Sildenafil to Facilitate Weaning From Inhaled Nitric Oxide and Mechanical Ventilation in a Patient With Severe Secondary Pulmonary Hypertension and a Patent Foramen Ovale

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We describe the case of a woman who presented to the intensive care unit with acute respiratory failure that required mechanical ventilation. She had severe pulmonary hypertension secondary to interstitial lung disease, and her history included sarcoidosis and tuberculosis. She was dependent on inhaled nitric oxide (INO) to maintain safe arterial oxygen saturation and could not be weaned from mechanical ventilation. Echocardiography revealed a patent foramen ovale with substantial right-to-left shunt, which probably contributed to her hypoxemia. Sildenafil enabled weaning from INO and substantially reduced the flow through the patent foramen ovale. She was successfully extubated and discharged home. To our knowledge, this is the first report of weaning from INO and mechanical ventilation in a patient with both severe secondary pulmonary hypertension and a right-to-left shunt through a patent foramen ovale. *Key words: sildenafil; pulmonary hypertension; mechanical ventilation; patent foramen ovale; sarcoidosis; tuberculosis.* [Respir Care 2011;56(10):1611–1613.

Introduction

Treatment with phosphodiesterase type 5 inhibitors (especially sildenafil) has rarely been described to facilitate weaning from mechanical ventilation in the intensive care unit (ICU) in patients who are dependent on inhaled nitric oxide (INO). We present a case of successful weaning from mechanical ventilation by the introduction of oral sildenafil in a patient with severe secondary pulmonary hypertension and a right-to-left shunt through a patent foramen ovale.

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Case Report

A 67-year-old woman was admitted to our hospital with severe dyspnea. Her medical history included diabetes mellitus, chronic renal failure, and hypertension. She had been hospitalized 2 years prior to this admission in another hospital, also with dyspnea. An echocardiography at that time revealed moderate dysfunction of the right ventricle and pulmonary hypertension, with a tricuspid gradient of 56 mm Hg. Chest computed tomogram showed enlarged mediastinal lymph nodes. Ultrasound-guided biopsy of the suspected lymph nodes showed non-caseating epitheliod granulomas, without giant cells. Sarcoidosis was diagnosed, and treatment with corticosteroids was initiated. Due to low arterial oxygen saturation (approximately 88–90%) on room air, continuous oxygen supplementation was prescribed.

Two years later she was again hospitalized, with shortness of breath, fever, and productive cough. This time she was diagnosed with tuberculosis, based on positive sputum staining for acid-fast bacilli and a positive sputum culture. She was transferred to a dedicated hospital for further tuberculosis treatment.

Two weeks after her discharge she presented to our hospital with severe dyspnea. On physical examination she was tachypneic and her S_{pO_2} was 66% on room air. Blood pressure was 160/82 mm Hg, heart rate was 109 beats/min, and she was apyrexial. She had crepitations at both lung bases and clubbing of the fingers. Her laboratory tests revealed mild acute renal failure (creatinine 171 μmol/L), leukocytosis (14.9 $\times$ 10^9 cells/L), and severe uncompensated metabolic acidosis (pH 7.22, HCO_3 15 mmol/L, P_{CO_2} 37.4 mm Hg). Due to the severe respiratory distress, she was intubated, but her arterial oxygen saturation remained low (60%) despite a high F_{IO_2}. Computed tomography angiography excluded pulmonary embolism, but was compatible with interstitial lung disease. The computed tomogram showed alveolar infiltrates and many enlarged lymph nodes (up to 15 mm) in the mediastinum and lung hila.

She was transferred to the medical ICU for further treatment, where she was mechanically ventilated with a pressure control mode. Due to the ongoing severe hypoxemia we added inhaled nitric oxide gas (INO) at 20 ppm, which allowed lower PEEP and lower F_{IO_2}. Intravenous vasopressors were required to maintain adequate systemic blood pressure. She received intravenous hydrocortisone (50 mg, 3 times a day) and broad-spectrum antibiotics, which were subsequently narrowed to cover recurrent growth of extended-spectrum β-lactamase *Klebsiella pneumoniae* in the sputum. We also resumed full anti-tuberculosis treatment.

Echocardiography showed severe enlargement of the right ventricle, with severe dysfunction, pulmonary hypertension (tricuspid gradient 48 mm Hg), mild to moderate mitral regurgitation, and preserved systolic function of the left ventricle. Bronchoscopy with bronchoalveolar lavage excluded any additional infectious cause. Due to the severe hypoxemia and diffuse pulmonary infiltrates we initiated a trial of high-dose corticosteroid (2 mg per kg of methylprednisolone). Her renal failure and metabolic acidosis resolved after fluid administration.

She remained dependent on mechanical ventilation and INO to maintain safe arterial oxygen saturation. Reducing the INO concentration even by 2–3 ppm suddenly decreased her P_{aO_2}. We then considered the possibility that an intracardiac shunt might be contributing to the hypoxemia. Transthoracic echocardiography, followed by transesophageal echocardiography, both with injection of agitated saline, showed severe pulmonary hypertension (tricuspid systolic gradient 70 mm Hg) and substantial right-to-left shunt through a large (0.7-cm) patent foramen ovale (Fig. 1).

To accurately measure the pulmonary pressures while varying the INO dose, we inserted a pulmonary artery catheter. Gradual increase in INO concentration reduced the pulmonary artery pressure. Oral sildenafil had an even greater effect (Table 1). We therefore initiated oral sildenafil, with dose escalation from 20 mg 3 times a day initially up to 60 mg 3 times a day. Sildenafil enabled weaning the patient from INO and mechanical ventilation in 5 days, after a total of 25 days of mechanical ventilation. Arterial oxygen saturation improved markedly, to $>$ 90% on oxygen at 2–3 L/min via nasal cannula. A repeat echocardiography before the patient was discharged showed ongoing severe right-ventricular dysfunction and severe pulmonary hypertension, but a substantial decrease in the flow through the patent foramen ovale.

Review of the initial lymph node biopsy specimen from 2 years prior confirmed epitheliod granulomas but no necrosis or giant cells and a negative stain for acid-fast bacilli (see Fig. 1). She was eventually discharged home.

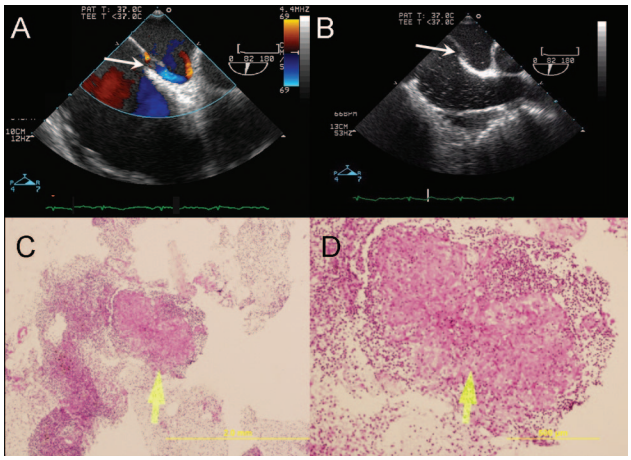

Fig. 1. Transesophageal echocardiogram of a patent foramen ovale (white arrows) with a right-to-left shunt. A: With colored Doppler scan. B: With agitated saline contrast. C and D: Mediastinal lymph node biopsy shows non-caseating granuloma (hematoxylin and eosin stain at (C) magnification 4, and (D) magnification 10.

Table 1. Pulmonary Artery Pressure, Measured With a Pulmonary Artery Catheter, With Increasing Concentration of Inhaled Nitric Oxide, Before and After Sildenafil

	Inhaled Nitric Oxide Concentration (ppm)	Pulmonary Artery Pressure (mm Hg)	
		Systolic/diastolic	Mean
Before Sildenafil			
	0	77/56	65
	10	68/49	57
	20	71/52	60
	30	68/52	60
	40	65/53	59
After Sildenafil			
	0	45/36	40

Discussion

Our patient had severe pulmonary hypertension secondary to interstitial lung disease (sarcoidosis/tuberculosis), and a patent foramen ovale, and was weaned from INO

with sildenafil. Although she was initially diagnosed with sarcoidosis based on a lymph node biopsy, 2 years later she had positive sputum cultures for tuberculosis. Differentiating between sarcoidosis and tuberculosis can be difficult[1,2] because sarcoidosis can be complicated by tuberculosis (due to treatment with corticosteroids or due to the interstitial lung itself[3]). A recent prospective study found 5.7% of patients with sarcoidosis to also have pulmonary hypertension, defined as estimated systolic pulmonary artery pressure $\geq$ 40 mm Hg, measured via Doppler echocardiography.[4] Pulmonary hypertension in sarcoidosis has been shown to be responsive to several treatments, including traditional pulmonary vasodilators (eg, INO)[5] and recently also sildenafil.[6] Pulmonary hypertension and cor pulmunale secondary to pulmonary tuberculosis have also been described, mostly in older reports.[7]

Our patient had a patent foramen ovale with a right-to-left shunt, which almost definitely contributed to her hypoxemia. Atrial septostomy is a treatment option for pulmonary hypertension in selected cases and enables a decrease in the pulmonary blood flow.[8] Therefore it could be postulated that a patent foramen ovale may have a beneficial effect on severe pulmonary hypertension. However, the importance of a patent foramen ovale in pulmonary hypertension is still unclear: one study found better survival in patients with pulmonary hypertension and patent foramen ovale,[9] whereas 2 other studies found no benefit.[10,11]

Treatment with phosphodiesterase type 5 inhibitors, especially sildenafil, for pulmonary hypertension has been well studied and described. There have also been a few reports of sildenafil used to facilitate weaning of pulmonary vasodilators after cardiac surgery or placement of a left-ventricular assist device.[12] However, in the English-language literature, we found only 2 reports of sildenafil used for an indication similar to that of our patient.[13,14] Two reports have described disappearance of right-to-left shunt through a patent foramen ovale after sildenafil in patients with primary pulmonary hypertension.[15,16] To our knowledge, our patient is the first reported weaning from INO and mechanical ventilation in a patient with both severe secondary pulmonary hypertension and a right-to-left shunt through a patent foramen ovale.

This case demonstrates several aspects of pulmonary hypertension in the ICU. The pulmonary hypertension in our patient was probably secondary to interstitial lung disease, and was responsive to INO and sildenafil. Therefore this case may suggest a role for sildenafil in weaning from INO and mechanical ventilation in patients with severe pulmonary hypertension in the ICU. We assume that our patient's right-to-left shunt contributed to her hypoxemia and to the difficulty in weaning from INO. Therefore this case emphasizes the importance of searching for a patent foramen ovale in patients with severe pulmonary hypertension and who are INO-dependent, and the role of sildenafil in reducing the flow through such shunts. Finally, this case highlights the possible relationship between sarcoidosis and tuberculosis and their impact on developing severe right heart failure.

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