Diastolic Pulmonary Arterial Pressure as a Prognostic Indicator for Closure of Atrial Septal Defect with Severe Pulmonary Arterial Hypertension

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Abstract

Background: In patients with atrial septal defect (ASD) and severe pulmonary arterial hypertension (PAH), diastolic pulmonary arterial pressure (DPAP) correlates closely with pulmonary vascular resistance (PVR) and can reflect the severity of pulmonary vascular disease. However, it is unclear whether DPAP has potential to become a prognostic indicator for closure of ASD with severe PAH.

Objectives: This study was performed to investigate the prognostic implication of DPAP in patients with ASD and severe PAH.

Methods: Among 232 patients with ASD and severe PAH (systolic pulmonary arterial pressure (SPAP)≥70 mm Hg measured with right heart catheterization), 85 patients (21M/64F) undergoing closure of ASD were followed up. Doppler-calculated SPAP was recorded to identify the normalized post-operative PAP (SPAP<40 mm Hg). According to the cut-off value of DPAP from a ROC curve, two subsets were classified: low-DPAP (<25 mm Hg, n=31) and high-DPAP (≥25 mm Hg, n=54).

Results: After closure of ASD, normalization of PAP occurred in 71% of patients with low-DPAP and 7.4% of patients with high-DPAP (P<0.001). Upon adjustment for PVR and SPAP/systolic aortic pressure, the hazard ratio of post-operative persistent PAH for high-DPAP was 4.48 (95%CI: 2.04-9.81, P<0.001). The follow-up (3.6 ± 1.3 years) demonstrated that normalized post-operative PAP tended to occur in patients with low-DPAP (Log Rank, P<0.001).

Conclusions: In patients with ASD and severe PAH, low-DPAP has the potential to become a predictor for the normalized post-operative PAP.

Keywords: Pulmonary arterial hypertension; Atrial septal defect; Diastolic pulmonary arterial pressure; Closure; Prognosis

Abbreviations and Acronyms

ASD: Atrial Septal Defect; PAH: Pulmonary Arterial Hypertension; DPAP: Diastolic Pulmonary Arterial Pressure; SPAP: Systolic Pulmonary Arterial Pressure; MPAP: Mean Pulmonary Arterial Pressure; PVR: Pulmonary Vascular Resistance; RHC: Right Heart Catheterization; TTE: Transthoracic Doppler Echocardiography

Introduction

In the patients with untreated atrial septal defect (ASD), severe pulmonary arterial hypertension (PAH) may develop and pulmonary vascular disease occurs in about 5~10% of patients [1]. In addition, it is more common in older and females [2-4]. To evaluate the reversibility of severe PAH, conventional predictors include the level of systolic pulmonary arterial pressure (SPAP), mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance (PVR) [5-7]. However, little attention was paid to the value of diastolic pulmonary arterial pressure (DPAP). It is accepted that SPAP and MPAP are determined mainly by stroke volume and pulmonary arterial compliance, respectively [8]. In comparison, DPAP is less influenced and has been assumed to be a reflection of left atrial pressure in normal subjects [9]. Furthermore, diastolic pulmonary pressure gradient has been considered a hemodynamic parameter for the diagnosis of pulmonary vascular disease [8,10].

In the ASD patients with severe PAH, SPAP usually increases highly (≥ 70 mm Hg). However, the level of DPAP might be high (high-DPAP subset) or low (low-DPAP subset). In some patients, DPAP can even be in normal limit (<15 mm Hg). In the absence of significant pulmonary valve insufficiency and coexisting cardiovascular malformations, it is

unknown about the mechanism of great differences in DPAP. In patients with PAH secondary to congenital heart disease, DPAP was closely associated with PVR and had the potential to reflect the severity of pulmonary vascular disease [11]. Therefore, we hypothesized that the ASD patients with low-DPAP, after closure of ASD, might have a better prognosis than those with high-DPAP. In this research, we investigated the prognostic implication of DPAP in patients with ASD and severe PAH.

Methods

Study patients

From January 2008 to January 2014, there were 232 (57M/175F) consecutive patients with ASD and severe PAH in National Center for Cardiovascular Diseases (204 patients with secundum ASD and 28 patients with primum ASD, SPAP≥70 mm Hg). After the examination of right heart catheterization (RHC), 88 patients underwent closure of ASD successfully, and 85 patients were followed up (3 patients were excluded because of insufficient tricuspid regurgitation to quantify post-operative SPAP after surgical closure of ASD and corrective tricuspid valve surgery). Among these 85 patients (surgical closure in 66 patients and transcatheter closure in 19 patients), none received the pre-operative treatment with specific pulmonary vasodilators. Patients with age <12 years, significant pulmonary valve insufficiency, coexisting cardiovascular malformations, left ventricular end-diastolic pressure >15 mmHg, coronary artery disease or identified causes for PAH were all excluded from the study. Doppler-calculated SPAP was recorded to identify the normalized post-operative PAP (SPAP<40 mmHg). The study was approved by our hospital research ethics committee, and informed consent was obtained from each adult patient (or the parents of children).

The indications for closure of ASD in this study [6]:

In patients with PVR<5 Woods, or PVR≥5 Woods but SPAP/systolic aortic pressure (Pp/Ps) <2/3, the closure of ASD was suggested.

In patients with PVR ≥ 5 Woods and Pp/Ps ≥ 2/3, the potential risk and conflicting evidences were informed and the closure was performed only under the insistence of patients. Furthermore, ASD closure was avoided in all patients with Eisenmenger physiology.

Definitions

PAH was defined as a resting MPAP ≥ 25 mmHg [12]. In this research, severe PAH was defined as SPAP ≥ 70 mmHg. Eisenmenger syndrome was defined as resting cyanosis with bidirectional shunt and supra-systemic pulmonary pressure (SPAP ≥ systolic aortic pressure). After surgical or transcatheter closure of ASD, the normalization of PAP was defined as Doppler-calculated SPAP<40 mmHg, and the persistent pulmonary hypertension (PH) was defined as Doppler-calculated SPAP ≥ 40 mmHg [13]. According to Doppler-calculated SPAP, the persistent PH was graded as mild (40–49 mmHg), moderate (50–59 mmHg) or severe (>60 mmHg).

RHC

Our procedure for cardiac catheterization has been described previously [14]. In brief, after percutaneous puncture of the femoral vein (6F Introducer, Cordis, Miami, Florida, USA) under local anesthesia, all patients underwent routine RHC with 6F MPA2 catheter (Cordis, Miami, Florida, USA). The complete hemodynamic data and

blood samples were obtained. The measurements included: mean right atrial pressure, right ventricular pressure, SPAP, DPAP and MPAP (the pressures were recorded in main pulmonary artery, left pulmonary artery and right pulmonary artery, respectively). The catheter was also introduced into left atrium through ASD to obtain the MLAP. Then, the catheter entered into left ventricle and aorta to record left ventricular pressure and aortic pressure. We calculated PA pulse pressure (PAPP=SPAP-DPAP), diastolic pulmonary pressure gradient (DPAP-MLAP) and Pp/Ps. According to the oxymetric principle of Fick, pulmonary blood flow (Qp), systemic blood flow (Qs), the ratio of pulmonary to systemic blood flow (Qp/Qs), PVR (PVR=MPAP-MLAP/Qp) and PVR index were calculated. Then, the patients were required to breathe oxygen (FiO$_2$>0.5) using a facemask for over 10 min, and hemodynamic measurements were repeated during inhalation of oxygen. A significant response to oxygen was defined as a drop in MPAP and PVR index by >20%. For the patients who underwent transcatheter closure of ASD, the immediate post-occlusion PAP was measured with catheter through the sheath.

Follow-up

After surgical or transcatheter closure of ASD, the follow-up was performed every 3-6 months. Post-operative SPAP was measured with Doppler transthoracic echocardiography (TTE) from the systolic right ventricular-to-right atrial pressure gradient using the modified Bernoulli equation, and the assessment of right atrial pressure was performed in accordance with previously described methods [15]. The arrhythmia was followed by twenty-four–hour ambulatory (Holter) electrocardiographic monitoring. The end-point was cardiac death. For patients with severe persistent PH after closure of ASD, pulmonary vasodilator therapy was commenced and the related cardiovascular drugs were stopped for one week (to exclude the potential influence of pulmonary vasodilator) before the evaluation of post-operative SPAP with Doppler-TTE. For the patients with mild to moderate persistent PH, no pulmonary vasodilator was administrated and the close follow-up was undertaken.

Statistical analysis

The data in the study were expressed as mean ± SD or count with percentage. Statistical significance between two groups was examined by t-test (continuous variables) and by chi-square test (categorical variables). Receiver-Operating Characteristics (ROC) curve was created to evaluate the predictive value of DPAP at baseline on the normalization of PAP during follow-up. Area under the curve and its 95% confidence interval (95%CI) were estimated. The best cut-off value was chosen at the value corresponding to the best diagnostic ability (which meant the maximum sum of sensitivity and specificity). According to the cut-off value of DPAP, two subsets were classified: low-DPAP and high-DPAP. Multivariate Cox regression model was constructed to establish the pre-operative predictor for the normalization of PAP after closure of ASD. The variables included the recommended references in guideline (Pp/Ps and PVR) [6] and the subsets of DPAP. In addition, Kaplan-Meier survival curves were generated and the difference of two subsets was compared by Log Rank test. The follow-up time was the interval from the date of RHC to final visit. A two-sided P<0.05 was considered statistically significant. Statistical software used in this study was SPSS 16.0.

Results

The cut-off value of DPAP from a ROC analysis

After the examination of RHC, 85 patients undergoing closure of ASD were followed up, and no cardiac death occurred. The cut-off value of DPAP was determined as 25 mmHg through a ROC analysis. This cut-off value gave the sensitivity and specificity at 86.4% and 84.6%, respectively (Figure 1). The area under the ROC curve was 0.89 and 95%CI was 0.81-0.96. According to the cut-off point of DPAP from the ROC curve, two subsets were classified: low-DPAP (<25 mmHg, n=31) and high-DPAP (≥25 mmHg, n=54).
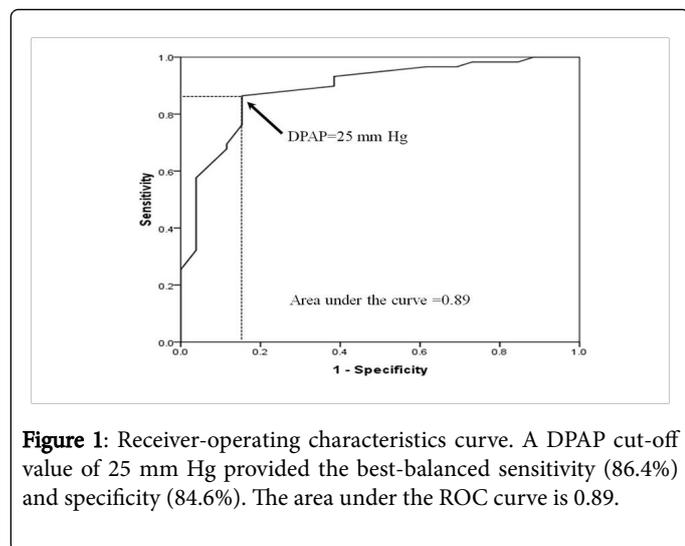

Figure 1: Receiver-operating characteristics curve. A DPAP cut-off value of 25 mm Hg provided the best-balanced sensitivity (86.4%) and specificity (84.6%). The area under the ROC curve is 0.89.

Clinical and hemodynamic characteristics of two subsets (n=85,21M/64F)

Clinical and hemodynamic characteristics of these patients are listed in Table 1. The DPAP was decreased with age (P for trend=0.001), but this association was absent for SPAP (P for trend=0.144).
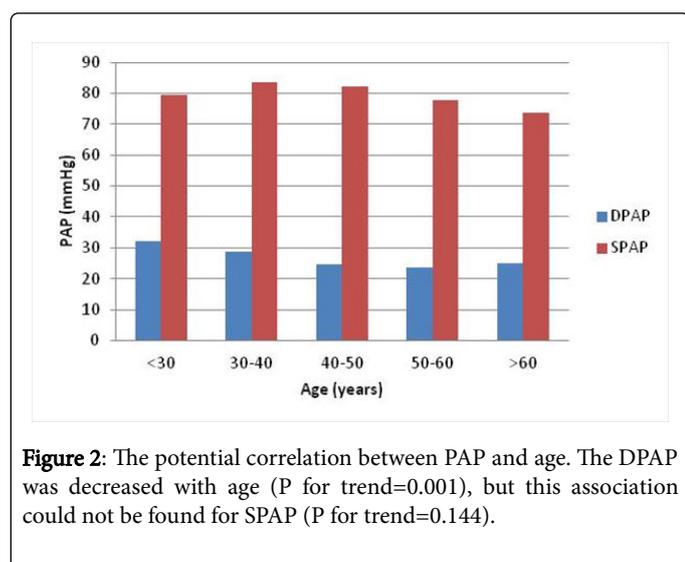
The potential correlation between PAP and age (Figure 2). Furthermore, DPAP was also associated with PVR (P<0.001). According to the current recommendations, 43 patients met the suggested criteria (PVR<5 Woods, or PVR≥5 Woods but Pp/Ps<2/3) and 42 patients were in borderline (PVR≥5 Woods and Pp/Ps≥2/3). In the former, there were 21 patients with low-DPAP (normalization of PAP occurred in 16 patients) and 22 patients with high-DPAP (normalization of PAP occurred in 4 patients). In the latter, there were 10 patients with low-DPAP (normalization of PAP occurred in 6 patients) and 32 patients with high-DPAP (no normalization of PAP occurred in these patients).

In two subsets, the level of SPAP was comparable (P=0.536). In addition, there were no significant differences in the level of systolic aortic pressure (P=0.135) and MLAP (P=0.202). Compared with high-DPAP subset, the patients with low-DPAP had lower PVR and higher Qp/Qs. After closure of ASD, mild residual shunt was detected in 3 patients. In the 19 patients with transcatheter closure, the immediate post-occlusion SPAP decreased from 81.8 ± 15.5 mmHg to 59.2 ± 15.2 mmHg, P<0.001. Though the reduction magnitude of SPAP was larger in low-DPAP than in high-DPAP, no immediate normalization of PAP was identified.

		Low-DPAP (n=31)	High-DPAP (n=54)	Total (n=85)	P
Age at RHC, years		48.3 ± 12.4	34.8 ± 13.7	39.7 ± 14.7	0.001
Male, n (%)		8(25.8%)	13(24.1%)	21(24.7%)	0.859
BSA, m^2		1.4 ± 0.15	1.5 ± 0.15	1.5 ± 0.15	0.05
CTR, %		60.2 ± 3.7	56.8 ± 6.2	58 ± 5.7	0.006
ASD, mm		30.3 ± 8.6	29.0 ± 7.8	29.5 ± 8.1	0.505
SAsat, %	Before O$_2$	94.0 ± 2.5	94.2 ± 3.3	94.1 ± 3.0	0.718
	During O$_2$	98.4 ± 1.2	98.4 ± 1.9	98.4 ± 1.7	0.992
SPAP, mm Hg	Before O$_2$	78.6 ± 12.0	80.2 ± 11.4	79.6 ± 11.5	0.536
	During O$_2$	69.1 ± 9.3	71.2 ± 11.1	70.4 ± 10.4	0.378
DPAP, mm Hg	Before O$_2$	20.9 ± 3.6	31.8 ± 6.6	27.8 ± 7.7	0.001
	During O$_2$	19.1 ± 3.4	27.7 ± 6.3	24.6 ± 6.8	0.001
MPAP, mm Hg	Before O$_2$	41.7 ± 5.5	48.6 ± 7.8	46.1 ± 7.8	0.001
	During O$_2$	36.1 ± 4.6	43.0 ± 7.1	40.5 ± 7.1	0.001
PAPP, mm Hg	Before O$_2$	57.6 ± 11.6	48.3 ± 8.7	51.7 ± 10.8	0.001
	During O$_2$	49.9 ± 8.6	43.4 ± 9.0	45.8 ± 9.4	0.002
PVR, Wood	Before O$_2$	5.1 ± 2.0	7.2 ± 3.2	6.4 ± 3.0	0.002

	During O$_2$	3.0 ± 1.3	4.3 ± 2.1	3.8 ± 2.0	0.006
Qp, L/min	Before O$_2$	8.7 ± 3.4	7.5 ± 2.8	7.9 ± 3.1	0.075
	During O$_2$	14.1 ± 7.1	11.9 ± 6.1	12.6 ± 6.4	0.183
Qp/Qs	Before O$_2$	2.5 ± 1.1	1.9 ± 0.8	2.2 ± 1.0	0.009
	During O$_2$	4.5 ± 2.2	2.9 ± 1.5	3.5 ± 1.9	0.001
Systolic aortic pressure, mm Hg		118.9 ± 16.0	113.8 ± 14.5	115.7 ± 15.2	0.135
Pp/Ps		0.67 ± 0.12	0.71 ± 0.11	0.69 ± 0.12	0.114
Response to oxygen, n(%)		5(16.1%)	8(14.8%)	13(15.3)	0.871
MLAP, mm Hg		8.71 ± 2.67	9.15 ± 3.86	8.99 ± 3.46	0.202
DPAP-MLAP, mm Hg		12.26 ± 4.13	22.7 ± 7.17	18.89 ± 8.01	0.063
Follow-up, years		3.8 ± 1.4	3.5 ± 1.3	3.6 ± 1.3	0.247
*SPAP after closure, mm Hg		38.0 ± 5.5	55.9 ± 12.7	49.4 ± 13.7	0.001
Normalization of PH, n(%)		22(71%)	4(7.4%)	26(30.6%)	0.001

Table 1: Clinical and hemodynamic characteristics of patients who were followed up after the closure of ASD (n=85).

Figure 2: The potential correlation between PAP and age. The DPAP was decreased with age (P for trend=0.001), but this association could not be found for SPAP (P for trend=0.144).

The follow-up after closure of ASD (3.6 ± 1.3 years)

In two subsets, there was no significant difference in the duration of follow-up (3.8 ± 1.4 years vs 3.5 ± 1.3 years, P=0.247). Furthermore, no patient developed signs of left ventricular diastolic dysfunction in the long-term follow up (estimated with Doppler-TTE). The Doppler-calculated post-operative SPAP was 38.0 ± 5.5 mmHg in low-DPAP and 55.9 ± 12.7 mmHg in high-DPAP (P<0.001). The persistent PH was identified in 59 patients: mild PH in 9 patients with low-DPAP and 14 patients with high-DPAP, moderate PH in 3 patients with low-DPAP and 18 patients with high-DPAP, severe PH with 15 patients with high-DPAP. For the patients with severe persistent PH, pulmonary vasodilator therapy was commenced (Sildenafil in 13 and Bosentan in 2). In addition, functional deterioration occurred in 2 patients (both belonged to high-DPAP).

The follow-up demonstrated that normalization of PAP occurred in 71% of patients with low-DPAP and 7.4% of patients with high-DPAP. Upon adjustment for PVR and Pp/Ps (Table 2), Cox regression analysis still showed that high-DPAP was associated with post-operative persistent PH (hazard ratio (HR)=4.48, 95%CI: 2.04-9.81, P<0.001). Kaplan-Meier curves showed clearly that, comparing to high-DPAP, low-DPAP was associated with the significant increase of normalized post-operative PAP in patients with ASD and severe PAH (Figure 3, Log Rank, P<0.001).

Subset of DPAP	Hazard Ratio	HR 95% CI	P-value
Unadjusted	4.55	(2.16- 9.61)	<0.001
Model 1	4.48	(2.04-9.81)	<0.001
Model 2	4.77	(2.14-10.62)	<0.001

Note: Model 1 was adjusted for PVR and Pp/Ps. Model 2 was adjusted for PVR, Pp/Ps and age.

Table 2: Hazard ratio of DPAP in multivariate Cox regression model.

Discussion

In patients with ASD and severe PAH, low-DPAP and high-DPAP were clinically different subsets, which were associated with different prognosis. Compared with high-DPAP, the patients with low-DPAP tended to have normalized post-operative PAP in the long-term follow up. Therefore, the presence of low-DPAP has the potential to become a predictor for the reversible severe PAH in patients with ASD. To our knowledge, it was the first report to investigate the prognostic implication of DPAP in patients with ASD and severe PAH.
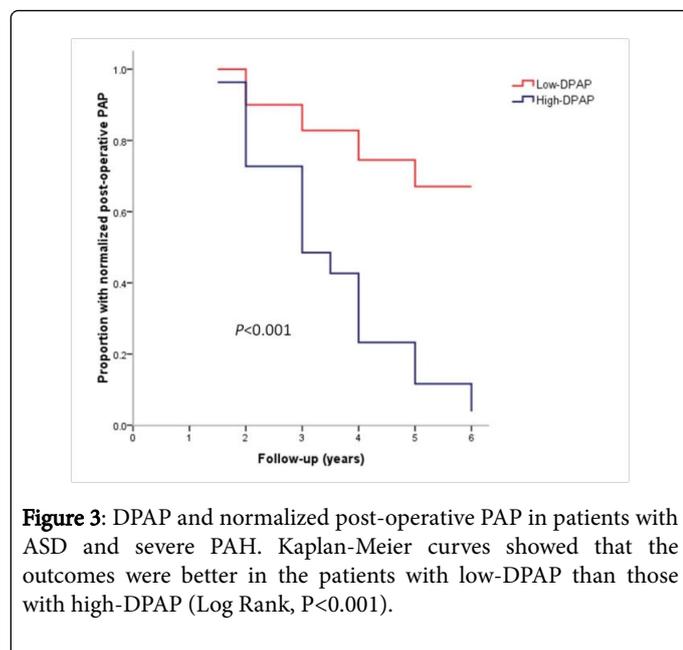
Figure 3: DPAP and normalized post-operative PAP in patients with ASD and severe PAH. Kaplan-Meier curves showed that the outcomes were better in the patients with low-DPAP than those with high-DPAP (Log Rank, P<0.001).

In this study, the cut-off value of DPAP was determined as 25 mmHg through a ROC analysis. The limit of DPAP was usually defined as <15 mmHg in normal subjects, however, there was no clear consensus as to the value limit in severe PAH. To determine the best cut-off value of DPAP, ROC analysis was carried out in this study. The cut-off point was determined as 25 mmHg, and this value of DPAP corresponded to the best diagnostic ability. Furthermore, according to this cut-off value, low-DPAP and high-DPAP accounted for 36.5% and 63.5%, respectively.

After closure of ASD, the patients with low-DPAP tended to have the normalization of PAP compared with high-DPAP. In this study, the normalization of PAP was identified in about 71% of patients with low-DPAP, but just 7.4% with high-DPAP. Previous research showed that there was a high correlation between DPAP and PVR in congenital heart disease with left to right shunt [11]. Though the invasive calculation of PVR has become an important predictor for reversible PAH, its accuracy was influenced by several variables, especially the measurement error in Qp. In comparison, the measurement of DPAP was less influenced and the diastolic pulmonary pressure gradient has been regarded as an indicator for pulmonary vascular disease [8,10]. In the absence of left ventricular diastolic dysfunction, the level of DPAP was probably associated with the reversibility of PAH in these patients. Up to now, however, no related reports are available. In this research, our findings proved the role of DPAP in the evaluation of severe PAH related to ASD.

In this study, normalization of PAP occurred in about 50% of patients with suggested indicators and only 14% of borderline patients (according to the recommendations in guideline) [6]. Therefore, the recommended indications in current guideline can't guarantee the normalized post-operative PAP. After closure of ASD, persistent PH has been recognized as a major determinant of poor outcomes in these patients [15-17]. Although conventional indicators for intervention (PVR, Pp/Ps or Rp/Rs) have proven to be valuable in clinical practice, they have lots of limitations [18]. Up to now, the reversibility of severe PAH remains a challenge in patients with untreated ASD, especially for those borderline patients. Therefore, it was urgent to seek additional

predictors for the pre-operative evaluation of reversible PAH. In this research, our findings showed that the level of DPAP might provide additional information in deciding the indication for ASD closure. However, persistent PH still occurred in 29% of patients with low-DPAP. Therefore, the prediction of reversible PAH should base on the combination of multiple indicators rather than any single parameter. Further studies were required to establish the feasible recommendations in guideline.

With the comparable SPAP, the level of DPAP varied greatly and had the prognostic implication in this study. It was usually considered that DPAP mainly reflected peripheral vascular resistance, and diastolic pulmonary pressure gradient had the potential to diagnose pulmonary vascular disease [19-21]. Therefore, the level of DPAP was probably associated with the prognosis, which was confirmed in the research. However, the mechanism was still unclear about the disproportional elevation between DPAP and SPAP. In addition, the patients with low-DPAP were older and had lower PVR. Considering that the compliance vessels were the same as the resistance vessels in PAH [21], it was probably secondary to the survivor selection bias in this study.

Study limitations

There are several limitations in the study. We analyzed only a limited number of patients. To generalize the results of this study, large population of patients was essential. In our center, it was oxygen but not nitric oxide that was traditionally used in patients with PAH related to congenital heart disease (nitric oxide may be more preferable). In the follow-up of patients after closure of ASD, repeated RHC was not the routine practice at our center and only Doppler-calculated SPAP was available in these patients. In comparison to recent research [22], the long-term follow up of this study demonstrated that left ventricular diastolic function remained in the normal limit (estimated with Doppler-TTE). In the absence of invasive measurement of left ventricular end-diastolic pressure, however, it was difficult to exclude the possibility of associated post-capillary component in this study.

Conclusions

In patients with ASD and severe PAH, the level of DPAP varies greatly. Furthermore, the patients with low-DPAP are more likely to develop normalized post-operative PAP than patients with high-DPAP. The presence of low-DPAP has the potential to become a predictor for the post-operative normalization of PAP.

Sources of Funding

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