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Prevalence and Characteristics of Pulmonary Hypertension Associated with COPD - A Pilot Study in Patients Referred to a Pulmonary Rehabilitation Program Clinic

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ABSTRACT

Objectives: *Pulmonary hypertension (PH) is a common complication of chronic obstructive pulmonary disease (COPD); its prevalence is currently unknown. The objectives of the study were: (a) to provide data on the prevalence of PH among the COPD patients referred to a pulmonary rehabilitation program; (b) to evaluate possible correlations of PH with the severity of COPD, the presence of hypoxemia and polycythemia.*

Material and methods: *We retrospectively studied 31 consecutive patients with the diagnosis of COPD hospitalised in our clinic in which echocardiography was performed. Spirometry, peripheral oxygen saturation, haematocrit, echocardiography data, history of exacerbations and cardiac comorbidities were obtained from patients records. PH was defined as systolic pulmonary arterial pressure (sPAP) greater than 35 mmHg or by the presence of right ventricle (RV) abnormalities.*

Outcomes: *The prevalence of PH was 38.7%. Resting hypoxemia was significantly more frequent in the PH group than in the non PH patients (p=0.019). Other differences were not statistically significant (severity of bronchial obstruction and polycythemia, cardiac comorbidities). The impact of PH on RV was found in only 5 patients with RV enlargement; no patient had RV hypertrophy or RV systolic dysfunction. Suspected "out of proportion" PH (sPAP greater than 50 mmHg) was encountered in 2 out of 12 patients with PH.*

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Conclusions: *The prevalence of PH in patients with COPD was 38.7%. Resting hypoxemia was significantly more frequent in PH patients. As PH has an important role in the prognosis of COPD patients, it should be evaluated in as many COPD patients as possible.*

Keywords: pulmonary hypertension, chronic obstructive pulmonary disease, echocardiography

INTRODUCTION

Chronic obstructive pulmonary disease has a rising incidence and is about to become the third leading cause of death worldwide in 2020 (1). The disease is characterised by slowly progressive airflow obstruction, resulting in dyspnoea and exercise limitation (1). Pulmonary hypertension (PH) is the major cardiac complication of the disease; it is defined by a mean pulmonary artery pressure at rest (mPAP) above 25 mmHg, as assessed by right heart catheterization (2). Due to the high prevalence of COPD, PH associated with COPD is one of the most frequent causes of PH (3). The current clinical classification of pulmonary hypertension includes PH secondary to COPD in subgroup 3, called "PH associated to Lung Diseases and/or Hypoxia" (2,4). PH due to COPD is a predictor of mortality (5), independent of the pulmonary obstruction severity (5-7). PH has been associated with an increased risk of severe acute exacerbation (3), and therefore with higher healthcare costs; it also additionally impairs the quality of life of these patients (8). It is therefore important to assess PH in COPD patients in the clinical management of the disease. In current practice the detection of PH is made mostly by echocardiography, as right heart catheterization, the "gold standard" diagnostic method for PH, is an invasive and expensive procedure, considered only in patients referred to surgical procedures. PH in patients with COPD is generally mild to moderate, with mean PAP values between 20 and 35 mmHg (6). A small proportion of patients may develop severe PH, known as ''out of proportion'' (or disproportionate) PH, with greater mortality (9).

The prevalence of PH in COPD is currently unknown, with different studies finding a wide range of prevalence, from 18% (10) to up to 91% (8), but most of the studies were based on pulmonary haemodynamic assessments performed in patients referred to surgical procedures; thus these results of prevalence can not be extended to the large population of COPD patients. PH prevalence is thought to be higher in more severe COPD patients, but a significant correlation between PH and the degree of bronchial obstruction defined by the maximum expiratory volume in the first second (FEV1) could not be found (11). There are no current data regarding the prevalence of PH associated with COPD in Romanian population.

The aims of the study were: (a) to provide data on the prevalence of PH among the COPD patients referred to a pulmonary rehabilitation program in Bucharest (b) to evaluate possible correlations of PH with the severity of COPD, the presence of hypoxemia and polycythemia. ❑

MATERIAL AND METHODS

We retrospectively studied 54 consecutive patients with the diagnosis of COPD hospitalised in our clinic during a two year period (2011-2012). Patients with asthma, congestive heart failure, major valvulopathies, obesity-hypoventilation syndrome or sleep apnea syndrome were excluded, as these diseases can also induce PH. Cardiac comorbidities (arterial hypertension, coronary heart disease and atrial fibrillation) were all treated and stable.

This pilot study was part of the implementation of a pulmonary rehabilitation program for COPD patients in Colentina Clinical Hospital. Our present study focused on the 31 patients in whom echocardiography was performed during hospitalisation.

Demographic and anthropometric data, COPD exacerbation at the time of hospitalization, spirometry results, GOLD stage, haematocrit, peripheral oxygen saturation at rest and after six minutes of walking were obtained from patients records at the time of hospital discharge.

Echocardiography data included continuous Doppler estimated systolic pulmonary arterial pressure (sPAP), left ventricular ejection fraction (LVEF) and left ventricular systolic and diastolic function (E/A ratio) and a complete

evaluation of the structure and function of the right ventricle (RV): end-diastolic diameter, wall thickness, systolic function, tricuspid annular plane systolic excursion (TAPSE). Doppler echocardiography was performed in order to obtain right ventricular systolic pressure (RVSP) by using the tricuspid regurgitation jet; sPAP was calculated by the sum of transtricuspid gradient and right atrial pressure, the later being estimated from the dimensions and collapsibility of the inferior vena cava (12).

PH was defined in this study by a systolic pulmonary arterial pressure (sPAP) greater than 35 mmHg; this cut-off value has been used in similar studies (11,13). In the absence or right heart catheterization these patients do not have a definitive diagnostic of PH, but for the simplicity of the text we will use the term "PH patients" instead of "probable PH". RV abnormalities were defined as recommended by current echocardiography guidelines for the assessment of the right heart (12), as follows:

- RV dilatation: mid-level end-diastolic diameter greater than 35 mm
- RV hypertrophy: RV wall thickness greater than 5 mm
- RV systolic dysfunction: TAPSE lower than 16 mm.

Patients in whom echocardiography was performed were then assigned to one of two groups: group 1 – patients with PH and group 2 – patients without PH, according to the level of sPAP assessed by echo-Doppler, using the cut-off of 35 mmHg. Patients in which no tricuspid regurgitation was detected (without an estimated value of sPAP) were included in the group 2, as none of them had RV abnormalities (RV enlargement, RV hypertrophy, RV systolic dysfunction) considered surrogate diagnostic markers of PH (10). It is known that increased size of right heart chambers, abnormal shape or function of the inter-ventricular septum, increased RV wall thickness and dilated main pulmonary artery are also suggestive of PH (4).

A subcategory of patients with suspected "severe PH" or suspected "out of proportion PH" was defined by sPAP greater than 50 mmHg.

Statistical analysis: the between groups differences were evaluated by Mann-Whitney analysis and Chi square test for nonparametric variables; a p value of less than 0.05 was considered to be statistically significant. ❑

RESULTS

Among the 54 consecutive patients with COPD, echocardiography was performed in 31 patients (57.4%) at the indication of the attending physicians, as a screening method for PH. These patients had a lower mean age (66.2 versus 70.5 years), a lower mean FEV1 (48.3 versus 55.3% of predicted) and a more severe COPD (20 of 31 patients in echo group with GOLD stages 3 and 4, versus 13 of 23 patients without echo). Resting hypoxemia was seen in 12 of 31 patients with echo versus 5 of 23 without echo; fewer patients had only exercise hypoxemia (without resting hypoxemia) (8 of 31 versus 7 of 23). No statistical significance was found in any of these differences.

Among COPD patients in whom echocardiography was performed, only 21 had tricuspid regurgitation (67.7%) which permitted the estimation of sPAP. Twelve patients had PH, defined by either sPAP greater than 35 mmHg or by the presence of RV abnormalities; the prevalence of PH in our COPD patients group was therefore 38.7%.

Left ventricular diastolic dysfunction was found in 70% of patients who performed echocardiography, but in all cases it was of the impaired relaxation pattern, therefore less probable to produce PH due to left heart disease.

Table 1 describes echocardiographic data (echo-Doppler evaluation) of the patients. The parameters of the subjects in the two groups (group 1 – PH group and group 2 – non PH group) were then studied comparatively (Table 2).

Mean FEV1 was lower in the PH group. FEV1 did not correlate with the level of sPAP. Mean age was similar in the two groups. The distribution of patients by GOLD classification indicated more severe GOLD stages in patients with PH. Resting hypoxemia was significantly more frequent in the PH group ($p=0.019$). Exercise hypoxemia (without resting hypoxemia) was encountered more frequent in patients without PH.

Cardiac comorbidities were found in a lesser proportion in the PH group. RV enlargement was found in 5 patients with PH. No differences in FEV1 were observed in patients with RV enlargement compared with the patients without RV enlargement: mean FEV1 44.4 versus 43.4%, $p=0.683$. No patient had RV hypertrophy or RV systolic dysfunction (either by TAPSE

Tricuspid regurgitation*	67.7%
Right ventricular diameter (mm)**	30 ± 4
Right ventricular dilatation*	16.1%
Right ventricular hypertrophy*	0
TAPSE (mm)** (4 subjects)	24 ± 5
sPAP (mm Hg)** (21 subjects)	35 ± 10
Left ventricular ejection fraction**	55 ± 5

TABLE 1. Echo-Doppler evaluation of study patients (31 subjects).

*Values represent the % of the total patient's number
**Values represent means ± standard deviations

measurement or by visual qualitative assessment of RV systolic function). Five patients in the PH group and seven patients in the non PH group were evaluated after a COPD exacerbation.

Suspected "out of proportion" PH was found in 2 out of the total 12 patients with PH (16.7% of PH patients). They both had severe bronchial obstruction (FEV1 predicted 36% and 37% respectively). One of them had resting hypoxemia and the other had only exercise hypoxemia. None of them had cardiac comorbidities. RV enlargement was found in one of these 2 patients. These patients had the indication for right heart catheterization in expert PH centers. ❑

DISCUSSIONS

The study evaluated data on PH prevalence in "common" COPD patients, as the majority of prevalence studies were made in selected patients referred for surgical procedures. The prevalence of PH was 38.7%. These are the first data on PH prevalence in Romanian COPD patients.

In the original group of 54 patients with moderate-severe COPD, echocardiography was performed in only 57.4%. In current practice the detection of PH is made mostly by echocardiography, as right heart catheterization, the "gold standard" diagnostic method for PH, is an invasive and expensive procedure. Although both GOLD guidelines for COPD and ERS/ESC guidelines for the diagnosis and treatment of PH recommend cardiac ultrasound as a screening method for detecting PH in patients with COPD (1,4), not all patients with COPD are systematically investigated for PH.

Clinically it is difficult to identify PH in COPD patients in the absence of right heart failure (14). On one hand, not all patients with cardiac comorbidities had echocardiography (19 out of 27 patients), even if ERS/ESC guidelines recommend assessing PH in COPD patients with left heart disease (4). On the other hand, not all the patients with resting hypoxemia were assessed for PH (12 out of 17 patients), even if the presence of hypoxemia should rise the suspicion of PH (15). The main reason for these limitations is the low accessibility of echocardiography in our hospital (lack of portable equipment with the impossibility of performing echocardiography at the bedside).

Among the 31 patients in whom echocardiography was performed, tricuspid regurgitation (TR) was found in 21 patients (67.7%); other studies found it in 77%, 47% or 38% of patients (16-18). Pulmonary hyperinflation, frequently seen in COPD patients, is responsible for the low quality of echocardiography (19), thus the likelihood of estimating sPAP is lower in patients with marked pulmonary hyperinflation. The quality of the tricuspid regurgitation was adequate in our study for the estimation of sPAP in all patients with TR, which is not always possible; one study estimated sPAP in only two thirds of the patients with TR (17). This is of great value, as the absence of an echocardio-

Characteristics	Patients with PH (12 subjects)	Patients without PH (19 subjects)	p value
Age (years, mean)	68.1	65.1	0.464
Male / female (number of subjects)	10 / 2	15 / 4	
FEV1 (% of predicted, mean)	43.8%	51.2%	0.133
GOLD I / II / III / IV (number of patients)	0 / 2 / 3 / 7	1 / 8 / 5 / 5	0. 255
Cardiac comorbidities*	58.3%	63.1%	0.788
Resting hypoxemia*	66.6%	21%	0.019
Exercise hypoxemia without resting hypoxemia*	8.3%	31.5%	0.332
Polycythemia*	25%	10.5%	0.286
Right ventricular dilatation*	41.6%	0	-
Right ventricular hypertrophy	0	0	-
Right ventricular systolic dysfunction	0	0	-
sPAP (mm Hg, mean)	42	26	0.000

TABLE 2. Clinical and echographic characteristics of patients with and without Pulmonary Hypertension.

*Values represent the % of the total patient's number

graphic high sPAP excludes important PH and further unnecessary invasive evaluation due to its high negative predictive value (87%) (10).

The systematic description of the structure and function of RV in our patients permitted the evaluation of PH even in those in which sPAP could not be assessed, as lack of RV abnormalities can be defined as an adjunctive measure of excluding significant PH. This RV evaluation method has a sensitivity and specificity comparable to the sPAP evaluation method (10), thus all the patients who performed echocardiography could be assessed for PH. The patients who did not have RV abnormalities (RV dilation, hypertrophy, or systolic dysfunction) were included in the non PH group, relying on the high negative predictive value of this RV evaluation (10). The authors want to encourage physicians to use this noninvasive and accessible procedure extensively in the evaluation of COPD patients.

The characteristics of COPD patients with PH could not be individualized, as no significant correlation could be found between the presence of PH and the severity of bronchial obstruction, presence of polycythemia or exercise hypoxemia (without resting hypoxemia). This is similar with other studies which did not find a significant correlation between PH and FEV1 (11). The fact that patients evaluated for PH were in higher GOLD stages could overestimate the prevalence of PH in our COPD patients.

Resting hypoxemia was significantly more frequent in PH patients ($p=0.019$), which can be related to the role of hypoxemia in the pathogenesis of PH. Hypoxic vasoconstriction in the small pulmonary arteries is the first mechanism of developing PH in COPD patients (1). Its determinant role was nevertheless reconsidered because vascular remodeling and endothelial dysfunction were observed in its absence, both in smokers with normal lung function, and in COPD patients without hypoxemia (20-22).

Surprisingly, as two thirds of the patients with PH had resting hypoxemia, only 25% of them had polycythemia; this can be partially explained by the use of domiciliary oxygenotherapy in some of the patients. It is known that before the use of long term oxygenotherapy, polycythemia among COPD patients was more frequent. On the other hand oxygenotherapy can not completely reverse PH (9).

Among patients with PH, RV enlargement was found in 5 cases. This is a beneficial adaptation in COPD patients, allowing the ventricle to cope with an increased afterload and thus to maintain a normal cardiac output (23). No differences in FEV1 were observed in patients with RV enlargement compared to the patients without RV enlargement: mean FEV1 was 44.4 versus 43.4% of predicted. As RV dilatation is progressive, it can be assumed that PH develops in patients with different degrees of bronchial obstruction. The rate of PH progression over time is not known (17). No patient was identified with RV systolic dysfunction (assessed by TAPSE or by subjective evaluation of the systolic function of RV), which is concordant with the fact that due to slow evolution of PH, RV has time to adapt and thus to preserve its contractility (9).

One of the characteristics of PH in COPD is its low degree of severity. In stable COPD, PH is usually mild or moderate, with mean PAP values between 20-35 mmHg (6).

The influence of PH on COPD prognosis depends on the severity of the pulmonary hypertension (24); it is therefore important to assess the correct degree of severity, knowing that there is a temporary increase in sPAP during sleep, exercise, or COPD exacerbations (19). Patients with severe PH associated with COPD usually have a distinct clinical pattern with moderate bronchial obstruction, marked hypoxemia, hypocapnia and a worse prognosis (8,24,25). In our group the percentage of suspected severe PH was greater than the one found in other studies. Both patients with severe PH defined as sPAP >50 mmHg were evaluated in the absence of a COPD exacerbation.

The main limit of our study is the small number of patients with limited statistical power. Another limit was incomplete exclusion of cardiac comorbidities. Also a limit was the fact that some of the patients were actually hospitalized for an exacerbation; among the patients with echo, 12 were in exacerbation (5 in the PH group and 7 in the non-PH group). Transient increase in pulmonary artery pressure occurs during COPD exacerbations, although the amount of this increase is unknown (19). One study found PH in 53% of COPD patients during an exacerbation (7), using echocardiography as a diagnostic tool. It is not known if transient PH during an exacerbation is a prognostic

factor for developing PH in a stable patient, similar to exercise induced PH being a prognostic factor for developing resting PH (26). Echography was performed in the majority of cases at the end of the hospitalization, when the patients were clinically stabilised, and the echocardiography findings were supposed to be similar with the stable state.

The study wanted to emphasize the utility of echocardiography in assessing PH in COPD patients even in the absence of PH confirmation by right heart catheterization. ❑

CONCLUSIONS

The prevalence of PH in patients with COPD was 38.7%. There were no significant correlations between the presence of PH and GOLD stage, severity of the bronchial obstruction and presence of polycythemia. Resting hypoxemia was significantly more frequent in PH patients. As PH has an important role in the prognosis of COPD patients, it should be evaluated in as many COPD patients as possible.

Conflict of interests: none to declare.
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