

Ultrasonographic Features and Clinical Significance of Fetal Isolated Redundant Foramen Ovale Flap

Guorong Lyu

Second Affiliated Hospital of Fujian Medical University

Shijie Zhang

Second Affiliated Hospital of Fujian Medical University

Shaosheng He

Second Affiliated Hospital of Fujian Medical University

Qiuyue Chen

Second Affiliated Hospital of Fujian Medical University

Liya Li (✉ lly7473@163.com)

Second Affiliated Hospital of Fujian Medical University <https://orcid.org/0000-0003-3099-0271>

Research Article

Keywords: Redundant foramen ovale flap, Aortic coarctation, Restrictive foramen ovale, Echocardiography, Ultrasonography, Fetal

Posted Date: March 2nd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-812287/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Little is known about the ultrasonographic features of fetal isolated redundant foramen ovale flap (RFOF). Additionally, false positive diagnosis of aortic coarctation (CoA) may be related to the presence of an RFOF. This study aimed to explore the ultrasonographic features of RFOF and its differential diagnosis with CoA.

Methods

This was a retrospective cohort study that included 54 fetuses: 15 with isolated RFOF, 9 with CoA, and 30 normal fetuses of matched gestational age. The correlations of foramen ovale flap diameter (FOFD)/left atrial diameter (LAD) with right atrial diameter (RAD)/LAD, right ventricular diameter (RVD)/left ventricular diameter (LVD), and pulmonary artery diameter (PAD)/aortic diameter (AoD) were analyzed, and a quadratic regression model was established. Differences in FOFD/LAD, RAD/LAD, RVD/LVD, PAD/AoD, and aortic isthmus diameter were compared among the three groups.

Results

(1) Noticeable RAD/LAD, RVD/LVD, and PAD/AoD increases, aortic arch dysplasia, and aortic isthmus narrowing were found in the RFOF group (all $p < 0.05$); ductus arteriosus aneurysm and premature atrial beats were also observed. (2) As the RFOF severity increased, the atrial and ventricular asymmetry and disproportion between the pulmonary artery and aorta became more pronounced ($r = 0.825, 0.862, 0.846$, all $p < 0.001$). (3) Other than the FOFD/LAD, no significant differences in the RAD/LAD, RVD/LVD, PAD/AoD, or aortic isthmus diameter were found between fetuses with an RFOF and fetuses with CoA ($p > 0.05$).

Conclusions

Isolated RFOF has specific ultrasound features, and the degree of disproportion between the left and right heart is consistent with the severity of RFOF. Measurement and calculation of FOFD/LAD may help distinguish between RFOF and CoA.

Background

The foramen ovale is an important channel for fetal blood flow distribution[1]. Approximately 70% of the oxygen-rich blood from the ductus venosus enters the left heart system through the foramen ovale, representing the dominant blood supply for vital organs[2]. Fetal congenital heart disease (CHD) complicated with a restrictive foramen ovale (RFO) can lead to a poor prognosis in newborns[3–6]. An

isolated RFO can also cause pulmonary arterial hypertension or other extracardiac malformations, resulting in adverse neonatal outcomes[7]. Approximately one-third of isolated RFO have a redundant foramen ovale flap (RFOF)[7]. Fetuses with isolated RFOF have better outcomes than those with isolated RFO, but few studies have explored the ultrasonographic features of RFOF[8–10]. In addition, some studies have shown that the ultrasonographic features of RFOF are similar to those of aortic coarctation (CoA), which often leads to a false positive diagnosis[8]. The purpose of this study was to explore the ultrasonographic features of RFOF and its differential diagnosis with CoA.

Methods

General data

This was a single-center retrospective study including 15 fetuses with isolated RFOF (RFOF group), 9 fetuses with CoA (CoA group), and 30 normal fetuses (control group) between 2015 and 2021 at the Second Affiliated Hospital of Fujian Medical University. The fetal diagnosis was confirmed after delivery by echocardiography or follow-up observation. The inclusion criteria for the RFOF group[7, 8] were (1) ventricular disproportion (2) foramen ovale flap diameter (FOFD)/left atrial diameter (LAD) ≥ 0.65 and (3) no RFO, i.e., a foramen ovale diameter (FOD) ≥ 2.5 mm, foramen ovale/atrial septum length > 0.33 , triphasic Doppler waveform for the foramen ovale, and flow velocity ≤ 40 cm/s. The exclusion criteria were (1) cardiac or extracardiac malformation, polyhydramnios or oligohydramnios, or intrauterine growth restriction (IUGR) of the fetus observed during the prenatal ultrasound examination or postpartum follow-up and (2) eclampsia, diabetes mellitus, hypertension, or infection in the mothers. Nine fetuses with CoA were selected for the CoA group, and 30 normal fetuses were randomly selected for the control group. These fetuses all had similar gestational ages and were delivered over the same time period as the RFOF group. The study was approved by the medical ethics committee of Fujian Medical University, approval number [2021251], and all gravidas gave their informed consent before the prenatal ultrasound examination. The data used for the analyses in this study are publicly shared in Supplemental Table 1.

Instruments And Methods

The prenatal ultrasound examinations were performed according to the practice guidelines for prenatal ultrasound examinations issued by the American Institute of Ultrasound in Medicine[11]. Ultrasound examinations of the fetal brain and heart were performed according to the practice guidelines for ultrasound examinations of the fetal central nervous system and heart issued by the International Society of Ultrasound in Obstetrics and Gynecology[12, 13]. Fetal echocardiographic examinations were performed using Voluson 730 Pro, Voluson E6, Voluson E8, and Voluson E10 (GE Healthcare Zipf, Austria) machines with 4–8 MHz transabdominal transducers. Fetal echocardiograms were reviewed by at least two of three experts (G.L., S.H., and Q.C.) with significant experience and expertise in the diagnosis of CHD. ImageJ (NIH, Bethesda, MD, USA) was used to obtain measurements from the two-dimensional datasets. Apical four-chamber views were used to measure the FOFD, LAD, right atrial

diameter (RAD), left ventricular diameter (LVD), and right ventricular diameter (RVD) at end systole. Left ventricular outflow tract views were used to measure the aortic diameter (AoD) of the aortic valve during systole. Right ventricular outflow tract views were used to measure the pulmonary artery diameter (PAD) of the pulmonary valve during systole. Aortic long-axis views were used to measure the aortic isthmus diameter (AID) at end systole, and the Z-score of the aortic isthmus was calculated[14, 15]. To assess reproducibility, 20 normal fetuses were selected randomly, and their measurements were performed by the same operator (G.L.) and by different operators (G.L. and S.H.).

Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, NY) and MedCalc version 16.8.4 (MedCalc Software Ltd., Ostend, Belgium) were used for statistical processing. Normality was evaluated using the Shapiro–Wilk test. The measurement data are described as the mean \pm standard deviation ($X \pm S$) or the median (M) and interquartile range (QL, QU). Repeatability was assessed using the intraclass correlation coefficient (ICC) and Bland–Altman plots. Spearman correlation analysis was used to measure the FOFD/LAD and heart structure parameters. Quadratic regression models of the FOFD/LAD and the measurement parameters of the heart structure were established. Comparisons between the RFOF group and the CoA group were carried out using the Mann–Whitney U test.

Results

Demographic data and repeatability test

The gestational ages of the RFOF, CoA, and control groups were 32.7 ± 3.1 weeks, 32.7 ± 3.0 weeks, and 31.7 ± 3.2 weeks, respectively, indicating comparable gestational ages ($p > 0.05$). The maternal ages of the three groups were 28.9 ± 2.6 years, 28.4 ± 1.9 years, and 29.3 ± 2.7 years, indicating comparable maternal ages ($p > 0.05$).

The intraobserver ICCs were between 0.91 (95% confidence interval (CI), 0.79–0.96) and 0.98 (95% CI, 0.96–0.99), and the interobserver ICCs were between 0.80 (95% CI, 0.57–0.92) and 0.91 (95% CI, 0.78–0.96). The Bland–Altman plots are shown in Supplemental Figs. 1 and 2.

Ultrasonographic Features Of Rfof

The ultrasonographic features of RFOF included atrial and ventricular asymmetry, disproportion between the pulmonary artery and aorta (Fig. 1), dysplasia of the aortic arch (Fig. 2), ductus arteriosus aneurysm, and premature atrial beats. The detailed ultrasonographic features, number of cases, and percentages are shown in Table 1.

Table 1
Detailed ultrasonographic features, number of cases, and percentages of the RFOF group

Ultrasonographic features	Details	Number of cases	Percentage
1. Atrial and ventricular asymmetry	(1) RAD/LAD ≤ 1.3	1	6%
	(2) $1.3 < \text{RAD/LAD} \leq 1.5$ in four cases	4	27%
	(3) RAD/LAD > 1.5 in 10 cases	10	67%
2. Disproportion between the pulmonary artery and aorta	(1) $1.3 < \text{PAD/AoD} \leq 1.5$	4	27%
	(2) PAD/AoD > 1.5	11	73%
3. Dysplasia of the aortic arch	The aortic arch view showed stiff and twisted aortic arches with changes in aortic spacing and narrowing of the inner diameter (similar to or slightly smaller than those of the adjacent carotid artery branches). Narrowing of the AID was especially prominent	15	100%
4. Ductus arteriosus aneurysm	Aneurysmal dilatation of the ductus arteriosus	3	20%
5. Premature atrial beats	Atrial premature beat	2	13%

Correlations Between The Fofd/lad And The Measured Parameters Of The Heart Structure

Analysis of the correlations between the FOFD/LAD and the measured parameters of the heart structure in the 15 fetuses with RFOF and the 30 normal fetuses showed that with increasing FOFD/LAD, the RAD/LAD, RVD/LVD, and PAD/AoD increased significantly, and the correlation r values were 0.825, 0.862, and 0.846 (all $p < 0.001$), respectively. The quadratic regression equations (Fig. 3) were $y = 2.42x^2 - 1.45x + 1.25$ ($R^2 = 0.936$, $p < 0.001$), $y = 2.26x^2 - 1.18x + 1.56$ ($R^2 = 0.936$, $p < 0.001$), and $y = 2.46x^2 - 1.43x + 1.24$ ($R^2 = 0.940$, $p < 0.001$) for the RAD/LAD, RVD/LVD, and PAD/AoD, respectively.

Comparison Of Parameters Of The Heart Structure Among The Rfof, Coa, And Control Groups

Except for the FOFD/LAD ($p < 0.01$), no significant differences in the RAD/LAD, RVD/LVD, PAD/AoD, or AID were found between fetuses with an RFOF and fetuses with CoA ($p > 0.05$). Table 2 shows a comparison of the three groups of fetuses.

Table 2
Comparison of cardiac structural parameters among the three fetus groups

Parameter Group	FOFD/LAD	RAD/LAD	RVD/LVD	PAD/AoD	Ao isthmus Z score
RFOF (n = 15)	0.73 (0.68, 0.82) ^a	1.54 (1.48, 1.70) ^a	1.57 (1.5, 1.71) ^a	1.61 (1.49, 1.75) ^a	3.0 (2.90, 3.10) ^a
CoA (n = 9)	0.40 (0.39, 0.44)	1.50 (1.40, 1.65) ^a	1.58 (1.40, 1.65) ^a	1.62 (1.44, 1.75) ^a	3.2 (3.0, 3.40) ^a
Control (n = 30)	0.47 (0.44, 0.54)	1.12 (1.08, 1.13)	1.10 (1.07, 1.14)	1.12 (1.09, 1.15)	0.08 (-0.33, 0.4)

Note: Compared with the control group, ^a $p < 0.01$.

Discussion

An isolated RFOF is rare and easily overlooked in prenatal ultrasound examinations. The incidence of isolated RFOF detected by ultrasonography is only 0.6–1.7%[9, 10]. To date, only two cases of prenatal diagnosis have been reported, including one case by Hagen et al.[9] and one by Devadasan et al.[10]. This study systematically analyzed the ultrasonographic features of isolated RFOF for the first time, including atrial and ventricular asymmetry, disproportion between the pulmonary artery and aorta, dysplasia of the aortic arch, narrowing of the aortic isthmus, aneurysmal dilatation of the ductus arteriosus, and premature atrial beats.

This study found that with increasing RFOF severity, the asymmetry of intracardiac structures and the disproportion between the pulmonary artery and aorta became more obvious, the dysplasia of the aortic arch became more serious, and the AID became thinner. These ultrasonographic features are similar to those of CoA (Table 2), which is consistent with the results reported by Vena et al.[8]. Fetal cardiovascular development depends on an increase in blood volume and the impact of blood flow[1, 2]. The main causes of the asymmetric development of intracardiac structures in RFOF are as follows: (1) the high activity of the foramen ovale flap affects the blood flow through the foramen ovale; (2) the protruding foramen ovale flap blocks the inflow of blood through the mitral valve; and (3) the flow of oxygen-rich blood from the ductus venosus is disturbed, causing turbulence[8, 16, 17]. These factors reduce the flow of blood through the left heart system, resulting in hypoplasia of the left heart.

Prenatal ultrasound diagnosis of fetal CoA has a high false positive rate[2]. Perolo et al.[18] reported the results of 10 years of diagnosing fetal cardiac malformation and found that the accuracy of prenatal diagnosis of CHD was as high as 91%. The false positive diagnosis rate was 3.4%, and the main false positive diagnosis was CoA. Stos et al.[19] reported that the diagnostic accuracy for 202 fetuses with severe CoA was only 19% if a PAD/AoD > 1.6 was used as the prediction index. Jung et al.[20] reported 44 fetuses with an isolated right dominant heart (RDH) whose RAD/LAD, RVD/LVD, and PAD/AoD were

greater than 1.5. Their results showed that 66% of fetuses with RDH were normal newborns after delivery and that 34% had cardiac disorders, with CoA and an interrupted aortic arch accounting for 27.2% of cases. The false positive diagnosis of CoA may be related to isolated RFOF[8, 10]. RFOF affects the blood flow into the left heart through the foramen ovale, increasing the blood volume through the ductus arteriosus and reducing the blood volume through the aortic arch, finally causing dysplasia of the aortic arch[1, 2, 16]. This may be one of the reasons why RFOF is misdiagnosed as CoA. Another reason is that both RFOF and CoA result in a disproportion between the left and right heart. In fetuses with RFOF, the foramen ovale and ductus arteriosus are closed after birth, and pulmonary vascular resistance decreases considerably. This process changes the blood flow through the pulmonary artery and aorta and increases aortic blood flow, causing the aortic arch to expand and continue to develop[2]. Therefore, fetuses with CoA and RFOF have different prognosis. In summary, the presence of RFOF must be considered for fetuses with suspected CoA on prenatal ultrasound examinations. In this study, the difference in the FOFD/LAD ratio between the RFOF group and the CoA group was statistically significant, which may be helpful in distinguishing between RFOF and CoA.

It should be emphasized that the ultrasonographic features of RFOF are also similar to those of RFO, including atrial and ventricular asymmetry and a narrowed aortic isthmus[6, 7, 9]. The asymmetric growth of intracardiac structures in RFO is mainly due to obstruction of the blood flow through the foramen ovale, and the normal functions of the left heart are mostly taken over by the right heart[16]. Although some studies have previously identified RFOF as RFO, their prognoses are different. The prognosis of fetuses with an RFO is poor, and that of fetuses with an RFO complicated with CHD is even worse[2, 6, 16]. However, the prognosis of fetuses with an isolated RFOF is better. The four fetuses with an isolated RFOF described by Devadasan and Hagen et al.[9, 10] had no adverse outcomes. Fetuses with an isolated RFOF described by Vena et al.[8] also had no adverse perinatal outcomes. Uzun et al.[7] reported 23 cases of RFO without an abnormal heart structure, including 21 cases of RFOF without structural heart disease. Among these cases, two newborns died, including one with VACTERL association and one with Menke syndrome, a posterior urethral valve, and bradycardia. Four newborns presented pulmonary arterial hypertension, all of whom had other abnormalities including hypothyroidism, anemia, edema, Down's syndrome, or hypospadias. The remaining fetuses had no adverse outcomes. In our study, none of the 15 fetuses with an isolated RFOF developed CoA or other adverse outcomes. Therefore, in view of the different prognoses of fetuses with isolated RFOF and RFO, an isolated RFOF should be clinically distinguished from an RFO. When atrial and ventricular asymmetry are found in prenatal ultrasound examinations, whether the foramen ovale flap is redundant or restrictive must be determined, and whether other maternal and fetal complications are present should be noted.

In summary, measurement and calculation of the FOFD/LAD, observation of blood flow through the foramen ovale, and observation of the activity of the foramen ovale flap contribute to the differential diagnosis between RFOF and CoA or RFO.

This study had some limitations, including its retrospective nature. The findings of this study need to be validated in prospective studies in the future. Furthermore, the sample size was relatively small due to the

strict selection criteria. According to the means and standard deviations of RAD/LAD, RVD/LVD, PAD/AoD, and aortic isthmus Z-score in our study, assuming an alpha of 0.05 and power of 0.8, the number of subjects needed to detect significant differences between the RFOF and CoA groups would be 106[21]. Hence, we cannot be sure whether the lack of a significant difference was caused by truly no difference or an insufficient sample size. However, based on the study by Vena et al.[8], we tend to favor the former explanation. In addition, according to the means and standard deviations of the FOFD/LAD, with group sample sizes of 15 and 9 in our study, assuming an alpha of 0.05, the statistical power to detect a difference between the RFOF and CoA groups was 1.0, indicating that the conclusion is still reliable.

Conclusions

Isolated RFOF has specific features and can be easily identified on ultrasound. The ultrasonographic features of RFOF are similar to those of CoA. Measurement and calculation of the FOFD/LAD may be helpful in distinguishing between RFOF and CoA.

List Of Abbreviations

AID
aortic isthmus diameter
AoD
aortic diameter
CHD
congenital heart disease
CI
confidence interval
CoA
aortic coarctation
FOD
foramen ovale diameter
FOFD
foramen ovale flap diameter
ICC
intraclass correlation coefficient
IUGR
intrauterine growth restriction
LAD
left atrial diameter
LVD
left ventricular diameter

PAD
pulmonary artery diameter
RAD
right atrial diameter
RDH
right dominant heart
RFO
restrictive foramen ovale
RFOF
redundant foramen ovale flap
RVD
right ventricular diameter

Declarations

Ethics approval and consent to participate: The study was approved by the medical ethics committee of Fujian Medical University, approval number [2021251], and all patients gave their informed consent before the prenatal ultrasound examination.

Consent for publication: All authors gave approval for submission.

Availability of data and materials: Data used for the analyses in this study are publicly shared in Supplemental Table 1.

Competing interests: The authors have no conflicts of interest to declare.

Funding: None.

Author contributions: G.L. and S.Z. contributed to the conception and design of the study, analysis and interpretation of data, and drafting of the article. S.H. and Q.C. contributed to the acquisition of data. L.L. was in charge of the research project. All authors revised the article critically for important intellectual content and gave final approval of the version to be submitted.

Acknowledgments: We sincerely thank all participants for their cooperation in obtaining the necessary medical data for publication.

Reference

1. Lyu GR, Jiang LX. Fetal echocardiography. Beijing: Peking University Medical Press; 2003. pp. 76–149.
2. Lyu GR. Ultrasound diagnosis of fetal central nervous system and cardiac malformations. Beijing: Peking University Medical Press; 2010. pp. 193–232.

3. Donofrio MT, Bremer YA, Moskowitz WB. Diagnosis and management of restricted or closed foramen ovale in fetuses with congenital heart disease. *Am J Cardiol.* 2004;94(10):1348–51.
4. Taketazu M, Barrea C, Smallhorn JF, Wilson GJ, Hornberger LK. Intrauterine pulmonary venous flow and restrictive foramen ovale in fetal hypoplastic left heart syndrome. *J Am Coll Cardiol.* 2004;43(10):1902–07.
5. Tuo G, Paladini D, Montobbio G, Volpe P, Cheli M, Calevo MG, et al. Prenatal echocardiographic assessment of foramen ovale appearance in fetuses with d-transposition of the great arteries and impact on neonatal outcome. *Fetal Diagn Ther.* 2017;42(1):48–56.
6. Gu X, Zhang Y, Han J, Liu X, Ge S, He Y. Isolated premature restriction or closure of foramen ovale in fetuses: echocardiographic characteristics and outcome. *Echocardiography.* 2018;35(8):1189–95.
7. Uzun O, Babaoglu K, Ayhan YI, Moselhi M, Rushworth F, Morris S, et al. Diagnostic ultrasound features and outcome of restrictive foramen ovale in fetuses with structurally normal hearts. *Pediatr Cardiol.* 2014;35(6):943–52.
8. Vena F, Donarini G, Scala C, Tuo G, Paladini D. Redundancy of foramen ovale flap may mimic fetal aortic coarctation. *Ultrasound Obstet Gynecol.* 2020;56(6):857–63.
9. Hagen A, Albig M, Schmitz L, Hopp H, van Baalen A, Becker R, et al. Prenatal diagnosis of isolated foramen ovale obstruction: A report of two cases. *Fetal Diagn Ther.* 2005;20(1):70–3.
10. Devadasan S, Batra M, Balakrishnan B, Sreeja PS, Patil Swapneel N, Gopinathan KK. Prenatal diagnosis of isolated redundant foramen ovale: a case report. *Journal of Fetal Medicine.* 2018/09/01;5(3):159–62.
11. AIUM-ACR-ACOG-SMFM-SRU. Practice parameter for the performance of standard diagnostic obstetric ultrasound examinations. *J Ultrasound Med.* 2018;37(11):E13–24.
12. International Society of Ultrasound in Obstetrics & Gynecology. Cardiac screening examination of the fetus: guidelines for performing the 'basic' and 'extended basic' cardiac scan. *Ultrasound Obstet Gynecol.* 2006;27(1):107–13.
13. International Society of Ultrasound in Obstetrics & Gynecology. Sonographic examination of the fetal central nervous system: guidelines for performing the 'basic examination' and the 'fetal neurosonogram'. *Ultrasound Obstet Gynecol.* 2007;29(1):109–16.
14. Editorial Committee of Chinese Ultrasound Doctors Association. Chinese guidelines for fetal echocardiography. Beijing: People's Health Publishing House; 2019. pp. 40–100.
15. García-Otero L, Gómez O, Rodríguez-López M, Torres X, Soveral I, Sepúlveda-Martínez Á, et al. Nomograms of fetal cardiac dimensions at 18–41 weeks of gestation. *Fetal Diagn Ther.* 2020;47(5):387–98.
16. Channing A, Szwaast A, Natarajan S, Degenhardt K, Tian Z, Rychik J. Maternal hyperoxygenation improves left heart filling in fetuses with atrial septal aneurysm causing impediment to left ventricular inflow. *Ultrasound Obstet Gynecol.* 2015;45(6):664–69.
17. Familiari A, Morlando M, Khalil A, Sonesson S-E, Scala C, Rizzo G, et al. Risk factors for coarctation of the aorta on prenatal ultrasound: a systematic review and meta-analysis. *Circulation.*

2017;135(8):772–85.

18. Perolo A, Prandstraller D, Ghi T, Gargiulo G, Leone O, Bovicelli L, et al. Diagnosis and management of fetal cardiac anomalies: 10 years of experience at a single institution. *Ultrasound Obstet Gynecol.* 2001;18(6):615–18.
19. Stos B, Le Bidois J, Fermont L, Bonnet D. Is antenatal diagnosis of coarctation of the aorta possible? *Arch Mal Coeur Vaiss.* 2007;100(5):428–32.
20. Jung E, Won H-S, Lee PR, Kim A, Park I-S. Clinical implication of isolated right dominant heart in the fetus. *Prenat Diagn.* 2007;27(8):695–98.
21. Zar JH *Biostatistical Analysis* (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey. 1984.

Figures



Figure 1

Ultrasonograms showing atrial and ventricular asymmetry in fetuses with an isolated RFOF.

A. RFOF; B. atrial and ventricular asymmetry; C. disproportion between the aorta and the pulmonary artery

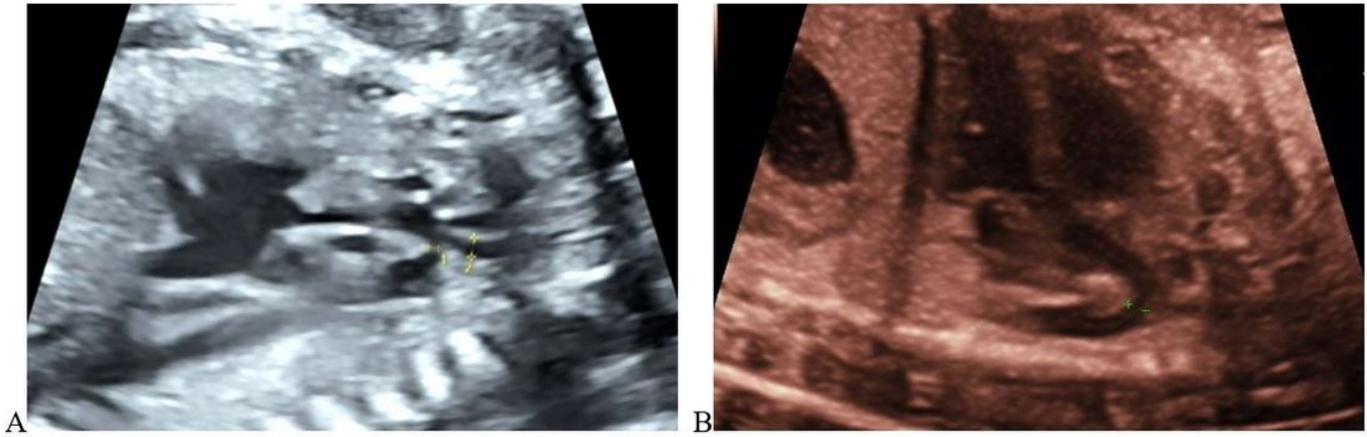


Figure 2

Ultrasonograms showing aortic dysplasia in fetuses with an isolated RFOF.

A. Aortic arch dysplasia; B. narrowing of the aortic isthmus

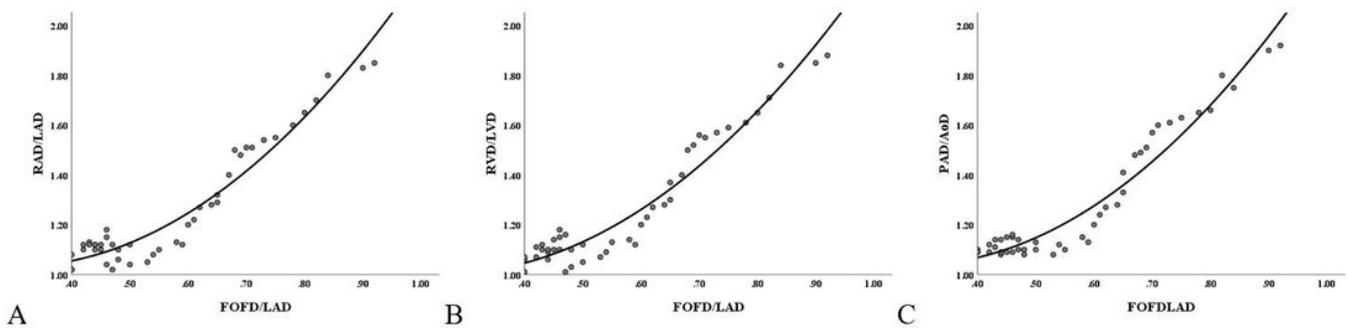


Figure 3

Quadratic regression equation for FOFD/LAD and measurement parameters of the heart structure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalFigure1.docx](#)

- [SupplementalFigure2.docx](#)
- [SupplementalTabel1.xlsx](#)