Disproportionate Pulmonary Hypertension in a Patient with Early-onset Pulmonary Emphysema Treated with Specific Drugs for Pulmonary Arterial Hypertension

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Abstract

Severe pulmonary hypertension in chronic obstructive pulmonary disease (COPD) is referred to as 'disproportionate' because the elevated pulmonary artery pressure does not match the degree of air flow limitation. We report a 41-year-old man presenting with early-onset pulmonary emphysema and pulmonary hypertension with a mean pressure of 74 mmHg. Continuous intravenous epoprostenol led to marked hemodynamic improvement, and epoprostenol was successfully replaced with bosentan. The patient has been followed for 3 years without exacerbation. This is the first report demonstrating the long-term efficacy of specific drugs for pulmonary arterial hypertension in disproportionate pulmonary hypertension in COPD.

Key words: early-onset pulmonary emphysema, pulmonary hypertension, epoprostenol, bosentan, chronic obstructive pulmonary disease

(Intern Med 50: 2341-2346, 2011)

(DOI: 10.2169/internalmedicine.50.5995)

Introduction

Definition of early-onset pulmonary emphysema includes disease onset before the age of 50 years irrespective of smoking history. If the disease is limited to Hugh-Jones classification of dyspnea higher than class II and forced expiratory volume in one second (FEV₁) <50% of predicted value, there is an estimated prevalence of less than 100 patients in Japan (1). Pulmonary hypertension occurs occasionally in patients with chronic obstructive pulmonary disease (COPD), and it is associated with a poor prognosis (2, 3). Pulmonary hypertension is relatively mild to moderate in most of the cases, but it could be very severe and 'disproportionate' to the degree of air flow limitation (3, 4). Therapeutic strategies for severe pulmonary hypertension include smoking cessation, pulmonary rehabilitation, and long-term oxygen supplementation, whereas the indications and effectiveness of specific drugs for pulmonary arterial hypertension remain controversial (2). We present a case of early-onset pulmonary emphysema complicated by severe pulmo-

nary hypertension. In the present case, continuous intravenous epoprostenol led to marked hemodynamic improvement, and epoprostenol was successfully replaced with bosentan in combination with beraprost without hemodynamic compromise.

Case Report

A 41-year-old man was admitted to the hospital because of dyspnea and general fatigue at rest in December 2007. He had experienced recurrent pneumothorax since the age of 25. He had been diagnosed with pulmonary emphysema based on findings of a CT scan at the age of 32 when he was admitted to the hospital because of pneumothorax. In addition, echocardiography had revealed pulmonary hypertension with an estimated peak pressure gradient of 65 mmHg. Until that time, he had smoked 20 cigarettes daily for 12 years, but he quit smoking ever since. He had been followed at another clinic with administration of inhaled anticholinergics, theophylline, and short-acting beraprost (120 µg/day). However, he developed exertional dyspnea at the

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Received for publication June 14, 2011; Accepted for publication July 19, 2011

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Figure 1. Anteroposterior chest radiograph (panel A) and computed tomography of the chest (panel B). The chest radiograph at admission shows enlarged hilar pulmonary arteries indicating pulmonary arterial hypertension. Computed tomography of the lungs demonstrates panlobular emphysema, which is an exceptional finding considering the patient's age.

age of 39, which progressively worsened to such a degree that he became dyspneic even at rest (Hugh-Jones grade IV). He was referred to our hospital for further management. He had no family history of pulmonary emphysema in first-degree relatives. He had not been engaged in any occupation related to irritant particles or gases, and denied using illegal drugs. On admission, his heart rate was 120 beats/min, and blood pressure was 120/86 mmHg. His pulse oximetry saturation was 88% on room air. The body mass index was 17.1 kg/m² (171 cm, 50 kg). Auscultation revealed a grade III systolic murmur with an accentuated second pulmonary sound. Prolonged expiration without any wheezes or rhonchi was noted. Laboratory findings were unremarkable, except for a uric acid of 8.1 mg/L and brain natriuretic peptide (BNP) of 361 pg/dL. Both KL-6 and α 1-antitrypsin were within normal range. Arterial-blood-gas analysis showed a pH of 7.45, a PCO₂ of 35 Torr, and a PaO₂ of 46 Torr during breathing of room air. Pulmonary function tests showed severe airflow obstruction and impaired diffusion capacity: forced vital capacity (FVC) 2.56 L (64.9% of predicted value), FEV₁ 1.15 L (32.6% of predicted value), FEV₁/FVC ratio 46.7%, residual volume 2.81 L (171.3% of predicted value) and carbon monoxide diffusion capacity (DLCO) 37.0% of predicted value. Given the patient's age, these findings fulfilled the criteria of early-onset pulmonary emphysema. An electrocardiogram revealed pulmonary P, right axis deviation, qR pattern in V₁, and clockwise rotation in precordial leads. A chest radiograph demonstrated enlarged pulmonary arteries and inflated lung fields (Fig. 1A). Computed tomography of the chest showed panlobular emphysema (Fig. 1B). A ventilation-perfusion lung scan showed no features of mismatched defect. A 6-minute walk test had to be discontinued in 2 minutes with a distance of less than 100 m. Echocardiography showed marked right ventricular dilatation with hypertrophy and flattened inter-

ventricular septum (Fig. 2A-C). No congenital abnormalities of the heart were found. Doppler echocardiography revealed an estimated right ventricular systolic pressure of 98.4 mmHg (mean: 60.1 mmHg) (Fig. 2D). The patient underwent right heart catheterization, which demonstrated mean right atrial pressure 8 mmHg, mean pulmonary arterial pressure 74 mmHg, pulmonary wedge pressure 10 mmHg, cardiac output 3.92 L/min, and pulmonary vascular resistance 1,265 dyne·sec·cm⁻⁵. The patient received 2.5 L/min of nasal oxygen, oral anticoagulation therapy, dobutamine, and human atrial natriuretic peptide. He was categorized as WHO functional class IV, and we considered that his symptoms were mainly due to severe pulmonary arterial hypertension. Then, intravenous epoprostenol infusion was initiated, the dose of which was gradually increased from 1 ng/kg/min to 19 ng/kg/min. The treatment with intravenous epoprostenol for 6 months resulted in marked improvement in exertional dyspnea and pulmonary hemodynamics (Table 1). The 6-minute walk distance increased to 420 m, and follow-up right heart catheterization showed mean pulmonary arterial pressure 49 mmHg, cardiac output 4.72 L/min, and pulmonary vascular resistance 891 dyne·sec·cm⁻⁵. The BNP level was 18.9 pg/dL. However, the patient developed psychiatric symptoms such as restlessness, a sense of palpitation, and a growing feeling of anxiety. He was prescribed antidepressants. Oral sildenafil was started at dosage of 40-60 mg in addition to epoprostenol, whereas sildenafil had to be discontinued after 3 months because the psychiatric problems became rather worse. We started bosentan therapy and attempted to gradually withdraw intravenous epoprostenol. The initial dosage of 125 mg bosentan was increased to 250 mg after 5 days. Fortunately, the patient was successfully weaned off intravenous epoprostenol without worsening of his symptoms. The psychiatric symptoms were almost relieved after withdrawal of epoprostenol, and the patient was

Figure 2. Echocardiographic examinations. Panels A, B and C show marked right ventricular dilatation (left: end-diastole, right: end-systole). Panel B demonstrates flat interventricular septum in the cross-sectional view, and panel C demonstrates hypertrophied right ventricular free wall in the apical four chamber view. Panel D shows that the peak velocity of tricuspid regurgitation is 4.7 m/s, suggesting an estimated right ventricular systolic pressure of 98.4 mmHg (mean: 60.1 mmHg). RV: right ventricle

Table 1. The Clinical Course of the First 14 Months

<div style="display: flex; justify-content: space-around; align-items: center;"> <div> <p>DOB</p> <p>hANP</p> </div> <div> <p>Sildenafil (mg)</p> <p>40 → 60</p> </div> <div> <p>Bosentan (mg)</p> <p>125 → 250</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div> <p>14 Epoprostenol (ng/kg/min)</p> <p>19</p> </div> <div> <p>Beraprost 120 (μg)</p> </div> </div> <div style="text-align: center; margin-top: 10px;"> <p>psychiatric symptoms</p> </div>									
BNP (pg/mL)	361	71			18.9			14.9	16.2
Catheterization									
PAP (mmHg)	100/61 (74)				54/44 (49)				
C.O. (L/min)	3.92				4.72				
Doppler									
mean PAP (mmHg)	60	53			47	42			40
6-minute walk distance (m)	<100	300	350		420			300	360
	2007 Dec	2008 Jan	Mar	May	Jul	Sep	Nov	2009 Jan	

DOB: dobutamine, hANP: human atrial natriuretic peptide, BNP: brain natriuretic peptide, PAP: pulmonary arterial pressure, C.O.: cardiac output

supplemented with long-acting oral beraprost (120 μg/day). The 6-minute walk distance was 360 m after 2 months of bosentan and beraprost treatment. A follow-up echocar-

diography showed that right ventricular dilatation and flattened interventricular septum became less prominent (Fig. 3). Mean pulmonary artery pressure was 40 mmHg.

Figure 3. Follow-up echocardiograms show that right ventricular dilatation is reduced and the interventricular septal curvature is less flattened. A: Parasternal long-axis view. B: Parasternal short-axis view. C: Apical four chamber view.

The patient returned to his previous job as a machine designer under bosentan, beraprost, and long-term oxygen therapy. He has been followed for 3 years without exacerbation of symptoms. His oxygen saturation at rest was maintained at 94%, and Doppler-estimated mean pulmonary artery pressure remained at less than 50 mmHg.

Discussion

Severe pulmonary hypertension constitutes an important clinical problem in patients with COPD. The present patient suffered from severe pulmonary hypertension with a mean pressure of 76 mmHg, which was not explained by left sided heart failure, congenital heart disease, or pulmonary embolism. Although pulmonary hypertension occurs occasionally in patients with COPD, most of them have only mild to moderate pulmonary hypertension (2). Severe pulmonary hypertension with a mean pressure >40 mmHg occurs in only 0.8% to 3.7% of COPD patients (3-6). It is characterized by less impaired respiratory function, and the elevated pulmonary pressure does not correlate with the degree of air flow limitation (3, 4). Because the elevated pulmonary arterial pressures do not correlate with the severity of COPD, it is called disproportionate pulmonary hypertension in COPD. Chaouat et al reported that the patients with disproportionate pulmonary hypertension had less severe air-flow limitation, decreased DLCO, more severe hypoxemia, and hypocapnia (3). As for the present patient, the markedly elevated pulmonary arterial pressure is disproportionate to his FEV₁, which is not in the most advanced stage of COPD. In

addition, the present patient had a very low DLCO, and blood gas analysis demonstrated marked hypoxemia requiring oxygen therapy and hypocapnia. Therefore, the severe pulmonary hypertension in the present patient is compatible with disproportionate pulmonary hypertension in COPD.

The mechanism of severe pulmonary hypertension in COPD remains not fully elucidated. Alveolar hypoxia, inflammation and genetic predisposition have been postulated as underlying causes of extensive vascular remodeling which leads to elevated pulmonary arterial pressure. Alveolar hypoxia causes constriction of resistance pulmonary arteries, and a close relationship has been reported between the severity of arterial hypoxemia and pulmonary vascular resistance (4, 6). However, arterial PO₂ was not an independent predictor of pulmonary artery pressure, suggesting the involvement of other factors (6). Recently, genetic factors have been identified that predispose to pulmonary hypertension. For example, single nucleotide polymorphisms from surfactant protein B are linked to pulmonary artery pressure in patients with severe COPD (7). The present patient had a smoking history of 240 pack years, when he was diagnosed with emphysema and moderate pulmonary hypertension at the age of 32. The pulmonary arterial pressure continued to rise even after the cessation of smoking. We believe that some genetic predisposition can be involved in the severe pulmonary hypertension in the present case.

While specific drugs for pulmonary arterial hypertension, including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostanoids have been tried in treating COPD-related pulmonary hypertension, their effectiveness

has not been established yet. Pulmonary hypertension associated with COPD has some histological similarities to idiopathic pulmonary arterial hypertension. Pathologic studies of lung specimens from patients with COPD have shown extensive vascular remodeling with prominent intimal thickening, medial hypertrophy, and muscularization of small arterioles (8, 9). These findings have prompted clinicians to treat pulmonary hypertension in COPD with specific drugs for pulmonary arterial hypertension. Stolz et al reported that the endothelin receptor antagonist bosentan not only failed to improve exercise capacity but also deteriorated hypoxemia and functional status in severe COPD patients without severe pulmonary hypertension at rest (10). In a study of the phosphodiesterase-5 inhibitor sildenafil, Blanco et al concluded that sildenafil improved pulmonary hemodynamics at rest and during exercise in patients with COPD-associated pulmonary hypertension, while these effects were accompanied by impaired arterial oxygenation due to the inhibition of hypoxic vasoconstriction (11). Since these studies included patients with only mild to moderate pulmonary hypertension or exercise-induced pulmonary hypertension, it is important to note that the results may not apply to severe pulmonary hypertension in COPD. Some reports have shown improvement in functional status and hemodynamic parameters after bosentan therapy in COPD patients with severe pulmonary hypertension (12-14). Oxygenation and cardiac output were well maintained after bosentan therapy. These results are supported by the fact that hypoxic pulmonary hypertension is characterized by an overproduction of endothelin-1, which causes vasoconstriction and vessel wall thickening (15). However, the long-term efficacy of bosentan for severe pulmonary hypertension in COPD has not been shown.

We initially administered continuous intravenous epoprostenol with supplemental oxygen to the present patient, as epoprostenol is the first-line therapy for patients with pulmonary arterial hypertension in NYHA/WHO functional class IV (16). Treatment with epoprostenol for six months resulted in marked improvement of BNP level, 6-minute walk distance, pulmonary arterial pressure, and pulmonary arterial resistance. However, the patient became intolerable to intravenous epoprostenol due to psychiatric symptoms. Intravenous epoprostenol treatment is complex and requires dedicated management by the patient, such as sterile preparation of the medication and aseptic management of the indwelling central venous catheter. Because epoprostenol has a very short half-life (2.7 minutes), abrupt discontinuation of the drug may lead to potentially life-threatening complications. These difficulties of intravenous epoprostenol treatment could cause substantial emotional stress for the patient. The addition of oral sildenafil therapy to epoprostenol did not lead to further clinical improvement but rather exacerbated psychiatric problems. We started bosentan therapy in place of sildenafil. Bosentan allowed successful withdrawal from epoprostenol without hemodynamic impairment (17). Long-acting oral beraprost was used as combination therapy.

Although the 6-minute walk distance decreased by 60 m, the psychiatric problems were almost relieved after epoprostenol discontinuation. Our experience with the present case suggests that specific drugs for pulmonary arterial hypertension such as epoprostenol and bosentan could be effective to severe pulmonary hypertension in COPD. Although some detrimental effects on gas exchange are to be expected with pulmonary vasodilation, his oxygen saturation at rest was maintained at 94% under long-term oxygen therapy. COPD patients with severe pulmonary hypertension have a very poor prognosis (2, 3). The survival of the present patient for more than 3 years would not have been achieved if epoprostenol and bosentan had not been applied. This is the first report demonstrating the long-term efficacy of specific drugs for pulmonary arterial hypertension in severe pulmonary hypertension in COPD.

We would like to stress that specific drugs for pulmonary arterial hypertension may not be applicable to severe COPD patients with less severe pulmonary hypertension, because pulmonary vasodilators also have the potential to worsen gas exchange and oxygenation (10, 11). These drugs should be used carefully in patients with severe pulmonary hypertension irrespective of the severity of COPD. Furthermore, as far as we have searched the literature, there are no reports demonstrating the effectiveness of sildenafil for severe pulmonary hypertension in COPD. It will be necessary to obtain further evidence before the use of specific drugs for pulmonary arterial hypertension can be recommended for severe pulmonary hypertension in COPD.

The authors state that they have no Conflict of Interest (COI).

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