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Research Article

The Effect of Chronic Obstructive Pulmonary Disease on Aortic Stiffness

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Abstract

Objective: The aim of this study was to compare the aortic stiffness in Chronic Obstructive Pulmonary Disease patients (COPDs) with the stiffness of the general population patients (GPPs) and to evaluate the determinants of vascular stiffness in COPDs.

Methods: The study group consisted of 93 COPD patients (aged 55.8 ± 10.3 years) and 45 matched control subjects (aged 54.9 ± 8.7 years). Pulse wave velocity (PWV) was assessed from time diversity propagation of the common carotid artery and femoral artery by Doppler ultrasonography. Biochemical analyses were determined in serum using standard laboratory procedures.

Results: The mean PWV values were: 8.56 ± 2.13 m/s in the COPDs and 7.28 ± 1.45 m/s in the GPPs ($p < 0.0001$). We found positive correlation between PWV and COPD duration ($r = 0.2729$, $p = 0.0078$). The results of linear regression we present by equation of simple linear regression: $y = 7.548 + 0.06481 \cdot x$. By multiple regression analysis, C-reactive protein (CRP) standardized coefficient β [(βst) = 0.1153, p = 0.0006], COPD duration (βst = 0.06222, p = 0.0164), fibrinogen (βst = 0.3258, p = 0.0493) and triglycerides (βst = 0.2237, p = 0.2433) were independently associated with PWV in COPDs.

Conclusion: Aortic arterial stiffness was more pronounced in the COPDs than in the GPPs. The independent determinants of arterial stiffness (PWV) in COPDs include markers of inflammation and triglycerides as traditional risk factor and duration of the chronic obstructive pulmonary disease.

Keywords: *Chronic Obstructive Pulmonary Disease; Pulse Wave Velocity; Aortic Stiffness; Doppler Ultrasonography; Markers of Inflammation; Traditional Risk Factors*

Introduction

Chronic obstructive pulmonary disease (COPD) is considered a complex and heterogeneous condition affecting multiple organ systems, including cardiovascular disease (CVD) as a major cause of death [1]. The pathophysiological link between COPD and CVD is persistent low-grade systemic inflammation [2]. CVD is a major comorbidity and significant contributor to morbidity and mortality in COPD

patients with 2 to3-fold higher risk for developing CVD compared with the normal population, independently from traditional risk factors such as ageing, smoking, and hypercholesterolaemia [3]. Vascular dysfunction such as carotid intima media thickness, endothelial dysfunction and aortic stiffness are important mechanisms that can explain the main link between COPD and CVD [4]. Arterial stiffness is a marker of early atherosclerosis and is an independent predictor of CVD and cardiovascular events [5]. Carotid-femoral Pulse Wave Velocity (PWV) is considered to be the gold standard for assessing central arterial stiffness, which represent the velocity of the pulse wave transit from the common carotid artery (CCA) to the common femoral artery (CFA) [6,7].

Aim

The aim of this study was to compare the aortic stiffness in COPD patients with the general population patients (GPPs) and to evaluate the determinants of vascular stiffness in COPDs.

Methods

In this longitudinal observational comparative study, we estimated 93 patients with COPD over the age of 18 years who were attending Asthma center at internal medicine department of our public clinical hospital. All patients fulfilled the America College of Chest Physicians and Europian Thoracic Society diagnostic criteria for COPD [8] and COPD was confirmed with spirometry, FEV1/FVC < 0.7.

The control group consisted of 45 patients from the general population (GPPs, general population patients). The total number of participants recruited from Asthma center was equal to their proportion in the general population according to predefined criteria: age, gender, body mass index (BMI) and smoking, compared with those of the study group COPD patients. All patients from the both groups involved in the study were active smokers and smokers who did not make a total break in smoking longer than 6 months. Pack-years was calculated by dividing the number of cigarettes smoked per day by 20 and multiplying this figure by the number of years a person has smoked. To reduce the impact of atherosclerotic factors, we used the following exclusion criteria in both groups: renal impairment with reduced glomerular filtration rate (GFR ≤ 60 mL/min/1.73 m^2), diabetes mellitus (raised fasting blood glucose ≥ 7.0 mmoles/liter), hyperlipidemia, history of ischemic CVD, valvular heart disease and arrhythmias, premature menopause, recent surgery and pregnancy. All participants from both groups signed an informed consent and Ethics Committee of our institution approved the study.

Assessment

PWV estimation

We used Doppler ultrasound machine General Electric Logiq pro 5 (GE Medical Systems – USA: 4855WElectric Avenue, Milwaukee, WI 53215) with linear array 10 MHz multi-frequency ultrasound probe GE 10L at sequential Doppler signals recording of left CCA (at base of the neck) and left CFA (in the groin) synchronized with R wave of the electrocardiography (ECG) signal. The principle of PWV calculation based of transition time ΔT and distance D is shown by Figure 1.

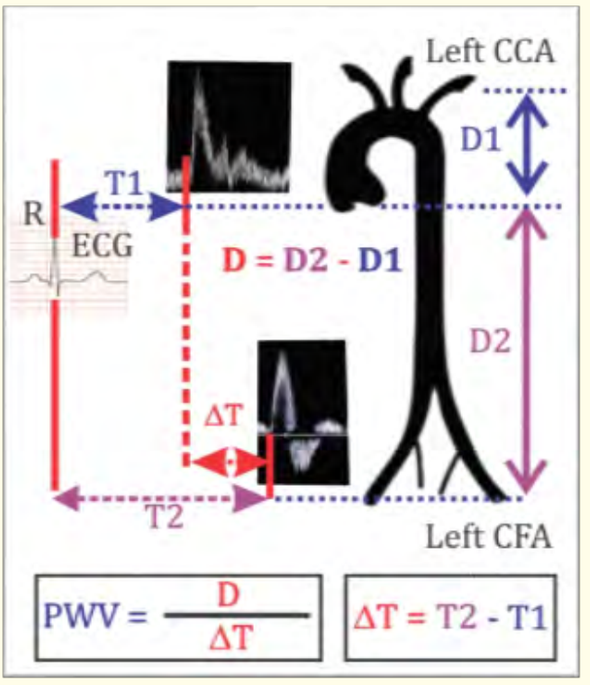

Figure 1: *Basic principles of Pulse Wave Estimation by time diversity (ΔT) of electrocardiographic and carotid-femoral Doppler.*

The distance lines marked as D1 (blue) and D2 (purple) presents the traveling paths that blood makes to access from the heart to the left CCA and left CFA, respectively. The time lines T1 (blue) and T2 (purple) corresponds with that distances (D1 and D2, respectively) and shows us the time needed for blood to cross the path. The synchronization start point for the both time lines (T1 and T2) is the R-wave of electrocardiography signal recorded simultaneously during patients Doppler examination. Distances between the sampling sites (D = D2 - D1) were measured as straight lines between the points on the body surface using a tape measure located at the same place as the ultrasound probe. The pulse traveling time, or time delay ΔT was calculated by the equation ΔT = T2 - T1. PWV was calculated by the standard equation for the speed (distance travelled per unit of time): S [m] = V [m/s] · ΔT or PWV = D/ΔT. The Doppler carotid-femoral PWV estimation has been previously described, reported and validated in my and many other studies [9-11].

Clinical and biochemical parameters

We determined clinical and biochemical parameters [plasma glucose, lipoprotein status, C-reactive protein (CRP), serum albumin, fibrinogen and erythrocyte sedimentation rate (ESR)] in all participants using standard laboratory procedures, performed on a Cobas Mira S Analyzer (Roche Diagnostics, Holliston, MA, USA).

Statistical analysis

The data were analyzed using MedCalc for Windows, 15.6. (MedCalc Software, Ostend, Belgium). The results were expressed as mean ± SD or percentage. We used Student's t-test for unpaired data to compare the COPDs and GPPs. Simple linear regression analysis was performed to assess the associations between PWV and independent variables. To show a relationship between variables we present a scatter diagram graphs pairs of numerical data. Multiple backward regression analysis was used to predict outcome of a response variable.

Results

We collected data from 93 COPDs (aged 55.8 ± 10.3 years) and 45 GPPs (aged 54.9 ± 8.7 years) during two-year period, with their BMI 22.9 ± 2.93 and 23.8 ± 1.76 kg/m^2, respectively. The mean duration of COPD state was 15.14 ± 7.3 years. Demographic and biochemical characteristics in both COPDs and GPPs are presented in part Results (Table 1). The mean PWV in COPDs was 8.56 ± 2.13 m/s and 7.28 ± 1.45 m/s in GPPs.

Characteristics	COPDs (n = 93)	GPPs (n = 45)	p value
Age, years	55.8 ± 10.3	54.9 ± 8.7	0.614
Male n (%)	68 (73.1)	33 (73.3)	0.98
BMI, kg/m^2	22.9 ± 2.93	23.8 ± 1.76	0.059
PWV, m/s	8.56 ± 2.13	7.28 ± 1.45	0.0004
FEV1/FVC	0.59 ± 0.12	0.82 ± 0.16	< 0.0001
Duration of COPD	15.14 ± 7.3	/	
Glucose, mmol/L	5.63 ± 0.57	5.23 ± 0.64	0.0003
Smokers, pack/years	24.8 ± 7.3	23.1 ± 9.1	0.2397
Hypertension, n (%)	24 (25.8)	13 (28.8)	0.71
Cholesterol, mmol/L	4.83 ± 0.9	5.57 ± 1.2	< 0.0001
HDL-Ch, mmol/L	1.42 ± 0.45	1.5 ± 0.37	0.303
LDL-Ch, mmol/L	3.2 ± 0.81	2.8 ± 1.1	0.017
Triglycerides, mmol/L	1.57 ± 0.62	1.37 ± 1.02	0.156
CRP, mg/L	6.57 ± 4.3	3.22 ± 2.1	< 0.0001
Albumin, g/L	38.2 ± 8.4	47.9 ± 9.2	< 0.0001
Fibrinogen, g/L	4.37 ± 1.94	2.71 ± 0.87	< 0.0001
ESR, mm/hour	27.8 ± 19.3	14.2 ± 5.1	< 0.0001

Table 1: *Demographic and Biochemical Characteristics of the Patients.*

COPDs: Chronic Obstructive Pulmonary Disease Patients.

GPPs: General Population Patients.

BMI: Body Mass Index.

PWV: Pulse Wave Velocity.

HDL-Ch: High Density Cholesterol.

LDL-Ch: Low Density Cholesterol.

CRP: C-Reactive Protein.

The unpaired t-test for PWV in COPDs and GPPs shows these results: Test statistics t = -5.400, DF = 136, Difference = -1.28, Significance level P < 0.0001. There was a high statistical significance between the mean PWV in the COPDs and GPPs.

Linear regression and scatter plot

The data from each of the 93 COPDs was displayed as a collection of blue circles determining the PWV [m/s] and COPD duration [years]. Each point (blue circle) had the value of one variable (COPD duration determining the position of the x (horizontal axis) and the value of the other variable (PWV) determining the position on the y (vertical axis).

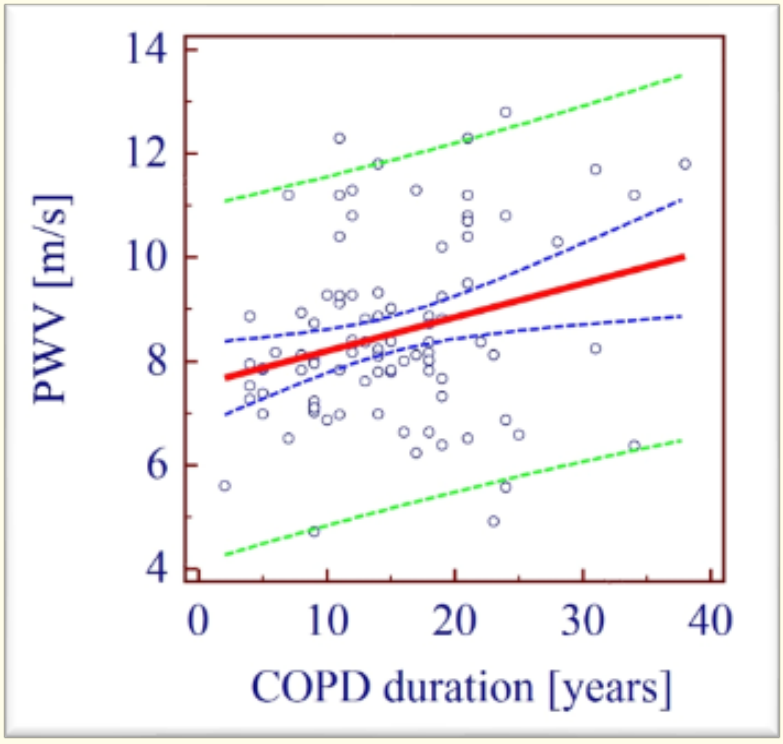

Figure 2: *Scatter plot of PWV and COPD duration.*

Figure 2 shows a scatter plot of PWV and COPD duration. There was a positive association between these variables showed by the thickened red line. The 95% confidence interval of intercept (95% CI = 6.754 to 8.342, p < 0.0001) is shown by the blue dashed line and prediction interval is shown by the green dashed line. There is a positive correlation between PWV and COPD duration, r = 0.2729, R2 = 0.074474 (p = 0.0078), 95% CI for r = 0.07436 to 0.4506.

The coefficient of determination R^2 (0.074474) showed that 7.447% of the total variability was explained with the linear relation between PWV [m/s] and COPD duration [year] or that 7.447 % from PWV was dependent on COPD duration. Only 7.447 % of the changes in PWV were the result of COPD value changes, and the remaining from the total variability between them were not explained (92.553% of PWV were dependent on other factors, which were not covered with the regression model). The results of linear regression represent the relationship between a scalar dependent variable Y (PWV, m/s) and an explanatory variable denoted X [Chronic Obstructive Pulmonary

Disease duration]. They were presented as equation of simple linear regression y = 7.548 + 0.06481 · x (p < 0.0001, intercept; p = 0.0078, slope) regression parameter bo = 7.5485, regression parameter b1 = 0.06481 and coefficient of determination R^2 = 0.07466. The regression parameter b1 = 0.06481 signified that with each increase of one unit (year) in COPD duration, the PWV score increased by 0.06481 m/s or 6.481 cm/s (0.6481 m/s per decade).

The correlation between FEV1/FVC and PWV was r = 0.327 (0.0013). In multiple regression analysis FEV1/FVC do not shows significant βst coefficient and p value (0.317) ant it was rejected by the regression model.

Multiple regression

Assessments [standardized coefficient β (βst), standard error of βst, t, and p-value of the independent predictor CRP or determinants (COPD duration, fibrinogen and triglycerides) for increasing of PWV as dependent variable Y in COPDs after backward multiple regression analysis are shown in Table 2.

	Multiple regression				
	Dependent Y	**(Pulse Wave Velocity, m/s)**			
	Method	Backward, Enter: if P < 0.1; Remove: if P > 0.3			
	Independence Variables	βst coefficient	Std. Error	t	P
COPDs	CRP	0.1153	0.0323	3.5640	0.0006
	COPD duration	0.06222	0.02546	2.444	0.0164
	Fibrinogen	0.3258	0.0163	1.9970	0.0493
	Triglycerides	0.2237	0.1902	1.176	0.2433
	smoking	0.2655	0.06995	0.380	0.7052

Table 2: *Multiple backward Regression Analysis of determinants of PWV in COPDs.*

Variables not included in the model: cholesterol, HDL-Ch, LDL-Ch, albumin, Smoking, FEV1/FVC and ESR.

Smoking is included after change of P > 0.8

βst, beta standardized; CRP, C-reactive protein; COPD, Chronic Obstructive Pulmonary Disease; HDL-Ch, high density lipoprotein cholesterol; LDL-Ch, low density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate;

FEV1/FVC, forced expiratory volume in one second/forced vital capacity;

The p-values followed the order of statistical significance: CRP (0.0006), COPD duration (0.0164), fibrinogen (0.0493), triglycerides (0.2433) and smoking (0.7052). There are statistically significant positive correlations between PWV and CRP, PWV and COPD duration and borderline correlation between PWV and fibrinogen. There is no statistical significance in correlation between PWV and triglycerides, and PWV and smoking estimated by backward multiple regression.

Discussion

There are no many studies which examined the aortic stiffness in patients with COPD, especially such studies which compared their results with the results of stiffness with the patients from general population [12,13]. We did not found enough studies which keep their attention on carotid-femoral aortic stiffness by comparing their results with GPPs and to determine the factors for increased PWV in COPD patients.

Our study is based on comparing data set of PWV in 93 COPDs and 45 matched control subjects without advanced atherosclerotic manifestation defined by exclusion criteria (renal impairment, diabetes mellitus, hyperlipidemia etc.). We found statistically significant difference between aortic PWVs as measure of aortic stiffness in the COPDs and the GPPs ($p = 0.0004$). Although we selected the patients with minimal traditional risk for atherosclerosis in both groups, with aim to eliminate the impact of natural process of atherosclerosis during ageing and under impact of traditional risk factors, the differences in aortic stiffness were still evident. These differences in PWV are generated by some other processes beside ageing and impact of traditional risk factors in COPDs, processes which further contribute to the advances progression of arterial stiffness in chronic obstructive pulmonary disease patients.

The results in our study for mean PWV in GPPs are matched with the mean PWV in GPPS in another study (7.28 ± 1.45 m/s, vs. range of another study results: 6.68 – 7.03 m/s) [14]. Our results for mean PWV in COPDs (8.56 ± 2.13, age 55.8 years) are nearly matched with results for PWV in older population of COPD patients (9.13 m/s, 68.8 years) [15]. The COPDs showed higher aortic PWV than GPPs of the same age, but whether increased PWV is a consequence of COPD or reflects only atherosclerosis is unknown. In the GPP group only traditional risk factors (hypertension, dyslipidemia and smoking) associated with progression of arterial stiffness in the elderly were evident. Unlike them, in COPDs, arterial stiffness expressed by PWV is accelerated due synergism between age and traditional risk factors plus factors related to the COPD (i.e., nontraditional risk factors: inflammatory markers CRP, fibrinogen, ESR, serum albumin and duration of COPD). That is the reason which suggests that classic risk factors do not explain excess vascular disease and stiffness increase.

Despite the fact that two-third of COPD population had a diagnosis of hypertension, it was so difficult to enroll in study the COPD patients without hypertension (about one-fourth in our study). It was with intended to neglect the hypertension influence on the vascular stiffness, in order to express only the impact of the COPD manifestation. Many studies declared that patients with COPD have increased arterial stiffness, blood pressure and systemic inflammation in comparison with control matched for age (our study, $p = 0.614$) and current smoking status (our study, $p = 0.2397$) [13]. By linear regression equation we detect that COPD patients in our study will increase the PWV for 0.648 m/s per decade. Tomlinson et al. proved that increase in PWV of one meter is equated to a 39% increased risk of cardiovascular events, and that data should not be underestimated [16].

The average age of our patients was 55.8 years and yet PWV values were similar to those of GPPs of 60 year olds, suggesting that COPD may results in premature ageing of the vasculature. Similar results were detected in other studies with more representative differences in PWV among COPD patients and healthy objects [17]. Arterial stiffness is also determined by the functional properties of the vessel wall with endothelium dependent vasomotor tone involved in the dynamic modulation of PWV. There is extensive evidence of endothelial dysfunction in cigarette smokers and in patients with atherosclerosis [18]. Interesting finding in our study is the fact that CRP has greater impact on vascular stiffness than COPD duration. Another marker of inflammation, fibrinogen has a smaller impact on PWV, but still with greater importance than other traditional factor for atherosclerosis (triglycerides, LDL-Cholesterol, HDL-Cholesterol). Systemic inflammation presented by markers of inflammation (CRP and fibrinogen, Table 2) is very important predictive factors for increase in aortic stiffness. It causes the degradation of elastic fibres by elastolysis and their replacement by collagen.

Elevated arterial stiffness in COPD patients can be predicted using age, blood pressure and thoracic calcification [21]. In our study, both CRP and COPD variables showed significant values as predictors in PWV determination. These two parameters affect the arterial stiffness. The action of CRP as inflammatory biomarker is more pronounced as the longer the disease, so these two markers act synergistically on the increase of arterial stiffness. Although we did not found significant value of hypoalbuminemia as predictor for PWV increase, its influence on COPD patients was evident. Hypoalbuminemia is the result of combined effects of inflammation and inadequate protein and caloric intake in patients with COPD [22]. Several studies have shown that hypoalbuminemia is associated with increased mortality in patients with COPD [23,24]. However, it may require further prospective study to verify whether albumin supplementation may reduce the arterial stiffness in COPD patients. Beside well-established factors for atherosclerosis, reduced FEV1/FVC was associated with increased PWV and elevated risk of cardiovascular mortality [25]. We found the similar correlation between arterial stiffness and mean FEV1/FVC in COPD patients.

Limitation of the Study

The first limitation of this study was the small number of patients sampled, especially the small number of GPPs. It was no easy to find smokers as control subject without symptoms of COPD and normal value of FEV1/FVC. Second, the critical factors during PWV estimation were the pulse traveling time ΔT and the length of the segment of aorta (D). Transcutaneous access of aorta, especially in tortuous aorta in elderly patients, may result with error in measured travel path (underestimation). Third, the COPDs with verified airflow limitation (FEV1/FVC) could not be precisely identified as having COPD. Because we did not perform post-bronchodilator function test, we may have overestimated the prevalence of participants with airflow limitation.

Finally, in order to improve the quality and accuracy of the further COPD studies, we certainly need to provide results of additional tests, chest radiograms, examination of medical records and gas analysis.

Conclusion

In conclusion, arterial stiffness was more pronounced in the COPDs than in the GPPs. The patients with COPD had stiffer arteries than GPPs. Non-traditional risk factors such as markers of inflammation (CRP, fibrinogen), FEV1/FVC and duration of COPD as well as the traditional risk factor of triglycerides are predictors for increase of vascular stiffness measured by PWV.

By incorporating carotid-femoral Doppler PWV measurements into standard regular diagnostic assessments for cardiovascular disease estimation in COPDs, the patients which are at increased cardiovascular risk can be identified, with recommendation for appropriate preventative therapy.

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