ULTRASONOGRAPHY

Pulmonary artery stiffness in fetuses with tetralogy of Fallot

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Purpose: This study evaluated the elastic characteristics of the pulmonary trunk and distal branches in fetuses diagnosed with tetralogy of Fallot (TOF) using Doppler echocardiography.

Methods: Data on 42 fetuses diagnosed with TOF and 84 gestational age–matched normal fetuses were prospectively collected from the Second Xiangya Hospital of Central South University between August 2022 and January 2023. The severity of TOF was classified into three categories based on the z-score of the pulmonary annulus diameter: mild (z-score ≥−2), moderate (−4<z-score<−2), and severe (z-score ≤−4). Pulmonary artery stiffness (PAS) in the main pulmonary artery (MPA), distal left pulmonary artery (DLPA), and distal right pulmonary artery (DRPA) was measured using pulsed-wave Doppler imaging. Differences in clinical data and echocardiographic parameters were compared between the TOF group and the normal group, as well as among TOF subgroups.

Results: Compared with the normal group, the MPA-PAS in fetuses with TOF was significantly higher, while the DLPA-PAS and DRPA-PAS were notably lower (all P<0.05). The MPA-PAS of fetuses with severe TOF was higher than that of those with mild and moderate TOF (all P<0.05). However, there were no significant differences in the DLPA-PAS or DRPA-PAS among fetuses with mild, moderate, and severe TOF (all P>0.05).

Conclusion: Fetuses diagnosed with TOF exhibited increased vascular stiffness in the MPA and reduced stiffness in the distal pulmonary artery (PA). Larger-scale follow-up studies are required to elucidate the relationships between these changes in vascular stiffness and PA development in patients with TOF.

Keywords: Ultrasonic cardiography; Pulmonary arterial stiffness; Pulmonary arterial elasticity; Tetralogy of Fallot; Fetus

Key points: This is the first study to systematically evaluate the elastic characteristics of the pulmonary trunk and its distal branches in terms of pulmonary artery stiffness in fetuses with tetralogy of Fallot (TOF). In fetuses with TOF, pulmonary artery stiffness was significantly elevated in the main pulmonary artery (MPA) but lower in the distal pulmonary artery. Fetuses with severe TOF had higher stiffness in the MPA than fetuses with mild and moderate TOF.

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Introduction

Tetralogy of Fallot (TOF) is the most prevalent cyanotic congenital heart disease in clinical practice [1]. The survival rate 36 years after heart repair is now 85% due to significant advances in cardiac surgery, which have increased the adult TOF patient population over the past 50 years [2]. Although major advances in cardiac surgery have resulted in very high surgical survival in patients with TOF, the development of right ventricular (RV) dilatation and dysfunction remains an important cause of late morbidity and mortality after surgical repair [3,4].

Recent reports indicate that patients with TOF exhibit structural abnormalities in the pulmonary trunk wall, including medionecrosis, fibrosis, and cystic medial necrosis. These abnormalities suggest a reduction in normal elastic fibers in the area [5]. The abnormal elastic tissue structure and the presence of moderate fibrosis in the pulmonary trunk of TOF patients may alter the stiffness of the pulmonary artery wall, which could lead to pulmonary regurgitation and contribute to RV dysfunction [5,6].

Most studies on pulmonary artery stiffness (PAS) have assessed the condition invasively [7–11], and PAS has been used relatively infrequently in clinical applications. PAS is an echocardiographic indicator that can be measured noninvasively as a way to assess the elasticity of the pulmonary vascular system [12]. Abnormally high PAS can impact ventricular–arterial coupling, leading to a 30%–40% increased load on the heart [13]. A study by Gorgulu et al. [12] suggested that PAS may be useful in clinical settings, as it correlates with pulmonary vascular impedance and pulmonary artery pressure. To date, only a few studies have utilized PAS to evaluate the elastic characteristics of the pulmonary artery in either adult patients or children [11,14,15], demonstrating that the abnormal cardiac hemodynamics of different diseases can affect the development of the pulmonary artery, resulting in reduced elasticity and increased hardness of vessels. No studies have yet assessed pulmonary vascular elasticity through PAS analysis in fetuses with TOF. This study aimed to explore PAS using a Doppler echocardiographic technique, introduced here for the first time, to evaluate the characteristics of pulmonary vascular elasticity in fetuses with TOF compared to normal fetuses.

Materials and Methods

Compliance with Ethical Standards

Written informed consent was obtained from all participating families, and the study received approval from the Ethics Committees of the Second Xiangya Hospital [(2018) No. 070].

Study Design

A prospective study was performed at the Department of Ultrasound Diagnosis, the Second Xiangya Hospital of Central South University in China between August 2022 and January 2023. The inclusion criteria were fetuses with TOF, including TOF with pulmonary stenosis. The severity of TOF was classified based on the z-score of the pulmonary annulus diameter as follows: mild (z-score ≥−2), moderate TOF (−4<z-score<−2) or severe TOF (z-score ≤−4). The diagnosis of fetal TOF was confirmed by postnatal echocardiography, surgical repair, or autopsy. For comparison, the control group consisted of gestational age (GA)–matched fetuses with normal cardiovascular anatomy, normal uterine placental function, and no extrinsic anatomical abnormalities. The exclusion criteria were as follows: (1) pregnant women carrying multiple fetuses; (2) fetuses with an estimated fetal weight (EFW) below the 10th percentile for their GA; (3) fetuses diagnosed with other cardiac or extracardiac malformations and genetic abnormalities; (4) fetuses with identifiable chromosomal abnormalities; (5) fetuses with a persistent non-sinus rhythm; and (6) pregnant women with high-risk factors such as poorly controlled hypertension or diabetes mellitus.

The Voluson E8 system (GE Healthcare, Milwaukee, WI, USA), equipped with a RAB 4-8-D curved probe, was utilized to conduct routine obstetric ultrasound examinations and complete fetal echocardiography. Fetal growth parameters were measured, and the EFW was calculated using Hadlock's formula [16]. Other parameters were recorded, including maternal age, maternal body mass index (BMI), maternal first menstrual period or menstrual history, GA, EFW, fetal heart rate (FHR) and diameter of the cardiac annulus and vessel.

Echocardiography of PAS

The Doppler flow trace of the main pulmonary artery (MPA) was recorded by positioning the pulsed-wave Doppler sample volume 1 cm distal to the pulmonary valve annulus in the pulmonary artery, using a rate of 100 mm/s from the outflow tract view of the right ventricle. The distal pulmonary artery was identified as the intraparenchymal segment at the first branching point within the lung. The pulsed-wave Doppler sample volumes encompassed the distal left pulmonary artery (DLPA) and distal right pulmonary artery (DRPA). During the measurement, the sample volume was maintained at 2–3 mm with an interrogation angle of less than 10°. The acceleration time (AcT) and maximal flow velocity shift (MFV) of the MPA, DLPA, and DRPA were measured. The MFV and AcT were incorporated into the following formula: PAS (kHz/s)=MFV/AcT (Fig. 1A) [12,17]. All measurements were taken while the fetuses were in a resting state with coordinated posture. Measurements from three consecutive heartbeats were averaged for analysis and were

conducted by an experienced prenatal sonographer.

Statistical Analysis

All statistical analyses were conducted using SPSS statistical software version 20.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA). The Shapiro-Wilk test was used to assess the normality of continuous variables. Data are presented as means with standard deviations or as frequencies with percentages. The TOF and normal groups were compared using the Student t-test. Analysis of variance was utilized to compare PAS among normal fetuses, and fetuses with mild, moderate, and severe TOF. To assess interobserver variability, PAS was independently measured by a second sonographer who was blinded to the clinical data of 36 normal fetuses and 12 fetuses with TOF that were randomly selected. To evaluate intraobserver variability, a single sonographer then analyzed the fetuses' data two times, with 1-day intervals between the analyses. A P-value <0.05 was considered statistically significant.

Results

During the study period, a total of 143 fetuses were enrolled. However, seven fetuses were excluded due to excessive fetal motion, and 10 were excluded due to poor image quality. Consequently, 126 fetuses were included in the final analysis: 42 fetuses diagnosed with TOF and 84 gestational age-matched normal fetuses. Table 1 presents the clinical demographics and pulmonary parameters of all the enrolled fetuses. There were no significant differences in maternal age, maternal BMI, GA at diagnosis, EFW at diagnosis, or FHR between the normal and TOF groups. In contrast, the fetuses with TOF showed a significantly higher aortic annulus diameter and significantly lower pulmonary annulus and MPA diameters compared to the controls (P<0.05 for all) (Table 1).

Distinct blood flow characteristic patterns were noted. The waveform of a normal MPA featured a unimodal systolic blood flow spectrum with asymmetric ascending and descending branches, and either low-velocity blood flow or no blood flow during the diastolic phase (Fig. 1A). Similarly, the waveform of a normal DLPA resembled that of the DRPA, characterized by the systolic "vertical gun sign," followed by minimal or no blood flow in the diastolic phase (Fig. 1B, C). In contrast, the MPA of most fetuses with TOF exhibited sharp systolic blood flow waves (Fig. 1D). Additionally, broad, blunted systolic acceleration followed by broad deceleration and moderate diastolic forward flow was observed in the distal pulmonary arteries

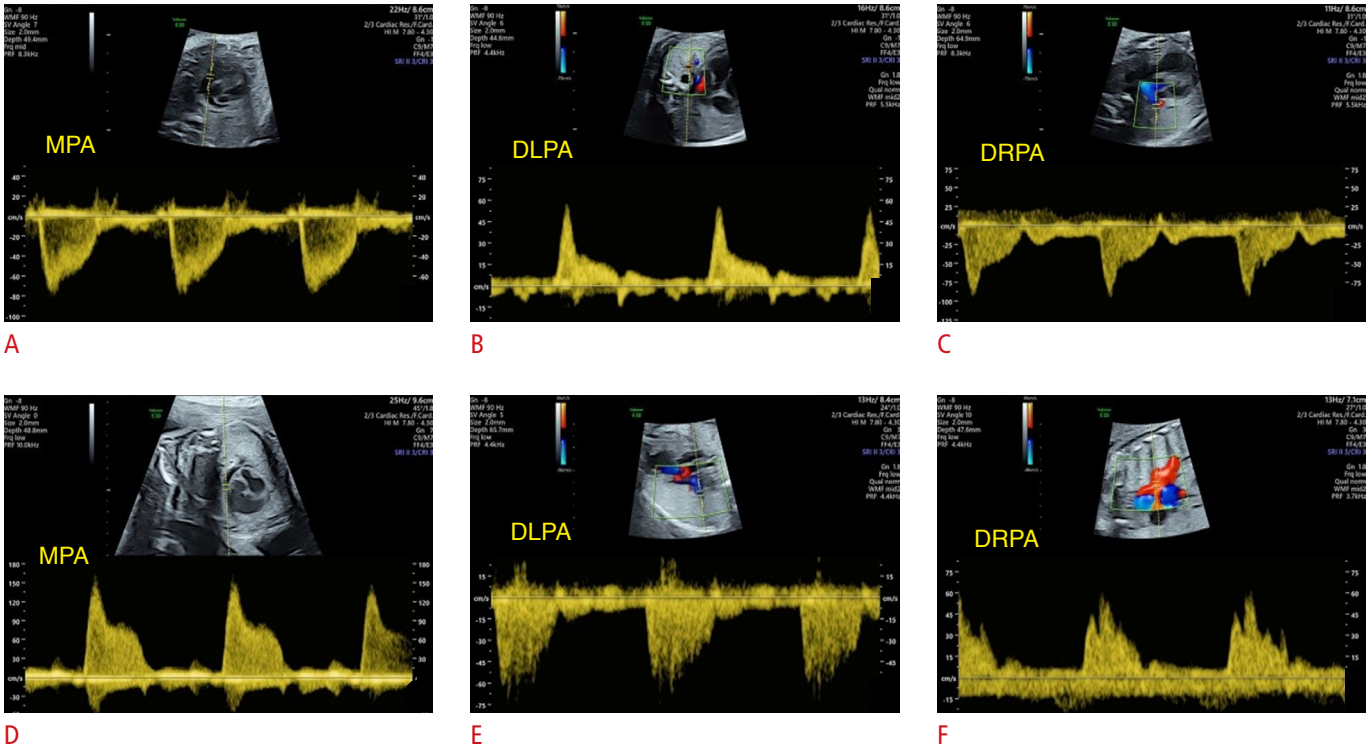

Fig. 1. Pulsed-wave Doppler measurements.
A–C. Waveforms of the main pulmonary artery (MPA) (A), distal left pulmonary artery (DLPA) (B), and distal right pulmonary artery (DRPA) (C) are shown in normal fetuses. D–F. Waveforms of the MPA (D), DLPA (E), and DRPA (F) are shown in fetuses with tetralogy of Fallot. Pulmonary artery stiffness was calculated by dividing the maximal flow velocity shift of pulmonary flow by the pulmonary acceleration time.

(Fig. 1E, F).

Among all fetuses, there were no significant differences in MPA-MFV, DLPA-MFV, or DRPA-MFV between normal fetuses and those with TOF (P<0.05 for all). The MPA-AcT was significantly longer in normal fetuses compared to those with TOF (P<0.05). Conversely, both the DLPA-AcT and DRPA-AcT were significantly shorter in normal fetuses than in those with TOF (P<0.05 for both). Consequently, the MPA-PAS was significantly higher in fetuses with TOF than in the controls (P<0.05). In the TOF group, both the DLPA-PAS and DRPA-PAS were markedly lower than in the normal group (P<0.05 for both) (Table 1).

The MPA-PAS in the severe TOF group was higher than that in the mild and moderate TOF groups (P<0.05 for all). However, there were no differences in the DLPA-PAS or DRPA-PAS among fetuses with mild, moderate, or severe TOF (P>0.05 for all). In fetuses with mild, moderate, and severe TOF, the MPA-PAS values were 32.18±3.79 kHz/s, 34.46±3.60 kHz/s, and 40.63±4.38 kHz/s, respectively. The DLPA-PAS values were 12.80±2.76 kHz/s, 12.97±3.45 kHz/s, and 13.43±3.78 kHz/s, respectively. The DRPA-PAS values were 12.71±2.39 kHz/s, 11.91±2.57 kHz/s, and 12.17±2.83 kHz/s,

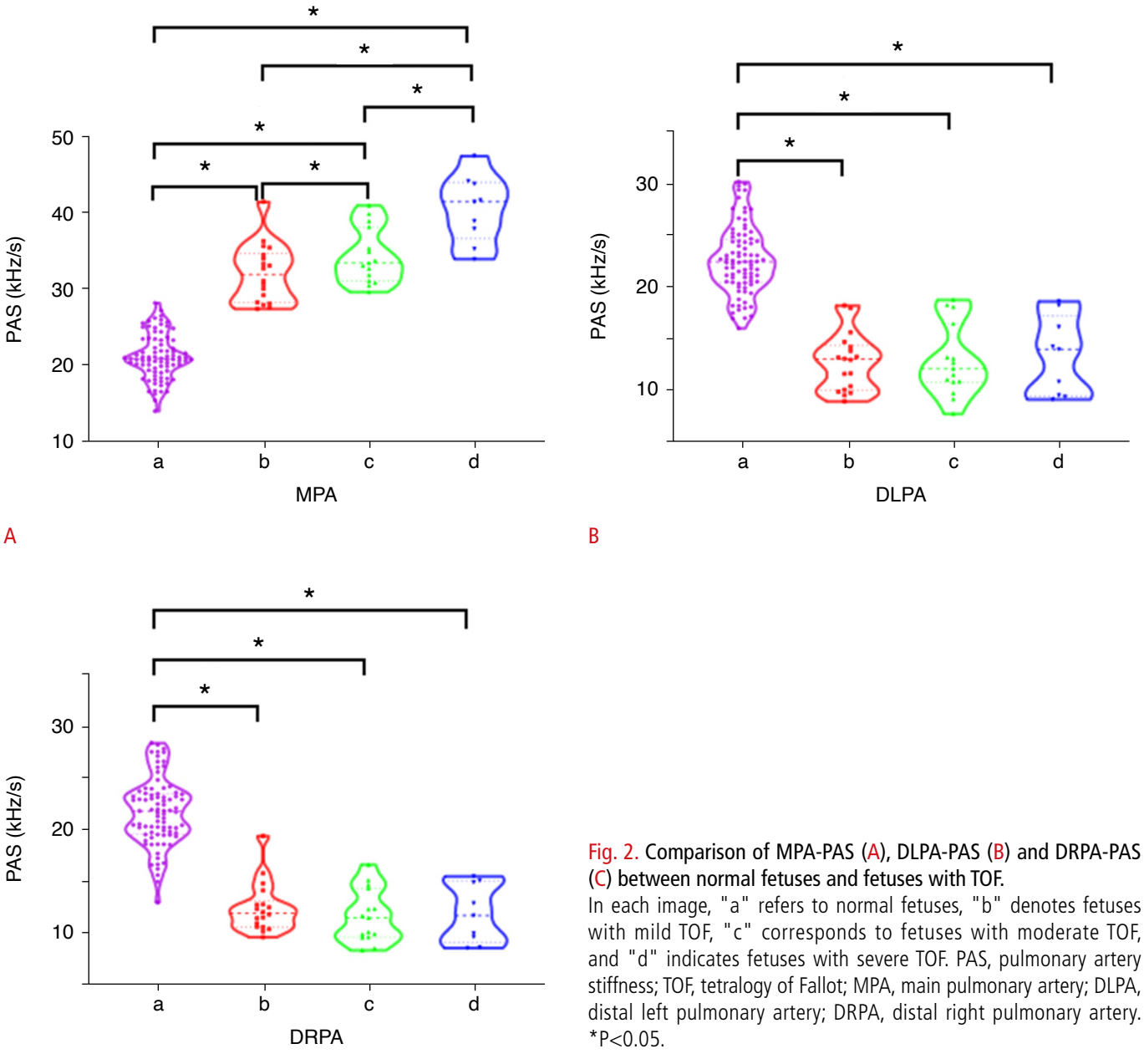

Fig. 2. Comparison of MPA-PAS (A), DLPA-PAS (B) and DRPA-PAS (C) between normal fetuses and fetuses with TOF.
In each image, "a" refers to normal fetuses, "b" denotes fetuses with mild TOF, "c" corresponds to fetuses with moderate TOF, and "d" indicates fetuses with severe TOF. PAS, pulmonary artery stiffness; TOF, tetralogy of Fallot; MPA, main pulmonary artery; DLPA, distal left pulmonary artery; DRPA, distal right pulmonary artery. *P<0.05.

Table 1. Clinical findings and echocardiographic data of the pulmonary artery in normal fetuses and those with TOF

Characteristic	Normal fetuses (n=84)	Fetuses with TOF (n=42)	P-value
Maternal age (year)	28.69±4.06	28.55±3.70	0.920
Maternal BMI	23.19±2.10	22.75±2.29	0.594
Primipara (no.)	51	24	
Multipara (no.)	33	18	
GA at diagnosis (week)	27.73±3.59	28.35±3.54	0.733
EFW at diagnosis (g)	1,158.45±550.49	1,168.07±529.20	0.543
FHR (beats/min)	142.71±8.52	145.43±8.31	0.596
Two-dimensional measurements			
Mitral annulus diameter (z-score)	1.13±0.67	1.44±0.73	0.874
Tricuspid annulus diameter (z-score)	1.44±0.60	1.72±0.85	0.110
Aortic annulus diameter (z-score)	1.37±0.79	4.16±1.00	0.036
Pulmonary annulus diameter (z-score)	1.28±0.85	−2.74±1.22	<0.001
Main pulmonary artery diameter (z-score)	1.01±0.77	−2.27±0.93	0.010
Left pulmonary artery diameter (z-score)	0.35±0.71	−0.92±0.75	0.981
Right pulmonary artery diameter (z-score)	−0.04±0.70	−1.44±0.87	0.191
Color Doppler flow imaging			
Antegrade flow in the DA (no.)	84	29	
Retrograde flow in the DA (no.)	0	13	
Hemodynamic parameters of the pulmonary artery			
MPA-MFV (m/s)	0.78±0.08	1.06±0.11	0.071
MPA-AcT (s)	0.04±0.006	0.03±0.004	<0.001
MPA-PAS (kHz/s)	21.32±2.91	34.80±4.96	0.013
DLPA-MFV (m/s)	0.62±0.07	0.59±0.08	0.869
DLPA-AcT (s)	0.03±0.004	0.05±0.014	0.001
DLPA-PAS (kHz/s)	22.67±3.29	12.99±3.17	0.019
DRPA-MFV (m/s)	0.62±0.07	0.57±0.06	0.772
DRPA-AcT (s)	0.03±0.004	0.05±0.013	0.002
DRPA-PAS (kHz/s)	21.98±3.21	12.31±2.51	0.022
Postnatal outcomes			
GA at birth (week)	38.89±0.83	38.31±0.53	0.005
Birth weight (g)	3,166.71±134.99	3,060.14±148.08	0.443
Admission to NICU (no.)	0	8	
Cardiac surgery (no.)	–	4	
Length of hospital stay (day)	–	18.25±5.87	

Values are presented as mean±standard deviation.
TOF, tetralogy of Fallot; BMI, body mass index; GA, gestational age; EFW, estimated fetal weight; FHR, fetal heart rate; DA, ductus arteriosus; MPA, main pulmonary artery; MFV, maximal flow velocity shift; AcT, acceleration time; PAS, pulmonary artery stiffness; DLPA, distal left pulmonary artery; DRPA, distal right pulmonary artery; NICU, neonatal intensive care unit.

respectively (Fig. 2).

The reproducibility analysis yielded the following results: intraclass correlation coefficients for interobserver and intraobserver variability were 0.84 and 0.81, respectively, for the MPA-PAS; 0.78 and 0.74 for the DLPA-PAS; and 0.80 and 0.75 for the DRPA-PAS.

Discussion

To the best of the authors' knowledge, this is the first study to systematically evaluate the elastic characteristics of the pulmonary trunk and its distal branches using PAS in fetuses diagnosed with

TOF. Compared to normal fetuses, those with TOF had significantly higher PAS in the MPA, but lower PAS in the distal pulmonary artery. Furthermore, fetuses with severe TOF exhibited higher stiffness in the MPA compared to those with mild and moderate TOF.

The finding that the MPA-PAS in fetuses with TOF was significantly higher than that in normal fetuses suggests the presence of increased vascular stiffness in the MPA of fetuses with TOF. Decreased blood flow in the pulmonary artery of fetuses with TOF may impact pulmonary vascular development [5], particularly during the crucial period of prenatal maturation. In fetuses with TOF, the media membrane of the pulmonary trunk develops abnormally due to insufficient blood flow, resulting in thin and sparse elastic fibers, and an increased content of collagen fibers and matrix [18]. There is a high prevalence of cystic medionecrosis, elastic fiber fragmentation, and collagen hyperplasia in the pulmonary trunk of infants with TOF and adult patients [5]. Notably, collagen is approximately 100 times harder than elastin [19]. Consequently, in fetuses with TOF, the MPA exhibits increased PAS. This increase in PAS not only promotes the proliferation of vascular smooth muscle but also activates fibroblasts through a feedback loop mechanism, leading to further deposition of extracellular matrix and fibrosis [20]. Furthermore, compared to fetuses with mild and moderate TOF, those with severe TOF exhibit particularly low blood flow in the pulmonary trunk, which may lead to more extensive pulmonary vascular remodeling. This could explain why the MPA-PAS in fetuses with severe TOF was higher than in those with mild and moderate TOF.

This research showed that AcT influenced PAS to a greater extent than the MFV. Decreased pulmonary artery distensibility shortens the RV–pulmonary artery systolic ejection time (ET) [21]. In other words, the AcT of the pulmonary blood flow trace is shorter in fetuses with increased PAS. Time-related parameters of fetal pulmonary arterial circulation, such as AcT and ET, are crucial in assessing pulmonary vascular maturity and pulmonary artery pressure through pulsed-wave Doppler analysis, with AcT being the primary parameter [22,23]. The reduction in AcT in the pulmonary blood flow spectrum is attributed to high impedance in the pulmonary artery during the systolic period, diminished blood perfusion, increased stiffness of the pulmonary vascular wall, and consequently, a forward shift in the peak of the pulmonary blood flow spectrum [24]. Numerous studies have established that AcT is inversely correlated with pulmonary artery pressure [25–27], and the formula fetal pulmonary artery pressure (FPAP)=90−(0.62×AcT) is commonly used in clinical settings to estimate the mean pulmonary arterial pressure [26,27]. Studies by Azpurua et al. [28] and Schenone et al. [29] have revealed that the fetal AcT/ET ratio is significantly inversely correlated with the lecithin/sphingomyelin ratio in amniotic fluid, indicating that pulsed-wave Doppler could be an effective new noninvasive method for assessing fetal lung maturity. Another study indicated that the fetal AcT/ET ratio has high positive and negative predictive values for forecasting the subsequent development and clinical outcomes of neonatal pulmonary hypoplasia [30]. Furthermore, research by Zuckerman et al. [8] suggested that PAS parameters could be utilized in diagnosing pulmonary hypertension. The excess accumulation of collagen is responsible for increased PAS in patients with pulmonary hypertension [31]. Collectively, these studies have demonstrated that AcT has an important effect on PAS and pulmonary hypertension.

In the present study, TOF was associated with decreased pulmonary vascular stiffness in the distal branches, suggesting an increase in compensatory blood flow to maintain normal lung tissue development. The fetal pulmonary vasculature has a unique ability to alter blood flow delivery to the lungs [32]. Normally, the fetal distal pulmonary circulatory system during pregnancy exhibits high impedance and elevated blood pressure. When TOF is accompanied by pulmonary stenosis, there is a reduction in blood flow within the pulmonary arterial system. This reduction triggers the self-regulation of the pulmonary circulatory system, resulting in a vasodilated state in the distal pulmonary vasculature [33]. In addition, a long-term decrease in pulmonary blood flow in patients with TOF can lead to atrophy of the distal pulmonary arterial smooth muscles, eventually causing the pulmonary vasculature to become thinner [19]. Thus, the dilation of the distal pulmonary arteries, driven by the self-regulation system, along with the thinning of the vessel walls in fetuses with TOF, facilitates more compensatory blood filling of the pulmonary vascular bed. This process increases vascular activity in the distal pulmonary artery. Ultimately, in fetuses with TOF, the distal pulmonary artery exhibits decreased PAS.

The results of this study indicated no statistically significant difference in the PAS of distal pulmonary artery branches in fetuses with TOF. In fetuses with TOF, but without reversed ductus arteriosus perfusion, the pulmonary circulatory system self-regulates, reducing vascular impedance in the distal branches. This adaptation increases blood flow into the pulmonary vascular bed, supporting normal lung tissue development [33,34]. However, in cases with severe obstruction of the pulmonary outflow tract, antegrade blood flow to the lungs is restricted, and some blood flow is provided retrogradely via the ductus arteriosus [35]. The study by Peyvandi et al. [34] demonstrated that in fetuses with TOF, characterized by severe pulmonary stenosis or pulmonary atresia, the pulsatility index of distal pulmonary vessels with retrograde ductal flow was lower. Additionally, these fetal pulmonary vessels were capable of vasodilation when anatomically obstructed. This mechanism also mitigated the inadequate blood flow in the distal pulmonary arteries,

leading to improved vascular activity and distensibility. Thus, there is no significant difference in the stiffness of the distal pulmonary artery in fetuses with mild, moderate, or severe TOF.

The limitations of this study are as follows. First, it was a cross-sectional study conducted during the second and third trimesters of pregnancy. It did not include a long-term longitudinal analysis to determine whether pulmonary vascular remodeling and complications occurred later in the children or adult patients with TOF. Second, only a small number of fetuses with TOF were included. A larger multicenter study is necessary to ascertain the characteristics of pulmonary arterial vascular stiffness in fetuses with TOF.

In fetuses with TOF, PAS was significantly higher in the MPA than in normal fetuses, whereas it decreased in the distal pulmonary artery. Fetuses with severe TOF exhibited greater stiffness in the MPA than those with mild and moderate TOF. Further large cohort studies are required to elucidate the impact of TOF on the development of PAS and related diseases affecting the pulmonary artery.

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Author Contributions

Conceptualization: Xu R, Zeng S. Data acquisition: Liu Y, Zhou D, Yang Y. Data analysis or interpretation: Liu Y, Xu G. Drafting of the manuscript: Liu Y. Critical revision of the manuscript: Xu R, Zhou D, Yang Y, Xu G, Zeng S. Approval of the final version of the manuscript: all authors.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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