Home inhaled nitric oxide therapy in a child with pulmonary arterial hypertension associated with pulmonary venous obstruction

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Case Report

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Abstract

We present the case of a child with severe pulmonary arterial hypertension associated with postoperative pulmonary venous obstruction who were treated with home inhaled nitric oxide therapy. The patient underwent corrective surgery at the age of 7 days; however, he developed postoperative pulmonary venous obstruction. Cardiac catheterization at the age of 2 months showed that mean pulmonary venous pressure and pulmonary vascular resistance were 53 mmHg and 9.0 Wood unit m$^2$, respectively. He underwent pulmonary venous reconstruction, but it resulted in recurrent pulmonary venous obstruction. Subsequently, he underwent stent implantation in the pulmonary vein. Histopathological findings of the lung specimen showed that intimal hyperplasia in the pulmonary arteries and arterialization in the pulmonary veins, suggesting intractable pulmonary arterial hypertension. Inhaled nitric oxide decreased mean pulmonary arterial pressure from 81 mmHg to 51 mmHg. Despite the introduction of pulmonary vasodilators including tadalafil and bosentan, inhaled nitric oxide could not discontinue. We implemented home inhaled nitric oxide therapy, which allowed the patient to be discharged for home-care medication. Our case suggested that home inhaled nitric oxide therapy was feasible in a child with intractable pulmonary arterial hypertension who were expected to be poor outcome.

Introduction

Inhaled nitric oxide (NO) is recognized as a useful therapy in the management of children with pulmonary arterial hypertension, especially in perioperative care for children with congenital heart disease [1]. Inhaled NO converts guanosine-5’-triphosphate to cyclic guanosine monophosphate in vascular smooth muscle cells and electively dilates pulmonary arteries, resulting in a decrease in pulmonary arterial pressure or an increase in pulmonary arterial blood flow [2]. However, inhaled NO therapy for patients with postcapillary pulmonary hypertension, such as pulmonary venous obstruction or left heart obstruction, remains controversial because pulmonary vasodilators deteriorate pulmonary venous congestion and compromise pulmonary circulation [3]. Total anomalous pulmonary venous connection (TAPVC) usually manifests soon after birth, which requires corrective surgery. Recent advances in cardiovascular surgery allows the majority of children with TAPVC to survive beyond childhood; however, 17% of children with TAPVC develops postoperative pulmonary venous obstruction, which is related to poor mortality and morbidity [4]. Pulmonary arterial hypertension associated with postoperative pulmonary venous obstruction occasionally consists with pre- and post-capillary pulmonary hypertension. Therefore, the indication of inhaled NO therapy should be individually determined in children with pulmonary arterial hypertension associated with postoperative pulmonary venous obstruction after corrective surgery for TAPVC. In addition, there are prolonged hospitalizations due to difficulty in weaning from inhaled NO therapy among them. We present the case of a child with pulmonary arterial hypertension associated with postoperative pulmonary venous obstruction who were treated with home inhaled NO therapy.

Case Presentation
A boy born at the 39 weeks' gestation with 2,112g of the birth weight was transferred to our hospital because of cyanosis. Echocardiography and contrasted computed tomography showed supracardiac TAPVC (Fig. 1). He underwent corrective surgery at 7 days of the age. However, tachypnea and cyanosis developed at 2 months after the surgery. Then, Doppler echocardiography showed that the velocity of the pulmonary vein increased up to 2.0 m/s, suggesting pulmonary venous obstruction. Cardiac catheterization at 2 months of the age showed that mean pulmonary arterial pressure and pulmonary vascular resistance were 53 mmHg and 9.0 Wood units m\(^2\), respectively. Contrasted computed tomography (CT) showed bilateral pulmonary venous obstruction. Subsequently, he underwent surgical release of pulmonary venous obstruction. At the intensive care units after reoperation, inhaled NO therapy was started because systemic arterial pressure was unstable and echocardiography suggested increased right ventricular pressure. Cardiac catheterization at 4 months of the age showed that mean pulmonary arterial pressure and pulmonary vascular resistance were 51 mmHg and 6.0 Wood units m\(^2\) on inhaled NO therapy, respectively. In addition, we tested whether inhaled NO therapy could be discontinued, which showed that mean pulmonary arterial pressure and pulmonary vascular resistance increased up to 81 mmHg and 12.1 Wood unit m\(^2\), respectively. We decided to continue further inhaled NO therapy. At 5 months of the age, he underwent stent implantation into the left pulmonary vein with a 6-mm Express™ vascular SD stent (Boston scientific corporation, Marlborough, USA), reconstruction of right pulmonary vein, and surgical creation of an atrial septal defect on cardiopulmonary bypass, because of deteriorated pulmonary venous obstruction. In addition, we performed lung biopsy. Histopathological findings showed medial proliferation of the pulmonary arterioles, which was classified as the Heath-Edwards class grade 3, and intimal fibrous thickening of the pulmonary veins (Fig. 2). Based on these histopathological findings, the combination therapy of pulmonary vasodilators, including tadalafil, macitentan and selexipag, was started. He repeatedly required re-dilation of right pulmonary vein and left pulmonary venous stent. Despite these intensive treatment for pulmonary arterial hypertension and pulmonary venous obstruction, severe pulmonary arterial hypertension remined, which had to give up on discontinuing inhaled NO therapy. At 10 months of the age, following cardiac catheterization showed that mean pulmonary arterial pressure and pulmonary vascular resistance during inhaled and discontinuing NO therapy were 80 and 112 mmHg, and 19.5 and 28.7 Wood units m\(^2\), respectively. Therefore, we introduced home inhaled NO therapy (Fig. 3). NO was steadily supplied to the patient by flowing NO through high flow nasal cannula (Optiflow® junior, Fisher & Pykel Healthcare, Auckland, New Zealand) using INOflo® DS (Mallinckrodt Pharmaceuticals, inc., Staines, UK). The concentrations of NO and NOx were continuously monitored by INOflo® DS. He could be discharged owing to this home inhaled NO therapy system at one year and ten months of the age. Home medical doctor checked his condition every 2 weeks, and he was stable without adverse events for one year and three months. However, he suddenly presented cardiac arrest probably due to the development of pulmonary hypertensive crisis followed by pulmonary venous obstruction, and he was deceased at 3 years of the age.

**Discussion**
We presented the case of a child with intractable pulmonary arterial hypertension associated with postoperative TAPVC in whom home inhaled NO therapy allowed to achieve home medical care. Patients with postoperative pulmonary venous obstruction associated with TAPVC have high mortalities, accounting for 58% of the 3-year-survival, despite repeated surgical or catheter interventions [4]. Histopathological changes in patients with pulmonary venous obstruction involve medial thickening both in the pulmonary arterioles and venous [5], which suggests that pulmonary arterial hypertension associated with pulmonary venous obstruction possesses the aspects of pre- and post-capillary pulmonary hypertension. It is commonly contraindicated to administrate pulmonary vasodilators in patients with pulmonary venous obstruction because it is precipitate life-threatening pulmonary edema [3]; however, pulmonary vasodilators contribute to reduce pulmonary arterial pressure and right ventricular workload in several cases with pulmonary venous obstruction [6]. Therefore, the effectiveness of pulmonary vasodilators should be individually evaluated among them. In our present case, invasive right heart catheterization revealed that inhaled NO reduced pulmonary arterial pressure, and clinical manifestations associated with heart failure were improved by inhaled NO therapy and administrations of tadalafil, macitentan, and selexipag. Creagh-Brown et al. suggested that inhaled NO trial test was useful to evaluate the effectiveness of pulmonary vasodilators, such as sildenafil, in patients with pulmonary venous obstructive disease [7]. Van Duin et al. reported that sildenafil which stimulated NO synthesize dilated both pulmonary arterioles and veins in animal models of pulmonary venous obstruction [8]. In our present case, inhaled NO might affect both pulmonary arterioles and veins, which relief intractable pulmonary arterial hypertension resulting in the achievement of his stable clinical condition after home inhaled NO therapy.

Previous reports have shown that home inhaled NO therapy was feasible and safe in patients with pulmonary arterial hypertension or SARS-CoV-2 infection [9–11]. The overall utility of home inhaled NO therapy is limited by interindividual variations in responses, costs, and logistics. Channick et al. reported that pulsed delivery of inhaled NO leads to significant improvements of clinical symptoms in ambulatory patients with idiopathic pulmonary hypertension [10]. Ivy et al. described the possibility of long-term safety, efficacy, and acceptability of home NO therapy using a pulsed delivery system in patients with idiopathic pulmonary hyertention [11]. However, because pulsed deliver of inhaled NO is not feasible in infants and toddlers because it requires synchronizer at a nasal prong. The equipment of Optiflow® junior and INOFlo® DS could provide steady supply of inhaled concentration of NO in our present case. However, it is controversial whether precise monitoring of inhaled concentration of NO in such small infants to avoid adverse effects of inhaled NO, including met-hemoglobinopathy, pulmonary congestion and emphysema. Fortunately, the accessibility to our institution and the trust for home medical care providers were satisfied in our present case.

Declarations

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**Informed consent:** written informed consent was obtained from his parents.

**Authorship contribution:**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jun Muneuchi, Hiromu Yamada, Mamie Watanabe, Takashi Matsumura and Yosie Ochiai. Histopathological analysis was performed by Naoki Masaki. The first draft of the manuscript was written by Yuichirou Sugitani and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**References**


Figures
Figure 1

Three dimensions contrast-enhanced computed tomography showed supracardiac Total anomalous pulmonary venous connection

All pulmonary veins formed common chamber and returned to superior vena cava via vertical vein

INV; innominate vein, SVC; superior vena cava
Figure 2

The histopathology of lung biopsy

a. Small pulmonary artery showed medial proliferation and the vascular lumen was almost lost. (Elastica Masson staining. 400X)
b. Peripheral pulmonary vein showed intimal proliferation. (Elastica Masson staining. 200X)

**Figure 3**

Home-inhaled NO therapy system

0.08%vol NO and Oxygen were connected (arrow; 0.08%vol NO, head arrow; Oxygen) and blended in Mediox 60™. The mixed gas was steadily supplied to a patient using optiflow TM flow. The concentration of NO and NOx was measured and monitored by INOflo® DS

NO; Nitric Oxide