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【 CASE REPORT 】

# Pulmonary Hypertension and Its Response to Treatment in a Patient with Kyphosis-related Alveolar Hypoventilation

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**Abstract:**
Pulmonary hypertension (PH) with kyphoscoliosis-related alveolar hypoventilation is uncommon, so little is known about the effectiveness of treatments for this condition. A 66-year-old man with kyphosis who had been treated with nocturnal noninvasive positive-pressure ventilation developed PH with a mean pulmonary arterial pressure (PAP) of 32 mmHg and a pulmonary vascular resistance (PVR) of 5.95 Wood units. After addition of oxygen therapy and tadalafil, his condition improved. One year later, his mean PAP and PVR were 25 mmHg and 3.62 Wood units, respectively. This case shows the therapeutic potential of vasoactive medications for alveolar hypoventilation-related PH.

**Key words:** alveolar hypoventilation, kyphoscoliosis, phosphodiesterase type 5 inhibitor, pulmonary hypertension, restrictive thoracic disease

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## Introduction

Pulmonary hypertension (PH) due to lung diseases and/or hypoxia (PH Group 3 in a recent classification) includes seven disease categories: (a) chronic obstructive pulmonary disease (COPD), (b) interstitial lung disease (ILD), (c) other pulmonary diseases with mixed restrictive and obstructive patterns, (d) sleep-disordered breathing, (e) alveolar hypoventilation disorders, (f) chronic exposure to high altitude, and (g) developmental lung diseases (1). Although they are in the same group, the pathophysiology involved in each disease category differs and can be roughly categorized as follows: (a) PH develops in lung disease, in which chronic inflammation-induced lung remodeling may affect PH development, and (b) PH with no or minimal lung disease develops in hypoxia or alveolar hypoventilation. Evidence has accumulated about the pathogenesis and pathophysiology of lung disease-related PH, such as COPD-related PH (COPD-PH) and ILD-related PH, and the effect of treatment with pulmonary artery hypertension (PAH)-approved vasoactive drugs (1, 2). However, although the prevalence of PH is high in some diseases with alveolar hypoventilation, there is little experience or knowledge regarding PH treatments in these conditions, especially concerning the potential role of PAH-approved vasoactive medications.

Recently, we treated PH in a patient with kyphosis-related alveolar hypoventilation who had undergone noninvasive positive-pressure ventilation (NPPV). We herein report the outcome of this patient's year-long treatment with vasoactive medication.

## Case Report

A 66-year-old man with kyphosis had been receiving nocturnal NPPV therapy for kyphosis-related alveolar hypoventilation since his first episode of right heart failure and $CO_2$ narcosis 8 years earlier in our hospital's outpatient clinic. His history of thoracic spine deformation and other findings indicated that he had Scheuermann's kyphosis, a form of idiopathic juvenile spinal kyphosis (Fig. 1) (3). He quit smoking after 38 pack-years, after his first episode of heart failure. During outpatient visits a few years thereafter, his daytime alveolar-arterial oxygen tension difference without NPPV support ranged from 5.0 to 19.7 mmHg, indicating that his lung function was within the normal range, apart from the kyphosis-induced restrictive thoracic movement. However, his daytime percutaneous oxygen saturation

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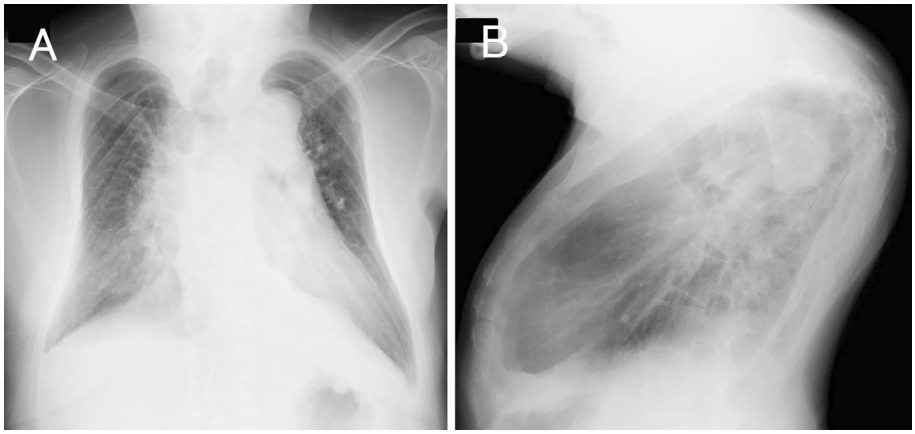


**Figure 1. Chest radiograph of the patient. (A) Posteroanterior view shows minimal scoliosis. (B) Lateral view shows severe thoracic spine kyphosis.**

($SpO_2$) during outpatient visits gradually decreased to around 90% over a period of 4 years after NPPV initiation. The NPPV setting had been changed several times to improve the $SpO_2$. The patient had refused to start oxygen therapy.

He was admitted to our hospital because of worsening exertional dyspnea and nocturnal orthopnea over the previous month. On admission, his arterial blood gas while breathing room air had a pH of 7.368, a partial oxygen pressure ($PaO_2$) of 37.6 mmHg, and a partial $CO_2$ pressure ($PaCO_2$) of 60.1 mmHg. An echocardiogram showed signs of PH and right heart overload, characterized by marked right ventricular enlargement and a flattened interventricular septum, estimated tricuspid regurgitation pressure gradient (TRPG) of 69.4 mmHg, and an inferior vena cava diameter of 20.7 mm (Fig. 2). The serum brain natriuretic peptide (BNP) concentration was 418.2 pg/mL. His white blood cell count, red blood cell count, and biochemical data were within normal ranges.

After several days of 24-h NPPV and oxygen therapy, right heart catheterization was performed under NPPV with 4 L/min of oxygen, during which the mean pulmonary arterial pressure (PAP) was 32 mmHg, the pulmonary capillary wedge pressure (PCWP) was 9 mmHg, the cardiac index (CI) was 2.58 L/min/$m^2$, and the pulmonary vascular resistance (PVR) was 5.95 Wood units. Furthermore, lung perfusion scintigraphy with technetium-99m aggregated albumin showed no blood perfusion defect in either lung region. Computed tomography of the chest showed no detectable lung abnormalities. Neither the anti-nuclear anti-topoisomerase I antibody nor any other autoantibodies were detected in his serum.

After the diagnosis of PH, administration of a phosphodiesterase type 5 (PDE5) inhibitor (tadalafil at 20 mg per day) was initiated to supplement NPPV and oxygen therapy. $SpO_2$ during the patient's daily movements without NPPV improved, and 24-h NPPV was changed to nocturnal use 3 days after the initiation of tadalafil. He was discharged from hospital the next day, with nocturnal NPPV and long-term oxygen therapy (LTOT). The spirometry results after controlling his symptoms were as follows: forced vital capacity (FVC) of 1.04 L (35.9% of predicted FVC) and forced expiratory volume in 1 second ($FEV_1$) of 0.75 L (for 72.1% of FVC and 32.0% of predicted $FEV_1$), which were the best recorded in his 8 years of monitoring. The diffusing capacity (DLCO) and lung permeability (DLCO/VA) were maintained at 10.69 mL/min/mmHg (73.7% of predicted DLCO) and 5.91 mL/min/mmHg/L (131% of predicted DLCO/VA), respectively. We diagnosed him with Group 3 PH.

The serum BNP concentration gradually decreased after these additional treatments and reached 10.4 pg/mL after 6 months. Given this rapid improvement, the PDE5 inhibitor dose was not increased. One year after the additional treatments, improvement of PH was observed on echocardiography (Fig. 2) and was confirmed by right heart catheterization, which recorded a mean PAP of 25 mmHg, a PCWP of 14 mmHg, a CI of 2.54 L/min/$m^2$, and PVR of 3.62 Wood units. He has been in good condition for more than a year with the use of LTOT, nocturnal NPPV, and a PDE5 inhibitor.

## Discussion

Few reports have been published on the treatment of PH in patients with kyphosis-related alveolar hypoventilation. In this report, we showed PH development in a patient with kyphosis who was already being treated with nocturnal NPPV. LTOT and vasoactive medication were effective in reducing the patient's PAP and PVR.

Kyphosis or kyphoscoliosis develops in various diseases, such as vitamin D deficiency, congenital kyphosis, and postural kyphosis, and as a sequela to tuberculosis or paraspinal muscle weakening, like that that can occur in syringomyelia, Friedreich's ataxia, spina bifida, and Duchenne muscular dystrophy. Although kyphosis and kyphoscoliosis have long been known to cause PH (4), we encounter few patients with these conditions, regardless of the cause of kyphoscoliosis. In a registry study of pediatric PH, only 2 patients

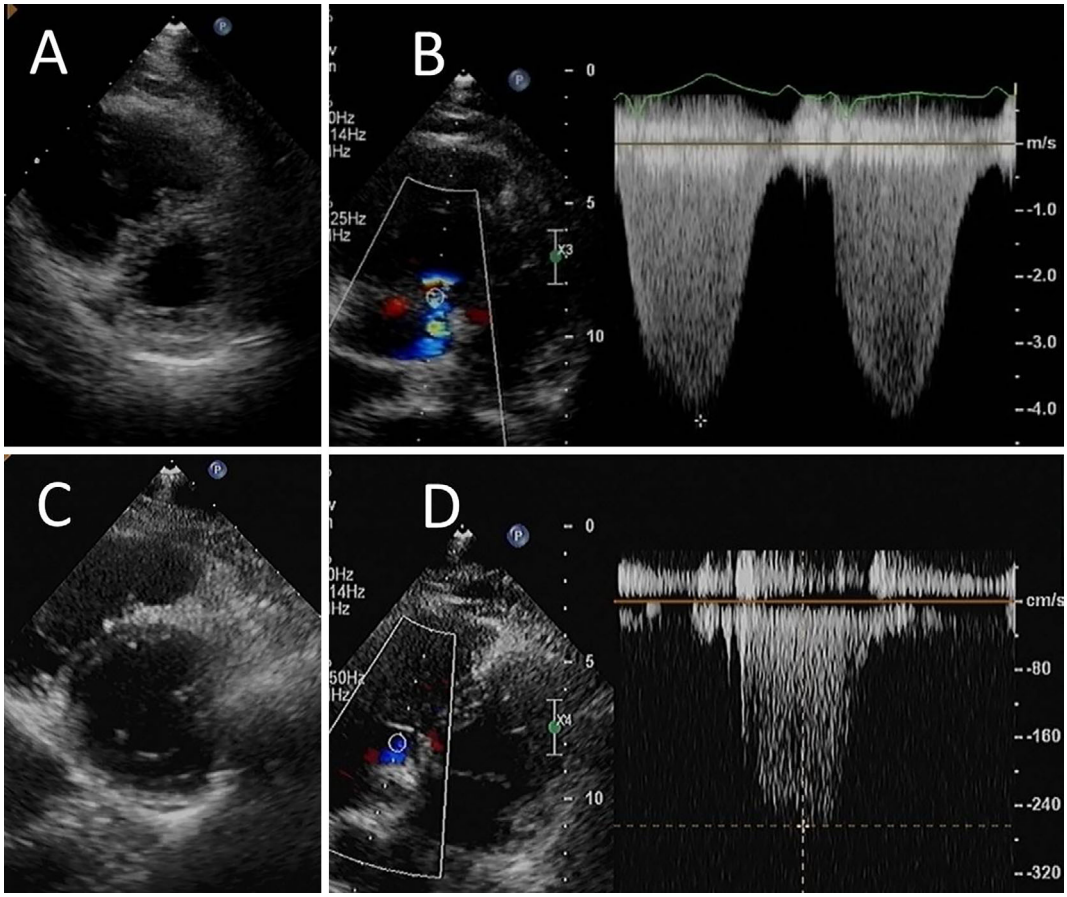


**Figure 2.** **Echocardiography of the patient before (A, B) and a year after (C, D) the addition of long-term oxygen therapy (LTOT) and a phosphodiesterase type 5 (PDE5) inhibitor. (A) Marked right ventricular enlargement and interventricular septum flattening and (B) increased tricuspid regurgitation pressure gradient (TRPG) (69.4 mmHg) were observed before the addition. (C) Right ventricular enlargement and interventricular septum flattening were not observed one year later. (D) TRPG decreased to 27.9 mmHg.**

with kyphoscoliosis were registered among 357 patients with confirmed PH, 52 of whom had Group 3 PH (5). In a similar study of adult PH, no patients with kyphoscoliosis were registered among 1,344 patients with PH (6). Since PH with kyphoscoliosis is uncommon, little is known about treating kyphoscoliosis-related PH, especially regarding the potential utility of vasoactive medications. We found only one report of the short-term effect of vasoactive medication on kyphosis-related PH. In that case, inhaled nitric oxide was effective for resolving pulmonary hypertensive crisis in a patient with severe kyphoscoliosis in an emergency care setting (7).

Alveolar hypoventilation, listed as a cause of PH in guidelines (1), is caused by various diseases and conditions, including central alveolar hypoventilation caused by central nervous system diseases and drugs, neuromuscular disorders, obesity hypoventilation syndrome (OHS), obstructive sleep apnea syndrome (OSAS), and restrictive thoracic diseases, such as sequelae of pulmonary tuberculosis and kyphoscoliosis. Although there are reports of a high PH prevalence and severity in OHS as compared to OSAS, and a high PH prevalence in patients with sequelae of pulmonary tuberculosis, the PH prevalence in most diseases in this group is unknown (8, 9). It has been reported that the prognosis of alveolar hypoventilation-related PH is better than that of other lung disease-related Group 3 PH types (6). Hypoxia is thought to play a major role in the development of alveolar hypoventilation-related PH. It has been reported that $PaO_2$, $PaCO_2$, and $FEV_1$ are related to increased PAP in OSAS patients (8). Furthermore, it has been reported that OSAS patients with PH showed a greater vasoconstrictive response to hypoxia, which may cause pulmonary artery remodeling, than those without PH (10). Hypercapnia, another consequence of alveolar hypoventilation, seems to have no relationship to PH development (11). Patients with some diseases involving alveolar hypoventilation develop PH in different conditions, in addition to hypoxic vasoconstriction of pulmonary vessels. In patients with OHS, frequent coexistence of PH and left heart dysfunction has been reported; this may be categorized as Group 2 PH (12). In the present case, increased PCWP over one year was observed, although the value was still within the normal range. It is possible that left ventricular dysfunction, which may differ from that of OHS in pathophysiology, only becomes prominent after

the preload to the left heart increases with dilatation of the pulmonary artery.

Regarding the treatment of alveolar hypoventilation-induced PH, supporting ventilation with NPPV has been reported to reduce PAP in PH patients with OHS or OSAS (13, 14). However, little is known about the potential of further treatment options, such as vasoactive medication. Supporting ventilation to improve oxygenation may also be the first line of treatment in restrictive thoracic disease-related PH, including kyphosis-related PH. This case shows the potential and safety of vasoactive medication as a next-step treatment for alveolar hypoventilation-related PH.

The present patient was a smoker until eight years previously. Severe inflammatory reaction and conformational changes in lung tissue in progressive lung disease are thought to mediate the development of COPD-PH. This case, with minimal obstructive change and minimal DLCO decrease, differs from typical COPD-PH. However, remodeling and narrowing of the pulmonary artery lumen have been reported in patients with mild COPD and even in smokers with a normal lung function, suggesting the possible influence of smoking on pulmonary artery remodeling and pulmonary endothelial dysfunction (15). Although this case is different from typical COPD-PH, the patient's history of smoking was undeniably related to the pulmonary artery dysfunction.

The effect of oxygen therapy cannot be ruled out in this case, because oxygen therapy which is performed for several days and that which is continued for one year do not have the same effect in reducing hypoxic vasoconstriction of the pulmonary artery.

In summary, our findings showed that LTOT and vasoactive medication, in addition to NPPV, were effective in treating alveolar hypoventilation-related PH in a patient with kyphosis. Since hypoxemia is the major cause of alveolar hypoventilation-related PH, resolution of hypoxemia by supporting ventilation may be the first line of treatment for kyphosis-related PH, as in cases of OHS (13). Vasoactive medications can therefore be used safely in the treatment of restrictive thoracic disease-related PH.

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

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