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Pulmonary Hypertension in COPD

Matthias Held*

Berthold Jany

Medical Mission Hospital, Department of Internal Medicine, Academic Teaching Hospital, Julius-Maximilian-University of Wuerzburg, Salvatorstrasse 7, 97064 Würzburg, Germany

e-mail addresses:

Matthias.held@missioklinik.de

Berthold.jany@missioklinik.de

*Corresponding author: Matthias Held

Conflict of interest statement

Matthias Held received honoraria and travel support from Actelion, Bayer Healthcare, Boehringer Ingelheim, Glaxo Smith Kline, Lilly, Novartis, Nycomed, Pfizer, Roche, Servier.

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Abstract

Pulmonary hypertension (PH) is a common consequence of chronic obstructive pulmonary disease (COPD). It has been speculated that patients showing serious PH and vascular remodelling 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 a follow-up of 12–16 weeks. We report on four patients with COPD and PH. Pulmonary arterial hypertension (PAH) associated diseases and pulmonary embolism were ruled out. PH persisted despite optimized treatment of underlying COPD and comorbidities. Therefore, Bosentan treatment was started in all the 4 patients. With Bosentan treatment, the mean pulmonary artery pressure (PAP) was found to improve. The average gain in six-minute walking distance (6MWD) at 2–3 months and 8–9 months was 36 m and 145 m, respectively. The maximum gain in 6MWD of the individual patients was noticed after the 9th, 13th, and 18th month. Oxygenation was found to be 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 lead to an underestimation of the treatment effects.

Key words:

COPD, Pulmonary Hypertension, hemodynamics, clinical trials, treatment, vasoactive drugs, follow-up.

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Pulmonary Hypertension in COPD

Introduction

Pulmonary hypertension (PH) is a common consequence of chronic obstructive pulmonary disease (COPD), although the actual overall prevalence of PH in COPD remains unclear.[1] Out of those 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 developing PH, pulmonary arterial pressure (PAP) is elevated only to a mild or moderate degree, [3] PH has an independent prognostic impact on survival.[3,4] Even in a range (>18 mm Hg), which does not represent PH as defined by a mean PAP of 25 mm Hg, the rate of hospital admission due to exacerbations of the COPD is higher compared to patients with a mean PAP <18 mm Hg.[3] The degree of PAP is a stronger prognostic factor in patients with COPD compared to FEV_1, hypoxemia or hypercapnia.[5]

Although it was proposed that PH develops due to loss of capillaries in emphysema and consecutive hypoxemia, elevated PAP 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 patients with severe PH, but only moderate ventilatory disturbance was identified[2] and classified as “Out-of-Proportion PH”.[4] Aberrant vascular remodelling 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 cases is the result of COPD or an independently coexisting idiopathic pulmonary arterial hypertension (PAH).[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 only advised if the PH is severe.[9] It was speculated that COPD patients with severe PH, but only

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mild to moderate ventilatory impairment, might benefit from vasoactive medication.[2] However, reported effects of vasoactive drugs are inconsistent[10–13] and reliable data corroborating this statement are lacking.

Case summary

We report on four patients with COPD and PH

In all four cases a complete staging of COPD with bodyplethysmography, analysis of capillary blood samples for oxygen and carbon dioxide, and a high resolution computed tomography (CT) of the lungs was done. Diagnostic workup for pulmonary hypertension was performed according to the guidelines.[8,9] Pulmonary embolism was ruled out by CT and ventilation perfusion scans. Anorexigen use, congenital heart disease, porto-pulmonary hypertension, collagen vascular disease, HIV infection, and chronic hemolysis were ruled out. There was no family history of PAH.

The characteristics of the four patients were as follows:

A: COPD, central sleep related breathing disorders, atrial fibrillation, coronary artery disease.

B: COPD, emphysema, hypoxemia, oxygen administration.

C: COPD, atrial fibrillation, coronary artery disease, prosthetic aortic valve.

D: COPD, atrial fibrillation, coronary artery disease.

Treatment of COPD and other accompanying medical conditions were optimized as follows: Patient A: Due to central sleep apnea (CSA), treatment with continuous positive airway pressure (CPAP) and night-time oxygen supplementation was started, and anti-obstructive treatment of COPD was intensified. The patient was treated with tiotropium bromide and

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formoterol. Additionally, digitoxin was given instead of a beta-blocker. Rehospitalization for baseline right heart catheter and six-minute-walking test was done 3 months later. Patient B: As an anti-obstructive treatment the patient received tiotropoium bromide and formoterol/budesonide. The treatment was not changed. The patient was admitted for a second look evaluation and baseline right heart catheter and six-minute walking test 4 weeks later. Patient C: Long-term oxygen treatment had been initiated five months before baseline right heart catheter. The current treatment with tiotropoium bromide and formoterol/budesonide was continued. Patient D: 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 patients were admitted at our hospital for a second look one to five months later. Their examinations did not show any significant improvement of PH. After excluding an exacerbation of the COPD by evaluating dyspnoea, cough and sputum according to the GOLD statement [14]and performing baseline right heart catheterization (RHC), six-minute walking test (6MWT) and cardiopulmonary exercise test, treatment with Bosentan was started.

Table 1 shows the baseline characteristics of the four patients one to five months after optimization of the treatment of the underlying diseases and before the start of Bosentan. At this point, the x-rays of the thorax ruled out pneumonia and no patient showed hypersecretion. There was no evidence of exacerbation and no further modification of COPD treatment was required. The four patients were at older age. While two of them showed severe airway obstruction, one showed moderate to severe airway obstruction, and one patient showed moderate airway obstruction. In two patients, the diffusion capacity for carbon monoxide was severely reduced, and the patients were on longterm oxygen supplementation. All patients were classified in WHO Functional Class III. In two patients, 6MWD was severely reduced. Three patients had concomitant coronary artery disease and one patient had a history of aortic

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valve replacement. Two patients had severe PH, while the other two had moderate PH. One patient showed a pulmonary wedge pressure of 22 mm Hg, but all patients had a transpulmonary vascular pressure gradient of at least 23 mm Hg.

After starting of Bosentan follow-up visits including WHO-functional class, 6-minute walking distance (6MWD), echocardiography, electrocardiography, body plethysmography, blood gas analysis and NT-proBNP serum levels were performed every 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 patients showed an improvement after the initiation of Bosentan therapy. There was an improvement of the 6MWD in all patients (Fig. 1). Maximum improvement was observed after 9, 13, and 18 months, respectively. The mean of the maximal gain in 6MWD of all the four patients during the complete follow-up period was 142.5 m. We compared the gain in 6-MWD of three patients at two different time points. The gain in 6-MWD 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 (TAPSE) measured by echocardiography (Fig. 2), as well as improvement in mean pulmonary artery (Fig. 3). Oxygenation was found to be stable (Fig. 4).

Discussion

We report on four patients 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] described that diastolic dysfunction is a frequent and relevant finding of patients with emphysema. In our patients, coronary artery disease and atrial fibrillation may suggest pulmonary venous hypertension. One of the four patients showed pulmonary artery wedge

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pressure (PAWP) >15 mm Hg. The other three patients showed a PAWP of 12–15 mm Hg, characteristic of precapillary pulmonary hypertension according to the Guidelines [8,9] and Dana Point Statement. In addition, acute vascular responsiveness was tested in Patient A. Under inhaled Iloprost, the mean PAP improved from 44 mg to 28 mm Hg. Furthermore, it is questionable whether in COPD patients, elevated PAWP exclusively reflects diastolic left ventricular dysfunction. Air trapping and hyperinflation may lead to an elevated intrathoracic pressure, and, consequently to elevated PAP and PCWP. This could be characterized by simultaneously measuring the esophageal pressure, which was not done in the clinical setting. Since transpulmonary vascular gradient was 23–28 mm Hg in all the four patients, we assumed a predominantly precapillary pulmonary hypertension. To uncover latent pulmonary venous hypertension, a "fluid challenge" procedure, which was not done in our patients, should be performed in patients with cardiac comorbidities, administering a rapid bolus of 500 ml NaCl and measuring pulmonary artery wedge pressure again.

Concomitant PAH associated with collagen vascular disease and even chronic thromboembolic pulmonary hypertension (CTEPH) was reported in COPD patients.[4] In our patients, those conditions were carefully ruled out.

Three of our patients showed severe airway obstruction. Only one patient showed criteria of the concept of "Out of proportion-PH", i.e., severe PH with only mild airway obstruction. For patients with PH and lung diseases, the current guidelines recommend the treatment of the underlying disease.[8,9] In our patients, treatment of COPD and the other concomitant diseases had been optimized one to five months before specific treatment of PH was considered. Despite optimized treatment severe PH persisted in two patients while moderate PH remained unchanged in the other two.

All patients showed improvement following vasoactive treatment with Bosentan. It is well known that in COPD patients, PAP rises during exacerbations.[15] In our patients, there were

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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 antiobstructive therapy, start of longterm oxygen therapy and treatment of concomitant coronary artery disease by angioplasty one to five months prior initiation of Bosentan therapy, this seems unklikely. Since Bosentan was started one to five 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 the functional capacity in COPD patients without severe PH, but this cohort was not investigated by RHC, and the group treated with Bosentan only had a mean systolic PAP of 32 mm Hg.

In our patients, the 6MWD as a marker of clinical performance improved even more after a longer follow-up period: three patients showed their maximum improvement after 9 months and the remaining patient after 18 months. The gain of 6MWD after eight and nine months was higher compared to the second and third month. Studies evaluating the benefit of PH therapy are mostly designed with a follow-up of 12–16 weeks. This time period 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 patients, oxygenation remained stable and the treatment was safe.

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This small retrospective case series cannot prove that the clinical and hemodynamic improvement seen in our patients is 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 pharmacological treatment in pulmonary hypertension in COPD.

Conclusion

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

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Table legend

Table 1: Baseline characteristics of the patients

Figure legends

Figure 1: 6-minute walking distance of the four patients.

Figure 2: TAPSE – tricuspid annular plane systolic excursion. Baseline: before start of Bosentan (red); follow-up (blue) at 9 months after start of treatment with Bosentan.

Figure 3: mPAP – mean pulmonary artery pressure. Baseline: before start of Bosentan (red); follow-up – right heart catheterization (blue). Right heart catheterization during follow-up was done at time points as follows: Patients A and B – 18 months; C – 9 months; and D – 8 months after start of Bosentan treatment.

Figure 4: pO_2. Baseline: before start of Bosentan (red); first follow-up after Bosentan treatment (blue). First follow-up was as follows: Patient A – 6 months; B – 2 months; C – 3 months; and D – 3 months after start of Bosentan treatment.

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Abbreviations List

CI	Cardiac Index
cm	centimeter
COPD	Chronic obstructive pulmonary disorder
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
CT	Computed tomography
FEV_1	Forced expiratory volume after 1 second
ITGV	intrathoracic gas volume
m	meter
min	minute
ml	milliliter
mm	millimeter
mmHg	millimeter mercury
mPAP	mean pulmonary artery pressure
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PH	Pulmonary Hypertension

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PCWP	Pulmonary capillary wedge pressure
pO_2	partial pressure of oxygen
PVR	Pulmonary vascular resistance
PCWP	Pulmonary capillary wedge pressure
RAP	Right atrial pressure
RHC	Right heart catheterization
sec	second
6-MWD	Six-minute walking distance
6-MWT	Six-minute walking test
TAPSE	Tricuspid annular plane systolic excursion
TLC	Total Lung Capacity
TLCO-VA	Transfer factor for carbonmonoxide per alveolar volume
VC	Vital capacity
WHO	World Health Organization
WHO-FC	World Health Organization functional class
% pred	% predicted

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	A	B	C	D
Sex	m	f	m	M
Age	78	73	74	75
BMI	31,6	30,3	31,1	25,8
FEV1/VC (%)	45	37	55	50
FEV1 (l) (% pred)	1,13(39 %)	0,65 (40 %)	1,42 (52 %)	2,27 (63 %)
VC (% pred)	2,46(61%)	1,73 (88)	2,55 (69)	4,51 (90)
ITGV (l) (% pred)	4,35 (115)	3,43 (137)	3.21 (91)	5,69 (138)
Diffusion capacity (% pred)	79	43	26	61
6 MWD (m)	240 m	165 m	135	400
WHO Class	III	III	III	III
mPAP rest (mm Hg)	44	38	50	38
PAWP (mmHg)	15	13	22	15
TPG(mmHg)	26	25	28	23
PVR (dynx sec x cm^{-5})	326	400	476	526
CI ($l/min/m^2$)	3.2	2,7	2.3	1,7
mPAP after Iloprost	28	Not done	No change	Not done

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Table 1: Baseline characteristics oft the 4 patients

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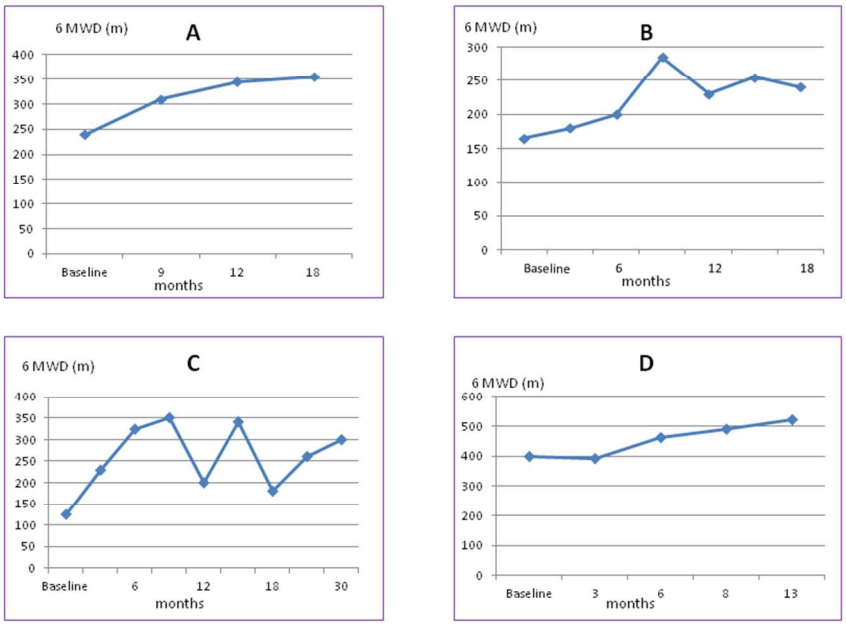

6-minute walking distance of the four patients
254x190mm (96 x 96 DPI)

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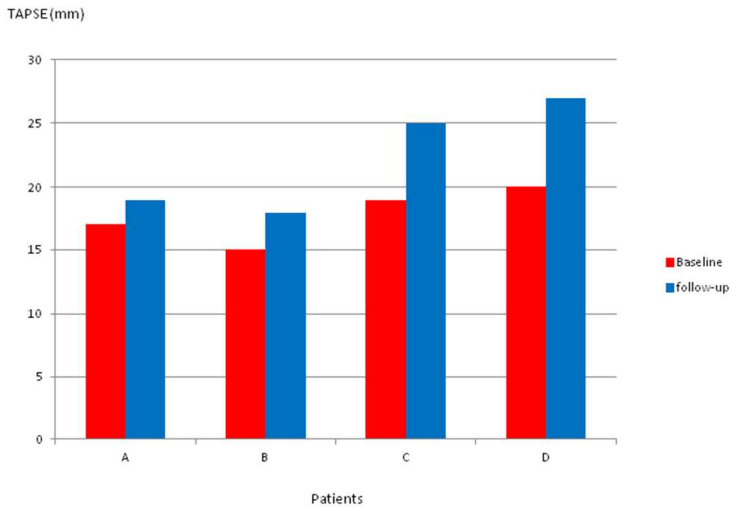

TAPSE – tricuspid annular plane systolic excursion. Baseline: before start of Bosentan (red). Follow-up (blue) 9 months after start of treatment with Bosentan.
254x190mm (96 x 96 DPI)

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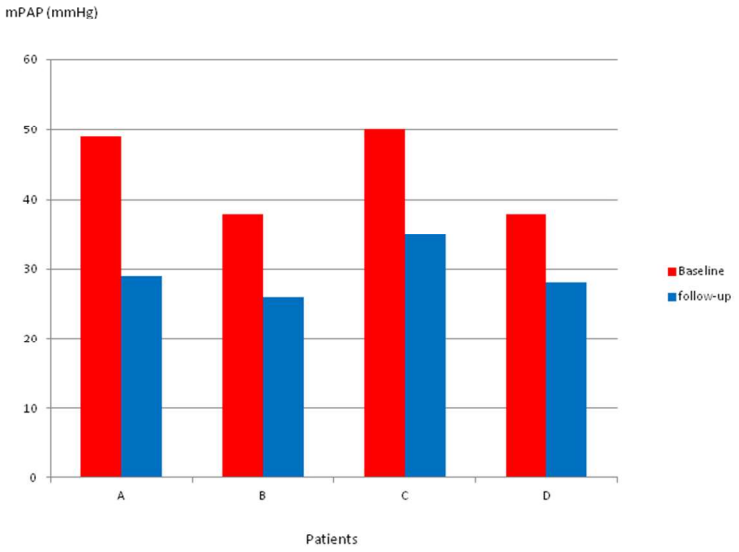

mPAP – mean pulmonary artery pressure. Baseline: before start of Bosentan (red). Follow-p: right heart catheterization during follow up (blue). Right heart catheterization during follow-up was done at timepoints as follows: Patient A, B 18 months, C 9 months and D 8 months after start of Bosentan treatment.
254x190mm (96 x 96 DPI)

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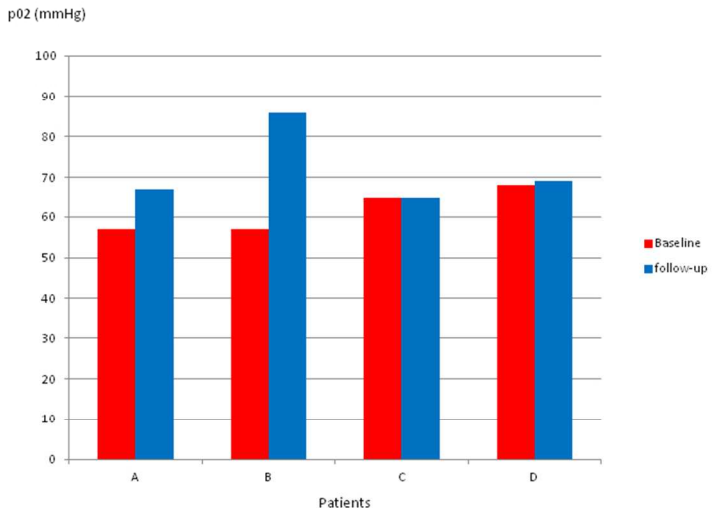

p02. Baseline: before start of Bosentan (red). First follow-up after Bosentan treatment (blue). First follow-up was as follows: A: 6months , B:2 months, C: months 3, D: 3 months after start of Bosentan treatment.
254x190mm (96 x 96 DPI)