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Effect of Physiological and Clinical Variables of Chronic Obstructive Pulmonary Disease on Atherosclerosis

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a debilitating condition associated with significant morbidity and mortality. Cardiovascular diseases are the major cause of mortality in COPD patients. Studies have shown that increased airflow limitation in COPD patients is associated with increased risk of atherosclerotic heart diseases. FEV1 has been shown to correlate significantly with carotid atherosclerosis as a marker of cardiovascular disease risk. This study tries to study the effect of physiological and clinical variables of COPD on atherosclerosis in terms of carotid intima media thickness.

Method: Patients admitted for acute exacerbation of COPD to our hospital were evaluated for carotid atherosclerosis, quantified by common carotid intima media thickness. 67 patients with significant CCIMT; quantified using B-mode ultrasonography and color doppler were evaluated in respect to physiological and clinical variables. Pearson's correlation, multiple linear regression, Anova and Independent sample t-tests were used, depending upon type of variable under test using IBM-SPSS software version17.

Results: Study included 67 subjects [Mean age = 61.91±9.07, Median = 63.00] including 38 males and 29 females of age 45 years and above. Mean common carotid intima media thickness (CCIMT) was 1.19 ± 0.35 mm. Lung function (represented by FEV1 % predicted, FEV1/FVC and PEFR) showed significant inverse correlation with CC=-IMT (p-value<0.05). Significant positive correlation was found between CC-IMT and age, arterial partial pressure of carbon di-oxide, total duration of illness (TDI) (p-value<0.01) and significant inverse correlation was seen with % of TDI on Proper monitored inhalation therapy. No significant correlation was found between arterial partial pressure of oxygen (PaO_2) and CC-IMT. Multiple linear regression analysis shows that PaCO2 (p-Value = 0.001) and Total Duration of Illness; TDI (p-Value < 0.001) are the two independent variables that have significant impact in predicting the CC-IMT.

Conclusion: our study shows that total duration of disease and PaCO2 is associated with increased carotid atherosclerotic thickening in COPD patients among all other physiological variables. Early diagnosis and management of COPD and early screening of atherosclerotic vascular heart disease in COPD patients may help reduce risk of atherosclerotic vascular complication.

Keywords: COPD, CC-IMT, Carotid atherosclerosis, PaCO2, FEV

INTRODUCTION

Chronic Obstructive Pulmonary Disease is a major cause of morbidity in adults and by far the fourth leading cause of death worldwide.[1] It is characterized by airway inflammation and remodeling leading to airflow limitation which is progressive. The airflow limitation which is irreversible or less often partially reversible makes the condition incurable but manageable. The inflammation associated with COPD is not limited to lungs and "spill-over" of inflammatory mediators into

systemic circulations have been discussed.[2] This concomitant systemic inflammation is believed to be responsible for the large array of co-morbidities associated with COPD. Acute exacerbations in COPD patients are acute events marked by sudden surge in inflammatory mediators which adds to the severity of the disease as well as the co-morbidities. Moreover, co-morbidities and their management play a major role in overall health status and health related quality of life of patients. Cardiovascular comorbidities in COPD need special attention because of shared common risk factors and high frequency of coexistence namely heart failure, ischemic heart disease, arrhythmias, peripheral vascular diseases and hypertension.[3] Atherosclerosis is a common pathophysiology associated with these conditions. Although smoking is common risk factor among atherosclerotic heart diseases and COPD, large scale epidemiological studies have shown COPD to be a major risk factor for heart diseases independent of smoking, hypercholestero-lemia and hypertension. Ongoing systemic inflammation in COPD is believed to be a cause for this. Researchers have argued that atherosclerotic heart diseases could be a distinct phenotype of COPD and a better understanding would help optimize diagnostic and management strategies.[4] Studies have shown that increased carotid intima media thickness and presence of atherosclerotic plaques in carotid arteries can be used as marker of cardiovascular disease and risk assessment.[6] Although severity of airflow limitation in COPD patients has been shown to be associated with increase cardiac related mortality as well as carotid intima media thickness in COPD patients, a recent study on Korean population has shown that pulmonary function represented by Forced expiratory volume in 1st second (FEV1) did not have significant association with cardiovascular risk factors; such as increased carotid intima media thickness, in general population without airflow limitation.[5] This could imply that inflammation associated with COPD and severity of the disease per se could be more responsible for increased atherosclerotic and cardiovascular risk rather than FEV1 alone. In this study we have evaluated carotid atherosclerosis quantified by carotid intima media thickness in relation to physiological and treatment related variables in COPD patients.

MATERIALS & METHODS

This was a single-centered observational study carried out at Sir Sunderlal Hospital, Institute of Medical, Banaras Hindu University, Varanasi, India. Prior approval from the institutional ethics committee was obtained. Patients admitted for acute exacerbations of COPD were enrolled after confirming the diagnosis and written informed consent was obtained. Inclusion criteria was COPD as diagnosed by Global Initiative for Chronic Obstructive Lung Diseases (GOLD) diagnostic criteria[7] in patients more than or equal to 45 years of age. The exclusion criteria were:

- Any other co-existing pulmonary disease
- Associated comorbidities like diabetes mellitus, systemic hypertension, renal disease, hepatic disease, neurological disease, coronary artery disease, left ventricular disease, arrhythmias, dyslipidemia, metabolic syndrome, obstructive sleep apneas and malignancy.
- Receiving treatment with antiplatelet, anticoagulant, statins or history of coronary revascularization/ intervention/ drug treatment etc
- Any cardiac abnormality other than of cor-pulmonale and pulmonary artery hypertension secondary to COPD.
- Multiple organ failure and/or hemodynamic instability requiring vasopressor support
- Active exposure to Cigarette/ Bidi or Biomass fuel smoke in last 5 years.
- History of stroke, transient ischemic attack

Relevant clinical history was taken and thorough physical examination was performed. Arterial blood gas analysis at admission, at discharge and at 4 weeks follow-up was done. Routine investigations included complete blood count, liver and renal function tests, fasting and post prandial blood sugar, C-reactive protein (CRP), electrocardiography, 2-dimensional echocardiography and chest x-ray postero-anterior view. High resolution computed tomography (HRCT) of chest to obtain imaging correlate of COPD and rule out other lung pathologies. Color Doppler flow imaging of neck for evaluation of extra cranial carotid arteries was performed using Toshiba Xario X2 model to study axial and sagittal sections of neck vessels by Linear probe (Frequency 8-12 MHz) and carotid intima media thickness was quantified (Figure 1).

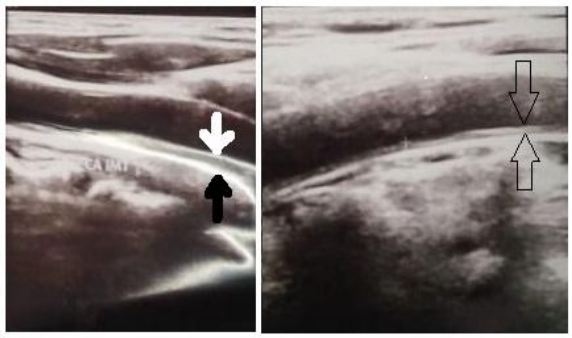

Figure 1: Common carotid ultrasound image showing significant intima media thickening 0f 1.26 mm (solid arrows) in a 52 year old male and insignificant 0.72 mm (hollow arrows) in 61 years old male.

COPD

COPD was diagnosed based on persistent clinical symptoms of cough, shortness of breath which worsened with exertion, sputum production, and was established by GOLD criteria of post bronchodilator spirometry values i.e. ratio of Forced expiratory value in 1st second (FEV1) to Forced Vital Capacity (FVC) <0.7 [FEV1/FVC <0.7]. Airflow limitation was graded based on percentage of predicted FEV1 values (%FEV1) as per GOLD criteria. Peak expiratory flow rate (Liter per second) was also recorded.

TDI & PMIT

TDI here refers to total duration of illness as reported by patient. PMIT is the Proper monitored inhalation therapy i.e. the duration for which patient has been on continuous inhalation therapy and treatment for COPD as per proper recommended standard of care and continuous follow-up.

Chronic Respiratory Failure (CRF)

Chronic respiratory failure was defined as arterial partial pressure of carbon dioxide (PaCO2) of ≥50 mm of Hg with normal (compensated) pH (>7.35) at 4 weeks follow-up when patients' symptoms (as assessed subjectively) returned to baseline i.e. similar to that before exacerbation.

Common Carotid-Intima Media Thickness (CC-IMT) was classified into significant and non-significant by reference cut-off values of upper limit (97.5 percentile) of IMT in common carotid in different patient age group as per study of Lim TK et al.[8] The following were the upper limit of normal reference cut-off values for different age groups:

Age Group:	35-39 yrs.	40-49 yrs.	50-59 yrs.	≥60 yrs.
CC-IMT	0.6mm	0.64mm	0.71mm	0.81mm

STATISTICAL ANALYSIS

Different variables were compared and tests such as Pearson's Correlation, Multiple Linear Univariate Regression, One way & Factorial (two way) Analysis of Variance [ANOVA], Independent sample t-test were applied depending upon type of variables under test. Necessary Post-Hoc Analyses were performed where ANOVA was used as test of significance. The tests were performed using IBM SPSS software version 17.

RESULTS

Total 67 patients were studied after meeting the inclusion and exclusion criteria. Baseline group characteristics are shown in Figure 2. The data obtained was normal in

distribution and parametric tests were used for statistical analysis.

Study group characteristics				
Size (N)	67			
Median Age	63			
Male	38 (56.7%)			
Female	29 (43.3%)			
Mean BMI (kg/m^2)	23.44±5.5			
Mean Total Cholesterol (mg/dL)	168.2±6.4			
Mean C-Reactive Protein (mg/L)	12.20±3.24			
Oxygen saturation % (mean)	90.1±2.8			
Mean FEV1/FVC (%)	58.4 ± 8.1			
Mean FEV1(%predicted)	42.3 ± 14			
Mean CC-IMT	1.19 ± 0.35			
Case distribution by TDI (in years)	≤2 yrs	>2-6 yrs	>6-10 yrs	>10 yrs
	9	27	17	14
Case Distribution by PMIT duration (% of TDI)	≤25%	>25-50%	>50-75%	>75%
	3	14	37	13
Mean arterial PaCO2	<50 mm of Hg		44.89±3.29 (n=47)	
	≥50mm of Hg		53.6±2.79 (n=20)	
	All		47.5±5.1 (n=67)	

Figure 2: Group Characteristics

13.4% of patients (N=9) were recently diagnosed of COPD with TDI ≤ 2 years, while 20.89% (N=14) had been suffering from COPD for >10 years. Rest of the patients fell within this TDI range.

There was wide variation in treatment for COPD taken by patients over the course of their disease. Treatment taken by patients was quantified as "percentage of TDI for which patients received PMIT" as defined under Materials and Methods.This included the duration immediately preceding inclusion into the study. Only 19.4% (N=13) were on PMIT for >75% of TDI while 4.5% (N=3) were on PMIT for <25% of TDI. 29.85% patients had chronic respiratory failure with mean PaCO2 of 53.6 (n=20, sd= 2.79).

Mean CC-IMT was 1.19mm (N=67, SD=0.35) with positive and significant (Pearson's) correlation with spirometric variables like FEV1/FVC ratio [p-value <0.001], percentage of predicted FEV1 [p-value <0.001] and PEFR [p-value <0.05].

There was found to be positive & significant correlation of CC-IMT with physiological and clinical variables like Age, PaCO2& TDI and inverse significant correlation with "percent of TDI with PMIT" as depicted in Figure 3-5.No significant correlation was found between arterial partial pressure of oxygen (PaO_2) and CC-IMT.

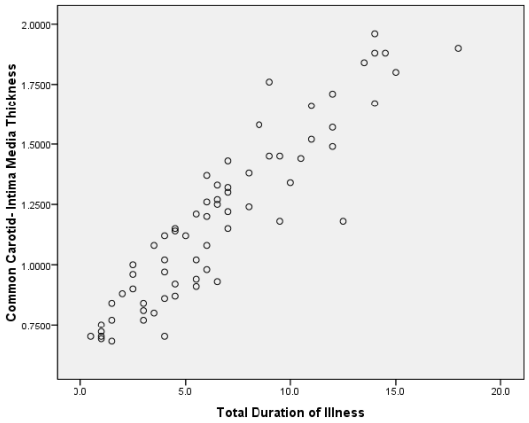

Figure 3: Scattered Dot Plot diagram : CC-IMT vs TDI

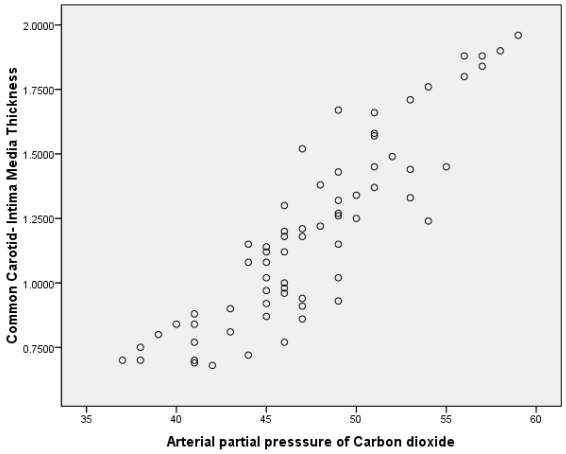

Figure 4: Scattered dot plot diagram: CC-IMT vs Arterial PaCO2

Based on percent of TDI on PMIT, patients were grouped into 4 groups: Group 1 (<25%), Group 2 (25 to <50%), Group 3 (50 to <75%) and Group 4 (≥75%). One-way Analysis of Variance reveals a significant

difference in the mean CC-IMT of different groups who received PMIT for different duration; p-value <0.001.

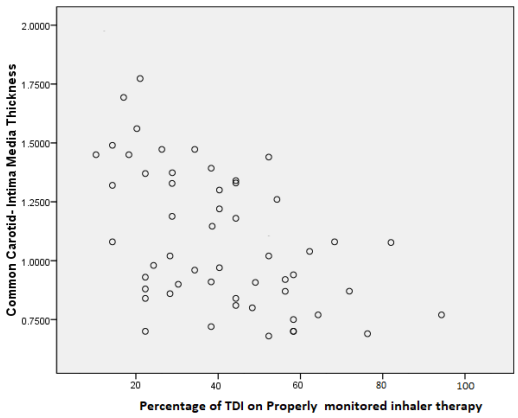

Figure 5: Scattered dot plot diagram: CC-IMT vs % TDI on PMIT

Post Hoc Analysis (Games-Howell) reveals that the mean difference in mean CC-IMT was significant for Group2 ↔ Group4 and Group3 ↔ Group4 (p-Value <0.001). The mean difference between Group2 ↔ Group4 (0.680) was higher than that of Group3 ↔ Group4 (0.366) with standard error of mean 0.113 and 0.059 respectively.

Similarly, there exists a statistically significant difference between the mean CC-IMT of patients with CRF (n= 20, M= 1.421mm, SD= 0.310) and patients without CRF (n= 47, M= 0.967, SD= 0.230) in the study group [t (65) = 6.806, p < 0.001, $\eta 2$ = 0.41] with 95% confidence interval range 0.320 to 0.587.

Multiple linear regression analysis shows that of all the variables which showed significant correlation with CC-IMT, PaCO2 (p-Value = 0.001) and Total Duration of Illness; TDI (p-Value < 0.001) are the two independent variables that have significant impact in predicting the CC-IMT value in presence of other independent variables.

DISCUSSION

This study evaluated carotid intima media thickness in relation to physiological and treatment related factors among patients of COPD in a hospital setting.

The mean CC-IMT in our study group was CC-IMT was 1.19mm (N=67, SD=0.35). A recent study by Cemal Koseouglu and colleagues to evaluate association between carotid intima media thickness and coronary artery disease among COPD patients found mean CIMT of 1.40±0.34 mm in COPD group and 1.24±0.28 mm in non COPD group. [5] In a study of Omer Karakas et al, Mean CIMT in the COPD group and control group were 0.62 ± 0.05 mm and 0.45 ± 0.03 mm, respectively (P < 0.001). [9] Another study by Sandip Chindi and colleagues on Indian population found Mean average CC-IMT in COPD patients to be 1.07 ± 0.49 mm. [10] It is evident from similar other studies that CC-IMT may vary widely among COPD patients depending on study population which could be attributed to ethnicity and demographic variations. Nonetheless, all such studies have demonstrated higher CC-IMT in COPD patients compared to their non-COPD control groups. Arterial wall thickness and plaque formation has been largely explained in light of lipid-driven atherosclerosis, endothelial injury and stasis.[11] Systemic inflammation and inflammatory mediators arising from oxidative stress play a major role in plaque formation and contribute to lipid core of the atherosclerotic plaque. COPD, although primarily a disease of airway and alveolar inflammation has been found to be a cause of systemic inflammation and systemic spill-over of inflammatory mediators play a significant role in development of co-morbidities in COPD patients.[12,13,14] This could explain higher mean CC-IMT levels in COPD patients than their non COPD counterparts in all of these studies.

Correlation of FEV1 to CC-IMT in our study was comparable to other similar hospital and population based studies, showing significant inverse correlation of CC-IMT with FEV1 values, thereby suggesting that increase in severity of airflow limitation is associated with increased carotid wall thickness.[6,9,10 ,15] Our study also found significant positive

correlation of CC-IMT with age, arterial partial pressure of carbon di-oxide and total duration of illness for which the subjects were suffering from COPD. An inverse and significant correlation was found between CC-IMT and the percentage of total duration of illness for which the patients were on properly monitored therapy for COPD as per recommended standard of care. Multiple linear regression analysis showed that PaCO2 and Total duration of illness had most significant impact on CC-IMT in presence of all the other independent variables studied. Our literature search did not yield any previous study evaluating this relationship. Since COPD is associated with significant airway and systemic inflammation, prolonged duration of illness subsequently leading to longer exposure to systemic inflammatory mediators may be responsible for positive correlation with increased CC-IMT. Similarly inverse correlation with "percentage of TDI on PMIT" may be attributed to better disease control and reduced inflammation. This is an important aspect in particularly rural and underserved regions of a developing country like India, with limited access to specialist care in remote rural areas, lack of patient education, less focus on counselling due to busy and crowded clinics and delayed referral to specialists. Many patients are diagnosed years after onset of their first symptoms which contributes to increased morbidity and mortality. Adding to this, cheap readily available over the counter drugs like prednisolone, betamethasone, theophylline and salbutamol tablets provide symptomatic relief and further delays the specialist consultation.

Increased baseline PaCO2 is found in severe of disease which is associated with decreased ventilatory function of lungs, as such positive correlation of its values with CIMT may be a surrogate for disease severity and direct effect of PaCO2 on atherosclerosis could be further investigated.

In our study, we tried to eliminate other factors which may directly contribute to systemic inflammation, oxidative stress and atherosclerosis by devising stringent exclusion criteria as discussed in materials and methods. Smoking itself is a risk factor for both COPD and atherosclerosis, as such we excluded subjects who had actively smoked or had exposure to biomass fuel smoke in daily routine in last 5 years. It may be noted that COPD is usually but not invariably associated with smoking and a substantial 3-11% prevalence of COPD has been reported in never smokers.[16] However, since smoking and exposure to other environmental and occupational exposure to noxious particles and gases may have long lasting effect, our exclusion criteria of "5 years" is open to criticism.

CONCLUSION

From the results and analysis of our study, we conclude that COPD plays an independent role in atherogenesis. Athesclerosis occurring in COPD, as quantified by common carotid intima media thickness may be due to hypoxic and systemic inflammatory effects of COPD which may add to other atherogenic factors that variably coexist with COPD like metabolic syndrome, smoking and coronary artery diseases. Since longer duration of COPD correlates with increased CC-IMT, it may be used as screening tool in early diagnosis of atherosclerotic vascular and heart diseases, which is a major cause of death in COPD patients.

Conflict of interest: None

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