricular function with chronic intermittent hypoxia in rats. Am J RespirCrit Care Med 172:915–920
51. Schroeder EB, Welch VL, Evans GW, et. al. Impaired lung function and subclinical atherosclerosis. The ARIC Study Atherosclerosis 2005; 180: 367–373.
52. Pike D, Kirby M, Lindenmaier TJ et al (2015) Pulmonary abnormalities and carotid atherosclerosis in ex-smokers without airflow limitation. COPD 12: 62–70
53. O'Brien KD, et. al. Vascular cell adhesion molecule-1 is expressed in human coronary atherosclerotic plaques. Implications for the mode of progression of advanced coronary atherosclerosis. J Clin Invest 1993;92: 945-951.
54. Dransfield MT, Huang F, Nath H, Singh SP, Bailey WC, Washko GR (2010) CT emphysema predicts thoracic aortic calcification in smokers with and without COPD. COPD 7(6):404–410
55. Chae EJ, Seo JB, Oh YM, Lee JS, Jung Y, Lee SD (2013) Severity of systemic calcified atherosclerosis is associated with airflow limitation and emphysema. J Comput Assist Tomogr 37(5):743–749
56. Pike D, Lindenmaier TJ, Sin DD, Parraga G (2014) Imaging evidence of the relationship between atherosclerosis and chronic obstructive pulmonary disease. Imaging Med 6(1):53–73

Publisher's Note