Long-term outcomes of percutaneous closure of patent ductus arteriosus accompanied with unilateral absence of pulmonary artery

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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ABSTRACT
Objective: This study aimed to evaluate the long-term outcome of patients with PDA associated with UAPA.
Methods: Patients diagnosed with PDA associated with UAPA were retrospectively enrolled from January 2005 to June 2019. Clinical data, treatment and follow-up information were evaluated.
Results: 11 patients (5 males and 6 females) were diagnosed with PDA associated with UAPA. Percutaneous closure was conducted in 9 patients successfully. The median age was 37 months. The mean diameter of the PDA and occluders were 5.3±1.8mm (range 2-8.1 mm), 11.5±3.9 mm (4-16 mm) respectively. The median in 5 patients with the pulmonary: systemic flow ratio (Qp:Qs) was 1.41(1.28-8.7) and total lung resistance

was 12 wood (1.8-13.6) . The mean systolic pulmonary artery pressure was 68.3±19.1mmHg（42-105mmHg). In 5 patients with pre- and post-

procedure catheter data, the systolic pulmonary arterial pressure decreased significantly after closure 77.0±20.2 v 58.8±17.5 mmHg (p = 0.024), and so was the mean pulmonary arterial pressure 58.2±14.6 v 39.0±14.1 mmHg (p = 0.18). The pulmonary artery pressure and heart size gradually decreased to normal in 8 patients, and the quality of life was significantly improved. The ratio of lung to systemic circulation pressure in all these patients was less than 0.75.
Conclusions: In appropriate patients with PDA associated with UAPA, transcatheter closure of PDA has the potential to improve the pulmonary artery hypertension. The ratio of lung to systemic circulation pressure less than 0.75 may be important reference index for predicting whether the pulmonary artery pressure could be reduced to normal after occlusion.
Keywords transcatheter closure; patent ductus arteriosus; absence of pulmonary artery; pulmonary hypertension; outcome

Introdcution

Unilateral absence of pulmonary artery (UAPA) is a very rare congenital cardiovascular malformation. It was first reported in 1868 and described the radiologic features of this lesion in 1942. Until 1952, the diagnosis by angiocardiogram was first reported by Madoff, Gaensler. and Strieder(1). The prevalence of isolated UAPA without associated cardiac anomalies ranged from 1 in 200,000 to 1 in 300,000 adults(2). In 2011, Bockeria et al. found 352 cases of UAPA in the world literature and an additional 67 cases were diagnosed in the Bakoulev Scientific Center for Cardiovascular Surgery. In 237 out of 419 cases, UAPA was associated with congenital heart defects(3).The common congenital heart defects accompanied with unilateral absence of pulmonary artery were tetralogy of Fallot(TOF), persistence of ductus arteriosus(PDA), septal defects(4). The most common symptoms include frequent pulmonary infections, dyspnea or limited exercise tolerance and hemoptysis. Moreover, pulmonary hypertension is reportedly present in 44% of patients(5). The incidence of pulmonary hypertension in patients with congenital heart defects can be as high as 88% (TOF has not been included in these statistics) which suggest that an increased pulmonary blood flow from the time of birth is an important factor in the development of pulmonary hypertension(1). Early intervention in patients with isolated pulmonary artery may reverse the pulmonary artery hypertension. While, there is limited data published in the literature reports on the outcome of percutaneous closure of PDA in patients with UAPA. The purpose of the present study aimed to determine therapeutic strategies and long-term outcome of PDA in patients with UAPA.

Methods

Study population

From January 2005 to June 2019, 11 patients were diagnosed with PDA associated with UAPA, including one case with right aortic arch associated with absence of the left pulmonary artery, and ten cases with absence of the right pulmonary artery. After admission, all patients passed clinical physical examination, chest X-ray, electrocardiogram, transthoracic echocardiogram, or multi-slice CT examination. All 11 cases underwent cardiac catheterization. One case was diagnosed with patent ductus arteriosus before operation, and was confirmed by angiography during interventional therapy as UAPA combined with patent ductus arteriosus. Among them, there were 5 males and 6 females, with a median age of 37 months, 1 case of fetal echocardiography found , 7 cases of repeated respiratory infections, 2 cases of hemoptysis, 5 cases of decreased exercise tolerance, 8 cases of audible precordial murmur (2 cases of continuous murmur) (Table 1). All patients signed an informed consent form before surgery.

This study was conducted in accordance with the Declaration of Helsinki (World Medical Assembly) and its amendments, and was approved by the Ethics Committee of Beijing Anzhen Hospital.

Procedure

The technique of transcatheter closure of PDA using Duct occluder was similar to that described in previous reports(6). After percutanous puncture of the femoral artery and vein, all patients underwent routine right and left heart catheterisation and complete haemodynamic data on each cardiac chamber and great artery were obtained. The descending aortogram in lateral or right anterior oblique view was performed with a 5 French pigtail catheter (Cordis, Miami, Florida, USA) to define the size and anatomy of PDA. If the patients have severe pulmonary hypertension, haemodynamic measurements were repeated during inhalation of oxygen, especially for measurement of pulmonary arterial pressure and aortic pressure.

The size of the occlusion device that we chose was 4-8 mm larger than the narrowest size of the PDA, which was measured through a descending aortogram. After screwing it to the delivery cable, the occluder was pulled into the loader and was introduced into the guiding sheath. Under fluoroscopic guidance, the occluder was deployed and pulled gently against the aortic ampulla. Then, the rest of the occluder was deployed into the PDA. After repeat the aortic angiography to confirm the correct position of the occluder, the duct occluder device could be released. Occlusion strategy for patients with severe pulmonary hypertension was similar to that described in previous reports(6).

Follow up

For each patient, a chest radiograph, an electrocardiogram and an echocardiogram were recorded at 1 day, 1 month, and serially at 6-12 month

intervals.

Statistical analysis

The data in the study were expressed as mean (SD), and range was also provided. The results before and after occlusion were compared using paired-samples t tests, and p<0.05 was considered significant. Statistical software used in this study was SPSS version 23.

Results

Baseline and procedural characteristics

11 patients were diagnosed with PDA accompanied with UAPA. No. 10 was a 52 year-old women, and she had symptoms of hemoptysis, and was diagnosed with absence of the right pulmonary artery with PDA and severe pulmonary hypertension in other hospital 13 years ago. She has been treated with intermittent oral medication and her symptoms have improved. Routine right and left heart catheterization were performed under local anesthesia. Total lung resistance and pulmonary arteriole resistance were 26 wood and 21.9 wood, respectively. Pulmonary artery pressure and aortic pressure were 143/73/101(systolic/diastolic/ mean pressure) mmHg and 159/82/111mmHg, respectively. The descending aortic blood oxygen saturation was 79%. Because pulmonary hypertension was severe to the extent of Eisenmenger syndrome, 'trial occlusion' treatment was not performed. She accepted medical therapy continuously. The latest review showed that the clinical symptoms were improved compared with the previous one. The pulmonary artery systolic pressure estimated by echocardiography was 108 mmHg, which was roughly the same as the pre-right heart catheterization (114mmHg). 1 patient was 1 year-old baby girl, and same as the first patient with Eisenmenger syndrome (QP:QS=0.47) accepted medical therapy.(Table. 2)

Closure was conducted successfully in 9 patients (Table. 2). The median age was 37 months (7 months to 135 months).Presentation on the ECG was non-specific, including Left ventricular high voltage (2cases) and right ventricular hypertrophy (5 cases). All patients' chest X-ray showed abnormal, such as decreased pulmonary volume, bilateral lung blood asymmetry and deviation of the mediastinum. 5 patients was

performed cardiac CT to confirm the diagnosis and exclude other cardiac malformations（Figure. 1）. All patients were diagnosed with TTE

pre-procedure except 1 patient who was confirmed during the intervention(Figure.2). No. 3 complained of haemoptysis, and was diagnosed with

PDA with UAPA and collateral arteries, and was treated with closure of PDA and selected collateral arteries（Figure. 2）. No. 7's results of first

cardiac catheterization and Iloprost inhalation test were negative, so treatment with Bosentan hopes to reduce pulmonary artery pressure. half a year later, the right heart catheterization and drug inhalation test showed positive, 'trial occlusion' indicating a large amount of residual shunt, so giving up, and after another six months, 'trial occlusion' was preformed again, pulmonary artery pressure gradually decreases and the device was released.

The mean diameter of the PDA was 5.3±1.8mm (range 2-8.1 mm). The diameter of the occluder was 11.5±3.9 mm (4-16 mm). The median in 5 patients with the pulmonary: systemic flow ratio (Qp:Qs) was 1.41(1.28-8.7) and total lung resistance was 12 wood (1.8-13.6) . In the whole, the

mean systolic pulmonary artery pressure was 68.3±19.1mmHg（42-105mmHg). In 5 patients with pre- and post-procedure catheter data, the

systolic pulmonary arterial pressure decreased significantly after closure 77.0±20.2 v 58.8±17.5 mmHg (p = 0.024), and so was the mean pulmonary arterial pressure 58.2±14.6 v 39.0±14.1 mmHg (p = 0.18). No complications occurred in the procedure.

Follow-up
The median follow-up time was 36 months (3-188months). No. 6 was lost to follow-up 28 months after interventional therapy. Before the loss to follow-up, echocardiogram showed normal heart size and pulmonary artery pressure. No. 7 had been treated with bosentan before and after interventional surgery , and was lost to follow-up 3 months later. One day, one month and three months after interventional therapy, the pulmonary artery pressures estimated by echocardiography were 66 mmHg, 84 mmHg, and 118 mmHg, respectively. No. 3 still had intermittent hemoptysis after interventional treatment, and another angiographic examination was performed nine months later showed that collateral arteries were small and could not be treated with embolization. All signs and symptoms had been improved markedly in other 7 patients. No. 9 complained of poorer physical activity than children of the same age, but echocardiogram showed normal heart size and pulmonary artery pressure. No complications, including residual shunt, device malposition, endocarditis occurred during the follow-up. No deterioration in pulmonary hypertension was identified in these patients.

Discussion
Unilateral absence of the pulmonary artery is a rare congenital malformation. In terms of embryology, An absent pulmonary arteries is caused by the involution of the proximal sixth aortic arch and persistence of the connection of the intrapulmonary pulmonary arteries to the distal sixth aortic arch(2). It has been pointed out that all reported cases of absent PA with satisfactory angiographical, surgical or autopsy documentation

had a ductus arteriosus or ligamentum ipsilateral to the absent pulmonary arteries (8,9).

UAPA is twice as common on the right side. Ten Harkel et al. (50) added a review of 107 cases of the right was absent in 63% of patients (67 of 107 patients). while in patients accompanied PDA in our study, this ratio is 10/11.Recurrent pulmonary infections, decreased exercise tolerance and mild dyspnoea during exertion are the most common symptoms(5). While in some patients, they are often asymptomatic or present with haemoptysis, cardiac murmur or are incidentally detected during chest radiography. In our study, one case of fetal echocardiography showed that the right pulmonary artery was unclear, and UAPA was suspected. She suffered repeated respiratory infections after birth, and received interventional treatment for patent ductus arteriosus in 7 months after birth. Other symptoms included cardiac murmur, pulmonary infections, and haemoptysis.

There is no consensus on treatment of UAPA. The choice of treatment is based on symptoms of the patients, pulmonary artery (PA) anatomy and associated aortopulmonary collaterals, associated cardiovascular anomalies and pulmonary hypertension(2). An 'ideal' surgical treatment for UAPA consists of the restoration of antegrade blood flow in the ipsilateral lung as well as the repair of congenital heart defects, if any. (10,11). However, very few studies reported the treatment and selective pulmonary vein angiogram was not performed routinely to evaluate pulmonary artery development (12). When the hilar artery in the route of the ipsilateral lung cannot be identified and the inclusion of this lung into pulmonary circulation is not possible, the surgical treatment is directed at the repair of concomitant congenital heart defects(10).

Patients with congenital heart disease and large persistent left-to-right shunts are exposed to persistent flow overload within the pulmonary circulation. Over time, this exposure to increased pulmonary blood flow would result in increased shear stress on the endothelial cells and might impair endothelial function and leading to pulmonary artery hypertension (13). In our study, all patients had different degrees of pulmonary hypertension, and two patients showed Eisenmanger syndrome. One of the patient with Eisenmenger syndrome was only one year old, suggesting that Eisenmenger syndrome is not simply related to time. Ling's report showed that pulmonary artery pressure decreased significantly after oral bosentan treatment for 6 months after interventional therapy(14). But In our study, one patient had been treated with bosentan orally, and the pulmonary artery pressure decreased significantly immediately after the closure, and the pulmonary artery pressure gradually increased during the 3-month follow-up process, suggesting that the damaged pulmonary vascular bed may get even worse after closure. Therefore, annual echocardiography or right heart catherization if necessary was recommended to monitor the development of pulmonary hypertension. The pulmonary artery pressure and heart size of the remaining 8 patients gradually decreased to normal, and the quality of life was significantly improved. In those patients, there were 3 cases of these patients with pulmonary artery systolic pressure greater than 70mmHg, and 5 cases with mean pressure greater than 45 mmHg. However, the ratio of lung to systemic circulation pressure in all these patients was less than 0.75,

suggesting that this may be important reference index for predicting whether the pulmonary artery pressure could be reduced to a normal one after occlusion. From our study, we supposed that simply close the PDA could be a help especially in decelerating the progress of pulmonary hypertension in the short and long-term for appropriate patient.

Hemoptysis occurs in about 20% of cases of UAPA and can be self-limiting for many years, but may also lead to massive pulmonary hemorrhage and death(5). Koga' report show hemoptysis and collateral arteries were found 50% of patients 20 years of age or older compared with only 0 and 13% of patients younger than 1 year, respectively(15). embolization of collateral arteries has been reported to be a useful option as a palliative treatment(16). In our study, 1 patient underwent both patent ductus arteriosus occlusion and pulmonary collateral embolization treatment. After treatment, there were still intermittent hemoptysis symptoms, and another angiographic examination was performed nine months later showed that collateral arteries were small and could not be treated with embolization. Pneumonectomy may be a better choice (17).

Limitations
This study is limited by its small sample size and retrospective nature. A patient with severe pulmonary hypertension was lost to follow-up 3 months after interventional therapy, which may affect the interpretation of results. Selective pulmonary vein wedge angiogram in the arterial phase was not obtained to evaluate peripheral pulmonary artery. A larger cohort of patients are needed to estimate the feasibility and long-term benefit.

Conclusion
Our study has shown the clinical characteristics, treatment in patients with PDA accompanied with UAPA. Transcatheter closure of PDA has the potential to decrease the pulmonary artery hypertension in appropriate patients. the ratio of lung to systemic circulation pressure may be important reference index for predicting whether the pulmonary artery pressure could be reduced to a normal one after occlusion. Further follow-up is required to monitor the long-term outcomes.

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Table.1 Clinical characteristics of patients with all patients

No.	Sex	Age (months)	Absence of PA	Symptoms	ECG	Cardiac CT
1	M	37	R	frequent pulmonary infections, limited exercise tolerance	N	Y

No.	Sex		Side	Symptoms	ECG	
2	F	7	R	frequent pulmonary infections, limited exercise tolerance, cardiac murmur	Right ventricular high voltage	N
3	M	47	R	hemoptysis, cardiac murmur	Right ventricular high voltage	Y
4	M	18	R	frequent pulmonary infections, cardiac murmur	Right ventricular high voltage	N
5	M	26	L	frequent pulmonary infections, limited exercise tolerance, cardiac murmur	Left ventricular hypertrophy	Y
6	F	135	R	frequent pulmonary infections, limited exercise tolerance, cardiac murmur	N	Y
7	M	50	R	frequent pulmonary infections ,limited exercise tolerance	Right ventricular high voltage	N
8	F	80	R	cardiac murmur	Right ventricular high voltage	Y
9	F	18	R	frequent pulmonary infections, limited exercise tolerance, cardiac murmur	Left ventricular hypertrophy	Y
10	F	624	R	hemoptysis, limited exercise tolerance	Right ventricular high voltage	Y
11	F	13	R	cardiac murmur	Right ventricular high voltage	Y

No.: number; M: male; F: female; R: right; L: left; PA: pulmonary artery; ECG: electrocardiogram Y: yes; N: none.
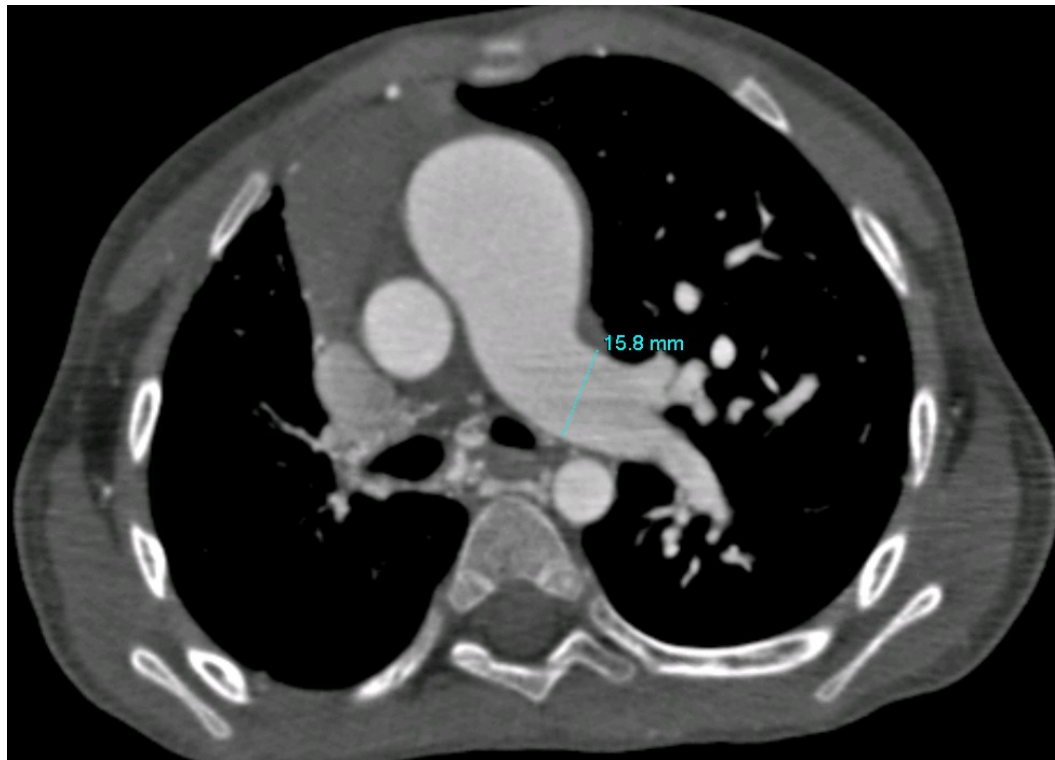
Table.2 haemodynamic data of all patients

No.	Qp:Qs	Woods	PAP(S/D/M)	Pp:Ps	PDA Size	Device Size	After PAP
1	1.3	6	42/25/30	0.47	2	4	N

No.							
2	N	N	70/33/47	0.71	3.8	10	N
3	N	N	71/38/53	0.7	7	16	55/23/38
4	1.28	12	88/48/67	0.72	4.3	10	64/21/41
5	N	N	52/24/36	0.57	4.7	10	32/10 (19)
6	1.41	13.6	63/41/52	0.51	5.6	12	N
7	N	N	105/53/74	0.93	8.1	16	80/42/59
8	1.66	13	69/57/61	0.73	6.7	16	63/20/38
9	8.7	1.8	55/26/42	0.63	5.6	10	N
10	0.83	26	143/73/101	0.9	15	N	N
11	0.47	25	83/48/66	1.04	3	N	N

No.: number; Y: yes; N: none; Qp:Qs: ratio of pulmonary blood flow to systemic blood flow; PAP: pulmonary artery pressure; Pp:Ps: ratio of pulmonary artery pressure to aortic pressure; PDA: patent ductus arteriosus.

Figure.1

CT showing absence of right pulmonary artery, widening of main pulmonary artery and left pulmonary artery
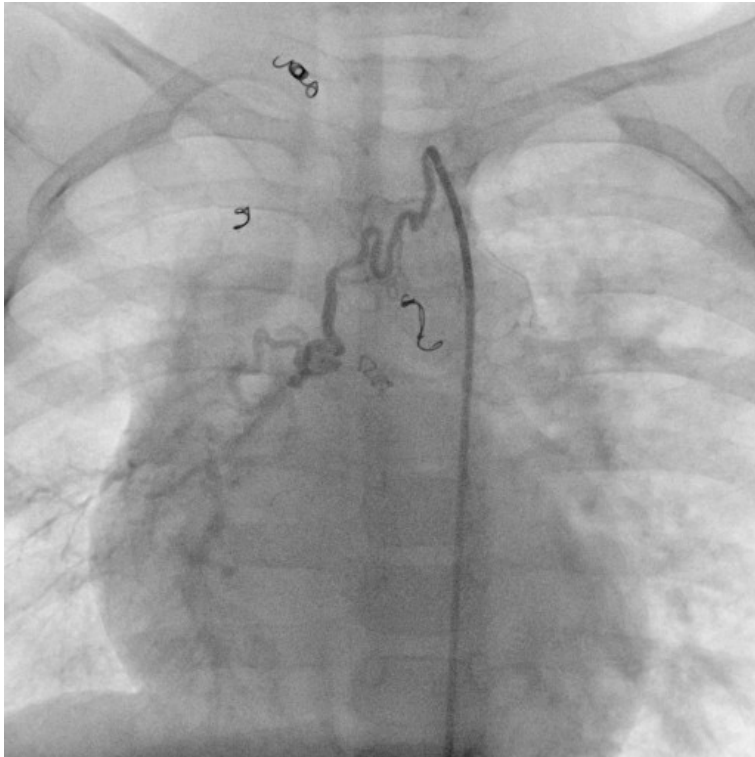
Figure.2

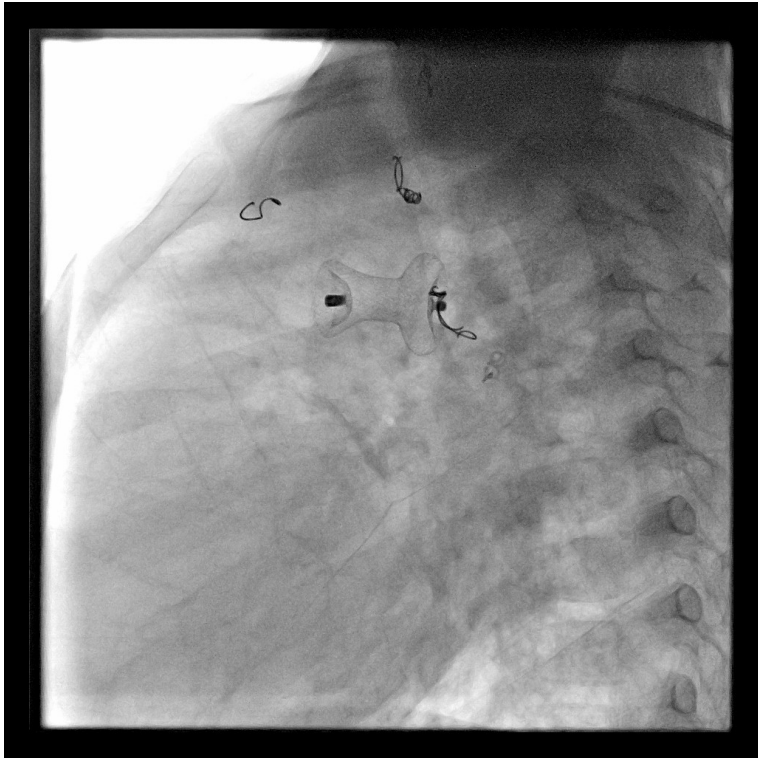RV angiogram showing the absence of the left pulmonary artery

Figuer.3

1.Aortic angiography showing patent ductus arteriosus

2.Selective collateral arteries angiography and collateral embolization

3.After collateral embolization and occluder release