Valvuloplasty of fetal pulmonary atresia with intact ventricular septum and hypoplastic right heart: Mid-term follow-up results

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A R T I C L E   I N F O

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A B S T R A C T

Objective: This study aimed to analyze and evaluate the results of mid-term follow-up after fetal pulmonary valvuloplasty (FPV) in fetuses with pulmonary atresia with intact ventricular septum (PA/IVS).

Methods: From August 31, 2018, to May 31, 2019, seven fetuses with PA/IVS and hypoplastic right heart were included in this study. All underwent echocardiography by the same specialist and were operated on by the same team. Intervention and echocardiography data were collected, and changes in the associated indices noted during follow-up were analyzed.

Results: All seven fetuses successfully underwent FPV. The median gestational age at FPV was 27.54 weeks. The average FPV procedural time was 6 min. Persistent bradycardia requiring treatment occurred in 4/7 procedures. Finally, five pregnancies were successfully delivered, and the other two were aborted. Compared to data before fetal cardiac interventions (FCI), tricuspid valve annulus diameter/mitral valve annulus diameter (TV/MV) and right ventricle diameter/left ventricle diameter (RV/LV) of all fetuses had progressively improved. The maximum tricuspid regurgitation velocity decreased from 4.60 m/s to 3.64 m/s. The average follow-up time was 30.40 ± 2.05 months. During the follow-up period, the diameter of the tricuspid valve ring in five children continued to improve, and the development rate of the tricuspid valve was relatively obvious from 6 months to 1 year after birth. However, the development of the right ventricle after birth was relatively slow. It was discovered that there were individual variations in the development of the right ventricle during follow-up.

Conclusion: The findings support the potential for the development of the right ventricle and tricuspid valve in fetuses with PA/IVS who underwent FCI. Development of the right ventricle and tricuspid valve does not occur synchronously during pregnancy. The right ventricle develops rapidly in utero, but the development of tricuspid valve is more apparent after birth than in utero.

1. Introduction

Pulmonary atresia with intact ventricular septum (PA/IVS) is a rare congenital heart disease with specific morphological characteristics, such as right ventricular outflow tract (RVOT) obstruction, varying degrees of right ventricular (RV) hypoplasia, tricuspid valve (TV) hypoplasia, and abnormal connections between the RV and coronary arteries. The majority of fetuses with severe RV hypoplasia die after birth or in utero because of their compromised biventricular circulation. Prenatal treatment, that is, FCI, is the most effective method currently available to promote the development of the RV. In 2002, Tulzer et al. successfully performed fetal pulmonary valvuloplasty (FPV) under ultrasound guidance, which made the right heart capable of supporting pulmonary circulation. In the years that followed, a number of institutions reported technological innovations and physiological success in facilitating the attainment of biventricular circulation after birth in PA/IVS patients.

The goal of FPV is to decompress the hypertensive RV and augment inflow and outflow through the RV simultaneously, thereby improving fetal circulation and development of TV and RV and making them amendable to biventricular repair postnatally. In the past five years, a growing interest in fetal cardiac interventions (FCI) has been noticed in China. However, there is relative inexperience with FPV in terms of indications, technical methods, and management of complications that may arise. Furthermore, a significant variation in the incidence of PA/IVS was noted between the Western
and Asia-Pacific populations. Finally, there is also a paucity of follow-up data regarding cardiac development in infants after FPV. As the center with the largest number of FPV operations in China, we report mid-term follow-up data in fetuses with PA/IVS following FPV.

2. Methods

2.1. Ethics

This retrospective study was approved by the ethics committee of our hospital (No. FELL-YX-2018-004). All participants provided written informed consent before participating in the study.

2.2. Study population

From August 31, 2018, to May 31, 2019, seven fetuses with PA/IVS and hypoplastic right heart syndrome (HRHS) were included in this study. HRHS is a rare congenital defect characterized by hypoplasia of the right ventricle and tricuspid malformation. Fetal echocardiography was performed by the same highly skilled echocardiographer in all cases. Two-dimensional data were recorded to analyze the ventricular and valvular dimensions and ratios, as well as the RV filling time (duration of TV inflow [TVI]/cardiac cycle length [CC]) and tricuspid regurgitation velocity (TR). Color Doppler flow imaging was used to depict the blood flow through the ductus arteriosus and assess the level of TR.

The inclusion criterion was the presence of either membranous atresia (rather than muscular) or critical stenosis of the pulmonary valve with a discernible RVOT. The FCI referential indication is based on four parameters (TV/MV ≤ 0.83, RV/LV ≤ 0.64, pulmonary valve annulus diameter/aortic valve annulus diameter (PV/AV) ≤ 0.75, TVI/CC ≤ 0.365) with 100% sensitivity and 92% specificity predicting a non-biventricular outcome if three of four criteria are present.8 After 2–3 weeks of observation, the fetuses with ventricular morphological development delay, complete retrograde flow through the ductus arteriosus, and severe TR were diagnosed as PA/IVS. The exclusion criteria include muscular atresia of the RVOT, severe TR with low velocity (<2.5 m/s), severe fetal edema, and large RV sinusoids.

2.3. Measurement of FPV

Since the ROVT is located posterior to the sternum of the fetus, insertion of the needle into the fetal ROVT requires the subcostal route or intercostal space adjacent to the sternum. We adjusted the fetal position such that the fetus was in the optimal position with the spine down and the right chest somewhat anteriorly. The mother was given general anesthesia so that the uterus was fully relaxed, enabling fetal anesthesia.

We assembled the balloon/lead unit prior to puncture (Fig. 1). After determining the optimum approach using ultrasound, a trocar (18 G or 19 G) was introduced into the ROVT through the maternal abdomen, uterus, amniotic cavity, and fetal chest. It was then passed through the pulmonary valve. The prepared balloon catheter and lead assembly were then pushed through the trocar. Once the balloon was at the pulmonary valve, it was inflated to achieve appropriate balloon-to-valve ratio to ensure approximately 80% dilatation because an excessively large balloon might damage the RVOT (Fig. 2). Following successful dilatation, the entire trocar with balloon/wire assembly was simultaneously removed. The entire procedure outlined above was performed under ultrasound guidance. Technical success was defined as visible balloon inflated valve and improved anterograde blood flow through it, confirmed by color Doppler imaging, with or without pulmonary regurgitation. The fetus was then monitored for 30–60 min to prevent complications.

Preparation for immediate pericardiocentesis or intracardiac injection of epinephrine or atropine was taken to tackle possible postoperative pericardial effusion, tamponade, or bradycardia. Following FPV, echocardiography was repeated every two weeks, Gomez scoring system parameters were recorded, development of the right ventricle was evaluated, and operation-related complications were noted. All live infants who received FPV were transferred to the cardiac intensive care unit after delivery for further intervention as required.

2.4. Data collection

Data on TV, TR, RV, TV/MV, and RV/LV measured by fetal echocardiography at 2 and 6 weeks after FPV were collected. The tricuspid annulus diameter and RV diameter measured by echocardiography at postnatal day, 6 months, 1 year, and 2 years of age were collected, and the Z-score was calculated. Further, we compared the changes in the related indicators between two adjacent time nodes.

3. Results

3.1. Demographical and baseline characteristics

All seven fetuses underwent FPV successfully. At the time of intervention, the median gestational age of the 7 fetuses was 27.54 weeks. The average FPV procedural time in all cases was 6 min (range, 4–8 min). No fetal fatalities occurred during the FPV. Persistent bradycardia requiring treatment occurred in 4/7 (57.12%) procedures. One case of fetal bradycardia occurred after anesthesia and in three cases during the intervention. All four fetuses needed injection epinephrine (0.1–1.0 μg/kg) or atropine (20 μg/kg) into the right atrium, which restored normal fetal heart rate. Five of the seven fetuses were delivered successfully, while the other two were aborted. One patient died of severe persistent bradycardia after FPV during the follow-up. One case was terminated during postoperative follow-up because of right ventricle-dependent coronary circulation. Anatomy, procedural details, complications, and outcomes of each patient are listed in Table 1. All fetuses were followed up for six weeks. TV/MV and RV/LV of all fetuses showed progressive improvement compared to values before FCI; the maximum TR velocity decreased from 4.60 m/s to 3.64 m/s (Table 2).

3.2. Postnatal intervention and outcomes

Five fetuses were born alive. Table 3 shows the fundamental information and first interventional treatment administered after delivery. The average follow-up time was 30.40 ± 2.05 months. During the follow-up

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*Fig. 1.* During the puncture, the pregnant woman takes the supine position (A), and the puncture needle (white arrow) points to the closed pulmonary valve (B).
4. Discussion

To achieve biventricular circulation, children with PA/IVS must have a TV and RV of optimal size to support the pulmonary circulation. Some fetuses with PA/IVS with severe RV hypoplasia lose biventricular circulation after birth, potentially leading to fetal edema or even death. FPV may quickly clear the obstruction of the RVOT, promote the continued development of the RV, and improve the long-term prognosis after birth. Currently, the indications for FPV are not clear, and the indicators that

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**Table 1**
Baseline characteristics of patients. GA, gestational age; PBPV, percutaneous balloon pulmonary valvuloplasty; PDA, patent ductus arteriosus; BV, biventricular.

| No. | GA Intervention (weeks) | Prediction Score before Intervention | Balloon(mm) | Pericardial Effusion | Bradycardia | GA Birth (weeks) | Tricuspid Annulus Z-Score | Postnatal Procedures | Circulation | Follow Up (months) |
|-----|-------------------------|-------------------------------------|-------------|---------------------|-------------|-----------------|------------------------|------------------------|-------------|-------------------|
| 1   | 26                      | 3.0                                 | 2.5         | No                  | Yes         | 38              | −0.23                  | PBPV, PDA stenting    | BV          | 34                |
| 2   | 28                      | 1.0                                 | 3.0         | No                  | No          | 38              | −2.5                   | BV                     | 31          |
| 3   | 28                      | 3.0                                 | 3.0         | No                  | No          | 40              | −2.8                   | BV                     | 30          |
| 4   | 28                      | 1.0                                 | 2.5         | No                  | Yes         | –               | –                      | –                      | –           |
| 5   | 28                      | 3.0                                 | 2.5         | No                  | No          | 38              | −2.34                  | –                      | BV          | 29                |
| 6   | 27                      | 3.0                                 | 2.5         | No                  | Yes         | 39              | −1.35                  | PBPV, PDA stenting    | BV          | 28                |
| 7   | 26                      | 4.0                                 | 2.5         | No                  | Yes         | –               | –                      | –                      | –           |

**Table 2**
Intrauterine follow-up data of 5 fetuses. TR, tricuspid regurgitation velocity; RV, right ventricular; LV, left ventricular; TV, tricuspid valve; MV, mitral valve.

| No. | TR(m/s) Pre-operation 2 weeks 6 weeks | RV/LV Pre-operation 2 weeks 6 weeks | TV/MV Pre-operation 2 weeks 6 weeks |
|-----|-------------------------------------|------------------------------------|-------------------------------------|
| 1   | 3.30 3.80 2.80                      | 0.80 0.86 0.90                    | 0.80 1.08 1.10                      |
| 2   | 4.60 4.00 3.00                      | 0.73 0.87 0.92                    | 0.57 1.02 1.05                      |
| 3   | 3.50 2.60 3.64                      | 0.65 0.88 0.92                    | 0.85 0.96 0.97                      |
| 4   | 3.90 3.20 3.50                      | 0.52 0.86 0.88                    | 0.88 0.92 0.92                      |
| 5   | 4.10 3.80 3.30                      | 0.53 0.68 0.82                    | 0.67 0.86 0.88                      |

**Table 3**
Postnatal clinical data of 5 fetuses. RVP, right ventricular pressure.

| Variables          | 1   | 2   | 3   | 4   | 5   |
|--------------------|-----|-----|-----|-----|-----|
| Gender             | Female | Female | Male | Male | Female |
| Birth weight (g)   | 3050 | 3900 | 3920 | 3500 | 3080 |
| Foramen ovale diameter (mm) | 3.5 | 4.0 | 3.5 | 3.0 | 3.5 |
| Tricuspid annulus diameter (mm) | 11.0 | 9.5 | 9.5 | 9.0 | 10.0 |
| Right ventricular diameter (mm) | 7.0 | 9.5 | 10.0 | 9.0 | 8.5 |
| Right ventricular z-Score | −1.43 | 0.12 | 0.43 | −0.18 | −0.50 |
| Age of first intervention (d) | 3.0 | 42.0 | 60.0 | 10.0 | 14.0 |
| Pre-operation RVP (mmHg) | 122 | 60 | 58 | 113 | 95 |
| Post-operation RVP (mmHg) | 62 | 45 | 32 | 60 | 50 |
| Balloon diameter (mm) | 8.0 | 8.0 | 12 | 4.5 | 8.0 |

**Table 4**
Postnatal development of right heart of 5 fetuses.

| No. | Tricuspid annulus growth rate(%) | Z-score difference of tricuspid annulus | Right ventricular growth rate(%) | Z-score difference of right ventricle |
|-----|---------------------------------|----------------------------------------|---------------------------------|-------------------------------------------|
|     | 6 months 1 year 2 years 6 months 1 year 2 years | 6 months 1 year 2 years | 6 months 1 year 2 years 6 months 1 year 2 years |
| 1   | 7.27 25.42 18.92                | −1.52 0.79 0.64                        | 21.42 8.24 17.39                | 0.48 0.29 0.49                           |
| 2   | 15.79 36.36 21.33                | 0.13 1.46 0.75                        | 15.79 10.90 4.92                | 0.06 0.40 0.05                           |
| 3   | 15.77 38.18 25.00                | 0.31 1.85 1.12                        | 15.29 7.14 10.48                | 0.14 0.24 0.22                           |
| 4   | 11.11 40.00 27.14                | −0.35 1.64 1.22                       | 21.11 7.34 6.84                | 0.31 0.24 0.05                           |
| 5   | 12.00 19.64 21.64                | −0.92 0.90 0.71                       | 9.41 9.68 11.76                | −0.22 0.47 0.28                          |
may be used as a reference are quite rudimentary. However, this study not only considered the aforementioned factors but also follow-up RV development. The indication for surgical intervention was more justified when RV progression remained stable for 2–3 weeks.

Currently, multicenter registry studies have focused on the development of intrauterine TV and RV after FPV treatment in fetuses with PA/IVS. However, given the low prevalence of PA/IVS in Western nations and the technological constraints of FPV, there are limited clinical studies on postnatal development. In this study, follow-up data of five live infants treated with FPV showed that the development of TV remained retarded in utero, while the RV size dramatically improved. This is consistent with Tulzer's finding that, after FPV, the RV/left ventricle ratio in children with PA/IVS continues to increase or remains constant until birth, although there may be a catch-up increase even after birth, and successful FPV intervention can promote the development of the RV until full-term delivery. Animal experiments demonstrated that fetal cardiomyocytes had a proliferative response to the increased cardiac load. Therefore, it is speculated that the over-proliferation of RV myocardium leading to myocardial hypertrophy could be prevented by FPV.

Although perioperative mortality in children with FPV is low, the majority of PA/IVS fetuses still exhibit severe pulmonary valve stenosis or even atresia after birth and different degrees of RV dysplasia requiring intervention again. The purpose of individualized intervention in the neonatal period is to restore forward blood flow through the pulmonary valve and stimulate the development of the RV and pulmonary vessels to achieve a favorable prognosis. The degree of postnatal RV dysplasia in children with PA/IVS is usually evaluated by the tricuspid annulus Z-score: it is > -2.5 in mild right ventricular dysplasia, from -4.5 to -2.5 in moderate right ventricular dysplasia, and < -5.0 in severe right ventricular dysplasia. A tricuspid annulus Z-score of < -5 is often used to determine the critical value of a single ventricular circulation, although actual implementations sometimes vary. The exact value of the tricuspid annulus has not been determined. In this study, the first Z-scores of the tricuspid annulus after birth ranged from -0.23 to -2.80. Most fetuses had mild to moderate RV dysplasia and finally achieved biventricular circulation aided by the FPV intervention at an early stage. The follow-up data in this study revealed that the development of TV and RV was not synchronized in patients undergoing FPV. TV development was retarded during pregnancy, whereas RV size improved significantly. After birth, TV continued to develop rapidly, while RV development was relatively slow and most infants required re-intervention. The sluggish RV development is mainly due to the loss of the proliferative ability of cardiomyocytes after birth. As described in the literature, the TV and right ventricle develop unevenly in children with PA/IVS following the procedure, and there is considerable individual variation.

Júnior et al. summarized the perinatal outcomes and intrauterine complications of FCI through a systematic review and meta-analysis of 279 cases of FCI in the PubMed and Scopus databases before 2015, including 16 cases of FPV. The mortality after pulmonary valvuloplasty was 25% (95% confidence interval [CI] 10–49%), while the rate of bradyarrhythmia requiring treatment was 44% (95% CI, 23–67%), 38% (95% CI, 18–61%) had hemopericardium requiring drainage after pulmonary valvuloplasty, with 25% (95% CI, 10–49%) fetal mortality. The neonatal fatality rate following pulmonary valvuloplasty was found to be 33%. Patel et al. analyzed the International Fetal Cardiac Intervention Registry data for fetuses who underwent fetal aortic valvuloplasty from 2002 to 2018 among a total of 108 fetuses. Complications occurred in 48.1% of the fetuses, including bradycardia (34.1%), pericardial effusion (22.2%), pleural effusion (2.7%) requiring drainage, and balloon rupture (5.6%). They found that a larger cannula size (>19 G) was associated with a higher rate of pericardial effusion. Multiple punctures were associated with a greater likelihood of procedural complications. These included bradycardia, pleural effusion, and intra-procedural death. Minimizing the number of cardiac punctures and size of the cannula used could diminish the risk associated with the procedure, while technical success would improve the odds of survival until delivery. This study reveals that bradyarrhythmia may develop in certain fetuses following anesthesia, and the dosage of narcotic drugs used during surgery should be carefully monitored. Atroline, which helps counteract the fetal vagus nerve response caused by anesthesia, can be used as a preventive measure before FPV. In addition to reducing the number of cardiac punctures and the size of the puncture needle, shortening the time of the puncture operation could also reduce the risk of bradyarrhythmia.

Although the evaluation and procedure-related data are robust, the sample size is small and potentially biased toward follow-up results. Additionally, the final declaration of ventricular status may have occurred several years after intervention. This study only presents data collected in a short period of time, and it is limited. Finally, the study lacked an appropriate control group, such as fetuses that did not undergo PCI. Future efforts should consider prospective trials or observational research with complete data collection and evaluation of the effect of PCI on long-term outcomes for mothers and fetuses.

In conclusion, the current investigation revealed that following FPV treatment, the indices of RV development in fetuses with PA/IVS improved progressively. In contrast to intrauterine RV development, the development was more obvious after birth. Bradycardia was the main complication of this intervention. Timely detection and adequate treatment are crucial to ensure the success of FPV.

Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

Declaration of competing interest

The authors declare that they have no conflicts of interest to disclose.

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