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[CASE REPORT]

Advanced Pulmonary Hypertension Due to Congenital Double-shunt Successfully Treated with Surgical Repair and Up-front Combination Therapy

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Abstract:

This case report concerns a 22-year-old woman with large patent ductus arteriosus and atrial septal defect. She was referred to our hospital because of exertional dyspnea and was revealed to have advanced pulmonary arterial hypertension (PAH) with a mean pulmonary arterial pressure (PAP) of 79 mmHg. Although both shunts had bidirectional flow, based on the results of acute pulmonary vasoreactive testing, one-stage surgical closure was performed followed by up-front combination therapy for post-operative pulmonary hypertensive crisis and residual PAH. At 14 months after the surgery, her symptoms were markedly improved, and her mean PAP had dramatically decreased to 13 mmHg.

Key words: atrial septal defect, patent ductus arteriosus, perioperative pulmonary hypertensive crisis, pulmonary arterial hypertension, surgical repair, up-front combination therapy

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Introduction

Although few epidemiological data are available on the relationship between adult congenital heart disease and pulmonary arterial hypertension (PAH), a European survey reported that approximately 5-10% of patients with adult congenital heart disease were found to have PAH (1). In most of these patients, prolonged exposure to pulmonary overcirculation due to a left-to-right shunt, as well as pressure overload in some cases, can lead to pulmonary arteriopathy that results in a significant increase in pulmonary vascular resistance (PVR). Ultimately, if the PVR exceeds systemic vascular resistance, the shunt is reversed to a right-to-left direction. For these patients (i.e., Eisenmenger pathophysiology), shunt repair should be avoided, as shunt closure does not improve their survival; indeed, a right-to-left shunt may be necessary to maintain the cardiac output, especially during episodic increases in the PVR. Thus, in daily clinical

settings, therapeutic decision-making is crucial for these patients with advanced PAH with regard to whether or not to close the shunt.

We herein report an adult case with advanced severe PAH due to a double shunt with a very large patent ductus arteriosus (PDA) and atrial septal defect (ASD) who was successfully treated with the combined therapy of surgical repair followed by aggressive up-front combination therapy for perioperative pulmonary hypertensive crisis and residual postoperative PAH.

Case Report

A 22-year-old Chinese woman was diagnosed with PDA and ASD at 3 years old but unfortunately did not receive any specific treatments for economic reasons. From childhood to adolescence, she was prohibited from participating in any competitive sports by an attending doctor, but she did not have any difficulties in day-to-day activities, such as go-

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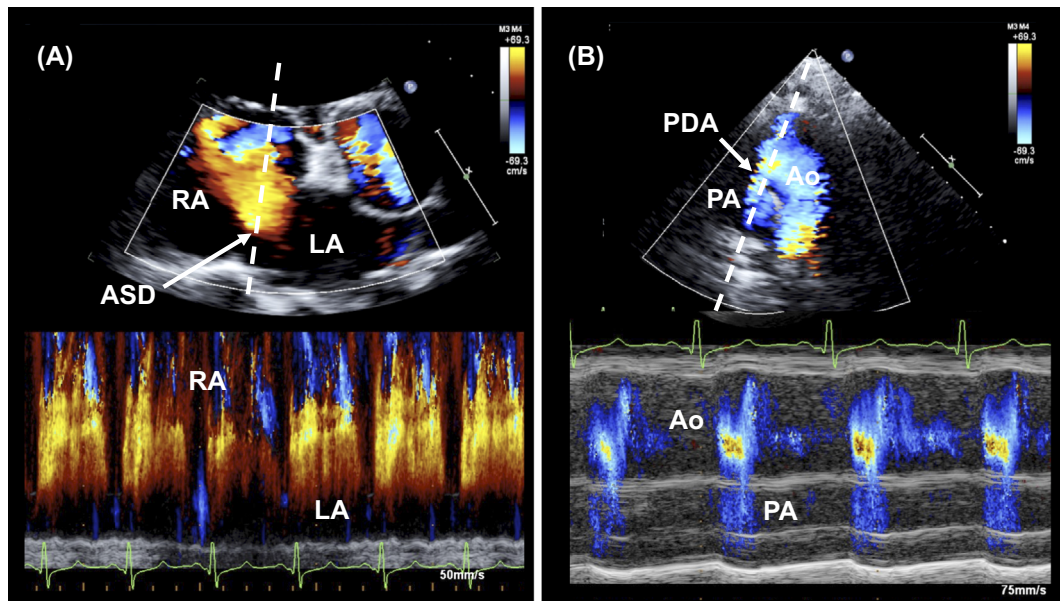


Figure 1. Transthoracic echocardiography showing the shunt flow across the atrial septal defect (ASD) and patent ductus arteriosus (PDA). Panel A shows a parasternal short-axis image of ASD flow (yellow arrow). Color M-mode echocardiogram shows the left-to-right shunt through the ASD. Panel B shows an image of the PDA (yellow arrow) from the supraclavicular view. Color M-mode echocardiogram clearly shows the left-to-right shunt through the PDA. LA: left atrium, RA: right atrium, Ao: aorta, PA: pulmonary artery

ing up stairs or slopes. At 16 years old, she migrated to Japan with her family, after which she did not receive any medical checkups. At 22 years old, she was referred to our hospital because of exertional dyspnea.

At the emergency department, her blood pressure was 104/60 mmHg, pulse rate was 60 bpm, and oxygen saturation was 99% at the right upper limb but 94% at the lower limbs. A physical examination revealed a prominent second heart sound with fixed splitting, but no heart murmur was auscultated. On a visual inspection, she did not have cyanosis or clubbing at her fingers and toes. Chest radiography showed cardiomegaly with dilation of the bilateral pulmonary arteries, and an electrocardiogram demonstrated right ventricular hypertrophy. Transthoracic echocardiography revealed normal left ventricular contraction with a dilated ventricle measuring 59 mm in end-diastolic diameter. Doppler echocardiography revealed a severely elevated pressure gradient of 84 mmHg across the tricuspid valve, which suggested near-systemic advanced PAH. A large PDA and secundum ASD with left-to-right shunts were clearly detected by color Doppler echocardiography (Fig. 1). On transesophageal echocardiography, however, both shunts of PDA and ASD were revealed to be left-to-right dominant with a bidirectional flow (Fig. 2), which was consistent with near-Eisenmenger pathophysiology. Multidetector-row computed tomography revealed that the PDA was quite large, measuring 20×14 mm in size, and could not be closed by a transcatheter approach. A large, oval-shaped secundum ASD (30×18 mm) and another small secundum ASD were also confirmed (Fig. 3). Although the shunt flow of both PDA and

ASD were bidirectional and the pulmonary artery pressure (PAP) was as high as 100/50 mmHg (mean 79 mmHg), the pulmonary vascular resistance index (PVRi) was borderline for surgical repair, with 6.3 Wood units·m² as measured by right heart catheterization (Table). To calculate the PVR, we used the deep right pulmonary artery oxygen saturation as the pulmonary artery oxygen content. However, the pulmonary vein oxygen saturation measured by right heart catheter was absurdly low at 95%, especially given the patient had no apparent lung disease, which suggested a sampling error. Because the right-to-left shunt flow through ASD was almost negligible in this patient based on the results of echocardiography, the oxygen saturation at the right upper limb was substituted for the pulmonary vein oxygen content. The VO₂ values used for the calculation of Qp and the PVR were estimated by using LaFarge formula.

In order to assess the possibility of surgical repair, acute pulmonary vasoreactive testing was then performed. During the inhalation of 100% oxygen, the mean PAP decreased from 79 mmHg to 69 mmHg, and the PVRi also decreased from 6.3 Wood units·m² to 4.5 Wood units·m² without a significant change in the cardiac output. Although the patient had been suffering from near-systemic advanced PAH and indeed showed differential limb oxygen saturation values, after a thorough discussion within the heart team, we eventually decided to perform one-stage repair for these shunts based on the baseline value of PVRi and the results of vasoreactive testing. Surgical closure of the PDA and ASD without fenestrated patch was then performed successfully and uneventfully.

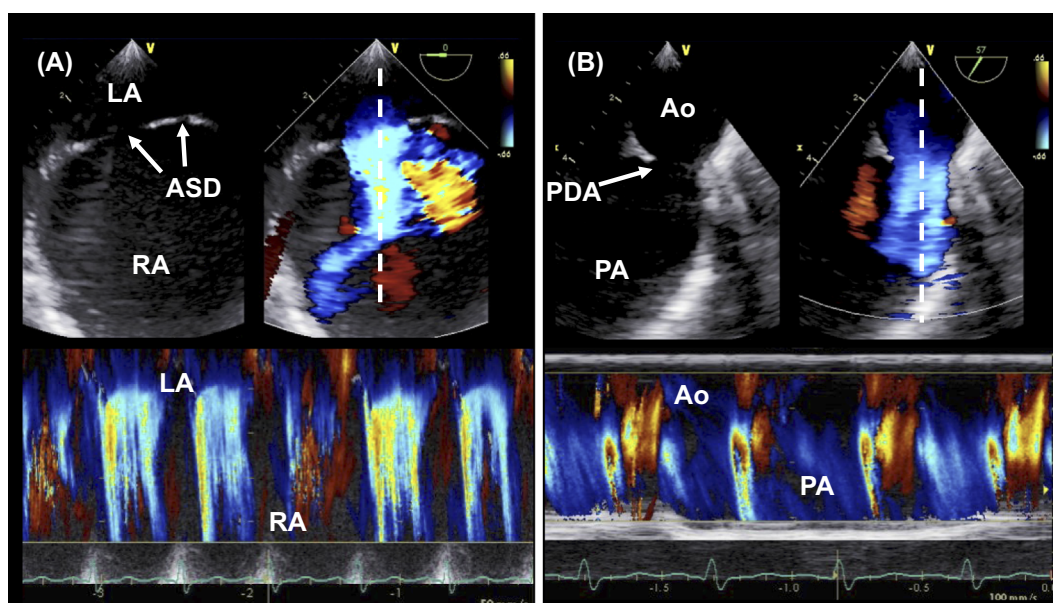


Figure 2. Transesophageal echocardiography showing the shunt flow across the atrial septal defect (ASD) and patent ductus arteriosus (PDA). Panel A is a mid-esophageal horizontal view showing two ASDs (yellow arrows). Color M-mode echocardiogram shows a left-to-right dominant bidirectional shunt through the ASD. Panel B is an upper-esophageal aortic arch short-axis view showing the connection (yellow arrow) between the aortic arch (Ao) and main pulmonary artery (PA). Color M-mode echocardiogram clearly demonstrates bidirectional shunt flow through the PDA. LA: left atrium, RA: right atrium

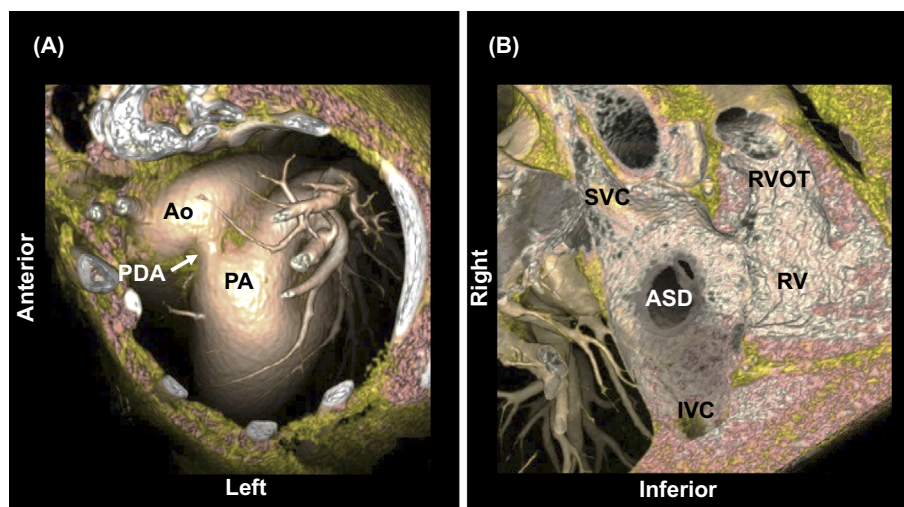


Figure 3. Volume-rendered images of multidetector-row computed tomography are shown. Panel A shows a window-shaped patent ductus arteriosus (PDA) between the anterior surface of the aortic arch (Ao) and left pulmonary artery (PA). Panel B shows a large, oval-shaped secundum atrial septal defect (ASD) and another small secundum ASD. SVC: superior vena cava, IVC: inferior vena cava, RV: right ventricle, RVOT: right ventricular outflow tract

She received milrinone to prevent pulmonary hypertensive crisis during the perioperative period, and we initially intended to gradually replace milrinone with oral PAH-specific drugs for the residual PAH. On the first postoperative day, after general anesthesia was discontinued, extubation was successfully performed. On the following day, however, the PAP suddenly rose to 80/40 mmHg (mean 53 mmHg) and the systemic blood pressure fell to 67/57 mmHg, triggered

by severe coughing. The patient received deep sedation, respiratory support with hyperventilation, introduction of inhaled nitric oxide, and the PAH-specific drugs sildenafil and bosentan to prevent the recurrence of pulmonary hypertensive crisis.

After the introduction of these PAH-specific drugs, her hemodynamics gradually improved, and the mean PAP was ameliorated to 30 mmHg while under sedation with drugs,

Table. Pressure Data and Results of Oxygen Saturation.

A. Pressure data by right heart catheterization			
Pressure	Rest	During inhalation of 100% oxygen	
PA, mmHg (mean)	100/50 (79)	100/50 (69)	
RV, mmHg (EDP)	100/0/8	96/-2/6	
RA, mmHg (mean)	7/7 (5)	4/4 (2)	
LA, mmHg (mean)	7/7 (5)	7/7 (4)	
PVRi, Wood units·m ²	6.3	4.3	
Cardiac output, L/m ²	2.89	3.03	

B. Results of oxygen saturation by oxymetry run			
SVC, %	60.4	Main PA, %	85.4
IVC, %	75.2	Right PA, %	90.5
RA high, %	63.5	Left PA, %	91.6
RA middle, %	83.1	Descending aorta, %	96.6
RA low, %	76.5	PV, %	95.2
RV inflow, %	82.9	Right upper limb, %	97.0
RV apex, %	82.8		
RV outflow, %	86.2		

PA: pulmonary artery, RV: right ventricle, EDP: end-diastolic pressure, RA: right atrium, LA: left atrium, PVRi: pulmonary vascular resistance index, SVC: superior vena cava, IVC: inferior vena cava, PV: pulmonary vein

but the mean PAP was elevated to 50 mmHg while awake. In addition to these PAH-specific drugs, epoprostenol was introduced for the residual PAH. On the 11th postoperative day, the mean PAP significantly improved to 30 mmHg, and the patient was able to be extubated. After the gradual discontinuation of intravenous epoprostenol, she was discharged at the 30th hospital day. After discharge from the hospital, she continued to receive close outpatient hemodynamic follow-up. PAH-specific drugs were then gradually withdrawn based on the results of a serial right heart catheter examination (Fig. 4).

At 14 months' follow-up, her symptoms had markedly improved to New York Heart Association functional class I. A right heart catheter examination revealed further improvement of the PAP to 24/4 mmHg (mean 13 mmHg). In light of these results, the oral PAH-specific drugs were able to be completely discontinued.

Discussion

The mainstay therapeutic approach for patients with significant pulmonary overcirculation is surgical or transcatheter shunt closure. However, for patients in the latter stages of pulmonary overcirculation complicated by advanced severe PAH, it is crucial to assess the presence of the residual reversible pulmonary vascular bed, as this will directly affect the clinical decision regarding whether or not to close the systemic-to-pulmonary shunts. The guidelines from the European Society of Cardiology and European Respiratory Society recommended that shunt closure be based on the baseline PVR for patients with PAH due to congenital heart diseases (2). However, systemic-to-pulmonary shunt flows

directly into the pulmonary artery in patients with PDA. Due to the confounding factors of streaming and sampling, the validity and accuracy of shunt calculations and consequently the precise estimation of PVR is often the major concern in the daily clinical setting for these patients. In the present case, we assessed the reversibility of the pulmonary artery with pulmonary vasoreactive testing and were able to prove the presence of the reversible vascular bed preoperatively. Although the possibility of surgical repair of a double-shunt PDA and ASD seemed unlikely at first, based on the results of the pulmonary vasoreactive testing and the presence of the volume overloaded left ventricle, we ultimately decided to perform surgical closure for the PDA and ASD complicated by near-systemic PAH.

For patients with severe PAH due to congenital intra- or extra-cardiac shunt, aggressive combination therapy with PAH-specific drugs is another cornerstone in treating these conditions. The main mechanisms of PAH include vasoconstriction, thrombosis, and inflammation leading to vessel wall remodeling. Thus far, up-front combination therapy using two or more classes of PAH-specific drugs has been the main treatment strategy for patients with advanced PAH (3). This reduces the risk of worsening obstructive pulmonary vascular disease by vasodilatation and may consequently promote reverse remodeling of the pulmonary vascular bed (4). Recently, some investigators reported the importance of targeted PAH-specific combination therapy for PAH patients with congenital heart diseases (5). In the present case, up-front combination therapy with PAH-specific drugs seemed to be quite effective in stabilizing perioperative pulmonary hemodynamics. Furthermore, these drugs may help reverse the pulmonary arterial damage in the chronic phase.

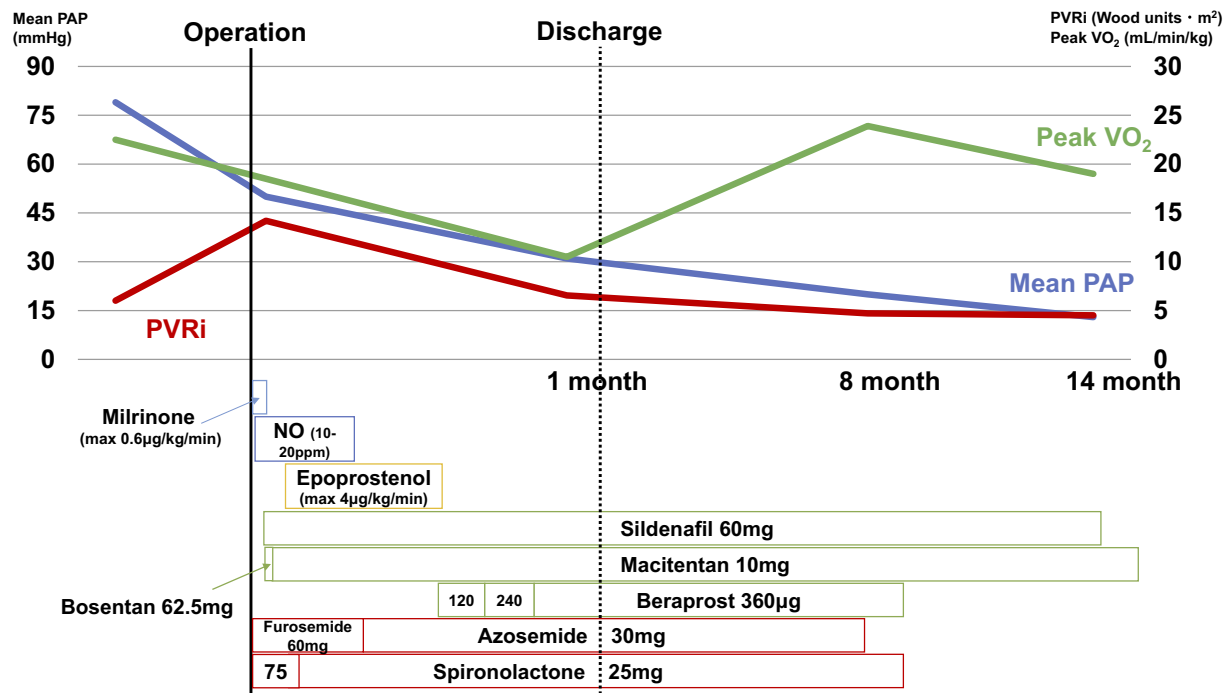


Figure 4. The clinical course after surgery is shown. The day after shunt repair, because pulmonary arterial hypertension (PAH) crisis occurred, the patient received PAH-specific drugs, inhaled nitric oxide (NO), and intravenous epoprostenol. After the titration of epoprostenol and oral diuretics, she was discharged on the 30th hospital day. PAH-specific drugs were gradually withdrawn based on the results of a serial right heart catheter examination. At 14 months' follow-up, the mean pulmonary arterial pressure (mPAP) had significantly improved. PVR: pulmonary vascular resistance, VO₂: oxygen uptake

Conclusion

We report a unique case in which a patient experienced an advanced stage of PAH due to double-shunt of a large PDA and ASD and was successfully treated with initial surgical repair followed by up-front combination therapy for residual PAH. This aggressive combined therapeutic strategy may expand opportunities for curative care even for patients with advanced PAH who were able to receive only supportive treatment in the past.

The authors state that they have no Conflict of Interest (COI).

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