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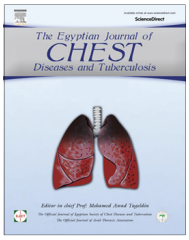

ORIGINAL ARTICLE

# Aortic stiffness and microalbuminuria in patients with chronic obstructive pulmonary disease

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**KEYWORDS**

Aortic stiffness;
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**Abstract** *Background:* Cardiovascular diseases (CVDs) remain a major leading cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD). Increased aortic stiffness is an independent predictor of cardiovascular disease. Microalbuminuria (MAU) reflects increased permeability of the glomerulus, usually due to microvascular damage and suggested as an early prognostic cardiovascular marker. So this study was done to determine the prevalence of aortic stiffness in patients with COPD and to evaluate the relationship of MAU levels with the degree of aortic stiffness.

*Subjects and methods:* This study was done at Respirology, Cardiology, Internal Medicine, and Clinical Pathology Departments, Farwaniya Hospital, Ministry of Health, State of Kuwait in the period between July 2013 and October 2014. A total 60 patients was distributed into 38 patients with COPD (group 1) and 22 control subjects (group 2). Patients with COPD and controls underwent spirometry, blood pressure, aortic stiffness assessment using aortic pulse wave velocity (aPWV) study and provided a spot urine sample for MAU measurement.

*Results:* Patients with COPD (group 1) had increased aortic stiffness compared with matched controls (group 2) 11.2 ± 2.3 vs. 7.8 ± 1.5 m/s, $P < 0.05$. Patients with GOLD III and IV had significant higher aPWV values as compared to patients with GOLD I and II ($P < 0.05$). Multiple logistic regression analyses revealed that the adjusted odds ratios of having MAU for aPWV quartile III and IV were 6.38 (95% confidence interval: 2.37–13.2) and 6.58 (95% confidence interval: 1.59–22.0) respectively, $P < 0.05$.

*Abbreviations*: MAU, microalbuminuria; aPWV, aortic pulse wave velocity; AIx, augmentation index; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GOLD, Global initiative for chronic Obstructive Lung Disease

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*Conclusions:* COPD is associated with increased aortic stiffness. MAU is independently related to aortic stiffness in patients with COPD. Further studies are necessary to investigate whether MAU could be an effective biomarker of aortic stiffness and potential cardiovascular compromise in patients with COPD.



## Introduction

Cardiovascular diseases (CVDs) remain a major leading cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD) and this appears to be independent of established risks such as smoking, gender and age [1]. The biological mechanisms of increased cardiovascular risk in COPD and cardiovascular disease are poorly understood. Current studies proposed that systemic inflammation and oxidative stress in COPD patients may contribute to the endothelial dysfunction and atherosclerosis [2,3]. Systemic inflammation can stimulate the remodelling process with degradation of elastic fibres in the arterial wall and replacement by collagen. This will lead to increased arterial stiffness and greater central aortic systolic pressures with increased afterload and risk of CVD. Additionally, the renal vascular beds will be susceptible to the increased pulsatile flow due to the reduced buffering capacity of the large arteries [4].

Microalbuminuria (MAU) reflects increased permeability of the glomerulus, usually due to microvascular damage and suggested as an early prognostic cardiovascular marker [5]. The proportion of patients with COPD having co-existent renal impairment has been highlighted. Casanova et al. [6] demonstrated increased urinary albumin creatinine ratio in patients with COPD compared to healthy smokers, which was related to hypoxaemia and systolic blood pressure. Other studies [7,8] hypothesized that the increased aortic stiffness in patients with COPD was related to the subclinical glomerular injury and could be related to the decline of renal function.

Increased central arterial stiffness in patients with COPD may explain the excess cardiovascular morbidity and mortality in these patients. However, a limited number of studies have evaluated the presence of aortic stiffness in patients with COPD and the association of MAU was not considered. So this study was done to determine the prevalence of aortic stiffness in patients with COPD and to evaluate the relationship of MAU levels with the degree of aortic stiffness.

## Subjects and methods

This study was done at Respirology, Cardiology, Internal Medicine, and Clinical Pathology Departments, Farwaniya Hospital, Ministry of Health, State of Kuwait in the period between July 2013 and October 2014. Demographic data and a full medical and therapeutic history were collected at study entry for all enrolled subjects. A total 60 patients were distributed into 38 patients with COPD (group 1) and 22 control subjects (group 2). All patients with COPD were older than 40 years with a post-bronchodilator forced expiratory volume in first second ($FEV_1$) to forced vital capacity (FVC) ratio of 0.70 or less with partial reversibility using 400 μg salbutamol (increase in $FEV_1$ of $\leqslant$12% or 200 ml) [9]. The patients were studied at clinical stability, defined as no change in regular therapy, no requirement for antibiotics and/or oral corticosteroids in the preceding 6 weeks and no change in symptoms beyond day to day variation. The St George's Respiratory Questionnaire (SGRQ) was performed [10]. The Global initiative for chronic Obstructive Lung Disease (GOLD) stage of airflow obstruction was used to classify patients into four GOLD stages I-IV based on post-bronchodilator $FEV_1$ levels. These are mild (GOLD-1, $FEV_1 \geqslant 80\%$ of predicted), moderate (GOLD-2, $50\% \leqslant FEV_1 < 80\%$ of predicted), severe (GOLD-3, $30\% \leqslant FEV_1 < 50\%$ of predicted) and very severe (GOLD-4, $FEV_1 < 30\%$ of predicted) according to the Global Initiative against Chronic Obstructive Lung Disease (GOLD) [9]. Another 22 subjects over 40 years of age with a smoking history (more than 10 pack years) were also recruited as the control group (group 2). Pack-years were calculated, by multiplying the number of years of smoking by the average number of cigarettes smoked per day and dividing by 20 [11]. All of control subjects had no evidence of airways obstruction or history of respiratory disease.

### *Exclusion criteria*

Patients with concomitant renal or presence of macroalbuminuria (urinary albumin to creatinine ratio $>300$ mg/g), cardiovascular and pulmonary diseases were excluded. Also, those with known alpha-1-antitrypsin deficiency, active or suspected malignancy or terminal disease, hypertension, diabetes mellitus or those with systemic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease) were also excluded. Electrocardiographic and Echocardiographic Studies were performed to rule out any cardiac disease.

### *Pulmonary function measurements*

Spirometry was performed according to the American Thoracic Society standards, using Jaeger Masterscreen full PFT system (CareFusion, Germany). $FEV_1$, FVC, and $FEV_1$: FVC ratio were determined. Total lung capacity (TLC, L) and residual volume (RV, L) were obtained by constant volume, different-pressure body plethysmography and expressed as percent of the predicted value. Air trapping was defined as increased RV/TLC and RV ($>0.4$ and $>140\%$ predicted, respectively): TLC values $>120\%$ predicted were indicative of lung hyperinflation [12].

### *Cardiovascular measurements*

All subjects underwent complete echo-Doppler evaluation utilizing the two-dimensional (2-D), M-mode, Doppler and tissue

Doppler echocardiographic techniques. Left ventricular ejection fraction was calculated in 2D-mode, in the apical 2- and 4-chamber apical views, using the Simpson biplane method. Early diastolic (E′) mitral annular velocity was measured and correcting transmitral E wave for the influence of myocardial relaxation (i.e. E/E′ratio) was calculated.

Aortic stiffness and peripheral vascular testing were done in the morning after an overnight fast from food and cigarette smoking for at least 8 h. Also, all subjects were directed to stop vasoactive medications for 2 h, bronchodilator therapy for 6 h, and caffeine for 3 h prior to the measurements and speaking or sleeping were not allowed during measurements. All tests were done in a temperature-controlled quiet room in resting supine position at 15°. Heart rate (HR) and peripheral blood pressure (BP) were initially measured and pulse pressure (PP) (systolic BP–diastolic BP) and mean arterial pressure (MAP) (1/3 (systolic BP–diastolic BP) + DBP) were calculated. After 15 min of rest, aortic pulse wave velocity (aPWV) was measured using Vicorder device (Skidmore Medical, Bristol, UK), by placing a neckpad (for measurement of right common carotid artery pulse) and a blood pressure cuff around the upper right thigh (for measurement of right common femoral pulse) and then aortic path length (the length between the cuffs) was measured. The cuffs were inflated simultaneously to 65 mmHg and 2 waveforms were simultaneously recorded. This procedure allowed calculation of the systolic pressure wave transit time and aPWV by the system software. Faster wave transit times reflect stiffer arteries (Fig. 1). With the integral software, Augmentation pressure is the difference between the systolic peak (forward wave) and first systolic inflection (reflected wave) pressures. This difference divided by the pulse pressure generates the augmentation index (Fig. 2) [13].

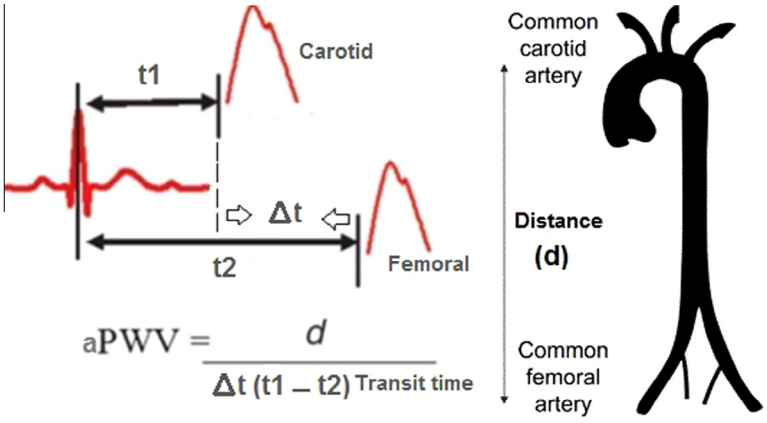


**Figure 1** Aortic pulse wave velocity measurement: aPWV calculated by dividing the distance (*d*) between the two arterial sites by the difference in time of pressure wave arrival between the carotid (*t*1) and femoral artery (*t*2) referenced to the *R* wave of the electrocardiogram.

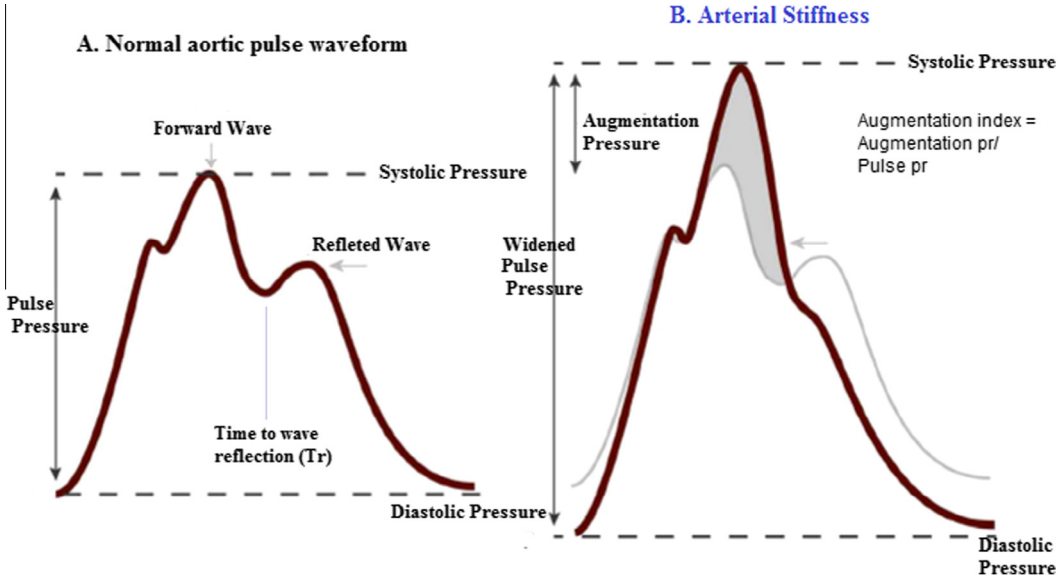


**Figure 2** Hemodynamic changes in arterial stiffness; (A) In normal aortic pulse waveform: forward wave precedes backward wave, (B) In arterial stiffness: due to increased aPWV, forward wave and reflected wave are integrated producing augmented pulse pressure.

*Biochemical assays*

Arterial blood gases were measured by arterial puncture, in the morning, sitting at rest (15 min), breathing room air for at least 45 min. A fasting venous blood was taken for measurement of fasting glucose, creatinine, triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol. Spot morning urine sample was collected for urinary albumin and creatinine to determine albumin/creatinine ratio (ACR). To define MAU, we used the ACR cut-off values of 30–300 mg/g for both men and women. Normoalbuminuria (NAU) was defined as the ACR of less than 30 mg/g and macroalbuminuria (or overt proteinuria) was defined as the ACR of more than 300 mg/g [14]. All analytes were measured on the Olympus AU2700 platform (Beckman Coulter, USA) according to manufacturer's settings. The baseline renal function was assessed based on estimated glomerular filtration rate (eGFR) using Cockcroft-Gault formula (creatinine clearance = (140 − age) × (Weight in kg) × (0.85 if female)/(72 × Cr in mg/dl)) [15].

*Anthropometry*

Height was obtained with subjects standing barefoot and was determined to the nearest 0.5 cm and weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated in kg/m$^2$. A low BMI was defined as less than 18.5 kg/m$^2$; while BMI greater than 25 kg/m$^2$ is considered overweight and above 30 kg/m$^2$ is considered obese [16].

*Statistical methods*

Statistical analysis was done using statistical software 'SPSS version 19.0 (SPSS Inc, Chicago, IL, USA). Continuous data were summarized as mean with standard deviation and compared between the two groups using Student's *t*-test. Chi-squared test and Fisher exact test were applied to compare the categorical data such as sex. Pearson's correlation coefficient was measured to determine the nature of associations of Pulse wave velocity and augmentation index to other parameters. Multiple logistic regression analysis was performed to assess odds ratios of having MAU in all subjects using aPWV quartiles as independent variables. For all analyses, $p$ value $<0.05$ was considered significant and $p$ value $<0.001$ was considered highly significant.

## Results

This study included 60 patients. They were 26 females and 34 males with mean age 60.1 ± 1.8 years. They comprised 38 patients (63.3%) with COPD aged 65.7 ± 2.3 with mean forced expiratory volume in 1 second (FEV1)% predicted was 40.1 ± 5.6. Of the 38 patients, 13 had mild to moderate COPD as defined by the Global initiative for Chronic Obstructive Lung Disease (GOLD COPD stage I and II respectively) and 25 had severe and very severe COPD (GOLD stage III and IV respectively). The mean arterial $PaO_2$ for patients was 72 ± 1.8 mmHg for all COPD cases. The baseline clinical and laboratory tests of both patient groups are shown in Table 1. Apart from pulmonary functional tests, all showed no statistical significant differences.

Table 2 shows that patients with COPD (group 1) had increased aortic stiffness compared with matched controls. Aortic PWV was significantly higher in patients with COPD compared with control subjects (11.2 ± 2.3 vs. 7.8 ± 1.5 m/s, $P < 0.05$). Augmentation index was similarly increased in patients with COPD in comparison with controls (34 ± 6.5

**Table 1** The baseline characteristics in both patient groups.

| Characteristics | | Group 1 (COPD) | Group 2 (Control) | *P*-value |
|---|---|---|---|---|
| No. (%) (total = 60) | | 38 (63.3%) | 22 (36.7%) | – |
| Age (years) | | 65.7 ± 2.3 | 58 ± 1.6 | >0.05 |
| Gender (No. (%)) | | *F* = 18 (47.4%) | *F* = 8 (36.4%) | >0.05 |
| | | *M* = 20 (52.6%) | *M* = 14 (63.6%) | |
| BMI (kg/m$^2$) | | 28 ± 5.5 | 25 ± 8.0 | >0.05 |
| Smoking | Current smokers | 13 (34.2) | 9 (40.9) | >0.05 |
| | Pack years | 41 ± 20 | 42 ± 08 | >0.05 |
| PFT | $FEV_1$ (% of pred.) | 40 ± 5.6 | 95 ± 1.3 | <0.001 |
| | FVC (% of pred.) | 87 ± 1.1 | 101 ± 6.3 | >0.05 |
| | $FEV_1$/FVC ratio | 47.6 ± 2.6 | 103 ± 5.3 | <0.001 |
| | RV (% of pred.) | 166.7 ± 4.7 | ND | – |
| | TLC (% of pred.) | 127.6 ± 2.6 | ND | – |
| | RV/TLC ratio | 48.1 ± 1.8 | ND | – |
| ABG | $PaO_2$ (mmHg) | 71 ± 1.2 | ND | – |
| | $PaCO_2$ (mmHg) | 41.5 ± 3.7 | ND | – |
| Cardiac Function | LVEF (%) | 61 ± 2.8 | 60.7 ± 6.2 | >0.05 |
| | E/E′ (MV) | 11.8 ± 2.3 | 8.1 ± 1.8 | >0.05 |
| Lipid Profile (mmol/l) | Total cholesterol | 5.2 ± 0.2 | 4.9 ± 0.8 | >0.05 |
| | Triglycerides | 1.8 ± 2.3 | 1.6 ± 1.7 | >0.05 |
| | HDL-cholesterol | 1.6 ± 1.7 | 1.5 ± 0.6 | >0.05 |
| | LDL-cholesterol | 3.3 ± 2.3 | 3.1 ± 0.1 | >0.05 |

All results are presented as mean ± SD unless specified.
$PaO_2$, partial pressure of oxygen in arterial blood; PaCO2, partial pressure of carbon dioxide in arterial blood; LVEF, left ventricle ejection fraction; E/E'(MV), mitral valve early filling wave in Doppler and tissue Doppler; HDL, high density lipoprotein; LDL, low density lipoprotein; ND, not done.

**Table 2** Arterial stiffness, haemodynamic measures, and biochemistry in both patient groups.

| Parameters | Group 1 (COPD) | Group 2 (Controls) | *P*-value |
|---|---|---|---|
| No. (%) (total = 60) | 38 (63.3%) | 22 (36.7%) | – |
| eGFR (ml/min) | 82 ± 9.7 | 91 ± 12 | >0.05 |
| MAU (mg/g) | 96 ± 1.1 | 22 ± 1.3 | <0.05 |
| Heart rate (bpm) | 70 ± 1.7 | 68 ± 1.9 | >0.05 |
| Peripheral SBP (mmHg) | 148 ± 1.5 | 135 ± 2.0 | >0.05 |
| Peripheral DBP (mmHg) | 81 ± 6.1 | 70 ± 0.5 | >0.05 |
| Peripheral MAP (mmHg) | 108 ± 12 | 98 ± 1.0 | >0.05 |
| Peripheral PP (mmHg) | 64 ± 6.3 | 57 ± 1.2 | >0.05 |
| Central SBP (mmHg) | 147 ± 5.3 | 128 ± 8.8 | >0.05 |
| Central DBP (mmHg) | 95 ± 6.3 | 81 ± 6.0 | >0.05 |
| Central MAP (mmHg) | 83 ± 4.2 | 78 ± 0.4 | >0.05 |
| Central PP (mmHg) | 50 ± 17 | 38 ± 1.1 | >0.05 |
| aPWV (m/s) | 11.2 ± 2.3 | 7.8 ± 1.5 | <0.001 |
| Augmentation pressure (mmHg) | 25 ± 1.8 | 14 ± 5.8 | <0.05 |
| Augmentation index AIx (%) | 34 ± 6.5 | 22 ± 0.7 | <0.05 |
| Time to reflection (ms) | 123 ± 7.8 | 142 ± 1.2 | >0.05 |

All results are presented as mean ± SD.
SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

vs. 22 ± 0.7%, $P < 0.05$). Consistent with these findings the time to wave reflection was reduced, although this difference was not statistically significant (123 ± 7.8 vs. 142 ± 1.2 ms, $P > 0.05$). Table 2 also shows that there were no significant differences in systemic systolic BP, diastolic BP or mean arterial pressure (MAP) between COPD patients and control subjects. Central BP indices also showed no significant differences. Regarding renal biomarkers, the eGFR was comparable in COPD patients and controls (68 ± 9.7 and 76 ± 12 ml/min respectively, $p > 0.05$). However, the MAU was significantly greater in patients than controls (96 ± 1.1 and 22 ± 1.3 mg/g creatinine respectively, $p < 0.05$).

Table 3 and Fig. 3 show the significant increased aPWV in patients with either GOLD I and II or those with GOLD III and IV compared to that of the healthy controls ($p < 0.05$). Additionally, patients with GOLD III and IV had significantly higher aPWV values as compared to patients with GOLD I and II ($p < 0.05$). Regarding Augmentation index, patients with GOLD III and IV had significantly higher indices when compared with either patients with GOLD I and II or with the healthy controls (Table 3 and Fig. 4). Patients with GOLD I and II had higher AIx values as compared to the healthy controls, although this difference was not statistically significant ($p > 0.05$). Table 3 also shows a high incidence of LVDD (E/E′) in patients with COPD than in control subjects although this difference was not statistically significant, even there was no difference among different stages of COPD.

Table 4 shows Pearson correlation analysis between the results of aPWV and different parameters of the patients with COPD (group 1). aPWV did not show any correlation either with smoking pack years, or with BMI (all $p > 0.05$). However, there were significant negative correlations between aPWV and age ($p < 0.05$, $r$: −0.31), the partial pressure of oxygen in arterial blood ($PaO_2$) ($p < 0.05$, $r$: −0.35) and between aPWV and $FEV_1$ levels ($p < 0.001$, $r$: −0.58). Regarding the other pulmonary function parameters, FVC showed a weak negative and insignificant correlation with aPWV ($p > 0.05$, $r$: −0.14), where the RV/TLC ratio showed a moderate negative and significant correlation ($p < 0.001$, $r$: −0.31). We did not find a significant correlation between aPWV and $PaCO_2$ (mmHg) levels in this study ($p < 0.05$, $r$: 0.21), or between aPWV and $SaO_2$, ($p < 0.05$, $r$: −0.06). In COPD patients, there was a significant inverse relationship between AIx and $FEV_1$ ($p < 0.05$, $r$: −0.43). A similar relationship was found between AIx and $PaO_2$ ($p < 0.05$, $r$: −0.33). There was no relationship between AIx and other lung functions. Interestingly, we found significant correlations between LVDD (E/E′) and aPWV and Aix ($p < 0.05$, $r$: −0.42 and $p < 0.05$, $r$: −0.37 respectively).

Table 5 shows the impact of COPD on the association between aPWV and MAU. We found that adjusted odds ratios were much higher among patients with high aPWV having MAU after adjusting for age, BMI, MAP, and smoking. Multiple logistic regression analyses revealed that the adjusted odds ratios of having MAU for aPWV quartile III and IV were 6.38 (95% confidence interval: 2.37–13.2) and 6.58 (95% confidence interval: 1.59–22.0) respectively, $p < 0.05$.

## Discussion

There is growing evidence that chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) coexist. Many studies [17–19] proved the importance of aortic stiffness as a predictor of cardiovascular co-morbidity in patients with

**Table 3** Cardiovascular parameters in both patient groups and according to GOLD staging of COPD.

| Parameters (total = 60) | Group 1 (COPD) 38 (63.3%) | | Group 2 (Controls) | *P*-value | | |
|---|---|---|---|---|---|---|
| | GOLD I and II | GOLD III and IV | | *P*1 | *P*2 | *P*3 |
| No. (%) | 13 (21.7%) | 25 (41.7%) | 22 (36.7%) | – | – | – |
| aPWV (m/s) | 9.5 ± 4.1 | 13.6 ± 3.6 | 7.8 ± 1.5 | <0.05 | <0.05 | <0.05 |
| AIx (%) | 28 ± 1.5 | 39 ± 1.8 | 22 ± 0.7 | <0.05 | >0.05 | <0.05 |
| E/E′ (MV) | 10.7 ± 0.1 | 11.2 ± 3.7 | 8.1 ± 1.8 | >0.05 | >0.05 | >0.05 |

P1, comparison of GOLD I and GOLD II patients with GOLD III and GOLD IV patients. P2, comparison of GOLD I and GOLD II patients with control group, P3, comparison of GOLD III and GOLD IV patients with the control group.

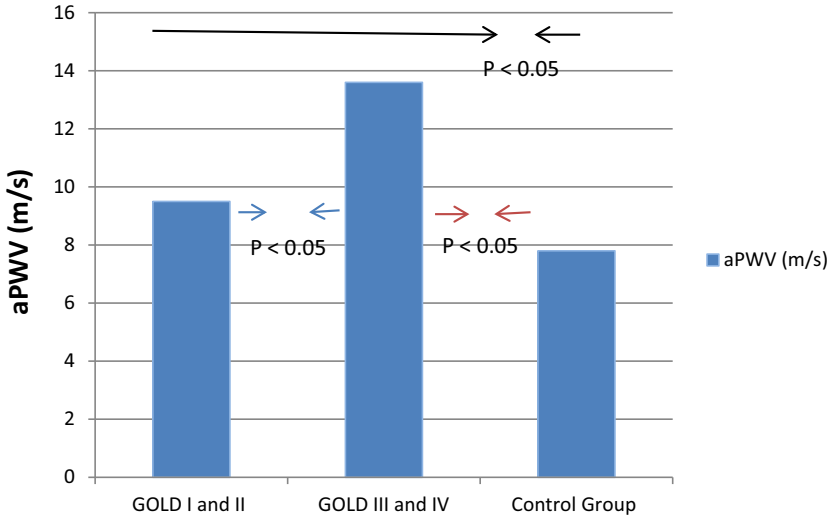


**Figure 3** Aortic pulse wave velocity (aPWV) in both patient groups according to GOLD staging of COPD.

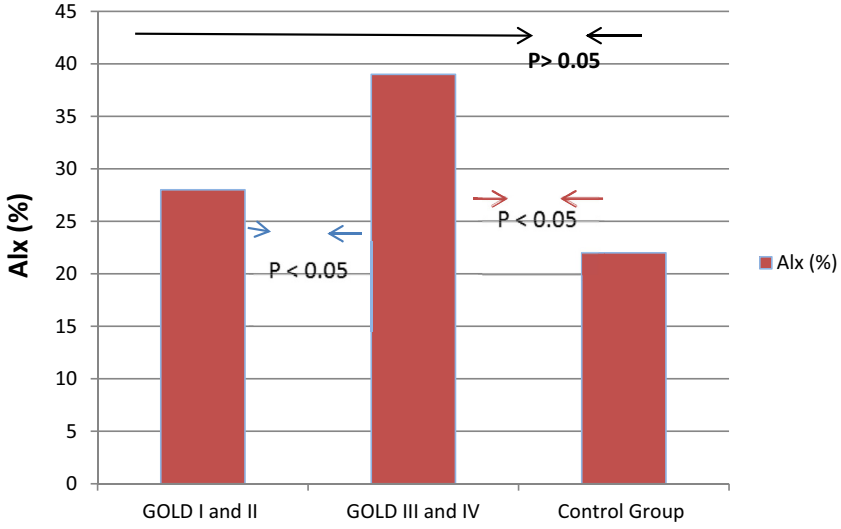


**Figure 4** Augmentation index (AIx) in both patient groups according to GOLD staging of COPD.

COPD. In future, chest physicians may need to measure arterial pulse wave velocity in routine clinical practice.

In this study we used a vicorder machine to measure aortic stiffness. We found that Aortic PWV was significantly higher in patients with COPD compared with control smoker subjects. Augmentation index is a measure of the augmentation of central blood pressure in systole by reflected pressure waves from the peripheral arteries. We established that augmentation index was similarly increased in patients with COPD. Moreover, we evaluate the relationship between obstructive lung function and central arterial stiffness. We observed higher aPWV values in COPD patients with greater disease severity as compared to that of patients with mild and moderate disease forms. In Pearson correlation model, our results showed that $FEV_1$ were significantly negatively correlated to aPWV, suggesting that pulmonary obstructive disorders may be implicated in arterial function stem or at least both sharing the same physiopathologic processes. Another possible explanation for our results is that inflammatory mechanisms may act as a contributing factor to both vascular stiffness and obstructive lung function.

In accordance with our results, McAllister et al. [20] confirmed that aortic stiffness is increased in patients with COPD which had statistically significant associations with $FEV_1$ (% predicted). Also, they showed that aPWV was higher in patients with severe and very severe COPD (GOLD stage 3 and 4) than in those with mild and moderate disease (GOLD stage 1 and 2). Sabit et al. [21] included 75 patients with stable COPD, and 42 healthy smokers and ex-smokers as control subjects. They observed greater mean aPWV in the COPD patients as compared to control subjects ($11.4 \pm 2.7$ vs $8.95 \pm 1.7$ m/s, $p < 0.001$). Furthermore, like our results, aPWV was correlated to the GOLD stage, thereby indicating that the more severe airflow limitations are associated with higher PWV values. Interestingly, in the Sabit et al. study, a significant correlation was found between IL-6 and aPWV

**Table 4** Pearson correlation between parameters of the patients in group 1 (with COPD) and aortic pulse wave velocity and augmentation index.

| Parameters | | Aortic pulse wave velocity (m/s) | | Augmentation index (%) | |
|---|---|---|---|---|---|
| | | *r*-Value | *P*-value | *r*-Value | *P*-value |
| Age (year) | | 0.31 | < 0.05 | 0.18 | > 0.05 |
| Smoking (pack-year) | | 0.09 | > 0.05 | 0.02 | > 0.05 |
| BMI (kg/m$^2$) | | 0.16 | > 0.05 | 0.08 | > 0.05 |
| SGRQ score | | 0.07 | > 0.05 | 0.13 | > 0.05 |
| MAP(mmHg) | | 0.15 | > 0.05 | 0.22 | > 0.05 |
| PFT | $FEV_1$ (% of pred.) | −0.58 | < 0.001 | −0.43 | < 0.05 |
| | FVC (% of pred.) | −0.14 | > 0.05 | −0.02 | > 0.05 |
| | RV (% of pred.) | 0.22 | > 0.05 | 0.18 | > 0.05 |
| | TLC (% of pred.) | 0.28 | > 0.05 | 0.20 | > 0.05 |
| | RV/TLC ratio | −0.31 | < 0.05 | −0.17 | > 0.05 |
| ABG | pH | −0.13 | > 0.05 | −0.29 | > 0.05 |
| | $PaO_2$ (mmHg) | −0.35 | < 0.05 | −0.33 | < 0.05 |
| | $PaCO_2$ (mmHg) | 0.21 | > 0.05 | 0.16 | > 0.05 |
| | $SaO_2$ | −0.06 | > 0.05 | −0.11 | > 0.05 |
| MAU (mg/g) | | 0.38 | < 0.05 | −0.35 | < 0.05 |
| E/E′ (MV) | | 0.42 | < 0.05 | 0.37 | < 0.05 |

*r*-Value; correlation coefficient.
SGRQ, St George's Respiratory Questionnaire.

and accordingly systemic inflammation may contribute to the increased aortic stiffness found in patients with COPD.

The association of impaired pulmonary function with aortic stiffness has also been reported in other studies. Zureik et al. [22] observed reduced pulmonary function in association with aortic stiffness in male patients free of cardiovascular diseases. They found that aPWV was negatively associated with $FEV_1$ even after adjustment for age, height and other cardiovascular risk factors. Taneda et al [23] were unable to find association of abnormal lung function with aPWV in 678 Japanese Americans Subjects whereas abnormal lung function defined as FVC% < 80% of predicted or $FEV_1$% < 80% of predicted. On the contrary, other studies [24,25] suggested that aortic stiffness may cause restriction of pulmonary function. Stiffening of the aorta can increase left ventricular pulsatile work and is associated with left ventricular dysfunction that could be correlated to abnormal pulmonary function. In this study we also observed correlation of lung hyperinflation parameters to aPWV. Stone et al. [26] included patients with a substantial degree of lung hyperinflation, with mean RV% values of 163.9%. They found no significant correlation between the extent of lung hyperinflation and aortic stiffness measurements regardless of which parameter for measuring lung hyperinflation was adopted like TLC or Inspiratory capacity (IC)/TLC.

In this study, COPD patients had a significant increase in MAU levels compared to controls, which was positively correlated to the increased aortic stiffness. Moreover, we proved that MAU is independently related to aortic stiffness in those patients with COPD. MAU increase would underline the glomerular damage leading to increased permeability in patients with increased aortic stiffness mediated via systemic inflammation, hypoxaemia, or increased sympathetic activation, all known to be affected in COPD, which can open the possibility of assessing new potential therapeutic strategies, such as statins [27], ACE inhibitors [28] beta blockers [29] in COPD management. It is important in this study that we evaluated the relationship of microvasculature to the macrovascular state in COPD.

Other previous studies have described the prevalence of MAU in patients with COPD. Casanova et al. [6] reported a higher prevalence of MAU in 129 patients with stable COPD compared with 51 control smokers with normal spirometry without known cardiovascular disease. MAB was observed in 24% of the patients compared with 6% of non-COPD control subjects. The MAU levels were inversely related to $PaO_2$ and positively with the alveolar-$PaO_2$ gradient. In Polatli et al. study [30], 33 patients with stable COPD, 26 patients with exacerbation, and 16 healthy subjects were assessed. The level of MAU was significantly increased only in the group with exacerbation. However, in the stable COPD group, the level of MAU was double than that of the control group. These results suggest that MAU is frequent in COPD and that it

**Table 5** Odds ratios of having MAU using aPWV quartiles as independent variables in both patients groups derived from multiple logistic regression analysis.

| Total 60 patients | Group 1 (COPD) 38 (63.3%) | | Group 2 (Controls) 22 (36.7%) | |
|---|---|---|---|---|
| aPWV | MAU no. = 22 | NAB no. = 16 | MAU no. = 8 | NAB no. = 14 |
| Quartile 1 (< 10.2 m/s) no. = 13 | 2.21 (0.78–13.7) | 2.01 (0.56–8.01) | 1.39 (0.15–34.9) | 1.33 (0.08–3.91) |
| Quartile 2 (10.2–13.7 m/s) no. = 14 | 3.23 (0.80–61.7) | 2.08 (0.59–3.12) | 1.41 (0.11–2.01) | 1.02 (0.50–2.33) |
| Quartile 3 (13.7–15.2 m/s) no. = 18 | 6.58 (1.59–22.0) § | 3.75 (1.08–5.91) | 3.65 (1.87–5.92) | 2.01 (1.26–4.03) |
| Quartile 4 (> 15.2 m/s) no. = 15 | 6.38 (2.37–13.2) § | 3.87 (1.63–4.09) | 3.78 (0.55–34.9) | 3.24 (1.88–5.91) |

Odds ratio was adjusted for age, BMI, MAP, smoking and $PaO_2$.
All results presented odds ratios with 95% confidence interval (lower limit-upper limit).
§$p < 0.05$.

appears to increase during exacerbations. In study of John et al. [8] 52 patients with COPD and 34 control smokers were included. All of them underwent spirometry, blood pressure, aPWV and a spot urine examination for MAU, with other renal biomarkers like serum kidney injury molecule and cystatin. They could prove the occurrence of glomerular damage in patients with COPD as evidenced by increased MAU, related to increased aortic stiffness, suggested that microvascular state in COPD management should be considered.

The present study observed incidence of LVDD in patients with COPD but there was no difference among different stages of COPD. In agreement with these results, Boussuges et al [31] found a high incidence of LVDD in patients with COPD. A recent study of Caram et al. [32] showed more frequent echocardiographic findings of mild LVDD in COPD patients, independently of COPD stage. Another recent study [33] showed a potentially highest prevalence of LVDD in patients with severe stable COPD ($FEV_1$of 30%–50%). The potential pathophysiologic mechanism for the association between COPD and LVDD could be systemic inflammation, which is associated with myocardial ischaemia and LVDD. However, in the present study, there was no correlation with stages of COPD. Therefore, there may be some other mechanisms involved in this process. Moreover, we found a significant relationship between arterial stiffness and left ventricular diastolic dysfunction. Hu et al. [34] report a similar result; they concluded that left ventricular diastolic dysfunction has a direct relationship to arterial stiffening, independent of cardiovascular risk factors. Furthermore they confirm the relation between several well-known baseline characteristics and both diastolic dysfunction and arterial stiffness. The authors concluded that the severity of left ventricular diastolic dysfunction correlates with the severity of arterial stiffness.

## Conclusions

COPD is associated with increased aortic stiffness. MAU is independently related to aortic stiffness in patients with COPD. Further studies are necessary to investigate whether MAU could be an effective biomarker of aortic stiffness and potential cardiovascular compromise in patients with COPD.

## Conflict of interest

We have no conflict of interest to declare.

## References

[1] K. Ghoorah, A. De Soyza, V. Kunadian, Increased cardiovascular risk in patients with chronic obstructive pulmonary disease and the potential mechanisms linking the two conditions: a review, Cardiol. Rev. 21 (4) (2013) 196–202.
[2] L. Moro, C. Pedone, S. Scarlata, et al, Endothelial dysfunction in chronic obstructive pulmonary disease, Angiology 59 (2008) 357–364.
[3] R. Barr, The epidemiology of vascular dysfunction relating to chronic obstructive pulmonary disease and emphysema, Proc. Am. Thorac. Soc. 8 (6) (2011 Nov) 522–527.
[4] G.F. Mitchell, Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage, J. Appl. Physiol. 105 (2008) 1652–1660.
[5] H.L. Hillege, W.M. Janssen, A.A. Bak, et al, Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factor and cardiovascular morbidity, J. Intern. Med. 249 (6) (2001) 519–526.
[6] C. Casanova, J.P. de Torres, J. Navarro, A. Aguirre-Jaime, P. Toledo, E. Cordoba, R. Baz, B.R. Celli, Microalbuminuria and hypoxemia in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 182 (2010) 1004–1010.
[7] R.A. Incalzi, A. Corsonello, C. Pedone, et al, Chronic renal failure: a neglected comorbidity of COPD, Chest 137 (4) (2010) 831–837.
[8] M. John, S. Hussain, A. Prayle, et al, Target renal damage: the microvascular associations of increased aortic stiffness in patients with COPD, Respir. Res. 5 (14) (2013 Mar) 31.
[9] J. Vestbo, S.S. Hurd, A.G. Agustí, et al, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary, Am. J. Respir. Crit. Care Med. 187 (4) (2013 Feb 15) 347–365.
[10] P.W. Jones, F.H. Quirk, C.M. Baveystock, P. Littlejohns, A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire, Am. Rev. Respir. Dis. 145 (1992) 1321–1327.
[11] C.M. Bernaards, J.W. Twisk, J. Snel, et al, Is calculating pack-years retrospectively a valid method to estimate life-time tobacco smoking? A comparison between prospectively calculated pack-years and retrospectively calculated pack-years, Addiction 96 (2001) 1653–1661.
[12] G.L. Ruppel, Lung volumes and gas distribution tests, in: G.L. Ruppel (Ed.), Manual of Pulmonary Function Testing, Mosby, St. Louis, 1998, pp. 69–94.
[13] I.S. Mackenzie, I.B. Wilkinson, J.R. Cockcroft, Assessment of arterial stiffness in clinical practice, QJM 95 (2) (2002 Feb) 67–74.
[14] B.J. Kim, H.A. Lee, N.H. Kim, M.W. Kim, B.S. Kim, J.H. Kang, The association of albuminuria, arterial stiffness, and blood pressure status in nondiabetic, nonhypertensive individuals, J. Hypertens. 29 (2011) 2091–2098.
[15] D.W. Cockcroft, M.H. Gault, Prediction of creatinine clearance from serum creatinine, Nephron 16 (1976) 31–41.
[16] BMI classification: World Health Organization (WHO). Retrieved 15 July 2013. <http://www.who.int/mediacentre/factsheets/fs311/en>.
[17] N.L. Mills, J.J. Miller, A. Anand, Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk, Thorax 63 (4) (2008 Apr) 306–311.
[18] A. Albu, D. Fodor, C. Bondor, O. Suciu, Carotid arterial stiffness in patients with chronic obstructive pulmonary disease, Acta Physiol. Hung. 98 (2) (2011 Jun) 117–127.
[19] H. Cinarka, S. Kayhan, A. Gumus, Arterial stiffness measured via carotid femoral pulse wave velocity is associated with disease severity in COPD, Respir. Care 59 (2) (2014 Feb) 274–280.
[20] D.A. McAllister, J.D. Maclay, N.L. Mills, et al, Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 176 (12) (2007) 1208–1214.
[21] R. Sabit, C.E. Bolton, P.H. Edwards, et al, Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 175 (2007) 1259–1265.
[22] M. Zureik, A. Benetos, C. Neukirch, et al, Reduced pulmonary function is associated with central arterial stiffness in men, Am. J. Respir. Crit. Care Med. 164 (2001) 2181–2185.
[23] K. Taneda, T. Namekata, D. Hughes, et al, Association of lung function with atherosclerotic risk factors among Japanese Americans: Seattle Nikkei Health Study, Clin. Exp. Pharmacol. Physiol. 31 (2004) S31–S34.

[24] P.D. Scanlon, Does cardiac dysfunction cause pulmonary restriction?, Chest 107 (1995) 6–7
[25] G. Engström, P. Lind, B. Hedblad, Et al Lung function and cardiovascular risk: relationship with inflammation-sensitive plasma proteins, Circulation 106 (20) (2002 Nov 12) 2555–2560.
[26] I. Stone, L. John, S.E. Petersen, N.C. Barnes, Reproducibility of arterial stiffness and wave reflections in chronic obstructive pulmonary disease: the contribution of lung hyperinflation and a comparison of techniques, Respir. Med. 107 (11) (2013 Nov) 1700–1708.
[27] R.P. Young, R. Hopkins, T.E. Eaton, Pharmacological actions of statins: potential utility in COPD, Eur. Respir. Rev. 18 (114) (2009 Dec) 222–232.
[28] L. Mascitelli, F. Pezzetta, Renin-angiotensin system blockade and COPD, Chest 129 (2006) 1734–1735.
[29] P.M. Short, S.I. Lipworth, D.H. Elder, et al, Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study, BMJ 10 (342) (2011 May) d2549.
[30] M. Polatli, Q. Cakir, O. Cildag, et al, Markers of the severity in COPD exacerbation, J. Thromb. Thrombolysis 26 (2008) 97–102.
[31] A. Boussuges, C. Pinet, F. Molenat, et al, Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study, Am. J. Respir. Crit. Care Med. 162 (2 pt 1) (2000) 670–675.
[32] L.M. Caram, R. Ferrari, C.R. Naves, et al, Association between left ventricular diastolic dysfunction and severity of chronic obstructive pulmonary disease, Clinics 68 (6) (2013) 772–776.
[33] M. López-Sánchez, M. Muñoz-Esquerre, D. Huertas, et al, High prevalence of left ventricle diastolic dysfunction in severe COPD associated with a low exercise capacity: a cross-sectional study, PLoS ONE 8 (6) (2013) e68034.
[34] Y. Hu, L. Li, L. Shen, H. Gao, The relationship between arterial wall stiffness and left ventricular dysfunction, Neth. Heart J. (2012), http://dx.doi.org/10.1007/s12471-012-0353-z.