Cardiology in the Young

cambridge.org/cty

Home-inhaled nitric oxide in a child with pulmonary arterial hypertension associated with post-operative pulmonary venous obstruction

Yuichiro Sugitani, Jun Muneuchi and Mamie Watanabe

Department of Pediatrics, Kyushu Hospital, Japan Community Healthcare Organization, Kitakyushu, Japan

Brief Report

Cite this article: Sugitani Y, Muneuchi J, and Watanabe M (2023) Home-inhaled nitric oxide in a child with pulmonary arterial hypertension associated with post-operative pulmonary venous obstruction. *Cardiology in the Young* **33**: 2673–2675. doi: 10.1017/S1047951123003591

Received: 18 March 2023
Revised: 12 July 2023
Accepted: 22 August 2023
First published online: 17 October 2023

Keywords:
Total anomalous pulmonary venous connection; pulmonary venous stenosis; NO; pulmonary veno-occlusive disease

Corresponding author:
Yuichiro Sugitani;
Email: sugitani505@yahoo.co.jp

Abstract

Home-inhaled nitric oxide therapy was effective and feasible in the patients with intractable pulmonary arterial hypertension. We present the case of a child with severe pulmonary arterial hypertension associated with post-operative pulmonary venous obstruction who was treated with home-inhaled nitric oxide therapy.

Introduction

Inhaled nitric oxide has been recognised as a useful therapy for management of children with pulmonary arterial hypertension, particularly in the peri-operative care.[1] However, inhaled nitric oxide in patients with post-capillary pulmonary hypertension remains controversial. Total anomalous pulmonary venous connection usually manifests soon after birth and requires corrective surgery. Despite recent advances in cardiovascular surgery, 17% of the patients develop post-operative pulmonary venous obstruction, which is associated with poor mortality and morbidity.[2] Pulmonary arterial hypertension associated with post-operative pulmonary venous obstruction occasionally comprises pre- and post-capillary pulmonary hypertension. We present the case of a child with pulmonary arterial hypertension associated with post-operative pulmonary venous obstruction, who was treated with home-inhaled nitric oxide.

Case presentation

A boy born at 39-weeks gestation with 2,112 g of birth weight was transferred to our hospital due to cyanosis. Echocardiography and contrast-enhanced CT revealed supracardiac total anomalous pulmonary venous connection (Supplemental figure S1). The patient underwent corrective surgery at 7 days of age. However, tachypnoea and cyanosis developed two months after surgery. Then, Doppler echocardiography showed that the velocity of the pulmonary vein increased up to 2.0 m/s. Cardiac catheterisation at 2 months of age showed that the mean pulmonary arterial pressure and pulmonary vascular resistance were 53 mmHg and 9.0 Wood units m^2, respectively. Contrast-enhanced CT showed bilateral pulmonary venous obstruction. Subsequently, the patient underwent surgical release of pulmonary venous obstruction using a sutureless technique. At the intensive care units after reoperation, inhaled nitric oxide was initiated because systemic arterial pressure was unstable. Moreover, echocardiography revealed increased right ventricular pressure. Cardiac catheterisation at 4 months of age showed that the mean pulmonary arterial pressure and pulmonary vascular resistance were 51 mmHg and 6.0 Wood units m^2 following inhaled nitric oxide, respectively. In addition, we assessed whether inhaled nitric oxide could be discontinued, which showed that the mean pulmonary arterial pressure and pulmonary vascular resistance increased up to 81 mmHg and 12.1 Wood unit m^2, respectively. Therefore, we decided to continue further with inhaled nitric oxide. At 5 months of age, the patient underwent stent implantation into the left pulmonary vein with a 6-mm Express™ vascular SD stent (Boston Scientific Corporation, Marlborough, USA), reconstruction of the right pulmonary vein by sutureless technique, and surgical creation of an atrial septal defect on cardiopulmonary bypass due to deteriorated pulmonary venous obstruction. In addition, a lung biopsy was performed. Histopathological findings showed medial proliferation of the pulmonary arterioles, which was classified as Heath-Edwards class grade 3, and intimal fibrous thickening of the pulmonary veins (Fig. 1). Based on these histopathological findings, combination therapy with pulmonary vasodilators including tadalafil, macitentan, and selexipag was initiated. He repeatedly required redilation of the right and left pulmonary veins. Despite these intensive treatments, severe pulmonary arterial hypertension was not resolved and therefore we had to give up on discontinuing inhaled nitric oxide.

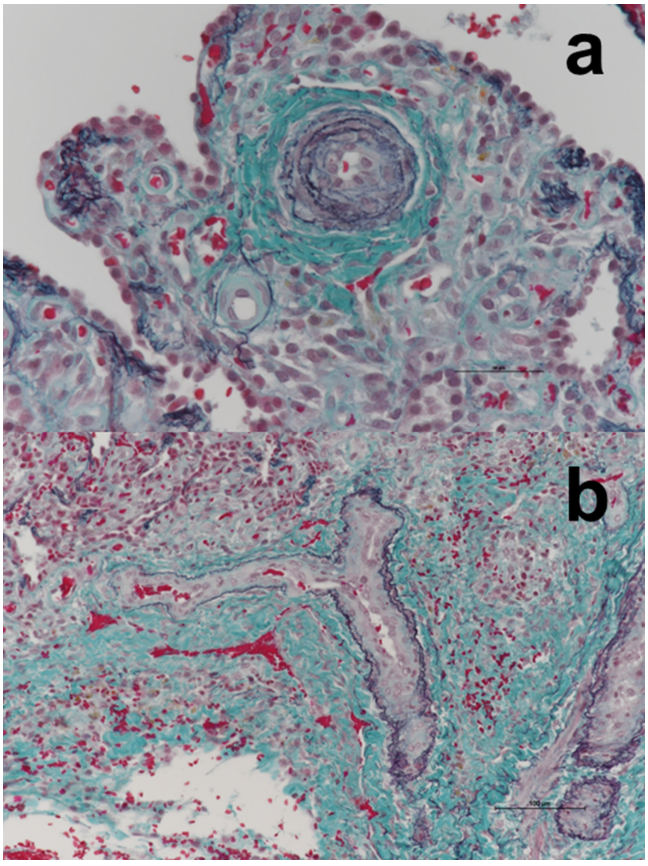

Figure 1. The histopathology of lung biopsy. (***a***) The small pulmonary artery shows medial proliferation and the vascular lumen is almost completely lost. (Elastica Masson staining). 400X). (***b***) Peripheral pulmonary vein shows intimal proliferation. (Elastica Masson staining. 200X).

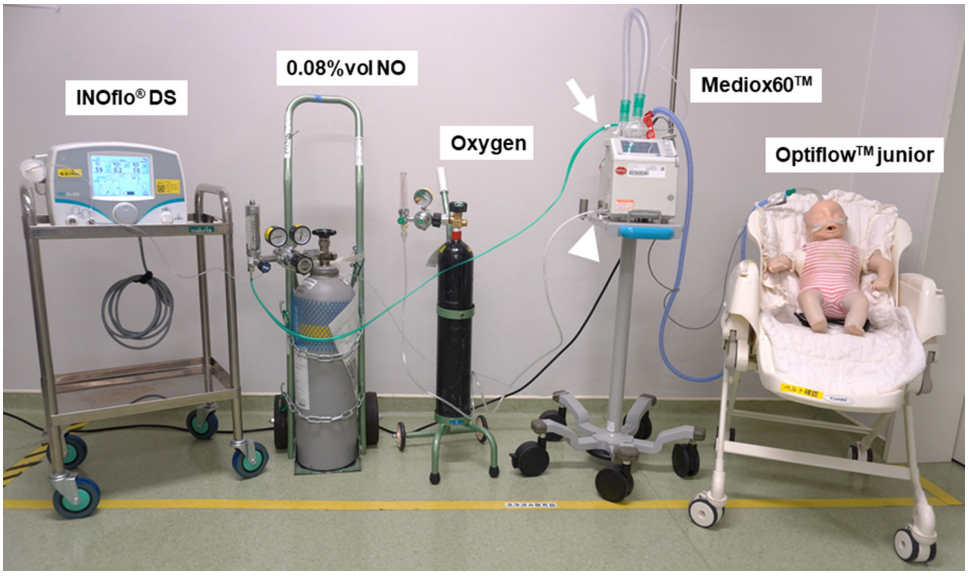

Figure 2. Home-inhaled nitric oxide therapy system. 0.08%vol NO and Oxygen are connected (arrow; 0.08%vol NO, head arrow; oxygen) and blended in Mediox 60™. The mixed gas is steadily supplied to the patient using an Optiflow TM flow. The concentrations of NO and NO_2 are measured and monitored using an INOflo® DS. NO = Nitric oxide; NO_2 = Nitrogen dioxide.

At 10 months of age, following cardiac catheterisation, the mean pulmonary arterial pressure and pulmonary vascular resistance during inhaled and discontinued nitric oxide were 80 and 112 mmHg, and 19.5 and 28.7 Wood units m^2, respectively. Therefore, we performed home-inhaled nitric oxide (Fig. 2). Nitric oxide was steadily supplied to the patient through a high-flow nasal cannula (Optiflow® junior, Fisher & Pykel Healthcare, Auckland, New Zealand) using INOflo® DS (Mallinckrodt Pharmaceuticals, Inc.,

https://doi.org/10.1017/S1047951123003591 Published online by Cambridge University Press

Staines, UK). The concentrations of nitric oxide and nitrogen dioxide were continuously monitored using INOflo® DS. The patient was discharged owing to this home-inhaled nitric oxide system at one year and ten months of age. The home medical doctor checked his condition every two weeks. The patient's condition was stable without adverse events for one year and three months. However, he expired at 3 years of age due to the development of a pulmonary hypertensive crisis.

Discussion

Patients with post-operative pulmonary venous obstruction associated with total anomalous pulmonary venous connection have high mortality rates, accounting for 58% of the 3-year survival, despite repeated surgical or catheter interventions.[2] Histopathological changes in patients with pulmonary venous obstruction involve medial thickening of both the pulmonary arterioles and veins.[3] This could suggest that pulmonary arterial hypertension associated with pulmonary venous obstruction is associated with pre- and post-capillary pulmonary hypertension. Pulmonary vasodilators are commonly contraindicated in patients with pulmonary venous obstruction because they precipitate life-threatening pulmonary oedema.[4] However, pulmonary vasodilators contribute to reduced pulmonary arterial pressure and right ventricular workload in several cases with pulmonary venous obstruction.[5] Therefore, the effectiveness of pulmonary vasodilators should be individually evaluated. In the present case, cardiac catheterisation revealed that inhaled nitric oxide reduced pulmonary arterial pressure, and clinical manifestations were improved by inhaled nitric oxide and pulmonary vasodilators. Van Duin et al. reported that sildenafil, which stimulates nitric oxide production, dilates both pulmonary arterioles and veins in animal models of pulmonary venous obstruction.[6] In the present case, inhaled nitric oxide might have affected both pulmonary arterioles and veins, resulting in the achievement of a stable clinical condition after home-inhaled nitric oxide.

The anatomical intervention performed for post-operative pulmonary venous obstruction had limited effectiveness in treating intimal fibrous thickening. Rapamycin, which is an inhibitor of mammalian target, has been found to effectively prevent intimal fibrous thickening for pulmonary venous obstruction.[7] Although systemic therapy of rapamycin was one of the effective therapies for post-operative pulmonary venous obstruction, the evidence of rapamycin had not been unfortunately established at the time when we treated the present case.

Previous reports have shown that home-inhaled nitric oxide was feasible and safe in patients with pulmonary arterial hypertension or severe acute respiratory distress syndrome coronavirus 2 infection.[8–10] Ivy et al. described the long-term safety, efficacy, and acceptability of home-inhaled nitric oxide using a pulsed delivery system in patients with idiopathic pulmonary hypertension.[10] However, pulsed delivery of inhaled nitric oxide is not feasible in infants and toddlers because it requires a synchroniser at nasal prong. The equipment of Optiflow® junior and INOflo® DS could provide a steady supply of inhaled nitric oxide concentrations in the present case. However, precise monitoring of inhaled concentration of nitric oxide in such small infants to avoid adverse effects of inhaled nitric oxide, including methemoglobinemia, pulmonary congestion, and emphysema, is controversial. Fortunately, accessibility to our institution and the trust of home medical care providers were satisfied in the present case.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/S1047951123003591

Acknowledgements. The authors would like to thank Dr Ryohei Matsuoka and Dr Takashi Furuta, Dr Hiromu Yamada, Mr. Takeshi Matsumura, Dr Naoki Masaki, and Dr Yosie Ochiai for providing the patient's data and approving the version for publication.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. None.

Informed consent. Written informed consent was obtained from the patient's parents.

References

1. Tominaga Y, Iwai S, Yamauchi S, et al. Post-extubation inhaled nitric oxide therapy via high-flow nasal cannula after fontan procedure. Pediatr Cardiol 2019; 40: 1064–1071. DOI: 10.1007/s00246-019-02122-2.
2. Seale AN, Uemura H, Webber SA, et al. Total anomalous pulmonary venous connection: outcome of postoperative pulmonary venous obstruction. J Thorac Cardiovasc Surg 2013; 145: 1255–1262. DOI: 10.1016/j.jtcvs.2012.06.031.
3. Yamaki S, Tsunemoto M, Shimada M, et al. Quantitative analysis of pulmonary vascular disease in total anomalous pulmonary venous connection in sixty infants. J Thorac Cardiovasc Surg 1992; 104: 728–735.
4. Humbert M, Kovacs G, Hoeper MM, et al. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2022; 30: 2200879. DOI: 10.1183/13993003.00879-2022.
5. Zhang L, Wang Y, Zhang R. Good response to pulmonary arterial hypertension-targeted therapy in 2 pulmonary veno-occlusive disease patients: a case report. Medicine (Baltimore) 2021; 100: e27334. DOI: 10.1097/MD.0000000000027334.
6. Van Duin RWB, Stam K, Uitterdijk A, et al. Intervening with the nitric oxide pathway to alleviate pulmonary hypertension in pulmonary vein stenosis. J Clin Med 2019; 8: 1204. DOI: 10.3390/jcm8081204.
7. Patel JD, Briones M, Mandhani M, et al. Systemic sirolimus therapy for infants and children with pulmonary vein stenosis. J. Am Coll Cardiol 2021; 77: 2807–2818. DOI: 10.1016/j.jacc.2021.04.013.
8. Zamanian RT, Pollack CV Jr, Gentile MA, et al. Outpatient inhaled nitric oxide in a patient with vasoreactive idiopathic pulmonary arterial hypertension and COVID-19 infection. Am J Respir Crit Care Med 2020; 202: 130–132. DOI: 10.1164/rccm.202004-0937LE.
9. Channick RN, Newhart JW, Johnson FW, et al. Pulsed delivery of inhaled nitric oxide to patients with primary pulmonary hypertension: an ambulatory delivery system and initial clinical tests. Chest 1996; 109: 1545–1549. DOI: 10.1378/chest.109.6.1545.
10. Ivy DD, Parker D, Doran A, Parker D, Kinsella JP, Abman SH. Acute hemodynamic effects and home therapy using a novel pulsed nasal nitric oxide delivery system in children and young adults with pulmonary hypertension. Am J Cardiol 2003; 92: 886–890. DOI: 10.1016/s0002-9149(03)00910-x.