DeVore Greggory (Orcid ID: 0000-0001-8814-572X)
Yeo Lami (Orcid ID: 0000-0001-6389-0993)

Cardiac Measurements of Size and Shape in Fetuses with Absent or Reversed End-Diastolic Velocity of the Umbilical Artery and Perinatal Survival and Severe Growth Restriction Less Than 34 Weeks of Gestation

Greggory R. DeVore, M.D.[1]

Percy Pacora Portella,M.D.[2,3]

Edgar Hernandez Andrade, M.D.[2,3]

Lami Yeo, M.D.[2,3]

Roberto Romero, M.D.[2-8]

1. Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, David Geffen School of Medicine, UCLA, Los Angeles, California, USA.
2. Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services (NICHD/NIH/DHHS), Bethesda, Maryland, and Detroit, Michigan, USA.
3. Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan, USA.
4. Department of Obstetrics and Gynecology, University of Michigan Health System, Ann Arbor, Michigan, USA.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jum.15532

5. Department of Epidemiology and Biostatistics, College of Human Medicine, East Lansing, Michigan, USA.
6. Center for Molecular Medicine and Genetics, Wayne State University, Detroit, Michigan, USA.
7. Detroit Medical Center.
8. Department of Obstetrics and Gynecology, Florida International University, Miami, Florida, US

Running Head: Measurements of Size and Shape in Fetuses

Corresponding Author:

Greggory R. DeVore, M.D.

Department of Obstetrics and Gynecology

David Geffen School of Medicine, UCLA

Suite 330, 50 Alessandro Place

Pasadena, California, 91105, USA

Tel: 626-840-6988

Fax: 626-583-8894

e-mail: grdevore@gmail.com

KEY WORDS: fetal echocardiography, fetal growth restriction, absent umbilical artery diastolic flow, speckle tracking, cardiomegaly, global sphericity index, perinatal death, fetal death

Funding: This research was supported, in part, by the Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, U.S.

Department of Health and Human Services (NICHD/NIH/DHHS); and, in part, with Federal funds from NICHD/NIH/DHHS under Contract No. HHSN275201300006C.

Dr. Romero has contributed to this work as part of his official duties as an employee of the United States Federal Government.

Abstract

Objective

The purpose of this study was to evaluate the end-diastolic size and shape of the four-chamber view as well as the right (RV) and left (LV) ventricles in growth restricted fetuses less than 34 weeks of gestation with absent or reversed end-diastolic velocity of the umbilical artery and compare the results between those with perinatal deaths and those who survived the neonatal period.

Methods

Forty-nine fetuses with growth restriction and absent or reversed end-diastolic velocity of the umbilical artery were studied. The size and shape and sphericity index of the four-chamber view (4CV) and the right (RV) and left (LV) ventricles were assessed. The number and percent of fetuses with z-score values <-1.65 and >1.65 were computed.

Results

Of the 49 fetuses, there were 13 perinatal deaths (27%) and 36 (63%) neonatal survivors. Measurements that were unique for neonatal survivors were an increased RV apical transverse widths and decreased measurements of the following: LV and RV widths, LV and RV areas, as well as RV sphericity indices.

Conclusions

Fetuses with a smaller RV and LV size and area and those with a globular-shaped RV were at significantly lower risk for perinatal death.

INTRODUCTION

In a recent meta-analysis of 31 studies evaluating 336 fetal deaths in growth restricted fetuses <34 weeks of gestation that had absent or reversed end-diastolic flow of the umbilical artery and/or ductus venosus, the authors reported the odds ratio for fetal death of 6.8 for absent or reversed umbilical artery end-diastolic flow (AREDV), and 11.6 for absent or reversed flow of the ductus venosus.[1] Since AREDV is associated with an increased placental resistance to blood flow resulting in increased fetal cardiac afterload with fetal and neonatal consequences, we were interested in the morphometric changes of the fetal heart in fetuses that experienced a perinatal death compared to those who survived the neonatal period. [1-13] Therefore, the purpose of this study was to determine (1) the frequency and z-score values of abnormal cardiac morphometric measurements of the four-chamber (4CV) view and the right (RV) and left (LV) ventricles in fetuses with AREDV, and (2) differences in the above measurements between fetuses who experienced a perinatal death and those who did not.

MATERIALS AND METHODS

Study Patients

The study was conducted at the Detroit Medical Center. All patients provided written informed consent and were enrolled in research protocols approved by the Human Investigation Committee of Wayne State University and the Institutional Review Board of the National Institutes of Child Health and Human Development. This cross-sectional retrospective descriptive study was performed in 49 fetuses with AREDV of the umbilical artery and a concomitant estimated fetal weight <10th centile which met the criteria for fetal growth restriction (FGR) using the Delphi Procedure.[14, 15] Fetuses with congenital or

chromosomal anomalies were not included in the study. The last examination before fetal death or delivery was used for analysis. Neonatal follow-up was available for all liveborn infants.

Control Fetuses

Two-hundred fetuses with accurate first- and/or second trimester dating sonograms were examined between 20- and 40-weeks' gestation, as previously reported. [8-12, 16-22] The fetuses were not at risk for congenital heart defects or growth restriction and were free of ultrasound-detected malformations and growth disturbances at the time of the examination using the criteria described by Altman and Chitty for deriving charts for fetal size.[23] All patients signed a consent form, allowing the use of images obtained during their routine examinations. All measurements were performed by a single examiner (G.R.D.) in an outpatient facility offering second- and third-trimester ultrasound screening for patients referred by obstetricians. The ethnicity of the patient population was Asian (6%), Caucasian (66%), African American (6%) and Hispanic (22%). Mean and standard deviation equations were derived for the 200 control fetuses by analyzing 44 fractional polynomial equations and selecting the equation with the best fit.[24]

Pulsed Doppler Measurements

Doppler velocimetry was performed in the umbilical artery (UA), middle cerebral artery (MCA), and the ductus venosus (DV). Doppler recordings were obtained in the absence of maternal or fetal movements with an angle of insonation as close as possible to 0° using a high-pass wall filter of 60 MHz. Three to five consecutive waveforms were obtained and the pulsatility index (PI) calculated for each of the above vessels. The cerebroplacental ratio was computed (MCA-PI/UA-PI.) The Z- score for the UAPI and MCAPI were automatically measured and the cerebroplacental ratio computed using gestational age as the independent variable.

Measurements of the Epicardial Global Size and Shape of the Four-Chamber View

Using a Digital Imaging and Communications in Medicine (DICOM) measurement package (Escape Medical Viewer, Thessaloniki, Greece), linear measurements of the end-diastolic basal-apical length, measured from the epicardium to the epicardium of the 4-chamber view in the longest dimension, and the end-diastolic transverse width, measured from the epicardium to the epicardium at the point of the greatest width (Figure 1A) were done for each fetus. From these measurements the following were computed:

1. The End-Diastolic Area = [(3.14*End-Diastolic Length*End-Diastolic Width)/4], (Figure 1A).[12]

2. Global Sphericity Index (GSI) = End-Diastolic Length/End-Diastolic Width (Figure 1A).[11]

Right and Left Ventricular Endocardial Measurements Derived from Speckle Tracking Analysis

Two-dimensional images of the four-chamber view were imported into an offline cardiac software program (2D Cardiac Performance Analysis (2D CPA) developed by TomTec Imaging Systems, Gmbh (Munich, Germany) using criteria for fetal applications that have been previously described.[25] The following end-diastolic measurements of ventricular shape and size were computed from the speckle tracking analysis from a single cardiac cycle (Figure 1B):

1. Right and Left Ventricular Size
    a. End-Diastolic Area (Figure 1C).[9]
    b. 24-Segment Transverse Widths. Segments 1 to 24 were measured using the end-diastolic 24-segment transverse width protocol (Figure 1C).[8]
2. Right and Left Ventricular 24-Segment Sphericity Index.

a. This was computed by dividing the end-diastolic length of the ventricular chamber by each of the 24 segment end-diastolic transverse widths (Figure 1C). [10]

3. Right-to-Left Ventricular Ratios.

a. This was computed as follows: right ventricular end-diastolic area/left ventricular end-diastolic area (mean 0.88, standard deviation (SD) 0.185) (Figure 1C)).

4. 24-Segment Transverse Width Ratios.

a. These were computed as follows for each segment: RV segment width/LV segment width.[8]

Measurements of Ventricular Wall Thickness.

The four-chamber view was reviewed to identify end-diastole by scrolling through the cine clip. The thickness of the right and left ventricular walls were measured in the mid-chamber using the protocol described by Garcia-Otero and the z-scores computed using the estimated fetal weight provided as an Excel calculator in the supplementary material associated with the above publication (Figure 1D).[26]

Statistical Analysis of Cardiac Measurements

The mean and standard deviation from control fetuses from the above studies were used to compute the Z-Score for the each of the 49 study fetuses using the following equation: [8-12, 16, 26]

Equation 1: Z-Score = (Individual Measured Cardiac Value $_{\text{Study Group}}$ – Mean $_{\text{Control Group}}$) / Standard Deviation $_{\text{Control Group}}$).

The 49 fetuses were separated by whether the fetus experienced a perinatal death (N=13) or survived the neonatal period (N=36). The results from the Z-Score computations were classified above the 95th centile (Z>1.65) or less than the 5th centile (Z<-1.65), depending upon the measurement. Once the z-scores were computed for each of the above measurements, the number of fetuses with abnormal z-

score values were compared to the expected number of abnormal values for the 5th and 95th centiles from control populations using the Chi-square analysis or the Fisher's exact test (NCSS 19, Kaysville, Utah, USA). [8-11, 16, 26] In addition, z-score values for the above measurements were compared between the two groups using the Student T-Test if the variables were normally distributed, or the Mann-Whitney U test if the measurements were not normally distributed. A $P<0.05$ was considered significant. The intraobserver and interobserver variability have been previously reported for each of the measurements described in this study, and therefore not repeated.[8-12, 16, 26]

RESULTS

The gestational age at the last examination, biometry and Doppler measurements are tabulated in Table 1. Perinatal deaths occurred in 13 (27%), with 36 (63%) neonatal survivors. There was a significant difference in gestational ages between those with perinatal deaths (25 1/7 ±2 5/7) and neonatal survivors (29 3/7 ± 3 4/7). The EFW was <10th centile in all fetuses, with 92% having an EFW <5th centile. While absent or reverse UA end-diastolic flow was present in 100% of fetuses, reverse flow of the ductus venosus was present in 31% (4/13) of those experiencing a perinatal death and only in 8.3% (3/36) of those who survived the neonatal period. There was a significant difference ($P<0.0001$) in the amniotic fluid index between those with a perinatal death (mean 2.6, SD 0.43) and those who survived the neonatal period (mean 8.24, SD 3.9).

Abnormal Measurements Common and Unique for Fetuses who Had a Perinatal Death and Neonatal Survivors

Four-Chamber View (Table 2)

The area, width and length >95th centile of the 4-chamber view were significantly more prevalent for both groups, when compared to controls. An abnormal GSI <5th centile was also significantly more frequent than controls for both groups. There was no significant difference in the frequency of abnormal findings of the area, length, width, and GSI between the perinatal deaths and neonatal survivors.

24-Segment Transverse Widths >95th Centile (Table 3)

Left ventricular end-diastolic transverse widths for basal segments 1 to 16 were significantly more frequent for both groups when compared to controls. However, only LV segments 17 to 24 >95th centile were unique for those with perinatal deaths. Similarly, RV segments 1 to 16 were significantly more frequent than controls and common for both groups. RV segments 17 to 24 were unique to neonatal survivors.

24-segment Transverse Widths <5th Centile (Table 4)

Left ventricular segments 1 to 24 as well as RV segments 17 to 24 less than the 5th centile were significantly more frequent than controls in the neonatal survivors. No fetuses with perinatal deaths had LV or RV 24-segment widths <5th centile.

Ventricular End-Diastolic Area, Length and Wall Thickness (Table 5)

The following were significantly more prevalent than in control fetuses and present in fetuses with perinatal deaths and neonatal survivors: (1) RV and LV ventricular length <5th centile, (2) RV ventricular area >95th centile, (3) RV and LV Area >95th centile, (4) and (5) RV and LV wall thickness >95th centile. RV and LV Area <5th centile was unique to neonatal survivors.

Ratios: Ventricular 24-Segment Sphericity Index <5th Centile and RV/LV Area >95th Centile (Table 6)

Both groups had a significantly higher prevalence of LV sphericity index values <5th centile for segments 1 to 8. However, RV sphericity index segments 1 to 16 and LV sphericity index segments 9 to 16 were only present in neonatal survivors. Abnormal RV/LV ratios >95th centile was present for all segments in both fetuses with perinatal deaths and neonatal survivors.

Comparison of Z-Score Measurements Between Fetuses with Perinatal Deaths and Neonatal Survivors

Supplement 1 lists z-score values and their corresponding mean percentiles between fetuses with perinatal deaths and neonatal survivors. The LV end-diastolic area was significantly smaller for neonatal survivors (13th centile) compared to those with perinatal deaths (43rd centile). The LV end-diastolic basal-apical length was significantly smaller for neonatal survivors (6th centile) compared to those with perinatal deaths (21st centile). The LV 24 segment transverse apical widths 20 to 24 were significantly smaller in neonatal survivors (10th to 14th centile) than those with perinatal deaths (35th to 48th centile). The RV 24 segment sphericity index for all segments (1 to 24) was significantly smaller for neonatal survivors (10th to 44th centile) than those with perinatal deaths (45th to 77th centile), suggesting a more globular shaped RV for fetuses who survived the neonatal period. The RV/LV ratios for the basal segments 1 to 8 of neonatal survivors (80th to 91st centile) were greater than those with perinatal deaths (51st to 52nd centile).

DISCUSSION

In the current study we identified 13 fetuses that experienced either fetal (46%) or neonatal death (64%) and 36 fetuses who survived the neonatal period. When we separated the study fetuses by those who survived the neonatal period and those that did not, there were similar as well as differing patterns of

fetal cardiovascular size and shape of the four-chamber view as well as the RV and LV, as manifest by the number of fetuses that had abnormal cardiac measurements $<5^{th}$ or $>95^{th}$ percentile and the difference in z-score values between the two groups. Absent or reversed ductus venosus flow was present in both groups. Our findings would suggest that in the presence of unique measurements (smaller RV and LV size, smaller area, or a globular-shaped RV) in neonatal survivors would not necessarily obligate the clinician to intervene as the result of abnormal ductus venosus findings. In addition, the absence of an abnormal ductus venosus waveform would not preclude the risk for perinatal death.

Four-Chamber View

Both groups had a high percentage of fetuses with an increased four-chamber view end-diastolic area, transverse width, and length. In addition, both groups had an abnormal GSI suggesting a round or globular-shaped four-chamber view. When comparing z-score values for the above measurements, there were no significant differences between the groups. Therefore, the size and shape of the four-chamber view did not discriminate between those fetuses who had a perinatal death, and those that survived the neonatal period.

Ventricular Size and Shape in Fetuses Who Had a Perinatal Death and Neonatal Survivors

Tables 2 to 6 list the abnormal findings for both groups when compared to control fetuses suggesting significant changes in the size and shape of the right and left ventricles and the unique findings between the two groups. From these tables three themes emerge. First, enlargement of the apex of the LV was unique to those who had perinatal deaths, but only occurred in 3 of 13 fetuses. Second, neonatal survivors had larger as well as smaller right ventricular transverse widths, smaller RV areas, as well as smaller LV transverse widths and LV areas. Third, neonatal survivors had more globular shaped chambers for all segments of the RV and LV. The above findings could be used as markers to separate

those fetuses at increased or decreased risk for fetal or neonatal death. For example, if the LV apical chamber was increased in transverse width >95th centile, this could suggest an increased risk for fetal death. Conversely, if the RV and LV chambers were decreased in area and width, as well as were more globular in shape for LV segments 9 to 16 and RV segments 1 to 16, this would suggest a decreased risk for perinatal death.

Categorization of Fetuses by Z-Score Results Gives Unique Information When Comparing Only z-score Values.

Tables 2 to 6 categorized results by the frequency of fetuses who had significant differences of abnormal measurements when compared to the control group. This approach provided unique information regarding the profile of these fetuses as we were able to identify measurements that were common and unique between the 2 groups. This allowed for a more detailed profile than if we only compared z-score values between the groups, which only identified significant differences for 5 measurement variables (Supplement 1).

Previous Studies Evaluating the Four-Chamber View Size and Shape.

In 2017 Rodriguez-Lopez classified fetuses with growth restriction by the phenotypes of the ventricles imaged from the four-chamber view as elongated, globular, or hypertrophic.[5] Irrespective of the phenotype of the ventricles, all had increased end-diastolic areas of the four-chamber view.[5] Review of Figure 3 from their study suggests that the GSI would be abnormally decreased, had it been measured, as manifest by a globular shaped four-chamber view.[5] Recently, Hobbins reported that there were no perinatal deaths in 25 fetuses with an EFW <10th centile with forward diastolic flow of the umbilical artery but an abnormal UAPI and/or CPR. [13] However, 29% of fetuses with an abnormal UAPI had an enlarged four-chamber view area >90th centile; 68 % had an increased four-chamber view transverse

width >90th centile; and 28% had an abnormal four-chamber view GSI <10th centile.[13] While their threshold for classifying an abnormal finding was 5% higher than our study (90th vs 95th centile; 10th vs 5th centile), the number of fetuses with an increased four-chamber view area were not significantly different than the current study.[13] The above studies would suggest that an increased four-chamber view area and width as well as an abnormal GSI are present early in the process of umbilical artery Doppler deterioration as it progresses from abnormal forward diastolic flow to AREDV.[13]

Previous Studies Evaluating Ventricular Size

Although a number of studies have reported end-diastolic widths for the RV and LV using M-Mode, 2-Dimensional, and 4D spatiotemporal image correlation,[8, 9, 27-38] few studies have measured these widths in fetuses with growth restriction.[5, 39] Increased ventricular widths in fetuses with growth restriction was first described using M-mode ultrasound by DeVore in 1988 in which enlargement of both the RV and LV end-diastolic mid-chamber widths were associated with fetal death.[39] In the study by Rodriguez-Lopez they also identified increased transverse widths for both the RV and LV in fetuses with globular and hypertrophic ventricular phenotypes, with the largest transverse width occurring in fetuses with the hypertrophic phenotype.[5] Studies in newborns with FGR have also found the RV and LV transverse widths to be increased when compared to controls.[2, 6] Hobbins et al measured the end-diastolic area of the RV and LV and found no increase in areas in fetuses with an EFW <10th centile with a normal UAPI, but reported a significant number of fetuses with decreased end-diastolic areas for both ventricles when the UAPI was abnormal.[13] Of interest, decreased LV and RV areas and 24-segment transverse widths were only identified in neonatal survivors in the current study.

Previous Studies Evaluating Ventricular Shape

In adults the change from an elliptical to a more spherical shape has been described in a number of diseases that include myocardial infarction, coronary artery associated disease, severe mitral regurgitation, and dilated cardiomyopathy.[40] The change from an elliptical to a globular shaped ventricular chamber results in increased wall tension, which is inversely proportional to the curvature of the wall.[41] Therefore, as the curvature increases, the wall tension decreases. Animal experiments have demonstrated that a change in left ventricular sphericity occurs before the onset of increased end-diastolic volume. Changes in ventricular shape have been shown to be an independent predictor of survival in adult patients with dilated cardiomyopathy as well as coronary artery disease.[41-44]

The sphericity index is a fixed constant in the fetus, irrespective of gestational age or changes in fetal biometry.[10] Except for the study by Channing, all previous fetal studies computed the sphericity index by dividing the end-diastolic basal-apical length by the basal (segment 1) transverse width.[5, 7, 44-46] In utero changes in the sphericity index may be a precursor for postnatal changes in cardiac function.[5 44, 47] In a previous study of 30 small for gestational age fetuses, DeVore and colleagues found that if only the basal segment 1 was used to compute the sphericity index, an abnormal sphericity index of the LV would be identified in only 30% of fetuses, while if all 24 segments were used, then 50% of fetuses would have been classified as having an abnormal sphericity index.[48] Similar findings were identified for the RV in which the detection rate increased from 23% with when only segment 1 was measured to 40% when all segments were measured.[48] Therefore, measuring the 24-segment sphericity index provides a more comprehensive evaluation of the shape of the ventricles than just measuring 1 segment located at the base of each ventricle.[5, 7, 44, 45] In the current study the neonatal survivors had significantly more fetuses with a sphericity index <5th centile for both base and mid sections. In addition, all 24 segments of the RV had significantly lower z-score values when compared to those with perinatal deaths.

Previous Studies Evaluating Ventricular Right /Left Ratios

The RV/LV ratio has been previously measured with M-mode and two-dimensional ultrasound from either the base of the ventricle or the mid-section of the chambers.[30, 39 49] In 2018 Rodriquez-Lopez reported that the RV/LV transverse diameter ratio computed from end-diastolic M-mode measurements obtained at the mid-chamber was significantly decreased in growth restricted fetuses with the phenotypical characteristics of an elongated four-chamber view, but was not different than controls for fetuses with a globular or hypertrophied phenotype.[2] Recently, Hobbins reported an increased RV/LV area ratio in 36% of fetuses with an EFW <10th centile and an abnormal umbilical artery Doppler PI with forward diastolic flow and/or an abnormal CPR, which was not significantly different from those fetuses with a perinatal death (46%) and those who survived the neonatal period (31%) in the current study.[13] This suggests that RV/LV area disproportion occurs early in the FGR process, and is not unique to FGR when the UA has AREDV.

Previous Studies Involving Wall Thickness

Hypertrophy of the ventricular walls was first reported by Veille in 1993.[50] Subsequent studies have demonstrated ventricular wall hypertrophy to be associated with increased vascular resistance in recipient twins with twin-to-twin transfusion, non-recipient twins with growth restriction, and singletons with growth restriction.[5, 51, 52] In addition, premature newborns with FGR have been shown to also have greater LV free wall ventricular hypertrophy and lower sphericity indices than controls.[3, 53] Recently, Sepulveda-Martinez demonstrated no significant differences when measuring RV and LV wall thickness as well as the interventricular septum between M-mode and 2-dimensional images.[54] Rodriquez-Lopez reported that fetuses with early FGR and the highest abnormal values for the UAPI had the greatest thickness of the left ventricular free wall (hypertrophic group).[5] Our results demonstrated a high incidence

of increased RV and LV wall thickness in both groups of fetuses but did not discriminate between those with perinatal deaths and neonatal survivors.

Integrating the Findings

When measuring the area and width of the 4CV the contributing anatomy that can increase the size are the thickness of the ventricular walls and septum as well as the size of the ventricular chambers. In fetuses with AREDV the wall thickness, present in 72% to 92% % of fetuses, is the main contributor since the 24 segment widths >95th centile was only present in 31% of fetuses with perinatal deaths and 44% in neonatal survivors. This would suggest that the increased size of the 4CV is primarily secondary to ventricular wall hypertrophy which is most likely the result of long-standing increased peripheral resistance. Since the size and the shape of the 4CV did not discriminate between the two study groups, evaluation of ventricular size and shape was more informative. The ventricular transverse widths >95th centile were of interest because only those with perinatal deaths had increased LV apical segments. However, when the RV apical widths were increased, this was only present in neonatal survivors. This would suggest that a dilated RV in the apical region is protective, while when the apical LV width is increased, perinatal death may occur. From our results the RV appears to be a marker for perinatal survival when it is decreased in width for the base, mid, and apical sections of the ventricle as well as more globular in shape for the base and mid sections. Therefore, when examining fetuses with AREDV, evaluation of the RV is important as it may be a marker for those fetuses who are not at risk for perinatal death. One important aspect of our analysis is that we did not use gestational age but used the estimated fetal weight as the independent variable for evaluating the size of the 4CV and ventricles as the size of the heart has been shown , from our experience, to correlate with the size of the fetus but not age when there is abnormal fetal growth. Observations from the current study can be integrated with current antepartum

surveillance such as the biophysical profile, non-stress test, amniotic fluid indices to identify the fetus at risk for perinatal death.

Strengths and Limitations

This was a retrospective study in which the measurements of the four-chamber view and ventricles were not used in clinical management. While perinatal death occurred in some fetuses at gestational ages below viability, others did not. The diagnostic tools described in this study could be applied to fetuses with AREDV to identify changes in ventricular size and shape to identify those fetuses at risk for perinatal death vs those who may survive the neonatal period. The limitation of the study was that we measured the four-chamber view and ventricular size and shape using the last examination prior to delivery or fetal death and did not study the fetuses longitudinally to determine the deterioration pattern of the cardiovascular measurements.

Conclusions

This study identified similarities of the size and shape of the four-chamber view and ventricles and differences between fetuses with growth restriction and AREDV who died in utero or the neonatal period and those who did not. Compared to those who experienced a perinatal death, neonatal survivors uniquely had the following: (1) the presence of smaller 24-segment diameters of the RV and LV (2) smaller RV and LV areas, and (3) sphericity index $<5^{th}$ centile for segments 9 to 16 of the LV and 1 to 16 for the RV. Therefore, fetuses with smaller RV and LV size and area and a more globular shaped RV may not be at increased risk for perinatal death, while those fetuses with an increased LV width for transverse segments 17 to 24 may be at increased risk for perinatal death.

References

1. Caradeux J, Martinez-Portilla RJ, Basuki TR, Kiserud T, Figueras F. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2018; **218**: S774-S782.e721.

2. Rodriguez-Guerineau L, Perez-Cruz M, Gomez Roig MD, Cambra FJ, Carretero J, Prada F, Gomez O, Crispi F, Bartrons J. Cardiovascular adaptation to extrauterine life after intrauterine growth restriction. *Cardiol Young* 2018; **28**: 284-291.

3. Sehgal A, Allison BJ, Gwini SM, Miller SL, Polglase GR. Cardiac Morphology and Function in Preterm Growth Restricted Infants: Relevance for Clinical Sequelae. *J Pediatr* 2017; **188**: 128-134.e122.

4. Arnott C, Skilton MR, Ruohonen S, Juonala M, Viikari JS, Kahonen M, Lehtimaki T, Laitinen T, Celermajer DS, Raitakari OT. Subtle increases in heart size persist into adulthood in growth restricted babies: the Cardiovascular Risk in Young Finns Study. *Open Heart* 2015; **2**: e000265.

5. Rodriguez-Lopez M, Cruz-Lemini M, Valenzuela-Alcaraz B, Garcia-Otero L, Sitges M, Bijnens B, Gratacos E, Crispi F. Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction. *Ultrasound Obstet Gynecol* 2017; **50**: 207-214.

6. Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, Ahmed A, Gratacos E. Fetal growth restriction results in remodeled and less efficient hearts in children. *Circulation* 2010; **121**: 2427-2436.

7. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, Figueras F, Gomez O, Sitges M, Bijnens B, Gratacos E. A fetal cardiovascular score to predict infant hypertension and arterial remodeling in intrauterine growth restriction. *Am J Obstet Gynecol* 2014; **210**: 552.e551-552.e522.

8. DeVore GR, Cuneo B, Klas B, Satou G, Sklansky M. Comprehensive Evaluation of Fetal Cardiac Ventricular Widths and Ratios Using a 24-Segment Speckle Tracking Technique. *J Ultrasound Med* 2019; **38**: 1039-1047.

9. DeVore GR, Klas B, Satou G, Sklansky M. Evaluation of the right and left ventricles: An integrated approach measuring the area, length, and width of the chambers in normal fetuses. *Prenat Diagn* 2017; **37**: 1203-1212.

10. DeVore GR, Klas B, Satou G, Sklansky M. The 24-Segment Sphericity Index: A New Technique to Evaluate Fetal Cardiac Diastolic Shape. *Ultrasound Obstet Gynecol* 2017. DOI: 10.1002/uog.17505.

11. DeVore GR, Satou G, Sklansky M. Abnormal Fetal Findings Associated With a Global Sphericity Index of the 4-Chamber View Below the 5th Centile. *J Ultrasound Med* 2017; **36**: 2309-2318.

12. DeVore GR, Satou G, Sklansky M. Area of the fetal heart's four-chamber view: a practical screening tool to improve detection of cardiac abnormalities in a low-risk population. *Prenat Diagn* 2017; **37**: 151-155.

13. Hobbins JC, Gumina DL, Zaretsky M, Driver C, Wilcox A, DeVore GR. Size and Shape of the Four-Chamber View of the Fetal Heart in Fetuses with an Estimated Fetal Weight Less than the Tenth Centile. *Am J Obstet Gynecol* 2019. DOI: 10.1016/j.ajog.2019.06.008.

14. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016; **48**: 333-339.

15. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* 1991; **181**: 129-133.

16. DeVore GR, Tabsh K, Polanco B, Satou G, Sklansky M. Fetal Heart Size: A Comparison Between the Point-to-Point Trace and Automated Ellipse Methods Between 20 and 40 Weeks' Gestation. *J Ultrasound Med* 2016; **35**: 2543-2562.

17. DeVore GR, Klas B, Satou G, Sklansky M. Longitudinal Annular Systolic Displacement Compared to Global Strain in Normal Fetal Hearts and Those With Cardiac Abnormalities. *J Ultrasound Med* 2017. DOI: 10.1002/jum.14454.

18. DeVore GR, Klas B, Satou G, Sklansky M. Twenty-four Segment Transverse Ventricular Fractional Shortening: A New Technique to Evaluate Fetal Cardiac Function. *J Ultrasound Med* 2017. DOI: 10.1002/jum.14455.

19. DeVore GR, Klas, B., Satou, G,, Sklansky, M. Quantitative Evaluation of the Fetal Right and Left Ventricular Fractional Area Change Using Speckle Tracking Technology. *Submitted* 2018.

20. DeVore GR, Klas B, Satou G, Sklansky M. Evaluation of Fetal Left Ventricular Size and Function Using Speckle-Tracking and the Simpson Rule. *J Ultrasound Med* 2018. DOI: 10.1002/jum.14799.

21. DeVore GR, Klas B, Satou G, Sklansky M. Longitudinal Annular Systolic Displacement Compared to Global Strain in Normal Fetal Hearts and Those With Cardiac Abnormalities. *J Ultrasound Med* 2018; **37**: 1159-1171.

22. DeVore GR, Berthold, K., Satou, G., Sklansky, M. Speckle Tracking of the Basal Lateral and Septal Wall Annular Plane Systolic Excursion of the Right and Left Ventricles of the Fetal Heart. *Submitted*

2019; **38**: 1309-1318.

23. Altman DG, Chitty LS. Design and analysis of studies to derive charts of fetal size. *Ultrasound Obstet Gynecol* 1993; **3**: 378-384.

24. DeVore GR. Computing the Z Score and Centiles for Cross-sectional Analysis: A Practical Approach. *J Ultrasound Med* 2017; **36**: 459-473.

25. DeVore GR, Polanco B, Satou G, Sklansky M. Two-Dimensional Speckle Tracking of the Fetal Heart: A Practical Step-by-Step Approach for the Fetal Sonologist. *J Ultrasound Med* 2016; **35**: 1765-1781.

26. Garcia-Otero L, Gomez O, Rodriguez-Lopez M, Torres X, Soveral I, Sepulveda-Martinez A, Guirado L, Valenzuela-Alcaraz B, Lopez M, Martinez JM, Gratacos E, Crispi F. Nomograms of Fetal Cardiac Dimensions at 18-41 Weeks of Gestation. *Fetal Diagn Ther* 2019. DOI: 10.1159/000494838. 1-12.

27. Allan LD, Joseph MC, Boyd EG, Campbell S, Tynan M. M-mode echocardiography in the developing human fetus. *Br Heart J* 1982; **47**: 573-583.

28. DeVore GR, Siassi B, Platt LD. Fetal echocardiography. IV. M-mode assessment of ventricular size and contractility during the second and third trimesters of pregnancy in the normal fetus. *Am J Obstet Gynecol* 1984; **150**: 981-988.

29. Tan J, Silverman NH, Hoffman JI, Villegas M, Schmidt KG. Cardiac dimensions determined by cross-sectional echocardiography in the normal human fetus from 18 weeks to term. *Am J Cardiol* 1992; **70**: 1459-1467.

30. Shapiro I, Degani S, Leibovitz Z, Ohel G, Tal Y, Abinader EG. Fetal cardiac measurements derived by transvaginal and transabdominal cross-sectional echocardiography from 14 weeks of gestation to term. *Ultrasound Obstet Gynecol* 1998; **12**: 404-418.

31. Firpo C, Hoffman JI, Silverman NH. Evaluation of fetal heart dimensions from 12 weeks to term. *Am J Cardiol* 2001; **87**: 594-600.

32. Schneider C, McCrindle BW, Carvalho JS, Hornberger LK, McCarthy KP, Daubeney PE. Development of z-scores for fetal cardiac dimensions from echocardiography. *Ultrasound Obstet Gynecol* 2005; **26**: 599-605.

33. Lee W, Riggs T, Amula V, Tsimis M, Cutler N, Bronsteen R, Comstock CH. Fetal echocardiography: z-score reference ranges for a large patient population. *Ultrasound Obstet Gynecol* 2010; **35**: 28-34.

34. Luewan S, Yanase Y, Tongprasert F, Srisupundit K, Tongsong T. Fetal cardiac dimensions at 14-40 weeks' gestation obtained using cardio-STIC-M. *Ultrasound Obstet Gynecol* 2011; **37**: 416-422.

35. Gagnon C, Bigras JL, Fouron JC, Dallaire F. Reference Values and Z Scores for Pulsed-Wave Doppler and M-Mode Measurements in Fetal Echocardiography. *J Am Soc Echocardiogr* 2016; **29**: 448-460.e449.

36. Krishnan A, Pike JI, McCarter R, Fulgium AL, Wilson E, Donofrio MT, Sable CA. Predictive Models for Normal Fetal Cardiac Structures. *J Am Soc Echocardiogr* 2016; **29**: 1197-1206.

37. Li X, Zhou Q, Huang H, Tian X, Peng Q. Response to "z-score reference ranges for normal fetal heart sizes throughout pregnancy derived from fetal echocardiography". *Prenat Diagn* 2016; **36**: 386.

38. Gu X, He Y, Zhang Y, Sun L, Zhao Y, Han J, Liu X. Fetal echocardiography: reference values for the Chinese population. *J Perinat Med* 2017; **45**: 171-179.

39. DeVore GR. Examination of the fetal heart in the fetus with intrauterine growth retardation using M-mode echocardiography. *Semin Perinatol* 1988; **12**: 66-79.

40. Izumo M, Lancellotti P, Suzuki K, Kou S, Shimozato T, Hayashi A, Akashi YJ, Osada N, Omiya K, Nobuoka S, Ohtaki E, Miyake F. Three-dimensional echocardiographic assessments of exercise-induced changes in left ventricular shape and dyssynchrony in patients with dynamic functional mitral regurgitation. *Eur J Echocardiogr* 2009; **10**: 961-967.

41. Gomez-Doblas JJ, Schor J, Vignola P, Weinberg D, Traad E, Carrillo R, Williams D, Lamas GA. Left ventricular geometry and operative mortality in patients undergoing mitral valve replacement. *Clin Cardiol* 2001; **24**: 717-722.

42. Sabbah HN, Kono T, Stein PD, Mancini GB, Goldstein S. Left ventricular shape changes during the course of evolving heart failure. *Am J Physiol* 1992; **263**: H266-270.

43. Douglas PS, Morrow R, Ioli A, Reichek N. Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1989; **13**: 311-315.

44. Perez-Cruz M, Cruz-Lemini M, Fernandez MT, Parra JA, Bartrons J, Gomez-Roig MD, Crispi F, Gratacos E. Fetal cardiac function in late-onset intrauterine growth restriction vs small-for-gestational age, as defined by estimated fetal weight, cerebroplacental ratio and uterine artery Doppler. *Ultrasound Obstet Gynecol* 2015; **46**: 465-471.

45. Channing A, Szwast 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**: 664-669.

46. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, Figueras F, Sitges M, Bijnens B, Gratacos E. Fetal cardiovascular remodelling persists at 6 months of life in infants with intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2015. DOI: 10.1002/uog.15767.

47. Shaddy RE PD. Chronic Cardiac Failure: Physiology And Treatment. In *Pediatric Cardiology*.Anderson RH BE PD, Redington AN, Rigby ML, Wernovsky G, (ed). Churchill Livingston/Elsevier: Philadelphia, PA, 2002.

48. DeVore GR, Zaretsky M, Gumina DL, Hobbins JC. Right and left ventricular 24-segment sphericity index is abnormal in small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol* 2018; **52**: 243-249.

49. Gabbay-Benziv R, Turan OM, Harman C, Turan S. Nomograms for Fetal Cardiac Ventricular Width and Right-to-Left Ventricular Ratio. *J Ultrasound Med* 2015; **34**: 2049-2055.

50. Veille JC, Hanson R, Sivakoff M, Hoen H, Ben-Ami M. Fetal cardiac size in normal, intrauterine growth retarded, and diabetic pregnancies. *Am J Perinatol* 1993; **10**: 275-279.

51. Mahieu-Caputo D, Salomon LJ, Le Bidois J, Fermont L, Brunhes A, Jouvet P, Dumez Y, Dommergues M. Fetal hypertension: an insight into the pathogenesis of the twin-twin transfusion syndrome. *Prenat Diagn* 2003; **23**: 640-645.

52. Kondo Y, Hidaka N, Yumoto Y, Fukushima K, Tsukimori K, Wake N. Cardiac hypertrophy of one fetus and selective growth restriction of the other fetus in a monochorionic twin pregnancy. *J Obstet Gynaecol Res* 2010; **36**: 401-404.

53. Leipala JA, Boldt T, Turpeinen U, Vuolteenaho O, Fellman V. Cardiac hypertrophy and altered hemodynamic adaptation in growth-restricted preterm infants. *Pediatr Res* 2003; **53**: 989-993.

54. Sepulveda-Martinez A, Garcia-Otero L, Soveral I, Guirado L, Valenzuela-Alcaraz B, Torres X, Rodriguez-Lopez M, Gratacos E, Gomez O, Crispi F. Comparison of 2D versus M-mode echocardiography for assessing fetal myocardial wall thickness. *J Matern Fetal Neonatal Med* 2019; **32**: 2319-2327.

Table 1. Biometry and Doppler Results for Perinatal Deaths and Neonatal Survivors.

	Perinatal Deaths (13)	**Neonatal Survivors (36)**	**P Value**
Estimated Fetial Weight <10th Centile	100% (13)	100% (36)	NS
Estimated Fetal Weight <5th Centile	92% (120	92% (33)	NS
Absent/Reverse Umbilical Artery Doppler Waveform	100% (13)	100% (36)	NS
Umbilical Artery Pulsatility Index	1.83 (SD 0.9)	2.33 (SD 0.89)	NS
Middle Cerebral Artery Pulsatility Index	1.16 (SD 0.29)	1.23 (SD 0.30)	NS
Cerebroplacental Ratio	0.70 (SD 0.38)	0.60 (SD 0.28)	NS
Reverse Flow Ductus Venosus	31% (4)	8.3% (3)	NS
Amniotic Fluid Index	2.6 (SD 0.43)	8.24 (SD 3.9)	P<0.0001
Amniotic Fluid Deepest Pocket	3.7 (SD 3.5)	3.61 (SD 1.54)	NS

Table 2. Number and Percent of Fetuses with Abnormal Values <5th Centile or >95th Centile for Measurements of the 4-Chamber View.

4-Chamber View End-Diastolic Measurements	Number of Fetuses (%)	Odds Ratio	95% Confidence Limits	P Value
Perinatal Deaths (N=13) *				
Area >95th Centile	10 (77%)	63.3	15 to 266.9	<0.0001
4-Chamber View Transverse Width >95th Centile	12 (92%)	228	26.9 to 1931	<0.0001
4-Chamber View Length >95th Centile	3 (23%)	5.7	1.3 to 24	<0.02
Global Sphericity Index <5th Centile	5 (38%)	11.9	3.2 to 42.9	<0.0002
Neonatal Survivors (N=36) *				
Area >95th Centile	17 (47%)	17	6.8 to 42.3	<0.0001
4-Chamber View Transverse Width >95th Centile	23 (64%)	33.6	13.2 to 85.3	<0.0001
4-Chamber View Length >95th Centile	10 (28%)	7.3	2.8 to 19.2	<0.0001
Global Sphericity Index <5th centile	15 (42%)	13.5	5.4 to 33.9	<0.0001

*There were no significant differences in the number of fetuses with abnormal values between the 2 groups for the above measurements.

Table 3. Number and Percent of Fetuses with Abnormal Values >95th Centile for Measurements of the Ventricular End-Diastolic 24-Segment Widths.

Ventricular 24-Segment Transverse Width >95th Centile	Number of Fetuses (%)	Odds Ratio	95% Confidence Limits	P Value	Unique Findings
Perinatal Deaths (N=13) *					
Left Ventricle					
Left Ventricular Basal Segments 1 to 8	4 (31%)	8.4	2.2 to 32.2	<0.002	
Left Ventricular Mid Segments 9 to 16	3 (23%)	5.7	1.3 to 24	<0.02	
Left Ventricular Apical Segments 17 to 24	3 (23%)	5.7	1.3 to 24	<0.02	Perinatal Deaths
Right Ventricle					
Right Ventricular Basal Segments 1 to 8	5 (38%)	11.9	3.2 to 42.9	<0.0002	
Right Ventricular Mid Segments 9 to 16	3 (23%)	5.7	1.3 to 24	<0.02	
Neonatal Survivors (N=36) *					
Left Ventricle					
Left Ventricular Basal Segments 1 to 8	7 (19%)	4.6	1.6 to 13	<0.004	
Left Ventricular Mid Segments 9 to 16	6 (17%)	3.8	1.3 to 11.2	0.02	
Right Ventricle					
Right Ventricular Basal Segments 1 to 8	16 (44%)	15.2	6 to 37.9	<0.0001	
Right Ventricular Mid Segments 9 to 16	10 (28%)	7.3	2.8 to 19.2	<0.0001	
Right Ventricular Apical Segments 17 to 24	9 (25%)	6.3	2.4 to 17	<0.0002	Neonatal Survivors

*There were no significant differences in the number of fetuses with abnormal values between the 2 groups for the above measurements that were not unique to each group.

Table 4. Number and Percent of Fetuses with Abnormal Values <5th Centile for Measurements of the Ventricular End-Diastolic 24-Segment Widths.

Ventricular 24-Segment Transverse Width <5th Centile	**Number of Fetuses (%)**	**Odds Ratio**	**95% Confidence Limits**	**P Value**	**Unique Findings**
Neonatal Survivors (N=36)					
Left Ventricle					
Left Ventricular Basal Segments 1 to 8	10 (28%)	7.3	2.8 to 19.2	<0.0001	Neonatal Survivors
Left Ventricular Mid Segments 9 to 16	8 (22%)	5.4	2 to 14.9	<0.0004	Neonatal Survivors
Left Ventricular Apical Segments 17 to 24	8 (22%)	5.4	2 to 14.9	<0.0004	Neonatal Survivors
Right Ventricle					
Right Ventricular Apical Section (Segments 17 to 24)	6 (17%)	3.8	1.3 to 11.2	0.02	Neonatal Survivors

Table 5. Number and Percent of Fetuses with Abnormal Values <5th or >95th Centile for Measurements of the Ventricular End-Diastolic Area, Length, and Wall Thickness.

End-Diastolic Ventricular Area, Length, and Wall Thickness	Number of Fetuses (%)	Odds Ratio	95% Confidence Limits	P Value	Unique Findings
Perinatal Deaths (N=13) *					
Ventricular Length <5th Centile					
Left Ventricle	3 (23%)	5.7	1.3 to 24	<0.02	
Right Ventricle	3 (23%)	5.7	1.3 to 24	<0.02	
Ventricular Area >95th Centile					
Right Ventricle	4 (31%)	8.4	2.2 to 32.2	<0.002	
Ventricular Wall Thickness >95th Centile					
Left Ventricle	12 (92%)	228	26.9 to 1931	<0.0001	
Right Ventricle	10 (77%)	63.3	15 to 266.9	<0.0001	
Neonatal Survivors (N=36) *					
Ventricular Length <5th Centile					
Left Ventricle	16 (44%)	15.2	6 to 37.9	<0.0001	
Right Ventricle	12 (33%)	9.5	3.7 to 24.3	<0.0001	
Ventricular Area <5th Centile					
Left Ventricle	10 (28%)	7.3	2.8 to 19.2	<0.0001	Neonatal Survival
Right Ventricle	6 (17%)	3.8	1.3 to 11.2	0.02	Neonatal Survivors
Ventricular Area>95th Centile					
Right Ventricle	7 (19%)	4.6	1.6 to 13	<0.004	
Ventricular Wall Thickness >95th centile					
Left Ventricle	26 (72%)	49.4	18.7 to 130	<0.0001	
Right Ventricle	26 (72%)	49.4	18.7 to 130	<0.0001	

*There were no significant differences in the number of fetuses with abnormal values between the 2 groups for the above measurements that were not unique to each group.

Table 6. Number and Percent of Fetuses with Abnormal Values <5th Centile or >95th Centile the 24-Segment Sphericity Index and the Right/Left Ventricular Ratios.

End-Diastolic 24-Segment Sphericity Index and RV/LV Ratios	Number of Fetuses (%)	Odds Ratio	95% Confidence Limits	P Value	Unique Findings
Perinatal Deaths (N=13) *					
Ventricular Sphericity Index <5th Centile					
Left Ventricular Basal Segments 1 to 8	3 (23%)	5.7	1.3 to 24	<0.02	
Right/Left Ventricular Ratio >95th Centile					
Area	6 (46%)	16.3	4.6 to 57.5	<0.0001	
Basal Transverse Segments 1 to 8	3 (23%)	5.7	1.3 to 24	<0.02	
Mid Transverse Segments 9 to 16	3 (23%)	5.7	1.3 to 24	<0.02	
Apical Transverse Segments 17 to 24	4 (31%)	8.4	2.2 to 32.2	<0.002	
Neonatal Survivors (N=36) *					
Ventricular Sphericity Index <5th Centile					
Left Ventricular Basal Segments 1 to 8	10 (28%)	7.3	2.8 to 19.2	<0.0001	
Left Ventricle Mid Segments 9 to 16)	9 (25%)	6.3	2.4 to 17	<0.0002	Neonatal Survivors
Right Ventricular Basal Segments 1 to 8	15 (42%)	13.5	5.4 to 33.9	<0.0001	Neonatal Survivors
Right Ventricle Mid Segments 9 to 16	12 (33%)	9.5	3.7 to 24.3	<0.0001	Neonatal Survivors
Right/Left Ventricular Ratio >95th Centile					
Area	11(31%)	8.4	3.2 to 21.7	<0.0001	
Basal Transverse Segments 1 to 8	14 (36%)	22.2	8.5 to 60.2	<0.0001	
Mid Transverse Segments 9 to 16	12 (33%)	9.5	3.7 to 24.3	<0.0001	
Apical Transverse Segments 17 to 24	10 (28%)	7.3	2.8 to 19.2	<0.0001	

*There were no significant differences in the number of fetuses with abnormal values between the 2 groups for the above measurements that were not unique to each group.

Legend

Figure 1. Measurements of the 4-chamber view and the right and left ventricles. (A) End-diastolic length (L) and width (W) of the 4-chamber view measured at the point of the greatest length and width. (B) Speckle tracking contour from the right ventricle at end-diastole. (C) 24-segment transverse widths and ventricular length computed from speckle tracking analysis of each ventricular chamber. The numbers 1, 12, and 24. identify segments 1, 12, and 24. (D) Measurements of ventricular wall thickness (double arrows) from the mid-section of the right and left ventricles. RV=right ventricle, LV=left ventricle.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

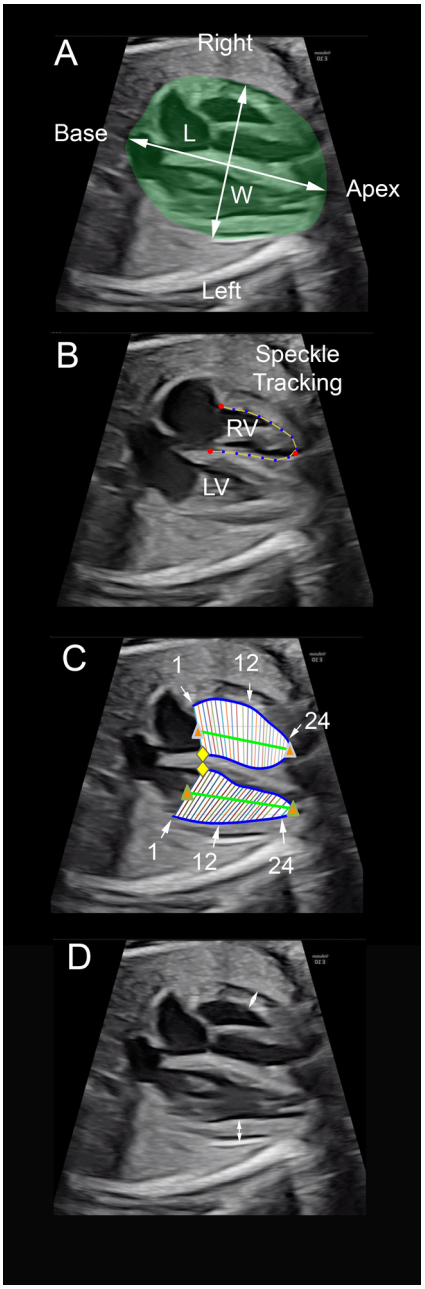
For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.



JUM_15532_Figure 1 Romero.tif

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.