

[ CASE REPORT ]

## Clinical Outcome of Closure of a Small Atrial Septal Defect in a Patient with Pulmonary Arterial Hypertension

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### Abstract:

The closure of small/coincidental atrial septal defects (ASDs) in patients with pulmonary arterial hypertension (PAH) has been described in recent major guidelines as useless or even contraindicated. We confirm the effectiveness of “Treat and Repair” for ASD closure through one patient diagnosed with idiopathic PAH with small ASD, under careful observation with right heart catheterization and cardiac magnetic resonance imaging. The clinical decision concerning the closure of ASD with PAH should be made not only by referring to the guidelines but also by evaluating the benefits and risks specific to that case.

**Key words:** atrial septal defect, pulmonary hypertension, percutaneous ASD closure

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### Introduction

Atrial septal defects (ASDs), accounting for approximately 10% of all congenital heart disease, can result in pulmonary hypertension (PH), right heart decompensation, atrial arrhythmias, and paradoxical embolism. Current guidelines recommended that patients with hemodynamically significant ASD undergo ASD closure to prevent these complications, regardless of symptom (1).

Many clinical studies have suggested that the clinical outcome of patients who have pulmonary artery hypertension (PAH) with associated ASD is also relatively good under combination therapy of PAH-specific drug and ASD closure (2, 3). However, the closure of small/coincidental ASDs in patients with PAH has been described as useless or even contraindicated in recent major guidelines for adult congenital heart disease (ACHD) (1, 4) and PH (5, 6). This is not only because there is no evidence of any beneficial effects, but also there is the potential risk of decompensated right ventricular (RV) failure due to the abolition of right-to-left shunting, which acts as a pop-off valve unloading the RV. However, RV failure can progress when the left-to-right shunt through the ASD is prominent, resulting in a degree

of RV volume overload.

The guidelines for ACHD also state that, in the absence of significant PH, ASDs that cause RV volume overload should be closed at any age, even if they are relatively small, to prevent the development of RV failure or its progression. When deciding whether or not to close the ASD for patients with PAH with a small/coincidental ASD, physicians should take into consideration the risk of RV failure as well as how to control PH.

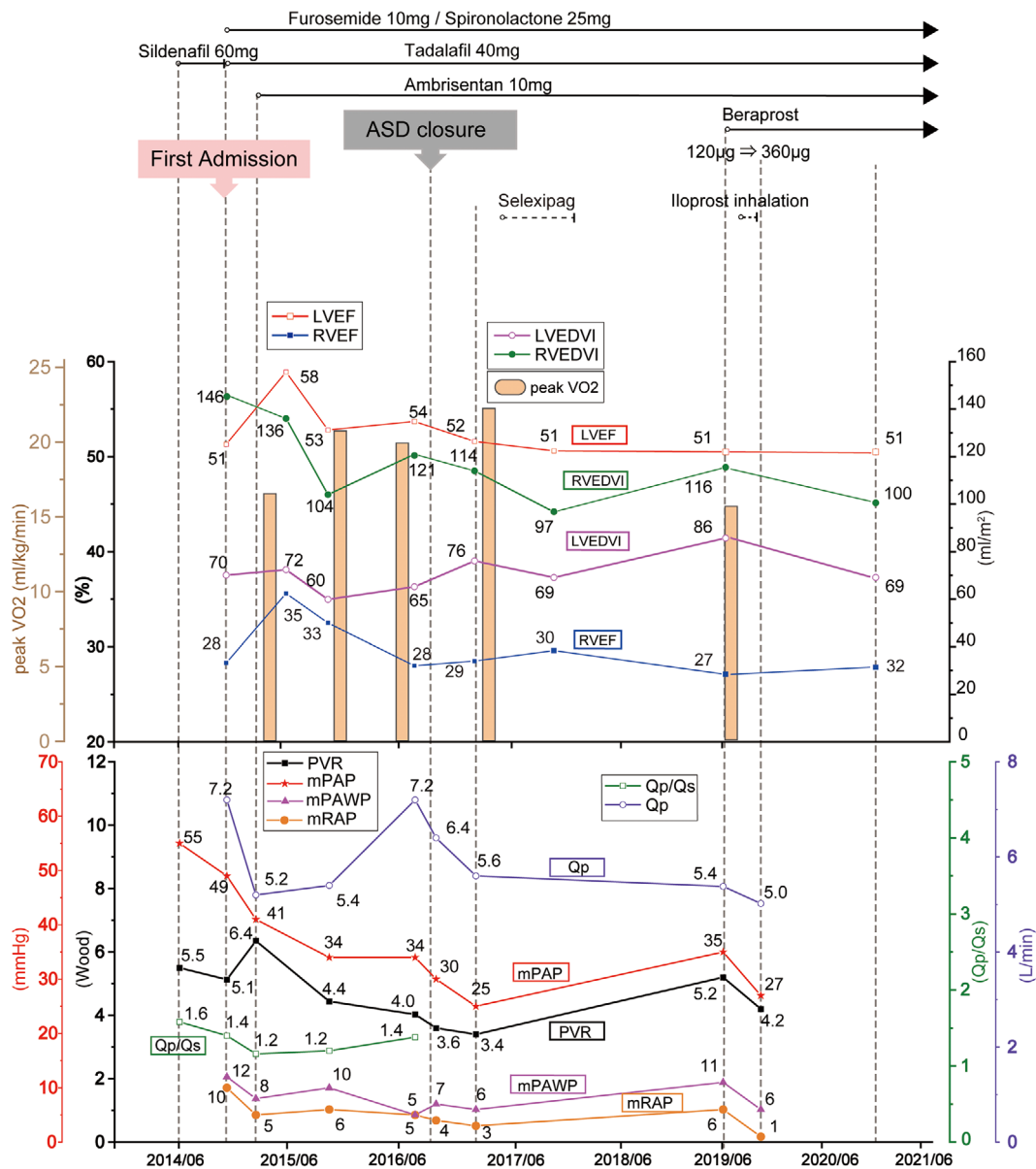
### Case Report

A 40-year-old Korean man living in Japan visited the hospital with exertional dyspnea-based symptoms (WHO functional class II). Based on a detailed clinical evaluation performed in his home country, the patient was diagnosed with idiopathic pulmonary arterial hypertension (IPAH), along with a small atrial septal defect (ASD); a genetic examination of the mutations in genes such as bone morphogenetic protein receptor (BMPR) II and activin-like kinase (ALK)-1 was not performed. As generally recommended (1, 7, 8), medical follow-up involving sildenafil was scheduled. In addition, the patient was advised to seek the medical opinion of a Japanese hospital specializing in ACHD and PH, since

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**Figure 1.** Time course of medications and important parameters of hemodynamics and cardiac magnetic resonance imaging. ASD: atrial septal defect, mPAP: mean pulmonary arterial pressure, mPAWP: mean pulmonary arterial wedge pressure, mRAP: mean right atrial pressure, LVEF: left ventricular ejection fraction, LVEDVI: left ventricular end-diastolic volume index, PVR: pulmonary vascular resistance, Qp/Qs: pulmonary to systemic perfusion ratio, RVEDVI: right ventricular end-diastolic volume index, RVEF: right ventricular ejection fraction, VO<sub>2</sub>: oxygen uptake

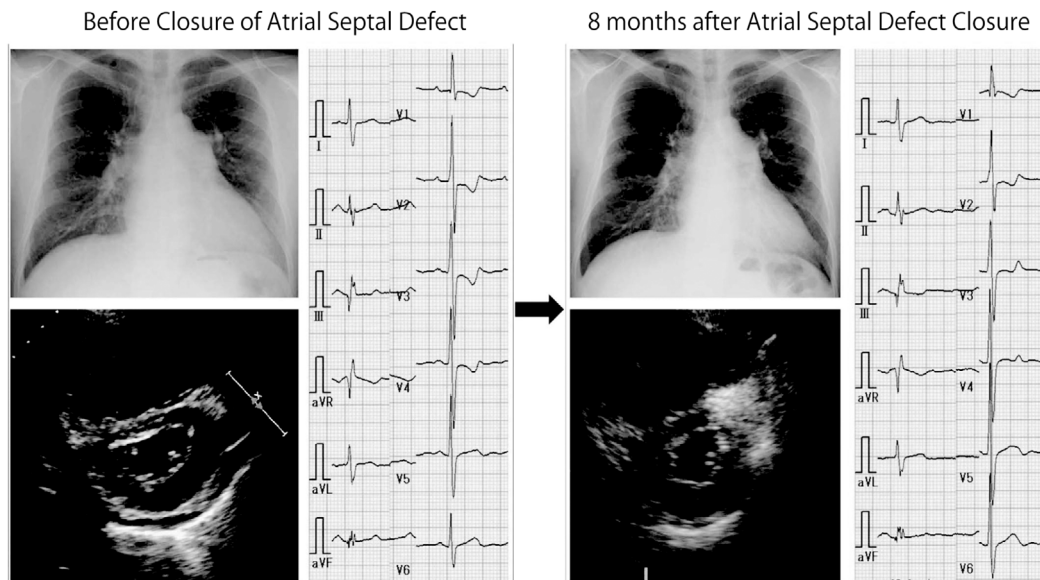
specialized hospitals in Japan have shown (9) or experienced (10) outstanding success in controlling IPAH.

The first right heart catheterization (RHC) procedure revealed that a mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), and pulmonary to systemic perfusion ratio (Qp/Qs) of 55 mmHg, 5.5 wood units (WU), and 1.6, respectively, which confirmed PH (Fig. 1).

Clinical evaluations conducted in other hospitals did not yield any data indicative of a specific disease for PH Groups 2 through 5; the PH exclusively belonged to Group 1 (PAH). Although the Qp/Qs (=1.6) was relatively high, the diameter of the ASD as measured by transesophageal echocardiography (TEE) was <20 mm, suggesting that the PAH

observed was not due to ASD-based left-to-right shunt. The final diagnosis of PH was thus IPAH with a small ASD.

We decided to evaluate the patient's physiological and hemodynamic status using cardiac magnetic resonance imaging (cMRI) and RHC. The time course of medications and important parameters of cMRI and RHC are summarized in Fig. 1. cMRI and RHC in November 2014 showed an increase in the RV end-diastolic volume index (RVEDVI) with a reduced RV ejection fraction (RVEF), along with an improvement in mPAP (49 mmHg) and the PVR (5.1 WU) with a prominent left-to-right shunt (Qp/Qs=1.4). The patient didn't strictly take sildenafil, and fluid retention was suspected from the high mean pulmonary arterial wedge



**Figure 2.** Changes in chest X-ray, electrocardiogram, and echocardiogram findings.

pressure (mPAWP) and mean right atrial pressure (mRAP). The short-acting sildenafil was replaced with long-acting tadalafil, and two diuretics were administered.

In March 2015, there was a reduction in the mPAP with normalization of the mPAWP and mRAP, although the PVR increased concomitantly with lower Qp/Qs. Ambrisentan was then added on to tadalafil. The patient's peak oxygen uptake (peak  $\text{VO}_2$ ) in cardiopulmonary exercise (CPX) testing just after this was 16.5 mL/kg/min (58% of the theoretical  $\text{VO}_2$  max). In August 2016, the RVEDVI and Qp increased with a reduction in the RVEF, while both the mPAP and PVR improved further. The high Qp likely has a harmful effect on the RV function in addition to a successive downstream negative effect on the pulmonary arteries. As a result, the percutaneous closure of the ASD was therefore selected.

With the informed consent of the patient, the ASD was percutaneously closed. The TEE-based assessment yielded a secundum ASD of 10.4 mm×6.0 mm with good circumferential rims except for the aortic rim and superior rim (1.9 and 1.7 mm, respectively). The ASD size was considered too small to induce PAH from the left-to-right shunt, suggesting again that IPAH was the main cause for his PAH. A septal occluder (15-mm Figulla Flex II; Occlutech GmbH, Jena, Germany) was chosen and placed. After confirming that the closure of the ASD did not acutely influence the hemodynamic status, the device was released for implantation. After the closure, we kept the Swan-Ganz catheter inserted until the next day and further observed that the mPAP (32-36 mmHg) slightly increased in proportion to an increase in the mPAWP (18-20 mmHg) until the next day.

On day 9 after repair, there was a slight reduction in Qp to 6.4 L  $\text{min}^{-1}$ , with slight decreases in the mPAP (30 mmHg) and PVR (3.6 WU). The patient had stable vitals and was discharged on day 10 after repair. A follow-up examination eight months later revealed apparent improve-

ments in cardiomegaly, inverted T waves, and RV enlargement with compressed LV cavity (Fig. 2). The RHC showed a further decrease in the mPAP (25 mmHg) without deterioration in the RV function. The patient's peak  $\text{VO}_2$  in CPX testing at that time improved to 22.2 mL/kg/min (73% of the theoretical  $\text{VO}_2$  max).

One year after ASD closure, cMRI further showed that the RVEDVI was markedly reduced with no marked change in the RVEF, implying that the RV had undergone reverse remodeling. However, three years after ASD closure, the patient's hemodynamic status worsened, supposedly due to his poor adherence to the medical treatment. We noted a slight increase in the mPAP (35 mmHg) and PVR (5.4 WU) on RHC and an increased RVEDVI with a slightly reduced RVEF on cMRI. The patient's peak  $\text{VO}_2$  in CPX testing decreased to 15.6 mL/kg/min (57% of the theoretical  $\text{VO}_2$  max).

We continued to educate the patient on medication adherence to him, and he has since been additionally taking beraprost (360  $\mu\text{g}$ ). The RHC showed a decrease in mPAP (27 mmHg) and PVR (4.2 WU). Four years after ASD closure, the most recent cMRI scan showed an improvement in the RVEF (32%) and a decrease in the RVEDVI (100 mL/m<sup>2</sup>). Recently, his WHO functional class stabilized to I. He has no particular complaints in his daily life.

## Discussion

Unrestricted ASD induces high Qp, leading to damage of the pulmonary endothelial cells and proliferation of vascular smooth muscle cells, which finally results in PAH, or so-called shunt associated PAH (sPAH). The global guidelines (1, 4) have recommended patients with RV enlargement due to unrestricted ASD undergo ASD closure regardless of the symptoms in order to prevent further complications, such as RV failure and sPAH. Recent reports on ASD-

sPAH have demonstrated safe closure of unrestricted ASD under controlled PAH using PAH-based therapeutics (2, 11, 12). However, the closure of a small ASD in patients with IPAH has been described as unnecessary and even contraindicated as per major guidelines for PH (7, 8) or ACHD (1).

The underlying reason for these guidelines is the lack of evidence concerning the beneficial effects of closing a small ASD and its potential for inducing RV failure with the further collapse of the systemic circulation. However, there are chances of progression of RV failure when the left-to-right shunt through the small ASD is prominent enough, especially under PH, to induce RV volume overload. Using cMRI, we were able to clearly predict the timing of the RV failure, which can occur due to volume overload through the small orifice of the ASD. Thus, percutaneous closure of the ASD was clinically feasible for preventing RV failure.

One year after ASD closure, cMRI (Fig. 1) showed a marked reduction in the RVEDVI (97 mL/m<sup>2</sup>), which strongly justified our treatment strategy and decision, in contrast to the contraindication described in the guidelines (1, 7, 8). In IPAH patients without a shunt, the prognosis has been outstanding in hospitals specialized in treating PH in Japan (9, 13), especially in patients with controlled mPAP (<42.5 mmHg) (9). Therefore, without the ASD, our patient can expect a longer survival, as his actual mPAP just before the ASD closure was 30 mmHg, and his expected mPAP after the ASD closure was 26.0 mmHg, as calculated using the formula (12):  $Qs \times PVR + mPAWP$ .

Although the mPAP increased over the expected value the first day after ASD closure mostly due to the transient elevation of mPAWP, the expected short-term outcomes were achieved in terms of the hemodynamics with no further progression of the RV failure one year after ASD closure. The patient's subsequent poor adherence to the medical treatment seemed to induce the later worsening of PAH, but education on medication adherence and the addition of beraprost were able to restore his hemodynamic status and RV function. In addition, his WHO-FC stabilized to I. We therefore conclude that our strategy of "Treat and Repair" for a patient with IPAH and a small ASD was successful and ultimately resulted in good long-term results.

We should touch on the important issue of compliance with medication in the present case. Recognition of our patient's poor compliance with medication was delayed. Therefore, it was somewhat difficult to predict potential worsening of his PAH in a timely manner, as shown in the RHC and cMRI data actually obtained three years after ASD closure. Adherence to oral PAH drugs was said to be around 60% (14), and patient education concerning medical treatment is critically important, especially for patients with progressive diseases like IPAH. We strongly suggest that even after successful ASD closure, periodic examinations and confirmation of the use of previously prescribed PAH drugs should be performed, especially for patients with IPAH.

## Conclusions

The clinical decision to close a small or coincidental ASD in a patient with IPAH should not be based solely on existing guidelines but rather consider the benefit-risk ratio associated with the specific case. Meticulous clinical monitoring, with attention to precise hemodynamic analyses using RHC and cMRI, and prior experience in effective strategies for controlling PAH are pertinent for making difficult clinical decisions with regard to closure of a small ASD in a patient with IPAH.

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

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