INTRODUCTION

Pulmonary hypertension (PH) is frequently encountered in patients of advanced age with atrial septal defects (ASD). In patients with overt PH, ASD closure might result in worse prognoses than not undergoing ASD closure. Based on guidelines for operability in patients with PH associated with ASD, shunt closure is usually discouraged in the presence of severe PH or Eisenmenger syndrome. Preoperative PH is a predictive factor for mortality and cardiac morbidity after shunt closure. However, recent advances in PH treatment have led to ASD closures even in patients with severe PH who are considered inoperable. ASD closure with fenestration is an important option for such high-risk patients. Few studies have performed hemodynamic evaluations in patients after partial closures of ASDs with fenestration. We evaluated changes in hemodynamic parameters after partial closure of ASD and the clinical implications of fenestration in patients with PH.

MATERIALS AND METHODS

This retrospective study enrolled 17 patients over 18 years of age who underwent partial closure of ASD with fenestration due to PH.
Partial closure of ASDs with fenestration

We collected clinical assessments of World Health Organization (WHO) functional class, age at the time of the operation, size of fenestration, body size, and evidence of volume overload (Qp/Qs > 1.5). The fenestrations were made with a punch on the surgical patch or via the use of a dilator on an Amplatzer Septal Occluder (ASO, St. Jude Medical Inc., St. Paul, MN, USA). The fenestration size depended on body size and the degree of PH, and was typically more than 5 mm.

Vasodilator testing with 100% oxygen was performed through a properly fitted face mask. Based on pre-closure PVRI, the patients were classified as mild (≤ 6), moderate (6 < PVRI ≤ 9), or severe (> 9 Wood units/m²) to observe the post-closure PVRI of each group.

Table 1. The Data for Each Patient

| No. | Sex | Age (yrs) | Fenestration | Pre-CTR | Vasodilator (mm Hg) | Pre-mPAP (mm Hg) | Pre-PVRI (Wood unit) | Pre-Qp/Qs | mPAP (O₂) | PVRI (O₂) | Post-CTR | Post-mPAP (mm Hg) | Post-PVRI (Wood unit) | Follow up | Fenestration | Vasodilator | Pre-Qp/Qs | mPAP (O₂) | PVRI (O₂) |
|-----|-----|-----------|--------------|---------|---------------------|-----------------|-------------------|----------|----------|----------|---------|-----------------|-------------------|---------|-------------|-----------|----------|----------|----------|
| 1   | F   | 27        | P            | 0.47    | 54                  | 11.4            | 1.5               | 48       | 8.3      | 0.44     | 35      | 8               | LR                 | Sil/60 months |
| 2   | F   | 28        | P            | 0.59    | 46                  | 10.3            | 2.15              | 44       | 7.2      | 0.48     | 22      | 6               | LR                 | Sil/16 months |
| 3   | F   | 31        | D            | 0.47    | 48                  | 8.5             | 1.8               | 44       | 5.6      | 0.42     | 25      | 5               | LR                 | Bos/18 months |
| 4   | F   | 29        | D            | 0.56    | 37                  | 5.5             | 1.8               | 34       | 2.8      | 0.46     | 22      | 2.16            | Closed             | Sil/12 months |
| 5   | F   | 24        | P            | 0.6     | 43                  | 7.2             | 2.1               | 41       | 3.5      | 0.52     | 22      | 2.7             | LR                 | Bos/30 months |
| 6   | F   | 23        | P            | 0.57    | 47                  | 12.19           | 2.21              | 48       | 8.35     | 0.41     | 29      | 6.9             | LR                 | Sil+Bos/10 months |
| 7   | F   | 22        | P            | 0.55    | 52                  | 9.3             | 2.05              | 45       | 6.76     | 0.41     | 13      | 2.2             | LR                 | Sil/1 months |
| 8   | M   | 42        | P            | 0.48    | 50                  | 9.53            | 2.49              | 48       | 5.74     | 0.47     | 41      | 9.77            | LR                 | Sil/60 months |
| 9   | F   | 32        | P            | 0.54    | 62                  | 11.3            | 1.79              | 61       | 5.1      | 0.56     | 70      | 15.8            | LR                 | Bos+Bera/12 months |
| 10  | F   | 34        | P            | 0.49    | 77                  | 16.7            | 1.3               | 66       | 8.6      | 0.51     | 37      | 8.9             | LR                 | Bera/60 months |
| 11  | F   | 24        | P            | 0.63    | 46                  | 8.8             | 2.3               | 47       | 7.1      | 0.47     | 18      | 2.7             | LR                 | Bera/60 months |
| 12  | F   | 18        | P            | 0.56    | 64                  | 9.8             | 1.7               | 60       | 5.7      | 0.53     | 55      | 8.8             | LR                 | Bos/24 months |
| 13  | M   | 22        | P            | 0.48    | 61                  | 14              | 1.5               | 57       | 7        | 0.46     | 44      | 10.8            | LR                 | Bera/48 months |
| 14  | F   | 29        | P            | 0.49    | 49                  | 4.5             | 2.1               | 47       | 4.1      | 0.41     | 23      | 2.9             | LR                 | Sil/6 months |
| 15  | F   | 51        | P            | 0.71    | 30                  | 13              | 3.6               | 64       | 2.7      | 0.64     | 27      | 1.8             | LR                 | Sil/6 months |
| 16  | M   | 36        | P            | 0.49    | 34                  | 6.9             | 1.2               | 44       | 2.5      | 0.56     | 39      | 7.3             | LR                 | Sil/6 months |
| 17  | F   | 62        | P            | 0.6     | 49                  | 9               | 1.5               | 44       | 2.5      | 0.56     | 39      | 7.3             | LR                 | Sil/6 months |

CTR, cardio-thoracic ratio; mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; Qp/Qs, shunt ratio; P, patch; D, device; Bos, bosentan; Sil, sildenafil; Bera, beraprost; LR, left to right.
echocardiography was performed to confirm the shunt patency.

After ASD closure, the patients were classified into two groups based on a post-closure PVRI threshold of 3.0 Wood units*m$^2$, which is one criterion for pulmonary arterial hypertension in adults with shunt lesions. Pulmonary vasodilation treatment was indicated when the PH remained on echocardiography immediately after closure.

Statistics
All measurements are expressed as means±the standard deviations, ranges, or medians. The nonparametric Mann-Whitney test was used to compare patients with high post-closure PVRIs to the other patients. The nonparametric Wilcoxon signed rank test and Fisher’s exact test were used to quantify the differences after closure. To correlate the post-closure and pre-closure parameters, the nonparametric Spearman correlation coefficient, logistic regression analysis, and the Kruskal-Wallis test were used. $p<0.05$ was considered statistically significant, and the statistical analyses were performed with SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Pre-closure hemodynamic data
The patients’ primary data are summarized in Table 1. The median age at cardiac catheterization was 29 years (range, 18.0–62.0). The Qp/Qs was 1.9±0.6 (1.2–3.6). The mPAP was 49.9±11.5 (30.0–77.0), and the PVRI was 9.2±3.6 (1.3–16.7). Pulmonary vasodilator tests were performed in 15 patients. The mPAP and PVRI after the pulmonary vasodilator tests with decreased oxygen were 48.9±8.5 (34.0–66.0) and 5.89±1.99 (2.5–8.6) Wood units*m$^2$, respectively, and both of these changes were significant ($p=0.01$). The ratios of the mPAP and PVRI decreases after the oxygen tests i.e., the (resting mPAP or PVRI-mPAP or PVRI after oxygen)/(resting mPAP or PVRI) were 6.1±4.9 (-2.2–14.3)% and 39.1±15.9 (8.9–72.2)%), respectively. The decrease in PVRI with oxygen was greater than 20% in all but 2 patients. There were 3 patients with mild PH, 5 patients with moderate PH, and 9 patients with severe PH.

Pulmonary vasodilators were prescribed for 7 patients at

| FC I/II/III | Pre-closure | Post-closure | $p$ value |
|------------|-------------|--------------|-----------|
| FC I/II/III | 0/14/3      | 9/8/0        |           |
| mPAP (mm Hg) | 49.9±11.5   | 32.5±14.4    | 0.001     |
| PVRI (Wood units*m$^2$) | 9.2±3.6       | 6.3±3.8      | 0.004     |
| CT ratio   | 0.54±0.06   | 0.48±0.06    | 0.001     |

CT ratio, cardiothoracic ratio; mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index.

There was a significant decrease in mPAP, PVRI, and CT ratio after shunt closure.

Fig. 1. Changes in mPAP (A) and PVRI (B) of each patient. We observed significant decreases from baseline after the oxygen test and after closure. mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index.
least 1 month prior to catheterization. Bosentan was the most common vasodilator (5 patients), followed by sildenafil (two patients). Beraprost was administered to 2 patients exclusively with bosentan (Table 1).

**Partial closure with fenestration**
The median age at the time of the operation was 29 years. Fenestrations were made in the surgical patches in 15 patients and in the ASOs in 2 patients. The median fenestration size was 6.5 mm (5–10 mm).

**Post-closure hemodynamic data** (Table 2)
Eleven patients (64.7%) exhibited improved functional class after closure. The median time interval from ASD closure to follow-up was 27 months (range, 4.0–99.0). The CT ratio decreased significantly after ASD closure ($p<0.05$). Additionally, the mPAP and PVRI decreased significantly after closure in all but 1 patient ($p<0.05$) (Fig. 1). The fenestrations maintained left-to-right flow patency in 15 of the patients with surgical patches and in 1 patient with an ASO device. Only a single patient with a fenestration in an ASO device exhibited spontaneous closure of the fenestration on follow-up echocardiography. Moreover, the post closure PVRLs exhibited strong linear correlations with the pre-closure PVRLs and mPAPs (Spearman’s rho coefficients=0.785 and 0.764, respectively, $p<0.01$). There were significant differences in the post-closure PVRLs between the patients with pre-closure PVRLs ≤6, 6<PVRL≤9, and >9 (2.3±0.6 vs. 4.5±1.9 vs. 8.6±3.7 Wood units*m², respectively; $p=0.015$) (Fig. 2). The PVRLs after closure with fenestration were over 3.0 Wood units*m² in 11 patients (64.7%), and their pre-closure PVRL, mPAP with oxygen, and pre-closure Qp/Qs values were significantly different from those of the other patients (6.1±3.0 Wood units*m² vs. 10.9±2.7 Wood units*m², 42.8±5.5 mm Hg vs. 52.0±8.2 mm Hg, and 2.3±0.6 vs. 1.7±0.4, respectively) (Fig. 3). However, the age at the time of operation and the pre-closure mPAP were not significantly different ($p=0.056$ and 0.580, respectively) (Table 3). Logistic regression analysis failed to reveal any pre-closure parameters that predicted a post-closure PVRI >3.0.

**Post-closure functional capacity and pulmonary vasodilator therapy**
Pulmonary vasodilators were prescribed for 13 patients after partial closure. A greater number of patients with post closure PVRLs >3.0 were treated with a pulmonary vasodilator after partial closure, although this difference was not significant (91%

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**Fig. 2.** Differences in post-closure PVRLs for the patients with mild, moderate, and severe pre-closure PH. PVRL, pulmonary vascular resistance index; PH, pulmonary hypertension.

**Fig. 3.** Significant differences in pre-closure PVRL (A), Qp/Qs (B), and pre-closure mPAP with the oxygen test (C) according to post-closure PVRL (<3 or ≥3). mPAP, mean pulmonary arterial pressure; PVRL, pulmonary vascular resistance index; Qp/Qs, shunt ratio.
vs. 51%, \( p=0.099 \)). Sildenafil was the most common vasodilator, and bosentan was the next most common (Fig. 4).

### DISCUSSION

This study found that, although ASD closure with fenestration relieves symptoms, right ventricular pressure, and volume overload, 11 patients (64.7%) continued to exhibit a high PVRI value (>3). The pre-closure PVRI, mPAP with oxygen test, and Qp/Qs values of these patients differed significantly from those of the other patients.

Although recent guidelines suggest that Qp/Qs >1.5 and PVRI <5 Wood units*m\(^{-2}\) are the upper limits for ASD closure,\(^2\) shunt closure in patients with PH remains controversial. PH after shunt closure has been reported to be associated with a worse prognosis than PH with a shunt.\(^1\) However, several promising studies of pulmonary vasodilators have led to a shift in treatment. As pulmonary vasodilators may lead to better hemodynamic status, even in patients with congenital heart disease,\(^14-16\) more aggressive shunt closure can be expected. There are still no significant predictors of the immediate or long-term outcomes of ASD with PH. Postoperative pulmonary hypertensive crises in ASD patients with PH can be lethal. The placement of a small atrial shunt (i.e., a fenestration) could hopefully be a safe option to prevent this situation. This study concluded that ASD closure results in clinical improvement with no deterioration of PH after partial closure. This study indicates that it may be possible to normalize PH with the help of pulmonary vasodilators, although PH might persist and progress. There was no evidence that ASD closure with fenestration could prevent a pulmonary hypertensive crisis; nevertheless, the persistence of PH suggests the need for this procedure in the long term. Among the patients in this study, PH was considered reversible or was concomitant with severe ventricular diastolic dysfunction. The patients also exhibited PH with high PVRIs (>3.0) and Qp/Qs ratios (>1.5).

We performed vasodilator tests with 100% oxygen to evaluate reversibility and observed decreases in the PVRIs greater than 20% in all but 2 patients. The mPAPs decreased significantly after the oxygen test; however, these decreases were much less than 20% and attributed to increased pulmonary blood flow. PVRI is reflected in the evaluation of the reversibility of PH with a shunt.\(^4,17\) Despite inaccuracies in PVRIs that are calculated during oxygen testing, we chose oxygen as a vasodilator due to convenience. The inhaled nitric oxide (iNO) and/or the balloon occlusion tests were applied to a limited number of patients. Barst, et al.\(^17\) reported that the combination of iNO and \(O_2\) may be more effective than \(O_2\) alone in identifying responders. Additionally, the balloon occlusion test has been useful in decisions regarding shunt closure,\(^18\) although there are technical difficulties related to total occlusion in large ASDs. The operability of patients with ASD and PH is also controversial. Patient responsiveness to oxygen testing for PH with a shunt may serve as a rationale for ASD closure with fenestration. Based on our observations, the factor that was related to low pulmonary vascular resistance after closure was the degree of responsiveness but the absolute PAP with oxygen. We used pulmonary vasodilators prior to catheterization in 7 patients; however, regrettably, we did not perform catheterization before the administration of the pul-

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Table 3. Pre-Closure Patient Parameters According to Post Closure PVRI

| Parameter                          | PVRI<3 | PVRI≥3 | \( p \) value |
|------------------------------------|--------|--------|---------------|
| Number                             | 6      | 11     |               |
| Age at closure (yr)                | 25.7±14.6 | 28.3±14.7 | 0.580         |
| Pre-closure CT ratio               | 0.59±0.07 | 0.53±0.06 | 0.055         |
| Pre-closure mPAP (mm Hg)           | 44.0±8.0  | 54.9±11.1 | 0.056         |
| Pre-closure PVRI (Wood units*m\(^{-2}\)) | 6.1±2.7  | 11.0±2.5  | 0.007         |
| Pre-closure Qp/Qs                  | 2.4±0.6  | 1.6±0.4  | 0.049         |
| Pre-closure mPAP with \(O_2\) (mm Hg) | 41.7±5.6  | 51.3±8.7  | 0.048         |
| Pre-closure PVRI with \(O_2\) (Wood units*m\(^{-2}\)) | 4.4±2.1  | 6.0±2.0  | 0.173         |
| Decrease in mPAP after \(O_2\) (%)  | 5.6±5.7  | 6.4±4.8  | 0.713         |
| Decrease in PVRI after \(O_2\) (%)  | 31.2±18.6 | 43.0±13.8 | 0.270         |
| Pulmonary vasodilator              | 3 pts. (50%) | 10 pts. (90%) | 0.099         |

CT ratio, cardiothoracic ratio; mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; Qp/Qs, shunt ratio.

There were significant differences between groups in pre-closure PVRI, Qp/Qs, and pre-closure mPAP with the oxygen test.

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**Fig. 4.** Various selective pulmonary vasodilators after defect closure.
monary vasodilators. Previously, we initiated vasodilator therapy without catheterization in some situations. Therefore, the effects of the application of pulmonary vasodilators before closure on the hemodynamic data are not clear.

The size of the fenestration depends on the patient’s size, although it should be sufficiently large to prevent spontaneous closure but not large enough to cause volume loading. Generally, a 5–10 mm fenestration is acceptable in adult patients. A punch on the patch is useful because the size is accurate and persistent. In the patients in this study, all of the fenestrations were greater than 5 mm. A fenestrated ASO is another good option. Fenestrations can be performed with a dilator or another device, and these approaches are easy and popular; however, such fenestrations can also close naturally. The CT ratio on chest X-ray decreased significantly after ASD closure with fenestration; this finding indicates that the right ventricular volume load was alleviated. The follow-up hemodynamic data demonstrated a significant decrease in PAP in all but one patient, which also indicates that the right ventricular pressure overload was alleviated. These changes resulted in symptomatic improvement in our patients. However, 11 patients still had high PVRIs (≥3.0 Wood units*m²) despite decreased mean PAPs. We were unable to observe any predictive value of the pre-closure parameters in terms of the occurrence of high post-closure PVRI. Our analysis revealed that pre-closure PVRI, shunt amount, and mPAP with oxygen were significantly different between the two groups. The pre-closure CT ratio and mPAP also exhibited weakly significant differences. However, the patients’ ages and the degrees of change after the oxygen tests were not different. Yong, et al. reported that in most patients with ASD, PH can be alleviated after ASD closure and that the factors associated with a reduction in mPAP include age, defect size, and baseline mPAP. Moreover, although a lower baseline mPAP was found to be an independent factor associated with normalization, only 48.8% of the patients with moderate or severe PH in the study of Yong, et al. normalized in terms of PAP; this finding is similar to that of the present study. D’Alto, et al. observed that the baseline PVRI in patients with PH after shunt closure was 10.1±2.7 Wood units*m², which was also similar to our results (10.9±2.7 Wood units*m²). These authors also found that a PVRI ≥6 and a PVR/SVR ≥0.33 at baseline were common among patients with PH after shunt closure. There was one patient whose follow-up mPAP and PVRI were higher than the corresponding baseline values (No. 9), but we were unable to identify the risk for this patient. However, this patient was alive and exhibited no changes at the end of the follow-up.

We prefer PVRI to mPAP as an indicator of PH after ASD closure because the fenestrations were maintained in our patients. We observed normalizations of PVRI after ASD closure with fenestration in some patients with pre-closure PVRIs ≥6 Wood units*m². However, we found that a pre-closure PVRI ≥6 Wood units*m² carries a high risk of post-closure PH; therefore, fenestration might be a safe option for these patients. Vasodilator therapy was applied after closure. Three (50%) patients with post-closure PVRIs <3.0 Wood units*m² required vasodilator therapy, whereas one (10%) patient with a post-closure PVRI ≥3 did not require vasodilators. The role of vasodilators in patients with post-closure PVRIs ≥3.0 Wood units*m² is unclear. Therefore, ASD closure with fenestration might be a reasonable treatment for patients with PH due to the uncertainty and long-term course of post-closure PH.

There are several limitations of this study due to its retrospective nature and small population. We were unable to propose uniform indications for fenestrated closure in PH associated with ASD. We considered the mPAP and PVRI values from the hemodynamic evaluations, but other factors, such as age and ventricular function, were simultaneously considered. Although hemodynamic evaluation is more accurate than echocardiographic evaluation, Fick’s principle has its limits regarding pressure and resistance. Oxygen consumption could not be measured precisely, which may have confounded the oxygen test. The resistance ratio (Rp/Rs) might be a more reliable parameter, but this value was only acquired on limited occasions. The time delay between the shunt closure and the hemodynamic evaluation at follow-up was not uniform. Therefore, the time required for complete normalization could not be assessed and differed across cases. We were therefore unsure whether high PVRI values were persistent. We also liberally treated the patients with pulmonary vasodilators that might have influenced the hemodynamic statuses. The evaluation and interpretation of PH in congenital heart disease during treatment with pulmonary vasodilators are unclear. Our follow-up hemodynamic evaluation reflected not only the closure effects but also the medical effects of these vasodilators, and the latter have not been well studied.

In conclusion, although right ventricular pressure and volume overload were alleviated by ASD closure with fenestration in the patients with severe PH, the PVRIs of a significant portion of the patients did not normalize. There were no significant predictors of high post-closure PVRI; therefore, PH should be monitored even after the partial closure of ASDs.

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http://dx.doi.org/10.3349/ymj.2016.57.2.306