

Effects of oxygen therapy in a pediatric normoxemic patient with pulmonary arterial hypertension and congenital heart disease

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Abstract

To shed light on the efficacy of oxygen therapy in pulmonary arterial hypertension (PAH) when hypoxemia is not present, we report seven years of observational data for a female patient recorded between February 2012 and February 2019 when she was aged 7.8–14.8 years. The patient was born with an atrial septal defect (closed spontaneously at 2.3 years) and ventricular septal defect (surgically repaired at 8.3 years) and then diagnosed with PAH at 8.9 years. The patient was prescribed bosentan soon after diagnosis and for the next 4.8 years, during which a first phase of oxygen therapy (nocturnal) was trialed for 2.8 years. Mean pulmonary arterial pressure (mPAP) and systolic PAP (sPAP) remained stable and at mild levels when oxygen was administered, but then increased progressively to severe levels over two years without oxygen. This coincided with worsening right ventricular pathology during the later part of this period without oxygen. Re-initiation of more intensive oxygen therapy while the patient was still on bosentan and before pharmacotherapy was changed coincided with a large and rapid fall in sPAP, confirmed by right heart catheterization measurements of mPAP. During this entire observation period, the patient remained normoxemic. These observations challenge the notion that oxygen therapy should be restricted to patients with hypoxemia and strengthen calls for further study of oxygen therapy in PAH.

Keywords

longitudinal study, pediatric, pulmonary hemodynamics, therapeutic benefit, O₂

Date received: 2 March 2019; accepted: 1 April 2019

Pulmonary Circulation 2018; 9(2) 1–3

DOI: 10.1177/2045894019845610

Case description

To shed light on the efficacy of oxygen therapy in pulmonary arterial hypertension (PAH) when hypoxemia is not present, we report seven years of observational data for a female patient recorded between February 2012 and February 2019 when she was aged 7.8–14.8 years. The patient provided permission to write and publish this report after it was described and read by her.

Early history and PAH diagnosis

The patient was born at ~980 m above sea level in May 2004; she lived at this altitude for 2.9 years before relocating to lower locations (<300 m) thereafter. She was born with a

large atrial septal defect (ASD) and moderate ventricular septal defect (VSD). Four weeks after birth, there was mild cardiomegaly and increased pulmonary vascularity (CXR). During early childhood, she exhibited exertional breathlessness and expiratory grunting. The ASD closed spontaneously by 2.3 years and the VSD was surgically closed at 8.3 years. Seven months later, in April 2013, right heart catheterization (RHC) measurements confirmed PAH (mPAP already defined in the Abstract mPAP = 40 mmHg, pulmonary capillary wedge pressure = 9 mmHg).

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Lung function

A sleep study performed two months after PAH diagnosis showed no evidence of sleep-disordered breathing (oxygen saturation = 93–97%) or obstructive sleep apnea. Lung function was assessed at 9.8 years; standard indices (FVC, FEV, FEV₁) were normal, but diffusion capacity (DLCO = 71% normal) was decreased and percentage of residual volume to total lung capacity (30%) was increased. Chest CT scans at 9.8 and 10.0 years did not reveal pulmonary embolism, focal lesions, or pleural effusion. There were no distinctive signs, symptoms, or risk factors for pulmonary embolism during the rest of the study period.

Pharmacotherapy

The patient began L-arginine (1.5 g daily) 10 days after PAH diagnosis. Ten days later, bosentan (62.5 mg daily) was introduced and the dose was doubled (125 mg daily) after one month and doubled again in February 2014 (250 mg daily). This treatment continued until 19 November 2018 when bosentan was replaced with macitentan (10 mg daily) and tadalafil (20 mg daily increased to 40 mg daily after two weeks).

Oxygen therapy

The patient engaged in oxygen therapy in two distinct phases. Phase-1 nocturnal-only oxygen therapy started in late May 2013. This phase was beset with difficulties (humidification, nasal discomfort, nasal congestion, device alarming, poor patient motivation linked to clinician discouragement) and characterized by intermittency. For the first seven months, 90% oxygen was delivered as 30-mL pulses/breath via nasal prongs using a portable oxygen concentrator for 4–8 h, 2–5 times per week. Later, a continuous oxygen concentrator delivering 90% oxygen via nasal prongs at 2 L·min⁻¹ was used, sometimes with an add-on air warmer-humidifier, again only for 4–8 h, 2–5 times per week. Based on resting measurements of expired minute ventilation in this patient (5 L·min⁻¹), the F_IO₂ associated with continuous O₂ delivery was ~0.5. The patient experienced frequent colds in mid-2015 resulting in a six-month interruption to therapy. Phase-1 stopped in December 2016 following prolonged nasal congestion and technical problems. Phase-2 started in late 2018 in an intensive way. Daytime therapy (30-mL pulse mode, 90% O₂) began on 26 October with the dose increasing over two weeks from 2–3 h daily to 5–9 h daily. Nocturnal therapy (continuous flow, 2 L·min⁻¹, 8–10 h daily) started on 11 November, following humidification troubleshooting, and is proceeding well to date due to strong patient engagement.

Pulmonary hemodynamics

Systolic pulmonary arterial pressure (sPAP) was measured by RHC or estimated by echocardiographic measurement of

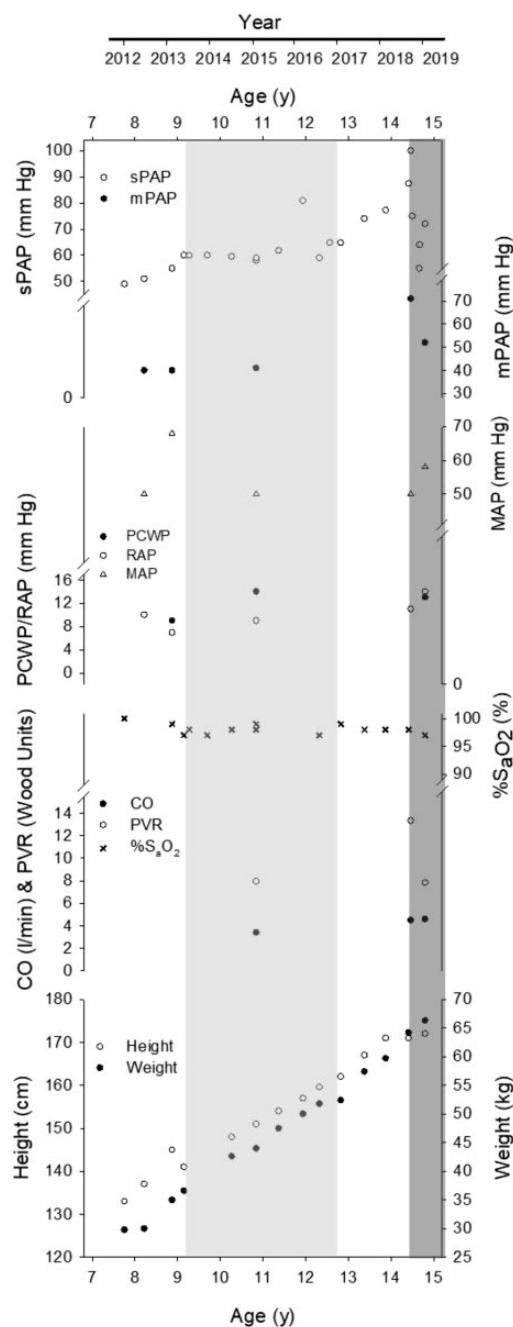


Fig. 1. Pulmonary hemodynamic and systemic arterial responses during a seven-year period of growth from childhood to adolescence in a female patient with PAH. Oxygen therapy is indicated by light grey shading (phase 1) and dark grey shading (phase 2). sPAP, systolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; MAP, mean arterial pressure; CO, cardiac output; PVR, pulmonary vascular resistance; %S_aO₂, percent oxygen saturation of hemoglobin in arterial blood.

tricuspid regurgitant jet velocity ($4v^2 + 10$). Twenty-two sPAP measurements are reported (Fig. 1) along with other RHC measurements, arterial oxygen saturation, weight, and height. There was no evidence of residual shunts during RHCs.

From December 2016 to October 2018, there was a 75 % increase in mean PAP (mPAP) to severe levels (Fig. 1). This coincided with increased limb edema and exertional breathlessness, diagnosis of vocal cord palsy (inactive left recurrent laryngeal nerve), and two episodes of gastritis treated successfully. Echocardiographic measurements (six-monthly intervals) showed an abrupt increase in right ventricular end-diastolic diameter (10%) and decrease in TAPSE (17%) from April to October 2018. NT-proBNP levels were normal in this late period (77–101 ng.mL⁻¹). Six-minute walk distance (6MWD) peaked in October 2018 (603 m, age = 14.4 years) after a gradual rise from initial measurements at 8–9 years (450–475 m).

Discussion

Current guidelines do not recommend oxygen therapy as a PAH treatment, unless patients develop hypoxemia.¹ This view is based on a lack of RCT evidence and a study of Eisenmenger patients who were severely hypoxemic but did not benefit from treatment.² There is, however, other evidence of improvements in pulmonary hemodynamics, fitness, and survival with oxygen therapy,^{3–5} although the relevance of hypoxemia is not clear. This case report provides evidence of significant benefit from oxygen therapy in the absence of hypoxemia.

The clinical history and sPAP data (Fig. 1) suggest early development of pulmonary vasculopathy before heart surgery and PAH associated with congenital heart disease, rather than of idiopathic or surgical origin. After initiation of bosentan and phase-1 oxygen therapy, pulmonary arterial pressures (PAPs) stabilized for three years at a level indicative of mild PAH. A temporary spike in sPAP coincided with interruption to oxygen therapy, suggesting that phase-1 therapy helped stabilize pulmonary pressures despite the intermittency of therapy.

Following the cessation of phase-1 oxygen therapy, there was a progressive increase in sPAP and mPAP over two years to levels consistent with severe PAH. This was associated with worsening signs, symptoms, and right ventricular pathology later during this period; whereas 6MWD peaked at this point, raising questions about its clinical utility in treating a young patient. The worsening scenario prompted the initiation of the intensive phase-2 oxygen therapy (day and night) while the patient was still on bosentan and several weeks before pharmacotherapy was altered. Re-initiation of oxygen therapy coincided with improvements in signs and symptoms and a rapid fall in sPAP, verified immediately before pharmacotherapy was changed, towards

levels observed two years earlier. RHC measurements confirmed the large and rapid reversal in pulmonary pressures, due to a reduction in pulmonary vascular resistance given that cardiac output did not change. These data suggest that oxygen acted as a rapid and potent pulmonary vasodilator, halted the rise in pulmonary pressures, and contributed substantially to the reversal in mPAP.

During the entire study, the patient remained normoxic (Fig. 1). The benefits of oxygen therapy for this patient are consistent with improvements in pulmonary hemodynamics during acute oxygen testing in normoxic patients⁶ and long-term survival benefit in a pediatric population which included patients who were normoxic before therapy.³ These observations challenge the notion that oxygen therapy should be restricted to patients with hypoxemia and strengthen calls for further study of oxygen therapy in PAH.^{3,5}

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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