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Case Report

A case of a middle-aged patient with a ventricular septal defect complicated by severe pulmonary hypertension-stepwise surgical repair with pulmonary vasodilators-

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ABSTRACT

We report a case of ventricular septal defect (VSD) in which we attempted to treat pulmonary arterial hypertension (PAH) with the goal of VSD closure in an adult with suspected Eisenmenger syndrome in childhood. Four years previously (age 41 years), she was referred to our department due to repeated hemoptysis requiring further treatment of PAH. We started combination therapy with several pulmonary vasodilators. Two years later, her pulmonary vascular resistance (PVR) was improved but still not at the level where VSD closure was possible. To control the increased PA flow resulting from intensive PAH treatment and to reduce the risk of hemoptysis, we performed pulmonary artery banding (PAB). As the risk of hemoptysis decreased, a prostacyclin analog was introduced, and the dose was increased. More than 1 year after PAB, active vasoactivity testing became positive, suggesting that the pulmonary vascular lesion was now "reversible". We performed VSD closure and atrial septal defect creation even though her PVR was still high. After the operation, her exercise capacity was remarkably improved. We suggest that stepwise surgical repair with pulmonary vasodilators is an important treatment option for select patients with VSD with severe PAH.

<**Learning objective:** Advances in pulmonary arterial hypertension (PAH) treatment have led to the use of a "treat-and-repair" strategy to close the intracardiac shunt after PAH treatment in select patients with adult congenital heart disease. In our case, ventricular septal defect (VSD) closure was achieved with stepwise surgical repair and a combination of pulmonary vasodilators, even though long-standing severe PAH with persistent hemoptysis remained. Even after a long period of exposure to high blood flow, this strategy may reduce pulmonary vascular resistance and permit eventual closure of the VSD.>

Introduction

Recent advances in disease-targeted therapy (DTT) for pulmonary arterial hypertension (PAH) have improved the exercise capacity and survival in patients with unrepaired congenital heart disease (CHD) with PAH. The "treat-and-repair" or "treat-to-close" strategy, which is shunt closure after intensive PAH treatment with DTT, has been applied for adult patients with advanced CHD-PAH, and has resulted in favorable outcomes in limited numbers of patients, especially those with atrial septal defect (ASD) [1]. Recently, the "treat-and-repair" strategy has been tried even in ventricular septal defect (VSD) patients with advanced PAH [2]. Most previous studies reported VSD patients with severe PAH whose baseline

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Table 1
Serial cardiac catheter examinations.

Catheter examination(The numbers correspond to Fig. 2)	①	②	③	④	⑤	⑥	⑦
Treatment	Bosentan 187.5 mg, Tadalafil 20 mg	Macitentan 10 mg, Riociguat 7.5 mg	Macitentan 10 mg, Riociguat 7.5 mg	Macitentan 10 mg, Tadalafil 40 mg	Macitentan 10 mg, Tadalafil 40 mg, Selexipag 1.6 mg, PA banding	Macitentan 10 mg, Tadalafil 40 mg, Selexipag 1.6 mg, PA banding	Macitentan 10 mg, Tadalafil 40 mg, Epoprostenol 15 ng/kg/min, VSD closure*
SAP (mmHg (mean))	NA	92/60 (73)	97/50 (67)	97/57 (73)	99/52 (68)	108/56 (76)	84/54 (64)
PAP (mmHg (mean))	96/40 (64)	93/38 (61)	91/34 (57)	94/30 (50)	82/32 (51)	95/27 (52)	60/25 (38)
RVP (syst/EDP, mmHg)	101/15	91/10	85/7	98/13	90/10	94/7	57/10
mRAP (mmHg)	9	4	5	7	8	4	9
PAWP (mmHg)	12	7	12	8	9	9	9
Qp/Qs	1.52	1.54	1.3	1.98	1.53	1.53	1.24
PVR (WU)	11.3	9.6	10.8	9	7.7	11.3	8.3
PVRI (WUm^2)	16.9	14.1	15.9	13.2	11.3	15.3	11.6
SVR (WU)	NA	NA	19.7	27.5	17.6	26.7	18.8
Rp/Rs	NA	NA	0.55	0.33	0.43	0.43	0.44
DPG (mmHg)	28	31	22	22	23	18	16
SaO_2 (%)	95	96	92	96	97	97	98
AVT	NA	NA	Response (-)	Response (-)	Response (-)	Response (+)	Response (-)
Plasma BNP level (pg/mL)	23.6	26.5	18.2	34.6	39.7	42.3	154.7

VSD, ventricular septal defect; SAP, systemic arterial pressure; PAP, pulmonary arterial pressure; RVP, right ventricular pressure; syst/EDP, systolic RV pressure/RV end-diastolic pressure; mRAP, mean right atrial pressure; PAWP, pulmonary arterial wedged pressure; Qp/Qs, pulmonary-systemic flow ratio; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SVR, systemic vascular resistance; Rp/Rs, pulmonary vascular resistance/systemic vascular resistance ratio; DPG, diastolic pressure gradient (diastolic PAP-PAWP); SaO2, oxygen saturation; AVT, acute vasoreactivity testing; BNP, B-type natriuretic peptide; NA, not applicable.
* VSD closure, atrial septal defect creation, and pulmonary artery de-banding.

pulmonary vascular resistance index (PVRI) was more than 8 wood units (WU)*m^2. This level was previously considered a contraindication for surgical repair [3].

Case report

A 41-year-old female patient with non-restrictive VSD was referred to our hospital from another hospital. At age 7 years, she was diagnosed with VSD for the first time. Her diagnostic catheter examination showed a mean pulmonary arterial pressure (PAP) of 77 mmHg, L-R shunt of 98%, and R-L shunt of 64%. Pediatric cardiologists suspected that she had already developed Eisenmenger syndrome, and her VSD was not indicated for surgery at age 8 years. From age 20 years, she was hospitalized due to hemoptysis one or two times per year. At age 25 years, home oxygen therapy was administered. At age 30 years, bosentan, an endothelin receptor antagonist, was started, but hospitalization due to hemoptysis was repeated. At age 41 years, she was referred to our hospital because hemoptysis had worsened.

She was 157 cm tall and weighed 48 kg. Her physical activity was estimated as World Health Organization functional class III. Clubbed fingers and cyanosis were observed. Chest X-ray (**Fig. 1a**) and electrocardiogram (**Fig. 1a**) showed enlargement of the PA and right ventricular (RV) hypertrophy. Echocardiogram showed perimembranous VSD (16 mm in diameter) with both directional snhunt flow but mainly an L-R shunt (**Fig. 1c–f**). The size of the VSD compared to that in her childhood was unclear. RV and left ventricular systolic functions were maintained (**Online Table 1**).

The overall time course is shown in **Fig. 2a**. The first catheter examination in our hospital showed severe PAH, including a mean PAP of 64 mmHg, pulmonary-systemic flow ratio (Qp/Qs) of 1.52, and PVRI of 16.9 WU*m^2 (**Table 1-**①). Because combination therapy with DTT is effective in reducing pulmonary vascular resistance (PVR) in patients with PAH [4], we added riociguat, a stimulator of soluble guanylate cyclase, and changed bosentan to macitentan. Catheter examination 5 months after the treatment change showed an improvement in PAH. Her mean PAP was 61 mmHg, Qp/Qs was 1.54, and PVRI was 14.1 WU*m^2 (**Table 1-**②). However, hemoptysis had worsened, and repeated catheter examination (5 months after the previous examination) showed that the mean PVRI had worsened to 15.9 WU*m^2 (**Table 1-**③), but the diastolic pressure gradient (DPG: diastolic PAP-PA wedged pressure), another marker for PVR [5], had improved. We performed acute vasoreactivity testing (AVT) with oxygen administration, but no response was observed (Online Table 2). Before this catheter examination, we performed cardiac magnetic resonance (CMR) imaging (**Online Table 3**). RV ejection fraction estimated with CMR imaging was 70%, suggesting that RV function was maintained. RV size remained in the normal range but the RV mass index (35.0 g/m^2) showed RV hypertrophy [6]. We switched her medication from riociguat to tadalafil, a phosphodiesterase 5 inhibitor. Repeated catheter examination after 1 year showed an improvement in PVRI (13.5 WU*m^2) and in Qp/Qs (1.3→1.98) (**Table 1-**④); however, her PVR was still high, and she showed no response with AVT (**Online Table 2**). To control the increased PA flow resulting from intensive PAH treatment and to reduce the risk of hemoptysis, we performed pulmonary artery banding (PAB) [7]. Because the RV function was preserved, it was decided that PAB would be feasible. Her main PA was constricted with an elastic band with a median sternotomy approach (the detailed method is described in the Online Text). Echocardiography after PAB showed that distal PA systolic pressure was physically reduced more than 30 mmHg compared to RV systolic pressure. Although PAB reduced the distal PAP, it increased the R-L shunt and worsened hypoxia in her systemic circulation. An increased amount of oxygen administration was required immediately after PAB due to hypoxia (**Fig. 2**). Interestingly, systemic hypoxia gradually improved within 1–2 months after surgery (Online **Fig. 1**). In addition to macitentan and tadalafil, a prostacyclin receptor agonist, selexipag, was started after PAB. The patient's 6 min walk test (6MWT) distance was improved with increased oxygenation (1.5 to 2 L/min) (**Fig. 2**). A catheter examination 1 year after PAB showed a substantial reduction in PVR (PVRI 11.3 WU*m^2), but the AVT response was modest (**Table 1-⑤, Online Table 2**). No increase in RV end diastolic pressure (RVEDP) or right atrial pressure (RAP) occurred, suggesting that right heart failure had not developed. We continued the treatment with DTT

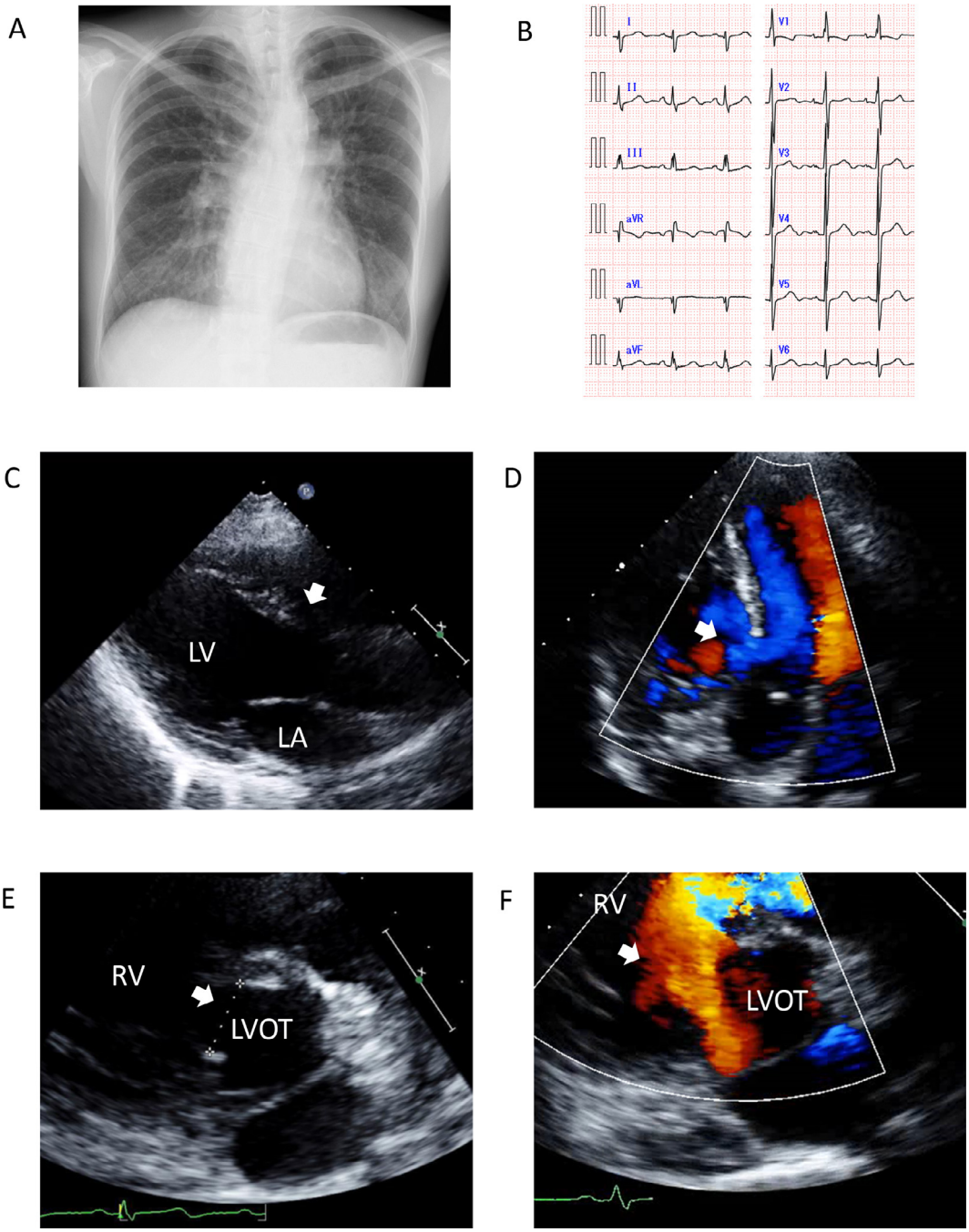

Fig. 1. Chest X-ray (**a**) and electrocardiogram (**b**) when the patient was referred to our hospital; (**c**–**f**) Echocardiography when the patient was referred to our hospital. Ventricular septal defect is indicated with the white arrow. The defect diameter was estimated as 16 mm; (**c**) Parasternal long-axis view; (**d**) Apical five chambers view with color Doppler; (e) Parasternal short-axis view; (**f**) Parasternal short-axis view with color Doppler. LV, left ventricle; LA, left atrium; RV, right ventricle; LVOT, left ventricular outflow tract.

and followed her with echocardiogram and catheter examinations (Table 1, **Online Tables 1 and 2**). RV function was maintained even after PAB. Plasma *B*-type natriuretic peptide was not increased. Almost 1.5 years after PAB, catheter examination was performed. PAP (proximal position of PAB) was still high, but the DPG had improved (23 to 18 mmHg), and AVT showed a significant response to oxygen exposure (Table 1-⑥, **Online Table 2**) [8]. Her baseline PVR was 11.4 WU, but oxygen exposure reduced PVR to 6.2 WU, representing a 45.6% decrease. The gradual decrease in pulmonary arterial resistance and the increase in vasoreactive response suggested the possibility of partial recovery of pulmonary vascular remodeling. Selexipag was switched to continuous transvenous infusion of the prostacyclin, epoprostenol. Surgical closure of VSD and ASD creation with a penetrated patch were successfully performed with a PA-debanding procedure. Four weeks after surgery, catheter examination was performed (Table 1-⑦, Online **Table 2**). Average PAP and PVRI were markedly improved (52 to 38 mmHg and 15.3 to 11.6 WU*m^2, respectively). Echocardiogram showed no VSD shunt flow and successful VSD closure (Fig. 2**b** and **c**) and maintenance of RV systolic function but decreased RV diastolic function

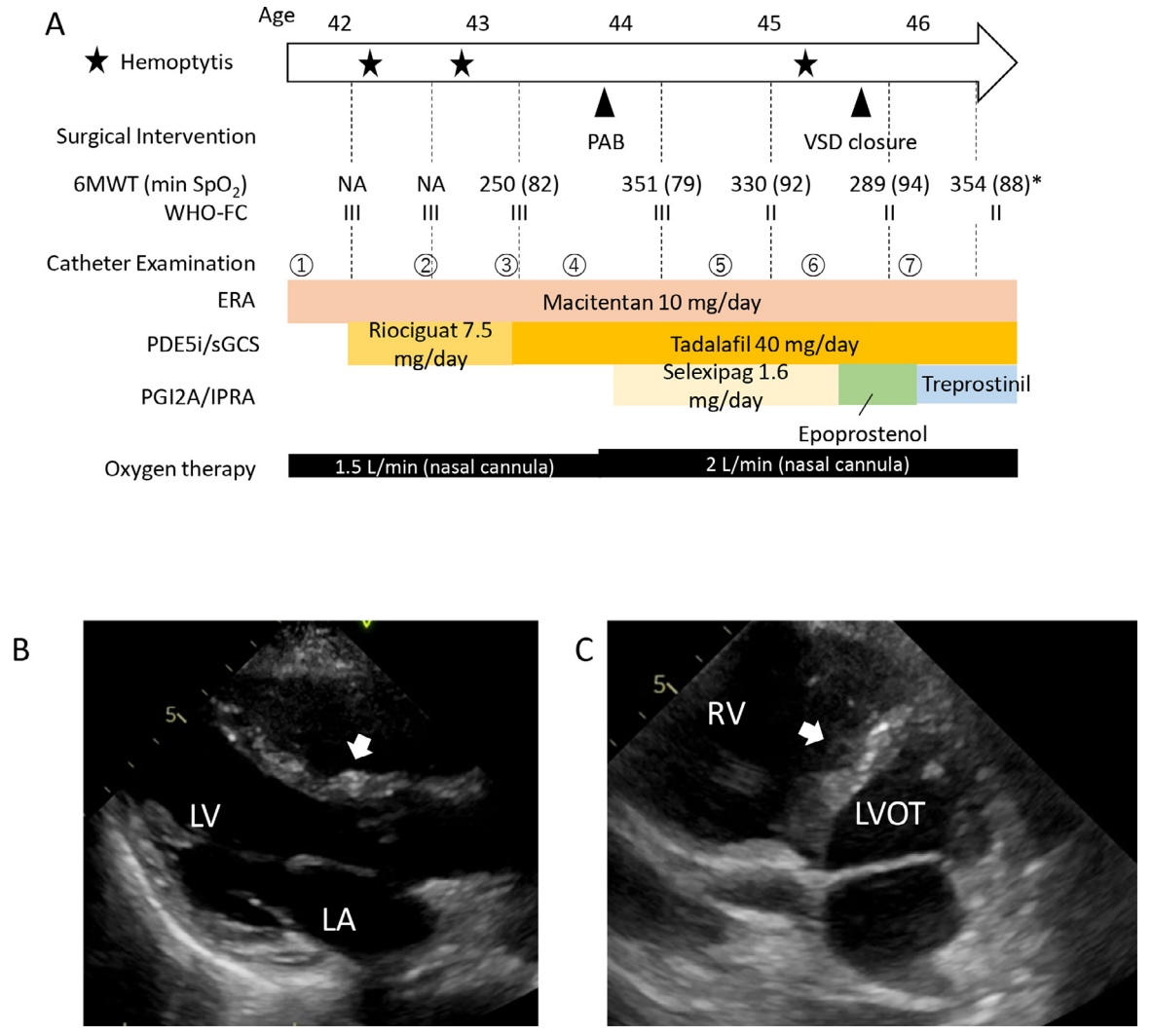

Fig. 2. **(a)** A time course of this case. Stars indicate hospitalization for severe hemoptysis. The numbers for catheter examination are detailed in Table 1. (**b**) and (**c**) Echocardiography after VSD closure. The closed VSD portion is indicated with a white arrow. (**b**) Parasternal long-axis view; (**c**) Parasternal short-axis view. 6MWT, six-minute walk test, walk distance (m) is described with minimum SpO_2 during exercise. The 6MWTs were performed under oxygenation as described below, whereas the test marked with * was performed without oxygenation; NA, not applicable; WHO-FC, World Health Organization functional class; PAB, pulmonary artery banding; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase 5 inhibitor; sGCS, soluble guanylate cyclase stimulator; PGI2A/IPRA, prostaglandin I2 analog/prostaglandin I2-receptor agonist; VSD, ventricular septal defect; LV, left ventricle; LA, left atrium; RV, right ventricle; LVOT, left ventricular outflow tract.

estimated by RV-E/e' (Online **Table 1**). Resting oxygen saturation was markedly improved. The 6MWT distance improved to 354 m without oxygenation. Six months after the operation, she continued to do well with DTT.

Discussion

A treat-and-repair strategy is thought to be more difficult in patients with PAH associated with VSD than in those with ASD. In patients with large VSD, pulmonary circulation is connected to the LV, resulting in high pressure and high flow, whereas ASD is associated with low pressure and high-flow PA pathology due to a pretricuspid shunt [9]. The dynamic high pressure of VSD contributes to the progression of pulmonary artery lesions and the susceptibility to Eisenmenger syndrome. This pathophysiology is closely related to the difficulty of PAH treatment in patients with VSD-PAH. Systolic PAP must remain unchanged even if PVR decreases due to DTT in patients with VSD [10]. Therefore, treatment with DTT could easily cause hemoptysis and/or heart failure. In this case, PAB was performed prior to VSD closure because hemoptysis reoccurred when intensive DTT was introduced. PAB can physically reduce the pressure load on the periphery of the PA, and may support "reverse remodeling" of pulmonary hypertensive lesions of the PA vasculature [2,4]. Although the usefulness of PAB for the treat-and-repair strategy in VSD remains controversial [10], it was effective for reducing the hemoptysis risk during DTT combination therapy in this case.

After long-term combination therapy with DTT and PAB, our case showed a positive AVT response in terms of a more than 20% decrease in PVR, but the final PVRI was still higher than 8 $WU^{*}m^{2}$. Therefore, our case was obviously challenging. Although continuation of DTT was mandatory, postoperative hemoptysis did not occur, cyanosis disappeared, and exercise tolerance has improved.

This report has several limitations. First, AVT is mainly used to determine whether surgical closure can be performed in pediatric shunting heart disease, and its significance in adult CHD re-

mains unclear [9]. Further experience will be required to confirm the significance. Second, we did not observe any pathological evidence of “reverse remodeling” in the PA. PVR was gradually reduced, and the AVT response became positive after long-term combination therapy with DTT and PAB in this case. The clinical course suggested that “reverse remodeling” of the PA may be achieved, but this idea is still speculation. Third, this is the report of one case. This treat-and-repair for VSD-PAH is still a challenging strategy and should be applied for only limited patients with careful informed consent. Fourth, because a risk of a progressive increase in PVR may be present, even several years after VSD closure [10], careful and long-term observation is required to determine the real efficacy of this strategy.

In conclusion, we report a middle-aged patient with VSD and severe PAH who was diagnosed with Eisenmenger syndrome in childhood. Even after a long period of exposure to high blood flow, upfront combination therapy with DTT and PAB may reduce PVR and permit eventual closure of the VSD. Further experience is required, but we suggest that stepwise surgical repair with DTT is an important treatment option for select patients with VSD, even those diagnosed with Eisenmenger syndrome, if the pulmonary vascular lesion is determined to be reversible.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jccase.2021.02.013.

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