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The fetal cardiovascular response to increased placental vascular impedance to flow determined with four-dimensional ultrasound using spatiotemporal image correlation and virtual organ computer-aided analysis

Neil Hamill, M.D.[1,2], **Roberto Romero, M.D., D. Med. Sci**[1], **Sonia Hassan, M.D.**[1,2], **Wesley Lee, M.D.**[4], **Stephen A. Myers, D.O.**[3], **Pooja Mittal, M.D.**[1,2], **Juan Pedro Kusanovic, M.D.**[1,2], **Mamtha Balasubramaniam, M.S.**[4], **Tinnakorn Chaiworapongsa, M.D.**[1,2], **Edi Vaisbuch, M.D.**[1,2], **Jimmy Espinoza, M.D.**[1,2], **Francesca Gotsch, M.D.**[1], **Luis F. Goncalves, M.D.**[1,2], **Shali Mazaki-Tovi, M.D.**[1,2], **Offer Erez, M.D.**[1,2], **Edgar Hernandez-Andrade, M.D.**[1,2], and **Lami Yeo, M.D.**[1,2]

[1]Perinatology Research Branch, NICHD, NIH, DHHS, Bethesda, Maryland, and Detroit, Michigan, USA

[2]Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan, USA

[3]Case-Metrohealth, Cleveland, Ohio, USA

[4]Division of Fetal Imaging, Department of Obstetrics and Gynecology, William Beaumont Hospital, Royal Oak, Michigan, USA

Abstract

Objective—To determine if increased placental vascular impedance to flow is associated with changes in fetal cardiac function using spatiotemporal image correlation (STIC) and Virtual Organ Computer-aided AnaLysis (VOCAL).

Study Design—A cross-sectional study was performed in fetuses with an umbilical artery pulsatility index > 95th percentile (ABN). Ventricular volume (end-systole, end-diastole), stroke volume (SV), cardiac output (CO), adjusted CO, and ejection fraction (EF) were compared to those of 184 normal fetuses (NL).

Address correspondence to: Lami Yeo, MD and Roberto Romero, MD, Perinatology Research Branch, NICHD/NIH/DHHS, Hutzel Women's Hospital, 3990 John R. Box 4, Detroit, MI 48201, USA, Telephone: (313) 993-2700, Fax: (313) 993-2694, lyeo@med.wayne.edu and prbchiefstaff@med.wayne.edu.

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Results—1) 34 fetuses were evaluated at a median gestational age of 28.3 (range 20.6 – 36.9) weeks; 2) mean ventricular volumes were lower for ABN than NL (end-systole, end-diastole) with a proportionally greater decrease for left ventricular volume (vs. right); 3) mean left and right SV, CO, and adjusted CO were lower for ABN (vs. NL); 4) right ventricular volume, SV, CO, and adjusted CO exceeded the left in ABN fetuses; 5) mean EF was greater for ABN than NL; and 6) median left EF was greater (vs. right) in ABN fetuses.

Conclusion—Increased placental vascular impedance to flow is associated with changes in fetal cardiac function.

Keywords

cardiac function; cardiac output; Contour Finder; ejection fraction; fetal echocardiography; fetus; 4D; IUGR; prenatal diagnosis; sonography; STIC; stroke volume; 3D; umbilical artery Doppler; ventricular volume; VOCAL

Introduction

Abnormal umbilical artery Doppler velocimetry reflects increased impedance to blood flow in the placenta.[1–4] Mathematical modeling of the placental circulation shows that initially, placental resistance and pulsatility index (PI) increase very slowly with fractional terminal vessel obliteration.[5] However, there is a steep increase of the PI after 60–90% of vessels are obliterated.[5]

In human pregnancies, structural heart disease,[6–8] small for gestational age with normal umbilical artery Doppler velocimetry,[9–10] intrauterine growth restriction (IUGR),[11–15] twin-to-twin transfusion syndrome,[16–18] and intra-amniotic infection[19–20] (reported in animal models also[21–22]) can result in fetal cardiac dysfunction. The heart is a central organ in the fetal adaptive mechanisms to placental insufficiency and hypoxia.[23] Therefore, it follows that placental insufficiency with increased placental vascular resistance may lead to fetal cardiovascular compromise,[24] and even fetal metabolic acidosis and death.[25] Indeed, severe IUGR due to placental insufficiency contributes to 30% of total perinatal loss and severe morbidity.[26] Monitoring of fetal cardiac function has been proposed as an adjunct to current methods to predict adverse outcome and death in IUGR.[27] Fetuses with abnormal umbilical artery Doppler velocimetry have been shown to have similar changes to those observed in adults with atherosclerosis. This may be important in relating placental vascular disease (detected by umbilical artery Doppler velocimetry) to the risk for adult cardiovascular disease.[28] Studies report that fetuses with abnormal umbilical artery Doppler velocimetry have evidence of higher red blood cell count and hemoglobin concentration,[29] endothelium activation,[28] platelet activation (which promotes thrombosis),[30] platelet consumption,[31] an atherogenic lipoprotein profile,[32] and evidence of intravascular inflammation.[33] Epidemiologic studies and animal models have also established that low birthweight babies have an increased risk of cardiovascular disease later in life.[34–35] Thus, the condition which is the focus of our study is the *in-utero* equivalent to fetal atherosclerosis, and this, along with fetal cardiac dysfunction may have important consequences in fetal programming of cardiac disease and the early-onset of disease.[23] Examining fetal cardiovascular parameters

is required to gain an understanding of the hemodynamic changes occurring in the setting of increased placental vascular impedance to flow.

However, the repeatability and reproducibility of most fetal echocardiographic measurements determined using two-dimensional (2D) sonography is poor, particularly for ventricular volume and volume flow estimations.[36] This has been attributed to measurement variation in the atrioventricular and semilunar valves, which can lead to large differences in the estimated cardiac output.[36–37] Errors in measuring velocity-time integral or valve area will greatly influence volume flow measurements, particularly because the valve area is related to the square of the radius, thus accentuating any errors.[38] Moreover, the use of 2D measurements to estimate ventricular volume requires assumptions about the three-dimensional geometry of the heart which may be invalid, leading to inaccuracy in estimations of cardiac output.[36–37]

Three-[39] and four-dimensional sonography have the potential to minimize the limitations inherent in 2D estimations of fetal cardiovascular parameters because: 1) geometric assumptions are not made when assessing ventricular volumes; 2) neither small outflow tract diameters nor angle-dependent Doppler measurements are required for calculation; and 3) from a single cardiac dataset obtained using spatiotemporal image correlation (STIC), all parameters required for calculation (left and right ventricular volumes) are present in the same volume, reducing the risk inherent in measuring two chambers at different times when using 2D ultrasound.[40] Indeed, three-[41–46] and four-dimensional echocardiography[47–57] have been used to evaluate cardiovascular parameters in normal fetuses.

Yet, there is insufficient data regarding the fetal cardiovascular response to increased placental vascular impedance to flow determined using four-dimensional sonography. We have previously described a repeatable and reproducible technique to quantify ventricular volume calculations using STIC and Virtual Organ Computer-aided AnaLysis (VOCAL).[58] Subsequently, we quantified fetal cardiovascular parameters (ventricular volume, stroke volume, cardiac output, and ejection fraction) in a group of 184 normal fetuses over a range of gestational ages.[40] Therefore, the objective of this study was to use the same technique to determine if increased placental vascular impedance to flow is associated with changes in fetal cardiac function.

Materials and Methods

Study population

A cross-sectional study was conducted to include pregnancies with increased placental vascular impedance to flow (umbilical artery PI > 95th percentile[59]) by searching our database of women enrolled into research protocols that included examination of the fetal heart by three- and four-dimensional ultrasound. Women were eligible for inclusion if gestational age was determined by either a first or second trimester sonographic examination and there was a singleton fetus (> 19 weeks of gestation). Women were excluded in the presence of fetal hydrops, chromosomal, or congenital abnormalities. A control group, consisting of 184 normal fetuses whose cardiovascular parameters had been previously reported,[40] was used for comparison.

IUGR was defined as an abdominal circumference < 5th percentile for gestational age[60–61] with an umbilical artery PI > 95th percentile.[59] Estimated fetal weight was not used to determine the presence of IUGR. Fetal Doppler recordings were obtained from the umbilical artery (free loop of cord), middle cerebral artery, and from the ductus venosus when possible. Preeclampsia was defined as the presence of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, and proteinuria of 300 mg/24 hours or ≥ +2 (dipstick) on two occasions six hours apart. All women provided written informed consent prior to undergoing sonographic examination. Participation was approved by the Institutional Review Board of the National Institute of Child Health and Human Development and by the Human Investigation Committee of Wayne State University.

Examination Technique

Ultrasound examinations were performed by eight experienced sonographers using systems with STIC capability (Voluson 730 Expert, Voluson E8 Expert; GE Medical Systems, Kretztechnik GmbH, Zipf, Austria) and utilizing a motorized curved array transabdominal transducer (2–5 or 4–8 MHz). Tissue harmonic imaging was used for each examination, and Compound Resolution Imaging (CRI) was used at the sonographer's discretion. A transverse view of the fetal chest at the level of the four-chamber view was obtained, from which STIC datasets were acquired. The transducer was oriented such that the fetal spine was located posteriorly for each acquisition. Acquisition time was 10 seconds with a sweep angle that was sufficient to encompass the fetal cardiac structures (25 – 35 degrees). Color Doppler sonography was not utilized during the acquisition process. Adequate cardiac datasets were accepted for post-processing if acoustic shadowing (signal loss in the sound path secondary to echogenic structures), dropout (signal loss in the sound path without intervening structures), and motion artifact were absent. When multiple STIC datasets were available, the dataset obtained closest to the time of delivery was selected for analysis.

Cardiac datasets were acquired to investigate the following fetal cardiovascular parameters: 1) ventricular volume (mL); 2) stroke volume (mL) (end-diastolic volume – end-systolic volume); 3) cardiac output (mL/min) (stroke volume×fetal heart rate); and 4) ejection fraction (%) (stroke volume/end-diastolic volume×100%). Fetal biometry of the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femoral diaphysis length (FL) were obtained using 2D sonography at the time of cardiac dataset acquisition. Cardiac output was expressed both as a function of estimated fetal weight,[62] and as a function of biometric parameters (HC, AC, FL).

Analysis was performed offline (4D View versions 5.0 – 7.0; GE Healthcare, Milwaukee, WI) in a standardized manner. In the A plane of the multiplanar display, the fetal heart was re-oriented such that the left ventricle was located on the left side of the screen with the apex of the heart directed upwards. Next, the ventricular septum was rotated to 90 degrees in both the A and C planes. The atrioventricular (AV) valves were located by scrolling from front to back in the A plane. The image was optimized by selecting Chroma Color 1 (Sepia) with the addition of speckle reduction (SRI 5). After image brightness and contrast settings were optimized, end-systolic and end-diastolic phases were identified by scrolling through each

frame, and locating the image preceding AV valve opening (systole) and following AV valve closure (diastole).

Ventricular volumes were calculated in a semi-automated fashion utilizing VOCAL. VOCAL II was selected and the Contour Finder: Trace option was utilized with 15 degrees of rotation and a sensitivity of 1 (default = 5). The image was enlarged and the reference dot repositioned into the ventricle of interest. Due to the complex geometry of the ventricles, the location of the reference dot within the ventricle was selected to meet the software requirement that the contour only cross the rotation line twice. With these selections, 12 rotational steps were made and a volume was computed. Datasets were accepted for analysis if the ventricular septum, ventricular walls, and AV valves were visible throughout each rotational step.

We previously reported the repeatability and reproducibility of ventricular volume measurements utilizing this technique.[58] Volume measurements were repeatable with good agreement [coefficient of variation (CV) < 10%] and excellent reliability [intraclass correlation (ICC) > 0.95] for both intraobserver and interobserver measurements. Additionally, ventricular volumes were reproducible with negligible differences in agreement (CV < 1%), good reliability (ICC > 0.9), and minimal bias (mean percent difference −0.4%; 95% limits of agreement, −5.4% to 5.9%) when different STIC datasets for the same patient were compared.[58]

Statistical Analysis

Data were first assessed using numerical and graphical techniques, including scatter plots of each response vs. gestational age, to determine whether they met assumptions of the statistical tests being used for analysis. All but two scatter plots revealed the presence of curvilinear relationships and heteroscedasticity; hence, natural logarithmic transformations (from the Box-Cox family of transformations) of each response and gestational age were performed to linearize the data and correct for heteroscedasticity.

Analyses of covariance (ANCOVA) based on weighted regression were performed on the transformed data (Table 2), with the weights computed according to the procedure described by Altman.[63–66] These weights are the best linear unbiased estimates (BLUE). Ejection fraction for the right and left ventricles were both linear and homoscedastic; therefore, analysis of covariance of two-factor interaction and main effects multiple regression models were used iteratively to analyze this untransformed data. Residual analysis was performed on all models as a diagnostic measure to assess the aptness of the models fit.

For bivariate analysis, the Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test for normal distribution. Student's t-test was used to determine the differences of the mean among groups, and Pearson's correlation coefficient was utilized to assess correlations. For nonparametric data, the Mann-Whitney U test and Wilcoxon signed-rank test were used to determine the difference between parameter medians, and Spearman's rank correlation coefficient (r_s) was utilized to assess correlations. A P-value <0.05 was considered statistically significant for all comparisons. Statistical analyses were performed using SPSS

package version 14 (SPSS Inc., Chicago IL), as well as The SAS System for Windows version 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient Population

Thirty-four women met the inclusion criteria; clinical and sonographic data are shown in Table 1. Ventricular volume (end-systole, end-diastole), stroke volume (SV), cardiac output (CO), adjusted CO, and ejection fraction (EF) were determined and compared to that of 184 normal fetuses (NL) previously reported by our group (each with normal umbilical artery PI and abdominal circumference measurements).[40]

Sonographic evaluation was performed at a median gestational age of 28.3 (range: 20.6 – 36.9) weeks. Umbilical artery (UA) waveform analysis demonstrated the presence of end-diastolic velocity in 74% (n=25), absence in 20% (n=7), and reversed in 6% (n=2). Since cardiovascular parameters did not statistically differ between these 3 groups, they were considered as a single group with an UA PI > 95th percentile (ABN). Doppler velocimetry of the middle cerebral artery and ductus venosus was available for 100% (n=34) and 85% (n=29) of women, respectively.

The median gestational age at delivery was 31.6 (range: 23.0 – 41.1) weeks, with 20% (n=7) of cases delivering at term (≥ 37 weeks of gestation). The median interval between acquisition of STIC datasets and delivery was 10 (range: 1 – 133) days. The median birth weight was 1000 (range: 282 – 3750) grams. Of the 34 ABN cases, IUGR occurred in 71% (n=24), preeclampsia in 53% (n=18), and perinatal death in 18% (n=6). Since no significant differences were found between cardiovascular parameters in those with and without IUGR, preeclampsia, or perinatal death, they were analyzed as a single group.

Ventricular volumes are lower in the presence of increased placental vascular impedance to flow

After adjusting for gestational age, mean volumes for the left ventricle (mL) were lower in end-systole (ABN: 0.12 vs. NL: 0.43; $p < 0.0001$) and end-diastole (ABN: 0.64 vs. NL: 1.28; $p < 0.0001$) (Figure 1 and Table 2). Similarly, after adjusting for gestational age, mean volumes for the right ventricle (mL) were also lower in end-systole (ABN: 0.39 vs. NL: 0.65; $p < 0.0001$) and end-diastole (ABN: 1.09 vs. NL: 1.57; $p < 0.0001$) (Figure 1 and Table 2). Moreover, there was a proportionately greater decrease [(1 – ABN/NL)×100%] in left ventricular volume as compared to the right, in both end-systole (left: −72% vs. right: −40%) and end-diastole (left: - 50% vs. right: −30%) (Table 2).

Right ventricular volumes are greater than the left in the presence of increased placental vascular impedance to flow

Median right ventricular volumes (mL) were significantly greater than the left in end-systole (ABN Right: 0.28 vs. ABN Left: 0.10; $p < 0.001$) and end-diastole (ABN Right: 0.75 vs. ABN Left: 0.53; $p < 0.001$) (Table 3). When a ratio of right to left ventricular volume was calculated, right ventricular volumes were greater in end-systole (median Right/Left: 3.2,

IQR: 1.8 – 5.4) and end-diastole (median Right/Left: 1.5, IQR: 1.1 – 2.6), an effect which was independent of gestational age (systole: $r_s = 0.15$; p = NS; diastole: $r_s = 0.15$; p = NS). For the same median ratio of right to left ventricular volume, this was significantly different between the ABN and NL groups in both end-diastole (ABN: 1.5, IQR: 1.1 – 2.6 vs. NL: 1.2, IQR: 0.9 – 1.7; $p < 0.05$) and end-systole (ABN: 3.2, IQR: 1.8 – 5.4 vs. NL: 1.6, IQR: 1.1 – 2.4; $p < 0.05$).

Stroke volume and cardiac output are lower in the presence of increased placental vascular impedance to flow

Mean stroke volume (adjusted for gestational age) (mL) was lower for the left (ABN: 0.53 vs. NL: 0.86; $p < 0.0001$) and right ventricle (ABN: 0.71 vs. NL: 0.92; $p < 0.0001$) (Figure 2 and Table 2). Similarly, mean cardiac output (adjusted for gestational age) (mL/min) was lower for the left (ABN: 71.9 vs. NL: 119.6; $p < 0.0001$) and right ventricle (ABN: 96 vs. NL: 127.5; $p < 0.0001$) (Figure 2 and Table 2). Median fetal heart rate (bpm) was not significantly different between the ABN and NL groups (ABN: 141, IQR: 131 – 145 vs. NL: 140, IQR: 134 – 147; p = 0.44).

Cardiac output adjusted for fetal size remains lower in the presence of increased placental vascular impedance to flow

Fetal cardiac output was adjusted for *estimated fetal weight* (EFW),[62] which was calculated using biometric parameters (BPD, HC, AC, FL) obtained at the time of cardiac volume acquisition. Adjustment for EFW (CO/EFW) demonstrated that neither the left nor the right cardiac output (mL/min/kg) changed significantly as gestation advanced (Left CO/EFW ABN: $r_s = 0.13$, p = NS; Right CO/EFW ABN: $r_s = 0.22$, p = NS).

For the left ventricle, the median CO adjusted for EFW (mL/min/kg) was significantly lower in the presence of increased placental vascular impedance to flow (ABN: 67.8, IQR: 44.7 – 84.1 vs. NL: 90, IQR: 56 – 127.5; $p < 0.05$) (Figure 3). However, for the right ventricle, the median CO adjusted for EFW (mL/min/kg) was not significantly different between ABN and NL groups (ABN: 77.4, IQR: 66.1 – 123.8 vs. NL: 99.9, IQR: 72.2 – 126; p = NS) (Figure 3).

Fetal cardiac output was also adjusted for *fetal size*, by dividing the CO (mL/min) by the following biometric parameters: *abdominal circumference* [AC, cm; CO(AC)], *head circumference* [HC, cm; CO(HC)], and *femoral diaphysis length* [FL, cm; CO(FL)]. In the presence of increased placental vascular impedance to flow, values adjusted for gestational age were significantly lower for the mean left CO(AC) (mL/min/cm) (ABN: 3.2 vs. NL: 4.8; p = 0.0001), CO(HC) (mL/min/cm) (ABN: 2.8 vs. NL: 4.4; $p < 0.0001$), and CO(FL) (mL/min/cm) (ABN: 14.2 vs. NL: 21.4; p = 0.0001) (Figure 4 and Table 2). Similarly, values adjusted for gestational age were significantly lower for the mean right CO(AC) (mL/min/cm) (ABN: 4.1 vs. NL: 5.1; $p < 0.0001$), CO(HC) (mL/min/cm) (ABN: 3.7 vs. NL: 4.7; $p < 0.0001$), and CO(FL) (mL/min/cm) (ABN: 18.4 vs. NL: 22.6; $p < 0.0001$) (Figure 4 and Table 2).

Right ventricular stroke volume, cardiac output, and adjusted cardiac output are greater than the left in the presence of increased placental vascular impedance to flow

Median right ventricular stroke volume (mL) was significantly greater than the left side (ABN Right: 0.5 vs. ABN Left: 0.43; $p < 0.05$). Median right cardiac output (mL/min) was also significantly greater than the left side (ABN Right: 65.9 vs. ABN Left: 61.1; $p < 0.05$) (Table 3).

After cardiac output was adjusted for EFW and each of the three biometric parameters, the median right ventricular cardiac output remained significantly greater than the left side: 1) EFW (mL/min/kg) (ABN Right: 77.4 vs. ABN Left: 67.8; $p < 0.05$); 2) abdominal circumference (mL/min/cm) (ABN Right: 3.11 vs. ABN Left: 3.06 ; $p < 0.05$); 3) head circumference (mL/min/cm) (ABN Right: 2.63 vs. ABN Left: 2.69; $p < 0.05$); and 4) femoral diaphysis length (mL/min/cm) (ABN Right: 14.0 vs. ABN Left: 13.3; $p < 0.05$) (Table 3).

Ejection fraction is higher in the presence of increased placental vascular impedance to flow, and is greater on the left side

Mean ejection fraction (adjusted for gestational age) (%) was significantly higher for the left (ABN: 82.4 vs. NL: 70.4; $p < 0.0001$) and right ventricle (ABN: 66.0 vs. NL: 60.8; $p < 0.0001$) (Figure 5 and Table 2). Moreover, the median left ejection fraction (%) was significantly greater than the right side (ABN Left: 83.7 vs. ABN Right: 64.7; $p < 0.001$) (Table 3).

Comment

Principal findings of this study

In the presence of increased placental vascular impedance to flow: 1) fetal ventricular volume (end-systole and end-diastole), stroke volume, and cardiac output are lower when compared to normal fetuses; 2) right ventricular volume, stroke volume, and cardiac output exceed those of the left side; 3) ejection fraction is higher when compared to normal fetuses; and 4) left ejection fraction is greater than that of the right side.

The fetal cardiovascular response to increased placental vascular impedance to flow determined using two-dimensional ultrasound

The heart is a central organ in the fetal adaptive mechanisms to placental insufficiency and hypoxia (crispi). Thus, placental insufficiency with increased placental vascular resistance may lead to fetal cardiovascular compromise,[24] and even fetal metabolic acidosis and death.[25] Examining fetal cardiovascular parameters in this setting could provide insight into the physiologic response to this condition. Fetuses with abnormal umbilical artery Doppler velocimetry have been shown to have similar changes to those observed in adults with atherosclerosis.[28–33] Therefore, placental vascular disease[28] (detected by umbilical artery Doppler velocimetry) along with fetal cardiac dysfunction may have important consequences in fetal programming of cardiac disease and the early-onset of disease.[23]

Several investigators have used 2D sonography to examine cardiovascular parameters (such as stroke volume and cardiac output) in fetuses with abnormal UA Doppler velocimetry.[69–74] The results suggests that left ventricular stroke volume and cardiac output are decreased.[72–73] Yet, for the right ventricle, some studies report an increased cardiac output,[727] while others report a decreased cardiac output.[71,73] One potential confounder is fetal size, which increases with gestational age.[75] Yet, even when cardiac output is adjusted by EFW, conflicting results have been reported. In the presence of abnormal UA Doppler velocimetry, fetal cardiac output adjusted by EFW has been reported to be increased,[72] decreased,[69] and no different,[73] when compared to that of control fetuses.

These discrepancies could be attributed to the limitations associated with using 2D methods to calculate fetal cardiovascular parameters. Errors in the calculation of stroke volume and cardiac output may arise from inaccurate measurement of vessel diameters and Doppler recordings.[36] Simpson and Cook determined the repeatability of fetal Doppler echocardiographic measurements, and reported that intra- and inter-observer errors were high for vessel dimension, stroke volume, and cardiac output.[36] Indeed, for Doppler measurements of the aorta (vessel diameter and velocity time integral), the coefficient of variation was > 10% for the calculated stroke volume (16%) and cardiac output (16%).[36] These limitations also apply to adults, in which 2D echocardiography lacks accuracy when compared to the gold standards of magnetic resonance imaging or radionuclide ventriculography for quantification of ejection fraction and volumes.[76]

However, assessing fetal cardiac function using four-dimensional sonography (STIC) appears to overcome many of these pitfalls, since geometric assumptions are not made, and angle-dependent Doppler measurements are not required. Moreover, the performance of STIC is feasible, and examination times are reduced since acquisitions generally take no more than 12.5 seconds to complete, making a change in the fetal status unlikely.[77–83]

We have previously described a repeatable and reproducible approach to quantify ventricular volume calculations utilizing STIC,[58] and then described cardiovascular parameters in a normal fetal population.[40] There is insufficient data about the fetal cardiovascular response to increased placental vascular impedance to flow determined using four-dimensional sonography. Therefore, we employed this technique to study a cohort of fetuses with abnormal UA Doppler velocimetry.

The right side of the fetal heart is dominant in the setting of increased placental vascular impedance to flow

Right ventricular volume, stroke volume, and cardiac output were significantly greater than the left side in the presence of increased placental vascular impedance to flow. When a median ratio of right to left ventricular volume was calculated, the ratio was greater in end-diastole for ABN fetuses (1.5) when compared to the ratio (1.2) in normal fetuses, and was also greater in end-systole for ABN fetuses (3.2) when compared to the ratio (1.6) in normal fetuses.

Cardiac output was also adjusted by the EFW,[62] and the right ventricular cardiac output remained significantly greater than the left side. However, estimates of fetal weight can

carry substantial variation,[84] which could introduce errors in the calculations. A systematic review of the literature evaluating sonographic estimation of fetal weight concluded that the size of random errors remains a major obstacle, with 95% CIs exceeding 14% of birth weight in all studies.[85] Moreover, since a large proportion of our fetuses were affected with IUGR (71%), this may have confounded the calculation of cardiac output. Therefore, in order to minimize variability introduced into these calculations, cardiac output was also expressed as a function of 3 fetal biometric parameters, each of which has a reliability coefficient that approaches 1,[86] and is measured directly without mathematical treatment or modeling of the observed results. The right ventricular cardiac output remained significantly greater than the left side after adjusting for HC, AC, and FL. In contrast, we previously reported in a population of normal fetuses no significant differences in stroke volume, cardiac output, or adjusted cardiac output (per estimated fetal weight and each of the 3 biometric parameters) between the right and left ventricles.[40] It is noteworthy that the changes in cardiac function were independent of the fetal heart rate, which did not differ between the ABN and NL groups.

In contrast to the other cardiac parameters, the left ejection fraction was significantly greater than the right side in the presence of increased placental vascular impedance to flow. Taken together, these findings provide evidence that increased placental vascular impedance to flow is associated with changes in fetal cardiac function.

Fetuses respond with increased cardiac inotropy in the setting of increased placental vascular impedance to flow

In ABN fetuses, left and right ventricular volumes in end-systole and end-diastole were lower when compared to a normal population. This effect was most pronounced for the left ventricle, especially in end-systole. Moreover, ejection fraction was significantly higher in both ventricles when compared to normal fetuses. These observations suggest that fetal hearts pumping against increased placental vascular impedance to flow may compensate by increasing ventricular inotropy, the hallmark of which is reduced end-systolic volume and an increase in ejection fraction.[87] In adults, the expected consequence of increased inotropy is an increase in cardiac output;[87] however, the findings reported herein demonstrate lower stroke volume, cardiac output, and adjusted cardiac output.

Due to the discrepancy in the expected findings, evidence was sought in support of these observations. This may be found when examining the neurohumoral pathways, including the adrenergic nervous system, which is activated *ex-utero* in those with increased inotropy.[88] There is empiric evidence in support of sympathetic activation in fetuses with growth restriction; specifically, norepinephrine concentrations are increased in amniotic fluid,[89–90] as well as blood samples obtained from cordocentesis.[91–92] Moreover, the pulsatility index of the UA has a significant correlation with norepinephrine concentrations in fetal blood.[93]

In growth restricted fetuses, M-mode echocardiography demonstrates significantly hypertrophied right and left ventricular free walls with greater cardiac size (adjusted for EFW) when compared to normal fetuses.[94] The larger heart may result from an increase in afterload, which subsequently affects wall thickness.[94] Indeed, Gruenwald reported that on

pathologic examination, heart weights were consistently and moderately elevated in growth restricted fetuses, when compared to normally grown fetuses.[95]

Taken together, it is plausible that fetuses increase cardiac inotropy when there is increased placental vascular impedance to flow. Moreover, the inotropic response appears to be disproportionate between the left and right ventricles. Specifically, there is a proportionately greater decrease in end-systolic volume for the left ventricle (−72%) compared to the right (−40%), along with a greater increase in the left ejection fraction (17%) compared to the right (10%). It is possible that the left ventricle is more receptive to inotropic stimulation as an adaptive and protective mechanism to preserve the cerebral circulation. Indeed, animal and human studies have demonstrated that in the presence of hypoxia, there is a redistribution of blood flow with preferential perfusion of the brain ("brain-sparing" effect).[96–99]

Diastolic dysfunction may be a component of the fetal cardiovascular response to increased placental vascular impedance to flow

In ABN fetuses, fetal stroke volume and cardiac output were lower for both ventricles when compared to normal fetuses. The left cardiac output adjusted for EFW was significantly lower in ABN fetuses when compared to normal fetuses. However, there was no significant difference in right cardiac output adjusted for EFW between these groups. Moreover, cardiac output adjusted by AC, HC, and FL for both ventricles was significantly lower in ABN fetuses when compared to normal fetuses. Collectively, the lower left ventricular volume in end-systole along with the higher ejection fraction indicates increased inotropy, while the lower cardiac output suggests that even with increased inotropy, for some fetuses the left ventricle's ability to compensate has been surpassed, suggesting that subclinical cardiac failure may have occurred.

Crispi et al. studied cardiac function longitudinally in growth restricted fetuses with abnormal UA Doppler velocimetry (pulsatility index > 2 SD).[23] Three stages were defined based upon the status of end-diastolic velocity (stage 1: present; stage 2: absent; stage 3: reversed). In growth restricted fetuses, cardiac dysfunction (determined by modified myocardial performance index[100] and early-to-late diastolic filling ratios) was identified in early stages, and increased progressively across stages. Therefore, the evidence suggests that in growth restricted fetuses with abnormal UA Doppler velocimetry, subclinical cardiac dysfunction is an early and progressive event across clinical stages of severity.[23]

In the adult, diastolic dysfunction has been recognized as a major cause of congestive heart failure. The major determinants of ventricular filling are ventricular relaxation and effective chamber compliance.[101–102] In the normal fetus, cardiac compliance increases with gestational age, and a reduction in ventricular stiffness has been reported.[103] In contrast, cardiac dysfunction in the growth-restricted fetus is characterized by increased peripheral resistance and decreased diastolic compliance, in which the heart can be described as being "stiff".[19] Indeed, Veille et al. reported that in growth-restricted fetuses, ventricles are not dilated, most likely because the fetal myocardium is inherently stiff.[94] Similarly, in our group of ABN fetuses, cardiac failure may result partially from diastolic dysfunction, since there were lower end-diastolic volumes in both ventricles. The suboptimal ability of the

heart to dilate could be due to a pathologic remodeling of the fetal heart, similar to the process present in adults with chronic hypertension.[104] Alternatively, when there is increased placental vascular impedance to flow, it is possible that diastolic dysfunction occurs not through a pathologic mechanism, but due to the innate immaturity of the fetus. Specifically, in the setting of increased inotropy, the fetus may not yet possess the ability to actively relax the ventricles. Therefore, the expected increase in cardiovascular parameters does not occur. Evidence for subclinical diastolic dysfunction in growth restricted fetuses with abnormal UA Doppler velocimetry was reported by Crispi et al.[23] In this population, cord blood levels of B-type natriuretic peptide (BNP) increased in a stage-dependent manner (based upon the status of umbilical artery end-diastolic velocity) compared with appropriately grown fetuses. In adults, BNP is considered the “gold standard” biomarker for heart failure, in which serum levels are elevated in early stages of subclinical diastolic dysfunction, and increase in proportion to severity.[105]

Limitations

There are several limitations of the current study. First, there is no invasive data to serve as a means of comparison to the calculation of fetal cardiovascular parameters. Due to the cardiovascular changes that occur shortly after delivery, neonatal data is not suitable to serve as a reference.[106] Second, it is noteworthy that STIC produces a single, computer-generated cardiac cycle, which is an assemblage of between 20 and 30 real cardiac cycles, and a smoothing or averaging of the ventricular borders could occur, introducing error into the calculations.[77] We have previously demonstrated that using STIC and VOCAL is both repeatable and reproducible for calculating fetal ventricular volumes.[58] Moreover, the validity of STIC has been addressed using balloon models. Bhat et al. investigated volumes ranging between 2.5 and 10 mL,[107] and Uittenbogaard et al. examined volumes ranging between 0.30 and 4.95 mL.[108] Both groups concluded that STIC was acceptably accurate over these volume ranges. However, in the current study, there were volume calculations of less than 0.30 mL. Therefore, it remains unclear whether STIC compilation affects volume calculation because the absolute error of STIC was not described in volumes less than 0.30 mL. Third, there were no differences in fetal cardiovascular parameters when UA Doppler was stratified by type of end-diastolic velocity (present, absent, reversed). However, the number of cases with absent (n=7) or reversed (n=2) end-diastolic velocity was small, introducing the possibility of a type II error. Fourth, although the acquisition time of a STIC volume is 12.5 seconds at most, there is a significant learning curve and time commitment required to orient and analyze the data. Finally, the cross-sectional design of our study did not permit an evaluation of longitudinal changes in fetal cardiac function in response to increased placental vascular impedance to flow; thus, the results reported herein should be interpreted within this context. Future longitudinal studies are required to describe the natural history of cardiac function in these fetuses, and its relationship to fetal and neonatal outcome.

Conclusions

The findings of this study suggest that increased placental vascular impedance to flow is associated with changes in fetal cardiac function. Ventricular volume (especially the left ventricle in end-systole), stroke volume, and cardiac output are lower when compared to

those of normal fetuses, and the right ventricle is dominant. Moreover, ejection fraction is higher when compared to normal fetuses, and the left ejection fraction is greater than the right. Taken together, the findings of lower left ventricular volume in end-systole and greater ejection fraction indicate increased inotropy. Yet, the lower cardiac output suggests that even with increased inotropy, in some fetuses the left ventricle's ability to compensate has been surpassed, suggesting that subclinical cardiac failure may have occurred. Diastolic dysfunction may be a component of the fetal cardiovascular response to increased placental vascular impedance to flow.

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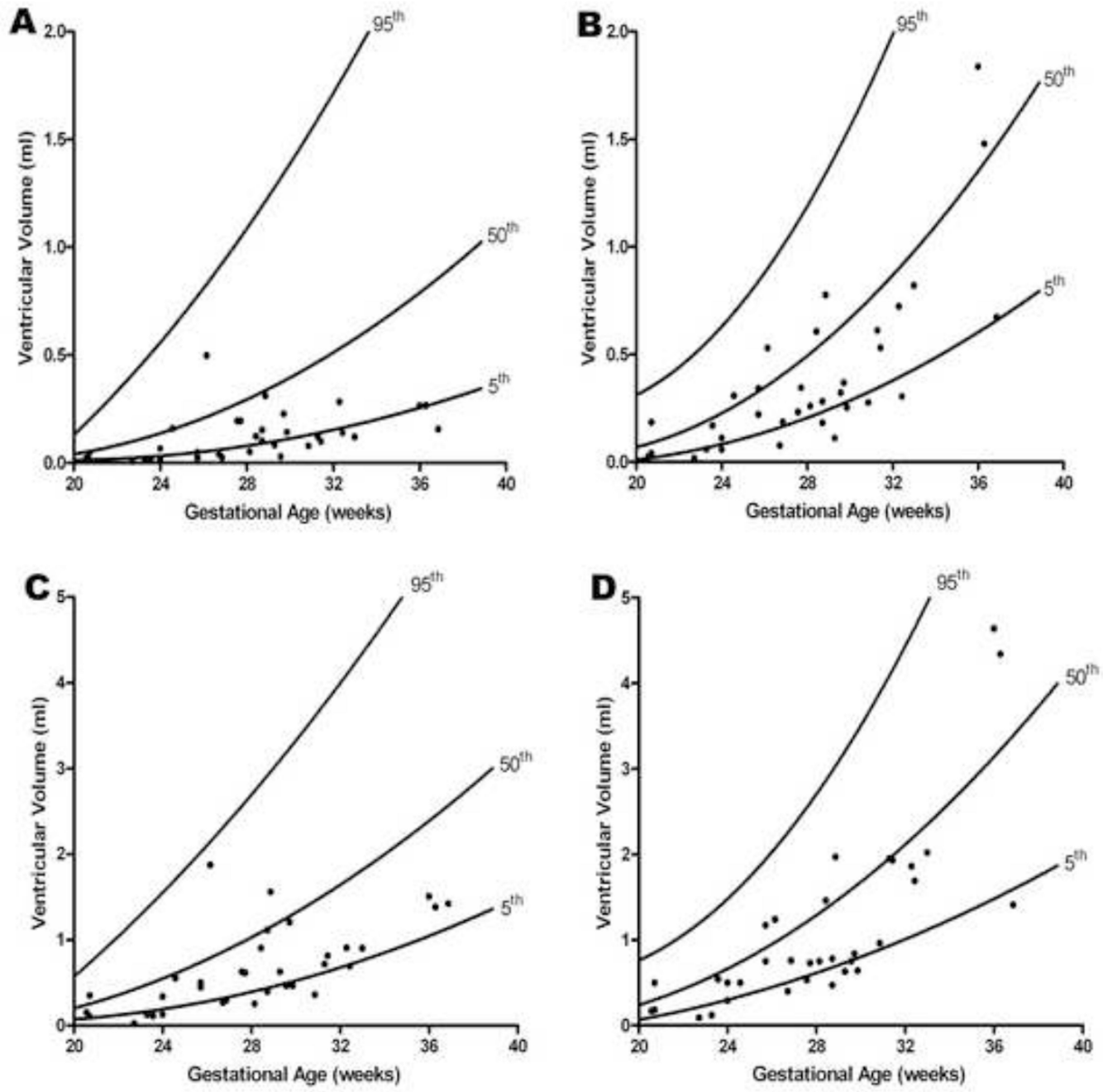

Figure 1. Ventricular volume in end-systole and end-diastole as a function of gestational age in the presence of increased placental vascular impedance to flow

Ventricular volume calculations in fetuses with an umbilical artery pulsatility index > 95th percentile (ABN) were compared to 184 normal fetuses (NL)[40] (A: left ventricle in end-systole; B: right ventricle in end-systole; C: left ventricle in end-diastole; D: right ventricle in end-diastole). For the left ventricle, mean volumes (adjusted for gestational age) (mL) were lower in both end-systole (ABN: 0.12 vs. NL: 0.43; $p < 0.0001$) and end-diastole (ABN: 0.64 vs. NL: 1.28; $p < 0.0001$). For the right ventricle, mean volumes (adjusted for

gestational age) (mL) were also lower in both end-systole (ABN: 0.39 vs. NL: 0.65; $p < 0.0001$) and end-diastole (ABN: 1.09 vs. NL: 1.57; $p < 0.0001$)

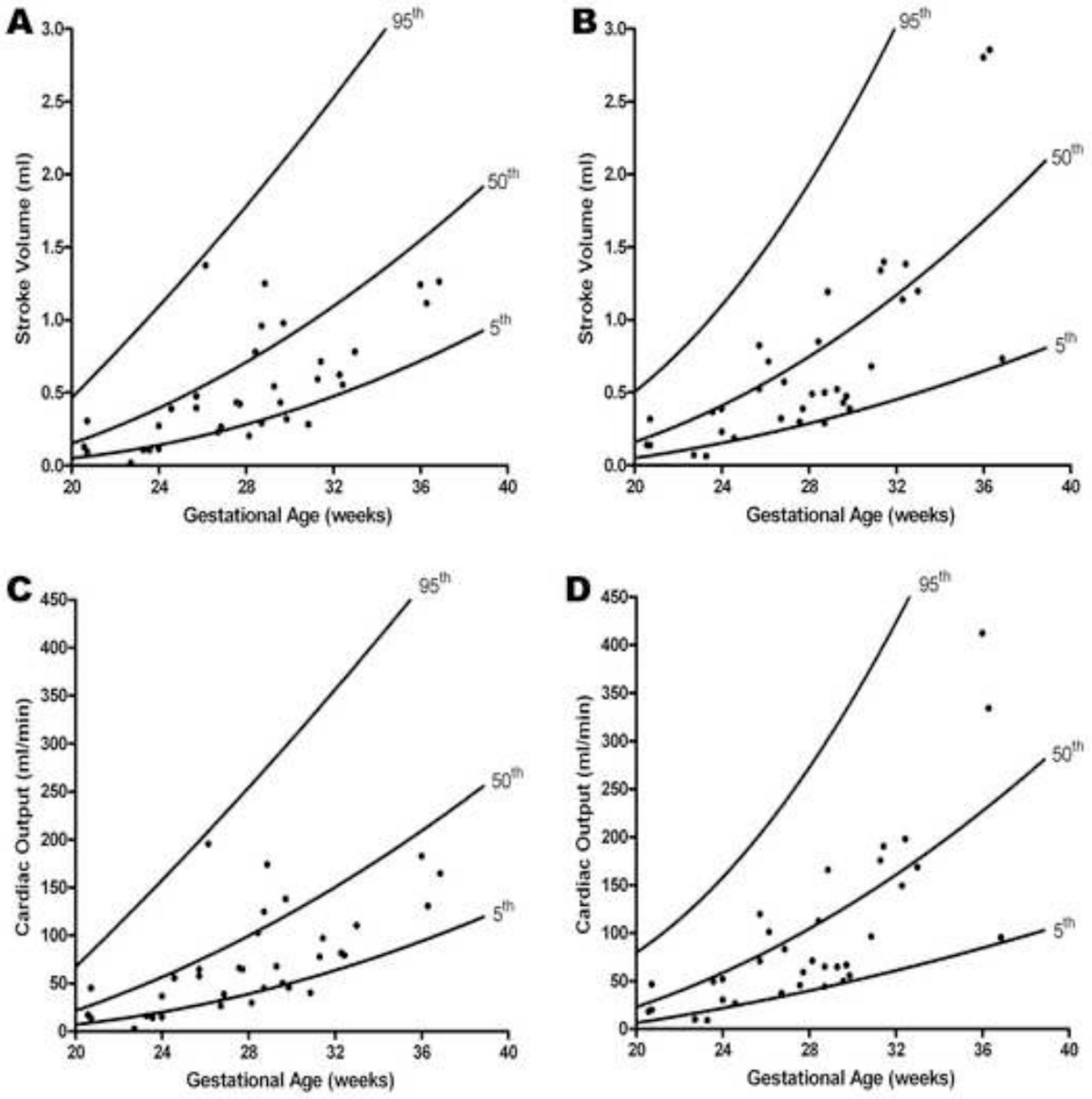

Figure 2. Stroke volume and cardiac output as a function of gestational age in the presence of increased placental vascular impedance to flow

Stroke volume (SV) and cardiac output (CO) calculations in fetuses with an umbilical artery pulsatility index > 95th percentile (ABN) were compared to 184 normal fetuses (NL)[40] (A: left ventricular SV; B: right ventricular SV; C: left ventricular CO; D: right ventricular CO). Mean SV (adjusted for gestational age) (mL) was lower for both the left ventricle (ABN: 0.53 vs. NL: 0.86; $p < 0.0001$) and right ventricle (ABN: 0.71 vs. NL: 0.92 ; $p < 0.0001$). Similarly, mean cardiac output (adjusted for gestational age) (mL/min) was lower for both

the left ventricle (ABN: 71.9 vs. NL: 119.6; $p < 0.0001$) and right ventricle (ABN: 96.0 vs. NL: 127.5; $p < 0.0001$)

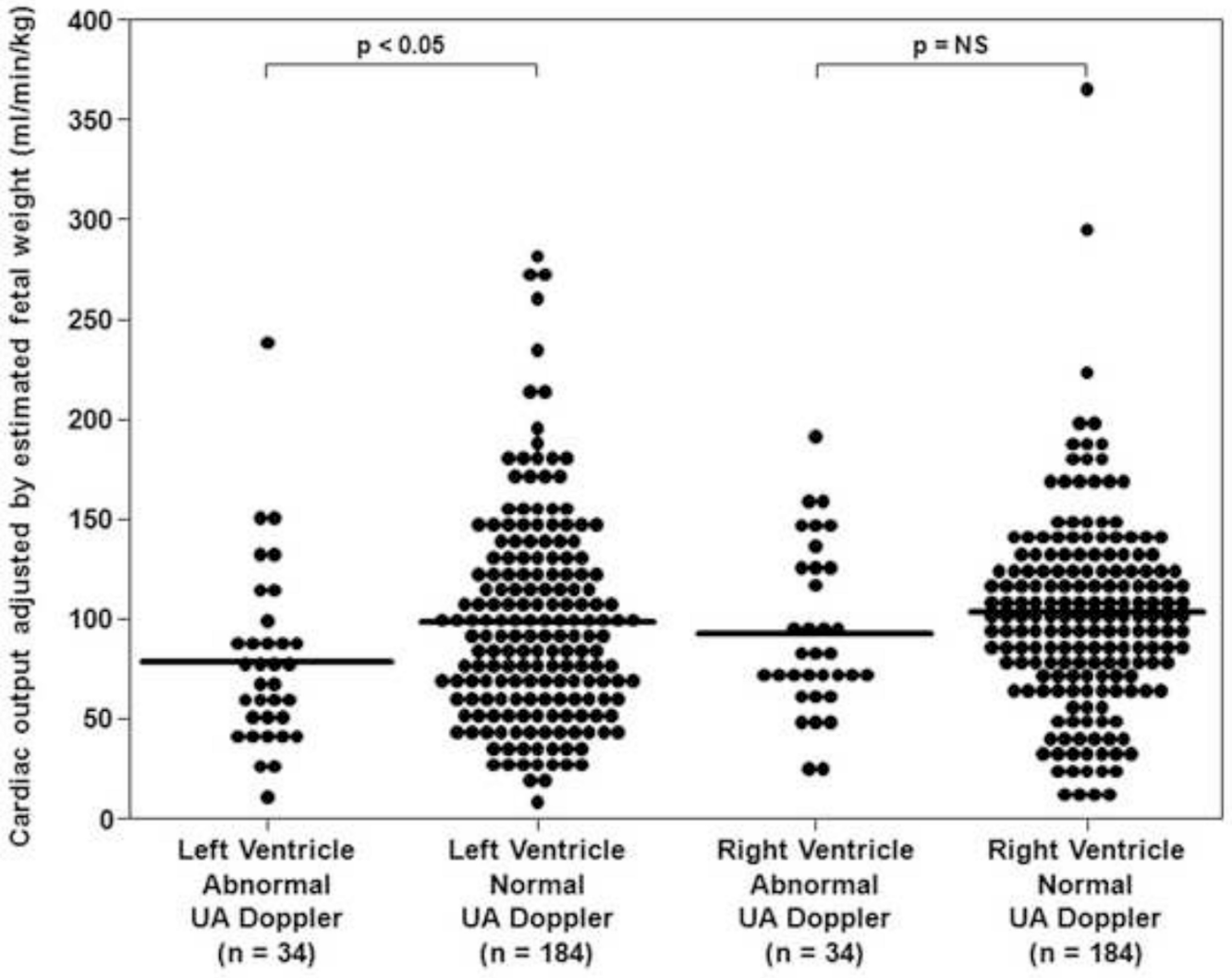

Figure 3. Cardiac output adjusted by estimated fetal weight of the left and right ventricles in the presence of increased placental vascular impedance to flow

Cardiac output adjusted for estimated fetal weight (EFW) in fetuses with an umbilical artery (UA) pulsatility index > 95th percentile (ABN) were compared to 184 normal fetuses (NL).[40] For the left ventricle, the median CO adjusted for EFW (mL/min/kg) was significantly lower in the presence of increased placental vascular impedance to flow (ABN: 67.8, IQR: 44.7 – 84.1 vs. NL: 90.0, IQR: 56.0 – 127.5; $p < 0.05$). However, for the right ventricle, the median CO adjusted for EFW (mL/min/kg) was not significantly different between ABN and NL groups (ABN: 77.4, IQR: 66.1 – 123.8 vs. NL: 99.9, IQR: 72.2 – 126.0; p = NS).

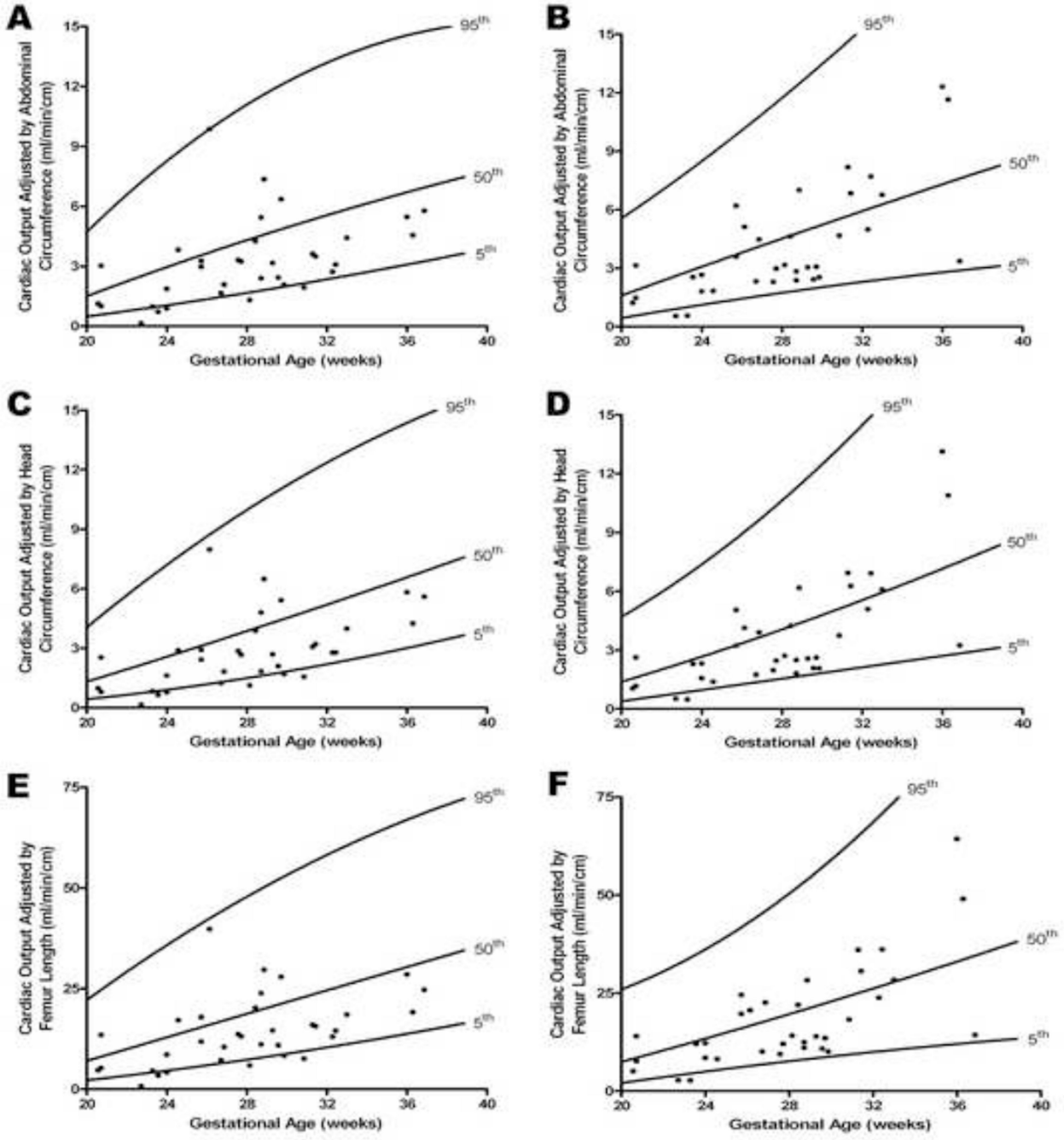

Figure 4. Cardiac output adjusted by fetal biometric parameters as a function of gestational age in the presence of increased placental vascular impedance to flow

Cardiac output (CO) obtained for left (A, C, E) and right (B, D, F) ventricles, divided by fetal biometric parameters: abdominal circumference [AC, cm; CO(AC)], head circumference [HC, cm; CO(HC)], and femoral diaphysis length [FL, cm; CO(FL)] in fetuses with an umbilical artery pulsatility index > 95th percentile (ABN) were compared to 184 normal fetuses (NL).[40] In the presence of increased placental vascular impedance to flow, values were significantly lower for the mean left CO(AC) (adjusted for gestational age) (mL/min/cm) (ABN: 3.2 vs. NL: 4.8; p = 0.0001), CO(HC) (adjusted for gestational

age) (mL/min/cm) (ABN: 2.8 vs. NL: 4.4; p< 0.0001), and CO(FL) (adjusted for gestational age) (mL/min/cm) (ABN: 14.2 vs. NL: 21.4; p = 0.0001). Similarly, values were significantly lower for the mean right CO(AC) (adjusted for gestational age) (mL/min/cm) (ABN: 4.1 vs. NL: 5.1; p < 0.0001), CO(HC) (adjusted for gestational age) (mL/min/cm) (ABN: 3.7 vs. NL: 4.7; p < 0.0001), and CO(FL) (adjusted for gestational age) (mL/min/cm) (ABN: 18.4 vs. NL: 22.6; p < 0.0001).

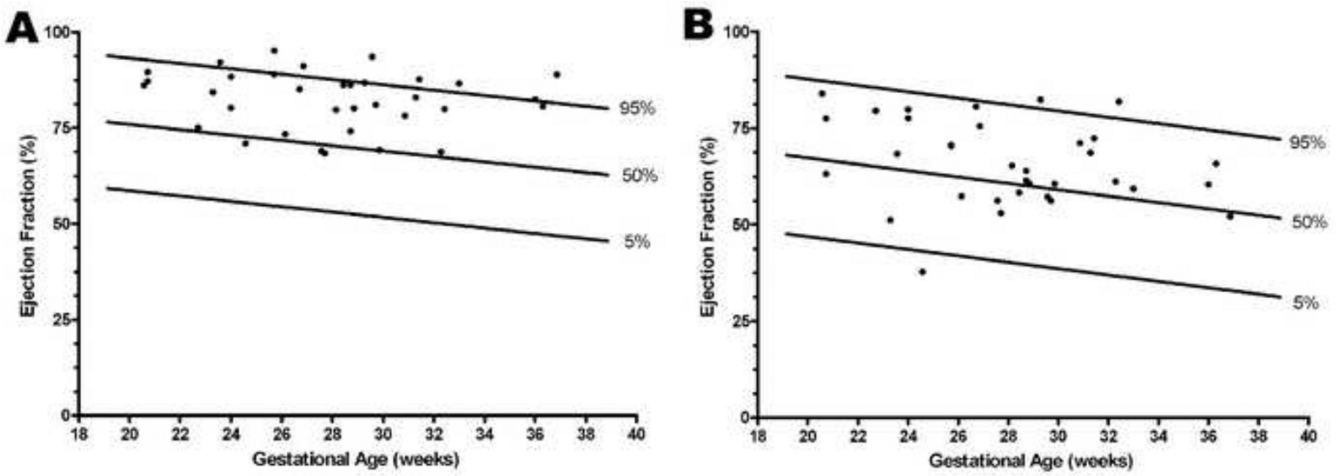

Figure 5. Ejection fraction as a function of gestational age in the presence of increased placental vascular impedance to flow

Ejection fraction (EF) in fetuses with an umbilical artery pulsatility index > 95th percentile (ABN) were compared to 184 normal fetuses (NL)[40] (A: left ventricular EF; B: right ventricular EF). Mean ejection fraction (adjusted for gestational age) (%) was significantly higher for both the left ventricle (ABN: 82.4 vs. NL: 70.4; $p < 0.0001$) and right ventricle (ABN: 66.0 vs. NL: 60.8; $p < 0.0001$).

Table 1

Clinical and sonographic characteristics of the study population (n = 34)

Parameter	Value
Clinical characteristics	
Gestational age at delivery (weeks)	31.6 (23.0 – 41.1)
Interval between acquisition of STIC datasets and delivery (days)	10 (1 – 133)
Birth weight (grams)	1000 (282 – 3750)
Term deliveries (≥ 37 weeks of gestation)	20% (7/34)
Preeclampsia	53% (18/34)
Perinatal death	18% (6/34)
Sonographic characteristics	
Gestational age at evaluation (weeks)	28.3 (20.6 – 36.9)
IUGR present	71% (24/34)
[a]Symmetrical IUGR	54% (13/24)
[b]Asymmetrical IUGR	46% (11/24)
HC < 10th percentile	50% (17/34)
Amniotic fluid index (mm)	67 (17 – 178)
UA end-diastolic velocity present	74% (25/34)
UA AEDV	20% (7/34)
UA REDV	6% (2/34)
MCA PI	1.7 (0.74 – 2.59)
[c]DV PIV	0.65 (0.24 – 3.06)
[c]DV (Reversed or absent a-wave)	7% (2/29)

AEDV, absent end-diastolic velocity; DV, ductus venosus; HC, head circumference;[67] IUGR, intrauterine growth restriction (defined as abdominal circumference < 5th percentile for gestational age); MCA, middle cerebral artery; PI, pulsatility index; PIV, pulsatility index for veins; REDV, reversed end-diastolic velocity; STIC, spatiotemporal image correlation; UA, umbilical artery.

[a]HC/AC < 95th percentile for gestational age[68]

[b]HC/AC > 95th percentile for gestational age[68]

[c]DV Doppler velocimetry results available in 29 cases

Data given as median (range) or %.

Table 2

Comparison of cardiovascular parameters between fetuses with an umbilical artery pulsatility index > 95th percentile (ABN) and normal controls (NL)

Cardiovascular parameter[a]	NL (95% CI)[b]	ABN (95% CI)[c]	Proportion Change[d]
Ventricular volume in end-systole (mL)			
Left	0.43 (0.4 – 0.5)	0.12 (0.02 – 0.2)	−72%
Right	0.65 (0.6 – 0.7)	0.39 (0.3 – 0.5)	−40%
Ventricular volume in end-diastole (mL)			
Left	1.28 (1.2 – 1.4)	0.64 (0.4 – 0.9)	−50%
Right	1.57 (1.5 – 1.7)	1.09 (0.8 – 1.3)	−30%
Stroke volume (mL)			
Left	0.86 (0.79 – 0.93)	0.53 (0.37 – 0.68)[e]	−38%
Right	0.92 (0.85 – 0.99)	0.71 (0.55 – 0.86)[e]	−23%
Cardiac output (mL/min)			
Left	119.6 (110 – 129)	71.9 (50 – 94)[e]	−40%
Right	127.5 (118 – 137)	96 (74 – 118)[e]	−25%
Cardiac output divided by HC (mL/min/cm)			
Left	4.4 (4.1 – 4.8)	2.8 (2.0 – 3.6)[e]	−36%
Right	4.7 (4.4 – 5.0)	3.7 (2.9 – 4.4)[e]	−21%
Cardiac output divided by AC (mL/min/cm)			
Left	4.8 (4.5 – 5.2)	3.2 (2.4 – 4.0)[e]	−33%
Right	5.1 (4.8 – 5.5)	4.1 (3.3 – 4.9)[e]	−20%
Cardiac output divided by FL (mL/min/cm)			
Left	21.4 (19.8 – 23.0)	14.2 (10.5 – 18.0)[e]	−34%
Right	22.6 (21.1 – 24.2)	18.4 (14.7 – 22.1)[e]	−19%
Ejection fraction (%)			
Left	70.4 (69 – 72)	82.4 (79 – 86)[e]	17%
Right	60.8 (59 – 63)	66 (62 – 70)[e]	9%

ABN, abnormal; AC, abdominal circumference; CI, confidence interval; FL, femoral diaphysis length; HC, head circumference; NL, normal

[a] Mean values adjusted for gestational age

[b] Data from Hamill N et al.[40]

[c] NL vs. ABN; $p < 0.0001$ (main effects ANCOVA)

[d] Proportion change calculated as [(1 – ABN/NL) × 100%]

[e] ABN right ventricle vs. ABN left ventricle for median stroke volume, cardiac output, cardiac output divided by HC, AC, FL, and ejection fraction; $p < 0.05$ for all, except $p < 0.001$ for ejection fraction (paired test)

Table 3

Comparison of fetal cardiovascular parameters between the left and right ventricles for fetuses with an umbilical artery pulsatility index > 95th percentile

Cardiovascular parameter	Left Ventricle	Right Ventricle	P value
Volume in end-systole (mL)	0.10 (0.03 – 0.17)	0.28 (0.16 – 0.55)	< 0.001
Volume in end-diastole (mL)	0.53 (0.29 – 0.91)	0.75 (0.5 – 1.52)	< 0.001
Stroke volume (mL)	0.43 (0.26 – 0.78)	0.5 (0.31 – 0.92)	< 0.05
Cardiac output (mL/min)	61.1 (34.9 – 104.9)	65.9 (45.3 – 127)	< 0.05
Cardiac output adjusted by EFW (mL/min/kg)	67.8 (44.7 – 84.1)	77.4 (66.1 – 123.8)	< 0.05
Cardiac Output adjusted by AC (mL/min/cm)	3.06 (1.82 – 4.3)	3.11 (2.36 – 5.39)	< 0.05
Cardiac Output adjusted by HC (mL/min/cm)	2.69 (1.48 – 3.91)	2.63 (1.94 – 5.06)	< 0.05
Cardiac Output adjusted by FL (mL/min/cm)	13.3 (7.5 – 18.7)	14.0 (10.1 – 24.0)	< 0.05
Ejection fraction (%)	83.7 (77.4 – 87.9)	64.7 (58.1 – 76)	< 0.001

Data given as group-level median (interquartile range); non-parametric comparisons were performed; median right to left ratios presented in the text were determined using ratios calculated within each fetus to account for the paired nature of these measures, and thus, are not consistent with the right to left ratios of the group level measures presented in this table.

AC, abdominal circumference; EFW, estimated fetal weight; HC, head circumference; FL, femoral diaphysis length