Targeted Therapy Is Required for Management of Pulmonary Arterial Hypertension After Defect Closure in Adult Patients With Atrial Septal Defect and Associated Pulmonary Arterial Hypertension

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Summary

Background: Therapeutic strategies for pulmonary arterial hypertension (PAH) associated with atrial septal defect (ASD) remain a matter of debate.

Methods and Results: We identified 5 outpatients who had been diagnosed with ASD–PAH and undergone ASD closure in combination with targeted therapy with certified PAH drugs. We assessed changes in hemodynamic parameters and exercise capacity. The combination of ASD closure and targeted therapy significantly increased systemic blood flow (Qs) from the baseline (from 3.3 ± 0.6 L/minute to 4.2 ± 1.0 L/minute, P < 0.05) with a significant improvement in the World Health Organization Functional Class (WHO-FC; from 2.8 ± 0.4 to 1.6 ± 0.5, P < 0.05). The hemodynamic data before and after ASD closure without targeted therapy showed further elevation of pulmonary vascular resistance shortly after ASD closure (678 dyne·s/cm² to 926 dyne·s/cm²) in 1 case, as well as after a long time since ASD closure (491.0 ± 53.7 dyne·s/cm² to 1045.0 ± 217.8 dyne·s/cm²) in 2 cases. This worsening was reversed after the targeted therapy, accompanied by an increase in Qs and an improvement in WHO-FC in all cases. Conclusions: Targeted therapy should be added to ASD closure in adult patients with ASD–PAH. (Int Heart J 2015; 56: 86-93)

Key words: Adult congenital heart disease, Therapeutic strategy

A subset of adult patients with open atrial septal defect (ASD) has pulmonary arterial hypertension (PAH). Persistent exposure of the pulmonary vasculature to increased blood flow results in pulmonary obstructive arteriopathy, which leads to an increase in pulmonary vascular resistance (PVR). If PVR approaches or exceeds systemic resistance, the shunt is reversed and the patient may finally develop Eisenmenger syndrome. It has been reported that 6.1% of adult patients with septal defects have a complication of associated pulmonary hypertension (defined by echocardiography), and 3.5% have Eisenmenger syndrome.1 The long-term outcome after surgical repair of ASD without PAH is generally excellent; therefore, ASD closure is recommended to prevent the development of PAH, reduce the risk of right heart failure and subsequent arrhythmia, and avoid paradoxical emboli.2,3 In contrast, the therapeutic strategies for patients with open ASD and associated PAH (ASD–PAH) remain a matter of debate. The Guideline of the European Society of Cardiology suggests that patients with a significant shunt (signs of right ventricular volume overload) and PVR < 400 dyne·s/cm² should undergo ASD closure regardless of symptoms (Class I, Level B).4 However, the findings were based on only 1 report by Attie, et al5 and thus require additional evidence. Recently, Beghetti, et al suggested that a baseline PVR index of < 480 dyne·s·m⁻²·cm⁻¹ and a PVR: systemic vascular resistance (SVR) ratio of < 0.3 may be considered indicative of a favorable outcome following ASD closure.6 These criteria are more restrictive than those provided by the guidelines,4,5 but they also lack adequate supporting evidence. In contrast, Engelfriet, et al reported that the prognosis appeared to be worse in patients with closed ASD–PAH than in those with open ASD–PAH.7 In addition, Manes, et al recently showed that the prognosis of patients with closed congenital heart disease (CHD)-associated PAH was far worse compared with that of patients with open CHD-associated PAH.8 Taken together, there has been no definitive strategy for patients with ASD–PAH.

In the last decade, there have been striking advances in treatment options for PAH, including the development of new drugs, such as prostanooids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and a soluble guanylate cyclase stimulator.9 Targeted therapy with these certified PAH drugs has led to the improvement of hemodynamic parameters or ex-

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exercise capacity not only in patients with idiopathic PAH, but also in those with CHD-associated PAH. In addition, several recent reports have shown that targeted therapy with certified PAH drugs allows adult patients with uncorrected ASD–PAH to undergo successful ASD closure.

The aim of this study was to determine if the targeted therapy with certified PAH drugs can improve hemodynamics and exercise capacity after defect closure in patients with ASD–PAH. We are convinced of the importance of hemodynamic correction and improvement of exercise capacity for longer survival in PAH patients. We examined outpatients at our hospital who had been preoperatively diagnosed with ASD–PAH and who had undergone ASD closure. We assessed hemodynamics and exercise capacity by consecutive catheter studies and cardiopulmonary exercise tests, respectively. Our results suggest that ASD closure alone is associated with a risk of worsening hemodynamics, although the addition of targeted therapy for PAH improves hemodynamics and exercise capacity.

**METHODS**

**Patient selection:** We conducted a retrospective review of outpatients who had undergone ASD closure after being preoperatively diagnosed with ASD–PAH at our hospital in December 2013. The diagnosis for PAH was decided in accordance with the global guidelines and satisfied the following criteria: mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, PVR ≥ 240 dyne·s/cm², and mean pulmonary capillary wedge pressure (mPCWP) ≤ 15 mmHg before surgery. We excluded patients who had other complex CHD or other possible causes of pulmonary hypertension, and those whose ASD diameters were < 15 mm. We identified 6 patients (2 males) with ASD–PAH who had undergone defect closure in our hospital. We excluded 1 female patient because of the coexistence of thromboembolism in her pulmonary artery. Thus, 5 patients were included in this study. All patients underwent cardiac catheterization/hemodynamic examinations before and after ASD closure.

**Hemodynamic measurements:** Right heart catheterization was used to obtain all hemodynamic measurements invasively and accurately. A Swan–Ganz catheter was introduced from the femoral or jugular vein. Next, the hemodynamic parameters, including mean right atrial pressure (mRAP), right ventricular pressure, mPCWP, mPAP, and mean left atrial pressure (mLAP, before ASD closure) were determined. Before ASD closure, the systemic blood flow (Qs or cardiac output (CO), L/minute) and pulmonary blood flow (Qp, L/minute) were calculated by the Fick method according to the following general equations:

\[ Qs (CO) = \text{estimated } O_2 \text{ consumption (mL/minute)} / \text{arteriovenous } O_2 \text{ difference (mL/L)} \]

\[ Qp = \text{estimated } O_2 \text{ consumption (mL/minute)} / \text{pulmonary arteriovenous } O_2 \text{ difference (mL/L)} \]

\[ \text{PVR (dyne-s/cm}^2) = \frac{80 \times (\text{mPAP (mmHg)} - \text{mLAP (mmHg)})}{Qp (L/minute)} \]

\[ \text{PVR after ASD closure was calculated according to the following equations:} \]

\[ \text{PVR} = \frac{80 \times (\text{mPAP (mmHg)} - \text{mPCWP (mmHg)})}{Qp (L/minute)} \]

\[ \text{SVR (dyne-s/cm}^5) \text{ was calculated according to the following equations:} \]

\[ \text{SVR} = \frac{80 \times (\text{mean arterial pressure (mmHg)} - \text{mRAP (mmHg)})}{Qs (L/minute)} \]

For these equations, estimated O₂ consumption was calculated according to the following equation as described previously:

\[ \text{Estimated } O_2 \text{ consumption} = \text{body surface area (m²)} \times \left[ (138.1 - C \times \ln (age)) + 0.378 \times \text{heart rate (bpm)} \right] \]

\[ C = 11.49 \text{ for male; 17.04 for female} \]

The mixed vein (MV) O₂ saturation (%) was calculated according to the following equation as described previously:

\[ \text{MV } O_2 \text{ saturation} = \frac{3 \times \text{superior vena cava } O_2 \text{ saturation} (\%)}{4} \]

Then, the arteriovenous O₂ difference (mL/L) and pulmonary arteriovenous O₂ difference (mL/L) were calculated according to the following equations:

\[ \text{Arteriovenous } O_2 \text{ difference} = \text{arterial } O_2 \text{ saturation (}% - MV \text{ } O_2 \text{ saturation (%))} \times \text{Hb (g/dL)} \times 1.36/10 \]

\[ \text{Pulmonary arteriovenous } O_2 \text{ difference} = \text{pulmonary vein } O_2 \text{ saturation (}% - \text{pulmonary arterial } O_2 \text{ saturation (%)} \times \text{Hb (g/dL)} \times 1.36/10 \]

After ASD closure (under the condition of no residual shunt), CO was measured by one method for each patient, the thermodilution or the Fick method. During cardiac catheterization, acute vasodilator challenge was performed by using inhaled nitric oxide (20 ppm) or oxygen (10 L/minute).

**Cardiopulmonary exercise test:** A cardiopulmonary exercise test (CPX) was performed on the day before the hemodynamic evaluation using an expired gas analyzer (AE-300S; Minato Ikagaku, Osaka, Japan) as described previously. An exercise protocol was selected by the attending physician to allow a patient’s individual performance to be assessed. In addition to the continuous measurement of O₂ consumption (VO₂), the peripheral arterial O₂ saturation (SpO₂) was monitored by a pulse oximeter during CPX. The peak VO₂ was expressed as a percent of the sex-, age-, body weight-, and body height-adjusted normal value for Japanese people.

**Therapeutic options:** The most appropriate intervention was selected for each individual defect. Decisions regarding the medical therapy were made on an individual basis by the attending physician who took into account all clinical data. We defined certified PAH drugs according to the global guidelines and excluded oral beraprost because it lacks proof of chronic efficacy.

**Statistical methods:** Data were analyzed by a two-tailed paired t-test or repeated measures analysis of variance, followed by the Tukey post-hoc test. P values < 0.05 were considered significant. GraphPad Prism v5.01 (GraphPad Software, Inc.) was used to analyze the data. All results are presented as the mean ± standard deviation.

**RESULTS**

**Patient characteristics:** The baseline data of the 5 patients are presented in Table I. The average age at the time of ASD closure was 40.4 ± 17.3 years (range, 28–70 years). The mean
values of mPAP, PVR, and Qp/Qs were 42.2 ± 4.6 mmHg, 485.0 ± 123.8 dyne s/cm², and 1.9 ± 0.4, respectively. Oxygen inhalation test and the histological analysis with lung biopsy were performed in case 3, showing a substantial decrease in PVR from 678 to 454 dyne s/cm² and 2.1 as an index of pulmonary vascular disease which had been defined by Yamaki, et al., respectively, both of which indicated a possible vascular reversibility after ASD closure. On the other hand, nitric oxide inhalation (20 ppm, 10 minutes) was performed during hemodynamic measurement in cases 1 and 2, showing a small decrease in mPAP (case 1; 35 mmHg to 30 mmHg, case 2; 43 mmHg to 37 mmHg) and PVR (case 1; 375 dyne s/cm² to 314 dyne s/cm², case 2; 390 dyne s/cm² to 314 dyne s/cm²). In 3 of the 5 cases (cases 1–3), CPX was performed before ASD closure and showed that the mean value of the percent peak VO₂ apparently decreased (61.0 ± 18.3%) and SpO₂ dropped at the end of the exercise by 6.7 ± 4.7% from the baseline.

Table II summarizes the information on medication. Bosentan was prescribed just after ASD closure in case 1 and before ASD closure in case 2. In case 3, the first hemodynamic evaluation following ASD closure was performed 1 month after the surgery, and sildenafil and ambrisentan were sequentially added to beraprost at 22 months after ASD closure. In case 4, tadalafil and bosentan were sequentially prescribed after the first hemodynamic evaluation, when 15 years had passed since the surgery. In case 5, beraprost was prescribed at some points between ASD closure and the first hemodynamic evaluation, and bosentan and riociguat were sequentially added after the first hemodynamic evaluation, when 40 years had passed since ASD closure.

Changes in hemodynamics and exercise capacity: Figure 1 shows the final results of the hemodynamic parameters after the combination therapy of ASD closure and targeted therapy with certified PAH drugs, which did not include beraprost. Cardiac output after ASD closure was measured by the Fick method in cases 1–3 and 5, and by the thermodilution method.
in case 4, because in case 4 there was no data of Fick analysis in the first catheterization after ASD closure. Tricuspid regurgitation was moderate in case 4. mPAP decreased in cases 1–3 and increased in cases 4 and 5, resulting in insignificant decreases in the values of mPAP and PVR (from 42.2 ± 4.6 mmHg to 34.2 ± 12.6 mmHg and from 485.0 ± 123.8 dyne·s/cm$^5$ to 419.6 ± 198.5 dyne·s/cm$^5$, respectively). On the other hand, Qs (CO) increased in all patients, showing a statistically significant increase in Qs (from 3.3 ± 0.6 L/minute to 4.2 ± 1.0 L/minute, $P < 0.05$).

Figure 2 shows the final change in exercise capacity after the combination therapy. The World Health Organization Functional Classification (WHO-FC) was significantly improved (from 2.8 ± 0.4 to 1.6 ± 0.5, $P < 0.05$). CPX performed in cases 1–3 demonstrated that the peak VO2 increased in all 3 patients (from 61.0 ± 18.3% to 87.0 ± 7.0% of the normal value, NS), accompanied by an improvement in desaturation at the end of the exercise (from −6.7 ± 4.7% to −2.0 ± 2.0%, NS), which is well known to be one marker for the severity of PAH.\footnote{18,26}

ASD closure alone increased PVR, which was reversed by additional targeted therapy: In cases 3–5, ASD closure was performed, followed by the hemodynamic evaluation without use of certified PAH drugs. The timing of hemodynamic evaluation and starting certified PAH drugs were different among the 3 cases (Table II). As shown in Figure 3A, in case 3, PVR was elevated at the time of the hemodynamic evaluation (1 month after ASD closure) before the use of certified PAH drugs (678 dyne·s/cm$^5$ to 926 dyne·s/cm$^5$) relative to that before ASD closure (baseline). Certified PAH drugs were introduced 22 months after ASD closure, and the latest hemodynamic evaluation revealed that the increase in PVR was reduced to a level similar to that at the baseline (926 dyne·s/cm$^5$ to 509 dyne·s/cm$^5$), suggesting that targeted therapy with certified PAH drugs exerted a beneficial effect on remodeling of the pulmonary artery. Qs (CO) increased (3.1 L/minute to 4.6 L/minute) and WHO-FC improved (from III to II) after the titration of certified PAH drugs, further confirming the beneficial effect of targeted therapy.

Also in cases 4 and 5 (Figure 3B), in which certified PAH drugs were started after a long time since ASD closure, PVR was elevated before the use of certified PAH drugs relative to the baseline (491.0 ± 53.7 dyne·s/cm$^5$ to 1045.0 ± 217.8 dyne·s/cm$^5$). The latest hemodynamic evaluation revealed that the increase in PVR was reduced to a level similar to that at the baseline (1045.0 ± 217.8 dyne·s/cm$^5$ to 583.0 ± 97.6 dyne·s/cm$^5$). Qs (CO) increased (3.5 ± 0.8 L/minute to 4.6 ± 0.6 L/minute) and WHO-FC improved after the titration of certified PAH drugs. These results suggested that certified PAH drugs had a beneficial effect even after a long period since ASD closure.

**Discussion**

There were several novel findings in this study. First, the targeted therapy with certified PAH drugs demonstrated improvement in the Qs (CO) and exercise capacity after ASD.
closure, assessed by right heart catheterization and CPX, respectively (Figures 1 and 2). Second, ASD closure alone resulted in an increase in PVR in the 3 patients with ASD–PAH. In addition, targeted therapy with certified PAH drugs effectively reversed their once-worsened PVR and increased CO, even after a long period since ASD closure (Figure 3B). Taken together, we advocate the importance of using certified PAH drugs for adult patients with ASD–PAH who plan to undergo or have already undergone ASD closure.

Hemodynamic alteration after ASD closure in patients with ASD–PAH: To date, hemodynamic changes after ASD closure in patients with ASD–PAH have remained unclear. As Manes, et al mentioned, hemodynamic data have often been lacking or were not obtained, even before and particularly after defect closure in patients with CHD-associated PAH, indicating that the decision for ASD closure had not been made properly, particularly in the era when certified PAH drugs were not available and when the medical treatment was inadequate through the following period. In this study, we demonstrated that hemodynamic changes were induced by ASD closure with or without certified PAH drugs in patients with ASD–PAH. Without use of certified PAH drugs, ASD closure alone exposes patients to the risk of PAH worsening, as indicated by an increase in PVR (Figure 3). In contrast, the concomitant use of certified PAH drugs before or just after ASD closure appeared to prevent an increase or even caused a decrease in PVR after ASD closure (cases 1 and 2), which is consistent with the findings of a recent report. In addition, the combination of ASD closure and targeted therapy with certified PAH drugs improved exercise capacity and ameliorated the decrease in SpO2 at the end of CPX in all 3 cases (cases 1–3, Figure 2). In contrast, before the targeted therapy was administered, CPXs performed 4 times did not show any improvement in peak VO2 after ASD closure in case 3 (data not shown). This observation also suggests the necessity of using certified PAH drugs for patients with ASD–PAH who have undergone or plan to undergo ASD closure.

Because we did not perform hemodynamic measurement after ASD closure before the titration of certified PAH drugs in cases 1 and 2, we cannot clarify whether ASD closure alone in the 2 cases worsened hemodynamics or not. However, we can declare the importance of applying the targeted therapy, because all 3 cases who had undergone ASD closure alone without certified PAH drugs had worsened hemodynamics (cases 3–5, Figure 3). In case 4, Qs (CO) before ASD closure was measured by the Fick method but after ASD closure we selected CO measured by the thermodilution method, because there was no data of Fick analysis in the first catheterization after ASD closure. We cannot rule out the possibility that the increase in CO after ASD closure (before the use of certified PAH drugs) might be due to the methodological inconsistency, because under a certain amount of tricuspid regurgitation the thermodilution method usually overestimates the CO.

**Figure 2.** Physiological parameters before and after the combination of ASD closure and targeted therapy. The data on WHO-FC (A), %peak VO2 (B), and decrease in SpO2 during CPX (C) in each patient before and after the combination therapy are presented. WHO-FC improved in 4 patients (P < 0.05). The %peak VO2 and desaturation during exercise improved in all patients. WHO-FC indicates World Health Organization Functional Classification; VO2, O2 consumption; SpO2, arterial O2 saturation of hemoglobin measured by pulse oximeter; CPX, cardiopulmonary exercise test; Pre, baseline data before the combination therapy; and Post-Combination, data after the combination of ASD closure and targeted therapy with certified PAH drugs.
When and how certified PAH drugs should be used for patients with ASD–PAH: Because several certified PAH drugs have become commercially available in Japan since 1999, cases 1 and 2 were given these drugs in the perioperative period. Theoretically, shunt closure alone decreases Qp, which substantially leads to a decrease in mPAP (= Qp × PVR – mLAP or mPCWP). However, PVR may suddenly increase because of surgical stress as implied by the observation at 1 month after ASD closure in case 3 (Table II and Figure 3A); consequently, the hemodynamic status of patients may worsen relative to their preoperative status. Therefore, we believe that it is important to start the PAH drugs in the perioperative period. Furthermore, before the targeted therapy was administered 22 months after ASD closure in case 3, consecutive echocardiography did not show any apparent change in estimated right ventricular systolic pressure (data not shown), suggesting the perioperative stress may not have transiently caused the elevation of PVR, but may have induced progression of PAH vasculopathy. In addition, an apparent increase in PVR was found long after the surgery (cases 4 and 5, Figure 3B). The reason for the elevated PVR after surgical closure must be different between case 3 and cases 4–5, because the timing of postoperative assessment was highly different. In cases 4 and 5, the sustained increase in PVR may have been caused by an auto-progression due to residual PAH after ASD closure and/or from the surgical stress. Delayed introduction of targeted therapy with certified PAH drugs improved the hemodynamics and symptoms. It is important to notice that PVR reversed to a similar value before ASD closure, which would suggest that the progression of vascular remodeling after ASD closure was mostly reversible. However, we could not deny the possibility that PVR would have been reduced further if adequate medical treatment had been given from the preoperative period as seen in case 2. Therefore, we emphasize that the medication should be started as early as possible if ASD closure is to be performed in patients with ASD–PAH.

It has been reported that the prognosis of PAH after shunt closure was worse than that of PAH with uncorrected shunt flow in the era without general application of targeted therapy. Thus, it is important to identify patients with ASD–PAH who could benefit from ASD closure without a substantial risk, even in this era with certified PAH drugs. We have not established the criteria for identification of these patients yet, but propose the use of certified PAH drugs for patients with ASD–PAH who plan to undergo or have already undergone ASD closure, even after a prolonged period.
Study limitations: Because the case series in this study consisted of outpatients at our hospital who had already undergone ASD closure, we cannot offer any suggestion about a proper method for choosing suitable candidates for ASD closure from adult patients with ASD–PAH. In patients with ASD–PAH, it is extremely important to revise the indication for ASD closure in combination with medical therapy. In addition, percutaneous ASD occlusion devices have become available that are expected to repair defects less invasively. Therefore, the indication for defect closure may be different between percutaneous and surgical procedures. Thus, randomized controlled studies and/or world-scale surveys on national registries, such as the REVEAL Registry, are required.

As mentioned above, there is as yet no consensus on when targeted therapy should be administered (pre- or post-operation). Further investigations are required to answer this question.

This investigation was a single-center retrospective (observational) study, and the sample size was quite small. However, we believe that the findings are sufficiently reliable to support the conclusion that targeted therapy should be administered for patients with ASD–PAH who plan to undergo or have undergone ASD closure percutaneously or surgically. To confirm our findings, randomized controlled studies and/or world-scale surveys on national registries are required.

To address all the questions associated with comparison of the prognoses of patients undergoing ASD closure and those without ASD closure will require a considerable amount of time because the long-term survival rates of patients in both groups are expected to be quite good. It is expected that the number of adult patients with ASD–PAH will decrease, particularly in developed countries, because of early diagnosis in childhood. Therefore, we believe that we should survey past experiences with a large number of patients as soon as possible to help existing patients with ASD–PAH. Considering this, our data may be useful for decision making in other hospitals.

Conclusion: The findings in this study clearly demonstrated improvements in hemodynamics and exercise capacity by the targeted therapy with certified PAH drugs after defect closure in adult patients with ASD–PAH. Our results suggest the importance of using certified PAH drugs for patients with ASD–PAH before or after undergoing ASD closure.

DISCLOSURE

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