Case Report

Pulmonary Circulation

Successful treatment of severe combined post- and pre-capillary pulmonary hypertension in a patient with idiopathic restrictive cardiomyopathy

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Abstract

Restrictive cardiomyopathy (RCM) is a rare form of cardiomyopathy that is characterized by restrictive ventricular filling. Elevated filling pressure leads to pulmonary hypertension (PH), which often progresses to combined post- and pre-capillary PH (Cpc-PH) with increased diastolic pulmonary vascular pressure gradient (DPG) and pulmonary vascular resistance (PVR) caused by long-standing backward hemodynamic consequences of left heart disease (LHD) leading to morphological changes in the pulmonary vasculature. Patients with high PVR undergoing left ventricular assist device (LVAD) implantation are at increased risk of post-operative right-sided heart failure requiring concomitant implantation of a right ventricular assist device (RVAD). We report a case of RCM with severe Cpc-PH due to extremely elevated DPG and PVR. The patient presented recurrent syncope caused by severe PH. Right heart catheterization (RHC) revealed highly elevated DPG 30 mmHg and PVR 25.3 Wood units (WU) and subsequent significant reduction of right ventricular afterload during vasoreactivity testing with inhaled nitric oxide (NO) to DPG 5 mmHg and PVR 10.5 WU. During the administration of pulmonary vasodilators, pulmonary congestion worsened. Second RHC revealed elevated pulmonary arterial wedge pressure (PAWP) and modest decrease of pulmonary arterial pressure (PAP) 87 mmHg and PVR 9.6 WU. Therefore, an inotropic agent and systemic vasodilator were added for the treatment of left-sided heart failure. Targeting elevated filling pressures with both PAH-specific and heart failure treatment, a further decrease of right ventricular afterload with DPG of 5 mmHg and PVR of 3.8 WU was achieved. In a next step, LVAD was successfully implanted, without need for RVAD, as a bridge to transplantation. This is the first reported case of Cpc-PH that revealed the potential reversibility of extremely elevated DPG and PVR, and suggests the importance of preoperative RHC-guided optimized medical PAH-specific and heart failure treatment before LVAD implantation.

Keywords

restrictive cardiomyopathy, pulmonary vascular resistance, diastolic pulmonary vascular pressure gradient, combined pre- and post-capillary pulmonary hypertension, pulmonary vasodilator, left ventricular assist device

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Introduction

Idiopathic restrictive cardiomyopathy (RCM) is characterized by the elevation of the left atrial pressure due to restrictive filling of the ventricle.[1] Chronic elevation of left atrial pressure can perturb pulmonary vascular structure and

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sometimes cause an irreversible high pulmonary vascular resistance (PVR).[2] We report an adult RCM case with extremely high PVR, which was successfully treated with a preoperative pulmonary vasodilator therapy and a left ventricular assist device (LVAD) implantation.

Case description

A 34-year-old woman was hospitalized at an outside institution because of worsening dyspnea and frequent syncope in February 2015 (Fig. 1a). She was diagnosed at the age of one year with idiopathic RCM and pulmonary hypertension (PH). After the diagnosis of RCM, she received regular ambulatory care with diuretics and home oxygen therapy and stayed in World Health Organization functional class (WHO FC) III before the hospitalization. Since the cause of syncope seemed to be low cardiac output (CO) due to high PVR, a small dose of epoprostenol was administered. The results of right heart catheterization (RHC) with 7 ng/kg/min of epoprostenol showed extremely elevated PVR and diastolic pulmonary vascular pressure gradient (DPG) and reduced CO as expected (Table 1). Vasoreactivity testing with inhaled nitric oxide (NO) showed decreased PVR and DPG and increased CO (Table 1). In particular, DPG decreased to 5 mmHg after inhalation of NO, which suggested that pulmonary vascular remodeling in this case might be reversible and pulmonary vasodilators would be effective for this case. Thereafter, epoprostenol was increased and tadalafil was administered sequentially. However pulmonary congestion worsened during the titration of these pulmonary vasodilators (Fig. 1b), and diuretics were increased to treat pulmonary congestion. A second RHC in December 2015 showed that treatment with these drugs remarkably decreased PVR, DPG, and transpulmonary pressure gradient (TPG) and increased CO. On the other hand, pulmonary artery wedge pressure (PAWP) was markedly elevated (Table 1). For further treatment, including implantation of LVAD, she was transferred to our hospital in January 2016 (Fig. 1c).

Echocardiography on admission revealed that PH was still severe (Fig. 2a and b). We tried to decrease PVR before LVAD implantation because high PVR is a risk factor for right ventricular assist device (RVAD) requirement.[3,4] To achieve this goal, intensive treatment of PH and left-sided heart failure were thought to be necessary. Initially, olprinone was started to decrease PAWP, and subsequently macitentan was carefully added while pulmonary congestion was monitored. The third RHC showed slightly decreased PAWP and increased CO with 0.2 μg/kg/min of olprinone (Table 1). In addition, it showed PVR, DPG, and TPG tended to be decreased when an inotropic agent was used together with pulmonary vasodilators, but systemic vascular resistance (SVR) was high at 21.4 WU. It was considered possible to increase CO and decrease PAWP by reducing left ventricular afterload, i.e., SVR, and thus an angiotensin-converting enzyme inhibitor, enalapril, was added to her regimen. Subsequently, the fourth RHC showed a marked increase in CO probably resulted from the reduction of left ventricular afterload by enalapril (Table 1). Echocardiography after these PAH-specific and heart failure treatment showed that a D-shaped left ventricle became less clear. Even though her hemodynamic parameters and pulmonary congestion improved (Fig. 1d), she remained in WHO FC III even with intravenous infusion of an inotropic agent. Since PVR decreased following preoperative comprehensive medical treatment targeting PH and left-sided heart failure, we decided to perform LVAD implantation as a bridge to transplantation. LVAD implantation was successfully performed without concomitant RVAD implantation in March 2016. After LVAD implantation, epoprostenol was increased to the final dose of 40 ng/kg/min without worsening of left-sided heart failure. The fifth RHC, performed nine months after LVAD implantation, confirmed the improvement of hemodynamic parameters (PAP 37/11/21 mmHg, PAWP 5 mmHg, RAP 9 mmHg, DPG 6 mmHg, TPG 16 mmHg, CO 4.9 L/min, PVR 3.1 WU) (Table 1 and Fig. 1e). She was in WHO FC II with 6-min walk distance of 408 m, and she was eventually discharged home ten months after LVAD implantation,

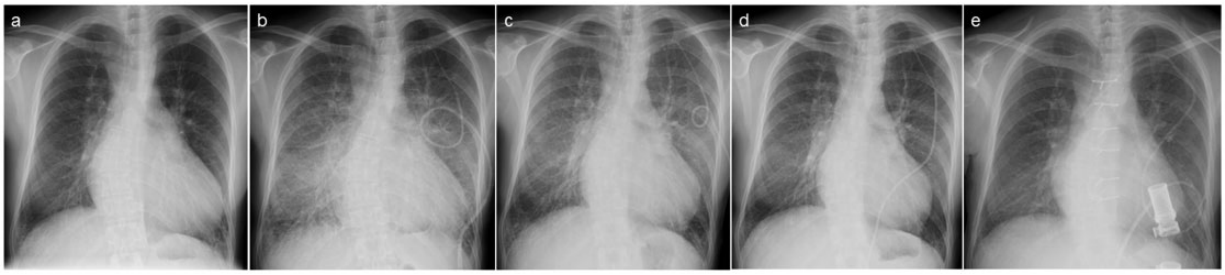
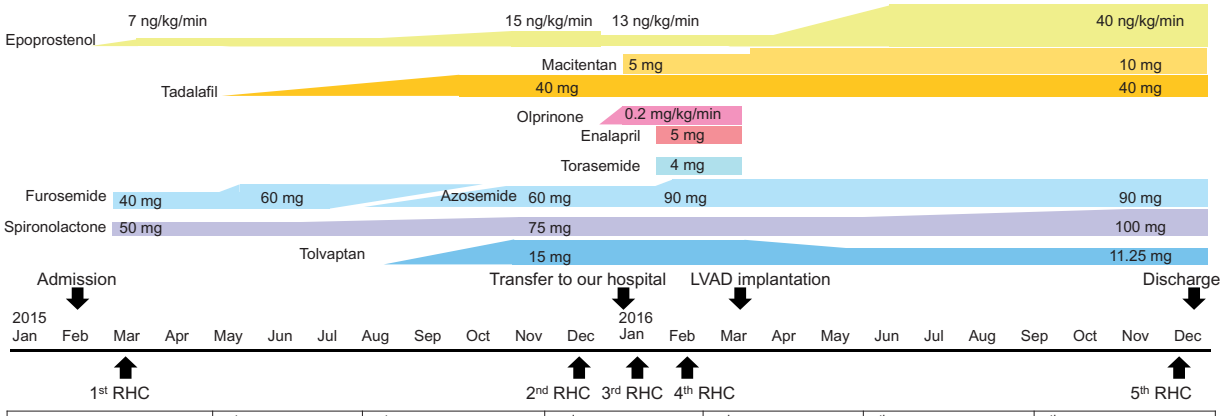


Fig. 1. Serial chest radiography images. (a) No pulmonary congestion on admission to an outside institution (February 2015); (b) pulmonary congestion worsened during the titration of pulmonary vasodilators (October 2015); (c) modest pulmonary congestion on admission to our hospital (January 2016); (d) addition of an inotropic agent and systemic vasodilator improved pulmonary congestion (February 2016); (e) after LVAD implantation with pulmonary vasodilators (December 2016).

Table 1. Treatments and hemodynamic measurements before and after LVAD implantation.



	1st RHC Mar, 2015	1st RHC Mar, 2015 (NO inhalation test)	2nd RHC Dec, 2015	3rd RHC Jan, 2016	4th RHC Feb, 2016	5th RHC Dec, 2016 (post-LVAD 9M)
O_2	FiO_2 0.3		6 L/min	6 L/min	6 L/min	Room air
BP (mmHg)	111/61/80	138/73/96	105/68/84	110/61/80	99/54/71	61/57/58
PAP (mmHg)	105/50/68	94/40/62	87/47/62	70/35/49	54/27/38	37/11/21
PAWP (mmHg)	20	35	40	31	22	5
RAP (mmHg)	16	10	21	10	9	9
DPG (mmHg)	30	5	7	4	5	6
TPG (mmHg)	48	27	22	18	16	16
CO (L/min)	1.9	2.6	2.3	3.3	4.2	4.9
CI (L/min/m²)	1.3	1.8	1.6	2.2	2.9	3.4
PVR (Wood units)	25	10.5	9.6	5.5	3.8	3.1
SVR (Wood units)	33.7	33.1	27.4	21.4	14.6	10.0
SVR/PVR ratio	1.35	3.15	2.85	3.89	3.85	3.23

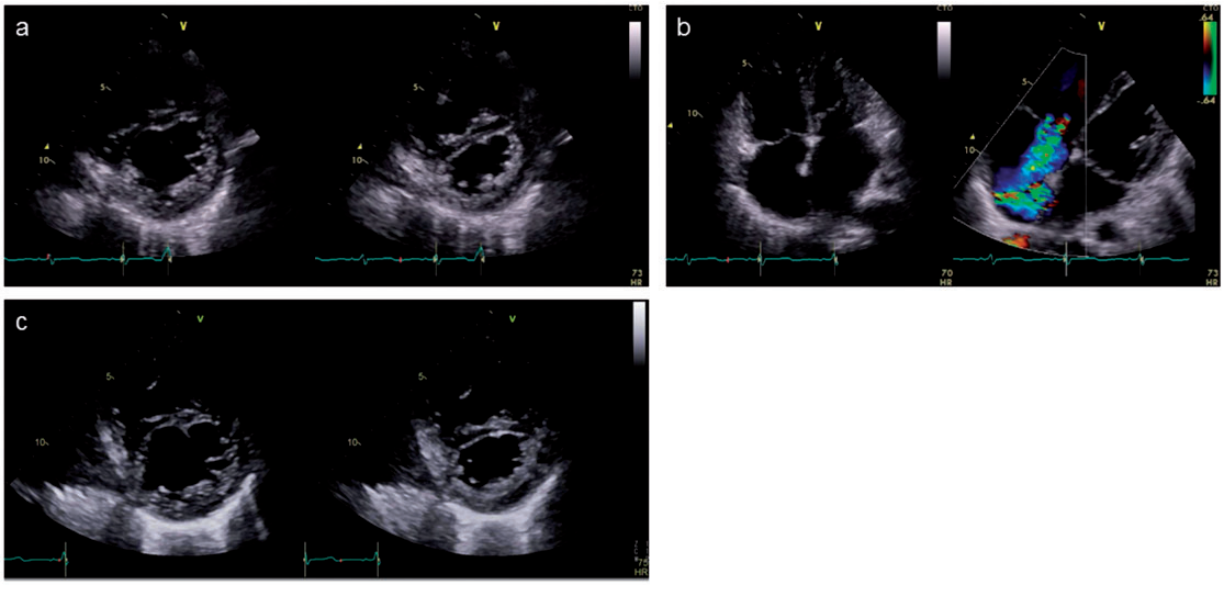


Fig. 2. Transthoracic echocardiography on admission to our hospital (a, b; January 2016) and after PAH-specific and heart failure treatment (c; February 2016). (a) Parasternal short-axis views (left, end-diastole; right, end-systole) show a D-shaped left ventricle caused by high pulmonary artery pressure; (b) four-chamber view shows a dilated right ventricle and atrium (left). Color Doppler echocardiography shows severe tricuspid regurgitation. The tricuspid regurgitation pressure gradient was 66 mmHg; (c) parasternal short-axis views (left, end-diastole; right, end-systole) after successful PAH-specific and heart failure treatment show that a D-shaped left ventricle became less clear.

where she was to wait for heart and lung transplantation. We performed whole-exome sequencing (WES) and detected several rare variants in several genes. Among them, we focused on previously reported PH-associated genes and identified a pulmonary arterial hypertension associated polymorphism in OR2T3 (olfactory receptor family 2 subfamily T member 3) gene (c.548 T > C, p. Phe183Ser) in the mutation database.[5] This mutation is predicted to be ''probably damaging'' by Polyphen-2 analysis although precise functional effect of this polymorphism on pulmonary vasculopathy has not directly been examined.

Discussion

PH with left heart disease (LHD) is hemodynamically classified into two subtypes, isolated post-capillary pulmonary hypertension (Ipc-PH) and combined post- and pre-capillary pulmonary hypertension (Cpc-PH).[6] According to current ESC/ERS guidelines, the combination of DPG and PVR represent a pre-capillary component in PH with LHD.[7] Idiopathic RCM is a rare form of cardiomyopathy[1] associated with a high incidence of PH, especially in patients who were diagnosed in childhood.[2,8,9] It is well-known that an elevated PVR is not only a risk factor for morbidity and mortality in heart failure patients,[10] but also that it increases the risk of death from right-sided heart failure after heart transplantation.[11] Furthermore, several studies reported that patients with high PVR undergoing LVAD implantation are at increased risk of requiring concomitant implantation of a RVAD.[3,4] Previous studies also showed that elevated DPG was associated with increased mortality with pathological pulmonary vascular remodeling.[12] In addition, it was reported that DPG was useful for the differential diagnosis of pulmonary vascular disease and the prediction of hemodynamic improvement with prostacyclin treatment.[13,14] The combination of PVR and DPG was a better predictor of outcome in heart failure with both reduced and preserved ejection fraction than PVR alone.[15] Therefore, medical management of PVR and DPG in patients with Cpc-PH is of clinical importance. However, a therapeutic dilemma exists in the management of heart failure with concurrent PH, namely decreased PVR reduces right ventricular afterload but in turn increases left ventricular preload and worsens pulmonary congestion.

There is no established treatment strategy for PH with LHD probably due to its pathological heterogeneity.[7,16] PH guidelines caution against the use of PAH-specific therapy for PH with LHD, out of concern for causing pulmonary edema, as well due to a lack of supportive evidence.[7] The elevation of DPG and PVR in Cpc-PH is thought to be characterized by various combinations of arteriolar medial hypertrophy, intimal proliferation, adventitial thickening and microthrombi, rarely fibrinoid necrosis, capillary congestion with hemosiderosis, thickened alveolocapillary membranes and sometimes interstitial fibrotic changes, venules undergoing medial hypertrophy and intimal fibrosis, dilated/muscularized lymphatics, but no plexiform lesions.[12,13,16] We were initially concerned that our patient's PH might be irreversible and difficult to treat even with pulmonary vasodilators, because her disease duration was very long and her PVR and DPG were extremely high compared to previous case reports.[17–20] NO inhalation test performed during the first RHC may be the key for the prediction of successful treatment by PAH-specific medications. After the inhalation of NO, PVR decreased from 25 WU to 10.5 WU and DPG decreased from 30 mmHg to 5 mmHg. It should be noted that DPG was decreased below the cut-off value for Cpc-PH ($\geq$ 7 mmHg), which might have predicted the reversibility of pulmonary vascular remodeling.[12] Careful stepwise increases in the dosages of PAH-specific medications, administered along with an inotropic agent, normalized PVR, and improved her hemodynamics. On the other hand, from the viewpoint of left-sided heart failure, elevation of PVR reduces left ventricular preload and protects against pulmonary congestion. This may partly explain why the patient survived until the age of 34 years without hospitalization for worsening of left-sided heart failure, despite being initially diagnosed with RCM and PH at one year of age.

The pathobiology of PH with LHD is complex and highly heterogeneous, and remains incompletely understood. Pulmonary arteriolar remodeling similar to that seen in PAH has been described in severe PH with LHD, especially in patients with Cpc-PH,[12] although plexiform lesions are not usually found. In addition, physiological assessment by the resistance-compliance relationship in patients with Cpc-PH suggests the presence of pulmonary vasculopathy similar to that in PAH patients.[16,21] Furthermore, genetic analysis of Cpc-PH, Ipc-PH and PAH in a large database[22] suggested that Cpc-PH genetically resembles PAH more than Ipc-PH. We performed WES and detected a PAH-associated polymorphism in the OR2T3 gene in this case.[5] It may be possible that this polymorphism might contribute to the development of severe PH and extremely elevated PVR although further research will be needed to address this issue. It was surprising that our patient's longstanding severe PH in association with a PAH-associated polymorphism was reversible in this case, although the pathogenic significance of the OR2T3 polymorphism in the development and progression of PH is unclear. Furthermore, it is also unclear why off-label use of pulmonary vasodilators was effective in this case. Future comprehensive study targeting genotype and phenotype of Group 2 PH may help to identify patient subgroup who can benefit from pulmonary vasodilator therapy.

In this report, RHC-guided optimized medical treatment for Cpc-PH and left-sided heart failure enabled successful implantation of an LVAD without concomitant RVAD implantation in a RCM patient. This case suggests that there may be some cases which respond to pulmonary vasodilator therapy even among patients initially not considered for heart transplantation due to high PVR. Further research is needed to identify subgroups of PH patients with LHD

who will benefit from pulmonary vasodilators and inotropic agents.

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Declaration of conflicting interests

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

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