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Original Research Article

Assessment of arterial stiffness in stable patients of chronic obstructive pulmonary disease: a prospective case control study

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide and represents a substantial socioeconomic burden. Co-morbidities are more in COPD patients. Cardiovascular disease is one of the co-morbid conditions in COPD. Arterial stiffness has a strong predictive value for cardiovascular events, which can be assessed non-invasively. Various predictors of arterial stiffness between stable COPD patients and healthy volunteers were measured and compared.
Methods: COPD patients attending pulmonary medicine outpatient services were screened for enrolment. It was a prospective case control study with enrolment of fifty COPD stable cases and fifty healthy control, who were matched for their age and sex. All eligible participants were subjected to focused history and physical examination as per structured questionnaire, followed by spirometric examination, periscope test, arterial blood gas analysis and six- minute walk test (6MWT).
Results: Increased arterial stiffness was observed in COPD patients over a wide range of severity of airway obstruction. Distance walked in 6MWT and spirometric values were significantly lower in COPD group as compared to healthy group.
Conclusions: It was concluded that vascular changes, which are predictive of cardiovascular disease remain as cardiovascular risks in mild or early lung disease. A strong relationship between COPD, systemic inflammation, arterial stiffness and cardiovascular disease had been found which needs to be explored further. It was finally concluded that targeted therapeutic approach has broad aspect in reducing cardiovascular risks and has potential for improved prognosis in COPD.

Keywords: Arterial stiffness, COPD, Periscope analysis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) as a "common, preventable and treatable disease is a major cause of morbidity and mortality worldwide and represents a substantial socioeconomic burden.[1]

The mortality due to COPD is showing an increasing trend. It was the fourth leading cause of death in 1990 and at present, it is the third leading cause of death globally.[2]

Clinically, the disease expresses in combination of chronic bronchitis and emphysema. The natural history of COPD is usually progressive, and patients commonly suffer from exacerbations of the disease.[3] Comorbidities are increasingly recognized in COPD patients and have significant negative impact on health status, healthcare utilization, all-cause hospital admissions and mortality in COPD patients.[4] Cardiovascular disease (CVD) is an important comorbid condition in COPD patients. Airflow obstruction profoundly affects cardiac function and gas

exchange, leading to systemic consequences, chronic inflammation both in lung and cardiovascular system may be associated with endothelial dysfunction, loss of elastin, and eventual vascular calcification.[5] Carotid intima-media thickness, endothelial function and arterial stiffness measurements are several subclinical markers of CVD that may have a role in identifying early changes in the cardiovascular system before the occurrence of major clinical events, such as myocardial infarction and stroke.[6] Among these markers, arterial stiffness has a strong predictive value for cardiovascular events beyond that of classic cardiovascular risk factors and is the most suited for use in routine clinical practice.[7]

Arterial stiffness has been independently associated not only with the severity of the COPD but also with inflammation, oxidative stress, and high sympathetic tone, the common processes of development of CVD in COPD patients.[8] Arterial stiffness is a potentially modifiable risk factor and has added predictive value beyond that obtained from traditional risk factors.[9,10] Arterial stiffness has been the target of pharmacologic and exercise interventions in patients with COPD.[11] Assessment of functional exercise capacity has gained importance in the evaluation of patients with various disease states. Six-minute walk test is a simple measure to assess the exercise capacity of patients with cardiopulmonary diseases.[12]

The present study was done to measure the arterial stiffness in stable patients of COPD and also to determine various predictors of increased arterial stiffness in stable COPD patients.

METHODS

The study was conducted in the Departments of Pulmonary Medicine and Pharmacology at Indira Gandhi Medical College, Shimla, which is a tertiary care center of Himachal Pradesh, located in north India in Asian Continent, which caters the majority of population of this state. A total of fifty patients fulfilling the inclusion and exclusion criteria and fifty healthy controls of similar age group, were enrolled in this study (Figure 1). It was conducted during July 2016 to June 2017. Written informed consent was obtained from all patients and study approval was taken from the Institutional ethical committee. It was a prospective case-control study. All consecutive patients diagnosed to have chronic obstructive pulmonary disease (COPD) and attending pulmonary medicine outpatient services were screened for enrolment in the study.

Inclusion criteria

- Patients with objectively confirmed stable COPD according to GOLD guidelines and aged 40 years or more.
- Written informed consent from patients willing to participate in the study.

Exclusion criteria

- History of COPD exacerbation within the last 6 weeks
- COPD patients with history of any cardiovascular disease, hypertension, dyslipidemia and diabetes mellitus were excluded.
- Other lung diseases.
- Inflammatory conditions, such as rheumatoid arthritis or psoriasis; or taking drugs that affect vascular function, including statins, angiotensin-converting enzyme inhibitors and beta-blockers.
- Patients receiving long-term oxygen therapy or corticosteroids.

Data collection

All eligible patients consenting to participate were subjected to focused history and physical examination as per structured questionnaire to record information related to socio-demographic profiles, duration of symptoms of chronic obstructive pulmonary disease, level of breathlessness using modified Medical Research Council scale (mMRC), history of any cardiovascular disease or peripheral arterial disease. Physical examination to record BP, HR, RR, anthropometrics, weight, height, waist circumference using appropriate tools and following standard guideline and arterial SaO_2 was measured with hand-held pulse oximeter.

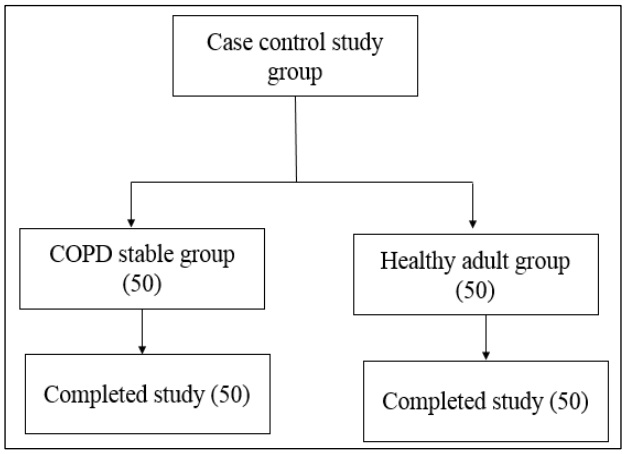

Figure 1: Flow chart of patients participating in study.

Investigations

Following investigations were carried out in each subject.

Lung function tests

Spirometric examination was done in all the patients using an electronic portable based spirometer with printer (Model Vitalgraph-Compact-Buckingham, England). It was post-bronchodilator spirometry according to global initiative for chronic obstructive lung disease (GOLD criteria). At least three measurements were made for each lung function variable to ensure reproducibility and

average measurement was accepted for final analysis. Grading of COPD was done as per GOLD guidelines. The spirometric classification of COPD was divided into four groups based on post-bronchodilator forced expiratory volume in 1 second (FEV1) levels. These are mild (GOLD-1, FEV1≥80% of predicted), moderate (GOLD-2, 50% ≤FEV1<80% of predicted), severe (GOLD-3, 30%≤FEV1<50% of predicted) and very severe (GOLD-4, FEV1<30% of predicted).

Periscope test

Periscope is a PC-based system for analysis of various parameters e.g., Blood Pressure (B.P.), pulse wave velocity (PWV), arterial stiffness Index (ASI), ankle brachial index (ABI), carotid-femoral index, ejection slope, mean arterial pressure (MAP), pulse pressure (PP), %MAP, ejection time and estimated ejection fraction. These parameters were calculated by measuring blood pressure from four limbs non-invasively and from ECG wave forms.

Arterial blood gas (ABG) analysis

ABG analysis of arterial blood sample drawn in 2ml heparinized syringe was done in all subjects in ABG analyzer instrument (Model No. GEM Premier 3000) and arterial pO_2, pCO_2, pH, saturation and bicarbonates were measured.

Six minutes walking test

The 6 minutes walking test was performed in the department of Pulmonary Medicine, where we used 30 metres long corridor. The test was completed according to the standards of ATS guidelines. The parameters that were recorded during the test included oxygen saturation levels before and after the 6 minutes walking test, the distance that the patients walked over 6 minutes and the lowest and the highest oxygen saturation levels. During the test, a decrease in oxygen saturation level of equal or more than 4% from the initial level was accepted as desaturation.

Statistical analysis

SPSS version 23 was used. Continuous variables are presented as the mean±SD, and categorical variables are expressed as a percentage. Independent student t-test was used for the continuous variables.

RESULTS

The present study was conducted on an outpatient basis in the Department of Pulmonary medicine at Indira Gandhi Medical College, Shimla from 1st July 2016 to 30th June 2017. It was a prospective case-control study which evaluated the arterial stiffness in stable patients of chronic obstructive pulmonary disease who attended the out-patient services.

Written informed consent was taken from all the patients. The controls were matched for age and sex. All patients were assessed for clinical examination, spirometry and other investigations. Socio-demographic characteristics including age, sex, level of education and socio-economic status were matched between the groups (Table 1). The percentage of illiterate subject were higher in COPD stable group than healthy adult group (20% vs 08%) p <0.001 and urbanization is more common in healthy adult group than COPD stable group (CSG); (37% vs 10%), p <0.0001.

The prevalence of current smoking was higher in the COPD patients than among healthy controls (14% vs 07%), p<0.0001.

The smoking index was significantly higher among patients with stable COPD. It was 458.50±285.48 in COPD and 145.44±179.83 in healthy controls (p <0.0001).

The percentage difference of exposure to biomass fuel smoke in stable COPD group was 47%. It was 28% in the healthy controls group, and the difference was statistically significant, p <0.0001. The mean difference in the duration of biomass fuel smoke in two groups was significant (16.62±8.35 vs 7.70±7.75), p <0.0001.

Most of the participants in COPD stable group were suffering from mMRC class II (27) and mMRC class I (14) dyspnea with minimum number of participants were in mMRCclass III (9) and none in mMRCclass-0, while healthy controls (group 2) exhibited 49, 1, 0 and 0 patients in class 0, class I, class II and class III respectively. The mean percentage of the cough among the stable COPD group was 49% vs. 0.00% in the healthy controls group (p <0.0001).

A total of 39% had presented with a history of productive cough, while 4% had a non-productive cough among stable COPD group. Most of the participants in COPD stable group had no cross ventilation in kitchen with only 25% cross-ventilation versus 41% cross ventilation in healthy adult group (p<0.001), which was statistically significant (Table 1).

Anthropometrically, COPD stable patients had lesser height, weight and BMI as compared to healthy group. The difference in mean height was 160.44±8.29 versus 164.12±7.81 (p <0.025, statistically significant), whereas difference in mean weight was 54.90±11.14 versus 60.54±10.64 (p <0.011 statistically significant). However, difference in BMI among two groups was 21.29±3.79 vs 22.40±3.09 which was not significant statistically (p=0.113). Mean SBP and DBP was lower in COPD patients as compared to healthy group which were not significant statistically. Average PR (83.76±10.87 vs 79.56±7.48) and average RR (21.68±2.49 vs 20.22±1.94) had significant difference among two groups with higher values in COPD group (Table 2).

Table 1: Distribution of clinical characteristics in study groups.

Variables		Group-1 COPD stable group	Group-2 healthy controls	P- value
Socio-demographic characteristics				
Age	40-49 (years)	3%	3%	0.9
	50-59 (years)	10%	10%	
	60-69 (years)	26%	27%	
	>70 (years)	11%	11%	
Sex	Male	34%	34%	1.0
	Female	16%	16%	
Urban		10%	37%	0.0001
Education	Illiterate	20	8	0.001
	Primary	15	7	
	Matriculate	10	16	
	Graduate	5	19	
	Post-Graduate	0	0	
Smoking	Never	4	23	0.0001
	Ex-smoker	32	20	
	Current Smoker	14	7	
Smoking index		458.50±285.48	145.44±179.83	0.0001
Exposure to biomass fuel		47	28	0.0001
Frequency of biomass fuel exposure	Occasionally	6	34	0.0001
	Frequently	23	13	
	Daily	21	3	
Duration of biomass fuel exposure (years)		16.62±8.35	7.70±7.75	0.0001
mMRC (Modified Medical Research Council) Dyspnea scale	mMRC0	0	49	0.0001
	mMRC1	14	1	
	mMRC2	27	0	
	mMRC3	9	0	
Cough		43%	00%	0.0001
Type of cough	Non-productive	4	0	0.0001
	Productive	39	0	
Duration of cough (months)		11.26±14.50	00%	0.0001
Type of kitchen	Open	1	0	0.35
	Closed	49	50	
Cross ventilation		25	41	0.001

Table 2: Comparison of anthropometric parameters between COPD stable group and healthy adult group.

Variables	COPD stable group (n-50)	Healthy controls (n-50)	Mean difference (95% C.I.)	P value
Height (cm)	160.44±8.29	164.12±7.81	-3.68 (-6.87 to -.48)	0.025
Weight (kg)	54.90±11.14	60.54±10.64	-5.64 (-9.96 to -1.31)	0.011
BMI	21.29±3.79	22.40±3.09	-1.106 (-2.48 to .267)	0.113
PR	83.76±10.87	79.56±7.48	4.20 (0.49 to 7.90)	0.027
SBP	123.28±9.77	124.80±9.18	-1.52 (-5.28 to 2.24)	0.425
DBP	77.12±6.02	78.44±5.22	-1.32 (-3.55 to .917)	0.245
RR	21.68±2.49	20.22±1.94	1.46 (0.57 to 2.34)	0.002

BMI=Body mass index, PR=Pulse rate, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, RR=Respiratory rate.

In present study, pulmonary function test showed decreased lung volume and lung capacity in COPD group. These parameters were recorded as SVC (62.38±12.34 vs 86.78±7.58); FVC (63.02±14.87 vs 88.50±9.80); FEV1 (60.34±17.56 vs 89.78±8.60); $FEF_{25-75\%}$ (37.92±24.12 vs 98.94±16.66) and FEV1/FVC (94.78±15.05 vs 101.60±9.57).

All these parameters showed significant difference (p <0.0001) among two groups (Table 3). Different variables of periscope analysis and their comparison among two groups had been shown in Table 4. There was significant difference in all the variables of periscope analysis between two groups. The mean of 6MWT in COPD stable group was 286.90±46 versus 399.38±28.4 in the healthy adult group, mean of SPO_2 at rest was 88.20±2.75versus 95.76±1.27, mean of SPO2 after 6MWT was 80.38±2.91versus 95±1.21. The mean HR at rest was 83.78±10.75versus 79.56±7.48. The mean of HR after 6MWT in COPD stable group was 93.24±11.35versus 86.24±7.77 in the healthy adult group. All variables of 6MWT had significant difference among two groups (Table 5).

Table 3: Comparison of pulmonary function test between COPD stable group and healthy adult group.

Characteristics	COPD stable group (n-50)	Healthy controls (n-50)	Mean difference (95% C.I.)	P value
SVC (%predicted)	62.38±12.34	86.78±7.58	-24.4 (-28.46 to -20.33)	0.000
FVC (%predicted)	63.02±14.87	88.50±9.80	-25.48 (-30.48 to -20.47)	<0.001
FEV_1 (%predicted)	60.34±17.56	89.78±8.60	-29.44 (-34.92 to -23.95)	0.000
$FEF_{25-75\%}$ (%predicted)	37.92±24.12	98.94±16.66	-61.02 (-69.24 to -52.79)	0.000
FEV_1/FVC (%predicted)	94.78±15.05	101.60±9.57	-6.82 (-11.82 to -1.81)	0.008

SVC=Slow vital capacity, FVC=Forced vital capacity, FEV1=Forced expiration volume in one second, FEF25-75%=Flow expiratory flow 25 to 75%.

Table 4: Comparison of arterial stiffness between COPD stable group and healthy adult group.

Variables	COPD stable group (n-50)	Healthy controls (n-50)	Mean difference (95% C.I.)	P value
RBAPWV (cm/s)	1600.51±682.61	1267.34±358.82	333.17 (116.74 to 549.60)	0.003
LBAPWV (cm/s)	1458.49±804.58	995.55±451.32	462.94 (204.03 to 721.84)	0.001
c-fPWV (cm/s)	964.02±555.94	782.07±212.68	181.94(14.89 to 348.99)	0.033
RBASI (mmHg)	32.25±10.80	25.92±6.24	6.32 (2.82 to 9.83)	0.001
LBASI (mmHg)	33.17±14.52	26.28±7.92	6.88 (2.24 to 11.53)	0.004
RAASI (mmHg)	40.18±12.16	35.35±8.74	4.83 (0.63 to 9.04)	0.025
LAASI (mmHg)	42.34±12.82	39.10±8.69	3.23 (-1.11 to 7.58)	0.143
ABI	1.075±.081	1.106±.082	-.0314 (-0.0639 to .00116)	0.059

RBAPWV=Right brachial ankle pulse wave velocity, LBAPWV=Left brachial ankle pulse wave velocity, c-fPWV=Carotid femoral pulse wave velocity, RBASI=Right brachial arterial stiffness index, LBASI=Left brachial arterial stiffness index, RAASI=Right ankle arterial stiffness index, LAASI=Left ankle arterial stiffness index, ABI=Ankle brachial index.

Table 5: Comparison of various distribution of 6-minute walk test on COPD stable group and healthy adult group.

Characteristics	COPD stable group (n-50)	Healthy controls (n-50)	Mean difference (95% C.I.)	P value
6MWT	286.90±46	399.38±28.4	-112.48 (-127.65 to -97.30)	0.000
SPO_2 at rest	88.20±2.75	95.76±1.27	-7.56 (-8.41 to -6.70)	0.000
SPO_2 after 6MWT	80.38±2.91	95±1.21	-14.62 (-15.50 to -13.73)	<0.001
HR at rest	83.78±10.75	79.56±7.48	4.22 (0.542 to 7.89)	0.025
HR after 6MWT	93.24±11.35	86.24±7.77	7 (3.13 to 10.86)	0.001

6MWT=Six minutes walk test, SPO_2=Blood oxygen saturation

Patients of COPD, when stratified by global Initiative for chronic obstructive lung disease (GOLD) stage, 4% patients were in stage I, 31% were in stage II, 13% stage III and 2% stage IV (Figure 2). The mean of pH in COPD stable group was 7.41±0.04 versus 7.37±0.03 in the healthy adult group (p<0.000) with mean difference (CI 95%) of 0.035 (.0209 to 0.0498), which was statistically significant. The mean of PCO_2 in COPD stable group was 43.67±7.22versus 39.72±2.54 in the healthy adult group p<0.001 with mean difference (CI 95%) of 3.94 (1.795 to 6.092), which was statistically significant. The mean of PO_2 in COPD stable group was 48.57±8.64 versus 89.49±4.64 in the healthy adult group (p<0.000) with mean difference (CI 95%) of -40.9 (-43.670 to -38.165), which was statistically significant. The mean of SPO_2 in COPD stable group was 88.44±2.54 versus 95.76±1.27 in the

healthy adult group (p<0.000), mean difference (CI 95%) of -7.32 (-8.117 to -6.522), which was statistically significant (Figure 3).

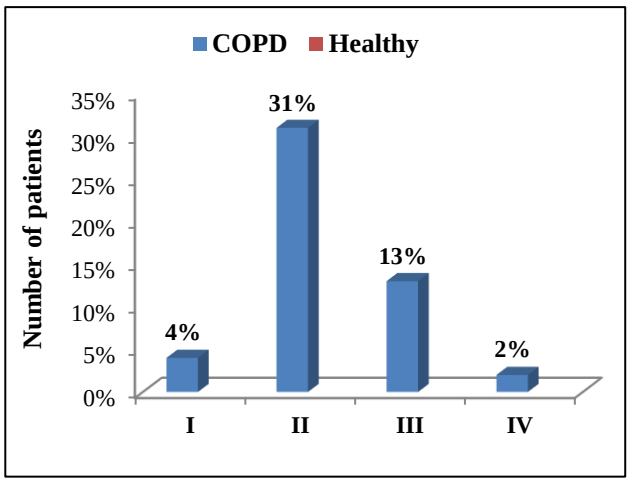

Figure 2: GOLD criteria staging of COPD stable group patients.

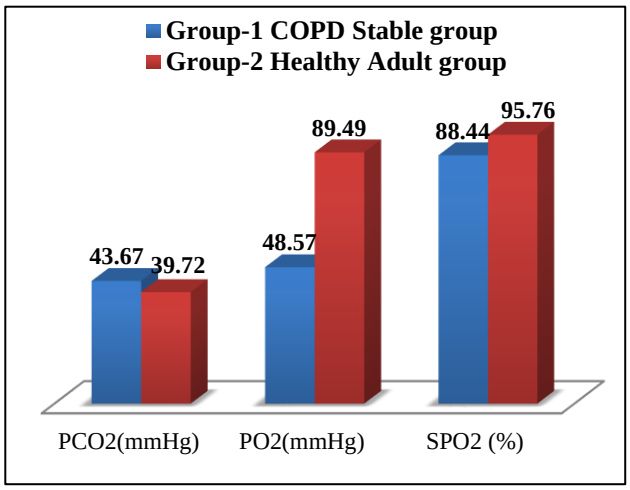

Figure 3: Comparison of ABG between two study groups.

Urbanization is related to well education and better awareness to cross ventilation among two groups. However, because of urbanization, exposure to tobacco product and biofuel along with increment in BMI were higher in the study group as compared to control group.

Level of education contributes in development of arterial stiffness as the knowledge regarding exposure to biofuel and tobacco was lowest when the population is illiterate.

DISCUSSION

A close connection exists between COPD and cardiovascular diseases Arterial pulse wave velocity (PWV) constitutes a useful and safe non-invasive method for assessing central arterial stiffness.[6,13]

In present study, majority of COPD patients were from the rural background and only 10% of the COPD patients resided in the urban locality. Another reason for rural predominance could be the widespread use of biomass combustion as cooking medium in the hilly rural areas. Illiteracy rate was also higher among the COPD patients (20% vs. 08%); p<0.001 compared to healthy control. These results correlated to other studies.[14,15]

Exposure to biomass fuel smoke (47% vs 28%), use of tobacco product (14% vs 07%) and mean smoking index (458.50±285.48 vs 145.44±179.83) were significantly higher (p<0.0001) in COPD patients as compared to the control group (Table 1). These results were also correlated to some other studies.[14,16]

Higher rate of pulse and respiration is usual in COPD patients. In the Copenhagen city heart study, which was a prospective population based study it was found that, resting heart rate increased with severity of COPD (p<0.001) and was associated with both cardiovascular and all cause mortality across all stages of COPD (p<0.001).[17] Similar trend had been observed in present study where pulse rate (83.76±10.87 vs. 79.56±7.48) and respiratory rate (21.68±2.49 vs. 20.22±1.94) demonstrated significant difference among two groups (p <0.001) (Table 2). It could be because of airwday obstruction, hyperinflation and hypoxemia.

Decreased values SVC, FVC, FEV_1, $FEF_{25-75\%}$ and FEV_1/FVC in COPD group had significant difference (p<0.0001) in comparison to healthy group (Table 3). It was in concordance with the previous studies which showed that patients of COPD had significant reduction in spirometric values as shown in the studies.[18,19]

Amongst different variables of periscope analysis, the mean of RBAPWV, LBAPWV and c-fPWV was significantly higher in the COPD stable group as compared to healthy control group (p <0.05). The mean of RBASI, LBASI and RAASI in COPD stable group was higher than in healthy control group and they found to be highly significant with a p-value for RBASI, LBASI and RAASI being 0.001, 0.004 and 0.025 respectively (Table 4). These enhanced levels of various variables in our study group are indicative of increased arterial stiffness. These results have positive correlation with some other studies.[20-22]

In COPD stable group, ABG parameters such as pH (7.41±0.04 vs 7.37±0.03); p<0.0001, PCO_2(mmHg) (43.67±7.22 vs 39.72±2.54); p<0.0001, PO_2(mmHg) (48.57±8.64 vs 89.49±4.64); p<0.0001, SPO_2 (%) (88.44±2.54 vs 95.76±1.27); p<0.0001 were significantly impaired as compared to the control group. These results have positive correlation with some other studies.[23,24]

The main contributing factors consistently reported for arterial stiffness are aging, smoking, BP, metabolic disorders, chronic inflammation, and oxidative stress. Airflow obstruction has been an independent predictor of

arterial stiffness in COPD. In a cross-sectional study involving 194 men, aged 30-70 years, who were free of coronary heart diseases, suggesting that both obstructive and restrictive lung disorders are associated with increased arterial stiffness.[25]

Arterial stiffness was increased even with a mild degree of airway obstruction, indicating its early occurrence in the natural history of COPD.[8] In a cross-sectional study, Sabit et al, measured arterial stiffness in 75 clinically stable COPD patients and 42 healthy current or ex-smoking participants. All participants were free of CVD. Both PWV and augmentation index (Alx) were significantly higher in COPD patients than in age matched controls. Increased aortic PWV was related to increased severity of airflow obstruction, systemic inflammation, and the presence of osteoporosis.

One possible explanation for low lung function and arterial stiffness could be an alteration of elastolytic activity in both the alveoli and the vasculature. Elastolysis in COPD can occur in both the pulmonary and systemic levels.[6]

In the present study, there were some predictors, which positively correlate the increased incidence of arterial stiffness. Subject who exposed to the tobacco product had higher incidence of mMRC ($p<0.005$). Urbanization is related to improvement in education ($p<0.005$) and those who had good educational background were less prone to develop cough ($p <0.005$) and related illness, but the urbanization also leads to obesity ($p <0.005$), that is another positive indicator to develop oxidative stress, that might also propagate arterial stiffness. Direct relationship was observed between cross ventilation and development of arterial stiffness with inclusion of mMRC and cough as predictors. Subjects who didn't had cross ventilation at their home gets higher incidence of cough ($p <0.005$), and severe mMRC scale ($p <0.005$) than those who had cross ventilation, which eventually culminate in development of arterial stiffness.

In the present study, there was significant correlation of the development of arterial stiffness with lifestyle and type of living. Most of the patients were illiterate who exposed themselves to the tobacco products, poor cross ventilation. It is clearly stated that, education and the living standard affect the development of arterial stiffness. This relationship was correlated with some other studies.[26-28]

Present study exhibited marked decrease in oxygen saturation at rest as well as after 6MWT in COPD stable group as compared to control group, also distance covered during 6MWT was severely affected in COPD group. It was in concordance with the earlier studies conducted by Miyamoto et al, which stated that 6MWT distance below 332 metre is an indicator of poor prognosis in cardiovascular diseases.[29] Another study says that 6MWT has prognostic value in disease severity and mortality in patients with heart diseases.[30]

CONCLUSION

It was concluded that vascular changes, which are predictive of cardiovascular disease remain as cardiovascular risks in mild or early lung disease. A strong relationship between COPD, systemic inflammation, arterial stiffness and cardiovascular disease had been found which needs to be explored further. It was finally concluded that targeted therapeutic approach has broad aspect in reducing cardiovascular risks and has potential for improved prognosis in COPD.

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