Pulmonary Arterial Hypertension-Specific Drug Therapy in COPD Patients with Severe Pulmonary Hypertension and Mild-to-Moderate Airflow Limitation

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Key Words

Chronic obstructive pulmonary disease · Severe pulmonary hypertension · Chronic hypoxemia · Pulmonary vasodilators · FEV₁/DLCO ratio

Abstract

Background: Patients with severe pulmonary hypertension (PH) associated with chronic obstructive pulmonary disease (COPD) present a poor outcome. Specific PH treatment could improve the clinical and hemodynamic status of these patients but may worsen arterial blood gases. **Objectives:** Our study retrospectively included 28 patients with severe pre-capillary PH (mean pulmonary arterial pressure >35 mm Hg) associated with mild-to-moderate COPD [forced expiratory volume in 1 s (FEV₁) >50% predicted]. All patients underwent specific pulmonary arterial hypertension (PAH) treatment as mono-, bi- or triple therapy. **Methods:** Our single-center study was conducted based on retrospective data of 537 right heart catheterizations (RHCs) performed on patients with COPD from January 2004 to June 2014. An echocardiography, comprehensive blood tests, pulmonary function tests, and a high-resolution computed tomography were performed before the RHCs. All patients underwent RHC

with a Swan-Ganz catheter. **Results:** Compared to baseline, patients treated with specific PAH drugs showed a significant increase in cardiac index at long term (2.5 ± 0.7 liters/min/m² at baseline vs. 3.2 ± 0.6 liters/min/m² at 6/12 months; $p = 0.003$) as well as a decrease in pulmonary vascular resistance in the long term (8.4 ± 4.2 Wood units at baseline vs. 5 ± 1.7 Wood units at 6/12 months; $p = 0.008$). There was a slight decrease in arterial oxygen tension (PaO₂) after 3 months of treatment (-2.4 ± 7.21 mm Hg; $p = 0.066$). During a median follow-up of 3 years, 12 patients (42.8%) died (including all causes of death). **Conclusions:** This preliminary report suggests that the use of specific PH therapy in severe PH associated with mild-to-moderate COPD can improve pulmonary hemodynamic parameters, with worsening of PaO₂, which had no clinical significance and did not lead to specific PAH therapy withdrawal in any patient.

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Introduction

Pulmonary hypertension (PH) is a frequent complication of chronic obstructive pulmonary disease (COPD) [1, 2]. Typical hemodynamic abnormalities usually in-

Fig. 1. Flowchart. FVC = Forced vital capacity; FC = functional class; PFTs = pulmonary function tests; 6MWT = 6-min walking test; PCWP = pulmonary capillary wedge pressure.

clude mild-to-moderate elevation in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) with a preserved cardiac output (CO). PH associated with COPD (PH-COPD) affects survival [3] and exercise capacity [4] and is associated with an increased risk of acute exacerbations [5]. Severe PH occurs in only 1–5% of patients with COPD [1, 2, 6]. There are many pathophysiological factors which could explain the severity of PH-COPD: higher susceptibility to alveolar hypoxia [2], vascular remodeling [7–9], inflammation, and genetic predisposition, or even the coexistence by chance of COPD and idiopathic pulmonary arterial hypertension (PAH) [2]. During the last PH symposium held in Nice in 2013, severe PH-COPD was defined by a resting mPAP ≥ 35 mm Hg, with a pulmonary capillary wedge pressure < 15 mm Hg [6]. Using the Aspire registry, the largest cohort of patients with severe PH-COPD, Hurdman et al. [10] showed that age, diffusing capacity of the lung for carbon monoxide (DLCO), mixed venous oxygen saturation (SvO₂), and World Health Organization functional class were independent predictors of survival. They also showed that severe PH-COPD has a poor prognosis, with survival at 3 years estimated at 33%.

As already known, specific PAH therapy could have deleterious effects on blood gas exchange [11–13]. Two prospective studies have evaluated the efficacy and safety of specific PAH therapy in COPD patients with second-

ary PH: in a first study, sildenafil showed no improvement in stroke volume or exercise capacity [11], but a second study revealed improvement in pulmonary hemodynamics at rest and during exercise, with an impairment of arterial oxygenation at rest [13]. However, none of these 2 studies did include patients with severe PH. In the study of Hurdman et al. [10], targeted therapies in 43 COPD patients [mean forced expiratory volume in 1 s (FEV₁): $71 \pm 23\%$ of predicted (pred.)] with severe PH was not associated with a survival benefit, although improvement in New York Heart Association (NYHA) functional class and/or a fall in PVR $> 20\%$ was associated with improved survival.

The main objective of our study was to determine the efficacy and safety of PAH-specific drug therapy for COPD patients with severe PH associated with mild-to-moderate airflow limitation. We also aimed to describe this particular phenotype and to determine the survival rate in this group of patients treated with PAH-specific drug therapy.

Materials and Methods

Study Design

Our single-center study was conducted based on retrospective data of 537 right heart catheterizations (RHCs) performed on patients with COPD from January 2004 to June 2014. It complied

with the Declaration of Helsinki and was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine – ‘Société de Pneumologie de Langue Française’ (CEPR No. 2015-010).

All patients investigated in the present study met the current definition of COPD [14]. An echocardiography, comprehensive blood tests, pulmonary function tests, and a high-resolution computed tomography were performed before the RHCs. All patients underwent RHC with a Swan-Ganz catheter.

Patients were excluded if they had: (1) an identifiable cause of PH other than COPD, drug-induced PAH, PH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or pulmonary veno-occlusive disease; (2) a concomitant chronic lung disease known to cause PH (pulmonary fibrosis, bronchiectasis, restrictive pulmonary disease, cystic fibrosis, or sarcoidosis), or (3) chronic thromboembolic PH. All patients were in stable state and at least 4 weeks had passed since acute exacerbation of COPD or any other acute event.

Following detailed assessment (fig. 1), 48 patients presented severe PH (mPAP ≥ 35 mm Hg and a pulmonary capillary wedge pressure < 15 mm Hg, measured during RHC) associated with COPD. The date of diagnosis of severe PH-COPD was taken as the date of the first RHC that demonstrated the PH. NYHA functional class, the pulmonary function tests, a 6-min walking test, echocardiography, and blood tests obtained close to the date of RHC (within 1 week) were recorded as the baseline measurements. The treatment of COPD patients was in accordance with the latest guidelines [15], and all patients were on long-term oxygen therapy. Concerning the treatment of PH, we used approved drugs on a compassionate basis after discussion in a multidisciplinary meeting.

Twenty patients had severe PH associated with severe COPD ($FEV_1 < 50\%$ pred.); of these, 13 patients did not undergo a specific PAH treatment because of severe chronic respiratory failure and were placed on a lung transplantation waiting list. Seven patients with severe PH associated with severe COPD were treated with targeted PAH drugs.

Twenty-eight patients with severe PH associated with mild-to-moderate COPD ($FEV_1 > 50\%$ pred.) underwent PAH-specific drug therapy (table 1). These latter patients were re-evaluated after 3 months and 6 or 12 months after the initiation of treatment. During follow-up visits, NYHA functional class was determined, and the 6-min walking test, arterial blood gases, an echocardiography, and an RHC were performed. We also collected survival data. We calculated the $FEV_1/DLCO$, which has been shown to be a potential predictor of precapillary PH in COPD patients [16].

Investigations

RHC was performed in patients who had been clinically stable for the last 4 weeks. CO was determined by the Fick method using measured oxygen consumption in room air. PVR was calculated by dividing mPAP minus pulmonary artery wedge pressure by CO. Pulmonary function tests, arterial blood gases, alveolar-arterial oxygen gradient ($A-a O_2$), 6-min walking distance (6MWD), and plasma B-type natriuretic peptide levels were obtained the week before RHC.

Statistical Analysis

SPSS Statistics version 20 was used for all statistical analyses. Continuous variables were described as the mean $\pm$ SD. Significant

Table 1. Therapy of patients with severe PH associated with mild-to-moderate airflow limitation

PAH-specific therapy	Baseline (n = 28)	3 months (n = 27)	6/12 months (n = 24)
ERA monotherapy	23	16	13
PDE-5I monotherapy	1	3	1
Oral bitherapy	1	6	9
Prostanoid monotherapy	1	0	0
Prostanoid in combination	0	1	2
Triple therapy	1	1	2
CCB	1	0	0

Data are the number of patients treated in each category. CCB = Calcium channel blocker. Oral monotherapy: PDE-5I or ERA. Oral bitherapy: PDE-5I and ERA. Prostanoid monotherapy: nebulized iloprost or intravenous epoprostenol. Prostanoid in combination: prostanoid in combination with any other targeted therapy/therapies. Triple therapy: combination of PDE-5I and ERA and prostanoid.

Table 2. Demographic and hemodynamic characteristics at baseline

Demographic variables	Severe PH $FEV_1 > 50\%$ pred. (n = 28)	Severe PH $FEV_1 < 50\%$ pred. (n = 20)	p value
Age, years	71.2 $\pm$ 9.4	64 $\pm$ 10.5	0.022
Males	22/28	10/13	
BMI	27.4 $\pm$ 5.5	25.4 $\pm$ 8.5	0.161 (n.s.)
NYHA class III or IV	22	19	
6MWD, m	259.2 $\pm$ 104.1	204.1 $\pm$ 71.8	0.115 (n.s.)
FVC, % pred.	93.7 $\pm$ 17.9	57.3 $\pm$ 18.8	< 0.0001
FEV_1 , % pred.	69.3 $\pm$ 13.8	28.4 $\pm$ 10.3	< 0.0001
$FEV_1/FVC\%$	57.7 $\pm$ 8	40.8 $\pm$ 10.6	< 0.0001
TLC, % pred.	95.7 $\pm$ 19.5	120.6 $\pm$ 29.2	0.004
RV, % pred.	108.8 $\pm$ 40.9	220.3 $\pm$ 80	< 0.0001
DLCO, % pred.	26.8 $\pm$ 11.8	28.1 $\pm$ 13.6	0.982 (n.s.)
$FEV_1/DLCO$	2.98 $\pm$ 1.2	1.17 $\pm$ 0.63	< 0.0001
PaO_2 , mm Hg	49.6 $\pm$ 9.5	49.7 $\pm$ 11.3	0.944 (n.s.)
$A-a O_2$, mm Hg	57.65 $\pm$ 12.28	42.9 $\pm$ 17.1	0.006
$PaCO_2$, mm Hg	34.1 $\pm$ 5.4	45.8 $\pm$ 11.6	< 0.0001
mPAP, mm Hg	44.2 $\pm$ 8.7	42.6 $\pm$ 8	0.607 (n.s.)
CO, l/min	4.8 $\pm$ 1.3	5.8 $\pm$ 1.7	0.038
CI, l/min/m ²	2.5 $\pm$ 0.67	3.4 $\pm$ 1.7	0.001
PVR, Wood units	8.5 $\pm$ 4.5	6.6 $\pm$ 2.8	0.253 (n.s.)
SvO_2 , %	57.6 $\pm$ 9.9	62.4 $\pm$ 9.2	0.101 (n.s.)
BNP, ng/l	296 $\pm$ 389	143 $\pm$ 152	0.141 (n.s.)

Data are presented as %, or mean $\pm$ SD. The Mann-Whitney U test was used for nonparametric data. BMI = Body mass index; n.s. = not significant; FVC = forced vital capacity; TLC = total lung capacity; RV = residual volume; $PaCO_2$ = arterial carbon dioxide tension; BNP = brain natriuretic peptide.

Fig. 2. Correlation test between FEV₁/DLCO, CI, PaO₂, and 6MWD.

differences at baseline, between the 2 subgroups (with or without severe airflow limitation), defined in the Results section, were determined using the Mann-Whitney U test. The hemodynamic data, 6MWD, and arterial blood gases, from the time of diagnosis to the 1st or 2nd follow-up, were compared between the groups by the Kruskal-Wallis test followed by the post hoc Mann-Whitney test. Correlation coefficients were calculated using Spearman's test. Survival was evaluated using the Kaplan-Meier method, and the survival rates were compared using the log-rank test. Overall survival was assessed until the 1st of June 2014. A p value <0.05 was considered statistically significant. All parameters with a p value <0.20 were entered into the multivariate Cox proportional hazards analysis.

Results

Baseline Patient Characteristics

The study population included 28 patients with severe PH associated with mild-to-moderate airflow limitation (FEV₁ $>50\%$ pred.). Among these patients, 6 had an FEV₁ $>80\%$ of the predicted value. The mean age was 71.2 ± 9.4 years, with a male predominance of 78.5%. In spite of a mild-to-moderate airflow limitation, these patients had a significant decrease in DLCO, with a mean value of $26.8 \pm 11.8\%$.

We compared, at baseline, the group with severe PH and mild-to-moderate COPD to the group with severe PH associated with severe COPD (table 2); patients with severe PH associated with mild-to-moderate COPD were older (71.2 ± 9.4 vs. 64 ± 10.5 years; $p = 0.022$), had, by definition, a higher FEV₁ (69.3 ± 13.8 vs. $28.4 \pm 10.3\%$; $p < 0.0001$), were hypocapnic (34.1 ± 5.4 vs. 49.5 ± 11.6

mm Hg; $p < 0.0001$), with an increased A-a O₂ (57.6 ± 12.3 vs. 42.9 ± 17.1 mm Hg; $p = 0.006$), and had more severe hemodynamic impairment [cardiac index (CI) at 2.5 ± 0.67 vs. 3.7 ± 1.7 liters/min/m²; $p = 0.001$]. Note that arterial oxygen tension (PaO₂) and mPAP were similar in both groups.

Correlations at Baseline

In the study population ($n = 28$) at baseline, the FEV₁ (% pred.)/DLCO (% pred.) ratio was 2.28 ± 1.35 and correlated negatively with CI ($r = -0.47$, $p = 0.041$), PaO₂ ($r = -0.505$, $p = 0.027$), and 6MWD ($r = -0.552$, $p = 0.022$), and positively with A-a O₂ ($r = 0.508$, $p = 0.027$; fig. 2).

At baseline, the functional class (NYHA) correlated with exercise capacity (6MWD: $r = -0.75$, $p < 0.0001$), respiratory function parameters (DLCO: $r = -0.717$, $p = 0.001$; PaO₂: $r = -0.408$, $p = 0.031$), hemodynamic status (CI: $r = -0.59$, $p = 0.001$; PVR: $r = 0.49$, $p = 0.007$), and echocardiographic parameters (tricuspid annular plane systolic excursion: $r = -0.922$, $p < 0.0001$).

Follow-Up Results

All 28 patients with severe PH associated with mild-to-moderate airflow obstruction underwent PAH-specific drug therapy: 23 patients were treated with endothelin receptor antagonist (ERA), 1 patient with phosphodiesterase-5-inhibitor (PDE-5I), 1 patient with oral bitherapy, 1 patient with prostanoid in monotherapy, 1 patient with triple therapy, and 1 patient with calcium channel blocker. After 6 or 12 months of treatment, only 14 patients were still treated by monotherapy.

Fig. 3. Evolution of CI and PVR. * $p < 0.05$; ** $p < 0.01$.

Table 3. Evolution of clinical and paraclinical parameters after specific PAH therapy

	Baseline (n = 28)	3 months (n = 28)	6/12 months (n = 16)	p value ¹
mPAP, mm Hg	44.1±8.7	43.4±8.35	39.43±6.56	n.s.
CO, l/min	4.8±1.2	5.4±1.1	5.9±0.9	0.018
CI, l/min/m ²	2.5±0.7	2.9±0.6	3.2±0.6	0.003
PVR, Wood unit	8.4±4.2	6.7±3	5±1.7	0.008
RAP, mm Hg	7.4±4.2	8.7±5	8±3.3	n.s.
SvO ₂ , %	57.5±10	55.9±9.2	58.8±9	n.s.
PaO ₂ , mm Hg	49.6±9.5	46.7±7.4	49.2±7.9	n.s.
A-a O ₂ , mm Hg	57.6±12.3	60.5±8.7	56.9±11.7	n.s.
PaCO ₂ , mm Hg	34.1±5.5	34.2±5.3	35±8.5	n.s.
6MWD, m	259.2±104	268.3±112.8	274.1±107.9	n.s.
NYHA class III or IV	22	21		

Data are presented as the mean ± SD. RAP = Right atrial pressure; PaCO₂ = arterial carbon dioxide tension.

¹ Kruskal-Wallis test for nonparametric data followed by the Mann-Whitney test (p value for the comparison between baseline and second follow-up at 6/12 months).

At follow-up, RHC data at 3 months were available for all 28 patients; at 6 or 12 months, only 16 patients had a hemodynamic re-evaluation by RHC.

After comparison at baseline, 3 months, and 6 or 12 months (fig. 3), we found a significant increase in CI at long term (2.5 ± 0.7 liters/min/m² at baseline vs. 3.2 ± 0.6 liters/min/m² at 6/12 months; $p = 0.003$) and a decrease in PVR at long term (8.4 ± 4.2 Wood units at baseline vs. 5 ± 1.7 Wood units at 6/12 months; $p =$

0.008). We observed a trend in hemodynamic improvement at 3 months: CI (2.5 ± 0.7 liters/min/m² vs. 2.9 ± 0.6 liters/min/m²; $p = 0.08$), PVR (8.4 ± 4.2 vs. 6.7 ± 3 ; $p = 0.46$) (table 3). We did not observe any significant difference between the mPAP value at baseline, 3 months, and at 6 or 12 months of treatment. Concerning blood gas exchange, there was a slight decrease in PaO₂ after 3 months of treatment (-2.4 ± 7.21 mm Hg; $p = 0.066$) and an increase in A-a O₂ (2.03 ± 8.9 mm Hg;

Fig. 4. Cumulative survival since the diagnosis.

Fig. 5. Cumulative survival by evolution of $\Delta A-a O_2$ at 3 months.

Table 4. Univariate analysis of factors associated with mortality

Variable	p value
$\Delta A-a O_2 > 0$	0.014
$\Delta PaO_2 > 0$	0.19
DLCO <27% pred.	0.09
6MWD at baseline >260 m	0.29
CO at baseline <4.8 liters/min	0.23
CI at baseline <2.5 liters/min/m ²	0.34
PVR at baseline >8.4 Wood units	0.53
SvO ₂ at baseline >57.5%	0.71
BNP at baseline >296	0.85

RAP = Right atrial pressure; BNP = brain natriuretic peptide.

Table 5. Multivariate analysis of factors associated with mortality

Variable	HR	95% CI	p value
$\Delta A-a O_2 > 0$	0.164	0.009–3.067	0.226
$\Delta PaO_2 > 0$	0.766	0.049–12.007	0.849
DLCO <27% pred.	0.229	0.042–1.247	0.88

HR = Hazard ratio; CI = confidence interval.

$p = 0.08$). Moreover, after 3 months of treatment, we observed that 16 patients had worsened PaO_2 (-6.83 ± 3.46 mm Hg; $p < 0.0001$), and 10 patients had improved PaO_2 (4.68 ± 5.82 mm Hg; $p = 0.032$). After comparison analysis, the patients with improved gas exchange had

a better CI (2.8 vs. 2.3 liters/min/m²; $p = 0.086$). In terms of A-a O_2 , 9 patients presented an improvement after 3 months of treatment and, in comparison with the 17 patients who showed worsened A-a O_2 , they had a better FEV₁ (76.7 vs. 65.8%; $p = 0.031$) and a lower residual volume (80 vs. 117.5%; $p = 0.018$). Worsening of PaO_2 did not lead to specific PAH therapy withdrawal in any patient.

After 3 months of treatment or more, we did not find any difference in terms of functional class or 6MWD, but we observed a trend of stabilization in walked distance (277 m at baseline vs. 268 m after 3 months of treatment; $p = 0.59$).

Survival and Prognostic Indicators

In our cohort of patients with severe PH associated with mild-to-moderate COPD, all treated with specific PH therapy, 12 patients (42.8%) died (including all causes of death) during the study period. The median survival was 36 months; the median follow-up time was 3 years (95% confidence interval 1.7–4.3; fig. 4). The cumulative survival rates at 1 and 2 years were 84 ± 7 and $63 \pm 10\%$, respectively.

Results of the univariate analysis are presented in table 4.

We found that patients with increased A-a O_2 had a better survival than those in whom A-a O_2 had decreased while treated with specific PH drugs ($p = 0.014$; fig. 5); however, this was no longer significant in multivariate analysis (table 5).

Discussion

Our study demonstrates that specific pulmonary vasodilators can significantly improve pulmonary hemodynamics in patients with severe PH associated with mild-to-moderate COPD. Hypoxemia worsened in 60% of patients, but did not lead to specific PAH treatment withdrawal.

There are limited data to support the use of specific pulmonary vasodilators in patients with severe PH-COPD; this phenotype is characterized by a poor prognosis [10] and similarities with idiopathic PAH [17].

Our study is the first, to our knowledge, to evaluate the efficacy, in terms of clinical and hemodynamic status, and the safety, regarding the risk of worsening arterial oxygenation of targeted drugs, and to describe the particularities of severe PH associated with mild-to-moderate COPD.

We observed a significant improvement in cardiopulmonary hemodynamic parameters at long term (6 or 12 months) and also a trend of hemodynamic improvement after 3 months of treatment. There are few studies in the literature which evaluated the hemodynamic status of PH-COPD in patients treated with specific PH therapy, and the results are contradictory [10, 13, 18–21]. A recent meta-analysis which included 9 randomized controlled trials concerning PH-specific therapy in PH-COPD patients showed an improvement in dyspnea, exercise capacity, and PAP [22].

In contradiction with our study, which assessed patients with severe PH, these studies were conducted in COPD patients with mild-to-moderate PH. It was shown that sildenafil could improve the hemodynamic status at rest and during exercise in mild PH-COPD patients, with worsening of PaO₂ at rest but not during exercise [13]. However, in a second prospective study, treatment with sildenafil had no effect on stroke volume or exercise capacity [11]. In the study of Hurdman et al. [10], COPD patients with all classes of severity of airflow limitation were included, but only a few patients had follow-up RHCs. They showed that improvement in NYHA functional class following treatment improved survival.

In our study, due to worsening of the clinical and hemodynamic status, 8 patients were switched to oral bi-therapy (PDE-5I and ERA), 2 to prostanoid plus PDE-5I or ERA, and 1 to triple therapy (prostanoid, PDE-5I, and ERA). Fourteen patients out of 25 remained on monotherapy after the 3rd evaluation.

Previous studies have raised concerns regarding acute worsening of arterial oxygen blood levels in patients with

COPD who received specific pulmonary vasodilators [18, 19, 23–25]. In our study, we observed a slight decrease in PaO₂ with an increase in A-a O₂, but these changes were not statistically significant. Interestingly, 38% of patients had improved PaO₂ after 3 months of treatment ($p = 0.032$). These patients had a higher CI in comparison to patients with worsened arterial oxygenation after the specific treatment.

In a recent retrospective study, NYHA functional class and 6MWD had improved after PH-targeted vasodilator therapy [19]. In our study, there was no statistical change over time under treatment, in terms of clinical status, exercise capacity, or respiratory function. Interestingly, we observed that the NYHA functional scale correlated with exercise capacity (6MWD), respiratory parameters (DLCO, PaO₂, and A-a O₂), and hemodynamic features (CI, PVR, SvO₂, and tricuspid annular plane systolic excursion).

We included patients with a phenotype of severe PH associated with mild-to-moderate COPD. This patient group was characterized by an elevated mPAP, a low CI, high PVR associated with a reduced DLCO, and severe hypoxemia associated with hypocapnia, despite mild-to-moderate airflow obstruction. By contrast, patients with a phenotype of severe PH associated with severe COPD, despite similar levels of mPAP and PaO₂, showed a higher CI and lower A-a O₂. We confirmed that the FEV₁/DLCO ratio could be a useful marker to assess the association of lung function impairment due to COPD and hemodynamic impairment and may be helpful in defining the indications for a hemodynamic evaluation in COPD patients.

In the literature, age, dyspnea scale, DLCO, and SvO₂ were independent predictors of survival in PH-COPD [10]. In the present study, we also confirmed the poor prognosis of this population, despite the use of specific PH therapy, with a median survival of 36 months. In the study of Hurdman et al. [10], in the patients with severe PH-COPD, 1-year survival was 70% and 3-year survival 33%. Surprisingly, patients with a deteriorated gas exchange (increased A-a O₂ after 3 months of treatment) showed better survival than those who had stable or decreased A-a O₂ in univariate analysis. This result could suggest a higher efficacy of PAH-specific drugs, resulting in higher ventilation/perfusion mismatches. Since impairment of A-a O₂ correlated with a higher degree of airflow limitation and hyperinflation, we could hypothesize that a targeted PH therapy which improves pulmonary hemodynamics deteriorates gas exchange if COPD is more severe.

It is clear that the vascular impairment is crucial in this disease. The particular phenotype of severe PH in mild-to-moderate COPD, also called 'out of proportion' PH, has a number of similarities with idiopathic PAH. Severe PH associated with severe COPD has different characteristics, with a better preserved cardiac function suggesting a different phenotype.

Randomized controlled trials are needed to prove the efficacy of specific therapy for selected patients with this particular phenotype of severe PH with mild-to-moderate COPD in which the pulmonary hemodynamic impairment is predominant and cannot be explained by the ventilatory defect.

Improvement in cardiac and vascular parameters was associated with a small decrease in PaO₂, which we considered acceptable (approximately 3 mm Hg). There were no patients in whom there was a clinically significantly reduction in PaO₂ that resulted in discontinuation of the PAH-specific therapy.

This study has certain limitations. It retrospectively analyzed a highly selected cohort of patients, in a regional PH center. Therefore, no estimate of the incidence or prevalence of severe PH-COPD in the COPD population can result from this study. Also, despite the routine use of RHC in our center, some results for the 3rd evaluation are missing. The delay between the 2nd and the 3rd RHC controls differs in our cohort of patients (at 6 or 12 months).

The dropout rate after 6/12 months may lead to biased results, as only those patients, who were in better condition, may have survived until this period of time or were able to be assessed by RHC.

Most importantly, we did not have a control group to compare the treatment efficacy, but this issue could be explained by the low prevalence of patients with severe PH associated with mild-to-moderate COPD and the difficult ethical question of not treating severe PH in mild-to-moderate COPD. In addition, our study was too small to evaluate the different specific PH therapies separately.

Conclusion

The hemodynamic status of severe PH with mild-to-moderate COPD improved after 6/12 months of treatment with specific pulmonary vasodilators. We confirmed a poor prognosis in our cohort. Patients with severe PH and severe COPD have different outcomes. A high FEV₁/DLCO ratio could indicate the need of hemodynamic screening for COPD patients. Given the poor outcome of this condition and the low prevalence, multicenter randomized controlled trials of specific PAH therapy in severe PH-COPD and mild-to-moderate airflow limitation are needed.

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