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 Before 34 Weeks' Gestation

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Abbreviations

4CV, 4-chamber view; AREDV, absent or reversed end-diastolic velocity; CPR, cerebroplacental ratio; DV, ductus venosus; EFW, estimated fetal weight; FGR, fetal growth restriction; GSI, global sphericity index; LV, left ventricle; MCA, middle cerebral artery; PI, pulsatility index; RV, right ventricle; UA, umbilical artery

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Objectives—The purpose of this study was to evaluate the end-diastolic size and shape of the 4-chamber view as well as the right ventricle (RV) and left ventricle (LV) in growth-restricted fetuses before 34 weeks' 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, shape, and sphericity index of the 4-chamber view, RV, and LV were assessed. The number and percentage of fetuses with z score values of less than −1.65 and greater than 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 width 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.

Key Words—absent umbilical artery diastolic flow; cardiomegaly; fetal death; fetal echocardiography; fetal growth restriction; global sphericity index; perinatal death; speckle tracking

In a recent meta-analysis of 31 studies evaluating 336 fetal deaths in growth-restricted fetuses before 34 weeks' gestation who had absent or reversed end-diastolic flow of the umbilical artery (UA), ductus venosus (DV), or both, the authors reported odds ratios for fetal death of 6.8 for absent or reversed end-diastolic velocity (AREDV) of the UA and 11.6 for absent or reversed flow of the DV.[1] Since AREDV is associated with increased placental resistance to blood flow, resulting in an

increased fetal cardiac afterload with fetal and neonatal consequences, we were interested in the morphometric changes of the fetal heart in fetuses who had 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 4-chamber view (4CV) and the right ventricle (RV) and left ventricle (LV) in fetuses with AREDV; and (2) differences in the above measurements between fetuses who had 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 *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development. This cross-sectional retrospective descriptive study was performed in 49 fetuses with AREDV of the UA and a concomitant estimated fetal weight (EFW) below the 10th centile, which met the criteria for fetal growth restriction (FGR) by 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 live-born neonates.

Control Fetuses

Two-hundred fetuses with accurate first- and second-trimester dating sonograms were examined between 20 and 40 weeks' gestation, as previously reported.[8–12,16–21] 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[22] for deriving charts for fetal size. 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%), white (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.[23]

Pulsed Doppler Measurements

Doppler velocimetry was performed in the UA, middle cerebral artery (MCA), and 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 5 consecutive waveforms were obtained and the pulsatility index (PI) calculated for each of the above vessels. The cerebroplacental ratio (CPR) was computed (MCA PI/UA PI.) The z scores for the UA PI and MCA PI were automatically measured and the CPR computed by using gestational age as the independent variable.

Measurements of the Epicardial Global Size and Shape of the 4CV

With a Digital Imaging and Communications in Medicine 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 4CV 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. End-diastolic area = $[(3.14 \times \text{end-diastolic length} \times \text{end-diastolic width})/4]$ (Figure 1A)[12]; and
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 4CV were imported into an offline cardiac software program (2-dimensional Cardiac Performance Analysis; TomTec Imaging Systems GmbH, Munich, Germany) using criteria for fetal

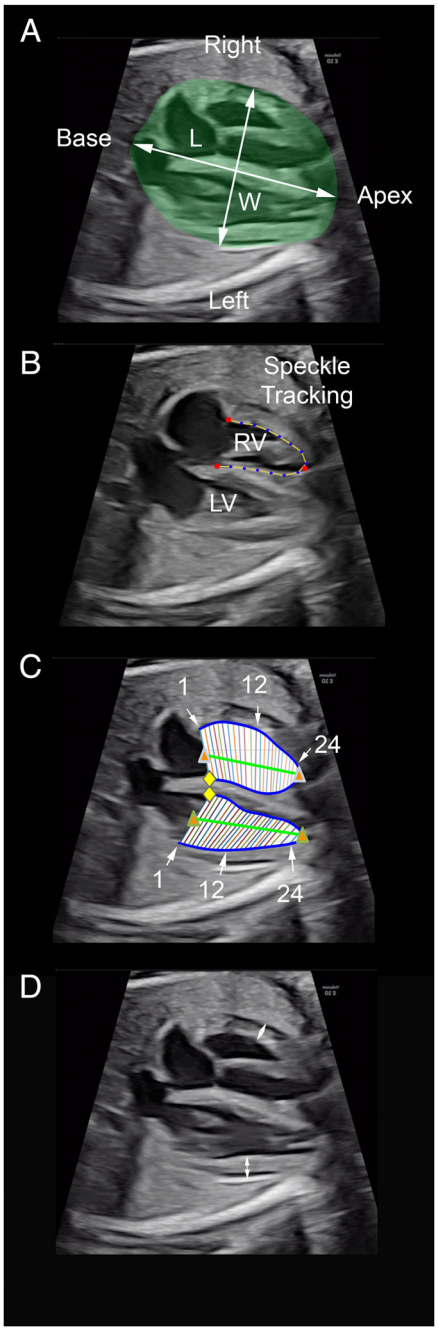

Figure 1. Measurements of the 4CV, RV, and LV. **A**, End-diastolic length (L) and width (W) of the 4CV measured at the point of the greatest length and width. **B**, Speckle-tracking contour from the RV at end diastole. **C**, Twenty-four–segment transverse widths and ventricular length computed from the speckle-tracking analysis of each ventricular chamber. Numbers identify segments 1, 12, and 24. **D**, Measurements of ventricular wall thickness (double arrows) from the midsection of the RV and LV.

applications that have been previously described.[24] 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. Twenty-four–segment transverse widths; segments 1 to 24 were measured by 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 area ratio;
   a. This was computed as follows: RV end-diastolic area/LV end-diastolic area (mean, 0.88; SD, 0.185; Figure 1C); and
4. Twenty-four–segment right-to-left 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 4CV was reviewed to identify end diastole by scrolling through the cine clip. The thickness of the RV and LV walls were measured in the mid chamber by the protocol described by Garcia-Otero et al[25] and the *z* scores computed by using the EFW provided as an Excel calculator (Microsoft Corporation, Redmond, WA) in the supplemental material associated with the above publication (Figure 1D).

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 by the following equation[8–12,16,25]:

$$z\ \text{score} = (\text{individual measured cardiac value}_{\text{study group}} - \text{mean}_{\text{control group}})/\text{SD}_{\text{control group}}$$

The 49 fetuses were separated by whether the fetus had a perinatal death (n = 13) or survived the

neonatal period (n = 36). The results from the z score computations were classified as above the 95th centile ($z > 1.65$) or below 5th centile ($z < -1.65$), depending on the measurement. Once the z scores were computed for each of the above measurements, the numbers of fetuses with abnormal z score values were compared to the expected numbers of abnormal values for the 5th and 95th centiles from control populations by the χ^2 analysis or the Fisher exact test (NCSS version 19; NCSS, Kaysville, UT).[8–11,16,25] In addition, z score values for the above measurements were compared between the two groups by the Student t test if the variables were normally distributed or the Mann–Whitney U test if the measurements were not normally distributed. $P < .05$ was considered significant. The intraobserver and interobserver variability have been previously reported for each of the measurements described in this study and, therefore, were not repeated.[8–12,16,25]

Results

The biometric 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 weeks 1 day ±2 weeks 5 days) and neonatal survivors (29 weeks 3 days ±3 weeks 4 days). The EFW was below the 10th centile in all fetuses, with 92% having an EFW below the 5th centile. Although absent or reversed UA end-diastolic flow was present in 100% of fetuses, reversed flow of the DV was present in 31% (4 of 13) of those who had a perinatal death and only in 8.3% (3 of 36) of those who survived the neonatal period. There was a significant difference ($P < .0001$) 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).

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

Parameter	Perinatal Deaths (n = 13)	Neonatal Survivors (n = 36)	*P*
EFW <10th centile, % (n)	100 (13)	100 (36)	NS
EFW <5th centile, % (n)	92 (120)	92 (33)	NS
Absent/reversed UA Doppler waveform, % (n)	100 (13)	100 (36)	NS
UA PI	1.83 (SD, 0.9)	2.33 (SD, 0.89)	NS
MCA PI	1.16 (SD, 0.29)	1.23 (SD, 0.30)	NS
CPR	0.70 (SD, 0.38)	0.60 (SD, 0.28)	NS
Reversed flow of DV, % (n)	31 (4)	8.3 (3)	NS
Amniotic fluid index	2.6 (SD, 0.43)	8.24 (SD, 3.9)	<.0001
Amniotic fluid deepest pocket	3.7 (SD, 3.5)	3.61 (SD, 1.54)	NS

NS indicates not significant.

Table 2. Fetuses With Abnormal Values Below the 5th or Above the 95th Centile for Measurements of the Four-Chamber View (4CV).

4CV End-Diastolic Measurement	Fetuses, n (%)	Odds Ratio	95% Confidence Limits	*P*
Perinatal deaths (n = 13)[a]				
Area > 95th centile	10 (77)	63.3	15–266.9	<.0001
4CV transverse width > 95th centile	12 (92)	228	26.9–1931	<.0001
4CV length > 95th centile	3 (23)	5.7	1.3–24	<.02
GSI <5th centile	5 (38)	11.9	3.2–42.9	<.0002
Neonatal survivors (n = 36)[a]				
Area > 95th centile	17 (47)	17	6.8–42.3	<.0001
4CV transverse width > 95th centile	23 (64)	33.6	13.2–85.3	<.0001
4CV length > 95th centile	10 (28)	7.3	2.8–19.2	<.0001
GSI <5th centile	15 (42)	13.5	5.4–33.9	<.0001

[a]There were no significant differences in the number of fetuses with abnormal values between the groups for the above measurements.

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

Four-Chamber View

The area, width, and length above the 95th centile of the 4CV were significantly more prevalent for both groups compared to controls. An abnormal GSI below the 5th centile was also significantly more frequent than in 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 (Table 2).

Twenty-four–Segment Transverse Widths Above the 95th Centile

Left ventricular end-diastolic transverse widths for basal segments 1 to 16 were significantly more frequent for both groups compared to controls. However, only LV segments 17 to 24 above the 95th centile were unique for those with perinatal deaths. Similarly, RV segments 1 to 16 were significantly more frequent than in controls and common for both groups. Right ventricular segments 17 to 24 were unique to neonatal survivors (Table 3).

Twenty-four–Segment Transverse Widths Below the 5th Centile

Left ventricular segments 1 to 24 as well as RV segments 17 to 24 below the 5th centile were significantly more frequent than in controls in the neonatal survivors. No fetuses with perinatal deaths had LV or RV 24-segment widths below the 5th centile (Table 4).

Table 3. Fetuses With Abnormal Values Above the 95th Centile for Measurements of the Ventricular End-Diastolic 24-Segment Widths

Ventricular 24-Segment Transverse Width > 95th Centile	Fetuses, n (%)	Odds Ratio	95% Confidence Limits	*P*	Unique Findings
Perinatal deaths (n = 13)[a]					
LV					
LV basal segments 1–8	4 (31)	8.4	2.2–32.2	<.002	
LV mid Segments 9–16	3 (23)	5.7	1.3–24	<.02	
LV apical segments 17–24	3 (23)	5.7	1.3–24	<.02	Perinatal deaths
RV					
RV basal segments 1–8	5 (38)	11.9	3.2–42.9	<.0002	
RV mid segments 9–16	3 (23)	5.7	1.3–24	<.02	
Neonatal survivors (n = 36)[a]					
LV					
LV basal segments 1–8	7 (19)	4.6	1.6–13	<.004	
LV mid segments 9–16	6 (17)	3.8	1.3–11.2	.02	
RV					
RV basal segments 1–8	16 (44)	15.2	6–37.9	<.0001	
RV mid segments 9–16	10 (28)	7.3	2.8–19.2	<.0001	
RV apical segments 17–24	9 (25)	6.3	2.4–17	<.0002	Neonatal survivors

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

Table 4. Fetuses With Abnormal Values Below the 5th Centile for Measurements of the Ventricular End-Diastolic 24-Segment Widths

Ventricular 24-Segment Transverse Width < 5th Centile	Fetuses, n (%)	Odds Ratio	95% Confidence Limits	*P*	Unique Findings
Neonatal survivors (n = 36)					
LV					
LV basal segments 1–8	10 (28%)	7.3	2.8–19.2	<.0001	Neonatal survivors
LV mid segments 9–16	8 (22%)	5.4	2–14.9	<.0004	Neonatal survivors
LV apical segments 17–24	8 (22%)	5.4	2–14.9	<.0004	Neonatal survivors
RV					
RV apical section (segments 17–24)	6 (17%)	3.8	1.3–11.2	.02	Neonatal survivors

Table 5. Fetuses With Abnormal Values Below the 5th or Above the 95th Centile for Measurements of the Ventricular End-Diastolic Area, Length, and Wall Thickness

End-Diastolic Ventricular Area, Length, and Wall Thickness	Fetuses, n (%)	Odds Ratio	95% Confidence Limits	*P*	Unique Findings
Perinatal deaths (n = 13)[a]					
Ventricular length < 5th centile					
LV	3 (23)	5.7	1.3–24	<.02	
RV	3 (23)	5.7	1.3–24	<.02	
Ventricular area > 95th centile					
RV	4 (31)	8.4	2.2–32.2	<.002	
Ventricular wall thickness > 95th centile					
LV	12 (92)	228	26.9–1931	<.0001	
RV	10 (77)	63.3	15–266.9	<.0001	
Neonatal survivors (n = 36)[a]					
Ventricular length < 5th centile					
LV	16 (44)	15.2	6–37.9	<.0001	
RV	12 (33)	9.5	3.7–24.3	<0.0001	
Ventricular area < 5th centile					
LV	10 (28)	7.3	2.8–19.2	<.0001	Neonatal survivors
RV	6 (17)	3.8	1.3–11.2	.02	Neonatal survivors
Ventricular area > 95th centile					
RV	7 (19)	4.6	1.6–13	<.004	
Ventricular wall thickness > 95th centile					
LV	26 (72)	49.4	18.7–130	<.0001	
RV	26 (72)	49.4	18.7–130	<.0001	

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

Table 6. Fetuses With Abnormal Values Below the 5th or Above the 95th Centile for the 24-Segment Sphericity Index and the RV/LV Ratios

End-Diastolic 24-Segment Sphericity Index and RV/LV Ratios	Fetuses, n (%)	Odds Ratio	95% Confidence Limits	*P*	Unique Findings
Perinatal deaths (n = 13)[a]					
Ventricular sphericity index <5th centile					
LV basal segments 1–8	3 (23)	5.7	1.3–24	<.02	
RV/LV ratio > 95th centile					
Area	6 (46)	16.3	4.6–57.5	<.0001	
Basal transverse segments 1–8	3 (23)	5.7	1.3–24	<.02	
Mid transverse segments 9–16	3 (23)	5.7	1.3–24	<.02	
Apical transverse segments 17–24	4 (31)	8.4	2.2–32.2	<.002	
Neonatal survivors (n = 36)[a]					
Ventricular sphericity index <5th centile					
LV basal segments 1–8	10 (28)	7.3	2.8–19.2	<.0001	
LV mid segments 9–16	9 (25)	6.3	2.4–17	<.0002	Neonatal survivors
RV basal segments 1–8	15 (42)	13.5	5.4–33.9	<.0001	Neonatal survivors
RV mid segments 9–16	12 (33)	9.5	3.7–24.3	<.0001	Neonatal survivors
RV/LV ratio > 95th centile					
Area	11 (31)	8.4	3.2–21.7	<.0001	
Basal transverse segments 1–8	14 (36)	22.2	8.5–60.2	<.0001	
Mid transverse segments 9–16	12 (33)	9.5	3.7–24.3	<.0001	
Apical transverse segments 17–24	10 (28)	7.3	2.8–19.2	<.0001	

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

Ventricular End-Diastolic Area, Length, and Wall Thickness

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 below the 5th centile; (2) RV ventricular area above the 95th centile; (3) RV and LV area above the 95th centile; and (4) RV and LV wall thickness above the 95th centile. Right ventricular and LV area below the 5th centile was unique to neonatal survivors (Table 5).

Ratios: Ventricular 24-Segment Sphericity Index Below the 5th Centile and RV/LV Area above the 95th Centile

Both groups had a significantly higher prevalence of LV sphericity index values below the 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 above the 95th centile were present for all segments in both fetuses with perinatal deaths and neonatal survivors (Table 6).

Comparison of z Score Measurements Between Fetuses With Perinatal Deaths and Neonatal Survivors

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

Discussion

In this study, we identified 13 fetuses who had either a 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 who did not, there were similar as well as differing patterns of fetal cardiovascular size and shape of the 4CV as well as the RV and LV, as manifested by the number of fetuses who had abnormal cardiac measurements below the 5th centile or above the 95th centile and the difference in z score values between the two groups. Absent or reversed DV flow was present in both groups. Our findings would suggest that 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 a result of abnormal DV findings. In addition, the absence of an abnormal DV waveform would not preclude the risk of perinatal death.

Four-Chamber View

Both groups had a high percentage of fetuses with an increased 4CV end-diastolic area, transverse width, and length. In addition, both groups had an abnormal GSI, suggesting a round or globular-shaped 4CV. When z score values were compared for the above measurements, there were no significant differences between the groups. Therefore, the size and shape of the 4CV did not discriminate between those fetuses who had a perinatal death and those who survived the neonatal period.

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

Tables 2–6 list the abnormal findings for both groups compared to control fetuses, suggesting significant changes in the size and shape of the RV and LV and the unique findings between the two groups. From these tables, 3 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 RV 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 were increased in transverse width above the 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 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 2–6 categorized results by the frequency of fetuses who had significant differences of abnormal measurements 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 two 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 (online Supplement 1).

Previous Studies Evaluating the 4CV Size and Shape

In 2017, Rodriguez-López et al[5] classified fetuses with growth restriction by the phenotypes of the ventricles imaged from the 4CV as elongated, globular, or hypertrophic. Irrespective of the phenotype of the ventricles, all had increased end-diastolic areas of the 4CV.[5] A review of Figure 3 from their study suggests that the GSI would be abnormally decreased, had it been measured, as manifested by a globular-shaped 4CV.[5] Recently, Hobbins et al[13] reported that there were no perinatal deaths in 25 fetuses with an EFW below the 10th centile with forward diastolic flow of the UA but an abnormal UA PI, CPR, or both. However, 29% of fetuses with an abnormal UA PI had an enlarged 4CV area above the 90th centile; 68% had an increased 4CV transverse width above the 90th centile; and 28% had an abnormal 4CV GSI below the 10th centile.[13] Although their threshold for classifying an abnormal finding was 5% higher than our study (90th versus 95th centile and 10th versus 5th centile), the number of fetuses with an increased 4CV area were not significantly different than in this study.[13] The above studies would suggest that an increased 4CV area and width as well as an abnormal GSI are present early in the process of UA 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 4-dimensional spatiotemporal image correlation,[8,9,26–37] few studies have measured these widths in fetuses with growth restriction.[5,38] Increased ventricular widths in fetuses with growth restriction were first described with M-mode ultrasound by DeVore[38] in 1988, in which enlargement of both the RV and LV end-diastolic midchamber widths was associated with fetal death. In the study by Rodriguez-López et al,[5] 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. Studies in neonates with FGR have also found the RV and LV transverse widths to be increased compared to controls.[2,6] Hobbins et al[13] measured the end-diastolic area of the RV and LV and found no increase in areas in fetuses with an EFW below the 10th centile with a normal UA PI but reported a significant number of fetuses with decreased end-diastolic areas for both ventricles when the UA PI was abnormal.[13] Of interest, decreased LV and RV areas and 24-segment transverse widths were only identified in neonatal survivors in our 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, which include myocardial infarction, coronary artery–associated disease, severe mitral regurgitation, and dilated cardiomyopathy.[39] 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.[40] Therefore, as the curvature increases, the wall tension decreases. Animal experiments have demonstrated that a change in LV 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.[40–43]

The sphericity index is a fixed constant in the fetus, irrespective of gestational age or changes in fetal biometric characteristics.[10] Except for a study by Channing et al,[44] all previous fetal studies computed the sphericity index by dividing the end-diastolic basal-apical length by the basal (segment 1) transverse width.[5,7,43,45] In utero changes in the sphericity index may be a precursor for postnatal changes in cardiac function.[5,43,46] In a previous study of 30 small-for-gestational-age fetuses, DeVore et al[47] found that if only 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, whereas if all 24 segments were used, then 50% of fetuses would have been classified as having an abnormal sphericity index. 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.[47] Therefore, measuring the 24-segment sphericity index provides a more comprehensive evaluation of the shape of the ventricles than just measuring one segment located at the base of each ventricle.[5,7,43,44] In this study, the neonatal survivors had significantly more fetuses with a sphericity index below the 5th centile for both base and mid sections. In addition, all 24 segments of the RV had significantly lower z score values compared to those with perinatal deaths.

Previous Studies Evaluating RV/LV Ratios

The RV/LV ratio has been previously measured with M-mode and 2-dimensional ultrasound from either the base of the ventricle or the mid section of the chambers.[29,38,48] In 2018, Rodriguez-Guerineau et al[2] 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 phenotypic characteristics of an elongated 4CV but was not different than in controls for fetuses with a globular or hypertrophied phenotype. Recently, Hobbins et al[13] reported an increased RV/LV area ratio in 36% of fetuses with an EFW below the 10th centile and an abnormal UA Doppler PI with forward diastolic flow, an abnormal CPR, or both, which was not significantly different from that in those fetuses with a perinatal death (46%) and those who survived the neonatal period (31%) in this 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 et al[49] in 1993. Subsequent studies have demonstrated ventricular wall hypertrophy to be associated with increased vascular resistance in recipient twins with twin-twin transfusion, nonrecipient twins with growth restriction, and singletons with growth restriction.[5,50,51] In addition, premature neonates with FGR have been shown to also have greater LV free wall ventricular hypertrophy and lower sphericity indices than controls.[3,52] Recently, Sepulveda-Martinez et al[53] showed no significant differences when measuring RV and LV wall thickness as well as the interventricular septum between M-mode and 2-dimensional images. Rodriguez-López et al[5] reported that fetuses with early FGR and the highest abnormal values for the UA PI and had the greatest thickness of the LV free wall (hypertrophic group). Our results showed 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

In measurement of the area and width of the 4CV, the contributing anatomic characteristics 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 above the 95th centile were 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 shape of the 4CV did not discriminate between the two study groups, evaluation of ventricular size and shape was more informative. Ventricular transverse widths above the 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, whereas 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 was that we did not use gestational age but used the EFW 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 this study can be integrated with current antepartum surveillance such as the biophysical profile, nonstress test, and 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 4CV and ventricles were not used in clinical management. Although perinatal death occurred in some fetuses at gestational ages below viability, it did not in others. 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 versus those who may survive the neonatal period. The limitation of the study was that we measured the 4CV and ventricular size and shape using the last examination before 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 4CV and ventricles and differences between fetuses with growth restriction and AREDV who died in utero or in the neonatal period and those who did not. Compared to those who had 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) a sphericity index below the 5th centile for segments 9 to 16 of the LV and 1 to 16 of the RV. Therefore, fetuses with a smaller RV and LV size and area and a more globular-shaped RV may not be at increased risk for perinatal death, whereas those fetuses with an increased LV width for transverse segments 17 to 24 may be at increased risk for perinatal death.

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