

Case Report

Reversible Cardiac Hypertrophy in Pulmonary Arterial Hypertension Treated With High-Dose Epoprostenol

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ABSTRACT

Although current guidelines recommend the use of prostanoid infusion that includes epoprostenol for high-risk pulmonary arterial hypertension patients, epoprostenol has many adverse effects. We report a case of a heritable pulmonary arterial hypertension patient who had transient biventricular hypertrophy during high-dose administration of epoprostenol. In this case, biventricular hypertrophy with worsening of dyspnea was observed during the uptitration of epoprostenol. Inflammatory diseases and endocrine disorders were ruled out as causes of the ventricular hypertrophy. After epoprostenol was changed to intravenous treprostinil, the biventricular hypertrophy normalized, in connection with dyspnea improvement. The use of high-dose epoprostenol may contribute to cardiac hypertrophy.

RÉSUMÉ

Bien que les lignes directrices en vigueur recommandent les perfusions de prostanoïdes comprenant de l'époprostenol chez les patients à risque élevé atteints d'hypertension artérielle pulmonaire, les effets indésirables de l'époprostenol sont nombreux. Nous décrivons ici le cas d'un patient atteint d'hypertension artérielle pulmonaire héréditaire ayant présenté une hypertrophie biventriculaire transitoire pendant le traitement par de l'époprostenol à dose élevée. Pour ce patient, une hypertrophie biventriculaire accompagnée d'une aggravation des symptômes de dyspnée ont été observées lors de l'ajustement à la hausse de la dose d'époprostenol. Les maladies inflammatoires et les troubles endocriniens ont été écartés comme facteurs étiologiques de l'hypertrophie ventriculaire. Après le remplacement de l'époprostenol par du treprostinil intraveineux, l'hypertrophie biventriculaire s'est résorbée, et les symptômes de dyspnée se sont atténués. Il semble donc que l'utilisation de l'époprostenol à dose élevée puisse contribuer à l'hypertrophie cardiaque.

A male patient, diagnosed with pulmonary arterial hypertension at a hospital, was referred to our institution at the age of 16 years.¹ The mean pulmonary arterial pressure, pulmonary vascular resistance (PVR), and cardiac index measured during diagnosis were 83 mm Hg, 12.9 Wood units, and 3.5 L/min per m², respectively. Tadalafil at 40 mg daily, sildenafil at 30 mg daily, and ambrisentan at 10 mg daily were administered as initial combination therapy. Continuous intravenous infusion of epoprostenol was initiated and was gradually increased to 75 ng/kg/min, because the initial combination

therapy was insufficient to improve the hemodynamics—mean pulmonary arterial pressure of 62 mm Hg, PVR of 10.9 Wood units, and cardiac output of 3.0 L/min. Although his symptoms remained in World Health Organization functional class III, the comprehensive risk of idiopathic/ heritable pulmonary arterial hypertension (HPAH) was intermediate; therefore, the patient was referred to our hospital at the age of 18 years. The patient carried a missense mutation of *BMPR2*, c.1472G > A, which caused an amino acid change to p.Arg491Gln. Echocardiography, on the 30th day after referral, showed normal left ventricular thickness. Despite the uptitration of epoprostenol to 133 ng/kg/min, plasma brain natriuretic peptide levels increased from 21 pg/mL at the 13th month to 156 pg/mL at the 21st month; ascites appeared, and dyspnea worsened, at the 30th month. Follow-up echocardiography at the 31st month showed marked concentric biventricular hypertrophy (Fig. 1A; Video 1, view video online), despite well-controlled blood pressure. However, none of the laboratory findings was suggestive of

Received for publication May 10, 2022. Accepted June 21, 2022.

Ethics Statement: The patient provided informed consent for the preparation of this report.

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Novel Teaching Points

- The delicate balance between the benefits and risks expected from use of high-dose epoprostenol, including the possibility of biventricular hypertrophy, needs to be explored, and the optimal dosage, with minimal side effects, needs to be determined.

infiltrative, inflammatory, or endocrine disorders (angiotensin-converting enzyme: 7.1 U/L; IgG4: 32.6 mg/dL; adrenocorticotropic hormone: 7.9 pg/mL; cortisol: 15.8 μ g/dL; free T3: 1.82 pg/mL; free T4: 1.57 ng/mL; serum growth hormone: 2.92 ng/mL; serum somatomedin C: 83 ng/mL). Cardiac magnetic resonance imaging (MRI) showed biventricular hypertrophy without abnormal signals on T2-weighted images, and late gadolinium enhancement. Endomyocardial biopsy of the right ventricle demonstrated cardiac hypertrophy associated with mild lymphocytic infiltration and fibrosis (Fig. 1B; Video 2, view video online). Although candidacy for cardiopulmonary transplantation was considered, due to uncontrolled pulmonary hypertension with

remarkable biventricular hypertrophy at the 32nd month, depression was considered to be a relative contraindication to cardiopulmonary transplantation. Sertraline at 25 mg daily and bromazepam at 8 mg daily were prescribed to treat depression; no other drugs or supplements were used. As further up-titration of epoprostenol, to 151 ng/kg/min, was ineffective, it was down-titrated from the 38th month, and switched to 92 ng/kg/min of treprostinil at the 40th month. Notably, afterward, his biventricular hypertrophy regressed, and almost-normalized hemodynamics were observed (Fig. 1C), along with improvement of ascites and normalized plasma brain natriuretic peptide level. During the 4-year follow-up period, no worsening of pulmonary hemodynamics (PVR: 4.4 Wood units [after transition to treprostinil] vs 4.2 Wood units [after 4 years]) or biventricular hypertrophy occurred (Fig. 2; Supplemental Table S1).

Discussion

The differential diagnosis of transient ventricular hypertrophy includes that caused by infiltrative or inflammatory diseases (eg, acute myocarditis and sarcoidosis), endocrine disorders (eg, acromegaly, Cushing syndrome, hypothyroidism), and drugs.² No clinical or laboratory findings were

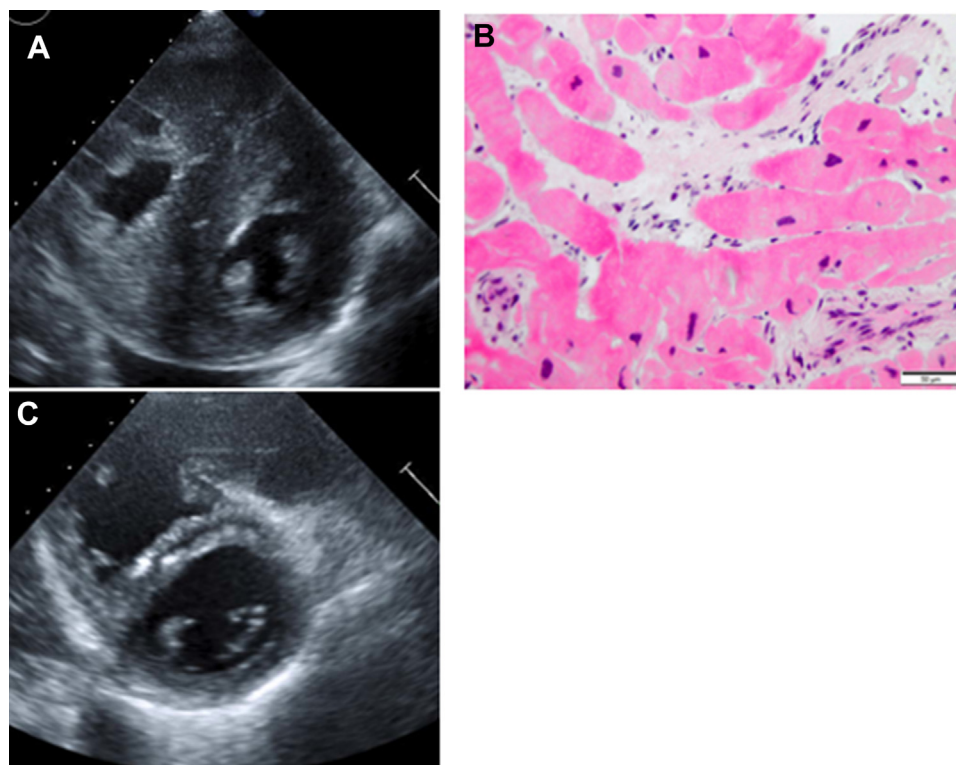


Figure 1. The ventricles, before and after discontinuation of epoprostenol. **(A)** Echocardiography showing remarkable biventricular hypertrophy during the up-titration of epoprostenol (151 ng/kg/min at the 31st month); left ventricular mass index and thicknesses of interventricular septum, left ventricular posterior wall, left ventricular wall, and right ventricular wall were 235 g/m², 24 mm, 14 mm, 13 mm, and 17 mm, respectively. **(B)** The photomicrography of ventricular myocardium following hematoxylin-eosin staining of the biopsy sample. A myocardial sample of the right ventricle shows hypertrophy and focal disarray of myocytes with mild lymphocytic infiltration and fibrosis; original magnification x400; **bar** = 50 μ m. **(C)** After discontinuation of epoprostenol (55th month), biventricular hypertrophy improved; the left ventricular mass index and the thicknesses of the interventricular septum, the left ventricular posterior wall, the left ventricular wall, and the right ventricular wall were 77 g/m², 9 mm, 8 mm, 9 mm, and 6 mm, respectively.

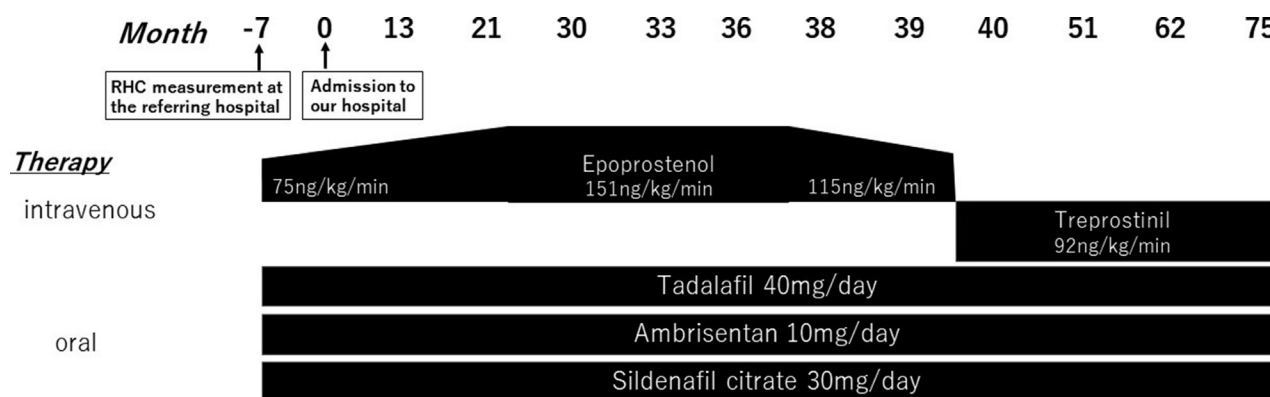


Figure 2. Clinical time-course changes of medical therapy in the present case. BNP, brain natriuretic peptide; CI, cardiac index; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; Rp/Rs, ratio of pulmonary to systemic vascular resistance; SVR, systemic vascular resistance.

suggestive of these diagnoses. Cardiac MRI did not reveal myocarditis, and the main finding of myocardial biopsy was cardiac hypertrophy without myocardial edema. Throughout the clinical course of this observation period, no medications, except treprostinil with epoprostenol, were changed. The combination of sildenafil and tadalafil was initiated before referral to our hospital, based on the evidence of the observational study,³ and was continued during the progression and regression of biventricular hypertrophy. Therefore, the use of high-dose epoprostenol could have contributed to cardiac hypertrophy in this case.

Although elucidating the mechanism by which epoprostenol induces hypertrophy is beyond the scope of this case report, we hypothesized that several mechanisms are possible. First, transient myocarditis could not be completely ruled out as the cause of hypertrophy. However, the findings of cardiac MRI and myocardial histology did not support the presence of myocarditis, which could contribute to significant hypertrophy, as mentioned previously. Second, although the effect of epoprostenol in nonvascular smooth muscle cells remains unclear, several case reports have indicated unexpected complications of using high-dose epoprostenol, possibly through mechanisms involving nonvascular smooth muscle cells (eg, organ enlargements such as the giant fold of the stomach⁴ and goiter⁵). To our knowledge, no prior studies have examined the effect of epoprostenol on cardiac myocytes, which merits further study. Third, excessive prostacyclin in pulmonary arterial hypertension can lead to a high cardiac output state, suggesting that it has a significant positive inotropic effect.⁶ However, the cardiac output state was not high during the treatment with epoprostenol or treprostinil, except during the initial assessment in our hospital.

Although current international guidelines recommend the use of prostanoid infusion including epoprostenol for high-risk idiopathic /HPAH patients, epoprostenol has many adverse effects, such as high cardiac output and thyroid gland enlargement.⁴ Given the situation in Japan, where the use of high-dose epoprostenol is eligible for insurance reimbursement, we have a unique opportunity to explore both the beneficial and adverse effects of using the

drug. To the best of our knowledge, this is the first reported case of HPAH with transient biventricular hypertrophy associated with continuous infusion of high-dose epoprostenol.

Determining the correct dosage of epoprostenol may be difficult because of its long-term side effects. The delicate balance between the benefits and risks expected from use of high-dose epoprostenol needs to be explored, and the optimal dosage with no or minimal side effects based on a pulmonary artery pressure-guided treatment strategy needs to be determined (ie, up-titration of epoprostenol until a sufficient decrease in pulmonary artery pressure occurs).⁷

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2022.06.009>.