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Original Article

The correlation between increased serum aldosterone level and presence and severity of PAH in patients suffering COPD

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ABSTRACT

Background: Based on the recent evidences it is now hypothesized a relationship between the level of aldosterone and deterioration of PAH especially in COPD patients which susceptible to PAH. Hence, the present study aimed to assess the correlation between increased serum aldosterone level and presence and severity of PAH in COPD patients. Methods: This cross-sectional study was performed on 87 consecutive patients who suffered COPD. All participants initially assessed by electronic spirometer. The morning fasting venous blood samples were taken to assess the serum level of aldosterone by radioimmunoassay technique. Then all patients were examined using three-dimensional echocardiography. Results: we found no significant correlation between level of aldosterone and SPAP ($r = -0.066$, $p = 0.542$). in this regard, the mean level of aldosterone in patients with normal SPAP was 83.00 ± 35.78pg/ml, in patients with mild PAH was 82.41 ± 42.09pg/ml and in those with moderate PAH was 82.50 ± 46.19pg/ml with no difference across the groups ($p = 0.446$). Based on the ROC curve analysis, determining the level of serum aldosterone had low value to predict PAH in COPD patients (AUC = 0.480, P = 0.753). In a multivariable linear regression model (Table 2), the main determinants of PAH included increased RV size (beta = 0.237, p = 0.019) and reduced FEV1/FVC ratio (beta = -0.233, p = 0.019). Conclusion: Measuring aldosterone levels does not play a prognostic role in predicting the incidence or severity of PAH in patients with COPD.

Keywords: COPD, pulmonary hypertension, aldosterone.

Introduction

Chronic obstructive pulmonary disease (COPD) is the main reason for mortality and morbidity loading high direct costs on healthcare systems and governments [1]. Corpulmonale as a prognostic sign can result in poor outcome in such patients manifested by hemodynamic instability as well as increase in cardiac volumes and pressures such as increasing pulmonary artery pressure (SPAP) [2]. It has been shown that with an increase in the mean SPAP of 10 mmHg is associated with a greater than fourfold increase in mortality [3]. The actual incidence of pulmonary artery hypertension (PAH) in COPD remains unknown, however some studies have emphasized that about 6% of COPD patients may suffer developing PAH each year [4]. Overall, extrapolation of the achieved data shows that a notable number of patients with COPD will develop PAH over the course of disease and increase the risk for morbidity and mortality as a result. More interestingly, PAH can adversely affect both cardiovascular and pulmonary functional parameters such as reduced functional capacity and pulmonary reservation, exercise intolerance and even patients' quality of life. Pathologically, exposure to cigarette smoking can affect pulmonary vasculature manifested by intimal thickening of vessels, increase in longitudinal muscle caused by smooth muscle cell proliferation, increased elastin, and deposition of collagen [5, 6]. These changes in pulmonary vascular bed along with hypoxia, endothelial dysfunction, and vascular remodeling can predispose the pulmonary vasculature to PAH [7-9].

Recent studies obtained some clear evidences on the close association between the activation of renin-angiotensin – aldosterone system (RAAS) and the pulmonary vasculopathy

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which characterized by perivascular fibrosis and intimal hypertrophy [10, 11]. In other words, using aldosterone inhibitors can attenuate perivascular fibrosis and also improve cardiopulmonary hemodynamics leading improvement of pulmonary vasculature [12, 13]. In this regard, it is now hypothesized a relationship between the level of aldosterone and deterioration of PAH especially in COPD patients which susceptible to PAH [14]. Hence, the present study aimed to assess the association between increased serum aldosterone level and presence and severity of PAH in patients suffering COPD.

Exclusion criteria included: severe LV failure, valvular disease contain MS and MR, symptomatic RV failure, COPD exacerbation, pulmonary artery disease and consumer of drugs that reduce load and tonicity of vessels (diuretics, ACEI, ARBS and etc).

Materials and Methods

This cross-sectional study was performed on 87 consecutive patients who suffered COPD with PAH referred to pulmonology clinic at Loghman hakim and Shahid modarres hospital in 2017. All participants initially assessed by electronic spirometer (Multi-functional spirometer H1-801, Japan) to determine respiratory parameters of FEV1 and FEV1/FVC. The morning fasting venous blood samples were taken to assess the serum level of aldosterone using a special kit (Switzerland 2013) and by radioimmunoassay technique. Then all patients were examined using three-dimensional echocardiography to determine SPAP and also left ventricular (LV) and right ventricular (RV) size and function. In this regard, PAH was categorized as mild (SPAP 30-50 mmHg), moderate (SPAP 50-70 mmHg), and severe (SPAP higher than 70 mmHg). Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t test or Mann U test. The association between quantitative variables was assessed using the Pearson's or Spearman's correlation tests. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

The average age of patients was 61.60 ± 9.97 years ranged 36 to 87 years and 92% of them were male. Regarding cardiovascular risk profile, 19.5% of patients were diabetics, 20.7% had hyperlipidemia, 33% had HTN,17.2% were obese and 9.2% had family history of COPD. The mean duration of disease was 7.07 ± 5.73 years and the mean time for smoking was also 31.07 ± 12.38 years. The mean number of cigarette use was 37.43 ± 18.13 packs per year. Regarding respiratory parameters, the mean FEV1 was 71.07 ± 14.99 and the mean FEV1/FVC ratio was 63.67 ± 8.64. in respect to cardiovascular parameters, mild, moderate and severe PAH was revealed in 41.4%, 51.7%, and 6.9% respectively. The mean LVEF was 54.15 ± 6.07% that 18.4% had LVEF lower than 45%. The mean RV size was 29.72 ± 3.32mm. The mean TAPSE index was also estimated to be 19.77 ± 4.38. Regarding valvular abnormalities, 77.0% suffered mild tricuspid regurgitation (TR), 21.8% suffered moderate TR and 1.1% suffered severe TR. The mean SPAP was 32.93 ± 10.04 mmHg.the mean serum level of aldosterone was also 82.71 ± 38.69pg/ml. we found no significant association between level of aldosterone and SPAP ($r = -0.066$, $p = 0.542$) (Figure 1). in this regard, the mean level of aldosterone in patients with normal SPAP was 83.00 ± 35.78pg/ml, in patients with mild PAH was 82.41 ± 42.09pg/ml and in those with moderate PAH was 82.50 ± 46.19pg/ml with no difference across the groups ($p = 0.446$). Based on the ROC curve analysis (Figure 2), determining the level of serum aldosterone had low value to predict PAH in COPD patients (AUC = 0.480, P = 0.753). In univariate analyses, the mean SPAP value was not different between men and women ($p = 0.923$), between obese and non-obese patients (0.595), and also between those with and without history of COPD ($p = 0.178$). However, diabetics had higher level of SPAP when compared to non-diabetic patients (37.11 ± 9.03mmHg versus 31.91 ± 10.07mmHg, $p = 0.047$). Similarly, patients with hyperlipidemia had significantly higher SPAP than in those without hyperlipidemia (37.22 ± 9.81mmHg versus 31.81 ± 9.46mmHg, $p = 0.041$). As shown in Table 1, of quantitative parameters assessed in our study, the SPAP value was directly associated with duration of cigarette use, the number of cigarette used per year, RV size and also adversely associated with FEV1/FVC ratio. In a multivariable linear regression model (Table 2), the main determinants of PAH included increased RV size (beta = 0.237, $p = 0.019$) and reduced FEV1/FVC ratio (beta = -0.233, $p = 0.019$) (Table 2).

Discussion

As we mentioned earlier, there are some assumptions that increase the activity of the RAAS system and consequently the occurrence of hyperaldosteronism in accompanied with increased risk of perivascular fibrosis, endothelial dysfunction and therefore increased SPAP that there are very few studies in this regard. Especially, a comprehensive study has not been done in patients with COPD so far. The present study and for the first time examined the relationship between serum aldosterone levels and systolic pulmonary arterial pressure and therefore the risk of PAH occurring in patients with COPD. This study did not show a significant correlation between SPAP and serum aldosterone level. In this regard, it seems that the mechanisms other than RAAS play role in occurrence of

pulmonary hypertension in COPD patients. Of course, this insignificant relationship might also be affected by some study limitations. First, the small sample size may have a potential impact on the correlation between SPAP and aldosterone. Secondly, few patient with moderate to severe PHTN and the forte of was that the patients entering our study mostly had normal RV systolic function (with RVEF mostly in the normal range). In addition, However, some studies have confirmed the association between the increase in aldosterone levels and the occurrence of PAH. In a study by Maron et al [15], patients with PAH had higher levels of serum aldosterone and higher lung vascular resistance while no difference was revealed between the two groups in terms of left ventricular ejection fraction. In other words, their study showed that even in the absence of systolic dysfunction, the relationship between aldosterone levels and SPAP can be predicted. In the study of Safdar et al [16], the mean aldosterone level was 9.9 pg/ml, which was significantly lower in comparison with our study. But in their study and similar to our study, the amount of Aldosterone was not significantly related to SPAP. In the study by De Man et al [17], an increase in renin-angiotensin activity was accompanied by PAH exacerbation, which was not consistent with our study of the relationship between aldosterone levels and PAH severity.

In sum, although in our study elevation of aldosterone levels was not considered as a stimulant for the progression of PAH, in the second step, we looked for the factors involved with the occurrence of PAH. In this regard, increased RV size and reduced FEV1/FVC were introduced as two prognostic factors for the occurrence of PAH. Similar to our study in Jing et al survey [18], patients with PAH have significantly decreased FEV1/FVC. Also, in the study by Badano et al [19], the relationship between increasing RV size and PAH was fully confirmed. In fact, in his study, the occurrence of right ventricular hypertrophy and right ventricular dilatation in patients with PAH were confirmed in comparison with healthy subjects. Therefore, echocardiographic evaluation of patients, as well as respiratory volume assessments can play a prognostic role in predicting PAH severity for patients [19]. This is especially important for patients with COPD with a risk for heart failure.

Conclusion

According our finding measuring aldosterone levels doesn't not play a prognostic role in predicting the incidence or severity of PAH. In this regard, other factors such as assessing the increase in RV size or decrease in FEV1/FVC can play this role.

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Table 1: Association between measured parameters and SPAP value

Index	r coefficient	P value
Duration of cigarette use	0.228	0.034
Number of cigarette use per year	0.275	0.010
RV size	0.250	0.019
FEV1/FVC	-0.271	0.011
Age	0.055	0.621
Disease duration	-0.020	0.856
FEV1	0.094	0.389
LVEF	0.001	0.993

Table 2: Multivariate linear regression analysis to determine main predictors of PAH

	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
(Constant)	28.462	12.969		2.195	0.031
Time for smoking	0.091	0.098	0.112	0.931	0.355
Cigarette use	0.063	0.067	0.113	0.931	0.355
FEV/FVC	-0.271	0.114	-0.233	-2.387	0.019
RVsize	0.715	0.298	0.237	2.399	0.019
IVC size	0.337	0.193	0.184	1.751	0.084
DM	-1.459	2.575	-0.058	-0.566	0.573
HLP	-3.900	2.381	-0.158	-1.638	0.105

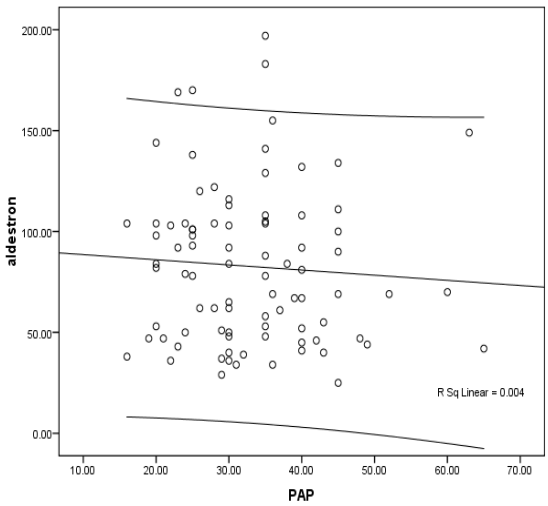

Figure 1: The association between level of aldosterone and SPAP

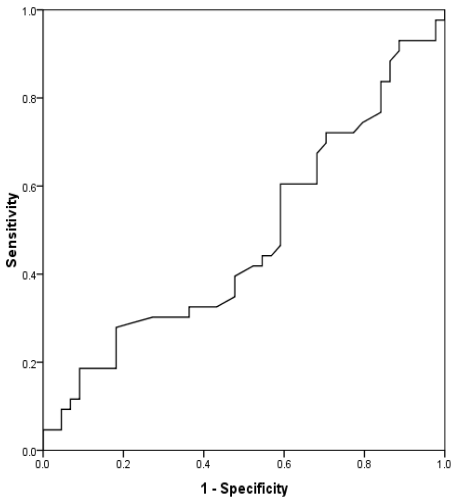

Figure 2: The ROC curve analysis to determine the value of aldosterone level for predicting PAH