Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease and Pulmonary Fibrosis: Prevalence and Hemodynamic Differences in Lung Transplant Recipients at Transplant Center's Referral Time

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ABSTRACT

Introduction. Single or bilateral lung transplantation is a therapeutic procedure for end-stage lung diseases. In particular, in cases of chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, patients can be referred to the transplant center late and with important comorbilities. Pulmonary hypertension (PH) associated with lung diseases not only is an index of poor outcome but also is an indication for bilateral procedure.

Methods. We conducted a retrospective observational study. We analyzed right heart catheterization in a consecutive series of patients who underwent lung transplantation from 2006 to 2014 for end-stage COPD and pulmonary fibrosis.

Results. We included in the study 73 patients (35 with fibrosis and 38 with COPD); prevalence of PH was higher in the COPD group (84.3% vs 31.4%), and with worse hemodynamic parameters (mean pulmonary artery pressure [30.3 mm Hg vs 24.1 mm Hg]). The majority of COPD patients presented mild or moderate PH, and fibrosis patients showed normal pulmonary arterial pressures.

Conclusions. COPD patients are referred to the Transplant Center with a higher prevalence of PH because of an echocardiographic screening or a late referral, but many patients survive on the waiting list and undergo the procedure. On the other hand, patients transplanted with interstitial diseases have a lower prevalence of PH; this can be explained by an earlier referral or a higher mortality on the waiting list and a more aggressive and rapidly progressing disease.

PULMONARY HYPERTENSION (PH) is defined as a mean pulmonary arterial pressure (mPAP) higher than 25 mm Hg, as measured by right heart catheterization (RHC) at rest [1]. Pulmonary arterial hypertension (PAH) and pulmonary venous hypertension (PVH) are traditionally distinguished on the basis that PAH patients have a pulmonary wedge pressure (PWP) lower than 15 mm Hg. In 2008, the Dana Point Symposium on Pulmonary Hypertension classified chronic obstructive pulmonary disease (COPD)–associated PH into Group 3, "Pulmonary hypertension associated with lung disease and/or hypoxemia" [2]. COPD is defined in terms of airflow obstruction that results from an inflammatory process affecting the airways and lung parenchyma. Different inflammatory mediators can have local and systemic activities and clinical consequences [3,4]. Changes in pulmonary vessels represent an important component of the disease. Alterations in vessel structure are very common, and abnormalities in their function impair gas exchange and result in PH [5]. Hurdman et al., in a recent article [6], have studied the characteristics and outcomes, in particular mortality,

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0041-1345/15
http://dx.doi.org/10.1016/j.transproceed.2015.01.031

of extensively phenotyped, consecutive patients with PH-COPD over a 9-year period. Survival has been studied on the basis of mPAP, age, diffusion lung capacity for carbon monoxide (DLCO), mixed venous oxygen saturation (SvO_2), and World Health Organization functional class. For all the parameters studied the patients were divided into 2 groups. In particular, in those with severe PH-COPD (mPAP > 40 mm Hg), 1-year survival was 70% and 3-year survival was 33%, which is significantly worse than the 83% and 55%, respectively, seen in mild–moderate PH-COPD (mPAP < 40 mm Hg).

In pulmonary fibrosis there is only a poor or even no correlation between PH severity and either lung function impairment [7] or high-resolution CT fibrosis score [8]. Increased dyspnea, deterioration of gas exchange at rest, low DLCO values, rapid desaturation during exercise, high brain natriuretic peptide (BNP) levels, gross right heart dilation on chest radiography, and limitation of exercise capacity caused by circulatory impairment have been linked to PH development in idiopathic pulmonary fibrosis (IPF) [9–11]. Doppler-defined PH (systolic PAP > 50 mm Hg) and even invasive mPAP values > 17 mm Hg [10] were associated with impaired survival in IPF, with mPAP and forced vital capacity (FVC) as independent predictors of survival [11]. Rapid progression of PH was reported in late-stage diffuse parenchymal lung disease (DPLD)/IPF patients [12]. In some studies, the prognosis of PH in lung fibrosis is not linked to the mPAP values but to pulmonary vascular resistance [13] or cardiac index (CI), with CI values < 2.4 L/min/m^2 correlated to survival of only a few months [14]. Assessment and definition of PH due to chronic lung diseases is a fundamental step in end-stage lung diseases (Group 3). Echocardiography is the initial modality for noninvasive diagnosis of PH in COPD and DPLD. Comparing echocardiographic data with RHC data in patients affected by lung diseases, positive predictive values of 32% and 68%, respectively, and negative predictive values of 93% and 67%, respectively, were reported [14,15]. Plasma levels of BNP or the N-terminal prohormone of BNP are elevated in severe COPD- and DPLD-associated PH, but their low sensitivity in moderate PH may be confounded by left heart abnormalities [16]. Nevertheless, BNP levels were found to be strongly predictive of mortality in a mixed DPLD population [17]. RHC, considered the gold standard for PH diagnosis, should be performed in patients with chronic lung disease when: 1) evaluation for lung transplantation is deemed necessary; 2) clinical worsening and progressive exercise limitation is disproportionate to ventilatory impairment; 3) progressive gas exchange abnormalities are disproportionate to ventilator impairment; 4) an accurate prognostic assessment is deemed to be critical; 5) severe PH is suspected by noninvasive measures and further therapy or inclusion in clinical trials or registries are being considered; and 6) there is suspicion of left ventricular systolic/diastolic dysfunction and categorization of the pulmonary artery occlusion pressure might alter management [18,19].

Table 1. Demographic Data

	Fibrosis	COPD	*P*
No. of patients	35	38	
Mean age (±SD)	56 (±8.9)	57 (±7.6)	
Gender male/female	26/9	28/10	
Mean BMI	26.98	24.52	
Ex smokers n. (%)	20 (57%)	32 (84%)	
Systemic arterial hypertension n. (%)	10 (28%)	19 (50%)	
History of coronary arterial disease n. (%)	4 (11%)	2 (5%)	
Diabetes n. (%)	8 (22%)	2 (5%)	
Osteopenia/osteoporosis n. (%)	13 (37%)	11 (28%)	
Obstructive sleep apnea syndrome n. (%)	4 (11%)	2 (5%)	
Mean %FEV1 (±SD)	55.1 (±19.6)	26.5 (±10.7)	
Mean %FVC (±SD)	54.4 (±18.9)	65.8 (±17.5)	
Mean %DLCO (±SD)	26.6 (±7)	32.2 (±19.9)	n.s.
Mean PaO_2 (±SD) (in mm Hg)	56.1 (±8.4)	55 (±8.5)	n.s.
Mean $PaCO_2$ (±SD) (in mm Hg)	41.8 (±5)	44.7 (±7.8)	n.s.
Mean %6MWT distance (±SD) (in m)	48.7 (±3.6)	45.9 (±2.6)	n.s.

Percentages refer to the total group population.
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV1, 1-second forced expiratory volume; FVC, forced vital capacity; DLCO, diffusion lung capacity for carbon monoxide; %6MWT, percent of the predicted distance at 6 minute walking test; n.s., not significant.

The aim of this study was to define the prevalence of PH in 2 populations who will undergo lung transplantation (COPD and pulmonary fibrosis patients) at the transplantation center referral. As a secondary objective we evaluated differences in hemodynamic parameters between these 2 groups.

METHODS

We conducted an observational retrospective study; we studied RHC in a consecutive cohort of patients who underwent lung transplantation from 2006 to 2014 for COPD and pulmonary fibrosis. Through the analysis of the corresponding medical records, for each patient the following information was gathered: demographics, body mass index, smoking habits, presence of comorbidities (coronary artery disease, systemic arterial hypertension, osteopenia/osteoporosis, diabetes, obstructive sleep apnea syndrome), arterial blood gas analysis, spirometric functional data (1-second forced expiratory volume [FEV1], forced vital capacity [FVC], DLCO) and 6-minute walking test distance performed (percentage of the predicted value, in accord with the Enright equation).

During the pretransplantation evaluation, all patients underwent RHC. The femoral or jugular venous approach was used for RHC. Cardiac output (CO) and CI were calculated by saturation measurement according to the Fick method. pulmonary artery pressure (PAP), pulmonary wedge pressure (PWP), right ventricular pressure, and right atrial pressure were measured during breath hold at baseline over at least 3 heart cycles. Mean pulmonary artery pressure was calculated by integration of the pressure curve using Metek software (Metek GmbH, Roetgen, Germany). Pulmonary vascular resistance was derived from pulmonary vascular resistance = (mean pulmonary artery pressure − pulmonary capillary wedge pressure)/cardiac output.

Diagnosis of PAH was made in accord with international guidelines [20]. We collected the following RHC data: systolic PAP,

Table 2. Prevalence of mPAP in the 2 Populations

mPAP (in mm Hg)		Fibrosis	COPD	
<25	n.	24	6	30
Normal	%	68.6	15.8	41.1
25≤mPAP<35	n.	6	22	28
Mild	%	17.1	57.9	38.6
35≤mPAP<45	n.	4	8	12
Moderate	%	11.4	21.1	16.4
≥45	n.	1	2	3
Severe	%	2.9	5.3	4.1

Division of mPAP values in 4 groups: normal, mild, moderate, and severe. Percentages refer to the total group population.

Abbreviations: mPAP, mean pulmonary arterial pressure; COPD, chronic obstructive pulmonary disease.

diastolic PAP, mean PAP, CO, CI, PWP and total pulmonary vascular resistances. Values of mPAP were divided into 4 categories: <25 mm Hg (normal), 25 to 35 mm Hg (mild PH), 35 to 45 mm Hg (moderate PH), >45 mm Hg (severe PH) [21]. A further speculative division of mPAP values provided 6 categories [22,23]: <25 mm Hg, 25 to 29 mm Hg, 30 to 34 mm Hg, 35 to39 mm Hg, 40 to 44 mm Hg, and ≥45 mm Hg.

Comparison between the groups of patients with pulmonary fibrosis and the group with COPD were conducted using the Student *t* test for continuous outcome variables such as DLCO, CO, continuous mPAP. Pearson χ^2 tests were used for categorical outcome variables such as categories of mPAP.

RESULTS

We retrospectively analyzed data of 73 patients; 35 of them belonged to the fibrosis group and 38 to the COPD group. Demographic and functional data are shown in Table 1. The fibrosis population had a higher prevalence of patients affected by osteopenia/osteoporosis or diabetes than the COPD one. On the contrary, COPD patients had a higher prevalence of smoking history and systemic arterial hypertension. We did not find any difference in PaO_2, $PaCO_2$, DLCO, and 6-minute walking test distance data between the 2 groups of patients. We did not search any difference in FEV1 and FVC values because the 2 leading pathologies had different functional spirometric characteristics.

On the basis of mPAP value, we first divided patients in 4 groups: <25 mm Hg (normal), 25 to 35 mm Hg (mild PH), 35 to 45 mm Hg (moderate PH), >45 mm Hg (severe PH) (21). There was evidence of difference between groups ($P < .0001$): in particular, the majority of fibrosis patients presented normal PAPm values (68.6% of them) and the PH prevalence was 31.4%; on the other hand, PH prevalence in COPD patients was 84.3% (57.9% had a mild, 21.1% a moderate, and 5.3% a severe PH) (data shown in Table 2). Secondly, we divided PAPm values into 6 groups: <25 mm Hg, 25 to 29 mm Hg, 30 to 34 mm Hg, 35 to 39 mm Hg, 40 to 44 mm Hg, and ≥45 mm Hg. In this subdivision, there also was evidence of difference between groups ($P < .001$); COPD patients had PAPm values between 25 and 29 mm Hg in 31%, between 30 and 34 mm Hg in 26%, and between 35 and 39 mm Hg in 15% of cases. These data confirmed that in fibrosis, values of mPAP > 25 mm Hg are equally distributed in all remaining 5 categories (Table 3).

Fibrosis and COPD RHC data are shown in Table 4. COPD patients presented with higher dPAP ($P < .005$), mPAP ($P < .001$), PWP ($P < .05$), and total pulmonary vascular resistances ($P < .01$) than the fibrosis group.

DISCUSSION

The prevalence of PH in the general COPD population is undefined because stable COPD patients do not routinely undergo RHC. Most studies published on this topic focus on patients with moderate to severe disease awaiting lung transplantation because hemodynamic data from cardiac catheterization are part of the standard transplant evaluation. These studies revealed that PH is common in advanced COPD. One of these studies evaluated patients with functionally very severe COPD (mean FEV1 <27% predicted) using a cutoff for definition of PH of a mPAP higher than 20 mm Hg; they found that 90.8% of those patients had PH. The majority (61.4%) of them had an elevated PWP (higher than 12 mm Hg), suggesting the cause of their PH was related, at least in part, to underlying cardiac abnormalities [22]. A second study followed up 215 patients evaluated for lung volume reduction surgery or lung transplantation (mean FEV1 24% predicted). Using a conventional definition of PH (mPAP >25 mm Hg), and excluding patients with elevated PWP, the prevalence of PH was 50.2% [23]. The largest study to date evaluated 4930 patients listed for lung transplantation with the primary diagnosis of COPD. Pulmonary hypertension was defined using World Health Organization Group 1 PAH criteria (mPAP >25 mm Hg with PWP <15 mm Hg) and pulmonary venous hypertension as mPAP ≥25 mm Hg with PWP more than 15 mm Hg.

Table 3. Prevalence of mPAP in the 2 Populations

mPAP (in mm Hg)	Fibrosis	COPD	
<25			
n.	24	6	30
%	68.6	15.8	41.1
25≤mPAP<29			
n.	4	12	16
%	11.4	31.5	21.9
30≤mPAP<35			
n.	2	10	12
%	5.7	26.3	16.4
35≤mPAP<40			
n.	1	6	7
%	2.8	15.7	9.5
40≤mPAP<45			
n.	3	2	5
%	8.5	5.2	6.8
≥45			
n.	1	2	3
%	2.8	5.2	4.1

Division of mPAP values in 6 groups. Percentages refer to the total group population.

Abbreviations: mPAP, mean pulmonary arterial pressure; COPD, chronic obstructive pulmonary disease.

Table 4. Hemodynamic Parameters in the 2 Populations

Hemodynamic parameters	Fibrosis	COPD	*P*
Mean sPAP (±SD) (in mm Hg)	41.1 (18.8)	43.1 (12.4)	n.s.
Mean dPAP (±SD) (in mm Hg)	15.9 (8.2)	22.2 (7.7)	<.005
Mean mPAP (±SD) (in mm Hg)	24.1 (8.2)	30.3 (6.9)	<.001
Mean PWP (±SD) (in mm Hg)	10.1 (0.8)	13.7 (1.1)	<.05
Mean CO	6.3 (1.6)	6.2 (2.5)	n.s.
Mean CI	3.3 (0.6)	3.7 (1.1)	n.s.
Mean total pulmonary vascular resistances	4 (2)	5.5 (2)	<.01

Abbreviations: mPAP, mean pulmonary arterial pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; CO, cardiac output; CI, cardiac index.

The prevalence of PH in this cohort was reported to be 31%, with an additional 17% having PVH [24]. Several studies in patients with previous GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage IV showed that up to 90% of these patients have a mPAP of >20 mm Hg, with most ranging between 20 and 35 mm Hg and about 3% to 5% of patients with mPAP >35 to 40 mm Hg [25]. In our experience, the prevalence of PH in COPD patients was 83.5% and is in line with literature data; in particular, the majority of the COPD population presented mPAP values consistent with mild PH. As reported in the literature, our population also had very compromised lung function with a severe degree of bronchial obstruction (mean FEV1 26.5%) and hypoxemia at rest (PaO_2 55 mm Hg) but, considering the functional impairment (DLCO, distance achieved during 6-minute walking test, PaO_2, $PaCO_2$), no differences with the fibrosis group were reported. Compared with the literature, we reported a lower percentage of COPD patients with PWP >15 mm Hg (18%).

In interstitial lung diseases, international guidelines suggest that PAP values are the most important predictor of mortality [10]. In the literature, the prevalence of PH in patients affected by IPF ranges from 8% to 21%, but higher percentages (30% to 50%) are found in advanced and end-stage cases [19,26]. Among those patients, a few may present with mPAP values >40 mm Hg [7]. Our results confirm these assumptions because the prevalence of PH in the fibrosis group in our study is 31.4%, and only 11.3% of them presented with mPAP <40 mm Hg.

The study of right heart pressure is really fundamental when a patient is evaluated for a lung transplantation, as we have to answer at least 2 questions: "is it the correct time?" and "What is the correct procedure (single or double lung transplant)?" The correct timing in COPD is given in particular by the BODE index [27,28], but the presence of PH is a mandatory indication [29]; moreover, the choice of procedure in COPD [30] and in fibrosis [31] is yet an open debate, because new procedures of organ procurement are now available (ie, ex vivo lung reperfusion and non–heart-beating donors) [32–35].

A remarkable problem in intensive care units is the postsurgical management in cases of a single procedure in COPD: in fact in PH-COPD patients immediately after transplantation almost all the blood flow is directed to the transplanted lung with high risk of reperfusion syndrome, while all the ventilation is directed to the more compliant lung (native COPD lung) but with low perfusion. In cases of reperfusion edema, we run the risk of having a transplanted lung perfused and unventilated and a native COPD lung ventilated but unperfused. The mPAP value used as cut-off to choose the procedure is conventionally 30 to 35 mm Hg, but this is an empirical behavior that needs more data [36].

In our study, there was a difference in hemodynamic values between 2 populations, with worse data for the COPD one. Possible explanations may be the following: 1) some severe COPD patients referred to transplant centers have two different diseases: a common (COPD) and a rare one (PAH); 2) PH is an indication for lung transplant in COPD, and patients with echocardiographic suspected disease are referred to transplant centers earlier; 3) other patients are referred to transplant centers too late with higher PH, very poor outcome, and a progressive disease; 4) patients with COPD and PH have worse symptoms (dyspnea) and a poorer quality of life, and clinicians are more prone to refer to a transplant center.

On the other hand, patients with interstitial lung diseases undergoing lung transplant have a lower prevalence of PH at RHC evaluation. These data have different possible explanations: 1) patients with pulmonary fibrosis have such a poor quality of life and shortness of breath that they are referred to transplantation centers before the development of PH; 2) patients with PH associated with interstitial diseases are so clinically and functionally compromised that they die on the waiting list before having a surgical opportunity; 3) PH leads to a higher risk of death on the waiting list because of an obligatory procedure choice (bilateral lung transplant), to avoid reperfusion syndrome, that limits the pool of donors.

Moreover, the bilateral procedure cannot be proposed for older patients; this limits both the number of potential recipients and, in the case of good donors, the number of patients undergoing lung transplantation with a single lung procedure.

CONCLUSIONS

Clinical symptoms and physical signs of PH may be difficult to identify in patients affected by respiratory disorders. COPD and diffuse parenchymal lung diseases, including IPF, are associated with a high prevalence of PH. In our center, during routine pretransplantation evaluation, the RHC revealed a higher prevalence of PH in COPD patients. On the contrary, the prevalence is lower in cases of fibrotic disease, and the majority of patients have normal mPAP values. A careful evaluation of clinical and hemodynamic data is mandatory because it may influence the prognosis of patients and the type of surgical approach.

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