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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

# Feasibility of Treat and Repair Strategy in Congenital Heart Defects With Pulmonary Arterial Hypertension

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## ABSTRACT

**BACKGROUND** A treatment strategy for congenital heart defects with moderate to severe pulmonary arterial hypertension (PAH) has not been established.

**OBJECTIVES** The purpose of this study was to identify patients in whom a treat and repair strategy was considered and to examine pretreatment variables associated with successful defect repair.

**METHODS** Patients with atrial or ventricular septal defect and PAH (pulmonary vascular resistance [PVR] ≥ 5 Wood units) eligible for the treat and repair strategy were included. Hemodynamics among pretreatment, pre-repair, and post-defect repair were compared. Clinical outcomes in patients with or without defect repair were also compared. Clinical outcomes included all-cause death, hospitalization for worsening pulmonary hypertension, and lung transplantation.

**RESULTS** Among 25 eligible for the treat and repair strategy, 20 underwent successful repair (repaired group) and 5 did not have a repair (unrepaired group). In the repaired group, PVR significantly decreased from 9.6 ± 2.6 WU at pretreatment to 5.0 ± 3.4 pre-repair (ß coefficient −4.6 [95% CI: −5.9 to −3.3]). The pulmonary to systemic blood flow ratio (Qp/Qs) increased from 1.5 ± 0.6 at pretreatment to 2.4 ± 1.3 pre-repair (ß coefficient 0.9 [95% CI: 0.4-1.38]). In the unrepaired group, pretreatment PVR decreased with treatment; however, PVR remained elevated. Qp/Qs did not change between pretreatment and post-treatment. The repaired group had a better prognosis than the unrepaired group (HR 0.092 [95% CI: 0.009-0.905]). Pretreatment mean pulmonary artery pressure, PVR, Qp/Qs, and arterial oxygen saturations were associated with undergoing defect repair.

**CONCLUSIONS** In this small cohort, a treat and repair strategy was successfully used in a significant proportion of the patients with congenital heart defects with moderate to severe PAH. (JACC Adv 2024;3:100887) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**ACC** = American College of Cardiology

**AHA** = American Heart Association

**ASD** = atrial septal defect

**ERA** = endothelin receptor antagonist

**ESC** = European Society of Cardiology

**PAH** = pulmonary arterial hypertension

**PAP** = pulmonary artery pressure

**PDE5i** = phosphodiesterase 5 inhibitor

**PVR** = pulmonary vascular resistance

**Qp/Qs** = pulmonary to systemic blood flow ratio

**Rp/Rs** = PVR systemic vascular resistance ratio

**$SaO_2$** = saturation of arterial oxygen

**VSD** = ventricular septal defect

Pulmonary arterial hypertension (PAH) is characterized by a remarkable elevation in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Recently, PAH-targeted drugs, such as endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE5is), soluble guanylate cyclase stimulators, and prostacyclins, have become available for treating PAH. Although these drugs are effective, the prognosis of PAH is less favorable if the diagnosis of PAH and initiation of PAH-targeted drugs are delayed.

Congenital heart defects, such as atrial septal defect (ASD) and ventricular septal defect (VSD), can be associated with PAH. PAH associated with congenital heart defects is classified as: 1) Eisenmenger syndrome; 2) PAH associated with a prevalent systemic-to-pulmonary shunt; 3) PAH with small/coincidental defects; and 4) PAH after defect correction.[1] There is no indication for cardiac surgery or catheter defect closure in Eisenmenger syndrome and PAH with small/coincidental defects. In these conditions, treatment with PAH-targeted drugs is recommended. In PAH with systemic-to-pulmonary shunts, cardiac defect repair should be considered when PAH is mild. However, when PAH is moderate to severe, cardiac defect repair is not recommended.

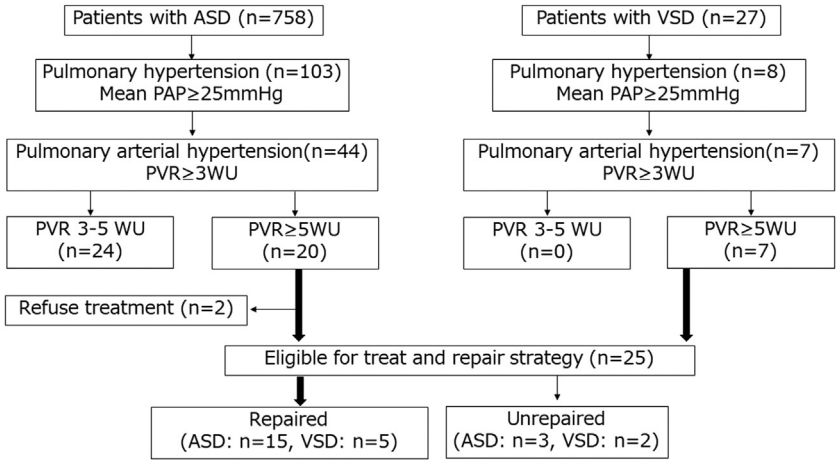
The "treat and repair" strategy has been attempted in patients with congenital heart defects with moderate to severe PAH. This approach involves initial "treatment" with PAH-targeted drugs used to improve PAH followed by a surgical or interventional "repair" of the cardiac defect. A few studies and case reports have shown that the treat and repair strategy is effective for moderate to severe PAH associated with ASD[2-4] and VSD.[5] However, no studies have described treat and repair hemodynamics or examined the predictors of a successful treat and repair strategy. Therefore, this study aimed: 1) to describe the cardiac hemodynamic changes in patients with moderate to severe PAH who did or did not undergo cardiac defect repair using a treat and repair approach; and 2) to examine potential pretreatment variables associated with undergoing cardiac defect repair using a treat and repair approach.

## METHODS

**STUDY DESIGN.** This study conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the Institutional Review Board and ethics committee of Okayama University (no. 2210-019). The requirement for informed consent was waived because of the low-risk nature of this retrospective study and the inability to obtain consent directly from all subjects. However, we extensively announced the study protocol at Okayama University Hospital, and provided patients with the opportunity to withdraw from the study.

**PATIENTS.** From January 2000 to December 2022, 758 consecutive adult patients with ASD and 27 with VSD were admitted to our hospital. All patients underwent chest radiography, electrocardiography, echocardiography, a blood examination, and right heart catheterization at pretreatment. Pulmonary hypertension was defined as a mean PAP of ≥25 mm Hg. PAH was defined as a mean PAP of ≥25 mm Hg, pulmonary artery wedge pressure (PAWP) of ≤15 mm Hg, and PVR of ≥3 WU at right heart catheterization. A flow diagram of this study is shown in Figure 1. Pulmonary hypertension was diagnosed in 103 patients with ASD and in 8 patients with VSD. PAH was diagnosed in 44 patients with ASD and in 7 patients with VSD. Patients with PVR ≥5 WU were candidates for treat and repair strategy (n = 27). We observed 2 patients with ASD because they rejected treatment. We initiated treatment with PAH-targeted drugs in 18 patients with ASD and in 7 patients with VSD. Information on age, sex, World Health Organization functional class, brain natriuretic peptide concentrations, 6-minute walk distance, PAH-targeted drugs, echocardiographic parameters, and hemodynamics were obtained from medical records. Echocardiography was used to evaluate the left ventricular ejection fraction, tricuspid regurgitation pressure gradient, tricuspid annular plane systolic excursion, and defect size of ASD and VSD. Hemodynamics included heart rate, systemic blood pressure (sBP), PAWP, PAP, PVR, systemic vascular resistance, the PVR systemic vascular resistance ratio (Rp/Rs), the pulmonary to systemic blood flow ratio (Qp/Qs), and saturation of arterial oxygen ($SaO_2$). Oxygen consumption was estimated by LaFarge formula (male: [138.1-11.49 × log age {years} + 0.378 × heart rate {beats/min}] × body surface area [$m^2$], female: [138.1-17.04 × log age {years} + 0.378 × heart rate {beats/min}] × body surface area [$m^2$]). Arterial oxygen content was calculated by (saturation [%] × 1.36 × hemoglobin [g/L]) without oxygen administration or was calculated by (saturation [%] × 1.36 × hemoglobin [g/L]) + (0.0031 × $PaO_2$ [mm Hg]) with oxygen administration. We obtained the blood samples from superior vena cava, inferior vena cava, right atrium, right ventricle,

**FIGURE 1** Study Flow Diagram




ASD = atrial septal defect; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; VSD = ventricular septal defect.

pulmonary artery, pulmonary vein (in case of ASD), pulmonary wedge (in case of VSD), and aorta.

**MEDICAL TREATMENT FOR PAH.** In Japan, intravenous epoprostenol and beraprost were available from 1999, bosentan from 2005, sildenafil from 2008, tadalafil from 2009, ambrisentan from 2011, subcutaneous/intravenous treprostinil from 2014, riociguat from 2014, and macitentan from 2015. The choice of PAH-targeted drugs was determined by a cardiologist who specialized in pulmonary hypertension and used what was available at the time. Until multiple oral PAH-targeted drugs became available, treatment was typically with monotherapy with beraprost or intravenous epoprostenol. Once multiple oral PAH-targeted drugs were available, treatment was with dual therapy with oral PAH-targeted drugs in ASD and monotherapy with oral PAH-targeted drugs in VSD. If patients did not meet the criteria of cardiac defect repair despite initial treatment, patients had sequential addition of oral PAH-targeted drugs or intravenous/subcutaneous prostanoids. Right heart catheterization was performed before administering PAH-targeted drugs (pretreatment), after administering PAH-targeted drugs (pre-repair of ASD or VSD), and after closing the cardiac defect (post-repair of ASD or VSD).

**DECISION OF CARDIAC DEFECT REPAIR OR UNREPAIR AFTER PAH TREATMENT.** The decision of ASD or VSD repair was made based on the hemodynamics after treatment with PAH-targeted drugs. Decisions were made by a multidisciplinary team with cardiologists and cardiac surgeon. Patients who had PVR <6 WU, a Qp/Qs >1.3, and $SaO_2$ ≥90% after PAH-targeted treatment were decided to perform cardiac defect repair. If the Qp/Qs was >1.3 and $SaO_2$ was ≥90%, but PVR was ≥6 WU, we performed an acute pulmonary vasoreactivity test with the breathing 100% oxygen for 10 minutes. If a considerable response defined as a decrease in PVR of >20% was obtained, the patients were decided to perform cardiac defect repair. Based on the above definition, cardiac defect repair was performed in 20 patients who fulfilled the criterion (repaired group). Five patients who did not meet the above criteria despite PAH treatment did not undergo cardiac defect repair (unrepaired group). Larger size ASDs were repaired with surgical closure. An ASD that was not large was repaired by transcatheter closure. VSDs were repaired with surgical closure.

**OUTCOMES.** The primary outcome of this study was all-cause death. We also investigated fatal and nonfatal adverse events: all-cause death, hospitalization for worsening pulmonary hypertension, and lung transplantation as secondary outcome. Worsening pulmonary hypertension was defined as elevation of brain natriuretic peptide concentrations, elevation of the tricuspid regurgitation pressure gradient, and symptoms of right heart failure.

**STATISTICAL ANALYSIS.** Baseline characteristics were compared between the repaired and unrepaired groups. Continuous variables were summarized as the mean ± SD or median (IQR) compared using Student's *t*-test for normally distributed data and the

**TABLE 1 Baseline Characteristics (Pretreatment)**

| | Repaired (n = 20) | Unrepaired (n = 5) | *P* Value |
|---|---|---|---|
| Age, y | 41 ± 17 | 30 ± 23 | 0.17 |
| Male | 3 (15) | 2 (40) | 0.25 |
| Type of congenital heart defect | | | |
| ASD | 15 (75) | 3 (60) | 0.60 |
| VSD | 5 (25) | 2(40) | 0.60 |
| WHO functional class | | | |
| II | 16 (80) | 2 (40) | 0.11 |
| III | 4 (20) | 2 (40) | 0.56 |
| IV | 0 | 1 (20) | 0.20 |
| BNP, pg/mL | 93 (31-114) | 96 (75-192) | 0.59 |
| 6MWD, m | 323 ± 114 | 472 ± 215 | 0.57 |
| Echocardiography | | | |
| LVEF, % | 72 ± 11 | 68 ± 6 | 0.54 |
| TRPG, mm Hg | 85 ± 29 | 83 ± 30 | 1.00 |
| TAPSE, mm | 20 ± 5 | NA | NA |
| ASD size, mm | 18 ± 5 | 13 ± 2 | 0.07 |
| VSD size, mm | 22 ± 6 | 19 ± 1 | 0.54 |
| Hemodynamics | | | |
| mPAP, mm Hg | 53 ± 13 | 75 ± 13 | 0.01 |
| PVR, WU | 9.6 ± 2.6 | 24 ± 8 | 0.02 |
| Rp/Rs | 0.5 ± 0.2 | 1.2 ± 0.5 | <0.01 |
| Qp/Qs | 1.5 ± 0.6 | 0.8 ± 0.2 | 0.08 |
| $SaO_2$, % | 95 ± 4 | 86 ± 4 | <0.01 |

Values are mean ± SD, n (%), or median (IQR).

6MWD = 6-minute walk distance; ASD = atrial septal defect; BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; Qp/Qs = pulmonary to systemic blood flow ratio; Rp/Rs = PVR systemic vascular resistance ratio; $SaO_2$ = saturation of arterial oxygen; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid regurgitation pressure gradient; VSD = ventricular septal defect; WHO = World Health Organization.

Mann-Whitney *U* test for non-normally distributed data; categorical variables were described as counts with proportions compared using Fisher exact test.

To evaluate the effect of PAH-targeted drugs and defect repair in the repaired group, we assessed the change of hemodynamic parameters (HR, systolic pulmonary artery pressure, mean pulmonary artery pressure, PAWP, sBP, PVR, systemic vascular resistance, Rp/Rs, systolic pulmonary artery pressure/sBP, Qp/Qs, and $SaO_2$) among pretreatment, pre-repair, and after repair using mixed effect linear regression models with a compound symmetry correlation matrix taking into account within-patient correlation of each measure (a random intercept model with fixed effects for explanatory variables and random intercepts for patients, as a longitudinal analysis). For this analysis, we modeled with linear spline terms (single knot at pre-repair) to assess the effect of PAH-targeted drugs alone and both drugs and defect repair separately. The same analytic approach was applied in unrepaired group to assess the change of hemodynamic parameters between pretreatment and post-treatment. We further conducted the same analysis in subgroups (ASD and VSD).

The 20-year cumulative incidence of all-cause death and fatal/nonfatal adverse events were examined using Kaplan-Meier curves. The cumulative incidence between repaired and unrepaired groups was compared by log-rank test. Cox proportional hazards regression models were used to estimate HR and 95% CI of cardiac defect compared with the unrepaired group as a reference.

Finally, to explore pretreatment variables associated with undergoing defect repair using a treat and repair strategy (ie, cardiac defect repair after PH treatment), univariable logistic regression models were created and pretreatment variables were examined (age, defect type [VSD vs ASD], World Health Organization functional class [III/IV vs II], heart rate, mean PAP, PVR, Qp/Qs, $SaO_2$, and brain natriuretic peptide). The decision of whether variables were included in models was based on previous literature.[6] Each model assumption is described in the Supplemental Methods. Two-sided $P < 0.05$ were considered statistically significant. Since this study was an exploratory analysis, no alpha adjustment was made to control for type 1 errors. All statistical analyses were performed using SPSS version 25.0 (IBM Corp) and R 4.1.2 version (The R Foundation for Statistical Computing).

## RESULTS

**BASELINE CHARACTERISTICS.** Characteristics at pretreatment are shown in Table 1. There were no significant differences in age, brain natriuretic peptide concentrations, 6-minute walk distance, and parameters obtained on echocardiography between the groups. Mean PAP and PVR were significantly lower in the repaired group than in the unrepaired group. $SaO_2$ was significantly higher in the repaired group than in the unrepaired group.

**PAH-TARGETED DRUGS AT PRE-REPAIR AND POST-REPAIR/FINAL FOLLOW-UP.** Details of PAH-targeted drugs at pre-repair and post-repair/final follow-up are shown in Table 2. In the repaired group, ERAs (average dosages: bosentan, 188 mg/day; ambrisentan, 7.5 mg/day; macitentan, 10 mg/day) were used in 19 patients, PDE5is (average dosages: sildenafil, 58 mg/day; tadalafil, 33 mg/day) were used in 16 patients, and prostacyclins (average dosages: beraprost, 260 μg/day; selexipag, 1.2 mg/day; epoprostenol, 60 ng/kg/min; treprostinil, 62 ng/kg/min) was used in 13 patients at pre-repair. There were 3 patients who received monotherapy, 6 had dual combination therapy, and 6 had triple combination

therapy. Six patients required triple combination therapy including intravenous or subcutaneous prostacyclin, all of whom had PVR of more than 10 WU at pretreatment. At post-repair, ERAs (average dosages: bosentan, 198 mg/day; ambrisentan, 7.5 mg/day; macitentan, 10 mg/day) were used in 20 patients, PDE5is (average dosages: sildenafil, 60 mg/day; tadalafil, 34 mg/day) were used in 15 patients, and prostacyclins (average dosages: beraprost, 288 μg/day, epoprostenol, 73 ng/kg/min; treprostinil, 77 ng/kg/min) was used in 10 patients. There were 1 patient on monotherapy, 10 on dual combination therapy, and 9 on triple combination therapy. In the unrepaired group, ERAs (average dosages: bosentan, 219 mg/day; macitentan 10 mg/day) were used in 5 patients, PDE5is (average dosages: sildenafil, 50 mg/day; tadalafil, 40 mg/day) were used in 3 patients, and prostacyclins (average dosages: beraprost, 240 μg/day; selexipag, 3.2 mg/day; epoprostenol, 97 ng/kg/min) was used in 5 patients at the final follow-up. There were 2 on dual combination therapy and 3 on triple combination therapy. There was no significant difference in the median duration from pre-repair to post-repair or the final follow-up between the repaired and unrepaired groups.

**TABLE 2** Treatment Pre-Repair, Post-Repair, and at the Time of Final Follow-Up

| | Repaired, n = 20 | | Unrepaired, n = 5 |
|---|---|---|---|
| | Pre-Repair | Post-Repair | Post-Treatment |
| Type of PAH-targeted drugs | | | |
| ERAs | 19 (95) | 20 (100) | 5 (100) |
| Bosentan | 7 (35) | 6 (30) | 4 (80) |
| Ambrisentan | 6 (30) | 5 (25) | 0 (0) |
| Macitentan | 6 (30) | 9 (45) | 1 (20) |
| PDE5is | 16 (80) | 15 (75) | 3 (60) |
| Sildenafil | 8 (40) | 5 (25) | 1 (20) |
| Tadalafil | 8 (40) | 10 (50) | 2 (40) |
| Riociguat | 0 (0) | 3 (15) | 0 (0) |
| Prostacyclins | 13 (65) | 10 (50) | 5 (100) |
| Beraprost | 6 (30) | 5 (25) | 2 (40) |
| Selexipag | 1 (5) | 0 (0) | 1 (20) |
| Epoprostenol/treprostinil | 6 (30) | 5 (25) | 2 (40) |
| Combination of PAH-targeted drugs | | | |
| Monotherapy | 3 (15) | 1 (5) | 0 (0) |
| Dual combination therapy | 6 (30) | 10 (50) | 2 (40) |
| Triple combination therapy | 11 (55) | 9 (45) | 3 (60) |

Values are n (%). Duration (days) from treatment to pre-repair: 428 (IQR: 175-1,231); from pre-repair to post-repair, 552 (IQR: 290-1,220); and, from treatment to post-repair/final follow-up, 1,021 (IQR: 742-1,699)/569 (IQR: 358-875). There was no significant difference of duration from treatment to post-repair/final follow-up between the repair and unrepair groups (Mann–Whitney *U* test for $P = 0.11$).

ERAs = endothelin receptor antagonists; PAH = pulmonary arterial hypertension; PDE5is = phosphodiesterase 5 inhibitors.

**HEMODYNAMIC CHANGES WITH THE TREAT AND REPAIR STRATEGY.** Hemodynamic parameters by right heart catheterization in the repaired group are shown in **Table 3** and Supplemental Figure 1. Mean PAP was significantly decreased at pre-repair compared with that at pretreatment (ß coefficient = −10.7 [95% CI: −19.11 to −2.29]), with a further reduction at post-repair (ß coefficient = −14.42 [95% CI: −22.96 to −5.88]). PVR was significantly decreased at pre-repair compared with that at pretreatment (ß coefficient = −4.6 [95% CI: −5.9 to −3.3]). The reduction in PVR continued at post-repair. The Qp/Qs was significantly increased at pre-repair compared with that at pretreatment (ß coefficient = 0.9 [95% CI: 0.4-1.38]). At post-repair, the Qp/Qs was significantly decreased compared with that at pre-repair (ß coefficient = −1.4 [95% CI: −1.9 to −0.91]). Heart rate, sBP, PAWP, and $SaO_2$ were not significantly changed among pretreatment, pre-repair, and post-repair. Additional follow-up results suggested no patients with worsening hemodynamic status after cardiac defect repair (Supplemental Table 1).

Similarly, in the unrepaired group, PVR significantly decreased from pretreatment to post-treatment (ß coefficient = −9.4 [95% CI: −14.78 to−4.02]). However, a high PVR persisted after treatment of PAH-targeted drugs. Heart rate, sBP, mean PAP, Qp/Qs, and $SaO_2$ were not significantly changed before and after treatment of PAH-targeted drugs (**Table 4**).

Stratified analysis results showed that mean PAP and PVR was significantly decreased at pre-repair compared with that at pretreatment in patients with ASD (**Table 5**). For Qp/Qs, significant increase was seen between pretreatment and pre-repair, while significant decline by defect repair was observed at post-repair compared with pre-repair. Conversely, in patients with VSD, mean PAP and PVR did not significantly decrease at pre-repair compared with that at pretreatment (**Table 6**). However, PVR at pre-repair decreased from 9.0 WU to 4.9 WU after the acute vasoreactivity test with oxygen (46% reduction in PVR). Mean PAP was significantly decreased at post-repair compared with those at pre-repair.

**SIDE EFFECTS OF PAH-TARGETED DRUGS AND COMPLICATIONS OF CARDIAC DEFECT REPAIR.** Side effects associated with PAH-targeted drugs, such as headache, flushing, nausea, diarrhea, and pain in the extremities, were observed in almost all patients. However, none of the patients discontinued PAH-targeted drugs before the cardiac defect repair. ASD was repaired by transcatheter closure without fenestrated device in 14 patients and by surgical closure with fenestrated patch in 1 patient. VSD was repaired by surgical closure in all patients. A case of VSD was

**TABLE 3 Right Heart Catheterization Hemodynamics Pretreatment, Pre-Repair, and Post-Repair in the Repaired Group (n = 20)**

| | | | | ß Coefficient (95% CI) | |
|---|---|---|---|---|---|
| | Pretreatment | Pre-Repair | Post-Repair | Pretreatment and Pre-repair (PAH Treatment Before Repair) | Pre- and post-Repair (PAH Treatment and Defect Repair) |
| HR, beats/min | 80 ± 12 | 74 ± 11 | 73 ± 14 | −5.61 (−11.91 to 0.69) | −1.55 (−7.85 to 4.75) |
| sPAP, mm Hg | 85 ± 22 | 68 ± 31 | 43 ± 17 | −16.15 (−29.3 to −3) | −26.03 (−39.39 to −12.67) |
| mPAP, mm Hg | 53 ± 13 | 43 ± 20 | 29 ± 12 | −10.7 (−19.11 to −2.29) | −14.42 (−22.96 to −5.88) |
| mRAP, mm Hg | 6.1 ± 3.6 | 5.2 ± 3.1 | 3.5 ± 2.3 | −0.86 (−2.74 to 1.01) | −1.73 (−3.57 to 0.11) |
| PAWP, mm Hg | 8 ± 4 | 8 ± 4 | 7 ± 3 | −0.49 (−2.73 to 1.75) | −0.61 (−2.82 to 1.6) |
| sBP, mm Hg | 108 ± 13 | 106 ± 22 | 105 ± 14 | −0.88 (−10.44 to 8.68) | −1.36 (−11.11 to 8.39) |
| PVR, WU | 9.6 ± 2.6 | 5.0 ± 3.4 | 4.8 ± 2.2 | −4.62 (−5.93 to −3.32) | −0.34 (−1.68 to 0.99) |
| SVR, WU | 24 ± 9 | 19 ± 9 | 18 ± 6 | −5.68 (−9.92 to −1.44) | −1.05 (−5.29 to 3.19) |
| Rp/Rs | 0.5 ± 0.2 | 0.3 ± 0.1 | 0.3 ± 0.1 | −0.2 (−0.27 to −0.13) | 0.02 (−0.05 to 0.1) |
| sPAP/sBP | 0.8 ± 0.2 | 0.6 ± 0.2 | 0.4 ± 0.2 | −0.16 (−0.26 to −0.05) | −0.22 (−0.33 to −0.11) |
| Qp/Qs | 1.5 ± 0.6 | 2.4 ± 1.3 | 1.0 ± 0.1 | 0.89 (0.4-1.38) | −1.4 (−1.9 to −0.91) |
| $SaO_2$, % | 95 ± 4 | 96 ± 2 | 97 ± 2 | 1.06 (−0.56 to 2.68) | 1.34 (−0.33 to 3.02) |

Values are mean ± SD. β coefficient was estimated by a mixed effect linear regression model (a random intercept model with fixed effects for explanatory variables and random intercepts for patients). To assess the treatment effect of PAH treatment before repair (treat) and PAH treatment and repair (treat and repair) separately, a model with linear spline terms (single knot at pre-repair when the timing of just before cardiac defect repair) was applied. Median follow-up duration: from diagnosis to PAH treatment, 16 (IQR: 4-37) days; and from PAH treatment to post-repair, 1,021 (IQR: 742-1,699) days.

HR = heart rate; mRAP = mean right atrial pressure; PAWP = pulmonary artery wedge pressure; sBP = systemic blood pressure; sPAP = systolic pulmonary artery pressure; SVR = systemic vascular resistance; and other abbreviations as in Table 1.

repaired with a patch and a flap valve. Two cases with VSD were repaired with a patch and creation of small atrial septal fenestration. A pulmonary hypertension crisis did not occur just after ASD and VSD closure.

**SURVIVAL ANALYSIS AND PRETREATMENT VARIABLES RELATED TO CARDIAC DEFECT REPAIR.** There was no death or lung transplantation in the repaired group. One patient was hospitalized for worsening pulmonary hypertension caused by catheter-related infection. In the unrepaired group, 2 patients died because of worsening pulmonary hypertension and 1 patient received lung transplantation (Supplemental Table 2). Lower mortality was observed in the repaired group compared to the unrepaired group (0% vs 40%). Figure 2A shows the 20-year cumulative incidence of all-cause death between repaired and unrepaired groups (median follow-up, 8.5 years vs 7.9 years). All-cause death did not occur until 8 years after the administration of PAH-targeted drugs in the repaired and unrepaired groups. However, after 8 years, the cumulative incidence curve in the unrepaired group showed a steep increase, while no patient died in the repaired group (log-rank test, $P = 0.02$). In the cumulative incidence of fatal and nonfatal adverse events (all-cause death, lung transplantation, and hospitalization for worsening pulmonary hypertension), the repaired group showed significantly better prognosis compared with unrepaired group (median follow-up, 8.9 years vs 13.5 years; HR 0.092 [95% CI: 0.009-0.905], $P = 0.04$).

An exploratory analysis for pretreatment variables and defect repair showed a possible association between mean PAP, PVR, Qp/Qs, and $SaO_2$ and cardiac defect repair using a treat and repair strategy (Table 7).

**TABLE 4 Right Heart Catheterization Hemodynamics Pretreatment and Post-Treatment in the Unrepaired Group (n = 5)**

| | Pretreatment | Post-Treatment | ß Coefficient (95% CI) |
|---|---|---|---|
| HR, beats/min | 93 ± 11 | 93 ± 16 | −0.58 (−8.38 to 7.22) |
| sPAP, mm Hg | 111 ± 20 | 108 ± 20 | −2.8 (−15.11 to 9.51) |
| mPAP, mm Hg | 75 ± 13 | 72 ± 15 | −1.8 (−8.07 to 4.47) |
| mRAP, mm Hg | 3.8 ± 2.3 | 6.8 ± 3.3 | 3 (1.76-4.24) |
| PAWP, mm Hg | 10.2 ± 6.2 | 11 ± 6.3 | 0.8 (−7.43 to 9.03) |
| sBP, mm Hg | 104 ± 6 | 103 ± 14 | 0.25 (−10.06 to 10.55) |
| PVR, WU | 27 ± 6 | 18 ± 4 | −9.4 (−14.78 to −4.02) |
| SVR, WU | 22 ± 6 | 24 ± 6 | 2.03 (−5.95 to 10) |
| Rp/Rs | 1.2 ± 0.54 | 0.8 ± 0.32 | −0.48 (−0.87 to 0.08) |
| sPAP/sBP | 1.1 ± 0.2 | 1.1 ± 0.2 | −0.07 (−0.16 to 0.03) |
| Qp/Qs | 0.8 ± 0.2 | 1.0 ± 0.7 | 0.18 (−0.45 to 0.81) |
| $SaO_2$, % | 86 ± 4 | 87 ± 5 | 0.76 (−4.8 to 6.32) |

Values are mean ± SD. β coefficient was estimated by a mixed effect linear regression model (a random intercept model with fixed effects for explanatory variables and random intercepts for patients). Median follow-up duration: from diagnosis to PAH treatment, 5 (IQR: 1-9) days; and from PAH treatment to post-repair, 569 (IQR: 358-875) days.

Abbreviations as in Tables 1 to 3.

## DISCUSSION

We investigated the feasibility, efficacy, and safety of the treat and repair strategy in ASD and VSD with

**TABLE 5** Right Heart Catheterization Hemodynamics in Patients With Atrial Septal Defects (n = 18)

| | | | | ß Coefficient (95% CI) | |
|---|---|---|---|---|---|
| | Pretreatment | Pre-Repair | Post-Repair | Pretreatment and Pre-Repair (PAH Treatment Before Repair) | Pre- and Post-Repair (PAH Treatment and Defect Repair) |
| HR, beats/min | 81 ± 11 | 72 ± 9 | 74 ± 14 | −8.09 (−15.33 to −0.84) | 2.13 (−5.11 to 9.37) |
| sPAP, mm Hg | 78 ± 21 | 55 ± 18 | 42 ± 19 | −22.8 (−36.08 to −9.52) | −13.28 (−26.82 to 0.27) |
| mPAP, mm Hg | 49 ± 12 | 35 ± 12 | 28 ± 13 | −14.6 (−21.96 to −7.24) | −6.84 (−14.37 to 0.68) |
| mRAP, mm Hg | 5.3 ± 3.9 | 5.0 ± 3.4 | 2.6 ± 1.6 | −0.32 (−2.7 to 2.06) | −2.43 (−4.76 to −0.1) |
| PAWP, mm Hg | 6.6 ± 3.0 | 7.2 ± 4.1 | 6.6 ± 3.0 | 0.63 (−1.95 to 3.21) | −0.63 (−3.21 to 1.95) |
| sBP, mm Hg | 106 ± 14 | 104 ± 18 | 109 ± 12 | −1.54 (−10.94 to 7.85) | 6.27 (−3.41 to 15.96) |
| PVR, WU | 9.5 ± 2.9 | 3.7 ± 1.9 | 4.6 ± 2.2 | −5.87 (−7.07 to −4.67) | 0.78 (−0.45 to 2.01) |
| SVR, WU | 23 ± 11 | 17 ± 8 | 18 ± 7 | −6.68 (−11.83 to −1.53) | 1.18 (−4.15 to 6.51) |
| Rp/Rs | 0.5 ± 0.2 | 0.2 ± 0.1 | 0.3 ± 0.2 | −0.26 (−0.34 to −0.18) | 0.05 (−0.04 to 0.13) |
| sPAP/sBP | 0.8 ± 0.2 | 0.6 ± 0.2 | 0.4 ± 0.2 | −0.22 (−0.34 to −0.1) | −0.13 (−0.26 to −0.01) |
| Qp/Qs | 1.4 ± 0.6 | 2.5 ± 1.5 | 1.0 ± 0.1 | 1.07 (0.44-1.69) | −1.5 (−2.14 to −0.87) |
| $SaO_2$, % | 95 ± 4 | 97 ± 2 | 97 ± 2 | 1.23 (−0.57 to 3.03) | 0.54 (−1.35 to 2.43) |

Values are mean ± SD. β coefficient was estimated by a mixed effect linear regression model (a random intercept model with fixed effects for explanatory variables and random intercepts for patients). To assess the treatment effect of PAH treatment before repair (treat) and PAH treatment and repair (treat and repair) separately, a model with linear spline terms (single knot at pre-repair when the timing of just before cardiac defect repair) was applied. Median follow-up duration: from diagnosis to PAH treatment, 15 (IQR: 3-27) days; and from PAH treatment to post-repair, 1,085 (IQR: 623-2,988) days.

Abbreviations are as in Tables 1 and 3.

moderate to severe PAH (Central Illustration). In the repaired group, PAH-targeted drugs significantly reduced PAP and PVR and increased the Qp/Qs, subsequently allowing closure of ASD and VSD without severe complications. This resulted in further improvement in PAH. Furthermore, the repaired group had a better prognosis than the unrepaired group. Baseline variables (pretreatment) associated with undergoing cardiac defect repair included mean PAP, PVR, Qp/Qs, and $SaO_2$. This study suggests that the treat and repair strategy is a reasonable therapeutic strategy in select patients with moderate to severe PAH associated with ASD and VSD who have a good response to PAH-targeted drugs.

Some studies have reported the efficacy of treat and repair strategy in ASD-PAH.[2-4] The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of ASD stated that cardiac defect repair should be considered in a Qp/Qs ≥1.5 and symptoms of right ventricular overload, no cyanosis, and a systolic PAP/sBP <50% and/or Rp/Rs <1/3.[7] The 2020 European Society of Cardiology (ESC) guidelines for the management of adult congenital heart diseases stated that the management of ASD-PAH.[8] The guidelines stated that in patients with ASD and PAH who had PVR <5 WU and a Qp/Qs >1.5, ASD closure should be considered. If PVR falls to <5 WU after PAH-targeted drugs and the Qp/Qs is >1.5, fenestrated closure may be considered. In the present study, 10 patients had met the ACC/AHA or ESC criteria of cardiac defect repair, but 5 patients did not meet these criteria (Supplemental Table 3). We repaired the ASD without pulmonary hypertension crisis or other complications. Although our method of closure differed from the guideline,[9] the criteria used for ASD closure in the present study had reasonable results.

There have been few studies and reports on the treat and repair strategy for VSD-PAH.[5,10] The 2018 ACC/AHA guidelines for managing VSD stated that cardiac defect repair may be considered in a Qp/Qs ≥1.5 and Rp/Rs <1/3 or systolic PAP/sBP <50% in VSD-PAH.[7] The 2020 ESC guidelines for the management of adult congenital heart diseases also have recommendations for the management of VSD-PAH.[8] In those guidelines, it is recommended that in patients with PAH with VSD who had PVR <5 WU and a Qp/Qs >1.5, VSD closure should be considered. In patients with PVR ≥5 WU, VSD closure may be considered if the Qp/Qs is >1.5, but a careful individual decision in an expert center is required. In the guidelines, the treat and repair strategy is not recommended for severe VSD-PAH. In the present study, PAH-targeted drugs increased the Qp/Qs to 2.1, but high PVR continued at pre-repair. However, PVR decreased to 4.9 WU after the acute vasoreactivity test with oxygen (46% reduction in PVR). We speculate that VSD closure was possible based on the acute vasoreactivity test results, and pulmonary hypertension crisis did not occur in the perioperative period. Even if PVR remains high after treatment of PAH-targeted drugs, VSD closure may be possible if there is a good response to the acute vasoreactivity test.

**TABLE 6 Right Heart Catheterization Hemodynamics in Patients With Ventricular Septal Defects (n = 7)**

| | | | | ß Coefficient (95% CI) | |
|---|---|---|---|---|---|
| | Pretreatment | Pre-Repair | Post-Repair | Pretreatment and Pre-Repair (PAH Treatment Before Repair) | Pre- and Post-Repair (PAH Treatment and Defect Repair) |
| HR, beats/min | 79 ± 15 | 80 ± 16 | 68 ± 12 | 1.4 (−9.87 to 12.67) | −12.2 (−23.47 to −0.93) |
| sPAP, mm Hg | 103 ± 12 | 107 ± 30 | 44 ± 12 | 3.8 (−19.98 to 27.58) | −62.8 (−86.58 to −39.02) |
| mPAP, mm Hg | 68 ± 6 | 66 ± 23 | 29 ± 9 | 1 (−19.99 to 21.99) | −36.8 (−57.79 to −15.81) |
| mRAP, mm Hg | 9 ± 2 | 6 ± 1 | 6 ± 2 | −2.2 (−4.43 to 0.03) | 0.2 (−2.03 to 2.43) |
| PAWP, mm Hg | 13 ± 3 | 9 ± 3 | 8 ± 2 | −4.45 (−7.71 to −1.19) | −0.6 (−3.63 to 2.43) |
| sBP, mm Hg | 112 ± 9 | 115 ± 30 | 96 ± 15 | 2.6 (−17.98 to 23.18) | −19.2 (−39.78 to 1.38) |
| PVR, WU | 10.2 ± 1.4 | 9.0 ± 1.3 | 5.3 ± 1.3 | −0.9 (−3.42 to 1.62) | −3.72 (−6.24 to −1.2) |
| SVR, WU | 27 ± 3 | 24 ± 3 | 17 ± 4 | −2.86 (−9.38 to 3.67) | −6.5 (−12.54 to −0.46) |
| Rp/Rs | 0.4 ± 0.1 | 0.4 ± 0.1 | 0.3 ± 0.1 | −0.04 (−0.13 to 0.05) | −0.06 (−0.15 to 0.03) |
| sPAP/sBP | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.5 ± 0.1 | 0.04 (−0.08 to 0.16) | −0.46 (−0.58 to −0.34) |
| Qp/Qs | 1.9 ± 0.4 | 2.1 ± 0.7 | 1.1 ± 0.2 | 0.36 (−0.19 to 0.91) | −1.1 (−1.65 to −0.55) |
| $SaO_2$, % | 94 ± 4 | 94 ± 2 | 98 ± 2 | 0.5 (−3.01 to 4.01) | 3.52 (0.01-7.03) |

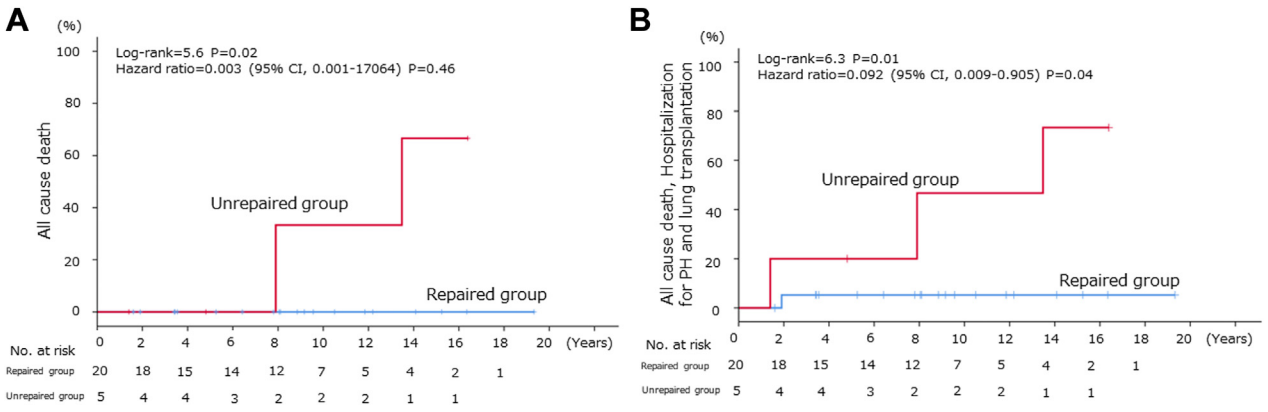
Values are mean ± SD. β coefficient was estimated by a mixed effect linear regression model (a random intercept model with fixed effects for explanatory variables and random intercepts for patients). To assess the treatment effect of PAH treatment before repair (treat) and PAH treatment and repair (treat and repair) separately, a model with linear spline terms (single knot at pre-repair when the timing of just before cardiac defect repair) was applied. Median follow-up duration: from diagnosis to PAH treatment, 131 (IQR: 21-239) days; and from PAH treatment to post-repair, 1,021 (IQR: 940-1,029) days. PVR decreased from 9.0 WU to 4.9 WU after the acute vasoreactivity test with oxygen at pre-repair (ß coefficient = −4, [95% CI: −9 to 1]).

Abbreviations are as in Tables 1 and 3.

In our study, 5 patients failed to complete the treat and repair strategy. PAH-targeted drugs tended to decrease PAP and PVR and increase the Qp/Qs in the unrepaired group, but severe PAH and a right-to-left shunt remained. The characteristics of the unrepaired group at pretreatment were: 1) a higher PVR than that in the repair group (27 vs 10 WU), 2) a low Qp/Qs than that in the repair group (0.6 vs 1.5); and 3) more severe hypoxia than that in the repair group ($SaO_2$ = 86% vs 95%). In patients with these hemodynamic characteristics at pretreatment, PAH-targeted drugs did not significantly improve PAH or lead to cardiac defect repair. Primary outcomes (all-cause death) and secondary outcomes (all-cause death, hospitalization for worsening of pulmonary hypertension, and lung transplantation) in the repaired group were significantly lower than that in the unrepaired group. Therefore, it is important to assess baseline and longitudinal change in hemodynamic parameters to predict whether treat and repair strategy should be considered or not. Specifically, among the parameters studied, PVR, Qp/Qs, and $SaO_2$ were associated with defect repair using a treat and repair strategy.

The treat and repair strategy has several advantages. PAH can further improve after cardiac defect repair. In the present study, mean PAP decreased from 43 mm Hg at pre-repair to 29 mm Hg at post-repair in all patients in the repaired group (35 mm Hg to 28 mm Hg in ASD-PAH and 66 mm Hg to 29 mm Hg in VSD-PAH). These further improvements in PAH might also contribute to improving symptoms, exercise capacity, and the long-term prognosis. PAH-targeted drugs are easy to use after cardiac defect repair. PAH-targeted drugs affect not only pulmonary vessels but also systemic vessels which sometimes cause hypotension and hypoxia under an unrepaired shunt. The use of PAH-targeted drugs before cardiac defect repair might worsen PAH because increased intracardiac and pulmonary flow through defects might increase the shear stress of pulmonary arteries, progress pulmonary artery remodeling, and deteriorate right ventricular function. In the present study, the average period from pretreatment to pre-repair was 428 days, and PAH did not worsen during this period. The long-term use of PAH-targeted drugs before cardiac defect repair might worsen PAH. Further studies are required to evaluate the effects of PAH-targeted drugs before cardiac defect repair. Previous studies showed that PAH after cardiac defect repair was associated with a poor prognosis compared with other types of PAH associated with congenital heart disease.[11,12] Our study showed that no patients died after cardiac defect repair. The continuation of PAH-targeted drugs after cardiac defect repair might contribute to good outcomes. The risk of a pulmonary hypertension crisis just after cardiac defect repair is a concern in patients with high PVR.[13] In this study, a pulmonary hypertension crisis did not occur. The criteria used for cardiac defect repair in this study may be less likely to result in a pulmonary hypertension crisis. However, further studies are required

**FIGURE 2** Cumulative Incidence for Study Outcomes




Each panel indicates the cumulative incidence of outcomes estimated by Kaplan-Meier estimator (A) all-cause death; and (B) fatal and nonfatal adverse events. Fatal and non-fatal adverse events included all-cause death, lung transplantation, and hospitalization for worsening pulmonary hypertension.

to evaluate a pulmonary hypertension crisis after cardiac defect repair in severe ASD-PAH and VSD-PAH.

**STUDY LIMITATIONS.** This study has several limitations. First, this was a single-center, observational study with a small sample size. Although multicenter, prospective studies with larger sample sizes are required, this study is important because of the number of severe PAH cases associated with ASD and VSD is limited even in PAH expert centers. However, the number of study participants was limited, and thus low statistical power might contribute the results of this study. Furthermore, the analyses did not avoid the influence of potential confounders and multiplicity issues in statistical testing. The findings of this study, therefore, should be interpreted as exploratory in nature. Second, our study included only Japanese patients (East Asian population), and thus, the generalizability of the results to other racial population is limited. Third, the criteria for cardiac defect repair after the treatment of PAH-targeted drugs and the criteria for the vasoreactivity test by oxygen have not been established. There are a few differences in criteria for cardiac defect repair between the AHA/ACC and ESC guidelines. Nine patients did not meet the AHA/ACC criteria or ESC criteria in the present study (Supplemental Table 3). If treatment strategy had been based on ACC/AHA or ESC criteria, 9 patients did not have an indication for cardiac defect repair, which might affect outcomes. We used PVR, Qp/Qs, and $SaO_2$ to determine the feasibility of cardiac defect repair. Desaturation during exercise in the 6-minute walk distance, the results of the cardiopulmonary exercise test, and secondary erythrocytosis might be candidates to determine the feasibility of cardiac defect repair. Further study is required to establish criteria for cardiac defect repair. Fourth, how to use PAH-targeted drugs has not been established before cardiac defect repair in severe PAH associated with ASD

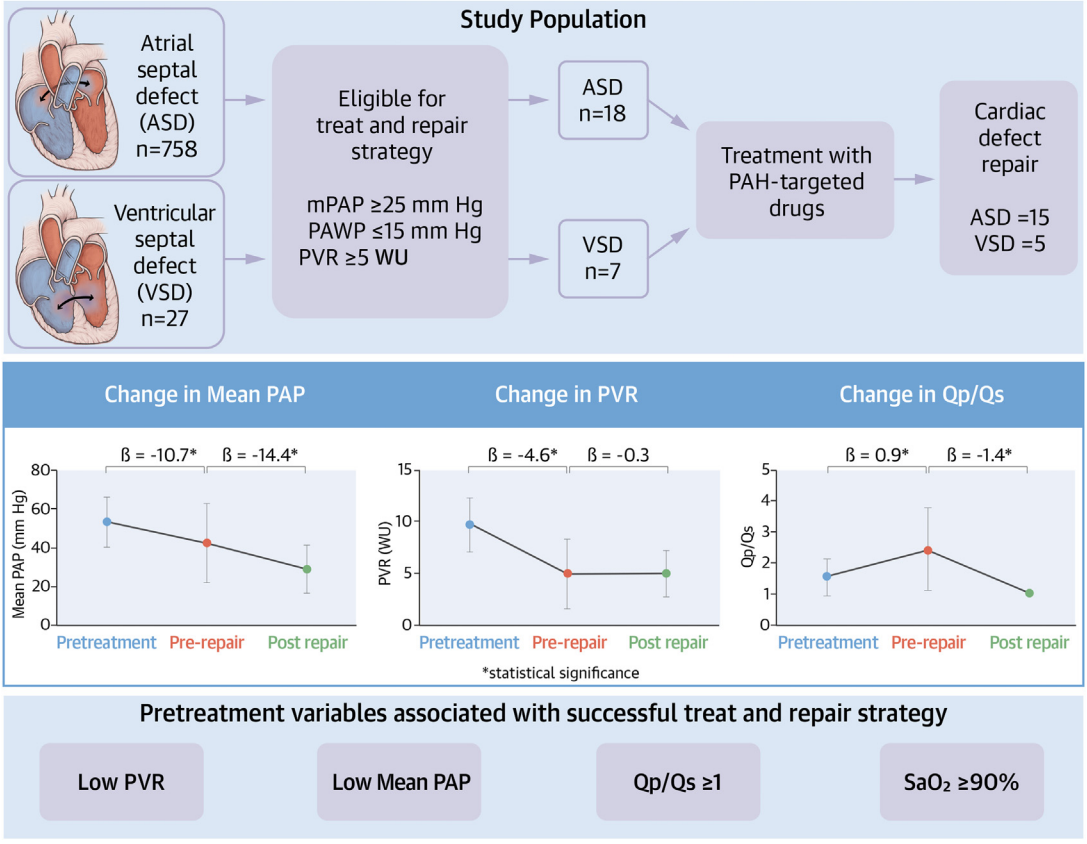
**TABLE 7** Pretreatment Variables Associated With Undergoing Cardiac Defect Repair

| | |
|---|---|
| Age, per 1 y | 1.04 (0.97-1.11) |
| Male (vs female) | 0.27 (0.03-2.63) |
| VSD (vs ASD) | 0.50 (0.06-4.62) |
| WHO functional class III/IV (vs I/II) | 0.17 (0.02-1.32) |
| Heart rate, bpm | 0.92 (0.84-1.01) |
| mPAP | |
| Per 1 mm Hg | 0.87 (0.73-0.96) |
| Per 10 mm Hg | 0.24 (0.04-0.64) |
| PVR | |
| Per 1 WU | 0.74 (0.47-0.89) |
| Per 5 WU | 0.22 (0.02-0.57) |
| Qp/Qs | |
| Per 0.1 | 4.08 (1.51-84.0) |
| <1.0 (vs ≥ 1.0) | 0.028 (0.001-0.29) |
| $SaO_2$ | |
| Per 1% | 1.60 (1.20-2.32) |
| ≥90% (vs <90%) | 36 (3.45-954) |
| BNP (log-transformed) | 0.81 (0.34-1.92) |

Values are OR (95% CI). Odds ratio of undergoing cardiac defect repair using a treat and repair approach was estimated by a logistic regression model without covariates due to small sample size. This analysis did not avoid the influence of potential confounders and multiplicity issues in statistical testing; and thus, the results should be interpreted as exploratory in nature.

Abbreviations as in Tables 1 to 3.

**CENTRAL ILLUSTRATION** **Feasibility of the Treat and Repair Strategy in Patients With Atrial Septal Defects and Ventricular Septal Defects With Moderate to Severe Pulmonary Arterial Hypertension**




**Akagi S, et al. JACC Adv. 2024;3(4):100887.**

PAH-targeted drugs significantly reduced PAP and PVR and increased the Qp/Qs, subsequently allowing ASD and VSD closure without severe complications, and further improving pulmonary hypertension. Low PVR, low mean PAP, Qp/Qs ≥1, and $SaO_2$ ≥90% at pretreatment were potential variables associated with undergoing defect repair using a treat and repair strategy. ASD = atrial septal defect; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; Qp/Qs = pulmonary to systemic blood flow ratio; $SaO_2$ = saturation of arterial oxygen; VSD = ventricular septal defect.

and VSD. The latest guideline recommends that PAH-targeted drugs should be considered.[1] However, whether monotherapy, initial combination therapy, or sequential combination therapy is appropriate is unknown. We started monotherapy or combination therapy and added more PAH-targeted drugs based on the patient's response. Although we continued PAH-targeted drugs with the same dose after cardiac defect repair in most patients, reducing the dose or number of PAH-targeted drugs may be possible. Furthermore, 5 patients continued to use intravenous epoprostenol or treprostinil after cardiac defect repair. In these patients, moderate PAH remained in study period. Further study is required to establish how to use PAH-targeted drugs before and after cardiac defect repair. Fifth, all patients in the unrepaired group continued to use PAH-targeted drugs during the study period. Several studies suggested that PAH-targeted drugs may improve outcome in Eisenmenger syndrome.[14] In our study, fatal and nonfatal adverse events in the repaired group were significantly lower than that in the unrepaired group. However, greater sample size and longer follow-up period may lead different results. Sixth, only patients with simple ASD and VSD were studied and not patients with complex congenital heart diseases. Finally, selection bias and residual confounding bias were inevitable in this type of observational study. To overcome these potential limitations, further multicenter prospective study is warranted.

## CONCLUSIONS

In patients with ASD and VSD with moderate to severe PAH, PAH-targeted drugs could reduce PAP and PVR and increase the Qp/Qs, subsequently allowing ASD and VSD closure without severe complications and further improving pulmonary hypertension. The treat and repair strategy could be a promising therapeutic approach in such patients. A low PAP, low PVR, Qp/Qs ≥1, and $SaO_2$ ≥90% at baseline could be associated with undergoing defect repair using a treat and repair strategy and deserve further investigation.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** In patients with PAH associated with congenital heart defects, initial treatment with PAH-targeted drugs and subsequent repair of the cardiac defect, called the treat and repair strategy, is a promising therapeutic strategy.

**TRANSLATIONAL OUTLOOK:** Additional prospective studies could improve understanding of the treat and repair strategy in patients with PAH associated with congenital heart defects.

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**KEY WORDS** atrial septal defect, hemodynamic parameter, ventricular septal defect

**APPENDIX** For supplemental methods, tables, and figures, please see the online version of this paper.