Original Article

Can Chronic Obstructive Pulmonary Disease be Associated with Arterial Stiffness?: A Case-control Multi-group Study

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Abstract

Background. Researchers have linked chronic obstructive pulmonary disease (COPD) to potential mechanisms increasing arterial stiffness. However, clinically the presence of COPD as risk factor for cardiovascular diseases is still unclear. The present study is aimed at assessing the COPD have an association with the risk of increased arterial stiffness.

Methods. This hospital-based, multi-group, case-control study comprised of three groups of patients: Group I: 50 COPD patients; Group II: 50 non-COPD smokers; and Group III: 50 normal healthy individuals who were non-smokers. Arterial stiffness of study subjects were measured by using non-invasive volume plethysmographic apparatus periscope.

Results. The mean brachio-ankle pulse wave velocity (baPWV) (cm/s) of COPD patients was found to be higher in comparison to healthy non-smokers (1696.4±341.3 *versus* 1405.4±622.7; p=0.005). The mean carotid femoral PWV was also significantly higher among COPD patients compared to control group (1197.7±273.5 *versus* 857.8±175.0; p<0.001). A weak negative correlation was found between forced expiratory volume in one second and baPWV among COPD patients (r=-0.024; p=0.871), however, for Global Initiative for Chronic Obstructive Lung Disease (GOLD) 3&4 patients it was statistically significant (r=-0.450;p=0.016).

Conclusion. Chronic obstructive pulmonary disease have no significant association with cardiovascular diseases independently, though in advance stage it can be consider as a strong predictor of increase in arterial stiffness. **[Indian J Chest Dis Allied Sci 2018;60:69-75]**

Key words: Lung, Vascular, Arterial stiffness, Brachio-ankle pulse wave velocity.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem, and predicted to be the third leading cause of death in 2020, after ischaemic heart disease and cerebrovascular disease.[1,2] There is considerable evidence that COPD and cardiovascular disease (CVD) co-exist and it has been cited that an increased risk of atherosclerosis is a direct consequence of COPD.[3] Various studies have shown that COPD is not limited to lungs but is a multi-system disease and researchers have linked COPD to potential mechanisms increasing atherosclerosis.[4-7] A spill over of inflammation from the pulmonary to the systemic circulation whose down-stream effects result in raised arterial stiffness could provide the mechanistic link between COPD and cardiovascular morbidity and mortality.[8] Therefore, we hypothesised that airflow limitation is associated with increased arterial stiffness. Brachio-ankle pulse wave velocity (baPWV), carotid femoral pulse wave velocity (cfPWV) and augmentation index (AIx) are non-invasive parameters by which arterial stiffness can be measured. Brachio-ankle PWV and cfPWV were estimated by measuring the transit time of the pulse wave between two pulse points and AIx was derived from pulse wave analysis (PWA) where peripheral artery waveforms are acquired and validated transfer functions are used to derive values of it.

Hitherto, the presence of COPD as risk factor for CVDs in the form of arterial stiffness as well association between baPWV, CfPWV, AIx and lung function indices was not studied thoroughly,[9] hence, the present study aims at assessing the same through non-invasive, multi-parameter cardiovascular analysis using periscope to find out the possibility of COPD as a risk factor for CVDs and also to explore any possible association between baPWV, cfPWV, AIx and lung function indices in patients with COPD.

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Material and Methods

This was a case-controlled, multi-group study approved by the ethics committee of our college and designed and conducted from October 2014 and December 2015, in the department of Respiratory Medicine. All subjects gave written informed consent.

The study subjects consisted of 150 participants who were enrolled from the general population living in rural areas of Haryana. The study comprised of three groups of patients: Group I: 50 COPD patients; Group II: 50 Non-COPD smokers; Group III: 50 Normal healthy individuals, non-smokers.

Cigarette smoking habit and the medical history of each person was obtained using a structured questionnaire. Smoking intensity (smoking index=no. of *bidi*/cigarette per day×years)[10] was obtained through the questionnaire. Patients with any of co-morbid conditions were excluded from the study: diabetes, hyperlipidemia, hypertension, human immunodeficiency virus (HIV)/ acquired immuno-deficiency syndrome (AIDS), renal disease, pregnant females and malignancy.

Cardiovascular Assessment

Brachio-ankle PWV, cfPWV and AIx were measured using a volume plethysmographic apparatus (Periscope (Recorders & Medicare System Pvt Ltd, Chandigarh). The baPWV was used as an index of arterial stiffness. To measure baPWV, cuffs were applied to both brachia and ankles, and all blood pressures were measured simultaneously by cuff oscillometric method. The pulse volume waveforms were also recorded simultaneously using a plethysmographic sensor connected to the cuffs. baPWV was calculated from the time interval between the wave fronts of the brachial and ankle wave forms, and the path length from the brachia to ankle (0.597 × height + 14.4014)[11] and we used the following formula for the cfPWV measurements: Estimated direct distance = [(0.45 × subtracted distance)+ (0.21 × height) + 0.08] × 0.8 and it was automatically analysed by the software.[12] The aortic AIx is a measure of pulse wave reflections, (AI=Augmentation pressure/Pulse pressure), which is an alternative, more indirect global measure of arterial stiffness that is dependent upon PWV but also on height, heart rate, endothelial dysfunction and changes in peripheral vascular smooth muscle cell tone.[13,14]

Pulmonary Functions

Pulmonary functions were measured by a forced vital capacity (FVC) maneuver on a computed spirometer with automated quality checks (BTL -08 Spiro PC, manufactured by Health and Medical Industry, United Kingdom, calibration 03-jun-14/003-0031080). Airflow limitation was defined as a ratio of FEV_1 to FVC of less than 70%. The severity of airflow limitation was graded by the ratio of FEV_1 to FEV_1 predicted value as per the GOLD.[15] Stage 1: $FEV_1 \geq 80\%$ of predicted — mild; Stage 2: FEV_1 $50 \leq FEV_1 < 80\%$ of predicted — moderate; Stage 3: FEV_1 $30 \leq FEV_1 < 50\%$ of predicted — severe; Stage 4: $FEV_1 < 30\%$ of predicted — very severe. Pulmonary functions were measured by a trained medical technologist according to a standardised protocol.

Statistical Analysis

Analysis was done by using Statistical Package for the Social Sciences (SPSS, version 20). All data were expressed as mean ± standard deviation (SD). Chi-square test used for categorical data and unpaired student 't' test used to compare means of non categorical variables while Pearson's correlation and regression analysis was performed to determine whether the FEV_1, baPWV, cfPWV or AIx results correlated with the examined risk factors of arterial stiffness. A p value of <0.05 was considered to be statistically significant.

Results

Data was analysed after being matched with mean age and sex in all study groups. Mean percent of predicted FEV_1 (52.8±20.5) for COPD patients was found to be significantly lower than asymptomatic smokers (64.5±31.3) as well as normal controls (111.2±16.3) ($p=<0.05$). The mean body mass index (BMI) was found to be lowest in the COPD group among all study subjects (19.8±2.8); p=0.000 (Table 1 and Figure 1).

We found significantly higher unadjusted values of baPWV and mean percent change of predicted in subjects with COPD (1696.4 cm/s, ±341.3; 21.8±24.0) in comparison to healthy controls (1405.4±622.7; 7.97±40.8; p=0.042). In asymptomatic smokers, it was found to be less than COPD patients. However, the difference was not statistically significant (1658.4±335.8; 16.7±40.4; p=0.44). Among smokers the percentage change of baPWV was higher than the control group which was not significant statistically (Table 1 and Figure 1).

By analysing cfPWV in various study groups, it was observed that mean value of cfPWV in both COPD patients (1197.7±273.5) as well as smokers (1143.9±289.7) were significantly higher than the control group (857.8±175.0; p=0.000). However, there was no significant difference was observed in percent change of cfPWV between COPD and asymptomatic smokers group (t=0.092; p=0.927) (Table 1 and Figure 1).

By calculating linear regression it was found that the dependency of baPWV on FEV_1 was less than cfPWV and AIx. It was also found that severity of arterial stiffness was maximum among COPD patients and increased with an increase in severity of airflow

Table 1. Characteristics of the study subjects with good quality of baPWV, cfPWV and AIx measurements and data of spirometry

Variables	COPD (N=50)	Smokers (N=50)	Controls (N=50)	p value COPD *versus* Controls	p value Smokers *versus* Controls	p value COPD *versus* Smokers
Mean age (in years)	58.9±15·2	56.4±11.7	56.1±9.2	0.204	0.917	0.293
Male:Female	21:4	21:4	19:6	>0.05	>0.05	>0.05
BMI	19.8±2.8	21.5±4.9	24.2±3.6	0.000	0.003	0.038
Smoking index	442.4±351.3	544.1±640.1	-	-	-	0.327
Mean observed baPWV (cm/s)	1696.4±341.3	1658.4±335.8	1405.4±622.7	0.005	0.013	0.576
Mean % change of predicted baPWV	21.8±24.0	16.7±40.4	7.9±40.8	0.04	0.284	0·448
Mean observed cfPWV (cm/s)	1197.7±273.5	1143.9±289.7	857.8±175.0	0.000	0.000	0·342
Mean % change of predicted cfPWV	19.2±27.1	18.7±30.4	3.0±15.1	0.000	0.001	0·927
Mean observed AIx	27.3±9.9	25.4±9.6	17.7±13.5	0.000	0.001	0.337
% Change of mean predicted AIx	47.4±51.7	48.0±58.1	33.7±77.3	0.301	0.300	0.957
% Predicted FEV_1	52.8±20.5	64.4±31.3	111.2±16.3	0.000	0.000	0.030
FVC	67.9±25.2	56.2±27.6	94.9±12.9	0.000	0.000	0.029
FEF_{25-75}	25.6±9.2	50.1±29.1	118.7±37.6	0.000	0.000	0.000
FEV_1/FVC	61.1±7.4	90.9±7.9	95.7±6.9	0.000	0.002	0.000

The results are presented as mean±SD with p value of significance

Definition of abbreviations: baPWV=Brachio-ankle pulse wave velocity; cfPWV=Carotid femoral pulse wave velocity; AIx=Aortic augmentation index; SD=Standard deviation; COPD=Chronic obstructive pulmonary disease; BMI=Body mass index; FEV_1=Forced expiratory volume in one second; FVC=Forced vital capacity; FEF_{25-75}=Forced expiratory flow at 25-75% of FVC

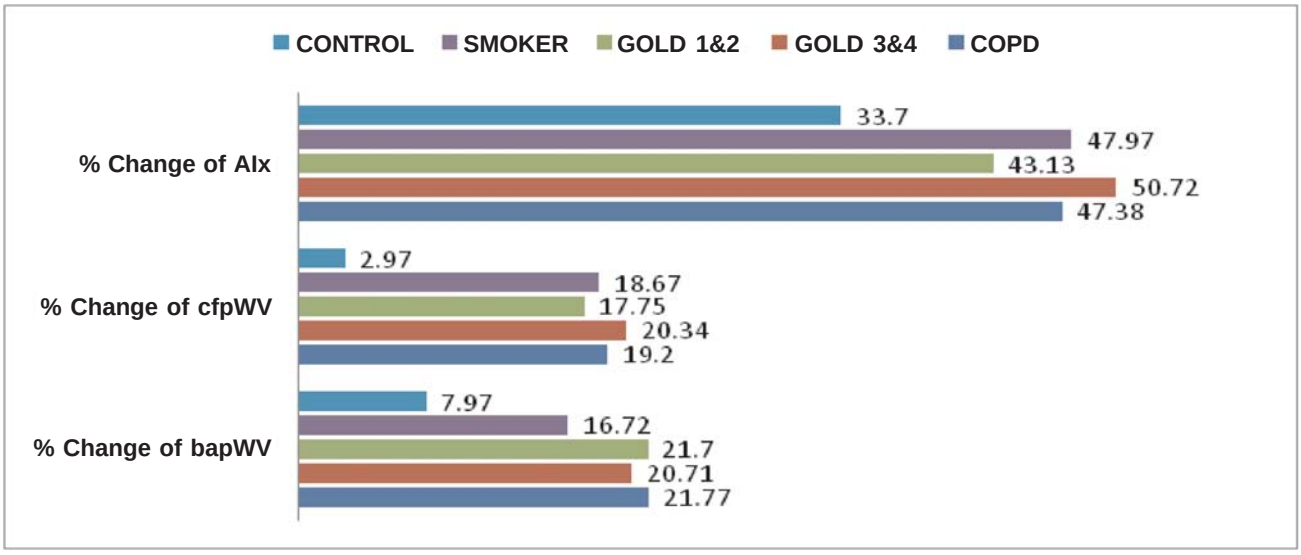

Figure 1. Bar diagram of mean percent change in periscopic indices among various study groups and sub-groups.

limitation. For GOLD 3 and 4 subjects (Mean % of predicted FEV_1=38.2±8.4), the airflow limitation was significantly correlated with baPWV (Mean % change of baPWV=20.7±21.5; r=-0.450; p=0.016) (Figure 2), similarly cfPWV (r=-0.462, F=7.037; p=0.013) and AI (r=-0.464, F=7.126; p=0.013). In addition to showing their robust association with the airflow limitation, the above findings also endorse the fact that severity of arterial stiffness increases with an increase in limitation in airflow in advance condition of COPD in comparison to mild form of COPD (Tables 2 and 3).

However, a weak negative correlation was found between diminution of FEV_1 and mean percent change in baPWV among COPD group as a whole, which was statistically insignificant (r=-0.024; p=0.871). Other PFT indices like FVC (r=-0.033; p=0.822) and FEF_{25-75} (r=-0.025;

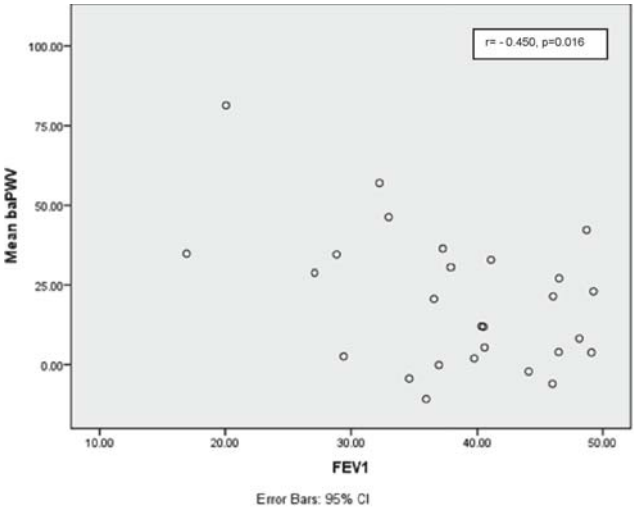

Figure 2. Scattered plot showing correlation in between baPWV and FEV_1 among GOLD 3 and 4 subjects.

Definitions of abbreviations: baPWV=Brachio-ankle pulse wave velocity; FEV_1=Forced expiratory volume in one second; GOLD=Global initiative for chronic obstructive lung diseases;

Table 2. Characteristics of the COPD (N=50) subjects distributed in GOLD stages 3 & 4, 1 & 2 with good quality of baPWV, cfPWV and AIx measurements and FEV_1

	COPD (N=50)		p-value
	GOLD 3 and 4 (N=28)	GOLD 1 and 2 (N=22)	
Mean % of predicted FEV_1	38.2±8.4	71.3±15.6	0.000
Mean % change of baPWV	20.7±21.5	21.7±27.2	0.886
Mean % change of cfPWV	20.3±27.9	17.7±26.7	0.742
Mean % change of AIx	50.7±53.7	43.1±50.0	0.611

Data are presented as mean±SD with p value of significance.

Definition of abbreviations: COPD=Chronic obstructive pulmonary disease; GOLD=Global initiative for chronic obstructive lung disease; FEV_1=Forced expiratory volume in one second; baPWV=Brachio-ankle pulse wave velocity; cfPWV=Carotid femoral pulse wave velocity; AIx=Augmentation index.

p=0.865) also showed a weak and negative correlation with baPWV (Table 4). Although cfPWV showed moderate negative correlation with FEV_1 (r=-0.265; p=0.063), FVC (r=-0.253; p=.076), FEF_{25-75} (r=-0.223; p=0.119) but this was found insignificant statistically (Table 4).

The mean observed value of AIx among COPD (27.3±9.9) is quite high compare to control group (17.7±13.5) which was statistically significant (p=0.000), for smokers (25.4±9.6) it was similar to COPD in compare to controls (p=0.337) (Table 1). There was moderate negative correlation between AIx and FEV_1 (r=-0.272; p=-0.272), FVC (r=-0.268; p=0.060) and FEF_{25-75} (r=-0.224; p=0.117) though it was statistically insignificant and very weak correlation with smoking index (r=-0.081; p=0.576) among COPD patients. However, among smokers AIx was significantly correlated with FEV_1 (r=-0.291; p=0.040) (Table 4).

By calculating linear regression among COPD group, it was found that the dependency of baPWV on FEV_1 (F=0.027, β=-0.024; p=0.871) was less than cfPWV (F=3.625, β=-0.265; p=0.063) and AIx (F=3.836, β=-0.272; p=0.056) but it was statistically insignificant, although among smokers AIx significantly dependent on FEV_1 (F=4.457, β=-0.291; p=0.040) (Table 4). However, among GOLD 3 and 4 subjects the dependency of baPWV (F=6.613, β=-0.450; p=0.016), cfPWV (F=7.037, β=-0.462; p=0.013) as well as AIx (F=7.126, β=-0.464; p=0.013) on FEV_1 was found statistically significant (Table 3).

By analysing different predictors of arterial stiffness to assess cardiovascular morbidity in COPD group we found statistically significant positive and robust correlation in between baPWV *versus* AIx (r=0.70; p=0.000); baPWV *versus* cfPWV (r=0.802; p=0.000); and cfPWV *versus* AIx (r=0.933; p=0.000).

Discussion

It was cited that arterial stiffness is mainly associated with hypertension, hypercholestrolaemia and aging, though the contribution of arterial stiffness to the cardiovascular morbidity in COPD is still debateable.[16] By analysing various epidemiological

Table 3. Correlation and regression analysis for baPWV, cfPWV and Alx with FEV_1 in subjects with COPD (GOLD 3&4 *versus* GOLD 1 & 2)

	Correlation and Regression with FEV_1 (GOLD 3 and 4)					Correlation and Regression with FEV_1 (GOLD 1 and 2)				
	Correlation		Regression			Correlation		Regression		
	r	p	F	β	p	r	p	F	β	P
% Change of predicted baPWV	-0.450	.016	6.613	-0.450	.016	-.061	.787	.075	-.061	.787
% Change of predicted cfPWV	-0.462	.013	7.037	-.462	.013	-.342	.119	2.65	-.342	.119
% Change of predicted AIx	-0.464	.013	7.126	-.464	.013	-.424	.049	4.378	-.424	.049

Definitions of abbreviations: COPD=Chronic obstructive pulmonary diseases; GOLD=Global initiative for chronic obstructive lung diseases; FEV_1=Forced expiratory volume in one second; baPWV=Brachio-ankle pulse wave velocity; cfPWV=Carotid femoral pulse wave velocity; AIx=Augmentation index

Table 4. Pearson's correlation and regression analysis for baPWV, cfPWV and AIx with physiological variables in patients with COPD and smokers

	Pearson's Correlation and Regression with % Change of Predicted baPWV						Pearson's Correlation and Regression with % Change Predicted cfPWV						Pearson's Correlation and Regression with % Change of Predicted AIx					
	COPD			Smoker			COPD			Smoker			COPD			Smoker		
	r	β	p	r	β	p	r	β	p	r	β	p	r	β	p	r	β	p
Age	-0.031	-.031	0.832	-0.081	-.081	0.578	-0.179	-.179	0.215	-0.107	-.107	0.465	-0.145	-.145	0.314	-0.242	-.242	0.092
SI	-0.240	-.240	0.094	-0.006	-.006	0.969	-0.134	-.134	0.353	0.051	.051	0.725	-0.081	-.081	0.576	-0.076	-.076	0.598
BMI	-0.074	-.074	0.611	-0.043	-.043	0.765	-0.295	-.295	0.038	-0.167	-.167	0.245	-0.262	-.262	0.067	-0.197	-.197	0.171
FEV_1	-0.024	-.024	0.871	-0.075	-.075	0.606	-0.265	-.265	0.063	-0.246	-.246	0.085	-0.272	-.272	0.056	-0.291	-.291	0.040
FVC	-0.033	-.033	0.822	-0.050	-.050	0.729	-0.253	-.253	0.076	-0.226	-.226	0.115	-0.268	-.268	0.060	-0.273	-.273	0.055
FEF_{25-75}	-0.025	-.025	0.865	-0.104	-.104	0.474	-0.223	-.223	0.119	-0.196	-.196	0.172	-0.224	-.224	0.117	-0.205	-.205	0.153
FEV_1/FVC	-0.069	-.069	0.632	-0.040	-.040	0.783	-0.154	-.154	0.285	-0.033	-.033	0.822	-0.121	-.121	0.401	-0.006	-.006	0.969

Definition of abbreviations: SI=Smoking index; BMI=Body mass index; baPWV=Brachio-ankle pulse wave velocity; cfPWV=Carotid femoral pulse wave velocity; FEV_1=Forced expiratory volume in one second; FVC=Forced vital capacity; FEF_{25-75}=Forced expiratory flow at 25-75% of FVC; r=Pearson's coefficient

studies it was found that a large proportion of patients with COPD die from cardiovascular cause rather than from respiratory failure and it appears to be independent of traditional risk factors for CVDs.[17] The present study was aimed to find out the answer whether COPD acts as risk factor for CVDs or it synergises the effect of tobacco smoke.

Researchers found that non-invasive parameters like pulse wave velocity used to assess cardiovascular risk among COPD patients is an ideal method. Besides this, it was also cited that baPWV is a robust predictor of CVD in COPD and provides qualitatively similar findings that are provided by aortic or carotid femoral pulse wave velocity.[18-20] Although few studies elucidate that measurement of cfPWV is highly reproducible in the assessment of cardiovascular risk and not affected by lung hyperinflation,[21,22] contrary to these findings Matsushima *et al*[23] reported moderate correlation with baPWV and coronary artery atherosclerosis by performing coronary angiography among COPD patients. According to them, carotid intima media thickness measurement by colour Doppler was found to be more accurate parameter to assess coronary artery disease, which needs further exploration to conceptualise and potentiate the hypothesis.[23]

One proposed mechanism linking COPD with increased arterial stiffness which leads to cardiovascular morbidity is systemic inflammation produced by inflammatory mediators that spill over from lungs to blood. Recent molecular studies have also demonstrated significant reduction in sirutin enzyme in rodent lungs exposed to cigarette smoke. In the lungs of patients with COPD, this enzyme has a prominent role in vascular biology and regulates key aspects of atherosclerosis.[6,7] In addition, the number of macrophages and interferon secreting TH1 lymphocytes increases in atherosclerotic plaque as well as in the peripheral lung regions in COPD patients, which accelerates and stimulates there modelling process with degradation of elastic fibres in the arterial wall and replacement by collagen.[12] This will lead to increased arterial stiffness with increased afterload, decreased perfusion of the coronary arteries and enhance the risk of CVD. However, contrary to this phenomenon, a study conducted by Vanfleteren and his team,[22] on 129 patients of COPD, did not find any significant correlation between arterial stiffness and systemic inflammation. Therefore, more comprehensive and detailed research with large sample size in future to challenge this phenomena are required. It was also elucidated that high coronary artery calcification was associated with higher pulse wave velocity in patients with COPD.[16] Similarly after doing Doppler echocardiography and measuring aortic pulse wave velocity in patients with COPD found sub-clinical left ventricular dysfunction related to arterial stiffness,[1] potentiate the present observation where we observed that COPD is associated with increased arterial stiffness, although smoking was common attribute in both the study groups, since significant arterial stiffness was found only among COPD subjects, which endorse that COPD can be consided as a factor responsible for arterial stiffness and cardiovascular risk. Although a large population based study conducted on 3374 subjects from the Copenhagen city found a weak association between COPD and arterial stiffness measured by AIx after controlling for confounders but only in men younger than 60 years of age, when mild COPD were excluded.[13] However, in one case control analysis,[22] moderate negative association of AIx with PFT indices was found; and elucidate that augmentation index increases with increment of severity of airflow

limitation. In the present study a high percent change in AIx was observed among COPD subjects in comparison to controls but it was statistically insignificant and similar changes were found among smokers; while in advance stage of COPD the correlation was found to be significant.

In the present study the cfPWV and baPWV were significantly high among COPD patients compared to controls and smokers group though statistically significant only with the control group. A similar case control analysis and couple of large population-based studies that included 8790 healthy community resident and multi-ethnic study of atherosclerosis with 3965 subjects from a general population, showed subjects with airflow limitation and smokers had significantly high baPWV and cfPWV. However in both the above-mentioned studies, the researchers took into account only the absolute values of both and not analysed percentage change of predicted value, which we have used in final analysis.[11,24,25]

Another potential factor responsible for atherosclerosis in COPD is hypoxia due to ventilation perfusion mismatch and disruption of alveoli by tobacco smoke leading to several atherogenic endothelial dysfunction, sympathetic nervous activity and elastolytic activity.[11] It has also been elucidated that decrease level of vascular endothelial growth factor (VEGF) and anti-apoptoic protein due to tobacco smoke and decrease VEGF receptors level in lung tissue of the patients of emphysema may be possible explanation of arterial stiffness among COPD patients. By these proposed theories, it seems that synergistic impact of tobacco smoke induced hypoxia and COPD induced inflammation may lead to vascular changes.[12] While a smoking habit in the absence of COPD has lesser impact on cardiovascular changes but statistically there is no significant difference found between the subjects having COPD and those who are presently smokers but without symptoms of airflow limitation.

On the other hand, recent research among COPD patients has revealed that increased arterial stiffness is more pronounced in severe stage of COPD,[26-29] which is endorsed also in the results of the present study.

Conclusions

Chronic obstructive pulmonary disease can not be associated with cardiovascular diseases independently, though the role of COPD in enhancing the risk of arterial stiffness in association with smoking can not be denied and it was found to be significant in comparison with healthy controls. However, COPD independently failed to create statistically significant change in cardiovascular system in compare to smokers. Though in advance stage of COPD (GOLD 3 and 4), the arterial stiffness was found to be significantly associated with airflow limitation in comparison to early stage of the disease.

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