

Original Paper

Study of Pulmonary Hypertension in Patients Suffering from Chronic Obstructive Pulmonary Disease

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ABSTRACT: Pulmonary hypertension (PAH) represents a frequent complication in patients suffering from chronic obstructive pulmonary disease (COPD), but the impact of accelerated inflammatory status on the pulmonary vascular bed is still insufficiently studied. Objectives: The study of the PAH's prevalence in patients suffering from COPD, its severity compared with lung function and the correlation with certain clinical, biological and functional parameters. Material and method: The study was performed on a group of 64 patients, average age 53 years, 42 of whom were men (65,62%), suffering from COPD who were admitted to the Emergency County Hospital Craiova, on the II-nd Medical Clinic, within a period of 18 months. When assessing the patients their clinical state was stable, without acute exacerbations items. The control group included 61 patients suffering from other diseases without inflammatory background, who were hospitalized in clinic in the same period. All the patients included in the study were evaluated by: physical examination, thoracic radiological examination, spirometry, inflammatory syndrome, echocardiography Doppler and oximetry. Results: The results of the study show a prevalence of 54.6 % PAH and a statistically significant impact of age, duration of the disease, Sa O₂, inflammatory status, which was quantified in the study by ESR, serum levels of CRP and serum level of TNF alpha over the risk of developing COPD in patients suffering from PAH. Conclusions: The occurrence and the severity of PAH in patients suffering from COPD seems to be correlated with their age, duration of the disease, Sa O₂ and serum levels of inflammatory markers.

KEYWORDS: COPD, inflammation, PAH

Introduction

PAH represents the growth of arterial pulmonary pressure over 25 mmHG at rest or over 30 mmHG during exercise, measured by catheterization of right cavities, and it is a frequent complication in patients suffering from chronic obstructive pulmonary disease (COPD)[1].

Pulmonary hypertension etiopathogeny is incompletely elucidated so far and it reflects a multifactorial process with a complex evolution that involves endothelial dysfunction mediated through various cellular and humoral links [2,3].

The growth of pulmonary vascular resistance represents the key factor of pathogenesis located at the crossroads of multiple pathogenic links, such as pulmonary vasoconstriction, endothelial dysfunction, vascular remodeling, inflammation and thrombosis [4, 5].

Endothelial dysfunction is initiated by disruption of balance between vasodilators factors of which the most important are thromboxane, which causes pulmonary vasoconstriction and platelet aggregation, and

endothelia, a strong vasoconstrictor and mitogen factor, that has elevated circulating levels and a high local production in arterial pulmonary endothelium [6,7,8].

The inflammation initiates endothelial injury by releasing chemotactic substances, that will after migrate in the vascular smooth cells from vascular wall; they promote a procoagulant status with consecutive vascular obstruction and causes in situ thrombosis, transforming the pulmonary vascular bed, which normally has anticoagulant characteristics, into an area with procoagulant characteristics, converging to a vascular remodeling process and a progressive degree of pulmonary vascular obstruction[9].

It is supposed that PAH develops in people who are prone to it, under the influence of certain triggers of pulmonary vasoconstriction in prone people such as: autoimmune diseases, certain drugs and toxins, pulmonary injuries and the increasing of sympathetic tonus. The systemic inflammation persisting in patients suffering from COPD promotes on the one hand endothelial dysfunction with the appearance of PAH and on the other hand progressive

obstruction of the airways, proteolysis, emphysema and fibrosis with consequences over the ventilation parameters (FEV1).

The inflammation and the damage of the endothelial function encourages the appearance Of PAH and contributes at the cardiovascular damage in COPD, and the accelerated impact of inflammatory status in patients with chronic pulmonary disease over the vascular pulmonary bed is still insufficiently studied.

The objectives of the study were the evaluation of the prevalence of PAH in patients with COPD, its severity in relation with lung function and the correlation with certain clinical, biological and functional parameters.

Material and method

The study which had a prospective nature, type event-control, was performed on a group of 64 patients, average age 53 years, 42 of whom were men (65,62%) who were admitted to the Emergency County Hospital Craiova, on the II-nd Medical Clinic, within a period of 18 months. When assessing the patients their clinical state was stable, without acute exacerbations items. The control group included 61 patients suffering from other diseases without inflammatory background, who were hospitalized in clinic in the same period of time.

Study inclusion criteria were chronic respiratory symptoms (cough, sputum, dyspnea, wheezing), smoking exposure or professional exposure at irritating substances, obstruction of the airways proved at spirometry.

Excluded from the study were patients with active pulmonary tuberculosis and with cardiac, hepatic or neoplastic comorbidities.

The main parameters monitored for the patients included in the study were age, gender, smoking status, duration of the disease, clinical, biological and imagistic evaluation.

Biological evaluation was performed in Craiova SCJU's laboratory and included hematological tests (complete blood count), inflammatory syndrome (ESR, reactive C protein, alpha tumor necrosis factor) and oximetry. Functional exploration was performed with COSMED spirometer in the II-nd Medical Clinic, and the radiological exploration was performed in the Radiology and Medical Imagistic Service.

Cardiac imagistic evaluation was performed using the Agilent-SONOS 5500 echograph, using a probe with a frequency of 3MHz in the Cardiology Center of Craiova, echocardiography (2B+Doppler) with a high informative value in the detection of vascular and cardiac abnormalities, highlighting the aspects and the regurgitations of the valves, the sizes of the cardiac cavities, assessment of the pressure in the pulmonary artery using the degree of tricuspid regurgitation.

Statistical analysis: database analysis was made by using **Excel** program from the package Microsoft Office, and the statistical analysis was made by using the following programs: **MedCalc** and **Epi Info 2000**.

Statistical indicators From the central tendency indicators were analyzed the following: **arithmetic mean, median, module**, and from the scattering data indicators were analyzed the following: **standard deviation, standard error of the mean** and the trust interval 95% of the mean.

The statistical tests used were **Chi square Test, Exact Test Fisher, ANOVA Test**. For the ANOVA positive tests **Student-Newman-Keuls Test** was also applied form making comparisons between the subgroups.

The results are expressed as mean values+/- standard deviation (SD).

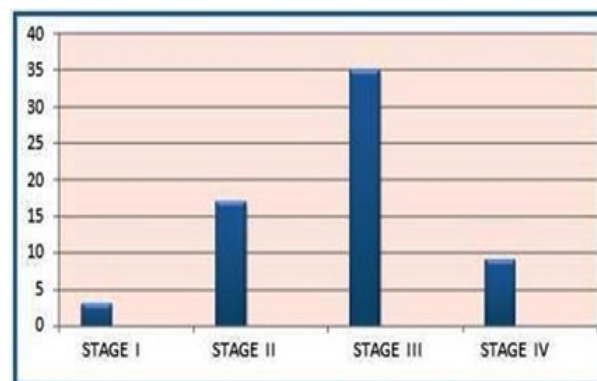
For describing the relation between two variables and for making one value predictions on the value of the other was used r^2 determination coefficient, F ratio and p value, whose statistical signification was accepted only for values under 0,05.

Results

Analyzing by comparison the main demographic and anthropometric parameters in the two study groups, there were no significant differences in terms of average age, 53+/-6.93 years in the case group and 51.7+/-6.2 in the control group, and the gender distribution (B/F)42/22 in the case group and 39/21 in the control group. Smoking status was at 57 patients in the COPD group (89%),in comparison with 15% in the control group (9 patients),polluted professional microclimate at 11 patients from the case group (11%) and 3 patients from the control group, and the intercurrent infections were present only in patients with COPD 34% (22 patients) (Table 1).

Table 1. Demographic and anthropometric parameters

Parameter	Patients with COPD(n = 64)	Control group(n = 61)
Gender(M/F)	42/22	39/21
Age	53+/-6,93	51,7+/-6,2
Smoking	57(89%)	9(15%)
Pollution of the professional microclimate	11(17%)	3(0,05%)
Intercurrent infections	22(34%)	0%

**Fig.1. Distribution of COPD patients according to the stage of the disease**

The study of the severity of the affection by evaluating the distribution of the cases with COPD depending on the disease stage reveals a predominance of the II and III stage of the disease (Fig.1), but the average duration of the disease progression was 12,64+/-5,76 years (Table 2).

The average saturation of the oxygen in the peripheral blood measured by pulse oximetry was 88,85+/-4,66 percent in the group of patients suffering from COPD, in comparison with the control group where the average value was 96,23+/-2,47 percent.

In what the inflammatory status is concerned in comparison at the two study groups was observed a significant inflammatory syndrome at the patients included in the study group, with an average value of the ESR at one hour of

36,18+/-10,28mm, CRP 3,22+/-2,48mg/dl and alpha TNF 4,37+/-0,96pg/dl, in comparison with the control group where the average value of the ESR at one hour was 14,03+/-5,46mm, CRP 1,15+/-0,36mg/dl and alpha TNF 1,34+/-0,48pg/ml.

The average value of the pressure in the pulmonary artery at the patients with COPD was 36,43+/-9,88mmHg in comparison with the patients from the control group 21,63+/-3,25mmHg, and the average values of FEV1 were 57,48+/-20,78ml at patients with COPD and 93,66+/-3,38ml at patients from the control group (Table 2).

PAH's prevalence was 54,6% was present at 35 patients included in the group with COPD, in comparison with 3,27%, respectively 2 patients from the control group (Fig.2).

Table 2. The average values of the main parameters studied (Results are shown as an average $M \pm$ standard deviation SD)

Parameter	Study Group(n = 64)	Control Group(n=61)
Duration of the disease(years)	12,64+/-5,76	-
Sa O2(%)	88,85+/-4,66	96,23+/-2,47
ESR 1h(mm)	36,18+/-10,28	14,03+/-5,46
CRP(mg/dl)	3,22+/-2,48	1,15+/-0,36
TNF alpha(pg/ml)	4,37+/-0,96	1,34+/-0,48
Pressure in the pulmonary artery(mmHg)	36,43+/-9,88	21,63+/-3,25
FEV1(ml)	57,48+/-20,78	93,66+/-3,38



Fig.2.PAH's prevalence-distribution of the cases depending of the pressure in the pulmonary artery at the two groups

Table 3. Factors correlated with the presence of pulmonary hypertension at patients with COPD

	ESR	CRP	TNF ALPHA	SaO2	Duration of the disease
R	0,6456	0,5825	0,5528	0,6113	0,5272
r ²	0,4168	0,3393	0,3056	0,3737	0,2780
IC 95%	0,4751 to 0,7693	0,3929 to 0,7246	0,3552 to 0,7031	0,7452 to 0,9301	0,3233 to 0,6844
p	<0,0001	<0,0001	<0,0001	<0,0001	<0,0001

The results of the study show a statistically significant impact of the inflammatory status, quantified in the study by ESR ($R=0,64$, IC95% 0,47-0,76, $p<0,0001$), serum levels of CRP ($R=0,58$, IC95% 0,39-0,72, $p<0,0001$), serum levels of alpha TNF ($R=0,55$, IC95% 0,35-0,7, $p<0,0001$), oxygen's saturation ($R=0,61$, IC95% 0,74-0,93, $p<0,0001$) and the duration of the disease ($R=0,52$, IC95% 0,32-0,68, $p<0,0001$) over the increasing risk of the patients with COPD of developing PAH (Table 3, Fig.3, 4).

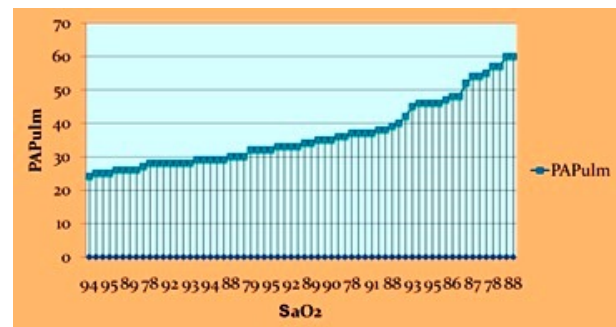


Fig.4. Pressure in the pulmonary artery according to the values of Sa O2

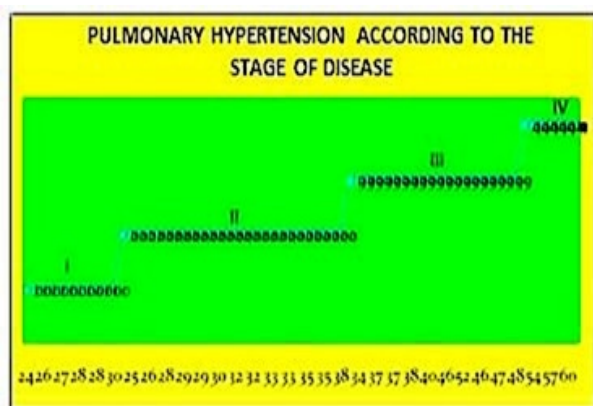


Fig.3.Pulmonary Hypertension and the severity of COPD

Discussions

The appearance and the severity of PAH in patients with COPD seem to be correlated with the patients' age, duration of the disease, SaO2 and serum level of the inflammatory markers.

The values of the inflammatory markers were correlated best with the systolic pressure from the pulmonary artery, showing the importance of the systemic inflammation in initializing the endothelial dysfunction in the pulmonary vessels.

Similar results were obtained in a study which included patients with severe COPD ($FEV_1\%$, 39.8 ± 16.2) at whom the average pressure in the pulmonary artery was 19.0 ± 4.3 and 23 patients (43%) presented PAH (mPAP >20 mmHg). From the 27 patients, 17 (63%) with mild and medium hypoxemia had PAH [10].

Similarly, another study proved a high medium pressure in the pulmonary artery $26,9 \pm 8,9$ mmHg, at 215 patients with severe COPD (FEV1% 24,3%), which suffered right cardiac catheterism before a pulmonary surgical intervention or a pulmonary transplant [11]. About half of them these patients had PAH (mPAP > 25 mmHg) ([11]).

Scharf and his contributors realized hemodynamic catheterism of the patients suffering from severe emphysema included in a group of patients with severe emphysema (FEV1%, 27% and PaO₂, $65,9 \pm 10,0$ mmHg) which suffered a right cardiac catheterism during the evaluation for the lung volume reduction surgery in National Emphysema Treatment trial (12). A mPAP of $26,3 \pm 5,2$ mmHg was identified. Over 90% of these patients had PAH, (mPAP > 20 mmHg). Although PaO₂ was conversely correlated with mPAP, this parameter was not an independent predictor of mPAP (Scharf et al 2002). Severe PAH, (mPAP > 35 mmHg) appeared at 6 patients (5%) [11]. Instead severe PAH's prevalence (mPAP > 45 mmHg) was 3,7%, respectively 8 from 215 patients evaluated for a lung volume reduction surgery or pulmonary transplant, while (in a retrospective analysis) only 11 (1,1%) from 998 patients suffering from COPD had this pressure level in the pulmonary artery (Chaouat et al 2005) (13). Otherwise, although the study of PAH's prevalence in patients with COPD identified rates situated between 20 and 50%, very few patients had severe PAH.

Similar to our results, the appearance and the progression of PAH with a duration of the basic disease was proved by Kessler and his contributors that studied the changes in pulmonary hemodynamic in time, in a group of 131 patients with moderate COPD (FEV1%, $34,6 \pm 15,7\%$ and PaO₂ $67,0 \pm 10,4$ mmHg). At the initial evaluation by right cardiac catheterism none of the patients had mPAP > 20 mmHg at rest, with values situated between 20-32,5 mmHg. The average growth rate of the arterial pulmonary pressure was 0,4 mmHg/year [14].

Although many studies had evaluated pulmonary hemodynamic in patients with COPD, PAH's prevalence is not exactly known. The analysis of these studies has as confusion factors the presence of various patient subgroups with various severity degrees of COPD and of

oxygenation, but also the generally small number of patients. However, the minimum prevalence of PAH in patients with at least one hospitalization for COPD was estimated at 10% - 30% [15] and is as big as at 90% of the patients who have been evaluated for a lung volume reduction surgery (12). Another aspect is PAH induced by physical exercise which can appear at two-thirds of the patients with COPD even when pulmonary pressures are normal at rest [16, 17].

The role of inflammation in the pathogenesis of PAH associated with COPD is uncertain. The degree of the inflammatory infiltrate in the pulmonary vascular adventitia in patients with COPD is correlated with the intimal thickening severity of the pulmonary arteries [9].

In addition, systemic inflammatory markers, reactive protein C (CRP) and the alpha tumor necrosis factor (TNF-alpha), are elevated at the patients with COPD and PAH [18] in comparison with patients with COPD without PAH. Similar to our study, Joppa P. et al had proposed to investigate the degree of systemic inflammation reflected by the serum levels of reactive protein C (CRP), alpha tumor necrosis factor (TNF-alpha) and interleukin (IL)-6 in patients with COPD with or without pulmonary hypertension. At 43 patients with COPD (average age [+/- SD], $65,0 \pm 10,5$ years, average FEV(1) $46,2 \pm 18,1\%$ from predicted), at whom pulmonary function was evaluated with the aid of plethysmography, and the pressure in the pulmonary artery (PPA) by echocardiography, PAH was present at 19 patients and was absent at 24 patients. At the patients with arterial pulmonary hypertension, serum levels of CRP and TNF-alpha was significantly higher compared to the patients without PAH (median, 3.6 mg/L [25th to 75th percentile, 1.4 to 13.0 mg/L] vs 1.8 mg/L [25th to 75th percentile, 0.8 to 2.8 mg/L; $p = 0.034$]; and median, 4.2 pg/mL [25th to 75th percentile, 3.4 to 10.9 pg/mL] vs 3.1 pg/mL [25th to 75th percentile, 2.1 to 4.2 pg/mL]; $p = 0.042$, respectively). There was no statistically significant difference between the level of IL-6 in patients with COPD with and without PAH. Two variables were identified as independent predictors of PAH: PaO₂ ($p = 0,011$) and the serum level of CRP ($p = 0,044$), concluding that PAH in patients with COPD is associated with high serum levels of CRP and TNF-alpha, raising the possibility of a pathogenic role of the systemic inflammation in the pathogenesis of pulmonary hypertension in patients with COPD.

Yet, the significance of these results is unclear and additional investigations are needed for analyzing the etiological analysis of the inflammation in the vascular remodeling which appears at smokers, patients with COPD and those with COPD and PAH.

COPD is a heterogeneous, multisystem affection with a complexity which extends far beyond the airways' obstruction. Although COPD is defined and classified according to FEV1, there is a consensus that this single parameter is insufficient for describing the complexity of the disease.

Pulmonary hypertension in patients with COPD is a well-known comorbidity, belongs to the third group of pulmonary hypertension associated to the pulmonary disease and hypoxemia [19].

In contrast to group 1 or arterial pulmonary hypertension, which has the diagnostic criteria well defined [means arterial pulmonary pressure (PAPm) 25 mmHg, with a capillary pulmonary pressure (PCP)<15 mmHg], hemodynamic definition of pulmonary hypertension linked to COPD was inconsistent in the literature.

The actual accepted criterion, according to which this supposes PAPm over 25 mmHg associated to hypoxic pulmonary diseases, doesn't succeed to reflect the complexity of this diagnosis in which vascular remodeling, cardiac comorbidities, hypoxia and changes in the pulmonary mechanics contribute to high pressures in the pulmonary artery.

In defining inconsistencies, the existence of multiple causes responsible for the occurrence of pulmonary hypertension and the difficulty in applying invasive diagnosis tests contributed to its prevalence appreciation problems.

This study aims to make an appreciation of the PAH's prevalence in patients with COPD and to highlight the complexity of the factors that contribute to the occurrence and severity of PAH.

The presence of systemic inflammatory syndrome can be considered an appreciation method for the severity of COPD and the risk of PAH.

Conclusions

-The results of the study show a prevalence of PAH of 54,6% in patients with COPD.

-The occurrence and severity of PAH in patients with COPD seems to be correlated with the patients' age, duration of the disease, Sa O2 and the serum levels of inflammatory markers.

-The values of inflammatory markers were best correlated with systolic pressure in the pulmonary artery, suggesting the importance of systemic inflammation in the initiation of the endothelial dysfunction in the pulmonary vessels.

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