Treat and Repair Strategy in Patients With Atrial Septal Defect and Significant Pulmonary Arterial Hypertension

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Background: A therapeutic strategy in patients with atrial septal defect (ASD) and significant pulmonary arterial hypertension (PAH) remains controversial. This study aimed to assess the effect of PAH-specific medications and subsequent transcatheter shunt closure (ie, a treat and repair strategy) in these patients.

Methods and Results: Among 646 patients with ASD, 22 patients (mean age of 56±20 years) who had PAH [mean pulmonary artery pressure ≥25mmHg and pulmonary vascular resistance (PVR) ≥3 Wood units] underwent successful transcatheter ASD closure. Prior to the procedure, 8 patients received PAH-specific medications (PHM group) and 14 patients did not (non-PHM group). Initially, the PHM group had higher PVR compared with non-PHM group (9.6±3.8 vs. 4.2±1.0 Wood units, P<0.01). After treatment with PAH-specific medications, PVR in this group decreased to 4.0±0.8 Wood units (P<0.01). No adverse events were observed in either the PHM or non-PHM group during or after the transcatheter procedure. In the PHM group, during a treatment period of 52±48 months, the World Health Organization Functional Classification significantly improved (3.0±0.5 to 2.0±0.0, P<0.01), as well as in the non-PHM group (2.1±0.6 to 1.5±0.5, P<0.01).

Conclusions: Treat and repair strategy provided substantial improvement and no worsening of the WHO-FC, even in patients with ASD and significant PAH. Long-term hemodynamic follow-up is mandatory to evaluate the ultimate efficacy and safety of this new strategy. (Circ J 2016; 80: 227–234)

Key Words: Atrial septal defect; Catheter intervention; Pulmonary hypertension; Treat and repair strategy
PAH (ie, ASD patients with elevated PVR) had transcatheter ASD closure performed and 22 patients achieved a successful operation. In 1 patient, the procedure was abandoned because of the morphological characteristics of the defect, and elective surgical closure was performed instead. Among the 22 patients, 8 patients who received PAH-specific medications (PHM group) because of their significant PAH prior to transcatheter ASD closure were the main study population. The remaining 14 patients who did not receive PAH-specific medications were considered as a subgroup of patients with ASD and mild to moderate PAH (non-PHM group) (Figure 1). The study was approved by the institutional ethics board and the patients provided written informed consent before participation in the study.

**Definition and Evaluation of PAH**

PAH was defined from hemodynamic variables at the initial cardiac catheterization study under the condition of no general anesthesia. The hemodynamic definition of PAH in this study consisted of PAP ≥25 mmHg with left atrial or pulmonary capillary wedge mean pressure of ≤15 mmHg and PVR ≥3 Wood units measured during a catheterization study. The effect of PAH-specific medications was evaluated by catheterization study, which was performed after treatment with PAH-specific medications prior to transcatheter ASD closure. Hemodynamic variables that were obtained from the catheterization study included PAP, PVR, and the pulmonary to systemic flow ratio (Qp/Qs). Qp/Qs was calculated using the Fick principle, using aortic, pulmonary arterial, and mixed venous oxygen saturations, which were obtained without supplemental oxygen. The mixed venous saturation value was derived from the superior and inferior venae cavae.

**Symptoms of PAH and Clinical Outcomes**

Symptoms of PAH were evaluated by the World Health Organization Functional Classification (WHO-FC), which was assessed at initial presentation and at follow-up. Symptomatic PAH was defined as WHO-FC ≥II. The clinical outcomes were evaluated during a medical interview with the patients at the time of follow-up. For patients who were followed by a physician outside our medical group, information was obtained by contacting the referring physicians. Adverse events were defined as a composite of all-cause death, hospitalization for heart failure or exacerbation of PAH, systemic arterial embolization, and procedure-related complications. Hospitalization for hemodynamic evaluation of the patients’ PAH was not included as an adverse event.

**PAH-Specific Medications**

PAH-specific medications included endothelin-receptor antagonists, phosphodiesterase type-5 inhibitors and oral and intravenous prostanoids. Other medications were not considered as
Treat and Repair for ASD and PAH

PAH-specific medication. The regimens of PAH-specific medications were used at the time of transcatheter ASD closure and were introduced by an individual cardiologist who specialized in pulmonary hypertension.

Transcatheter Procedure

Transcatheter ASD closure was recommended if the patient responded to the PAH-specific medications. The decision to undergo transcatheter ASD closure was based on the patient’s hemodynamics, which were measured in a catheterization study. References for the hemodynamic criteria for recommendation of closure of the interatrial shunt were Qp/Qs ≥1.5 and PVR <8 Wood units.13 Transcatheter closure of the ASD was performed under general anesthesia with fluoroscopic and transesophageal echocardiographic guidance. The procedure was performed using an Amplatzer septal occluder (St. Jude Medical, St. Paul, MN, USA). A Swan-Ganz catheter was inserted from the right jugular vein prior to the transcatheter procedure. Hemodynamics were monitored from the beginning of the transcatheter procedure until at least 1 day after the procedure to evaluate the safety of the procedure. A significant decrease in systemic blood pressure with hypoxia, a significant elevation of PAP, and any other symptoms suggesting the state of a so-called pulmonary hypertensive crisis were included as procedural complications.

Echocardiographic Evaluation

Transthoracic echocardiography was performed to evaluate the effect of transcatheter closure with or without prior PAH-specific medications. The echocardiographic evaluation was performed at the time of initial examination, after treatment with PAH-specific medications (ie, before ASD closure), at 1 day after the procedure, and at follow-up (≥3 months). Estimated systolic PAP (ESPAP) was derived from right ventricular systolic pressure estimates using tricuspid regurgitation velocity (v) and the Bernoulli equation as follows: 4v^2 + right atrial (RA) pressure. RA pressure was estimated from the diameter of the inferior vena cava and respiratory collapse, as previously described.14

Table 1. Clinical Details of the PHM Group (A) and the Non-PHM Group (B)

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(Table 1 continued the next page.)
Statistical Analysis

Data analysis was performed using JMP software (version 9; SAS Institute, Cary, NC, USA). Continuous variables are expressed as mean±standard deviation. Discrete variables are expressed as number and percentage. Comparisons between serial hemodynamic measures with cardiac catheterization and echocardiographic measures were performed using the paired t-test. Comparison of continuous variables between the PHM and non-PHM group were performed using the unpaired Student’s t-test. Comparisons between discrete variables were performed using Fisher’s exact test. A P value of <0.05 was considered statistically significant.
Results

Study Population
The mean age at the time of ASD closure in the total study population was 56±20 years.

PHM Group  Detailed demographics and clinical characteristics of the PHM group are shown in Table 1A. The mean age at the time of ASD closure was 66±13 years and all 8 patients had symptomatic PAH (WHO-FC ≥II) at initial presentation. PAH-specific medications consisted of endothelin-receptor antagonists (bosentan, n=5; ambrisentan, n=2), phosphodiesterase type-5 inhibitors (sildenafil, n=5; tadalafil, n=1), an oral prostanoid (beraprost, n=3), and an intravenous prostanoid (epoprostenol, n=3). Notably, 3 patients (Cases 1, 4, and 7) who had experienced a severe degree of PAH were treated with a high dose of intravenous epoprostenol. The treatment duration of PAH-specific medications prior to ASD closure ranged from 2 weeks to 120 months. In 1 patient (Case 3), initial hemodynamic evaluation in a catheterization study was performed after PAH-specific medications had been introduced for 1 month. Hemodynamic evaluation prior to the PAH-specific medications could not be performed because this patient visited the emergency room at a local hospital with unstable hemodynamics. Consequently, this patient was primarily treated with PAH-specific medications prior to a complete hemodynamic evaluation.

Non-PHM Group  Demographics and clinical characteristics of the non-PHM group are shown in Table 1B. The mean age at the time of ASD closure was 66±13 years and 12 (86%) patients had symptomatic PAH at initial presentation.

Clinical Outcomes
All 22 patients in the PHM and non-PHM groups safely achieved transcatheter ASD closure. No procedure-related complications occurred in any of the patients during or after the transcatheter procedure.

In the PHM group, no adverse events were observed during a mean follow-up period of 19±27 months after the procedure. The mean follow-up period during the entire treatment strategy was 52±48 (range, 6–127) months. Regimens of PAH-specific medications at the time of follow-up did not differ from those at the time of ASD closure, except in 3 patients. The patient in Case 1 had the longest follow-up period of 83 months and ambrisentan 5 mg was added. Additionally, epoprostenol was decreased to 57 ng·kg⁻¹·min⁻¹. With regard to the other patients, in Case 5 the patient had a risk of liver damage and the dose of bosentan decreased from 187.5 to 125 mg, and in Case 6 the patient abandoned beraprost as her symptoms improved and she remained on bosentan 125 mg and sildenafil 60 mg. Although the WHO-FC improved in 7 patients, all the patients remained symptomatic for PAH after the entire treatment process of combined PAH-specific medications and transcatheter ASD closure (Figure 2A). The mean WHO-FC significantly improved (from 3.0±0.5 to 2.0±0.0, P<0.01) after the entire treatment.

In the non-PHM group, no adverse events were observed during a mean follow-up period of 19±16 (range, 4–61) months. There were 12 out of 14 patients who were symptomatic for their PAH, and the WHO-FC improved in 7 patients but did not improve in 5 patients (Figure 2B). The mean WHO-FC in the non-PHM group significantly improved (from 2.1±0.6 to 1.5±0.5, P<0.01). No patients in either the PHM or non-PHM group had deterioration of the WHO-FC after closure of their ASD. There was no significant difference in the decrement value of the WHO-FC in the PHM vs. the non-PHM group (−1.0±0.5 vs. −0.6±0.6, P=0.13).

Effect of PAH-Specific Medication
Comparison of the hemodynamic variables at the initial catheterization and after treatment with PAH-specific medications...
Hemodynamic variables in the non-PHM group are shown in Table 2. Initially, the PHM group had significantly higher mean PAP and PVR compared with the non-PHM group (P<0.01 for both). After treatment with PAH-specific medications, mean PAP and PVR were not significantly different between the PHM and non-PHM groups (P=0.13 and P=0.73, respectively).

**Echocardiographic Evaluation**

Echocardiography-derived ESPAP in the PHM group at each stage during the treat and repair process are shown (* vs. †P=0.02; * vs. †P<0.01; * vs. †P<0.01). (B) ESPAP values in the non-PHM group before and after ASD closure and at the follow-up are shown (* vs. †P<0.01). ASD, atrial septal defect; ESPAP, estimated systolic pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PHM, PAH-specific medications.

Comparison of the PHM and Non-PHM Groups

Comparison of the clinical variables in the PHM and non-PHM groups is shown in Table 3. Patients in the PHM group were significantly younger (P<0.01) and had significantly greater values for the WHO-FC (P<0.01) than those in the non-PHM group. There was no significant difference in the defect size between the PHM and non-PHM groups (P=0.81).

Hemodynamic variables in the non-PHM group are shown in Table 2. Initially, the PHM group had significantly higher mean PAP and PVR compared with the non-PHM group (P<0.01 for both). After treatment with PAH-specific medications, mean PAP and PVR were not significantly different between the PHM and non-PHM groups (P=0.13 and P=0.73, respectively).
1 patient whose initial echocardiographic evaluation was performed after treatment with PAH-specific medications (Case 3) and a patient who had an early increase of ESPAP after ASD closure (Case 1). Of the 6 patients who showed a decrease in ESPAP over time. As a result, ESPAP significantly decreased after treatment with PAH-specific medications (ie, before ASD closure) compared with the initial evaluation (104±27 vs. 72±19 mmHg, P=0.02). ESPAP at the follow-up evaluation (40±9 mmHg) was significantly lower compared with before ASD closure (P<0.01).

Echocardiography-derived ESPAP in the non-PHM group before ASD closure, after ASD closure, and at the follow-up are shown in Figure 3B. An early increase in ESPAP after ASD closure was observed in 2 cases (Cases 12 and 14) and ESPAP remained higher compared with before ASD closure in 2 cases at follow-up (Cases 12 and 21). Mean ESPAP at follow-up (38±10 mmHg) was significantly lower than before ASD closure (vs. 61±19 mmHg, P<0.01).

Discussion

PAH-specific medications improved the hemodynamics in patients with ASD and coexisting significant PAH, and there were no procedure-related complication or adverse events, including death, during or after transcatheter ASD closure. The present study showed symptomatic improvement with the combined strategy of “treat” (using PAH-specific medications) and “repair” (undergoing subsequent transcatheter shunt closure) in serial patients with ASD and significant PAH. Symptomatic improvement in the PHM group was similar to that in the non-PHM group, which had less severe PAH with their ASD. Our results for short-term outcomes imply or may further lead to a potential long-term benefit of this treat and repair strategy.

Transcatheter ASD closure using the Amplatzer septal occluder in adults is reported to be efficient and safe with excellent success rates.7-17 This procedure is also reported as safe and effective for patients with PAH.7-9 The benefits of the transcatheter procedure over standard cardiac surgery are avoidance of thoracotomy and cardiopulmonary bypass, and reduced requirement for blood products.18-20 These factors may have contributed to our result that none of our PAH patients had a complication or adverse event during or after transcatheter ASD closure.

A strength of the present study is that all of our study population had the potential to be classified as having significant PAH associated with congenital heart disease according to a recent classification and definition, because we excluded patients with PAH associated with other diseases and those who did not meet the recent criteria of PAH.12,13 In this patient population, we found that PAH-specific medications can modify hemodynamics significantly, to the extent that transcatheter shunt closure could be considered as a therapeutic option. Notably, as previously demonstrated in idiopathic PAH patients,20 a high dose of intravenous epoprostenol improved hemodynamics to a certain degree in patients with ASD and severe PAH (Cases 1, 4, and 7).

A recent report suggested that transcatheter ASD closure is effective in patients with severe PAH who fulfill the criteria of systolic PAP ≥60 mmHg and PVR ≥6 Wood units, as measured by catheterization.21 However, those investigators excluded patients who were treated with PAH-specific medications. Only a few reports have discussed the effects and safety of transcatheter ASD closure for PAH patients who have been treated with recent disease-targeted therapy for PAH.22-24 Fujino et al describe, in a small number of serial patients, that treating patients with ASD and significant PAH using “certified” medications resulted in improvement of hemodynamics.25 In their report, they also demonstrate that ASD closure alone could provoke an elevation of PVR and thus advocated the importance of “certified” PAH medications for these patients. Those results, with the results from the present study, suggest that PAH-specific medications have the potential to extend the consideration of interatrial left-to-right shunt closure for patients with severe PAH from the hemodynamic standpoint. However, whether the hemodynamics of PAH ameliorate or deteriorate with ASD closure alone remains uncertain without an evaluation by catheterization study.

A few previous reports have suggested that ASD closure may not always improve PAH.26-27 Patients with congenital heart disease who develop PAH after shunt closure have a worse prognosis than patients not undergoing shunt closure.28,29 Thus, there is a concern that patients with ASD complicated by significant PAH who require PAH-specific medications do not benefit from transcatheter ASD closure. In Case 1, ESPAP increased from 50 mmHg to 65 mmHg after ASD closure, and decreased to 49 mmHg at follow-up. This early increase in ESPAP was observed in 2 cases in the non-PHM group. One can speculate that left-to-right shunt closure led to an immediate increase of PVR or enhanced cardiac output occurred because of a hyperkinetic constriction of the right ventricle. These immediate, vital reactions might be adjusted during the time after shunt closure. Because some patients in the non-PHM group as well as in the PHM group remained symptomatic or had high ESPAP values at follow-up, hemodynamic evaluation by catheterization study would be necessary for patients who had residual PAH symptoms, regardless of the severity of their PAH prior to ASD closure. In the current era, a catheterization study after ASD closure should be performed in order to evaluate residual PAH and whether the patient requires PAH-specific medications.

Study Limitations

There are 4 limitations to this study. First, the institution is a regional hospital with patients who are referred from various regions of Japan. Therefore, we encountered wide variability in the timing of the follow-up after the procedure at which clinical data were available. Cardiac catheterization, which is the gold standard examination to evaluate hemodynamics, was not routinely performed after ASD closure. Second, because our patients were referred from various institutions, the required criteria for treating them with PAH-specific medications were not uniform. Third, although PAH patients who responded well to PAH-specific medications were included in our study, we do not know how many patients did not respond and were not referred to us. The decision to undergo ASD closure was based on hemodynamic criteria at rest. However, hemodynamic changes under special conditions (eg, challenge with 100% oxygen or with nitric oxide, test occlusion of a defect) also supported our decisions in some cases. Because there is not an established criterion to interpret these responses, these results were not included in this study. Fourth, the number of patients included in the study was small and the follow-up period was short. Therefore, a multicenter, large-volume clinical study with long-term follow-up results is needed to confirm the safety and effect of this treatment strategy.

Conclusions

In patients with ASD and coexisting significant PAH, PAH-
specific medications improved the hemodynamics, and subsequent transcatheter ASD closure was accomplished without any immediate severe complications. Substantial improvement in the WHO-FC was observed with this therapeutic strategy. Treat and repair strategy can be considered as an alternative to watchful waiting under medical therapy alone for patients with ASD and significant PAH, although precise hemodynamic evaluation in the long-term period is mandatory to confirm the efficacy and safety of this strategy.

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Conflict of Interest Statement

T.A. serves as a consultant to St. Jude Medical Inc. None of the other authors has any conflicts of interest to declare regarding this study.

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References