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The Effect of Arterial $PaCO_2$ in COPD Exacerbations with and without Peripheral Edema

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Introduction. Studies often suggest hypoxemia is an important factor for sodium retention in chronic obstructive pulmonary disease (COPD), although hypercapnia is also associated with sodium retention in these patients. Hence, we have presented the major role of $PaCO_2$ in edema due to COPD.

Method. COPD patients who were hospitalized due to exacerbation were enrolled in the study and divided into two groups: with and without edema. Exclusion criteria included primary hepatic diseases, nephrotic syndrome and other renal diseases, left heart failure, or using drugs that would interfere with these organs or endocrine function. Data were coded and analyzed by SPSS software. Arterial blood gas variables including bicarbonate, pH, and PaO_2, $PaCO_2$ and O_2 saturation, and FEV1, FVC, FEV1/FVC were measured and compared between the groups.

Results. No significant difference was found between the averages of bicarbonate, pH, PaO_2, O_2 saturation, FEV1, FVC and FEV1/FVC in COPD in the two groups. $PaCO_2$ levels were significantly higher in patients with edema, compared to those without edema ($p = 0.05$). A reverse and significant correlation between $PaCo_2$ and FEV1 levels ($p = 0.03$) ($r = -0.501$) was observed in patients with edema.

Conclusion. This study suggests that hypercapnia is a major factor in causing edema in COPD patients compared to hypoxemia.

Key words: Arterial, $PaCO_2$, Edema, Chronic obstructive pulmonary disease.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) includes a group of respiratory diseases that are characterized by air flow limitation, and is a major problem for public health worldwide because it significantly impairs health status [1, 2]. The most important systemic complications of this disease are activity intolerance, musculoskeletal dysfunction, osteoporosis, metabolic disorders, anxiety, depression, cardiovascular diseases, and death [3-5]. Men are more at risk than women, and the maximum prevalence rate of COPD is in the seventh and eighth decades [6]. Smoking is considered the most common risk factor for COPD [7]. Capillary dynamic changes and sodium retention in the kidneys are two basic requirements for peripheral edema development. Also, there are some evidences about the association between edema and right heart failure (cardiac theory) [8]. The pathogenesis of edema in cor-pulmonale is different from the other types of heart failure. In this disorder, the resting cardiac output and glomerular filtration rate (GFR) and during activity indexes are often normal or remain near normal. It seems that edema occurs in hypoxemic patients only, PaO_2 might be the cause of sodium retention. On the other hand, hypercapnia with a proportionate increase in bicarbonate reuptake minimizes the changes in pH. Increase in bicarbonate absorption on proximal tubes leads to water and NaCl reuptake, so it might cause edema [9]. Although the cardiac theory might have a role in some patients, edema is developed in the absence of heart dysfunction in many patients. The fluid homeostasis disorder in COPD might have a nephrogenic base. There might be a direct relation between CO_2 and sodium retention; if so, the most important factor would be the sodium-hydrogen antiporter in proximal tubules [10]. Water retention and hyponatremia appear in the last stages of COPD, and edema is associated with poor prognosis. Gas exchange disorders lead to hormonal imbalances including renin, angiotensin II, aldosterone, and atrial natriuretic peptide (ANP), vasopressin and endothelial factors. The systemic response to

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hypercapnia decreases renal blood flow causing edema and water and sodium retention causing hyponatremia. Changes in renal blood flow might be caused by a reflex mechanism depending on the afferent nerves of the kidneys and stimulation of chemical receptors [11, 12]. Edema is considered to be the worse prognostic factor [13]. The aim of this study was to investigate the role of $PaCO_2$ in edema in COPD patients.

MATERIALS AND METHODS

Patients and assessments

This cross sectional study was conducted on patients hospitalized due to exacerbation during 2013, and divided into two groups: with and without edema. Based on medical history, physical examination and chest radiography, patients with other diseases such as primary hepatic diseases and hypoalbuminemia, nephrotic syndrome and renal diseases, left heart failure and endocrine diseases, and interaction between drugs and liver, kidney, or endocrine function, were excluded from this study.

In order to rule out left heart failure as a justifying factor for edema, an echocardiography was performed by an experienced cardiologist for all the patients. Arterial blood gases (ABG) were recorded at the patient's arrival. Arterial blood sample was taken from radial artery and sodium, potassium, urea and creatinine serum and a spirometry test were also conducted. Forced expiratory volume per one second (FEV1), forced vital capacity (FVC) and FEV1/FVC were estimated by spirometry (Spiro lab II), and maximum levels were chosen for the three maneuvers.

COPD diagnosis was confirmed via medical history, physical examination, chest X-ray and pulmonary function test (PFT).

Written informed consent was initially obtained from all patients. The study protocol was approved by the Ethics Committee of the Mashhad University of Medical Sciences.

Statistical analysis

The data was expressed as mean ± standard deviation if distribution of data was normal or median (minimum, maximum) if distribution was not normal. Student'test or Mann-Whitney U were used to compare the two groups, depending on the distribution of variables. The P value <0.05 was considered as statistically significant. Statistical analyses were conducted by SPSS software (version 11.5).

RESULTS

There were 40 individuals studied in this research, 20 with edema and 20 without. Patients' mean age in the edematous and non-edematous group was 66 ± 11.95 and 60.45 ± 11.95 years, respectively. No significant difference was detected between groups (p = 0.14).

Of the individuals 77.5% were men and X^2 test results showed no significant difference in sex between the two groups. Fourteen patients in the edema group, and 16 in the other group were suffering from severe or very severe COPD based on the GOLD criteria.

No significant difference was found among the averages of ABG variables including bicarbonate, PH, PaO_2, O_2 saturation and spirometric variables in COPD patients with and without edema. The $PaCO_2$ levels were significantly higher in patients with edema compared to those without (p = 0.049) as shown in Table 1.

Table 1
Comparison of gasometric and spirometric variables in COPD patients with and without edema

		Edematous group (n = 20)	Non-edematous group (n = 20)	P value
Gasometric parameters	pH	7.37 ± 0.10	7.38 ± 0.06	0.71
	$PaCO_2$ (mm Hg)	63.90 ± 25.28	50 ± 17.09	0.049
	HCO_3 (mEq/L)	34.6 ± 15.15	28.9 ± 10.30	0.17
	O_2SAT (%)	84.15 ± 15.36	79.30 ± 17.37	0.36
	PaO_2 (mm Hg)	64.95 ± 32.95	58.85 ± 30.87	0.55
Spirometric parameters	FEV1	40.30 ± 12.08	39.55 ± 16.95	0.93
	FVC	55 ± 12.08	54.35 ± 16.75	0.88
	FEV1/FVC	57.95 ± 10.27	55.6 ± 14.69	0.56

The results proved an association between arterial blood gas and spirometric variables in COPD patients with and without edema. Hence, there was an inverse significant correlation between $PaCO_2$ and FEV1 levels in patients with edema (p = 0.03) (r = -0.501) although there was

no significant correlation between these two in the other group (p = 0.61). Also, no other significant correlation was found between the other spirometric and arterial blood gas variables between groups.

DISCUSSION

Capillary dynamic changes and sodium retention are the two main mechanisms of edema. $PaCO_2$ is suggested to be more effective in sodium retention than heart dysfunction and a positive correlation has been detected between CO_2 and sodium retention in previous studies [6]. In our study $PaCO_2$ levels were significantly higher in patients with edema and a reverse and significant correlation was observed between $PaCO_2$ and FEV1 levels in the edematous group. Hodgkin has reported a higher mortality in COPD patients with edema [14]. Howes *et al*. focused on renal hemodynamics in order to test the hypothesis of nephrogenic vasoconstriction regression after oxygen therapy. They found that mean arterial velocity increases in kidneys after oxygen therapy in normocapnic hypoxemic patients, but not in hyercapnic hypoxemic patients. Decrease in renal blood flow causes GFR reduction and, therefore, sodium retention [15, 16]. Hypoxemia and hypercapnia have an inverse relation with renal blood flow and the ability of water and sodium excretion. Total body sodium is enhanced in COPD patients with or without edema [17]. Skwarski *et al.* showed the imbalance in endogenous urinary dopamine output during hypoxic exacerbation of COPD [18]. Many researches indicate that hypoxemia in COPD patients causes a reduction in renal blood flow although the exact mechanism is unknown. Additionally, sodium excretion disorders are associated with the hypercapnia degree [16-20]. In our study, $PaCO_2$ levels were significantly higher in patients with edema in comparison with the non-edematous group, because of the correlation between hypercapnia and sodium excretion disorders leading to edema. In Anand *et al*.'s researches done on 9 COPD patients admitted with respiratory failure, water and sodium retention in patients with edema was considered to be an outcome of hypercapnia that affects the kidneys and neurohumoral system [20]. Hypoxemia in the presence of hypercapnia also has a role in sodium retention in these patients based on Mannix *et al*.'s and Sin *et al*.'s study [21, 22], because hypoxemia influences urinary sodium excretion by renal vasoconstriction [22].

In our study, the gasometric indexes except $PaCO_2$ and spirometric variables showed no significant difference between the two groups. Edema is associated with gas exchange disorders [23] and, therefore, water retention in COPD patients is considered as a consequence of ion chemical or nephrogenic hemodynamic disorders [24]. Hypoxemia causes a great reduction in urinary sodium excretion, while no changes occur in water excretion. Mild and moderate hypoxemias increase the renal blood flow in normal individuals and only severre hypoxemia (PO_2<40) can reduce it [25].

In this study, COPD severity was defined by FEV1 and the GOLD criteria, most of the patients in both groups were classified into a severe or very severe grade. According to the present study, edema in COPD has a different pathogenesis other than heart failure. Hence, $PaCO_2$ might be the underlying cause of sodium retention in this disease instead of heart dysfunction, and permanent hypercapnia in COPD patients often leads to disorders in water and sodium excretion. While a hypoxemic-hypercapnic state has a crucial impact on sodium retention in COPD patients with significantly higher $PaCO_2$ levels in edematous patients, hypercapnia can be considered the more probable factor for developing edema.

The main limitation of this study was the small sample size, and so we suggest investigating our finding in larger clinical trials.

CONCLUSION

Hypercapnia has a leading role in edema due to COPD, leading to sodium retention and edema.

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Conflict of Interests: Authors have no conflict of interest.

Introducere. *Hipoxia este un factor important pentru retenţia sodiului şi boala pulmonară cronică obstructivă (BPOC) deşi şi hipercapnia este asociată cu retenţia de sodiu la aceşti pacienţi. Articolul se concentrează pe rolul pe care îl joacă $PaCO_2$ pentru apariţia edemelor la pacienţii cu BPOC.*

Materiale şi metode. *Au fost incluşi în studiu pacienţi spitalizaţi cu BPOC. Aceştia au fost împărţiţi în două grupe – cu şi fără edeme. Criteriile de excludere au fost boli hepatice, sindrom nefrotic sau alte afectări renale, insuficienţă cardiacă stângă, sau medicaţie care ar fi putut să interfere cu funcţia endocrină. Datele au fost analizate utilizând softul SPSS. Au fost studiate gazele sanguine (PaO_2, $PaCO_2$), pH, nivelurile ionului bicarbonat alături de VEMS (volumul expirator maxim în prima secundă), CVF (capacitatea vitală forţată) şi raportul VEMS/FVC.*

Rezultate. *Nu au fost găsite diferenţe semnificative între cele două grupuri exceptând valorile $PaCO_2$ care au fost mai mari la grupul de pacienţi cu edeme ($p = 0.05$).*

Concluzii. *Studiul sugerează că hipercapnia este şi ea un factor determinant important pentru dezvoltarea edemelor la pacienţii cu BPOC.*

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