Original Research Paper

Volume-9 | Issue-8 | August - 2019 | PRINT ISSN No. 2249 - 555X

Medical Science

EVALUATION OF ANGIOTENSIN II AND ACE ACTIVITY IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Dr Preeti Chauhan Associate Professor, Department of Biochemistry, Lady Hardinge Medical College, New Delhi-01

Dr Parijat Gogoi* Associate Professor, Department of Biochemistry, Lady Hardinge Medical College, New Delhi-01 *Corresponding Author

Dr Rajesh Chetiwal Department of Medicine, ESI PGIMSR, Basaidarapur, New Delhi

ABSTRACT COPD represents an important public health challenge and is a major cause of chronic morbidity and mortality throughout the world. Salt and water retention eventually resulting in edema formation is a frequently occurring feature in advanced COPD patients and it indicate a poor prognosis. This study was done to explore the potential role of Renin Angiotensin Aldosterone System (RAAS) in the pathogenesis of salt and water retention and pulmonary hypertension in patients of acute exacerbation of COPD. Our study reveals that in such patients there is significant alteration of RAAS system which correlated with changes in ABG. These alterations may play an important role in the pathogenesis of salt and water retention and pulmonary hypertension.

KEYWORDS : Chronic obstructive pulmonary disease (COPD), Renin angiotensin aldosterone system (RAAS), Angiotensin II (Ang II), Angiotensin Converting Enzyme (ACE), Arterial blood gas (ABG),Arginine Vasopressin (AVP)

INTRODUCTION

COPD represents an important public health challenge and is a major cause of chronic morbidity and mortality throughout the world. The Global Burden of Disease studies ranked COPD as the sixth commonest cause of death worldwide in 1990, and it was predicted to become the third commonest cause by 2020[1].

It is a chronic inflammatory disease, and in some patients, extra pulmonary manifestations can worsen prognosis[2]. Salt and water retention eventually resulting in edema formation is a frequently occurring feature in advanced COPD patients. Edema formation in such patients indicate a poor prognosis[3,4]. This is usually attributed to cor pulmonale or "backward failure" of the right ventricle, secondary to development of pulmonary hypertension that frequently complicates severe COPD. However, the demonstration that the cardiac output remains normal at rest has led to the exploration of alternate mechanisms such as abnormalities of salt and water regulatory systems including Renin Angiotensin Aldosterone system(RAAS), Arginine vasopressin (AVP) and the Atrial Natriuretic Peptide[5,6,7].

Severe hypoxia, as at high altitude and during acute respiratory failure in COPD have been shown to stimulate renin activity and increase aldosterone level due to reduced renal blood flow[8,9]. However, chronic hypoxia, as in cyanotic congenital heart disease or interstitial fibrosis does not cause edema[10]. Increased plasma level of renin activity and aldosterone levels are assumed to play an important role in impaired renal water excretion function with aldosterone contributing to sodium retention and increased AVP level to hyponatremia[11,12]. The stimulus for these alteration is not clear. Although derangements of arterial blood gases have been implicated, their effect on RAAS or role in renal abnormality has remained unclear[11,13].

The impairment in sodium and water extraction is related to the degree of hypoxia, while hypercapnia, being a systemic vasodilator, acts by evoking a reflex increase in sympathetic activity and may also act indirectly at level of distal tubule through increased aldosterone production[14,15].

The alteration in the final product in the RAAS activation, Ang II and the ACE activity have not been studied in AECOPD. Ang II might stimulate AVP directly, but this notion was debated[13]. Ang II, being a potent vasoconstrictor, especially of the pulmonary vasculature, may play a role in elevation of the pulmonary artery pressure that usually occurs during episodes of AECOPD. Very few studies are available on the potential role of Ang II and ACE activity in AECOPD. Further, the association of these changes with hypoxemia and hypercapnia is not well established.

Hence, with the objective to address the above gaps in knowledge, we carried out this study to investigate the alterations in these components of RAAS during AECOPD and relate them to changes in ABG abnormalities.

MATERIAL AND METHODS

The study was carried out in the outpatient (emergency room) setting of a tertiary care hospital. 22 patients of COPD, presenting with an acute exacerbation and acute hypoxaemic-hypercapnic respiratory failure were included and 20 age-matched healthy volunteers were included as controls. The study was approved by the Institutional Ethics Committee and written informed consent was taken from the participants.

The diagnosis of COPD had been established earlier based on their clinical presentation and spirometry as per the GOLD criteria[16], and they were receiving severity-appropriate regular treatment using one or more of the inhalational drugs. The diagnosis of an acute exacerbation was made clinically by an acute increase in intensity of symptoms over the usual day-to-day variation and necessitating an emergency room visit. None of these patients had a history of any other concurrent respiratory or systemic disease. Prior to the presentation, none of the patients had been documented to have cor pulmonale or respiratory failure.

The ABG analysis in the patients were done before initiating treatment. Plasma Ang II level was measured by ELISA kit. Ang II was extracted from plasma on C 18 sep columns by using 1% trifluroacetic 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 the dried extract was stored at -20^{0}C.

The ACE activity measured by spectrophotometric method of buttery *et.al*. using the synthetic substrates, N- {3-(2-furly) acryloly}-L-phenylalanylglycylglycine (FAPGG) (SIGMA)[17].

Plasma Aldosterone was measured by Radioimmunoassay by a method based on polyclonal antibody and a radio iodinated tracer.

STATISTICAL ANALYSIS

The data obtained was analysed using SPSS 19 and Graphed prism 4.01 software. It was expressed as mean ±SD and 95% confidence intervals. Student's unpaired t-test was applied to compare data of patients and controls. Welch correction was applied where the assumption of equal variances was violated and correlations were computed using Pearson correlation coefficient. For data that was not normally distributed, non-parametric tests, Mann Whitney u test and Spearmen rank coefficient tests were applied. A multiple linear regression was carried out to identify the determinants of the three dependable variable.

RESULTS

The mean ±2SD age of the patients was 52.68 ± 8.39 and that of controls was 49.6 ± 5.56 years (p>0.05). All patients were smokers with a history of 42.77 ± 19.48 pack-years of smoking while the controls were non-smokers. All patients had a normal ECG except one who had a right axis deviation. None of the patients had a clinical evidence of cor pulmonale.

The level of Ang II was increased in patients with more than 30-fold higher values in patients than in controls (12.77±5.76 and 0.37±0.30, respectively, p<0.0001, mean difference 12.40 ± 1.23, 95% CI 9.84 to 14.97). **(Fig 1)**

Plasma ACE activity in patients was greater at 85.14±33.11 compared to controls in whom the values were 41.22±15.22 (p<0.001), mean difference 43.94 ± 11.03, 95% CI of 21.40 to 66.47**. (Fig 2).**

In patients, the Aldosterone levels were higher (95.55 ±64.03) as compared to controls (57.24±18.99) (p<0.05), mean difference 38.31 ± 14.91, 95% CI of 7.70 to 68.91. **(Fig 3)**

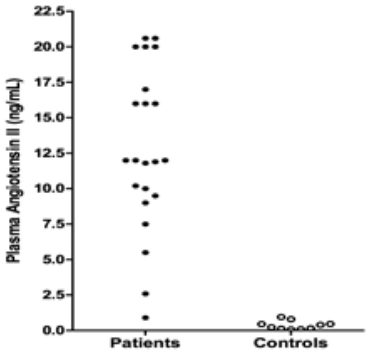

Fig 1: Plasma Angiotensin II levels in patients and controls

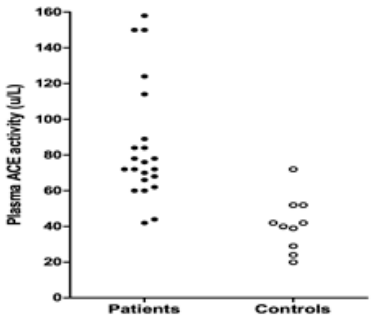

Fig 2: Plasma ACE activity in patients and controls

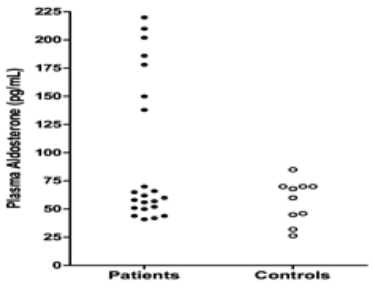

Fig 3: Plasma Aldosterone levels in patients and controls

Serum osmolality (mosm/kg) was significantly lower in patients (280.43±9.34) than in controls (285.13±2.55) (p<0.05) with a mean difference of -4.69 ± 2.15 and 95% confidence interval of -9.12 to -0.2792.

Arterial blood gas analysis showed a pH of 7.30± 5.4, $PaCO_2$ 52.6±6.39 mmHg, PaO_2 49.87±9.48 mm Hg and bicarbonate 29.98±5.28 meq/L in the patients. Table 2 shows the correlations between the arterial blood gas parameters and the RAAS study parameters.

Table 2. Correlations between RAAS and arterial blood gas parameters in patients

Sl.No.	Parameters	pH r	PaO_2 r	$PaCO_2$ r
1	Plasma Angiotensin II	0.56**	0.11	-0.08
2	Plasma ACE levels	-0.13	0.19	0.47*
3	Plasma Aldosterone	0.27	0.22	0.01

*p<0.05, **p<0.01, r - Spearman's coefficient of correlation

Eight patients had uncompensated acidosis while it was compensated in the remaining 14. Table 3 shows the comparison of RAAS parameters in patients with compensated and uncompensated acidosis.

Table 3. RAAS parameters in patients with compensated and uncompensated acidosis

Parameters	Compensated acidosis	Uncompensated acidosis
Plasma Angiotensin II	15.21±5.51**	8.51±3.26
Plasma ACE levels	77.79±28.82^{ns}	98.00±38.07
Plasma Aldosterone	108.50±70.44^{ns}	72.88±46.48

**p<0.01 ns: not significant p>0.05

DISCUSSION

The present study shows that patients with COPD in acute exacerbation with acute respiratory failure, and without any evidence of cor pulmonale, have an activation of RAAS system, showing increase in Ang II, ACE and Aldosterone.

In contrast to our findings, Milledge *et. al.* reported a decrease in plasma ACE activity during hypoxia[18]. Since ACE is primarily a membrane bound enzyme, plasma ACE activity may not accurately reflect the in vivo conversion rate of Ang I to Ang II[19]. Moreover, variation in ACE activity is known to exist in the population as the result of an insertion/deletion polymorphism of ACE gene. Individuals homozygous for the deletion have a higher ACE activity[20,21]. We have not done genotyping in our patients. In another study in chronic stable COPD patients, elevated ACE specific activity but normal ACE activity was observed, raising the possibility that in this condition different isozymes of ACE with higher specific activity might be released[22].

A higher ACE activity could potentially explain the elevation of Ang II in our study subjects. Umran Toru et.al. in their study had stated that activation of ACE pathway may lead to pulmonary hypertension through the vasoconstrictor effects of Ang Ii[23].

This pulmonary vasoconstriction and hypoxemia caused by Ang II could contribute to ventilation perfusion imbalance during acute exacerbation of COPD[24,25]. Peacock AJ, Mattews A. *et.al*. had observed elevated levels of Ang II in stable patients with airflow obstruction and arterial hypoxemia[26]. It has also been reported to promote the growth of cultured vascular smooth muscle cells, which may play a role in vascular remodeling leading to pulmonary hypertension[27,28]. It also stimulates the secretion of AVP out of proportion to the serum osmolality leading to syndrome of inappropriate ADH secretion. Ang II may also be generated via an alternate pathway, independent of ACE through the action of inflammatory protease [19,29].

In this study the variation in Ang II was significantly correlated with changes in pH. Interestingly, we found Ang II level to be higher in patients with compensated respiratory acidosis compared to those in whom acidosis had not been compensated, suggesting that Ang II increase throughout the compensatory process and reaches peak when the acidosis is compensated. This significant correlation between Ang II levels and alteration in arterial blood gases was not observed in previous studies.

The increased Aldosterone levels in our study subjects is consistent with an increased RAAS activity during acute exacerbation and would promote salt and water retention in the distal parts of the nephrons.

The present study shows that salt and water retention may occur in AECOPD even without evidence of cor pulmonale and is likely the result of abnormalities in blood gases and activation of RAAS. These factors together with severity of COPD could also be contributors to the pathogenesis of pulmonary hypertension.

CONCLUSION:

Activation of RAAS in AECOPD gives us an insight into the

pathogenesis of increase in pulmonary arterial pressures and edema formation in AECOPD. It also offers a rationale for addition of ACE inhibitors and angiotensin receptor blocking drugs in such cases.

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