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Long-Term Response to Vasoactive Treatment in a Case of Kyphoscoliosis-Associated Pulmonary Hypertension

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 61
Final Diagnosis: Pulmonary hypertension
Symptoms: Dyspnoea
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Unusual setting of medical care

Background: Kyphoscoliosis is an anatomical deformity of the spine often accompanied by an array of respiratory complications, pulmonary hypertension being among the most severe ones. At present, evidence-based treatment options for kyphoscoliosis-related pulmonary hypertension remain limited to the correction of hypoxemia through ventilatory support and long-term oxygenation.

Case Report: We report a case of a 61-year-old female with severe kyphoscoliosis-related pulmonary hypertension who was admitted to a university hospital in September 2018 due to progressive dyspnea and respiratory failure. She was diagnosed with pulmonary hypertension in 2016 and had been on endothelin receptor antagonist (ambrisentan) and oxygen therapy ever since. Upon admission, the patient presented with severe depression of peripheral oxygen saturation (SpO_2 at 75%). The patient declined further treatment hours after hospitalization, despite optimized supportive oxygen therapy. Ambrisentan was discontinued and replaced by inhaled iloprost. Over the course of the next 4 days, the patient showed symptomatic improvement and was discharged on Day 5. Right heart catheterization follow-up in February 2019 showed no worsening in pulmonary hemodynamic parameters compared to the time of initial diagnosis.

Conclusions: Managing the respiratory decline in kyphoscoliosis-related pulmonary hypertension can be challenging since these patients tend to deteriorate despite current treatment options. Our case reports on the use of vasoactive agents as a safe and effective treatment option in addition to established therapeutic regimen.

MeSH Keywords: Hypertension, Pulmonary • Kyphosis • Scoliosis

Abbreviations: **PH** – pulmonary hypertension; **RHC** – right heart catheterization; **PAH** – pulmonary arterial hypertension; **NYHA** – New York Heart Association; **TTE** – transthoracic echocardiogram; **RSVP** – right ventricular systolic pressure; **LTOT** – long-term oxygen therapy; **SpO_2** – percutaneous oxygen saturation; **CT** – computer tomography; **6MWT** – 6-minute walk test

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/917154

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Background

Respiratory complications are a common entity for restrictive chest wall diseases such as kyphoscoliosis. While mild spinal deformities rarely require medical attention, patients with severe anatomical distortions face an increased risk of respiratory failure associated with poor clinical outcomes [1]. Kyphoscoliosis is primarily a deformation of the thoracic and cervical spinal segments, and an ensuing malformation of the thoracic cavity is often inevitable. The combination of reduced lung volume, increased thoracic muscle workload, and restriction in thoracic chest wall compliance and movements of diaphragm favored the development of alveolar hypoventilation [2]. Similar to other alveolar hypoventilation disorders, namely obesity hypoventilation syndrome and obstructive sleep apnea, aggravation of hypoxia provokes a vasoconstrictive response contributing to increased pulmonary vascular resistance and subsequent development of pulmonary hypertension (PH) [3]. The 2015 European Society of Cardiology (ESC) guidelines define PH as an increase in mean pulmonary artery pressure ≥25 mmHg, assessed by right heart catheterization (RHC). PH is classified into 5 groups depending on hemodynamic parameters and pathologic characteristics of the disease [4].

Alveolar hypoventilation remains the predominant contributor towards development of PH in kyphoscoliosis. It, however, allows for the condition to be classified into the third group: PH due to lung disease and/or hypoxia. Although a single group, the pathogenic mechanism differs. PH develops either in the setting of lung disease or in a state of hypoxemia and alveolar hypoventilation with the absence of structural changes. The underlying condition determines which therapeutic options can be considered for the respective case. Since the kyphoscoliosis patient with concomitant PH is rarely encountered in modern-day practice, little progress has been made in improving or changing therapeutic regimens. Current recommendation for the management of the condition are limited to the administration of ventilatory support. The use of pulmonary arterial hypertension (PAH)-approved vasoactive medications and potential benefits of such an approach remain largely undiscovered [1,5]. This study provides insight into a long-term vasodilator therapy in a patient with congenital kyphoscoliosis and PH.

Case Report

A 64-year-old Caucasian female was admitted to Pauls Stradins Clinical University Hospital in September 2018 with complaints of progressive dyspnea on exertion (New York Heart Association [NYHA] functional class IV) and increased fatigue during daily activities. The patient has been suffering from severe congenital kyphoscoliosis (Figure 1). An attempt of surgical correction at the age of 10 was unsuccessful. She had no history of smoking or prior drug abuse.

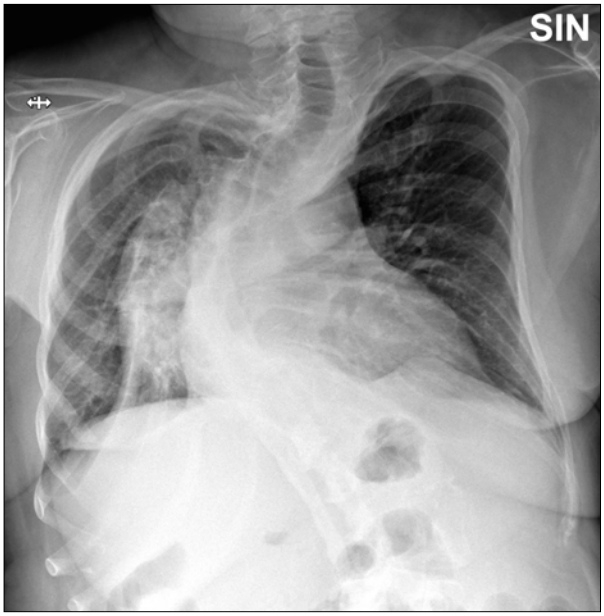

Figure 1. Posteroanterior (PA) chest X-ray shows marked scoliosis of thoracic spine.

Table 1. Right-heart catheterization.

Parameter	Date	
	04.07.2016	12.02.2019
PASP, mmHg	62	67
PADP, mmHg	30	31
mPAP, mmHg	43	43
CO, l/min	6.4	6.4
CI, l/min/m²	2.8	2.9
PVR, Wood units	6	5.62
PCWP, mmHg	7	7

PASP – pulmonary arterial systolic pressure; PADP – pulmonary arterial diastolic pressure; mPAP – mean pulmonary artery pressure; CO – cardiac output; CI – cardiac index; PVR – pulmonary vascular resistance; PCWP – pulmonary capillary wedge pressure.

Symptoms (dyspnea) were first noticed in mid-2015. To rule out a cardiac origin of symptoms a transthoracic echocardiography (TTE) was performed in June 2016 showing signs of right ventricular overload with elevated right ventricular systolic pressure (RSVP) of 90 mmHg. Right heart catheterization (July 2016) confirmed the diagnosis of PH (Table 1). Long-term oxygen therapy (LTOT) was initiated together with the endothelin receptor antagonist ambrisentan at 5 mg once daily (OD)

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Table 2. Pulmonary function test.

Parameter	Date 11.09.2018	
	Best	% Pred
FVC, L	0.97	36.99
FEV1, L	0.76	34.53
FEV1/FVC, %	72.11	93.72
DLCO, ml/min/mmHg	16.34	74
DLCO/VA, ml/min/mmHg/L	6.50	145

FVC – forced vital capacity; FEV_1 – forced expiratory volume in 1 seconds; DLCO – diffusing capacity for carbon monoxide; DCLO/VA – diffusing capacity for carbon monoxide divided by alveolar volume; % Pred – % predicted.

off-label. Supportive therapy included spironolactone 25 mg OD, torsemide 10 mg OD and atorvastatin 20 mg OD.

During current admission, the patient presented with peripheral edema and mild acrocyanosis. Lung auscultation revealed bilaterally diminished breath sounds at the bases. Vital signs were within normal range apart from mild tachycardia (92 beats per minute) and low blood pressure 100/60 mmHg. Peripheral oxygen saturation displayed severe hypoxemia with 75% on admission. Several hours after hospitalization, the patient's SpO_2 further declined to 64%, despite supplemental oxygen therapy by non-rebreathing face mask (12 L/minute). A complete blood count showed minor erythrocytosis (5.51×10^{12}/L), while white cell count and blood biochemistry (chem-8) results were within normal ranges. Serum brain natriuretic peptide (BNP) also proved to be within normal range (80.8 pg/mL). Ambrisentan was immediately discontinued and replaced by an inhaled prostanoid every 4 hours (iloprost 5 mcg via nebulizer), complemented by supplemental oxygen via simple face mask (5 L/minute). A TTE performed on admission revealed dilatation of right ventricle and left atrium, tricuspid regurgitation grade I–II with tricuspid annular plane systolic excursion of 2.9 cm, RVSP of 65 mmHg, preserved ejection fraction of 65%. Chest computer tomography (CT) with intravenous contrast displayed bilateral basal hypoventilation, focal atelectasis in right basal lobe, and prominent thoracic malformation. There were no signs of pulmonary embolism. Anti-nuclear antibody and extractable nuclear antigen panel were negative. Pulmonary function tests (Table 2) were coherent with the CT findings, demonstrating a highly restrictive ventilation pattern with largely maintained diffusing capacity (DLCO 74% of predicted) and lung permeability (DLCO/VA 145% of predicted). Over the following days, the patient's condition slowly improved with SpO_2 levels raising over 90% with increase in functional capacity to NYHA class III. The 6-minute walk test (6MWT) results on Day 4 of hospitalization was improved to 241 meters compared to 153 meters measured on Day 2 after admission. Due to financial limitations, long-term therapy of inhaled prostanoids could not be provided, therefore the patient's therapy was reverted to ambrisentan. The patient was discharged in satisfactory condition 4 days after admission. The continuation of LTOT and the start of a non-invasive positive pressure ventilation therapy was recommended.

A follow-up right heart catheterization performed in February 2019 (Table 1) revealed similar hemodynamic parameter values compared to the values obtained during the initial diagnosis, with a slight improvement in pulmonary vascular resistance. The patient remained in NYHA class III with moderate exertional dyspnea. She covered 260 meters on the repeated 6MWT.

Discussion

Kyphoscoliosis is linked to varying degrees of cardiopulmonary deterioration; the development of PH marks a more severe outcome. Although the first reports on kyphoscoliosis complicated by PH appeared several decades ago, the amount of publications reporting novel therapeutic approaches remains scarce [6]. A recent registry study of adult PH patients reported that none of the 1344 enrolled participants were affected by kyphoscoliosis [7]. A pediatric PH study counted 2 patients with kyphoscoliosis among 362 confirmed cases of PH [8]. Similar to other alveolar hypoventilative disorders, management is largely directed towards improvement of oxygenation state and ventilatory support [5,9]. Although a mainstay in combating respiratory decline, the isolated LTOT therapy is nowadays largely avoided. A combinatory approach of LTOT in conjunct with non-invasive ventilation has proven more effective in opposing pulmonary vasoconstriction, resulting in improved long-term survival and exercise capacity [10]. Despite the general improvement, adequate ventilation/oxygenation remains unable to prevent the cardiopulmonary deterioration of kyphoscoliosis patient [9,11].

The literature on the use of vasoactive medication in PH patients with deformative thoracic diseases is limited. A first report on the utilization of inhaled nitric oxide in a case of PH secondary to Potts disease indicated marked improvement of cardiopulmonary condition in a short-term emergency setting [12]. A more recent case reported clinical improvement following initiation of phosphodiesterase-5 inhibitor and oxygen therapy: a patient with severe kyphoscoliosis and multiple years of nocturnal noninvasive positive-pressure ventilation was prescribed the vasodilator therapy following the diagnosis of PH [11]. It is necessary to address the safety concerns that are generally valid when using a PAH-approved vasoactive drugs in cases of PH with concomitant lung disease. Vasoactive drugs oppose hypoxic vasoconstriction in poorly ventilated lung areas, creating a ventilation-perfusion mismatch,

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subsequently impairing blood oxygenation [13]. However, these concerns might not be attributable to PH in kyphoscoliosis, as the analysis of lung parenchyma in these patients has shown no structural abnormalities with the exception of focal atelectasis [2]. It can be expected that the deterioration of blood oxygenation is reduced to minimum in these cases.

In the present case, we initially decided to commence a monotherapy with an endothelin receptor antagonist (currently approved in PAH therapy), as PH was already far progressed at the time of diagnosis. On admission, however, the endothelin receptor antagonist could not be excluded as a cause for the declining state of the patient. Choosing the alternative, an inhaled prostanoid, was therefore largely based on its mode of distribution as this drug primarily accesses well-ventilated lung segments and hence does not interfere with hypoxic vasoconstriction and does not worsen oxygenation [14]. CT imaging and pulmonary function test did not show any evidence of concomitant lung disease, underlining the unlikelihood that the severe hypoxemia was due to the treatment with ambrisentan. Subsequently, the continuation of oral vasodilator therapy was deemed safe. Considering that PH in kyphoscoliosis progresses despite ventilatory and oxygen treatment, the addition of a vasoactive medication proposes a safe option in combating cardiopulmonary decline, not only in an acute but also in a long-term setting.

Conclusions

Pulmonary hypertension in kyphoscoliosis remains a condition associated with high mortality. Despite maximizing the effect of current management options, gradual development of pulmonary hypertension seems inevitable. So far, the reports on PAH-approved drugs in the case of kyphoscoliosis-related PH are associated with positive outcome and possibly limit progression of disease. As kyphoscoliosis remains a relatively rare encounter in clinical practice and PH is often not diagnosed in a timely manner, attention should be directed to identifying those patients who might benefit from vasoactive agents in addition to ventilation/oxygenation therapy. Each patient must be evaluated individually, as currently there are no guidelines available on treatment of this condition.

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Department and Institution where work was done

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Conflicts of interest

None.

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