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ORIGINAL ARTICLE

Endothelial Function and Subclinical Atherosclerosis in Patients of Chronic Obstructive Pulmonary Disease

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) has systemic consequences, including cardiovascular disease. The endothelial functions are impaired in COPD patients, correlating with the severity of the disease. Our study is designed to examine the endothelial function in COPD patients by studying Flow Mediated Dilatation (FMD) and its correlation to severity of disease.

Methods: Patients more than 35 years of age with stable COPD were included in the study. Focused examination was carried out to record blood pressure, ankle brachial index and signs of heart failure. Detailed biochemical investigations were done along with ECG, Chest X-ray, Spirometry, FMD and carotid intima media thickness in all patients. Age and sex matched healthy subjects without any evidence of systemic disease were recruited as controls.

Results: Fifty-nine consecutive COPD patients along with their age and sex matched controls were evaluated. Of the 118 patients, 06 (10.2%) in control group had carotid plaque, while 26 (44.1%) patients in the COPD group were observed to have carotid plaque ($p<0.0001$). Mean FMD in the control group was 13.765±4.428 and among COPD patients was 5.7440±3.2698 ($p<0.0001$).

Conclusions: Endothelial dysfunction measured by FMD was independently associated with Forced Expiratory Volume in the first second (FEV1) i.e., severity of COPD. We also found that there was higher likelihood of subclinical atherosclerosis and peripheral vascular disease to be present in COPD patients. Hence, cardiovascular risk factors should be evaluated in all COPD patients.

Keywords: Endothelial Function; Flow Mediated Dilatation; Atherosclerosis; COPD; FEV1.

Introduction

It now accepted that Chronic Obstructive Pulmonary Disease (COPD) is not solely a pulmonary disease but one with important measurable systemic consequences, including cardiovascular disease (CVD) that represents a considerable burden in terms of both morbidity and mortality in patients with COPD. Coexisting COPD could also lead to

poor prognosis in patients with CVD, for which the former is an independent risk factor.[1] The cumulative evidence from clinical trials and meta-analyses indicates that there may be a 'COPD effect' that contributes to CVD, including coronary artery disease (CAD), in patients with COPD. Arterial wall stiffness, which relates to cardiovascular risk, is increased in patients with COPD.[1, 2]

Recent studies have shown that endothelial functions are impaired in COPD patients, correlating with severity of the disease.[3, 4] Increased systemic inflammatory processes with activated inflammatory cells, increased plasma levels of pro-inflammatory cytokines, hypoxia, and increased oxidative stress may be the leading causes of endothelial dysfunction in COPD patients.

Endothelium is the largest organ in the body. The term 'Endothelial Function' is widely used for the ability of the endothelium to cause vasodilatation dependent on a stimulated endothelium. The most important endothelium derived vasodilating substance is nitric oxide (NO). In addition to the vasodilatory effects, NO has been found to be a principal factor involved in anti-atherosclerotic properties of the endothelium. NO interferes with key events in the development of atherosclerosis, such as monocyte and leucocyte adhesion to vascular endothelium and platelet aggregation and adhesion. NO also decreases the endothelial permeability and inhibits the vascular smooth muscle cell proliferation.[5]

Endothelial dysfunction plays a major role in the pathogenesis of various diseases including atherosclerosis, hypertension and heart failure.[5] All the well-known risk factors of atherosclerosis including age, smoking, hypertension, hyperlipidemia, diabetes and hyper-homocysteinemia contribute to cardiovascular mortality and morbidity by impairing normal endothelial function.[6]

Brachial artery flow-mediated dilatation (FMD) is a well-studied measure of endothelial function that has been used to noninvasively assess conduit artery and microvascular endothelial function. The stimulus provokes the endothelium to release nitric oxide, with subsequent vasodilatation that can be imaged and quantified as an index of vasomotor function.[7m]

Only a few studies have examined endothelial function in COPD. Our study was designed to examine the endothelial function in COPD patients by studying FMD and its correlation to severity of disease.

Material and Methods

This study was conducted at Indira Gandhi Medical College (IGMC), Shimla, one of the tertiary care centres of Himachal Pradesh, located in the north of India. Patients were included if they met the inclusion criteria, were capable of consenting, ambulatory and not receiving treatment for life-threatening conditions. Ethical approval was taken from the medical ethics committee of IGMC, Shimla (Ref. HFW(MS)G-5/Ethics Committee/09-11732). Written informed consent was obtained from all patients. Patients aged more than 35 years with stable COPD were included in the study. Patients with acute exacerbation of COPD within the last 6 months were excluded, as well as patients with diabetes, hypertension, ischemic heart diseases, heart failure, peripheral vascular disease, chronic renal disease, asthma and tuberculosis. Patients with interstitial lung diseases, rheumatoid arthritis and kyphoscoliosis were also excluded.

The demographic profile of patients was recorded, including age, place of residence (rural/urban) and its distance from IGMC, Shimla. History regarding smoking, symptoms of COPD, diabetes, hypertension, dyslipidemia, prior coronary artery disease (CAD) and peripheral vascular disease were elicited and noted. Focused examination was carried out to record systemic blood pressure, ankle brachial index and signs of heart failure. Detailed biochemical and other investigations were done, including ECG (electrocardiogram), chest X-ray, spirometry, FMD and carotid intima media thickness in all patients. ABG was done in patients with severe and very severe COPD cases only. Age and sex matched healthy controls without any evidence of systemic disease were recruited. Severity of COPD was decided as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines: GOLD classification, as shown in Table 1.

Table 1: Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV1

Classification	Severity of Airflow Limitation	FEV_1
GOLD 1	Mild	≥80%
GOLD 2	Moderate	50-79%
GOLD 3	Severe	30-49%
GOLD 4	Very severe	<30%

FEV1: Forced Expiratory Volume in the first second.

Ankle Brachial Index (ABI): A standard cuff was taken for both upper limb and lower limb blood pressure measurement. In the lower limb, the cuff was applied in such a way that it just covered the medial malleolus. The systolic pressure of posterior tibial artery was taken as the ankle pressure, and the higher of systolic pressure in both upper limbs was taken as brachial pressure. ABI was calculated as the ratio of systolic blood pressure measured at ankle and systolic blood pressure measured below elbow. The mean of three readings was taken. ABI of >1 was taken as normal and <0.9 was suggestive of Peripheral Vascular Disease (PVD).

Flow mediated dilatation (FMD): FMD was assessed with the patient in the supine position. The right brachial artery was scanned over a longitudinal section, 3 to 5 cm above the elbow. Depth and gain settings were optimized to identify the lumen-to-vessel wall interface. FMD was assessed by measuring the change in brachial artery diameter after 10, 30 and 60 seconds of reactive hyperaemia, compared with baseline measurements, after deflation of a cuff placed around the forearm that had been inflated to 50 mm Hg above systolic blood pressure for 5 minutes. Arterial diameter was determined as the internal dimension of the vessel wall from the anterior to posterior interface between the lumen and the intima. The mean diameter was calculated from three measurements of arterial diameter performed at end-diastole coincident with the R wave on a continuously recorded ECG. Because of circadian variations of peripheral vascular tone, detection of brachial artery vasomotion was performed in all patients between 8 and 9 AM in a quiet, temperature-controlled room (22^0C to 24^0C). All subjects were studied after a 12-hour overnight fast. Smokers refrained from smoking in the 12 hours preceding the study. Vasoactive drugs were discontinued in the same time period. Overall, 10% of the recordings were interpreted by another cardiologist to limit inter-observer bias.

$$FMD = \{(D2-D1) \times 100\}/D1$$

where D1 is brachial artery diameter at baseline and D2 is brachial artery diameter at 60 sec after release of BP cuff.The distribution of categorial variables between study groups was expressed as percentages and continuous variables as mean ± SD. The significance of differences in the categorical variables were analysed using chi-square test and continuous variables with unpaired student-t test. P value <0.05 was taken as statistically significant. Analysis was done using software SPSS v 16.0.

Results

We evaluated 59 consecutive COPD patients along with age and sex matched controls from the medicine and pulmonary medicine outpatient departments. Overall**,** among 118 patients, 81 (68.6%) were male and 37 (31.4%) were female. In the control group, 40 (67.8%) were male and 19 (32.2%) were female whereas among cases, 41 (69.5%) were male and 18 (30.5%) were female. This difference in sex distribution was statistically insignificant (p= 0.843). Of the 118 patients, 14 (23.7%) patients were either smokers or ex-smokers in the control group and 59 (100%) patients were either smokers or ex-smokers among cases (p<0.0001). Of the 118 patients, 17 (28.8 %) were illiterate in the control group and 28 (47.5%) were illiterate among the cases (p=0.037). Of the 118 patients, 4 (6.8%) patients in the control group had and 1 (1.7%) among cases had dyslipidemia (p=0.157). Baseline clinical characteristics of cases and controls were matched as shown in Table 2.

Of the 59 cases, 9 (15.3%) patients had mild COPD, 25 (42.4%) had moderate COPD, 12 (20.3%) had severe COPD and 13 (22%) had very severe COPD. Of the 118 patients, 14 (10.2%) patients in the control group had increased maximum carotid intima media thickness (CIMT) (either of right or left) and among cases, 33 (55.9%) patients showed an increase in maximum CIMT (either

of right or left) (p<0.0001). Of the 118 patients, 06 (10.2%) in the control group and 26 (44.1%) patients among cases were noted to have carotid plaque (p<0.0001). Of the 118 patients, 10 (16.9%) in control group and 50 (84.7%) among cases had FMD <10% (p<0.0001). These results are depicted in Table 3.

Discussion

Brachial artery flow-mediated dilatation (FMD) is a well-studied measure of endothelial function that has been used to noninvasively assess conduit artery and microvascular endothelial function. The stimulus provokes the endothelium to release nitric oxide with subsequent vasodilatation that can be

Table 2: Baseline clinical characteristic of cases and controls

Characteristic	Controls (n= 140)	Cases (n= 142)	P value
Age (years)	62.42±8.42	62.154±8.26	0.852
Smoking Index	43.14 ±92.01	399.29 ±43.14	<0.0001
Body Mass Index (kg/m^2)	24.198 ±3.28	23.824 ±4.02	0.515
Systolic Blood Pressure (mm Hg)	125.05 ±8.81	124.88 ±8.46	0.915
Diastolic Blood Pressure (mm Hg)	78.14 ±5.89	78.44 ±6.37	0.788
Total Cholesterol (mg/dl)	141.73±28.95	151.97 ±26.95	0.049
Triglyceride (mg/dl)	116.51 ±35.54	116.93 ±24.95	0.94
High Density Lipoproteins (mg/dl)	48.02±21.8	44.36±7.35	0.224
Low Density Lipoproteins (mg/dl)	82.10±30.78	93.32±22.61	0.026

Smoking Index is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Table 3: Results of the study

Characteristic	Controls (n= 140)	Cases (n= 142)	P value
ABI	1.258±0.15	1.119±0.14	<0.0001
FEV1	2.1828±0.57	1.1025 ±0.36	<0.0001
FEV1/FVC	82.1695 ±7.48	58.879 ±15.99	<0.0001
CIMT(LEFT)	0.7341 ±0.31	1.04492 ±0.63	0.001
CIMT(RIGHT)	0.73475 ±0.25	1.03746 ±0.52	<0.0001
CIMT (max)	0.7953 ±0.29	1.1825 ±0.68	<0.0001
CIMT (Average)	0.73442±0.27	1.04118 ±0.52	<0.0001
FMD	13.765±4.43	5.7440±3.27	<0.0001

ABI: Ankle Brachial Index. FEV1: Forced Expiratory Volume in first second. FVC: Forced vital capacity. CIMT: Carotid Intima Media Thickness. CIMT (max): Maximum Carotid Intima Media Thickness CIMT (Average): Average Carotid Intima Media Thickness. FMD: Flow Mediated Dilatation.

imaged and quantified as an index of vasomotor function.[7]

In the present study, the mean FMD in COPD patients was weak when compared to controls. Similar results were observed by Leo Moro et al,[4] where a total of 44 COPD patients were studied along with age and sex matched controls. The mean FMD in COPD patients was 5.4% and 8.2% among controls, with a significant p value ($p<0.001$). In the study by RG Barr et al,[3] FMD was assessed in a cohort of former smokers and was correlated with severity of COPD in relationship to pulmonary function tests and CT percentage of emphysema. They reported a mean FMD of 3.8±3.1% and demonstrated the mean FMD to be significantly lower in COPD patients as compared to the non-COPD group ($p=0.001$). The result of lower mean FMD in COPD patients and its severity in our study were consistent with findings of Leo Moro et al[4] and RG Barr et al.[3]

The pathologist A. A. Liebow postulated almost 50 years ago that changes in the local vascular milieu modulate alveolar destruction in COPD.[8] More recent research has shown that smoking causes acute endothelial dysfunction. Intima medial thickness (IMT) of the common carotid artery measured by carotid ultrasonography is considered to be an excellent non-invasive measure of generalized atherosclerosis. In the study by Gestel et al,[9] 23% of patients without COPD demonstrated increased carotid wall IMT, whereas 32% of patients with mild COPD and 36% of patients with moderate/severe COPD had increased IMT ($p < 0.01$). Hiroshi Iwamoto et al.[10] found that the mean carotid IMT was significantly higher in smokers with airflow limitation (0.78 mm) than in both control smokers (0.73 mm) ($p <0.01$) and control never-smokers (0.73 mm) ($p < 0.005$). The results of higher CIMT among COPD patients in our study, as well as its severity, are consistent with findings of Gestel et al[9] and Hiroshi Iwamoto et al.[10]

The mean ankle brachial index in our study was significantly lower in the COPD group when compared to the control group. The ARIC Study,[11] a cohort study, examined the cross-sectional relationship between lung function (measured by FEV1) and three markers of subclinical atherosclerosis, namely ankle–brachial index (ABI), carotid intimal–medial thickness and presence of carotid plaques in 14,000 adults. They found a direct association between mean FEV1 and ABI in the full cohort and in each of the smoking groups, such that individuals with lower ABI tended to have lower FEV1 ($p=0.04$). Increased CIMT and carotid plaques were both associated with decreased FEV1.

Some of the limitations of the present study need to be noted. COPD is characterized by a high prevalence of co-morbid conditions such as diabetes mellitus and hypertension, known to affect both structure and function of the arterial wall. As our study population excluded other co-morbidities and included a pure COPD population, such a population may be poorly representative of the overall COPD population. Secondly, as we did not measure serum or plasma biomarkers of inflammatory or oxidative pathways, we could not verify whether some of these pathways mediated the observed relationship between impaired vasodilation and bronchial obstruction. Thirdly, COPD is associated with both a prooxidative and hypercoagulable state, and this per se might impair the FMD. Further research is needed to understand the contribution of COPD and other comorbidities like diabetes and hypertension on endothelial dysfunction in the COPD population.

Conclusions

Our study revealed that endothelial dysfunction measured by FMD was independently associated with FEV1 i.e. the severity of COPD. These associations were linear across a spectrum of disease, from normal lung function to mild to severe COPD. Our findings are consistent with basic science research hypothesizing a primary vascular role in the pathogenesis of COPD. We also found that there is a higher likelihood of subclinical atherosclerosis and peripheral vascular disease to be present among COPD patients. Therefore, cardiovascular risk factors should be evaluated in all COPD patients. These findings are indicative of a biologically plausible link between bronchial obstruction and atherosclerosis. Our study adds to the evidence that COPD is not merely a respiratory disease, but a systemic one, and this calls for new priorities and objectives of research, especially

relative to the atherogenic effect of COPD.

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