Reverse Remodeling of Pulmonary Arterioles After Pulmonary Artery Banding in Patients ≥ 2 Years Old with Severe Pulmonary Arterial Hypertension and Congenital Heart Disease

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Abstract

The purpose of this study was to evaluate the pathological changes of the pulmonary arterioles in patients ≥ 2 years of age who first underwent a pulmonary artery banding (PAB) procedure, followed by bidirectional Glenn or Fontan according to their specific conditions. This was a prospective study of 15 children diagnosed and treated with PAB at the Department of Cardiothoracic Surgery of Anzhen Hospital between January 2009 and December 2012. The percentage of media area (%MS) of pulmonary arteriole, the percentage of media thickness (%MT), and pulmonary arterial density (APSC) were calculated from lung tissue sections. Pulmonary artery pressure decreased significantly after PAB surgery ($P < 0.01$). Post-operative mean pulmonary artery pressure declined significantly ($P < 0.01$), the cardiothoracic ratio was reduced ($P < 0.05$), and percutaneous oxygen saturation (inhaled air) decreased to 80–85% ($P < 0.01$). %MT (from $35.1 \pm 5.6\%$ to $26.9 \pm 4.3\%$, $P < 0.01$), %MS (from $51.4 \pm 6.7\%$ to $32.2 \pm 7.4\%$, $P < 0.01$), and APSC (from 108.3 ± 38.5 to 83.6 ± 19.6 , $P < 0.01$) were decreased significantly after PAB. Five patients underwent the bidirectional Glenn procedure and four underwent Fontan. In conclusion, the results suggest that PAB can reduce pulmonary artery pressure and that pulmonary arterial lesions can be reversed after PAB.

Keywords Pulmonary artery banding · Pulmonary artery · Pathological alteration · Pulmonary arterial hypertension · Congenital heart disease

Introduction

For complex congenital heart defects combined with severe pulmonary arterial hypertension that can only be managed using single ventricular repair (such as single ventricle, tricuspid atresia, mitral atresia, crisscross heart, double outlet right ventricle with ventricular septal defect far from the two arteries, ventricular disequilibrium complete atrioventricular pathway, and complex transposition of the great arteries), pulmonary artery banding (PAB) is usually recommended to be performed at least within 6 months, followed by bidirectional Glenn or total cavopulmonary anastomosis (Fontan), according to the each patient's specific conditions [1, 2]. Otherwise, with the progression of pulmonary arterial

hypertension, irreversible obstructive lesions would occur in pulmonary arterioles, resulting in the loss of surgery opportunity.

Patients who have missed the optimal age for surgery and are ≥ 2 years of age are usually considered to have irreversible pulmonary vascular lesions, and single ventricle repair cannot be performed. Therefore, the only therapeutic option for these patients is heart transplantation. Nevertheless, the characteristics of the pulmonary arterioles of these patients are mostly unknown, and it is also unknown whether there could be a reversal of the pulmonary arterial lesions after PAB. Furthermore, it is still controversial whether the patients can safely undergo PAB and then single ventricular repair [3–10].

In recent years, our hospital successively performed surgical treatment for the pediatric patients who had missed the optimal age of operation, and we achieved good early and mid-term results. Masaki et al. [10] reported that reverse remodeling occurs after PAB, but that the magnitude of this reversal was more important before 6 months of age.

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Therefore, the aim of the present study was to evaluate the pathological changes of the pulmonary arterioles in patients ≥ 2 years of age who first underwent PAB, followed by bidirectional Glenn or Fontan according to their specific conditions. The results could provide some basis to support our clinical experience.

Material and Methods

Patients

This was a prospective study of children diagnosed and treated at the Department of Cardiothoracic Surgery of Anzhen Hospital between January 2009 and December 2012. The study was approved by the ethics committee of Anzhen Hospital. Written informed consent was obtained from the legal guardians.

The inclusion criteria were: (1) ≥ 2 but < 18 years of age; (2) congenital heart disease combined with severe pulmonary arterial hypertension (mean pulmonary artery pressure [mPAP] > 25 mmHg [11]); (3) scheduled for single ventricular repair; (4) baseline percutaneous oxygen saturation (SpO_2) $\geq 85\%$; and (5) pulmonary blood significantly increased preoperatively on chest X-ray. Patients with pulmonary malformations were excluded such as pneumatocele, pulmonary emphysema, pulmonary fibrosis, pulmonary tumor, pulmonary hypoplasia.

Infantile cadaver specimens who were with normal cardiopulmonary system (i.e. without congenital heart disease or secondary or primary pulmonary arterial hypertension) were selected between January 2001 and December 2010. Lung specimens were obtained as the control group. The cadavers were preserved with formalin, and the cause of death was liver and kidney dysfunction or trauma.

Grouping

The subjects were divided into three groups. The control group included 16 cases of infantile cadavers. The PAB group included 15 patients ≥ 2 years of age who suffered from congenital heart disease combined with pulmonary arterial hypertension treated using PAB. The Glenn/Fontan group included nine patients who were selected from the PAB group to undergo stage II Glenn/Fontan procedure.

Surgery

PAB surgery was performed first. An incision was made through the middle of the chest under intravenous-inhalation anesthesia. A piezometric tube was implanted into the distal end of the aorta and the pulmonary artery to continuously measure the pulmonary artery pressure intraoperatively.

Pneumonia, if present, was treated before surgery. After dissociating the aortopulmonary septum, the root of the aorta and the pulmonary artery was wrapped by a Gore-Tex strip of 3–5 mm in width. The banding was adjusted to achieve $\text{SpO}_2 \geq 80\%$, pulmonary arterial systolic pressure ≤ 25 mmHg, and mPAP ≤ 20 mmHg, under inhaled oxygen at 40%. After observation for 10–15 min, changes in arterial systolic pressure, heart rate, and SpO_2 were verified. Arterial blood gas was reviewed. The concordance between arterial SpO_2 and transcutaneous SpO_2 was verified. The absence of metabolic acidosis and normal PCO_2 were verified. If all parameters were correct, the banding was fixed to avoid slippage.

Two to three years after PAB, superior vena cava pulmonary anastomosis (Glenn) and total cavopulmonary anastomosis (Fontan) were performed according to the age, SpO_2 , mPAP, and pulmonary artery development of the children. Pulmonary vasodilator therapy was not continued during the interval between the PAB surgery and Glenn/Fontan surgery.

Perioperative Medication

Nitric oxide at 10–20 ppm was inhaled by patients with residual pulmonary arterial hypertension in the perioperative period. Prostacyclin was inhaled by nebulization or continuously intravenously infused at 3–10 ng/kg/min. After weaning from the ventilator, sildenafil at 0.5–3 mg/kg/days was administered and oral bosentan at 15.6–31.25 mg was given once a day.

Pathological Examination of Lung Tissue

For the PAB and Glenn/Fontan groups, the pleura was cut off intraoperatively and the middle lobe of the right lung was clipped using an auricle clamp after lung inflation. A lung tissue specimen of 1.0×1.0 cm was harvested, washed with 0.9% normal saline, fixed with formalin, dehydrated, embedded in paraffin, and sectioned to 5 μm to perform hematoxylin and eosin (HE) staining and elastic fiber staining. Normal lung tissues of the cadaver were harvested from the same location as the patients. HE grading was performed for each case [12]. Lung tissue sections were quantitatively analyzed under a microscope computer system (BX53 microscope, DP73 image acquisition system, Olympus, Tokyo, Japan). The percentage of media area (%MS) of pulmonary arteriole, the percentage of media thickness (%MT), and pulmonary arterial density (APSC; i.e. the number of pulmonary arterioles in each square centimeter) were calculated. The lung tissue area was measured using cellSens Dimension 1.7 software (Olympus, Tokyo, Japan). The number of blood vessels was manually counted in sections stained for smooth muscle actin (SMA), performed twice to obtain the mean values. The SMA-stained sections were scanned using a NanoZoomer 2.0 HT C9600-13 digital slide scanner

(Hamamatsu Photonics K.K., Hamamatsu, Japan). The total area of tissue on SMA staining sections and SMA stained area were measured by cellSens Dimension 1.7. Measurements were performed three times and the percentages were calculated by two approximations.

The formulas were:

$$\% \text{ MT} = \left[\left(\frac{\text{Cavity diameter of outer elastic layer} - \text{cavity diameter of inner elastic layer}}{\text{Cavity diameter of outer elastic layer}} \right) \right] \times 100\% ,$$

$$\% \text{ MS} = \left[\left(\frac{\text{Cavity area of outer elastic layer} - \text{cavity are of inner elastic layer}}{\text{Cavity area of outer elastic layer}} \right) \right] \times 100\% ,$$

$$\text{APSC} = \left(\frac{\text{The number of pulmonary arterioles in a section}}{\text{The area of the section}} \right) \times 100\% .$$

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD) and were compared using the Student *t* test. Categorical variables were expressed as frequency (percentage). Two-sided *P* values < 0.05 were considered statistically significant.

Results

Characteristics of the Subjects

There were 15 patients in the PAB group (nine males and six females). They were 7.8 ± 3.8 years of age and weighed 8.82 ± 4.24 kg. The preoperative mPAP was 62.2 ± 36.8 mmHg. The preoperative SpO₂ was $90 \pm 4\%$ (85–100%).

Table 1 Baseline characteristics of the patients

Variable	PAB (<i>n</i> = 15)	Glenn/Fontan (<i>n</i> = 9)
Gender, <i>n</i> (%)		
Male	9 (60)	6 (67)
Female	6 (40)	3 (33)
Age (years)	7.8 ± 3.8	5.8 ± 3.2
Weight (kg)	8.82 ± 4.24	13.92 ± 5.24
Preoperative mPAP (mmHg)	62.2 ± 36.8	18.6 ± 3.1
Preoperative SpO ₂ (%)	90 ± 4	80 ± 2
Cardiothoracic ratio	0.66 ± 0.09	0.66 ± 0.09

Data are expressed as mean $\pm$ standard deviation or *n* (%)

PAB pulmonary artery banding, SpO₂ percutaneous oxygen saturation, mPAP mean pulmonary artery pressure

There were seven patients whose SpO₂ was only 75–80% at the first visit, and they achieved $> 85\%$ after cardiac and diuretic therapy. Pulmonary blood flow was significantly higher than normal according to preoperative chest X-ray and the cardiothoracic ratio was 0.66 ± 0.09 (Table 1). The heart malformations included four cases of single ventricle,

four cases of tricuspid atresia, two cases of double outlet right ventricle with ventricular septal defect far from the two arteries combined with left ventricular dysplasia, two cases of severe tricuspid stenosis, two cases of ventricular disequilibrium complete atrioventricular pathway, and one case of crisscross heart. ECG showed that all patients were with sinus rhythm; there were five cases of right ventricular hypertrophy, eight cases of biventricular hypertrophy, and two cases of left ventricular hypertrophy. All patients in the PAB group were diagnosed by echocardiography. There were seven patients combined with pneumonia preoperatively.

There were nine patients who underwent Glenn/Fontan (six males and three females). They were aged 5.8 ± 3.2 years and weighed 13.92 ± 5.24 kg. Their preoperative mPAP was 18.6 ± 3.1 mmHg. Their preoperative SpO₂ was $80 \pm 2\%$, and their cardiothoracic ratio was 0.66 ± 0.09 (Table 1). The cardiac malformations included five cases of single ventricle, two cases of tricuspid atresia, one case of double outlet right ventricle with ventricular septal defect far from the two arteries combined with left ventricular dysplasia, and one case of ventricular disequilibrium complete atrioventricular pathway.

Table 2 Preoperative and postoperative data of patients who underwent PAB

Variable	Pre-PAB (<i>n</i> = 15)	Post-PAB (<i>n</i> = 15)	<i>P</i>
mPAP (mmHg)	62.0 ± 36.8	16.8 ± 3.1	< 0.01
SpO ₂ (%)	89 ± 9	80 ± 2	< 0.01
Cardiothoracic ratio	0.66 ± 0.09	0.63 ± 0.07	< 0.05

Data are expressed as mean $\pm$ standard deviation

PAB pulmonary artery banding, SpO₂ percutaneous oxygen saturation, mPAP mean pulmonary artery pressure

Table 3 Ventilator-assisted breathing, ICU stay, and postoperative hospitalization

Variable	PAB (<i>n</i> = 15)	Glenn/Fontan (<i>n</i> = 9)
Ventilator use (h)	10.0 ± 4.2	15.5 ± 17.2
Duration of ICU stay (h)	43.2 ± 17.4	60.2 ± 50.4
Postoperative hospitalization stay (days)	10.6 ± 4.3	11.6 ± 5.1

Data are expressed as mean ± standard deviation

PAB pulmonary artery banding, ICU intensive care unit

Characteristics of the Surgeries

There was no operative mortality in the PAB group. Postoperative non-fatal complications included two cases of pericardial effusion, which were cured after cardiac and diuretic therapy.

For the PAB group, the duration of ventilator use was 10.0 ± 4.2 h, the duration of intensive care unit (ICU) stay was 42.2 ± 17.4 h, and the postoperative hospitalization was 10.6 ± 4.3 days. Postoperative mPAP declined significantly ($P < 0.01$), the cardiothoracic ratio was reduced ($P < 0.05$), and SpO₂ (inhaled air) decreased to 80–85% ($P < 0.01$) (Tables 2 and 3).

For the Glenn/Fontan group, the duration of ventilator use was 15.5 ± 17.2 h, the duration of ICU stay was 60.2 ± 50.4 h, and postoperative hospitalization was 11.6 ± 5.1 days (Table 3).

Pathological Examination of the Lung Tissues

There were 15 patients with available specimens of lung tissue before PAB, including three cases of HE grade I, eight cases of HE grade II, and four cases of HE grade III. Among the patients in the Glenn/Fontan group (*n* = 9), HE grade was I in three (33%) patients, II in five (56%) patients and III in one (11%) patient before PAB, and I in four (44%) patients and II in five (56%) patients before Glenn/Fontan, respectively (Table 4). One patient with HE

Table 4 HE grading of pulmonary arteriole lesions before PAB and Glenn/Fontan

Variable	PAB (<i>n</i> = 15)	Glenn/Fontan (<i>n</i> = 9)	
		Stage I surgery	Stage II surgery
HE grade, <i>n</i> (%)			
I	3 (20)	3 (33)	4 (44)
II	8 (53)	5 (56)	5 (56)
III	4 (27)	1 (11)	0 (0)

PAB pulmonary artery banding, HE hematoxylin and eosin

Table 5 Quantitative analysis of the pathological alteration of pulmonary arterioles

Variable	PAB (<i>n</i> = 13)	Glenn/Fontan (<i>n</i> = 9)	Control (<i>n</i> = 16)
MT%	35.14 ± 5.78* ^{&}	26.92 ± 4.27 ^{#&}	16.72 ± 3.27 ^{*#}
MS%	51.39 ± 6.72* ^{&}	32.23 ± 7.42 ^{#&}	27.05 ± 5.74 ^{*#}
APSC	108.26 ± 38.49* ^{&}	83.63 ± 19.61 ^{#&}	43.53 ± 20.81 ^{*#}

PAB pulmonary artery banding, MT% percentage of media thickness, MS% percentage of the medial area, APSC pulmonary artery density

* $P < 0.01$ control versus PAB groups

[#] $P < 0.01$ control versus Glenn/Fontan groups

[&] $P < 0.01$ PAB versus Glenn/Fontan groups

grade III was alleviated to grade II, and one patient with grade II was alleviated to grade I after PAB.

The calculations could not be completed for two of the 15 patients in the PAB group. For SMA staining, %MT, %MS, and APSC were decreased significantly before the stage II procedure (*n* = 9). It suggested that pathological alterations of the pulmonary arterioles were reversible after PAB (Table 5; Figs. 1 and 2).

Discussion

Reverse remodeling occurs after PAB [10], but that the magnitude of this reversal is unknown in children operated at ≥ 2 years of age. Therefore, the present study aimed to evaluate the pathological changes of the pulmonary arterioles in patients ≥ 2 years of age that first underwent PAB, followed by bidirectional Glenn or Fontan according to their specific conditions. The results strongly suggest that PAB can reduce pulmonary artery pressure and that the pulmonary arterial lesions can be reversed after PAB. It could be possible for patients ≥ 2 years of age to undergo PAB and stage II procedure.

Severe pulmonary arterial hypertension is defined as mPAP > 25 mmHg [11]. The course of pulmonary arterial hypertension depends on the type of lesion, the size of the heart defect, and location and postnatal changes of pulmonary vascular resistance [13]. Severe pulmonary arterial hypertension can cause pulmonary vascular lesions and the opportunity for surgery can be lost [13]. Whether congenital heart disease combined with secondary severe pulmonary arterial hypertension can be cured depends on the age of the child, as well as the severity of preoperative pulmonary vascular lesions [14]. Nevertheless, it is still controversial whether the patients can safely undergo PAB and then single ventricular repair [3–10].

In recent years, advanced treatment of pulmonary arterial hypertension (including the application of endothelin receptor antagonists such as bosentan and the 5-phosphodiesterase

Fig. 1 Lung sections before pulmonary artery banding ($\times 10$ hematoxylin–eosin and smooth muscle actin)

Fig. 2 Lung sections before Glenn/Fontan ($\times 20$ hematoxylin–eosin and smooth muscle actin)

inhibitor sildenafil) can effectively reduce pulmonary vascular resistance in patients with congenital heart disease combined with secondary severe pulmonary arterial hypertension. Moreover, it can improve symptoms, reduce the perioperative risk, and expand the potential of radical surgical indications [15–18]. A strategy was used to select the appropriate patients who had a good response to advanced pulmonary arterial hypertension therapy and who could benefit from radical surgery for advanced pulmonary arterial hypertension treatment. Cardiac diuretics were used and, if necessary, sildenafil or bosentan was administered orally. Radical surgery was performed for the patients with an improved situation. Otherwise, it was a contraindication to surgery.

In 1958, Heath and Edwards [12] divided pulmonary vascular diseases into six grades according to the order of occurrence. Grade I is medial hypertrophy of vessels, without intimal hyperplasia. Grade II is medial hypertrophy of vessels combined with response of endothelial cells. Grade III is intimal fibrosis combined with medial hypertrophy, and

may have early extensive vasodilatation. Grade IV is extensive vasodilatation and regional vascular occlusion as well as plexiform lesions caused by endothelial fibrosis. Grade V is other dilated lesions of the vessels such as spongiform and hemangiomatous lesions. Finally, Grade VI is grade V lesions showing necrotizing arteritis. It is generally believed that grades I–II lesions are reversible, grade III is borderline lesions, and grades IV–VI are irreversible lesions. The appearance of plexiform lesions is thought to be a sign of the development of pulmonary vascular disease to a severe stage of pulmonary arterial hypertension. Even if the cardiac malformations are repaired by surgery, pulmonary vascular disease is difficult to reverse and even continues to develop postoperatively. Irreversible lesions can lead to fatal results [19–21]. More recent studies performed morphometric quantitative and semi-quantitative analyses according to the degree and quantity of pulmonary artery muscularization, as well as the thickness of the middle layer of the tube and extracellular matrix protein [22–24]. Furthermore, they divided pulmonary vascular lesions into three grades: A,

B, and C. Compared with normal tissues, smooth muscle in grade A is usually seen in the periphery, combined or not with smooth muscle hypertrophy in normal muscular media vascular. Smooth muscle eccentric expansion occurs in grade B and the media is 1.5–2 times that of the normal vessels (mild grade B) or more than 2 times that of the normal vessels (severe grade B). For grade C, compared with alveolus, those with the decline of the density of peripheral arteries < 50% is mild grade C, and those > 50% is severe grade C.

Pathological alterations of pulmonary arterial hypertension include pulmonary vasoconstriction, pulmonary vascular remodeling, and in situ thrombosis. Pulmonary vascular remodeling is a pathological feature of pulmonary arterial hypertension, manifesting as non-muscular arteriolar muscularization, muscular arterial medial hypertrophy, neointimal formation, and formation of plexiform lesions [25]. Moreover, the latter two features are the iconic changes of severe pulmonary arterial hypertension [13, 16, 26]. In the present study, the %MS, %MT, and APSC of pulmonary arterioles were significantly higher than in the control group. There were no grade IV lesions among the 24 cases with pathologic alteration of the pulmonary arterioles; HE grade I lesions accounted for 29%, while the grades II and III lesions accounted for 71% of all patients, suggesting that pulmonary vascular diseases in these patients were not severe. Among the patients in the Glenn/Fontan group, the HE grade was I in three (33%) patients, II in five (56%) patients and III in one (11%) patient before PAB, and I in four (44%) patients and II in five (56%) patients before Glenn/Fontan, respectively. These results are supported by Mooi et al. [27].

Plexiform lesion is usually a sign of severity and irreversibility of pulmonary arterial hypertension. In the 24 cases with severe pulmonary arterial hypertension, there was no HE grade IV case combined with plexiform lesion. Nevertheless, results of the follow-up demonstrated that the mPAP decreased after the operation, the diameter of the main pulmonary artery declined, transcutaneous oxygen saturation was normal, and weight and height increased. After PAB, the %MS, %MT, and APSC all significantly decreased, suggesting that although grade III was the critical state of the lesion, it was still reversible. These results are supported by a study by Masaki et al. [10], who showed that pulmonary arterial remodeling could be reversed after PAB. They also showed that this reversal was more important for children < 6 months of age [10], as supported by previous studies [28, 29]. Nevertheless, the present study suggests that significant vascular remodeling takes place even when PAB is performed after 2 years of age.

In addition, targeted drugs of pulmonary arterial hypertension (such as endothelin receptor antagonist therapy) contribute to the reversal of pathological alterations of pulmonary arterioles in patients with pulmonary arterial

hypertension. Endothelin receptor antagonists have roles of anti-proliferation and reverse remodeling [30–34].

The present study is not without limitations. Because of the rarity of such severe congenital heart diseases, the sample size was small. Nevertheless, this study provides data for the management of these patients.

Conclusion

The results suggest that PAB can reduce pulmonary artery pressure and that the pulmonary arterial lesions can be reversed after PAB. It could be possible for patients ≥ 2 years of age to undergo PAB and stage II procedure. Additional studies are necessary to determine the best strategy for these patients, which should be based on a combination of medical and surgical procedures.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no competing interests.

Research Involving Human Participants The study was approved by the ethics committee of Anzhen Hospital. Written informed consent was obtained from the legal guardians.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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