



OPEN ACCESS

Original research

Efficacy of treat-and-repair strategy for atrial septal defect with pulmonary arterial hypertension

Yoichi Takaya ¹, Teiji Akagi,¹ Ichiro Sakamoto,² Hideaki Kanazawa,³ Gaku Nakazawa,⁴ Tsutomu Murakami,⁵ Atsushi Yao,⁶ Mamoru Nanasato,⁷ Mike Saji,⁷ Mitsugu Hirokami,⁸ Yasushi Fuku,⁹ Shinobu Hosokawa,¹⁰ Norio Tada,¹¹ Kensuke Matsumoto,¹² Masao Imai,¹³ Koji Nakagawa,¹ Hiroshi Ito¹

For numbered affiliations see end of article.

Correspondence to

Dr Yoichi Takaya, Department of Cardiovascular Medicine, Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan; takayaoyoichi@yahoo.co.jp

Received 29 January 2021

Accepted 21 May 2021

Published Online First

15 June 2021

ABSTRACT

Objective Therapeutic strategies for atrial septal defect (ASD) with severe pulmonary arterial hypertension (PAH) are controversial. This study aimed to evaluate the efficacy of PAH-specific medications and subsequent transcatheter closure (ie, treat-and-repair strategy) on clinical outcomes.

Methods We enrolled 42 patients who were referred to 13 institutions for consideration of ASD closure with concomitant PAH and underwent the treat-and-repair strategy. The endpoint was cardiovascular death or hospitalisation due to heart failure or exacerbated PAH.

Results At baseline prior to PAH-specific medications, pulmonary to systemic blood flow ratio (Qp:Qs), pulmonary vascular resistance (PVR), and mean pulmonary artery pressure (PAP) were 1.9 ± 0.8 , 6.9 ± 3.2 Wood units and 45 ± 15 mm Hg. Qp:Qs was increased to 2.4 ± 1.2 , and PVR and mean PAP were decreased to 4.0 ± 1.5 Wood units and 35 ± 9 mm Hg at the time of transcatheter ASD closure after PAH-specific medications. Transcatheter ASD closure was performed without any complications. During a median follow-up period of 33 months (1–126 months) after transcatheter ASD closure, one older patient died and one patient was hospitalised due to heart failure, but the other patients survived with an improvement in WHO functional class. PAP was further decreased after transcatheter ASD closure.

Conclusions The treat-and-repair strategy results in low complication and mortality rates with a reduction in PAP in selected patients with ASD complicated with PAH who have a favourable response of medical therapy.

INTRODUCTION

Atrial septal defect (ASD) of secundum type is a common congenital heart disease. Pulmonary arterial hypertension (PAH) occurs in 6%–35% of patients with ASD¹ and is associated with increased mortality and functional limitations.² Transcatheter ASD closure has been established as an effective treatment.^{3–6} Transcatheter closure can be safely performed if PAH is mild or appears reversible after shunt closure,^{7–9} while transcatheter closure is contraindicated in severe PAH. The guidelines indicate that shunt closure can be performed in patients with pulmonary vascular resistance (PVR) of ≤ 2.3 Wood units, but shunt closure is not recommended in those with PVR of > 4.6 Wood units.^{10–12}

Treatments for PAH have dramatically advanced because of development of PAH-specific medications, including endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and prostacyclins. These medical treatments improve survival in patients with PAH.^{13 14} Recently, a few studies have reported that PAH-specific medications and subsequent transcatheter closure (ie, treat-and-repair strategy) are effective for ASD with severe PAH.^{15–18} There has been increasing interest in the potential for the treat-and-repair strategy. However, these data are limited to case reports. Clinical outcomes of the treat-and-repair strategy remain unclear. Therefore, this study aimed to evaluate the efficacy of the treat-and-repair strategy on clinical outcomes in patients with ASD complicated with PAH.

METHODS

Study design

This multicentre cohort study involved 13 institutions in Japan. This study enrolled a total of 42 patients with ASD complicated with PAH, who were referred to the institutions for consideration of ASD closure with concomitant PAH and underwent PAH-specific medications and subsequent transcatheter closure (treat-and-repair strategy) between January 2008 and December 2019. All patients underwent transcatheter ASD closure using non-fenestrated devices. PAH was defined as mean pulmonary artery pressure (PAP) of ≥ 25 mm Hg, pulmonary arterial wedge pressure of ≤ 15 mm Hg and PVR of ≥ 3.0 Wood units at cardiac catheterisation. The regimens of PAH-specific medications were determined by cardiologists at each institution who specialised in pulmonary hypertension. The decision of performing transcatheter ASD closure was made on the basis of the patient's haemodynamics after PAH-specific medications. PVR of < 5.0 – 7.0 Wood units and significant left-to-right shunt of pulmonary to systolic blood flow ratio (Qp:Qs) of > 1.5 were used to determine transcatheter ASD closure. We also confirmed no remarkable increase in PAP after balloon occlusion to test whether the patient tolerated transcatheter ASD closure.

The primary endpoint was cardiovascular death or hospitalisation due to heart failure or exacerbated PAH after transcatheter ASD closure. The secondary endpoints were changes in mean PAP

 Check for updates

© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Takaya Y, Akagi T, Sakamoto I, et al. *Heart* 2022;**108**:382–387.

and PVR evaluated by cardiac catheterisation and estimated systolic PAP evaluated by transthoracic echocardiography. Changes in WHO functional class and plasma B-type natriuretic peptide (BNP) levels were evaluated. The regimens of PAH-specific medications were assessed at the time of transcatheter ASD closure and at the latest follow-up after transcatheter ASD closure. Patients were followed up until the first documentation of death or the end of follow-up.

Clinical assessments

We collected data, such as age, sex, haemodynamic parameters, WHO functional class, BNP levels and transthoracic echocardiographic parameters. Data collection was conducted at baseline prior to PAH-specific medications, at the time of transcatheter ASD closure after PAH-specific medications, and at the latest follow-up after transcatheter ASD closure. Haemodynamic parameters included PVR, mean PAP and Qp:Qs. Transthoracic echocardiography evaluated estimated systolic PAP, which was derived from right ventricular systolic pressure estimated using tricuspid regurgitation velocity (v) and the Bernoulli equation as $4v^2 + \text{right atrial pressure}$. Right atrial pressure was estimated from the diameter of inferior vena cava and respiratory collapse.¹⁹ Adverse events, such as death and hospitalisation, were investigated during the follow-up period after transcatheter ASD closure. The regimens of PAH-specific medications were collected.

Statistical analysis

Data are presented as mean \pm SD for continuous variables and as number and percentage for categorical variables. Differences were analysed using the Wilcoxon signed-rank test for continuous variables and the marginal homogeneity test for categorical variables. Event-free survival rate was estimated by Kaplan-Meier analysis. Statistical analysis was performed with JMP V.14.0 (SAS Institute, Cary, North Carolina, USA), and significance was defined as a p value of <0.05 .

Patient and public involvement

Participants were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Patient characteristics

Forty-seven patients with ASD complicated with PAH received PAH-specific medications in the 13 institutions. Of the 47 patients, 42 subsequently underwent transcatheter ASD closure. Five patients abandoned shunt closure during treatment of

PAH-specific medications because of no significant decrease in PVR.

Clinical characteristics of the 42 patients are shown in table 1. The age at the time of transcatheter ASD closure was 51 ± 18 years (range 17–80 years). The median maximal defect diameter was 23 mm. At baseline prior to PAH-specific medication, 24 (57%) patients were in WHO functional class III or IV. Qp:Qs was 1.9 ± 0.8 (range 0.9–3.9), and PVR and mean PAP were 6.9 ± 3.2 Wood units (range 3.0–15.9 Wood units) and 45 ± 15 mm Hg (range 25–104 mm Hg). Estimated systolic PAP was 78 ± 26 mm Hg.

PAH-specific medications

At the time of transcatheter ASD closure, 31 (74%) patients received a combination therapy with either two ($n=13$) or three PAH-specific medications ($n=18$). The remaining 11 (26%) patients received a single therapy. PAH-specific medications consisted of endothelin receptor antagonists (bosentan: $n=11$, ambrisentan: $n=8$ and macitentan: $n=15$), phosphodiesterase type-5 inhibitors (sildenafil: $n=13$ and tadalafil: $n=20$), prostacyclins (beraprost: $n=13$, selexipag: $n=6$, epoprostenol: $n=4$ and treprostinil: $n=2$) and soluble guanylate cyclase stimulators (riociguat: $n=1$). Six patients were treated with intravenous administration of epoprostenol or treprostinil. The median duration of PAH-specific medications before transcatheter ASD closure was 9 months (range 1–87 months).

After PAH-specific medications, Qp:Qs was 2.4 ± 1.2 (range 1.2–6.3), which was increased, compared with that at baseline ($p=0.03$). PVR and mean PAP were 4.0 ± 1.5 Wood units (range 1.5–7.1 Wood units) and 35 ± 9 mm Hg (range 18–61 mm Hg), which were decreased, compared with those at baseline ($p<0.01$ and $p<0.01$).

Transcatheter ASD closure

Transcatheter closure was performed using the Amplatzer Septal Occluder (Abbott, Chicago, Illinois, USA) with a median size of 25 mm in 31 patients, and using the Occlutech Figulla Flex II Occluder (Occlutech GmbH, Jena, Germany) with a median size of 26 mm in 11 patients. There were no complications related to the procedure. No patients developed pulmonary hypertensive crisis during the procedure.

Clinical outcomes

One patient who was 80 years old at the time of transcatheter ASD closure died at 25 months after transcatheter closure. The cause of death was unknown, but we included it as cardiovascular death. One patient was hospitalised due to right heart failure at 14 months. During the median follow-up period after transcatheter ASD closure of 33 months (range 1–126 months), the other patients survived without any hospitalisations (figure 1).

WHO functional class was improved at the latest follow-up after transcatheter ASD closure, compared with that at baseline ($p<0.01$). All the 24 patients with WHO functional class III or IV at baseline had WHO functional class I or II at the latest follow-up. No patients had deterioration (figure 2). Plasma BNP levels were decreased at the latest follow-up, compared with those at baseline (158 ± 192 to 85 ± 86 pg/mL, $p=0.03$).

PAH after transcatheter ASD closure

Twenty-six of the 42 patients had cardiac catheterisation performed during the follow-up period after transcatheter ASD closure. Among these 26 patients, mean PAP was decreased, compared with that at the time of transcatheter ASD closure

Table 1 Clinical characteristics ($n=42$)

| | |
|---|---------------|
| Age at transcatheter ASD closure (years) | 51 \pm 18 |
| Female | 32 (76) |
| Maximum defect diameter (mm) | 23 |
| WHO functional class I or II | 18 (43) |
| WHO functional class III or IV | 24 (57) |
| B-type natriuretic peptide (pg/mL) | 158 \pm 192 |
| Pulmonary vascular resistance (Wood unit) | 6.9 \pm 3.2 |
| Mean PAP (mm Hg) | 45 \pm 15 |
| Pulmonary to systemic blood flow ratio | 1.9 \pm 0.8 |
| Estimated systolic PAP (mm Hg) | 78 \pm 26 |

Data are presented as mean \pm SD, median or number (%) of patients. ASD, atrial septal defect; PAP, pulmonary artery pressure.

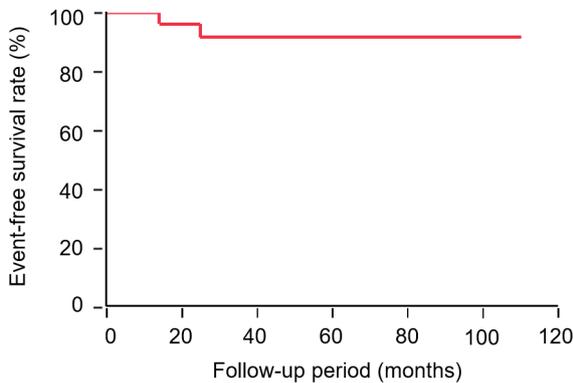


Figure 1 Event-free survival rate. Survival rate without cardiovascular death or hospitalisation due to heart failure or exacerbated pulmonary arterial hypertension.

(34 ± 9 to 25 ± 7 mm Hg, $p < 0.01$) (figure 3). Mean PAP ranged from 12 to 42 mm Hg. Mean PAP of < 25 mm Hg was observed in 13 (50%) of the 26 patients. PVR tended to be decreased, compared with that at the time of transcatheter ASD closure (4.1 ± 1.6 to 3.2 ± 1.7 Wood units, $p = 0.08$).

Estimated systolic PAP was obtained during the follow-up period after transcatheter ASD closure in all the 42 patients. Estimated systolic PAP was decreased at the time of transcatheter ASD closure, compared with that at baseline (78 ± 26 to 66 ± 22 mm Hg, $p = 0.02$). Further reduction was observed at the follow-up period (66 ± 22 to 38 ± 10 mm Hg, $p < 0.01$) (figure 4). Normalisation of estimated systolic PAP, which was defined as < 40 mm Hg, was observed in 21 (50%) of the 42 patients.

PAH-specific medications after transcatheter ASD closure

The regimens of PAH-specific medications remained unchanged in 29 (69%) of the 42 patients. A reduction in PAH-specific medications was observed in eight (19%) patients. Three

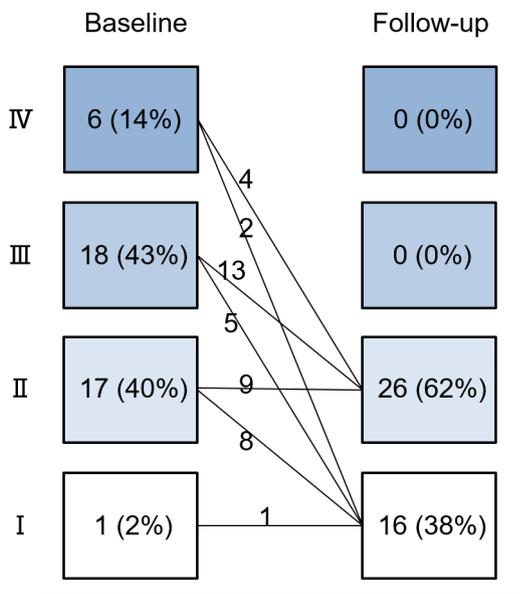


Figure 2 WHO functional class. WHO functional class at baseline prior to pulmonary arterial hypertension-specific medications and at the follow-up after transcatheter atrial septal defect closure. WHO functional class was significantly improved ($p < 0.01$).

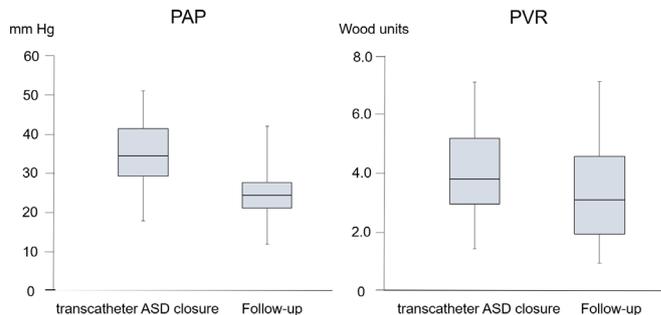


Figure 3 Mean PAP and PVR after transcatheter ASD closure. Mean PAP was significantly decreased ($p < 0.01$). PVR tended to be decreased ($p = 0.08$). ASD, atrial septal defect; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

patients had a reduction from three medications to two medications, and two patients had a reduction from two medications to one medication. The remaining three patients had discontinuation of PAH-specific medications. These eight patients had no PAH exacerbation. An increase in PAH-specific medications was observed in five (12%) patients. Three patients had one medication added, and one patient had two medications added. In one patient, the dose of PAH-specific medication was increased. These five patients had a Qp:Qs of 1.5 ± 0.4 , a PVR of 6.1 ± 3.8 Wood units and a mean PAP of 50 ± 15 mm Hg at baseline. During the follow-up period, PVR and mean PAP were decreased to 2.5 ± 1.2 Wood units and 25 ± 6 mm Hg.

Severe PAH

When severe PAH was defined as a mean PAP of ≥ 40 mm Hg and a PVR of ≥ 5.0 Wood units with a Qp:Qs of < 1.5 , 14 of the 42 patients had severe PAH at baseline. During the median follow-up period of 37 months (range 8–110 months), all the 14 patients survived without any hospitalisation. Among the 11 patients who had cardiac catheterisation performed during the follow-up period, the mean PAP and PVR were decreased, compared with those at baseline (61 ± 14 to 27 ± 7 mm Hg,

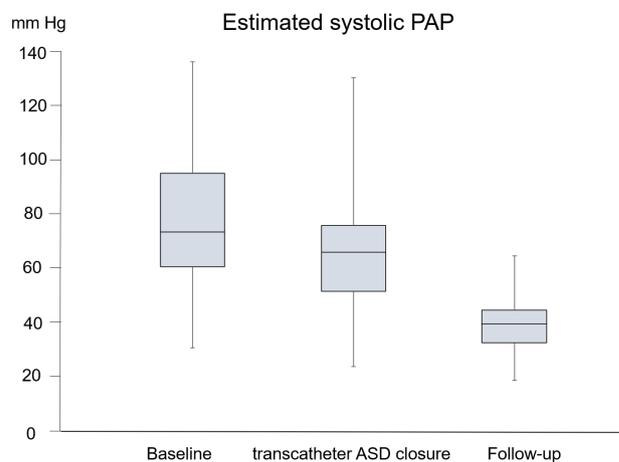


Figure 4 Estimated systolic PAP. Estimated systolic PAP was significantly decreased at the time of transcatheter ASD closure after PAH-specific medications, compared with that at baseline prior to PAH-specific medications ($p = 0.02$). Estimated systolic PAP was further decreased at the follow-up after transcatheter ASD closure ($p < 0.01$). ASD, atrial septal defect; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure.

$p < 0.01$; 9.7 ± 3.2 to 3.6 ± 1.6 Wood units, $p < 0.01$). No patients had an increase in PAH-specific medications.

DISCUSSION

ASD complicated with PAH

ASD is often complicated by PAH.¹ Previous studies reported that shunt closure did not always improve PAH.^{20–21} Patients who developed PAH after shunt closure had a worse prognosis compared with those treated with medical therapy.^{22–23} Therefore, ASD closure has been considered to be unsuitable in patients with PAH. The European Society of Cardiology guideline indicates a PVR of < 5.0 Wood units as the upper limit for operability in patients with ASD.²⁴ In several guidelines, shunt closure is not recommended in patients with a PVR of > 4.6 Wood units.^{10–12} However, data are limited in patients complicated with PAH, especially those with severe PAH.

In recent years, PAH-specific medications have advanced. Furthermore, effective usage of PAH-specific medications, such as combination therapy, has been demonstrated.²⁵ Additionally, transcatheter closure, which is less invasive and has fewer complications, has been performed. Because treatments for ASD and PAH are remarkably developing, the therapeutic strategy for ASD complicated with PAH needs to be modified. A few studies have reported the benefits of PAH-specific medications and subsequent transcatheter closure (treat-and-repair strategy) in patients with ASD complicated with PAH,^{15–17} but the number of patients was small. One study reported the data of 19 patients who underwent ASD repair following PAH-specific medications, but these included surgical closure.²⁶

The present study showed that patients with ASD complicated with PAH who underwent the treat-and-repair strategy had low complication and mortality rates. Most patients survived without hospitalisation due to heart failure or exacerbated PAH. Additionally, WHO functional class was improved after transcatheter ASD closure. PAP was significantly decreased after transcatheter ASD closure. One 80-year-old patient died, but transcatheter ASD closure might not be suitable for this patient because of old age. To the best of our knowledge, this is the first study to show the efficacy of the treat-and-repair strategy for ASD complicated with PAH in a large population. Unlike previous studies,^{27–28} transcatheter ASD closure was performed using non-fenestrated devices in all the patients with PAH. Our study population was in relatively good condition with predominantly left-to-right shunt at baseline prior to PAH-specific medications. Transcatheter ASD closure using non-fenestrated devices can be effective in this population.

The further reduction in PAP after transcatheter ASD closure was considered to contribute to the clinical outcomes in our study. In patients with PAH, an adequate decrease in PAP plays an important role in improving prognosis. One study showed that patients with PAH with mean PAP of < 42.5 mm Hg by aggressive treatment of PAH-specific medications survived for a long time.²⁵ In the present study, all the 26 patients who repeated cardiac catheterisation during the follow-up period had a mean PAP of < 42.5 mm Hg, including 13 patients with a mean PAP of < 25 mm Hg. This value of mean PAP may be useful as an indicator for managing PAH-specific medications after transcatheter closure.

The upper limits of PVR for transcatheter ASD closure after PAH-specific medications remain unclear. In the present study, the majority of patients had a PVR of ≤ 5.0 Wood units at the time of transcatheter ASD closure. This result suggests that a PVR of ≤ 5.0 Wood units is appropriate as the criterion for performing

transcatheter closure and as the goal of PAH-specific medications before transcatheter closure. Additionally, with regard to PVR at the time of diagnosis before starting PAH-specific medications, the present study included patients with high PVR values, but transcatheter ASD closure was performed following PAH-specific medications, such as combination therapy. An ASD which is previously considered unreparable due to severe PAH can become a candidate for transcatheter closure if the patient responds to PAH-specific medications. Our study suggests that the treat-and-repair strategy should be applied, regardless of the value of PVR at the time of diagnosis. Aggressive treatment for PAH is important to extend the indication of transcatheter ASD closure.

However, once Eisenmenger syndrome develops, ASD closure is contraindicated. This is because shunt closure may sacrifice the right-sided pressure relief role, leading to worsening right heart failure. In patients with Eisenmenger syndrome, medical management with PAH-specific medications becomes the focus. Our study did not include patients with ASD causing Eisenmenger syndrome.

PAH-specific medications

After transcatheter ASD closure, the optimal regimens of PAH-specific medications remain unknown. The present study showed that PAH-specific medications were largely unchanged during the follow-up period. In patients with PAH, pulmonary vascular histopathology is changed by intimal proliferation and progressive distortion. The development of PAH after shunt closure is related to a poor prognosis.^{22–23} Maintaining low PAP contributes to an improvement in prognosis.²⁵ Additionally, PAH is associated with ASD, but PAH is not caused by only increased blood flow to the lungs.²⁹ Therefore, it seems necessary to continue PAH-specific medications even after the ASD is closed in patients with severe PAH. The regimens of PAH-specific medications should be carefully determined in individual patients. Further studies are required to clarify the appropriate regimens of PAH-specific medications.

Clinical implication

Prognosis is worse in unclosed patients with ASD with PAH,³⁰ whereas ASD closure is reported to be a risk for mortality in patients with PAH.^{2–30} Therefore, the appropriate therapeutic strategies for ASD with PAH, especially severe PAH, remain controversial.^{7–9 22–23} Physicians are confused about how to treat ASD with PAH because of the lack of evidence. The present study showed low complication and mortality rates after PAH-specific medications and subsequent transcatheter closure. The present study indicates that the treat-and-repair strategy has the potential to improve clinical outcomes in patients with ASD complicated with PAH.

Study limitations

First, this was a retrospective study. There was no control group. In this study, we involved the institutions where the patients were referred for consideration of transcatheter closure of ASD complicated with PAH, and enrolled patients who responded to PAH-specific medications and underwent transcatheter closure. The study population was likely a less sick cohort. We did not investigate the entire ASD with PAH population, including Eisenmenger syndrome. Therefore, this study showed the results of the treat-and-repair strategy in selected patients with a favourable response to PAH-specific medications. Furthermore, clinical outcomes in patients who did not

respond to PAH-specific medications and did not get transcatheter closure were not assessed. It was uncertain whether transcatheter ASD closure led to the clinical outcomes, including the reduction in PAP. The indication for ASD closure could not be clarified. Second, this was a relatively large-scale study for evaluating the effect of the treat-and-repair strategy, but the number of patients was small. Third, the follow-up period after transcatheter ASD closure was not long. Fourth, this study did not include patients who underwent surgical closure. Transcatheter closure has become an alternative to surgical closure. Therefore, this study evaluated the effect of PAH-specific medications and subsequent transcatheter closure. Finally, the regimens of PAH-specific medications were not uniform because these treatments were introduced by individual cardiologists. The decision to undergo transcatheter ASD closure was based on judgement by cardiologists.

CONCLUSIONS

This multicentre, relatively large-scale observational study shows low complication and mortality rates with a reduction in PAP after PAH-specific medications and subsequent transcatheter ASD closure. Our findings suggest that the treat-and-repair strategy may be a reasonable therapeutic option in selected patients with ASD complicated with PAH who have a favourable response of medical therapy.

Key messages

What is already known on this subject?

- ▶ Atrial septal defect (ASD) is often complicated by pulmonary arterial hypertension (PAH). However, therapeutic strategies for ASD with PAH are controversial. The efficacy of the treat-and-repair strategy remains unclear.

What might this study add?

- ▶ This multicentre, relatively large-scale observational study showed that the treat-and-repair strategy resulted in low complication and mortality rates with an improvement in WHO functional class. Pulmonary artery pressure was further decreased after transcatheter ASD closure.

How might this impact on clinical practice?

- ▶ The treat-and-repair strategy may be a reasonable therapeutic option in patients with ASD complicated with PAH. Patients with PAH can become candidates for transcatheter ASD closure.

Author affiliations

¹Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

²Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

³Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

⁴Department of Cardiology, Kindai University Faculty of Medicine, Osaka, Japan

⁵Department of Cardiology, Tokai University Hospital, Isehara, Japan

⁶Division for Health Service Promotion, University of Tokyo, Tokyo, Japan

⁷Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan

⁸Department of Cardiology, Teine Keijinkai Hospital, Sapporo, Japan

⁹Department of Cardiovascular Medicine, Kurashiki Central Hospital, Kurashiki, Japan

¹⁰Department of Cardiology, Tokushima Red Cross Hospital, Komatsushima, Japan

¹¹Department of Cardiology, Sendai Kousei Hospital, Sendai, Japan

¹²Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

¹³Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan

Contributors All authors contributed to the collection of data, discussion and interpretation of the data, and the writing of the report. All authors reviewed and approved the manuscript for submission. The study was designed by YT, TA, KN and HI. The analysis was performed by YT. The manuscript was written by YT.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study was in accordance with the Declaration of Helsinki and approved by the ethical committee of our institution. Informed consent was obtained before entering this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement This study is based on data from our institutions. The data are available from the corresponding author on reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Yoichi Takaya <http://orcid.org/0000-0003-4872-8669>

REFERENCES

- 1 Geva T, Martins JD, Wald RM. Atrial septal defects. *Lancet* 2014;383:1921–32.
- 2 Engelfriet PM, Duffels MGJ, Möller T, et al. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 2007;93:682–7.
- 3 Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. *J Am Coll Cardiol* 2005;45:505–7.
- 4 Salehian O, Horlick E, Schwertzmann M, et al. Improvements in cardiac form and function after transcatheter closure of secundum atrial septal defects. *J Am Coll Cardiol* 2005;45:499–504.
- 5 Butera G, Carminati M, Chessa M, et al. Percutaneous versus surgical closure of secundum atrial septal defect: comparison of early results and complications. *Am Heart J* 2006;151:228–34.
- 6 Du ZD, Hijazi ZM, Kleinman CS, et al. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 2002;39:1836–44.
- 7 de Lezo JS, Medina A, Romero M, et al. Effectiveness of percutaneous device occlusion for atrial septal defect in adult patients with pulmonary hypertension. *Am Heart J* 2002;144:877–80.
- 8 Balint OH, Samman A, Haberer K, et al. Outcomes in patients with pulmonary hypertension undergoing percutaneous atrial septal defect closure. *Heart* 2008;94:1189–93.
- 9 Yong G, Khairy P, De Guise P, et al. Pulmonary arterial hypertension in patients with transcatheter closure of secundum atrial septal defects: a longitudinal study. *Circ Cardiovasc Interv* 2009;2:455–62.
- 10 Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34–41.
- 11 Opatowsky AR. Clinical evaluation and management of pulmonary hypertension in the adult with congenital heart disease. *Circulation* 2015;131:200–10.
- 12 Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint Task force for the diagnosis and treatment of pulmonary hypertension of the European Society of cardiology (ESC) and the European respiratory Society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), International Society for heart and lung transplantation (ISHLT). *Eur Heart J* 2016;37:67–119.
- 13 Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. *Circulation* 2010;121:20–5.
- 14 Berger RMF, Beghetti M, Galiè N, et al. Atrial septal defects versus ventricular septal defects in BREATHE-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: a subgroup analysis. *Int J Cardiol* 2010;144:373–8.
- 15 Kijima Y, Akagi T, Takaya Y, et al. Treat and repair strategy in patients with atrial septal defect and significant pulmonary arterial hypertension. *Circ J* 2016;80:227–34.
- 16 Taniguchi Y, Emoto N, Miyagawa K, et al. Subsequent shunt closure after targeted medical therapy can be an effective strategy for secundum atrial septal defect with

- severe pulmonary arterial hypertension: two case reports : strategy for ASD with severe PAH. *Heart Vessels* 2014;29:282–5.
- 17 Bradley EA, Chakinala M, Billadello JJ. Usefulness of medical therapy for pulmonary hypertension and delayed atrial septal defect closure. *Am J Cardiol* 2013;112:1471–6.
 - 18 Murakami T, Nakazawa G, Horinouchi H, *et al.* Transcatheter closure of atrial septal defect protects from pulmonary edema: septal occluder device gradually reduces LR shunt. *Heart Vessels* 2017;32:101–4.
 - 19 Rudski LG, Lai WW, Afilalo J, *et al.* Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of echocardiography endorsed by the European association of echocardiography, a registered branch of the European Society of cardiology, and the Canadian Society of echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713.
 - 20 O'Donnell C, Ruygrok PN, Whyte K, *et al.* Progressive pulmonary hypertension post atrial septal defect device closure-early symptomatic improvement may not predict outcome. *Heart Lung Circ* 2010;19:713–6.
 - 21 D'Alto M, Romeo E, Argiento P, *et al.* Hemodynamics of patients developing pulmonary arterial hypertension after shunt closure. *Int J Cardiol* 2013;168:3797–801.
 - 22 van Loon RLE, Roofthoof MTR, Hillege HL, *et al.* Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. *Circulation* 2011;124:1755–64.
 - 23 Manes A, Palazzini M, Leci E, *et al.* Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. *Eur Heart J* 2014;35:716–24.
 - 24 Baumgartner H, De Backer J, Babu-Narayan SV, *et al.* 2020 ESC guidelines for the management of adult congenital heart disease. *Eur Heart J* 2021;42:563–645.
 - 25 Ogawa A, Ejiri K, Matsubara H. Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan. *Life Sci* 2014;118:414–9.
 - 26 Bradley EA, Ammash N, Martinez SC, *et al.* "Treat-to-close": Non-repairable ASD-PAH in the adult: Results from the North American ASD-PAH (NAAP) Multicenter Registry. *Int J Cardiol* 2019;291:127–33.
 - 27 Dalvi B, Jain S, Pinto R. Device closure of atrial septal defect with severe pulmonary hypertension in adults: patient selection with early and intermediate term results. *Catheter Cardiovasc Interv* 2019;93:309–15.
 - 28 Yan C, Pan X, Wan L, *et al.* Combination of F-ASO and targeted medical therapy in patients with secundum ASD and severe PAH. *JACC Cardiovasc Interv* 2020;13:2024–34.
 - 29 Jain S, Dalvi B. Atrial septal defect with pulmonary hypertension: when/how can we consider closure? *J Thorac Dis* 2018;10:52890–8.
 - 30 Steele PM, Fuster V, Cohen M, *et al.* Isolated atrial septal defect with pulmonary vascular obstructive disease--long-term follow-up and prediction of outcome after surgical correction. *Circulation* 1987;76:1037–42.