

Original Research Article

Renin angiotensin system and pulmonary hemodynamics in chronic obstructive pulmonary disease

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ABSTRACT

Background: Pulmonary hypertension in chronic obstructive pulmonary disease (COPD) due to chronic alveolar hypoxia is probably the main contributor to the pathogenesis of pulmonary hypertension in COPD. Angiotensin II is a potent vasoconstrictor in renin angiotensin aldosterone system (RAAS), it has been shown to promote growth response in vascular smooth muscle cell contributing towards pulmonary hypertension. So, the Echocardiographically measured MPAP and its correlation with RAAS in patients of COPD was evaluated.

Methods: A prospective observational study was done in 32 patients with COPD and 10 age matched healthy, non-smoker subject included as controls. Stable patients requiring no change in their medication in the previous four weeks and not having had an acute exacerbation in that period were included. MPAP was calculated. Measurement of Ang II and aldosterone was done.

Results: Thirty-two cases of COPD, meeting inclusion criteria were enrolled comprising of 32 males and the mean age of patients $\pm 2sd$ was (55.6 \pm 16.8), while mean age of controls $\pm 2sd$ was 49.60 \pm 5.56. Arterial blood gas analysis, PaO₂ was ranged from (mean $\pm 2sd$ 75.44 \pm 12.1), PaCO₂ ranged from (mean $\pm 2sd$ 41.36 \pm 3.79) and SpO₂ ranged from (mean $\pm 2sd$ 94.03 \pm 2.74). Mean $\pm 2sd$ of plasma Ang II in COPD cases was (4.9 \pm 3.8) ng/dl, significantly higher in comparison with controls ($p < 0.001$). Mean $\pm 2sd$ of plasma ACE activity was (51.12 \pm 26.9) in COPD. Mean $\pm 2sd$ of plasma aldosterone was (182.35 \pm 364.2) in COPD cases with significant ($p < 0.01$). The MPAP in COPD cases was (mean $\pm 2sd$ 34.53 \pm 7.70).

Conclusions: Use of Doppler has the advantage of being noninvasive and has been shown to be extremely reproducible in evaluation of MPAP and CO. The increased level of Ang II with increase MPAP in the present study would suggest that this may be a suitable model for investigating effects of novel vasodilator drugs for the treatment of pulmonary hypertension developed due to COPD.

Keywords: Aldosterone, Angiotensin, COPD, Pulmonary hypertension, Renin

INTRODUCTION

Pulmonary hypertension is the main cardiovascular complication of chronic obstructive pulmonary disease (COPD), it is associated with substantial increase in morbidity and mortality.¹⁻³ Structural remodeling of the pulmonary vasculature as a consequence of chronic

alveolar hypoxia is probably the main contributor to the pathogenesis of pulmonary hypertension in COPD.⁴ Other factors may be involved including hyperinflation and loss of alveolar capillaries in emphysema.⁵ Hypoxia and Hypercapnia both increases pulmonary vasculature and induces pulmonary hypertension (PH).⁶ Long term oxygen therapy improves survival but does not revise the

pulmonary vasculature changes.⁷ There is imbalance in vasoactive factors and the definite role of these vasoactive factors in PH has been studied, the biochemical and hormonal mediators of hypoxia induces PH are poorly defined.

Angiotensin II (Ang. II) is a potent vasoconstrictor and in COPD there is activation of renin angiotensin aldosterone system (RAAS).^{8,9} Direct elevation of Ang. II and Angiotensin converting enzyme (ACE) activity in relation to mean pulmonary arterial pressure has not been explored. Indeed Ang. II has been shown to promote growth response in vascular smooth muscle cell.¹⁰ So Ang. II could contribute directly to vascular remodeling.

Therefore, the present study has been carried out to evaluate the role of RAAS in patients of COPD and abnormalities of Arterial blood gas (ABG) in relationship with the echocardiographically measured MPAP. Moreover, pulmonary artery pressure rises markedly in COPD patients on minimal exertion and it is likely that pulmonary hypertension contributes partly to exercise limitation in these patients. The aims and objectives of the present study were to evaluate and analyze abnormal Arterial blood gas (ABG) and its correlation with the echocardiographically measured MPAP and the role of RAAS in patients of COPD.

METHODS

A Prospective observational study was done in 32 male COPD patients in the outpatients setting in a teaching institute, New Delhi. Ten age matched healthy, nonsmoker subject included as controls. The study was approved by the institutional review committee and an informed consent was taken.

The diagnosis of COPD was based on the criteria of British thoracic society and established by history of smoking greater than 20 pack years, cough with expectoration accompanied by progressively increasing dyspnoea on exertion. Patients of asthma were excluded from the study. Only stable patients requiring no change in their medication in the previous four weeks and not having had an acute exacerbation in that period were included.

The inclusion criteria included an FEV1/FVC ratio of less than 70% and a post dilator increase in FEV1 of less than 12% and 200ml from the initial value. Patients with clinical cor pulmonale, congenital, rheumatic or any valvular heart disease, systemic hypertension, coronary artery disease and any other past or concurrent pulmonary disease, diabetes mellitus, renal failure, carcinoma, connective tissue disorder and liver disease were excluded clinically and on the basis of biochemical test where relevant. None of the patients consumed alcohol on regular basis or had any dietary deficiency of vitamins (B group) or had any disease such as malabsorption that could cause vitamin deficiency. These patients were not

on any medication other than that required for COPD. These drugs included inhaled bronchodilator (salbutamol and ipratropium bromide) and corticosteroids (budesonide, beclimethasone or fluticasone)

The investigations were carried out in the morning between 10am to 12 noon. The patients were asked not to take bronchodilator 12 hour before the tests. Inhaled corticosteroids were allowed in the same dosage as being already taken. A light dinner was permitted at least 12 hours before the test. Spirometry was performed on dry, rolling -seal spirometer of the Transfer test C model lung function machine (P.K.Morgan, Kent, UK).

Maximal expiratory flow volume (MEFV) curves were obtained. Three acceptable and at least two reproducible curves were obtained in each subject. The highest FEV1 obtained were recorded. Reference equations for north Indian adults were used to calculate the percentage-predicted values. Arterial blood gas analysis was carried out on a sample drawn from the radial artery in a heparinized glass syringe and measured in instrumentation ABG machine (model 1312).

Echocardiographic assessment was done by using all standard echocardiographic windows (parasternal long axis view, parasternal short axis view, apical four chamber view, subcostal view). Following M-mode and 2D assessment of morphology, color flow mapping was done to identify the pulmonary and tricuspid regurgitant jets. A pulsed doppler study was next applied confirm and localize the above regurgitant jets and then continuous wave doppler study was done to record their maximal velocity. MPAP was calculated from the right ventricular outflow tract acceleration time using Mahan's equation.

Measurement of Ang. II and aldosterone was done in 10 ml venous sample collected in chilled tube containing EDTA (12.5mmol/l) and o-phenanroline (2.6mmol/l). It was placed immediately on ice, centrifuged at 4°C at approximately 6000 rpm for 4 minutes and plasma was stored in aliquotes at -80°C till the time of measurement, 5ml venous sample was also collected at the same time for measurement of angiotensin converting enzyme activity in tubes containing Acid citrate dextrose (ACD) (1%). It was centrifuged at 37°C at 3000rpm for 10 minutes and plasma was stored at -80°C.

Procedure

By ELISA kit (Peninsula Laboratories, USA) measured plasma ANG II level. Ang. II was extracted from plasma on C 18 sep columns by using 1% trifluoroacetic acid (TFA) in 95% distilled water and 60% acetonitrile in 1% TFA in 39% distilled water. The eluent was evaporated to dryness by lyophilisation and dried extract was stored at -200°C. The assay of Ang. II resides in the competition between biotinylated peptide for antibody binding site with the standard peptide and the sampled Ang. II. Separation of bound antibody from free fraction is

achieved by washing and SA-HRP, TMB is allowed to react with the bound HRP. The color intensity depend on quantity of biotinylated peptide bound to immobilized antibody. The minimum detectable range for kit was .02-.04 ng/ml. the range of the kit was 0-20ng/ml and it has 100% cross reactivity with Ang. II (human), val 5 Ang II (human) and 0.9% with renin substrate. Plasma aldosterone was measured by Radioimmunoassay (immunotech, France) and expressed as pg/ml. aldosterone assay was performed using a radio immunologic method based on a polyclonal antibody and a radio iodinated tracer.

The technique proposed involves the separation of the free fraction and it has 100% cross reactivity with aldosterone and .002% with 18 OH-corticosteroid. Within assay and between assay variability was 8.2% and 14%.

The ACE activity was measured spectrophotometrical method of Buttery et al using the synthetic substrate, N-{3-(2-furyl)acryloyl}-L-phenylalanyl-glycylglycine (FAPGG) (SIGMA). The ACE activity was measured in U/L.¹¹

RESULTS

Thirty-two cases of COPD, meeting inclusion criteria were enrolled comprising of 32 males and the majority of the patients were in age group ranged from 32 to 72 years mean±2sd (55.6±16.8). The age of controls ranged from 38 to 56 years old. The mean±2sd 49.60±5.56. All the controls were nonsmoker and in COPD pack years of smoking is (mean ±2sd 46±4.43) years. Seven patients were classified having stage II COPD and eight patients were in stage III and two patients were in stage I COPD (Table1).

Table 1: Age sex distribution.

Characteristic	Control N=10	COPD N=32
Age (in years)	49.60±5.56	55.6±16.8
Sex		
Male	9	32
female	1	
Duration of smoking	No history of smoking	27.5±9.16
No of cigarettes	---	31.21±10.66
Pack year of smoking	---	41.62±18.48

Expressed as mean ± 2standard error

Table 2: ABG analysis

Abg	Range	Copd patients
pH	7.30-7.49	7.30±5.35
PaO ₂	71.0-80.23	75.44±12.1
PaCO ₂	39.5-43.6	41.36±3.79
HCO ₃	22.7-26.9	25.25±2.7
SPO ₂	88.2-96.5	94.03±0.74

Expressed as mean±2standard error

Arterial blood gas analysis, PaO₂ was (mean±2sd 75.44±12.1), PaCO₂ was (mean±2sd 41.36±3.79) and SpO₂ was (mean±2sd 94.03 ±0.74). Bicarbonates were (mean±2sd 25.25±2.7) (Table 2).

In the controls mean ±2sd of plasma Ang. II was (0.37±0.30) while in COPD it was (4.9±3.8) ng/dl. The plasma Ang. II level in control and cases compared by student t test showed that plasma Ang. II level were significantly (p < 0.001) higher in COPD cases (Table 3).

Table 3: ACE, Aldosterone and Ang II.

Components	Control N=10	COPD N=32	P value
Ace activity	41.2±15.22	51.12±26.9	<0.01
Aldosterone	57.24±18.99	182.35±364.2	<0.01
Ang. II	0.37±0.3	4.9±3.8	<0.001

P<0.01 significant

Table 4: Correlation between MPAP and plasma Ang II, ACE Activity and Aldosterone in patients.

COPD N=32	R (Spearman's coefficient of correlation)	P
Ang II	0.55	<0.01
ACE Activity	0.14	ns
Aldosterone	0.26	ns

P<0.01 significant, ns is not significant

In the controls mean ±2sd of plasma ACE activity was (41.2±15.22) while in COPD it was (51.12±26.9). The plasma ACE activity showed not much difference but, in some cases, it was disproportionately high. In the controls mean ±2sd of plasma aldosterone was (57.24±18.99) while in COPD cases it was (182.35±364.2). The plasma level of aldosterone as compared by student t showed (p<0.01). The MPAP in COPD cases was (mean±2sd 34.53±7.70) (Table 4).

DISCUSSION

The result of the present study showed that there is direct correlation of Ang. II with MPAP in stable patients of COPD. This suggests that the elevated levels of Ang. II in cor pulmonale, along with hypoxemia may be involved in pathophysiology of raised peripheral vascular resistance. In our study we have not found direct correlation of Ang. II with PaO₂ and SpO₂. It is also in contrast of studies which show the direct presser effect of Ang. II also facilitate the vasoconstrictor response to hypoxemia as suggested by animal studies.¹²⁻¹⁴ However, hypoxemia need not be present at all the time. Even transient or shortterm hypoxia as can occur during exercise, acute exacerbation or in sleep may be sufficient to cause increase in MPAP and can cause pulmonary hypertension. In another study PaO₂ and PaCO₂ was not found to correlate with MPAP as measured by cardiac catheter (wright). The pulmonary vasculature has an inherently lower resistance as compared to systemic

circulation. So Ang. II has greater response in pulmonary circulation.^{15,16} So, a lower level of basal vascular tone in pulmonary circulation produces more presser effect of Ang. II on infusion in men and their might be the possibility that the pulmonary vascular response as measured as MPAP in our patient might be attenuated either because of raised basal level of vascular tone or as a consequences of tachyphylaxis due to persistently high level of Ang. II found in COPD patients. So, the MPAP measured in COPD may not be giving us clear picture of pathophysiological changes occurring in Cor Pulmonale.

Although patients were clinically stable, in most of them there was a disproportionate increase in the ACE activity. Since ACE is primarily membrane bound enzyme plasma ACE activity may not accurately reflect the in vivo conversion rate of Ang. I to Ang. II. Variation in ACE activity is known to exist in the population as the result of insertion/deletion polymorphism of ACE gene.^{17,18}

In another study in chronic stable COPD patients elevated ACE activity was observed raising the possibility that in this condition different isoenzymes with higher specific activity might be released.¹⁹ In the setting of cor pulmonale, role of drugs such as ACE inhibitors have been studied. There is however conflicting evidence in the literature regarding their role in reduction of MPAP even with the long-term use of this drugs.²⁰⁻²⁶

Our finding of raised MPAP in these patients is also in favor of not finding correlation with ACE activity. Plasma Aldosterone level increases in COPD when hypoxia and hypercapnia are present. In our patients also increase in aldosterone was found as compared to controls although the difference was significant. It was not correlated with high MPAP.

CONCLUSION

Use of Echodoppler to measure MPAP and Cardiac output (CO), Doppler has the advantage of being noninvasive and has been shown to be extremely reproducible in evaluation of MPAP and CO. The increased level of Ang. II with increase MPAP in the present study would suggest that this may be a suitable model for investigating effects of novel vasodilator drugs for the treatment of pulmonary hypertension developed due to COPD.

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