Pulmonary Hypertension in COPD

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Pulmonary hypertension (PH) is a common consequence of COPD. It has been speculated that patients showing serious PH and vascular remodeling without severe airway obstruction might benefit from vasoactive treatment. There is no approved drug available for COPD-induced PH. Most trials assessing the efficacy of vasoactive drugs in PH have had a follow-up of 12–16 weeks. We report on 4 subjects with COPD and PH. Pulmonary arterial hypertension associated diseases and pulmonary embolism were ruled out. PH persisted despite optimized treatment of underlying COPD and comorbidities, so bosentan was started in all 4 subjects. With bosentan the mean pulmonary artery pressure improved. The average gains in 6-min walk distance at 2–3 months and 8–9 months were 36 m and 145 m, respectively. The maximum gains in 6-min walk distance of the individual subjects were at the 9th, 13th, and 18th month. Oxygenation was stable, and no side effects were observed. We suggest from this experience that in clinical trials of PH in COPD, a follow-up of 16 weeks might cause underestimation of the treatment effects. *Key words: COPD; pulmonary hypertension; hemodynamics; clinical trials; treatment; vasoactive drugs; follow-up.* [Respir Care 2013;58(8):e86–e91. © 2013 Daedalus Enterprises]

Introduction

Pulmonary hypertension (PH) is a common consequence of COPD, although the actual overall prevalence of PH in COPD remains unclear.[1] Among COPD patients who were to undergo lung-volume-reduction surgery or lung transplantation, mild PH was observed in 50.2%, moderate PH in 9.8%, and severe PH in 3.7%.[2] While in most COPD patients who develop PH, pulmonary arterial pressure is only mildly or moderately elevated,[3] PH has an independent prognostic impact on survival.[3,4] Even in a range (> 18 mm Hg) that does not represent PH as defined by a mean pulmonary artery pressure of 25 mm Hg, the rate of hospital admission due to COPD exacerbation is higher than in patients with a mean pulmonary artery pressure < 18 mm Hg.[3] Pulmonary artery pressure is a stronger prognostic factor in patients with COPD than is FEV_1, hypoxemia, or hypercapnia.[5]

Although it has been proposed that PH develops due to loss of capillaries in emphysema and chronic hypoxemia, elevated pulmonary artery pressure was not correlated with oxygenation in patients with severe emphysema. Rather, it was associated with elevated pulmonary wedge pressure, reflecting left diastolic dysfunction, despite preserved systolic ventricular function.[6]

A subgroup of subjects with severe PH but only moderate ventilatory disturbance was identified[2] and classified as "out of proportion PH."[4] Aberrant vascular remodeling induced by tobacco smoke was found, and a correlation with small airway disease and emphysema was established.[7] It is still unclear whether severe PH in these subjects is the result of COPD or an independently coexisting idiopathic pulmonary arterial hypertension.[4]

In PH occurring due to respiratory disorders and hypoxemia, treatment of the underlying disease and oxygen administration has been recommended.[8,9] Further evaluation is advised only if the PH is severe.[9] It was speculated that COPD patients with severe PH but only mild to moderate

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Table. Baseline Characteristics of the 4 Subjects

	Subject Number			
	1	2	3	4
Sex	M	F	M	M
Age, y	78	73	74	75
Body mass index, kg/m^2	31.6	30.3	31.1	25.8
FEV_1/FVC, %	45	37	55	50
FEV_1, L	1.13	0.65	1.42	2.27
FEV_1, % predicted	39	40	52	63
FVC, L	2.46	1.73	2.55	4.51
FVC, % predicted	61	88	69	90
Intrathoracic gas volume, L	4.35	3.43	3.21	5.69
Intrathoracic gas volume, % predicted	115	137	91	138
Diffusion capacity, % predicted	79	43	26	61
6-min walk distance, m	240	165	135	400
World Health Organization functional class	3	3	3	3
Mean pulmonary artery pressure at rest, mm Hg	44	38	50	38
Pulmonary artery wedge pressure, mm Hg	15	13	22	15
Transpulmonary pressure difference, mm Hg	26	25	28	23
Pulmonary vascular resistance, dyn/s/cm	326	400	476	526
Cardiac index, L/min/m^2	3.2	2.7	2.3	1.7
Mean pulmonary artery pressure after iloprost	28	Not measured	No change	Not measured

Transpulmonary pressure difference = difference between mean pulmonary arterial pressure and pulmonary arterial wedge pressure.

ventilatory impairment might benefit from vasoactive medication.[2] However, the reported effects of vasoactive drugs have been inconsistent[10-13] and reliable corroborating data are lacking.

Case Reports

We report on 4 subjects with COPD and PH. In all 4 subjects we did a complete staging of COPD, including body plethysmography, analysis of capillary blood samples for oxygen and carbon dioxide, and high-resolution computed tomography of the lungs. Diagnostic workup for PH was performed according to the guidelines.[8,9] Pulmonary embolism was ruled out by computed tomography and ventilation-perfusion scans. Anorexigen use, congenital heart disease, porto-pulmonary hypertension, collagen vascular disease, human immunodeficiency virus infection, and chronic hemolysis were ruled out. There was no family history of pulmonary arterial hypertension.

The characteristics of the 4 subjects were as follows:

Subject 1: COPD, central sleep related breathing disorders, atrial fibrillation, coronary artery disease

Subject 2: COPD, emphysema, hypoxemia, oxygen administration

Subject 3: COPD, atrial fibrillation, coronary artery disease, prosthetic aortic valve

Subject 4: COPD, atrial fibrillation, coronary artery disease

Treatment of COPD and other accompanying medical conditions were optimized as follows.

Subject 1: Due to central sleep apnea, treatment with CPAP and night-time oxygen supplementation was started, and anti-obstructive treatment of COPD was intensified. The subject was treated with tiotropium bromide and formoterol. Additionally, digitoxin was given instead of a β-blocker. Rehospitalization for baseline right heart catheter and 6-min walk test was done 3 months later.

Subject 2: As an anti-obstructive treatment the subject received tiotropium bromide and formoterol/budesonide. The treatment was not changed. The subject was admitted for a second-look evaluation and baseline right heart catheter and 6-min walk test 4 weeks later.

Subject 3: Long-term oxygen treatment had been initiated 5 months before baseline right heart catheter. The current treatment with tiotropium bromide and formoterol/budesonide was continued.

Subject 4: Coronary angioplasty was performed, and tiotropium bromide was started 4 weeks before baseline right heart catheter.

To evaluate the effects of these interventions, all the subjects were admitted at our hospital for a second look 1–5 months later. Their examinations did not show any important improvement of PH. After excluding COPD exacerbation by evaluating dyspnea, cough, and sputum according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement[14] and performing base-

line right heart catheterization, 6-min walk test, and cardiopulmonary exercise test, treatment with bosentan was started.

The Table shows the baseline characteristics of the 4 subjects 1–5 months after optimization of the treatment of the underlying diseases and before the start of bosentan. At this point the x-rays ruled out pneumonia, and no subject showed hypersecretion. There was no evidence of exacerbation, and no further modification of COPD treatment was required. The 4 subjects were of older age. While 2 of them showed severe airway obstruction, one showed moderate to severe airway obstruction, and one subject showed moderate airway obstruction. In 2 subjects the diffusion capacity for carbon monoxide was severely reduced, and those subjects were on long-term oxygen supplementation. All subjects were classified in World Health Organization functional class 3. In 2 subjects 6-min walk distance (6MWD) was severely reduced. Three subjects had concomitant coronary artery disease, and one subject had a history of aortic valve replacement. Two subjects had severe PH, while the other 2 had moderate PH. One subject showed a pulmonary wedge pressure of 22 mm Hg, but all subjects had a transpulmonary vascular pressure difference of at least 23 mm Hg.

After starting bosentan, at the follow-up visits we measured World Health Organization functional class, 6MWD, echocardiography, electrocardiography, body plethysmography, blood gas analysis, and serum amino-terminal pro-brain natriuretic peptide (NT-proBNP) 2–6 months, for an overall follow-up period of 9–18 months. Right heart catheterization follow-up was performed once a year.

All the subjects improved with bosentan. There was an improvement of 6MWD in all subjects (Fig. 1). The maximum improvements were at 9, 13, and 18 months, respectively. The mean maximal 6MWD gain of all 4 subjects during the complete follow-up period was 142.5 m. We compared the 6MWD gain of 3 subjects at 2 different time points. The 6MWD gain was 36 m after an early time point of 2 or 3 months, and 145 m after a later time point of 8 or 9 months. There was an improvement in tricuspid annular plane systolic excursion measured by echocardiography (Fig. 2), as well as improvement in mean pulmonary artery (Fig. 3). Oxygenation was stable (Fig. 4).

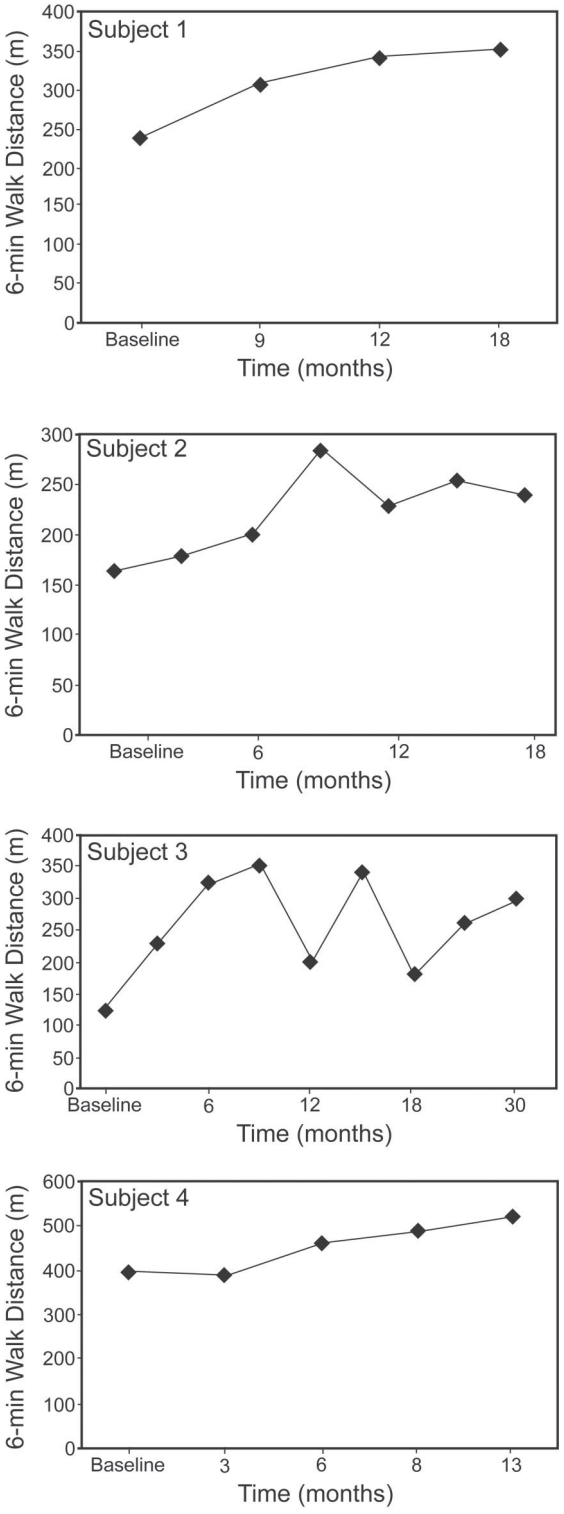

Fig. 1. Six-min walk distance of the 4 subjects.

Discussion

We report on 4 subjects with COPD and PH. Three of them had coronary artery disease and atrial fibrillation, which are common comorbidities in COPD patients. Scharf et al[6] reported that diastolic dysfunction is a frequent and relevant finding of patients with emphysema. In our subjects, coronary artery disease and atrial fibrillation may suggest pulmonary venous hypertension. One of the 4 subjects showed pulmonary artery wedge pressure $>$ 15 mm Hg. The other 3 subjects showed a pulmonary artery wedge pressure of 12–15 mm Hg, characteristic of precapillary PH according to the guidelines[8,9] and the Dana Point statement. In addition, acute vascular responsiveness

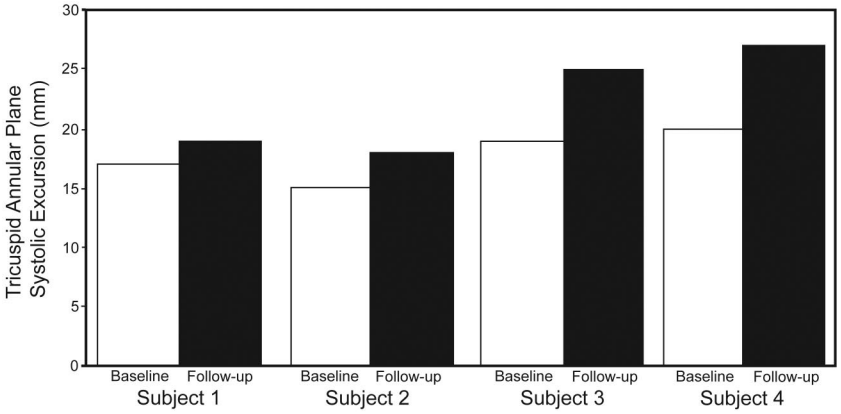

Fig. 2. Tricuspid annular plane systolic excursion at baseline and after 9 months of bosentan.

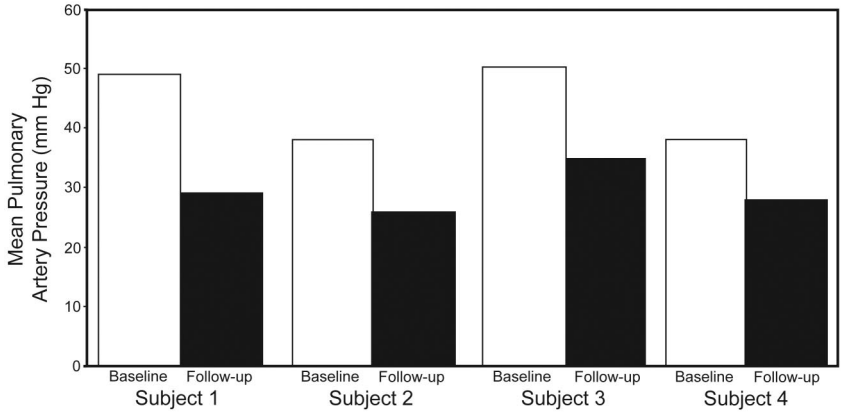

Fig. 3. Mean pulmonary artery pressure at baseline and at follow-up. After starting bosentan, right heart catheterization was done at 18 months in subjects 1 and 2, at 9 months in subject 3, and at 8 months subject 4.

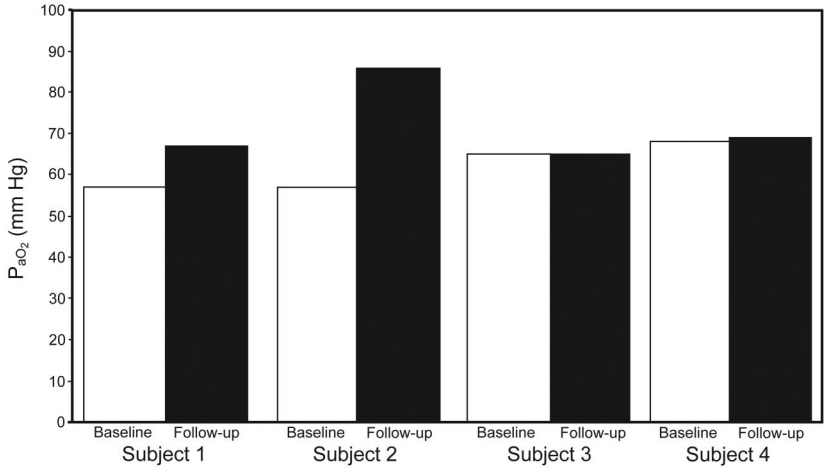

Fig. 4. P_{aO_2} at baseline and after starting bosentan therapy, at 6 months in subject 1, at 2 months in subject 2, and at 3 months in subject 3 and 4.

was tested in Subject 1. Under inhaled iloprost, the mean pulmonary artery pressure improved from 44 mm Hg to 28 mm Hg. Furthermore, it is questionable whether in COPD patients, elevated pulmonary artery wedge pressure exclusively reflects diastolic left ventricular dysfunction. Air trapping and hyperinflation may increase intrathoracic

pressure and, consequently, pulmonary artery pressure and pulmonary capillary wedge pressure. This could be characterized by simultaneously measuring the esophageal pressure, which was not done in the clinical setting. Since transpulmonary vascular difference was 23–28 mm Hg in all the 4 subjects, we assumed a predominantly precapillary PH. To uncover latent pulmonary venous hypertension, a "fluid challenge" procedure, which was not done in our subjects, should be performed in patients with cardiac comorbidities, administering a rapid bolus of 500 mL NaCl and measuring pulmonary artery wedge pressure again.

Concomitant pulmonary arterial hypertension associated with collagen vascular disease and even chronic thromboembolic PH has been reported in COPD patients.[4] In our subjects those conditions were carefully ruled out.

Three of our subjects showed severe airway obstruction. Only one subject showed criteria for the concept of "out of proportion PH" (ie, severe PH with only mild airway obstruction). For patients with PH and lung disease the current guidelines recommend treatment of the underlying disease.[8,9] In our subjects, treatment of COPD and the other concomitant diseases had been optimized 1–5 months before specific treatment of PH was considered. Despite optimized treatment, severe PH persisted in 2 subjects, while moderate PH remained unchanged in the other 2.

All 4 subjects showed improvement following vasoactive treatment with bosentan. It is well known that in COPD patients, pulmonary artery pressure rises during exacerbation.[15] In our subjects there were no clinical signs of COPD exacerbation, according to the GOLD criteria,[14] when bosentan treatment was started. Although it is conceivable that hemodynamic and functional improvement was influenced by the optimization of the treatment of the underlying COPD by modifying anti-obstructive therapy, start of long-term oxygen therapy, and treatment of concomitant coronary artery disease by angioplasty 1–5 months prior to initiation of bosentan therapy, this seems unlikely. Since bosentan was started 1–5 months after these modifications, the hemodynamic and clinical improvement of PH might be the consequence of starting bosentan. The presence of a pulmonary vasculopathy in COPD with concomitant PH has been postulated by other authors.[3,4,7]

The positive effect of the endothelin receptor antagonist bosentan on PH due to hypoxic PH and COPD was shown in animal models as well as in humans.[10-12] Stolz et al[13] concluded that bosentan failed to improve functional capacity in COPD patients without severe PH, but this cohort was not investigated by right heart catheterization, and the group treated with bosentan had a mean systolic pulmonary artery pressure of only 32 mm Hg.

In our subjects the 6MWD as a marker of clinical performance improved even more after a longer follow-up period: 3 subjects showed their maximum improvement after 9 months, and the remaining subject after 18 months. The gain of 6MWD after 8 and 9 months was higher, compared to the second and third month. Studies evaluating the benefit of PH therapy have mostly had a follow-up of 12–16 weeks, which might be too short for assessing treatment effects.

Due to increasing shunt perfusion, pulmonary vasodilatation could lead to worsening of oxygenation in COPD patients.[1,16] In our subjects, oxygenation remained stable and the treatment was safe.

This small retrospective case series cannot prove that the clinical and hemodynamic improvement in our subjects was due to bosentan treatment. We suggest that in future prospective clinical trials a longer follow up-period could be useful to investigate the true effect of pharmacologic treatment of PH in COPD.

To identify COPD patients who could possibly benefit from specific pharmacologic PH treatment, prospective clinical trials are needed. Patients should be carefully selected for inclusion in these trials. A follow-up period of only 16 weeks might lead to an underestimation of the treatment effects.

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