Transcatheter Closure of Atrial Septal Defect Associated With Pulmonary Artery Hypertension using Fenestrated Devices

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In patients with pulmonary artery hypertension (PAH) associated with atrial septal defect (ASD), closure of ASD may carry significant risks. We aimed to evaluate the safety and efficacy of transcatheter closure of ASD in selected patients with PAH using a fenestrated device followed by pulmonary vasodilator therapy. During the 14.8-year period, 51 ASD patients (10 males, age 46 ± 18 years) with a mean pulmonary artery pressure (PAP) ≥ 35 mm Hg and/or systolic PAP ≥ 60 mm Hg, underwent closure with a fenestrated device. Of them, mean Qp/Qs ratio, systolic PAP and mean PAP were 2.6 ± 1.2, 73 ± 14 mm Hg, and 44 ± 8 mm Hg, respectively. A total of 35 patients received pulmonary vasodilator therapy. The New York Heart Association (NYHA) functional class improved at 3 to 6 months follow-up. ($p < 0.001$) Nineteen patients underwent repeated catheterization. A comparison of the hemodynamic parameters between baseline and repeated catheterization revealed significant decreases in both systolic and mean PAP (77 ± 11 vs 55 ± 14 mm Hg, $p < 0.0001$ & 48 ± 7 vs 37 ± 8 mm Hg, $p = 0.001$, respectively), pulmonary vascular resistance (PVR) (5.1 ± 2.3 vs 4.0 ± 1.7 WU, $p = 0.011$) and PVRi (7.7 ± 3.3 vs 6.2 ± 2.4 WU*m2, $p = 0.024$). After a follow-up period of 84 ± 45 months, 6 mortalities were noted in which 2 were due to cardiac causes. In conclusion, catheter closure of ASD in patients with PAH using a fenestrated device followed by vasodilator therapy is safe and effective. © 2021 Published by Elsevier Inc. (Am J Cardiol 2021;147:122−128)

Atrial septal defect (ASD) accounts for approximately 8% of congenital heart disease. Because the symptoms are generally subtle, ASD frequently remains undetected in childhood. Adults with unrepaired ASD may have pulmonary artery hypertension (PAH), heart failure, arrhythmia and even death.[1−3] Since PAH is common in adults with an open ASD and pulmonary vascular disease may progress with time, closure of ASD should be performed within the appropriate time period. If patients have Eisenmenger syndrome or severe pulmonary vascular obstructive disease, closure of ASD is contraindicated.[4]

Partial closure of ASD has been advocated in patients with PAH and can be achieved by creating a small fenestration in the surgical patch.[5] This enables gradual reduction in left-to-right shunt and prevents drastic changes in hemodynamics in those patients. We developed a strategy to close ASD with moderate-to-severe PAH by using fenestrated devices followed by targeted therapy.[6−8]

Methods

In a 14.8-year period between July 2002 and March 2017, 55 patients diagnosed as having unrepaired secundum type ASD and moderate-to-severe PAH, defined as a mean (PAP) ≥ 35 mm Hg and/or systolic PAP ≥ 60 mm Hg[9,10] and PVR < 12 Wood Unit (WU), underwent attempted transcatheter closure with a fenestrated device. Clinical evaluation, ECG and echocardiography were performed before the procedure. Four patients were excluded from this procedure, because of very high PVR or intolerance to balloon occlusion test. This study has been approved by the ethical committee of this institution. There were 51 patients, 41 women (80%) and 10 men, undergoing transcatheter closure using a fenestrated device. Their ages ranged from 16 to 75 years (46 ± 18 years, median 43 years). Before intervention, 3 patients had been treated with pulmonary vasodilators in other hospitals. One had undergone an unsuccessful surgical closure 8 years in a foreign country before the intervention. Twelve patients (24 %) had atrial arrhythmia: atrial fibrillation in 8 and atrial flutter in 4. Of them, 1 with atrial fibrillation underwent catheter ablation and 2 patients with atrial flutter underwent cardioversion prior to the procedure.

Informed consent was obtained from each patient. After local anesthesia was administered, hemodynamic studies were performed and PVR was obtained. An acute vasodilation test was performed in selected patients with PVR > 6 WU*m2 or PVR/SVR > 0.3.[6,7] Following general anesthesia, transesophageal echocardiography (TEE) was used to monitor the procedure.

Department of pediatrics, National Taiwan University Hospital, and medical college, National Taiwan University, Taipei, Taiwan. Manuscript received September 25, 2020; revised manuscript received and accepted January 13, 2021.

This study is supported by a grant from National Science Council, Taiwan, grant no. NSC 101-2314-B-002-143-MY3

See page 127 for disclosure information.

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0002-9149/© 2021 Published by Elsevier Inc.
https://doi.org/10.1016/j.amjcard.2021.01.025

The Amplatzer septal occluders (AGA Medical Corporation, Plymouth, MN, USA) were used in all patients. The device size selected is usually equal to or up to 2 mm larger than the balloon sizing diameter. Since 2006, the majority of patients did not undergo balloon sizing. Without balloon sizing, the device size selected was generally 4−7 mm or 20%−25% larger than maximal diameter of ASD on TEE images.[11] A fenestration approximately one-fourth of device diameter was manually created by removing part of the patch.[8,12] In many patients, an additional fenestration of approximately 4−5 mm in diameter was made to ensure adequate flow across the fenestration after deployment (Figure 2). After closure, Aspirin 200 mg was administrated for at least 6 months except to those who were taking warfarin. Clinical evaluation, electrocadiogram and transthoracic echocardiography were performed at 1 day, 1 week, 1 month, 3 months and 6 months after the procedure, then every 6 months afterwards. The NYHA functional class was evaluated before intervention and at 3- or 6-months follow-up in each patient. Pulmonary vasodilators were given in patients with echocardiographic estimated tricuspid valve regurgitation gradient > 46 mm Hg[13] or systolic PAP > 50 mm Hg during the 1- or 3-months follow-up.

Data are presented as mean ± standard deviation (STD). Student's *t* test or 1 way analysis of variance (ANOVA) were used for a numerical data comparison. Paired *t* test was used to compare the hemodynamic parameters at baseline and during follow-up. The Chi-square test and Fisher's exact test were used for a categorical data comparison. Logistic regression was used for multivariate risk factor analysis of persistent PAH.

Results

The demographic data and follow-up data of the 51 patients are summarized in Table 1. A fenestrated occluder was successfully deployed in all 51 patients. Shunt flows across fenestrations were observed on TEE images for all patients immediately after device implantation. Fourty nine patients were discharged within 2 days after the procedure. No patients developed pulmonary hypertension crisis during and after the procedure.

In the 3 patients who received pretreatment, pulmonary vasodilator therapy was continued immediately after the procedure. In 32 patients, Sildenafil 20 mg twice or 3 times daily was given as first-line therapy after evaluation with Doppler echocardiography in the 1- or 3-month follow-up. A total of 35 patients received vasodilator therapy. Bosentan was added based on echocardiographic estimation of systolic PAP in 5 patients for more efficient control of PAH during follow-up. Forty-nine patients received at least 6-month of follow-up. Two were lost to follow-up after the third month visit. A second cardiac catheterization was performed to evaluate the hemodynamics in 19 patients at 4.5−92 (mean 40 ± 35) months after the procedure. The mean Qp/Qs was 1.4 ± 0.4 (1−2.6). A comparison of hemodynamic parameters obtained at baseline with those obtained at repeated catheterization were shown in Figure 1. The

Table 1
clinical characteristics and follow-up data in ASD patients associated with pulmonary artery hypertension

	Baseline	Follow-up	p value
Age (years, mean ± STD)	46±18		
Women	41 (80%)		
Function class			
I	0	11 (22%)	***<0.001***
II	27 (53%)	33 (65%)	
III	19 (37%)	7 (14%)	
IV	5 (10%)	0	
Pro-brain natriuretic peptide (pg/mL)	1722 ± 3506 24	412 ± 705 16	0.044
Atrial flutter/fibrillation (%)	12 (24%)	8 (16%)	0.318
Estimated PAP by echocardiography (mm Hg)	76 ± 21	48 ± 24	***<0.001***
Cardiac catheterization			
systolic PAP (mm Hg)	73 ± 14(50∼105)	55 ± 14*(33∼80)	***<0.001****
mean PAP (mm Hg)	44 ± 8 (28∼61)	37 ± 8* (24∼50)	***0.001****
Qp/Qs	2.6 ± 1.2(1∼5.8)		
estimated PVR (WU)	4.9 ± 2.9 (1.2∼13.7)	4.0 ± 1.7*(1.8∼10.5)	***0.011****
estimated PVRi (WU*m2)	7.3 ± 4.3(1.9∼19.4)	6.2 ± 2.4*(3∼14.8)	***0.024****
ASD			
Maximal diameter on echocardiography (mm)	27 ± 6		
Device size (mm)	33 ± 6(22−40)		
Follow-up period (months)	84 ± 45		

ASD- atrial septal defect, PAP- pulmonary artery pressure, PVR- pulmonary vascular resistance, PVRi- PVR times body surface area. STD- standard deviation .

P valuue < 0.05 was regarded as statistically significant and marked as "bold".

* for 19 patients received follow-up cardiac catheterization paired-t test

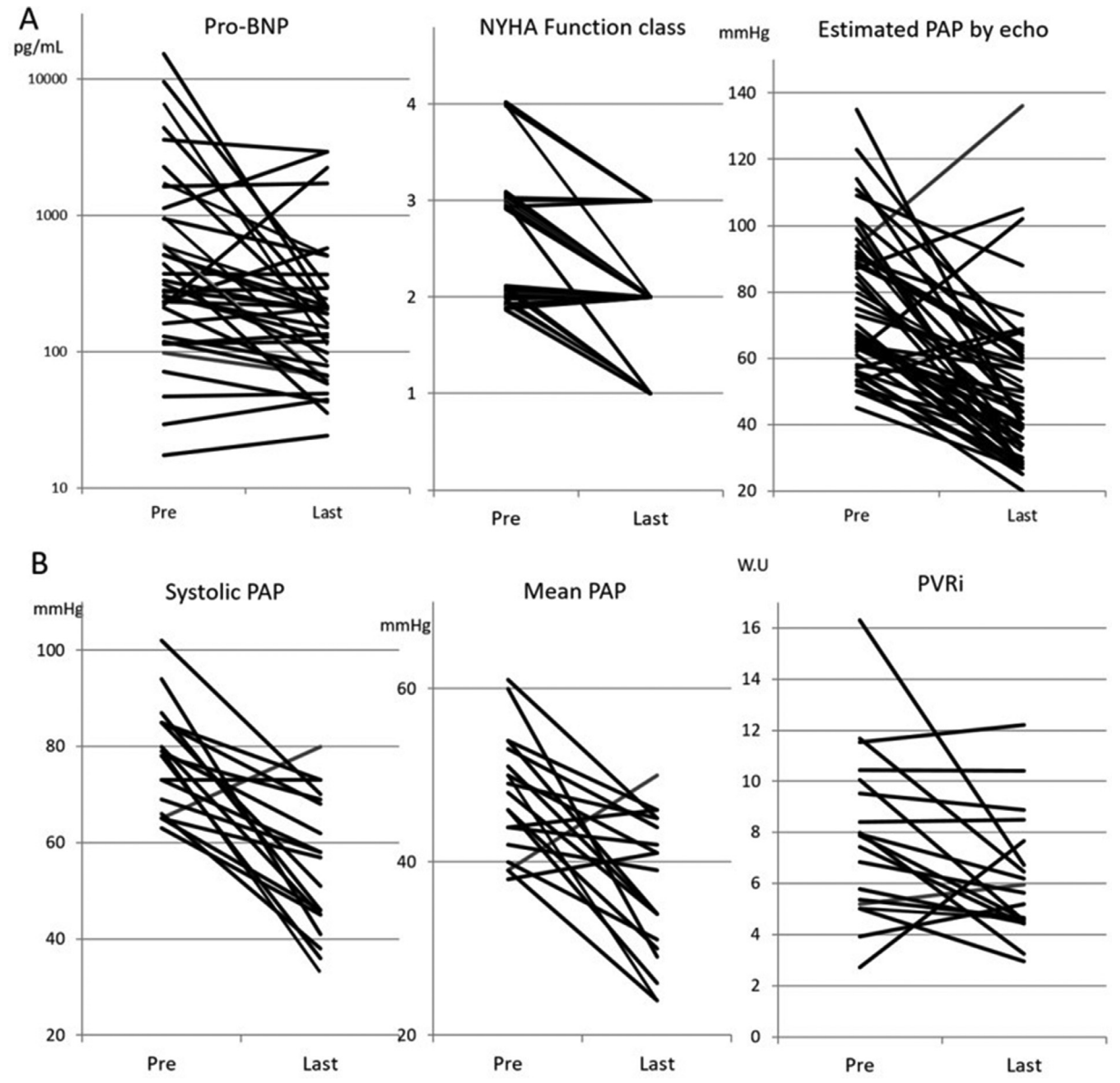

Figure 1. A. Significant improvement of follow-up echocardiographic data in Pro-brain natriuretic peptide (Pro-BNP, $p = 0.044$), NYHA functional class ($p < 0.001$), and estimated pulmonary artery pressure (PAP, $p < 0.001$) in 51 patients of ASD with PAH. B. Significant improvement of follow-up data of systolic PAP ($p < 0.001$), mean PAP ($p = 0.001$), and pulmonary vascular resistance index (PVRi, $p = 0.024$) in 19 of 51 patients receiving follow-up cardiac catheterization.

fenestrations were still patent in 15 of 19 (79%) patients at the time of second catheterization. Transcatheter closure of the fenestration was performed in the three patients who had a significant shunt across the fenestration with Qp/Qs ratio > 2. Two patients underwent balloon dilation of the fenestration and 7 patients underwent concomitant stent implantation (Express SD stent, 7 mm diameter by 19 mm long, Boston Scientific) at the fenestration to maintain interatrial communication, because PAP remained high (mean PAP > 25 mm Hg) (Figure 2). After a mean follow-up period of 84 ± 45 months, there were 6 deaths: 4 were non-cardiac death and 2 mortalities were likely cardiac causes. (Figure 3) Of the 2 patients dying of cardiac causes, 1 received vasodilator treatment and the other had poor compliance to vasodilator treatment (Table 2). Two patients had uneventful deliveries of babies after the second catheterization. In the most recent follow-up, left-to-right shunt across the fenestrations could be observed on precordial echocardiography in 21 patients. No 1 had desaturation during follow up. Significant improvements in NYHA functional class was observed during follow-up (Table 1).

We divided the 51 patients into 3 groups according to their baseline PVRi (PVRi <4, PVRi 4−8 and PVRi >8 WU*m2)[4,13] to compare various parameters including hemodynamics, percentages of atrial arrhythmia, ASD diameter and device size, baseline and changes in NYHA functional class, NT pro-BNP level and systolic PAP (Table 3). We also analyzed the risk factors for persistent PAH defined as tricuspid regurgitation pressure gradient > 46 mm Hg[13] or mean PAP ≥ 25 mm Hg. Baseline systolic

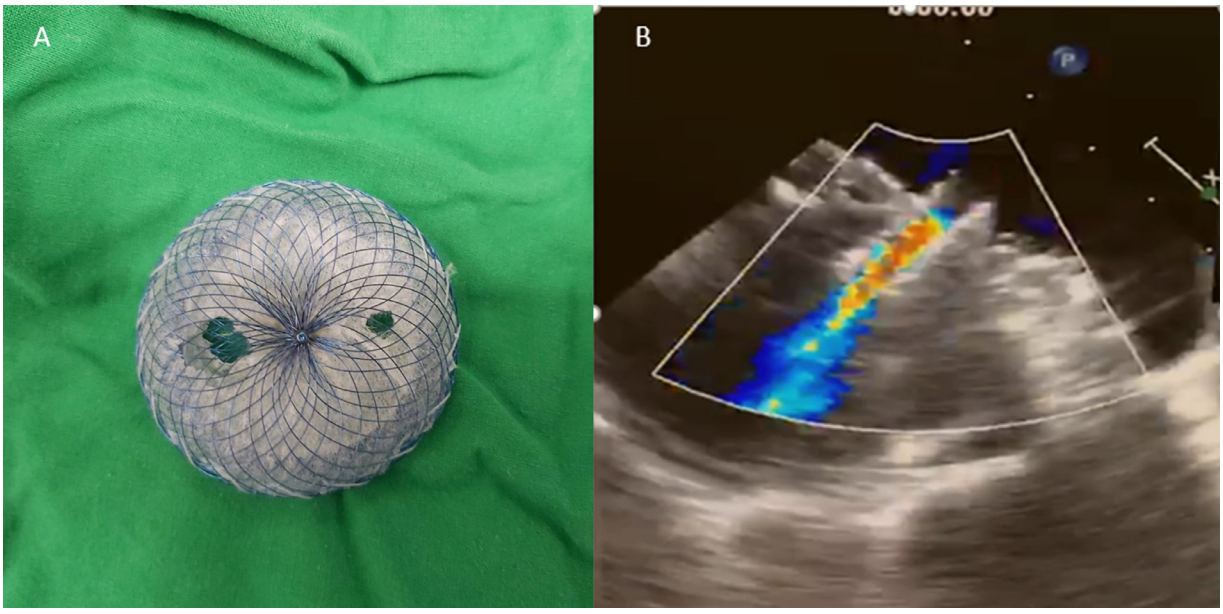

Figure 2. A. Two fenestration were made in a device. B. A TEE image showed a stent deployed at the fenestration of the device to keep patency of atrial communications. A left-to-right shunt was seen.

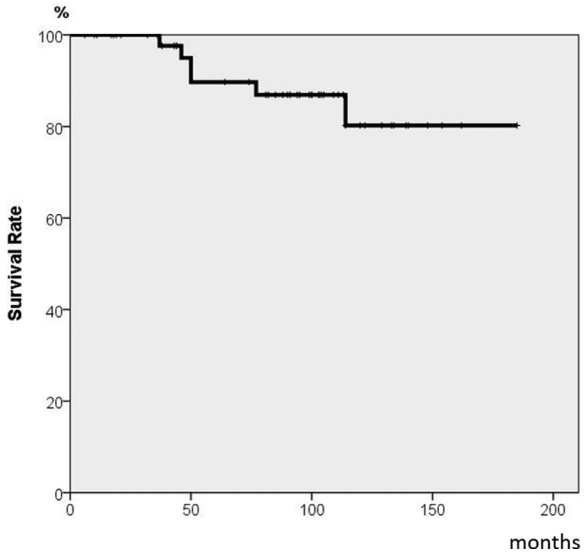

Figure 3. Survival curve analysis in 51 patients of atrial septal defect with pulmonary artery hypertension (PAH)

PAP and mean PAP, baseline left atrial pressure and ASD diameter were risk factors for persistent pulmonary hypertension in univariate analysis and baseline mean PAP and left atrial pressure were risk factors for persistent pulmonary hypertension in multivariate analysis (Table 4). Receiver operating characteristic curve (ROC) analysis showed that baseline PVRi > 5.69 WU*m2 and mean PAP > 42 mm Hg are the most efficient predictors of persistent PAH (Figure 4).

Discussions:

PAH is prevalent in 6% to 35% adults with open ASD.[1,14] Pulmonary vascular bed changes including intima proliferation, medial thickening and even progression to plexiform and occlusive lesions may occur, if the defect is not closed in a timely manner.[14,15] Decision making regarding closure can be difficult in those with moderately elevated PVR, because a subset of patients may develop

Table 2
Demographic features of 6 mortalities

No	Age	Sex	baseline PAP (mm Hg)	Latest Systolic PAP (mm Hg)	PVRi baseline	Defect diameter	FU interval	comorbilities	Cause of death
			(Cath)(pre)	(Echo)	WU*m2	(mm)	(months)		
1	81	F	88/15(37)	44	3.2	19	116	cancer	cancer
2	67	F	105/31(61)	82	15.7	21	43	DM	cardiac
3	76	M	61/19(35)	57	3.8	36	48	AF	stroke
4	72	M	51/27(39)	22	4	33	85	DM, uremia	infection
5	61	F	90/43(50)	37	5.9	26	36	DM, CAD	cardiac
6	41	F	57/18(35)	68	3.3	30	46	cancer	cancer

AF = atrial fibrillation, CAD = coronary artery disease, DM = diabetes mellitus.

Table 3
Comparisons of baseline and follow-up data in three groups of patients according to Pulmonary vascular resistance index (PVRi)

PVRi (WU*m2)	PVRi < 4 (12)	PVRi 4~8 (23)	PVRi > 8 (16)	p values
Age (years, mean ± STD)	47.7 ±22.9	49.4 ± 14.9	40 ±17.1	0.143
Women	8 (67%)	17 (74%)	16 (100%)	0.051
Body weight (kg)	53 ± 8	56 ± 10	49 ± 7	0.050
Baseline FC				
I	0	0	0	0.749
II	5(42%)	14(61%)	8(50%)	
III	5(42%)	7(30%)	7(44%)	
IV	2(17%)	2(9%)	1(6%)	
FC improve	10(83%)	15(65%)	6(38%)	0.140
Atrial flutter/fibrillation (n, %)	5(42%)	5(22%)	2(13%)	***0.041***
pro-BNP				
Baseline value (pg/mL)	1845 ± 4362	2626 ± 4243	544 ± 669	0.173
Baseline abnormal data (n,%)	3(33%)	9(53%)	5(36%)	0.514
FU abnormal data (n,%)	3 (30%)	2 (11%)	4(29%)	0.368
Echocardiography				
baseline estimated PAP (mm Hg)	59.8 ± 8.7	72.5 ± 18.2	94.0 ± 18.7	***<0.001***
estimated PAP change (mm Hg)	-14.5 ± 15.6	-35.3 ± 18.3	-29.7 ± 37.9	***0.016***
FU TR gradient <46mm Hg	8 (67%)	16 (70%)	4 (25%)	***0.015***
Baseline cardiac catheterization				
systolic PAP (mm Hg)	65 ± 10	68 ± 13	84 ± 12	***<0.001***
mean PAP (mm Hg)	39 ± 5	42 ± 8	51 ± 6	***<0.001***
Qp/Qs	3.7 ± 1.2	2.6 ± 0.8	1.9 ± 1	***<0.001***
PVRi (WU*m2)	3.1 ± 0.7	5.8 ± 1.1	12.5 ± 3.5	***<0.001***
ASD				
Maximal diameter of echocardiography (mm)	28 ± 7	27 ± 6	26 ± 7	0.717
Device size (mm)	32 ± 6	32 ± 6	32 ± 6	0.796
Follow-up period (months)	84 ± 49	85 ± 45	83 ± 44	0.971

ASD = atrial septal defect, FC = functional class, PAP = pulmonary artery pressure, PVR = pulmonary vascular resistance, PVRi = PVR times body surface area, STD = standard deviation, TR-tricuspid valve regurgitation.

P valuue < 0.05 was regarded as statistically significant and marked as "bold".

persistent PAH with a pathophysiology similar to idiopathic pulmonary hypertension after closure.[15–17] The upper limits of PVR for "operability" have been proposed in a few studies, but no universal consensus has been reached yet.[4,6] The 2010 guidelines from the European Society of Cardiology advocated that in the presence of significant shunt with a pulmonary vascular resistance (PVR) of ≤ 5 Wood units WU, ASD can be safely repaired.[18] However, recent guidelines suggest that in ASD patients with PVR ≤ 2.3 WU or pulmonary vascular resistance index (PVRi) ≤ 4 WU*m2, surgical or transcatheter closure can be performed with low complication and mortality rates, but with PVR > 4.6 WU or PVRi > 8 WU*m2, defect closure is not recommended. In patients with PVR between 2.3 and 4.6 WU or PVRi between 4 and 8 WU*m2, the decision to close the defect should be

Table 4
Cox regression analysis for the risk of persistent PAH in these patients of ASD with PAH receiving fenestrated device implantation

Persistent PAH	Univariate factors			Multivariate factors		
	OR	C.I	p values	OR	C.I.	p values
Age	0.99	0.97−1.01	0.158			
Gender (M/F)	0.79	0.30−2.10	0.635			
Baseline systolic PAP by catheterization	1.03	1.00−1.06	***0.029***			
Baseline mean PAP by catheterization	1.07	1.02−1.12	***0.004***	1.08	1.03−1.14	***0.001***
Baseline Qp/Qs	1.00	0.71−1.39	0.975			
Baseline LA pressure	1.08	1.00−1.16	***0.042***	1.113	1.03−1.12	***0.005***
Baseline PVRi	1.09	1.00−1.18	0.051			
Baseline ASD diameter by echocardiography	1.11	1.02−1.20	***0.012***			

ASD = atrial septal defect, FC = functional class, LA = left atrium, PAP = pulmonary artery pressure, PVRi = PVR times body surface area, STD = standard deviation.

P valuue < 0.05 was regarded as statistically significant and marked as "bold".

The definition of persistent PAH is either tricuspid regurgitation pressure gradient greater than 46 mm Hg by last echocardiography or mean pulmonary pressure greater than 25 mm Hg by last cardiac catheterization.

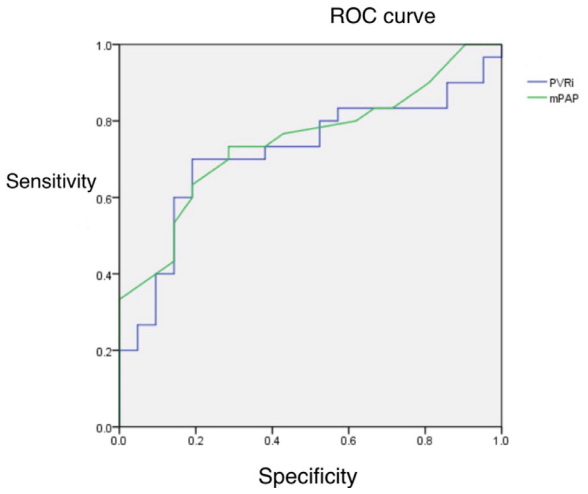

Figure 4. Receiver operating characteristic (ROC) curve analysis to evaluate the best PVRi value to predict those with persistent PAH. The definition of persistent PAH is either tricuspid regurgitation flow velocity > 3.4m/sec by last echocardiography or mean pulmonary pressure greater than 25 mm Hg by last cardiac catheterization. The result showed that PVRi > 5.69 WU*m2 and mean PAP > 42 mm Hg predict those with persistent PAH best. The area under the curve was 0.747 for mean PAP and 0.716 for PVRi.

evaluated individually in each patient.[4,16,19,20] Other recent guidelines suggested that patients with PVRi < 6 WU*m2 and PVR/systemic vascular resistance (SVR) < 0.3 can be safely operated.[6,7,18,20,21] The most recent guidelines from AHA/ACC suggested that PVR of < 1 of 3 SVR, systolic PAP of < 50% systemic pressure and Qp/Qs ratio > 1.5 with right ventricular enlargement as operable conditions.[22]

Evaluation of pulmonary vasoreactivity by various pulmonary vasodilators has been considered a necessary procedure in ASD patients with PVRi between 6- and 9 WU*m2 and a PVR/SVR ratio of 0.3−0.5. Favorable responses to acute vasodilators have been defined as a systolic or mean PAP decrease of more than 20% or PVR/ SVR < 0.3 and PVRi < 6 WU*m2 without a fall in systemic pressure or increase in ventricular end-diastolic pressure.[6,7,18,20−24] Such "responders'' can undergo closure of the defect with or without a fenestration.[6,7,13,16] However, no long-term follow-up data have indicated that responders to the acute vasodilator test can undergo ASD closure safely and will present more favorable long-term outcomes compared with those on medical therapy.[18,20] In addition to the acute pulmonary vasoreactivity test, the balloon occlusion test can be helpful for evaluating "operability".[25]

The "treat-and-repair" strategy has been applied in clinical practice with favorable short to mid-term results.[26−28] Long-term data of application of treat-and-repair strategy are very few. However, providing pulmonary vasodilator therapy before closure may increase the magnitude of left-to-right shunt and aggravate the severity of pulmonary vascular occlusive disease during therapy. In PAH association with ASD patients, partial surgical closure by creating a small fenestration on a patch or device has been reported to be safe and effective.[5,8,12,29] Most left-to-right shunts were abolished to prevent further deterioration in pulmonary vascular obstruction and a small fenestration in the device can serve as a "pop-off" for those with severe pulmonary hypertension or heart failure. However, the case number are limited. This strategy of partial closure with a fenestrated device followed by vasodilator treatment was effective in majorities of our patients. Most patients tolerated the procedure with a significant decrease in systolic PAP, mean PAP and PVR at follow-up. In recent reports, normalization of systolic PAP (< 40 mm Hg) was expected following ASD closure in most patients with mild-to-moderate pulmonary hypertension but normalization of systolic PAP is less likely (nearly 25%) in patients with severe pulmonary hypertension (systolic PAP > 60 mm Hg).[9,10] In this study, receiver operating characteristic curve (ROC) analysis showed that baseline PVRi > 5.69 WU*m2 and mean PAP > 42 mm Hg are the most efficient predictors of persistent pulmonary hypertension. Normalization of systolic PAP (tricuspid valve regurgitation gradient > 46 mm Hg) is less likely in patients with a PVRi > 8 WU*m2. (Table 3)

Fenestrations created in the laboratory underwent spontaneous closure in most patients.[30] Among our patients with a persistently high systolic PAP or PVR after closure, despite medical treatment, stenting or balloon dilation of the fenestration was performed to prevent progression to idiopathic pulmonary hypertension like pathophysiology.[15]

There were some limitations in this study. The oxygen consumption could not be measured in all patients. For some reasons, this was not performed in a few patients in whom the oxygen consumption was assumed using a formula to obtain PVR. In 3 patients, pulmonary vasodilators were given in peripheral hospitals prior to the procedure and their baseline systolic PAP and PVR could have been underestimated. The NYHA functional class in each patient was evaluated at the 6-month visit, except in the 2 patients who lost to follow-up after 3 months, the functional class evaluated at the 3- month visit was used for analysis.

ASD patients with moderate-to-severe PAH can be managed by using a fenestrated device and followed by vasodilator treatment. Most patients benefited from this strategy of treatment. Long term follow-up is mandatory in those patients.

Authors' contributions

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.

Disclosures

There is no conflict of interests.

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