

Fetal Ventricular Longitudinal Strain Does Not Predict Neonatal Hypoxemia in D-Transposition of the Great Arteries: A Prospective Multi-Center Study by the Fetal Heart Society Research Collaborative

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Research Article

Keywords: Transposition of the great arteries, Ventricular longitudinal strain, Fetal echocardiography, Balloon atrial septostomy

Posted Date: October 15th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11197059/v1>

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Additional Declarations: No competing interests reported.

Abstract

Introduction:

Neonates with transposition of the great arteries (TGA) and intact ventricular septum (IVS) can develop life-threatening hypoxemia after birth. There are no known reliable fetal echocardiographic markers of postnatal hypoxemia. Using a large, multi-center prospectively recruited cohort, we analyzed fetal ventricular strain and its association with postnatal hypoxemia.

Material and Methods:

Eighteen centers enrolled maternal-fetal dyads. Fetal ventricular longitudinal strain and strain rate measurements were obtained. The primary outcome measure was preoperative neonatal hypoxemia. The secondary outcome measure was reported need for balloon atrial septostomy (BAS). Intra- and inter-rater reliability was assessed. Fetal longitudinal strain was compared to normative data from a previously published study evaluating strain in fetuses without congenital heart disease.

Results:

Longitudinal strain was performed on 79 fetuses with TGA/IVS. Of those, 29 (37%) developed postnatal hypoxemia. A BAS was performed in 45 (57%). There was no statistically significant difference in fetal longitudinal strain between those with postnatal hypoxemia and those without. Similarly, fetal longitudinal strain did not differ among those who received a BAS and those who did not. Among fetuses with TGA/IVS, while right and left ventricular longitudinal strain was similar, right ventricular free wall strain was significantly higher than left ventricular longitudinal strain. Compared to the previously published normative data, longitudinal strain for both ventricles were significantly higher in fetuses with TGA/IVS.

Conclusion:

This prospective multi-center study identified no association between fetal longitudinal strain and postnatal hypoxemia or need for BAS in neonates with TGA/IVS, highlighting the importance of delivery planning for all fetuses with TGA to include preparations for BAS.

Introduction

Dextro-transposition of the great arteries (TGA) is a critical cyanotic congenital heart defect (CHD) with a prevalence of 2–3 per 1,000 live births and a 2:1 male preponderance.^{1–3} TGA is characterized by atrioventricular concordance and ventriculoarterial discordance resulting in parallel systemic and pulmonary circulations. Infants with TGA and an intact ventricular septum (TGA/IVS) may have inadequate atrial level mixing of oxygenated and deoxygenated blood and develop life-threatening hypoxemia and acidemia. Those with hypoxemia and acidemia may emergently require a balloon atrial septostomy (BAS) to enlarge the foramen ovale, thereby improving systemic oxygenation.

While prenatal detection of TGA has been shown to improve outcomes²⁻⁴ and is of clear benefit for affected pregnancies, prenatal identification of those at higher risk for profound hypoxemia after birth remains challenging.^{2,5,6-13} The anatomic arm of this Fetal Heart Society (FHS) study evaluated fetuses with TGA/IVS and aimed to identify fetal echocardiographic anatomic and physiologic predictors of postnatal hypoxemia. Unfortunately, no sensitive fetal echocardiographic predictors were identified.¹⁴ Identification of a sensitive fetal echocardiographic predictor would allow for improved delivery planning and postnatal outcomes.

Ventricular longitudinal strain (LS) evaluates the fractional change in length of a ventricular segment. Using speckle tracking echocardiography, the ventricular motion is tracked frame-by-frame in a largely angle-independent manner, making it a more optimal measurement of ventricular function in a mobile fetus than classic techniques such as ejection fraction and fractional shortening.¹⁵⁻¹⁸ Fetal LS has been shown to detect subclinical changes in myocardial function associated with extracardiac conditions, such as maternal diabetes, fetal growth restriction, congenital diaphragmatic hernia, and twin-twin transfusion syndrome.^{15,19-23} Additionally, changes in fetal ventricular strain have been associated with certain types of CHD, including tetralogy of Fallot, pulmonary atresia with intact ventricular septum, Ebstein's malformation, critical aortic stenosis, coarctation of the aorta, and single ventricular heart defects.²⁴⁻²⁹ To date, studies evaluating ventricular strain in fetuses with TGA have been largely retrospective and/or single center studies with often times conflicting results.

Using a large, multi-center, prospectively recruited and examined cohort, our study aimed to determine if changes in left (LV) and right (RV) ventricular LS and strain rate (SR) are associated with postnatal hypoxemia or need for BAS in infants prenatally diagnosed with TGA/IVS. We also sought to identify changes in strain between the LV and RV in fetuses with TGA/IVS, as well as changes in ventricular strain between fetuses with TGA/IVS and fetuses without CHD.

Based on prior studies evaluating strain in fetal TGA, we hypothesized that neonates with hypoxemia would have lower fetal LV LS and SR values. Additionally, when evaluating interventricular strain differences among the cohort, we hypothesized that RV LS would be higher than LV LS due to prior reports describing increased RV cardiac output, increased LV preload, and decreased LV function in fetal TGA.^{5,30}

Material and Methods

This study represents one arm of a multicenter, multi-arm prospective longitudinal cohort study designed by the Fetal Heart Society (FHS) Research Collaborative to identify predictors of postnatal hypoxemia in fetuses with TGA/IVS for improved delivery planning and postnatal outcomes. Centers across North America prospectively enrolled maternal-fetal dyads with a fetal diagnosis of TGA/IVS from 2018 to 2022. Each center obtained appropriate ethics approval and as required by their institution, informed consent from participating maternal subjects, as well as appropriate data use agreements with the FHS Data Coordinating Center (DCC, University of Utah, Salt Lake City, Utah).

Any maternal-fetal dyad with a prenatal diagnosis of TGA/IVS was eligible for inclusion. Subjects were excluded if there were additional cardiac defects expected to require intervention, non-cardiac anomalies expected to affect mortality, or if there was interruption of pregnancy or lack of postnatal data.

Participating centers uploaded de-identified fetal echocardiograms to the DCC and images were stored in Digital Imaging and Communication in Medicine (DICOM) format. The type of ultrasound machine and choice of ultrasound probe used for each subject was at the discretion of the individual participating centers. The offline cardiac software program 2D Cardiac Performance Analysis (2D CPA) developed by TomTec Imaging Systems, GmbH (Munich, Germany) was used to analyze the stored cine clips.

Fetal ventricular strain measurements were primarily performed at the core lab at AdventHealth for Children in Orlando Florida, by an investigator (JS) with expertise in fetal echocardiography and strain analysis. For inter-rater reliability testing, some measurements were also performed at Monroe Carell Jr. Children's Hospital at Vanderbilt by two investigators (AKM and PG), also with expertise in fetal echocardiography and strain analysis. All investigators performing strain measurements were blinded to the outcome.

For each subject, a 2-dimensional (2D) cine clip of a fetal 4-chamber view was selected from the stored fetal echocardiogram for fetal strain analysis. The most recent fetal echocardiogram was selected to attempt to analyze late third trimester studies. Left and right ventricular analyses were performed separately. The clip with the highest frame rate and most optimal contrast between the endocardium and ventricular cavity was selected. Subjects were excluded if image quality was deemed suboptimal for adequate tracking. The investigator performing the strain measurements qualified the tracking as either good, fair, or poor. Four-chamber endocardial LS measurements were performed as per recommendations in the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) consensus documents.^{17,31} Each measurement was performed three separate times by the same investigator on the same cardiac cycle, and the averaged value was used for final data analysis.

The fetal strain measurements analyzed for this study included: LV and RV systolic longitudinal strain (LV LS and RV LS respectively), RV free wall strain (RV FWS), and LV and RV strain rate (LV SR and RV SR respectively). For the purposes of this study, LS refers to the average longitudinal component of strain over all segments of the endocardium for each respective ventricle and is expressed as a percentage. RV FWS refers to the average longitudinal component of strain over the endocardium of the RV free wall. Strain rate describes the rate of deformation over time, or how fast the deformation occurs, and is expressed as 1/sec or sec^{-1} .

Ventricular strain is described as an absolute value of the number, such that a described increase in the strain value is noted when the value becomes more negative, and a decrease when the value becomes less negative as ventricular function deteriorates, as described in the recommendation in the EACVI and ASE consensus document.^{17,31}

Statistical Analysis

The primary outcome was profound pre-operative hypoxemia, defined as $\text{PaO}_2 < 30 \text{ mmHg}$, or $\text{SpO}_2 < 75\%$. Participating centers recorded the lowest PaO_2 and/or SpO_2 between 5 minutes after birth and prior to BAS or cardiac surgery. The secondary outcome was whether a BAS was performed. The urgency of the BAS was noted by the participating centers at the time of data collection as “urgent” or “elective” defined by their clinical assessment.

Categorical variables are presented as counts and percentages, and continuous variables are presented as medians and interquartile ranges. Associations were determined using Fisher’s exact test for categorical variables and Wilcoxon rank-sum test for continuous or ordinal variables. Maternal and postnatal characteristics were evaluated according to pre-operative hypoxemia status. Fetal ventricular strain measures were also evaluated according to pre-operative hypoxemia status, as well as the combined outcome of pre-operative hypoxemia and need for BAS. Univariable logistic regression analysis was conducted comparing fetal strain measures to pre-operative hypoxemia. Analyses were also repeated excluding those with poor strain tracking quality. A signed-rank test was conducted comparing the LV and RV strain measurements.

For the purposes of this study, a normal control population was not analyzed. However, to understand how the ventricular strain measurements in fetuses with TGA/IVS compared to normal fetuses without CHD, the data were compared to previously reported data on normal fetuses in the study by Van Oostrum et al.¹⁵ A one-sample t-test was used to compare mean Z-score differences.

Intra-rater reliability was assessed using intraclass correlation [ICC(1,1) and ICC(1,3)] with 95% confidence intervals using three separate fetal strain measurements on the same subject performed by the same investigator. Inter-rater reliability was assessed between two independent investigators (each blinded to the outcome) using intraclass correlation [ICC(3,1)] with 95% confidence intervals on 11 subjects with LV fetal strain data and 10 subjects with RV fetal strain data. A p-value of < 0.05 was considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute; Cary, NC).

Results

Eighteen centers prospectively enrolled maternal-fetal dyads diagnosed with TGA/IVS from 2018 to 2022. A total of 100 maternal-fetal dyads met the inclusion criteria with a fetal echocardiogram uploaded for review. Of those, 79 contained the required fetal 4-chamber view for ventricular strain analysis, creating the final cohort.

Demographics/baseline characteristics

Maternal and postnatal characteristics are summarized in Table 1. No significant differences in maternal characteristics were identified between those that developed postnatal hypoxemia and those that did

not.

Of the final cohort, 29 (37%) had the primary outcome of profound postnatal pre-operative hypoxemia. The median age at lowest pre-operative SpO₂ was 2.5 hours [IQR 1–24 hours] and the median age at lowest pre-operative PaO₂ was 5 hours [IQR 1–26 hours].

A BAS was performed in 45 (57%) of the final cohort, at a median age of 2 hours [IQR 1–4 hours]. The BAS was noted to be urgent or elective by the respective centers. Of the 45 requiring a BAS, urgency status was missing in one subject. The BAS was noted to be urgent in 39 (89%) and elective in 5 (11%).

A BAS was performed more often in those with reported hypoxemia as opposed to those without (79% vs 44%, $p = 0.002$). However, even in those without reported hypoxemia, a BAS was still performed in almost half of those patients. There was no difference in the reported urgency of the BAS between the two outcome groups, with 86% noted as urgent in the hypoxemia group, and 91% noted as urgent in the non-hypoxemia group.

The median age at surgical intervention was 5 days, with no difference between the hypoxemia and non-hypoxemia groups. However, the total hospitalization and intensive care unit length of stays were significantly longer in the hypoxemia group ($p = 0.039$ and $p = 0.005$ respectively). Of the final cohort, all (100%) survived to hospital discharge.

Fetal ventricular strain & postnatal hypoxemia

The last fetal echocardiogram prior to delivery was analyzed for each subject. The median gestational age at fetal strain analysis was 34 6/7 weeks (interquartile range of 31 0/7 weeks to 36 0/7 weeks).

Fetal ventricular strain measurements are reported in Tables 2 and 3. There were no statistically significant fetal ventricular strain predictors of neonatal hypoxemia identified. Fetal ventricular strain values were also evaluated for possible association with need for BAS and similarly, there were no statistically significant predictors identified.

In an attempt to capture the most critical neonates, the analyses were performed again combining those that both developed hypoxemia and underwent BAS. As shown in table 4, fetal strain values remained nonsignificant for those 23 neonates that both developed hypoxemia and required a BAS.

Fetal ventricular strain can be affected by suboptimal images and poor endocardial tracking. Both LV and RV strain measurements were significantly lower in those with poor endocardial tracking (supplemental table 1). Of note, strain rate measurements were not as affected by tracking quality. Given this information, the analysis was again performed after excluding those with poor endocardial tracking. The fetal ventricular strain values continued to remain non-significant (supplemental table 2).

Comparing fetal ventricular strain differences between ventricles

When evaluating inter-ventricular differences in strain among the entire cohort of fetuses with TGA/IVS (regardless of hypoxemia or BAS status), LV LS and RV LS values were similar ($p = 0.332$), and LV and RV SR measurements were also similar ($p = 0.370$). However, when analyzing RV FWS separately, RV FWS was significantly higher than LV LS ($p = 0.025$).

Comparing fetal ventricular strain in TGA/IVS vs fetuses without CHD

The mean gestational age-adjusted LV LS Z-score was -0.27 ($SD = 0.57$, $p < 0.001$) relative to gestational age normals, indicating a statistically significant increase in LV LS in those with TGA/IVS compared with gestational age-matched values. Similarly, the mean gestational age-adjusted RV LS Z-score was -0.53 ($SD = 0.058$, $p < 0.001$), indicating a statistically significant increase in RV LS in those with TGA/IVS compared with gestational age-matched values from the referenced manuscript¹⁵.

Intra- and inter-rater reliability testing

Intra-rater reliability was tested using three separate fetal ventricular strain measurements on the same subject performed by the same investigator blinded to outcome. Intra-rater reliability was high for both LV and RV strain measurements. For single measurements ($ICC(1,1)$), LV LS had an ICC of 0.82 (95%CI 0.79–0.90) and RV LS had an ICC of 0.85 (95% CI: 0.79–0.90) indicating excellent consistency.

Inter-rater reliability was tested using 11 subjects with LV fetal strain data and 10 subjects with RV fetal strain data. For each subject, fetal strain measurements were performed three separate times by two independent investigators blinded to outcome. Inter-rater reliability for LV LS was good ($ICC[3,1] = 0.85$; 95% CI: 0.53, 0.96), indicating substantial agreement between providers. Although the lower bound of the confidence interval suggested moderate reliability, the point estimate supported strong consistency in LV LS measurements. Inter-rater reliability for LV SR was poor ($ICC[3,1] = 0.29$; 95% CI: -0.34 , 0.74). The wide confidence interval indicated substantial uncertainty in the reliability estimate. Inter-rater reliability for the RV measurements (RV LS, RV FWS, and RV SR) was good based on the point estimate ($ICC[3,1] = 0.78$, $ICC[3,1] = 0.80$ and $ICC[3,1] = 0.75$), respectively; however, the wide confidence interval (0.30–0.94), (0.35–0.95) and (0.23–0.93), respectively, indicates considerable uncertainty.

Discussion

To the best of our knowledge, this study represents the first prospective, multi-center study evaluating ventricular strain in fetuses with TGA/IVS. While we found inter-ventricular differences in strain among our cohort, as well as higher LV and RV LS compared to a previously reported normal fetal cohort, we ultimately found no differences in ventricular strain associated with postnatal hypoxemia or need for BAS. Ventricular strain values for both the LV and RV were similar in those presenting with postnatal

hypoxemia or those undergoing a BAS compared to those without hypoxemia and/or not undergoing a BAS.

Profound postnatal pre-operative hypoxemia was noted in 37% of the cohort and a BAS was performed in 57%. Our BAS rates are similar to previously published BAS rates in the literature that range from 48% to 57%.^{2,5-8,30}

Centers may have differing criteria on indications for performing a BAS. Our study showed that a BAS was not limited to those with postnatal hypoxemia. While a BAS was performed more often in those with hypoxemia (79%), it was still performed in nearly half of those (44%) without reported hypoxemia, with no difference in the reported urgency of BAS between the two groups. As a result, using BAS as the primary outcome measure potentially tempered the results, as less critical neonates also underwent the procedure.

Fetal ventricular strain

Ventricular strain has been well documented as a sensitive and specific marker of ventricular function in adult and pediatric subjects. Recent data show similar findings in fetal patients.¹⁵

Our study found no difference in fetal LV and RV strain values between those that developed postnatal hypoxemia and those that did not. This is surprising given a prior retrospective study that evaluated ventricular size and function parameters in 39 fetuses with TGA/IVS. The authors found that the RV in the non-BAS group demonstrated abnormalities in contractility, including abnormal RV free wall strain measurements.⁵ While our study chose postnatal hypoxemia as the primary outcome measure, fetal strain values were also analyzed in those that underwent a BAS compared to those who did not. There remained no significant differences in fetal strain between the two groups. To further attempt to capture the most critical neonates, the data were re-analyzed combining the two outcomes of postnatal hypoxemia and need for BAS. Fetal ventricular strain values remained non-significant in our prospectively collected cohort.

A possible reason for the lack of an association identified in our study could be related to differences in gestational age and/or endocardial tracking between the two outcome groups. It is known that fetal ventricular strain changes with advancing gestation,¹⁵ however, in our study there was no difference in gestational age between the two outcome groups. Fetal ventricular strain is also affected by suboptimal images with poor endocardial tracking. Higher frame rates are known to improve speckle tracking and poor image quality can lead to falsely low strain values. Our study showed no difference in frame rates between the two outcome groups and our sub-analysis excluding those with poor tracking remained non-significant.

Comparing fetal ventricular strain: inter-ventricular difference and controls

In fetuses with a structurally normal heart, the literature differs regarding relative strain values between the LV and RV. Some studies report that RV strain is higher than the LV, as the RV ejects to the low resistance placenta.^{19,32} However, other studies report that the LV strain is higher than the RV.^{15,20,33}

Similarly, in small study populations of fetuses with TGA, there are similar conflicting data regarding LV and RV strain. One study evaluated ventricular strain in 13 fetuses with TGA and demonstrated increased RV LS compared to normal fetuses, as well as reduced LV basal circumferential strain. The authors demonstrated relatively lower LV LS compared to RV LS and hypothesized it could be related to the smaller diameter of the ductus arteriosus leading to increased LV afterload.³⁰ In another single center retrospective study evaluating fetal ventricular strain in different types of CHD, including 15 fetuses with TGA, no significant difference was found between LS in fetuses with TGA compared to the control group. Additionally, the LV and RV LS values were similar in TGA fetuses (-22.9% and -21.3% respectively).³³ Similar conflicting results have been reported in larger study populations as well. A systematic review and meta-analysis evaluated LV and RV LS in different types of CHD. Among those with TGA, there was no difference in LV or RV LS compared to controls.²⁷ Another retrospective study evaluated RV strain in 49 fetuses with TGA and found RV LS to be lower than the control group.³⁴ The authors postulated that this could be related to insufficient coronary oxygen supply in fetuses with TGA, or related to the inherent differences in the RV structure.

In our multicenter study evaluating a larger and prospectively collected cohort, when comparing fetal ventricular strain differences between the LV and RV, longitudinal strain values were similar between ventricles however when analyzing RV FWS separately, RV FWS was significantly higher than LV LS ($p = 0.025$) among the entire cohort. RV FWS excludes the interventricular septum in analysis, which is known to be systematically lower in magnitude than that of the RV free wall. Therefore, the finding of higher RV FWS could be related to the known lower septal strain values, or may be at least in part related to other proposed theories such as that noted in the manuscript by Patey et al where a smaller ductus arteriosus in TGA/IVS fetuses could affect LV afterload.³⁰

As our study did not analyze a separate normal fetal control population, we compared our ventricular strain values in fetuses with TGA/IVS to the ventricular strain values in normal fetuses reported in the manuscript by Van Oostrum et al.¹⁵ When referencing to gestational age-matched normal values reported in the manuscript, both LV and RV LS values were significantly higher in fetuses with TGA/IVS compared to the normative values. One possible reason could be related to differences in oxygen content resulting in lower afterload; in the aorta due to cerebral autoregulation and in the lungs due to oxygen reactivity. As our study analyzed late-gestation fetal echocardiograms, this difference was apparent as these regulatory factors are appreciated later in gestation.

Intra- and inter-rater reliability

Our data showed good intra-rater reliability. While the inter-rater reliability results were good for LV LS, the results were poor or had wide confidence intervals suggesting uncertainty for LV SR and RV strain

measurements. The suboptimal inter-rater reliability is similar to prior studies.^{30,35} While strain measurements performed in the same manner by the same investigator over time have good reliability, measurements between investigators are not as reliable. The study from McFarland et al showed feasibility but poor reliability of retrospective fetal strain measurements from images obtained in clinical practice across multiple institutions.³⁶ Our study reinforces this finding and underscores the importance of utilizing a focused strain imaging protocol during image acquisition.

Limitations

While our study represents the first multi-center prospective study to evaluate fetal ventricular strain in TGA/IVS, there are several limitations to consider.

Given the variability between centers in the decision to perform and timing of BAS, hypoxemia (as measured by lowest PaO₂) was chosen as a more objective measure of neonatal status. However, we observed that most centers do not place an indwelling arterial catheter until after the neonate was stabilized, or even after the BAS, thereby limiting the utility of this measure in describing neonatal compromise. As a result, SpO₂ was chosen as a surrogate marker to capture an alternate measure of hypoxemia. The site of SpO₂ (pre vs post ductal) was not captured on all subjects however, given that the lowest SpO₂ was requested, we would expect that recorded measures represented pre-ductal saturations since saturations are expected to be higher in the lower extremities in neonates with this condition. Despite using these two measures of hypoxemia, it remained difficult to fully capture the true clinical status, as some with critically low PaO₂ or SpO₂ did not receive a BAS, and others with a higher PaO₂ or SpO₂ underwent a BAS “urgently”. The inconsistency highlights the variability of clinical practice across centers.

Suboptimal image quality with low axial and lateral resolution can lead to falsely low strain values. While we attempted to correct for suboptimal images and excluded those where reliable tracking was not feasible, values could still be falsely underestimated. The position of the fetal heart could result in potential imaging dropout of the endocardial borders, thereby underestimating true strain values. One study suggested that imaging the fetal 4-chamber when the apex is perpendicular to the ultrasound beam may be more ideal than when the apex is parallel.³⁷ For the purposes of our study, we were unable to standardize the orientation of the fetal heart prior to strain analysis.

Ventricular strain is also highly dependent on temporal resolution. The EACVI/ASE consensus documents suggest using the highest frame rate possible to improve accuracy.^{17,31} Although no set number has been agreed upon, experts suggest above 80–90 frames per second.³⁷ In our study, despite utilizing a study protocol aimed to collect high-frame rate images, the frame rates obtained were ultimately lower than this target for many subjects, likely because many manufacturers export images at the default DICOM frame rate of 30 frames per second. These low frame rates could also falsely underestimate true strain values, thereby impacting the findings of this study. As such, it should be noted based on these results that fetal longitudinal strain, as measurable from routinely exported clinical

DICOM clips at typical frame rates, does not predict postnatal hypoxemia. Nevertheless, the results of this study are important and impactful contributions to the field of fetal cardiology by providing valuable insights into the technical challenges of frame rate, which highlights a potential opportunity to advance technology, improve research protocols, and inform the conduct of future multicenter research studies.

Lastly, there are challenges in using strain analysis in clinical practice. Ventricular strain is both vendor and platform specific and values have been found to vary significantly between vendors and platforms.^{17–18,27,37} Therefore, it is difficult to make exact comparisons between our study and prior studies evaluating fetal ventricular strain that used different vendors or platforms. A systematic review and meta-analysis of ventricular strain in different types of CHD found substantial heterogeneity with variations in ultrasound device, software, frame rate, sample size and gestational age.²⁷ Therefore, the variability inherent in this multicenter study may have affected the ability to detect a significant difference.

Conclusions

In fetuses with TGA/IVS, the RV free wall strain was significantly higher than LV longitudinal strain, although the RV and LV longitudinal strain values were similar. No differences were identified between fetal RV or LV strain or strain rate in association with postnatal hypoxemia or need for BAS in neonates with TGA/IVS. Postnatal stability remains difficult to predict prenatally. Therefore, delivery planning for infants with prenatally diagnosed TGA/IVS should include delivery at a cardiac center with preparation for BAS as there currently are no reliable predictive measures for expected urgent intervention.

Declarations

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgements

The authors gratefully acknowledge the generous support of the Mend-a-Heart Foundation and to the donors of the Fetal Heart Society collaborative (see www.fetalheartsociety.org) in the completion of this investigation.

We would also like to acknowledge Paula Gordon for contributing to this study.

Sources of Funding

This research was supported financially by the Mend-a-Heart foundation and the Fetal Heart Society.

Author Contribution

Every co-author contributed to the development of the manuscript and reviewed the manuscript.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Supplementary Files

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