

Correlation between ductus venosus velocity and right ventricular diastolic function in fetuses with isolated single umbilical artery in third trimester

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Abstract

Background The cardiac diastolic functions in fetuses with isolated single umbilical artery (SUA) in the third trimester were evaluated using the spectrum of blood flow in the fetal ductus venosus (DV).

Methods Color Doppler was employed to visualize the spectra of the fetal DV and tricuspid orifice in 34 fetuses with isolated SUA aged 28–39 weeks and in age-matched healthy controls. The DV flow velocities and velocity ratios were measured. The E/A ratio at the tricuspid orifice and tissue Doppler Tei index of fetal right ventricular in the two groups were measured.

Results During the third trimester, the DV atrial systolic peak velocity “a” was lower in the isolated SUA group than in the control group ($P < 0.05$). The correlations between the velocity ratios and the E/A ratio at the tricuspid orifice in the two groups were analyzed, and the correlation between the v/D and E/A ratios was the best (R^2 of 0.520 in the isolated SUA group and 0.358 in the control group). The correlations between the velocity ratios and the tissue Doppler Tei index of fetal right ventricular in the two groups were analyzed, and the correlation between the PIV and tissue Doppler Tei index ratios was the best (R^2 of 0.865 in the isolated SUA group and 0.627 in the control group).

Conclusions In the isolated SUA group, the atrial systolic peak velocity “a” decreased, which might be related to changes in fetal cardiac functions. v/D was more closely related to the E/A ratio at the tricuspid valve and could be used to identify changes earlier in the isolated and healthy fetuses’ right ventricular diastolic functions. PIV was more closely related to the tissue doppler Tei index of fetal right ventricular and could be used to identify the isolated and healthy fetuses’ right ventricular overall functions.

Background

Normal umbilical cords contain two umbilical arteries and one umbilical vein. A single umbilical artery (SUA) is the most common malformation of the umbilical cord in which only one umbilical artery instead of two is present. SUA is a soft marker for chromosomal abnormalities, congenital structural malformations, and preterm birth. According to whether other structural malformations and/or karyotype abnormalities are present, SUA is divided into isolated SUA and non-isolated SUA, with the former accounting for approximately 65% of all SUA cases[1–3]. However, isolated SUA result in the development of certain obstetric complications, such as fetal growth restriction and increased perinatal mortality[4–7].

The presence of an isolated SUA can cause blood circulation disorder in the fetus and thus structural and functional changes of the fetal heart, affecting both maternal and fetal circulation[6, 8]. Existing studies indicate that in the fetal heart, diastolic function changes before systolic function[9]. Anatomically, the ductus venosus (DV) enters directly into the right atrium or is connected to the right atrium via the inferior vena cava (IVC). Right ventricular diastolic function in the fetus can be evaluated by the DV blood flow spectrum[10–12]. Currently, particle image velocimetry (PIV) is now clinically used as the major indicator for evaluating changes in the DV blood flow spectrum[12]. However, since there are four different stages

throughout the fetal cardiac cycle, including ventricular systole, ventricular diastole, atrial diastole, and atrial systole, DV is greatly affected by factors such as the cardiac cycle, volume, and pressure[13–14]. As a result, evaluating fetal cardiac functions using PIV alone may not be objective and accurate. Understanding the cardiac function changes in fetuses with isolated SUA in the third trimester helps assess the intrauterine conditions and perinatal outcomes in fetuses and right ventricular function in isolated SUA is altered as early as in fetal third trimester[15]. In this study, fetal DV flow velocities, flow velocity ratios, and the tricuspid orifice spectral parameters were used to evaluate changes of the right ventricular diastolic function in fetuses with isolated SUA in the third trimester, in an attempt to identify sensitive indicators for evaluating right ventricular diastolic function in fetuses with isolated SUA and thereby provide an objective basis for clinical practice.

Methods

Study subjects

We prospectively studied 34 fetuses from 28 to 39 weeks of gestational age with prenatally identified isolated SUA and 34 gestational age-matched healthy fetuses from the Gansu Provincial Maternity and Child-care Hospital between July 2017 and December 2018. The study protocol was approved by the Medical Ethics Committee of Gansu Provincial Maternity and Child-care Hospital ethics committee(No.2017-04), and the pregnant mothers provided their written informed consent. We excluded pregnant mothers with multiple gestations; pregnancies presenting associated fetal anomalies, including structural abnormalities, congenital heart disease, and abnormal karyotype; and pregnant mothers with conditions that may affect fetal hemodynamics, such as maternal diabetes, pre-eclampsia, preterm labor, or endocrinological disorders such as thyroid disease.

The diagnosis of isolated SUA was made or confirmed using color Doppler ultrasonography at the level of the fetal abdominal cord insertion by observing the absence of one of the two umbilical arteries (UAs) that normally encircle the fetal bladder. In all cases, the diagnosis of isolated SUA was confirmed by postnatal pathological examination, and all newborns were determined to be anatomically normal at delivery. The newborns were diagnosed as small-for-gestational-age (SGA) when their birth weight was below the 10th percentile for gestational age. Demographic data including maternal age, weight, height, body mass index, parity, and medical history were collected. Gestational age was calculated based on the first day of the last menstrual period and was confirmed by crown–rump length measurement at the first-trimester ultrasound scan.

Instruments and methods

E10 (GE Healthcare, USA) and EPIQ5 (Philips, Netherlands) ultrasound systems were used. Fetal biometric measurements were performed during each scan. The pregnant women were asked to lie in a supine position. The median sagittal section or oblique transection of the upper abdomen of the fetus was assessed, which clearly displayed the long axis of the umbilical vein and tracked it toward the head

of the fetus. Before the umbilical vein turned toward the left branch of the portal vein, a small tubular structure was shown to be connected to the IVC. After turning on the color Doppler function, the bright blood flow signals were identified as the DV blood flow (Figs. 1) and spectrum (Figs. 2a). Blood flow parameters including the ventricular systolic peak flow velocity (S), the ventricular late diastolic velocity (v), the ventricular diastolic peak flow velocity (D), and the atrial systolic peak velocity (a) were measured (Figs. 2a), and the velocity ratios including S/v, S/D, S/a, v/D, v/a, and D/a were calculated according to these parameters. During measurement, the sample volume was placed inside the DV to reduce the interference of the surrounding vessels. A four-chamber view of the fetus was obtained, and the sample volume was placed at the tip of the tricuspid valve to measure E peak and A peak blood flow velocities to calculate the E/A ratio (Figs. 2b).

Right ventricular overall function was evaluated using the tissue Doppler Tei index described by literature¹⁶. In a four-chamber view, the tissue Doppler sample volume was placed at the junction of the free wall of the right ventricle and the posterior leaflet of the tricuspid valve, the sample line was parallel to the direction of movement (angle <20 °), the tissue Doppler sample volume was 2mm, and the scanning speed was adjusted to 10-15cm / s to obtain tissue Doppler spectrum images to measure isovolumic contraction time (ICT), ejection time (ET) and isovolumic relaxation time (IRT). The tissue Doppler Tei index was calculated according to the measurement method (as shown in Figs. 3a), $Tei = (ICT + IRT) / ET$ (Figs. 3b). When the fetal position is not good, measure again after the fetus changes position. The above parameters were measured three consecutive times, and the average values were calculated.

Statistical analysis

The data analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the mean \pm SD or median (interquartile range), as appropriate. The independent sample t test was used for comparisons between groups, and $P < 0.05$ was considered statistically significant. Velocity ratios of DV with the E/A ratio at the tricuspid orifice and the tissue doppler Tei index of fetal right ventricular were analyzed using a linear regression, and the regression coefficient R^2 was calculated respectively.

Results

The color flow Doppler of the umbilical cords in all 34 healthy fetuses showed two umbilical arteries and one umbilical vein. The color flow Doppler of the umbilical cords in the 34 isolated SUA fetuses showed only one umbilical artery and one umbilical vein. Among the latter group, the left branch was absent in 20 cases, and the right branch was absent in 14 cases. One of the healthy fetuses (1/34) displayed tricuspid regurgitation (TR), whereas five of the fetuses in the isolated SUA group (5/34) had TR. TR was considered abnormal if holosystolic with a maximum velocity of more than 2 m/sec^[17]. In the control group, the fetal DV spectrum "a"-wave was a forward wave. In the isolated SUA group, the "a"-waves of 32 fetuses were forward, and the "a"-waves of two fetuses, both of which were SGA, were backward(Figs.

2c). A comparison of the blood flow parameters between the two groups showed that the DV atrial systolic peak velocity “a”-wave was lower in the isolated SUA group than in the control group ($P < 0.05$), whereas the PIV, S/v, S/D, S/a, v/D, v/a, D/a, and E/A ratios at the tricuspid orifice did not change significantly ($P > 0.05$) (Table 1). The correlations between the velocity ratios and the E/A ratio at the tricuspid orifice in the two groups were analyzed, and the correlation between the v/D and E/A ratios was the best in both groups (R^2 of 0.520 in the isolated SUA group and 0.358 in the control group) (Figs. 4a, b). The correlations between the velocity ratios and the tissue doppler Tei index of fetal right ventricular in the two groups were analyzed, and the correlation between the PIV and tissue doppler Tei index of fetal right ventricular was the best in both groups (R^2 of 0.865 in the isolated SUA group and 0.627 in the control group) (Figs. 4a, b). During follow-up of all fetuses until birth, the general conditions of the newborns at birth were analyzed, and the bodyweight and placental mass were compared between newborns of the two groups. The differences were statistically significant ($P < 0.05$). In the univariate analysis, the presence of an isolated SUA was associated with lower birth weight (2940 vs 3260 g) and with a higher prevalence of SGA (13.0% vs. 3.9%; $P < 0.01$). There was no statistically significant difference in the pregnant women’s age, gravidity and parity, and gestational age ($P > 0.05$) (Table 2).

Discussion

In fetuses, diastolic function changes before cardiac function. The fetal DV directly delivers the umbilical venous blood with high oxygen saturation through the IVC to the right atrium, the pressure of which is the major factor affecting DV blood flow[18]. Previous studies demonstrated that when dynamic changes in fetal heart blood flow lead to changes in right atrial pressure, this manifests as a change in the DV spectral blood flow parameters, most evidently PIV[19–20]. This study evaluated the relationship between the DV Doppler flow velocity ratios and right ventricular function.

The fetal DV spectral waveform is closely related to the four periods of the cardiac cycle[13]. The “S”-wave corresponds to ventricular systole, which is produced by an increase in the venous forward blood flow velocity caused by atrial diastole during ventricular systole and followed by the “v”-wave during end-systolic ventricular relaxation and the ascent of the atrioventricular (AV) valves before the onset of diastole. With the opening of the AV valves, the “D”- and “a”-waves correspond to early passive and late active diastolic filling, respectively. In particular, the highest velocity occurs at the “S”-wave and the lowest at the “a”-wave. The S/v ratio quantifies relative forward flow into the atria as the ventricle relaxes before the AV valves open. The v/D ratio reflects early diastolic filling immediately following this event. The D/a ratio is a diastolic parameter relating the magnitude of forward flow during passive and active diastolic filling; it is analogous to the E/A ratio but for the AV valves. Three ratios describe non-consecutive cardiac events: the S/D ratio quantifies ventricular systolic to early passive diastolic filling[13], the S/a ratio quantifies ventricular systolic to active diastolic filling[21], and the v/a ratio quantifies end-systolic relaxation and active diastolic filling. Existing studies have shown that the relative decrease in the “a”-wave is closely associated with the increase in PIV. Currently, PIV is used as the primary indicator for evaluating changes in the DV blood flow spectrum[22–24]. However, this study showed that in both

isolated SUA and healthy fetuses, the v/D ratio was significantly correlated with the E/A ratio at the tricuspid orifice. The E/A ratio can be used for evaluation of conventional Doppler fetal cardiac diastolic function[25]. The PIV ratio was significantly correlated with the tissue doppler Tei index of fetal right ventricular. The tissue doppler Tei index can be used for evaluation of fetal cardiac overall function. This suggests that when evaluating cardiac function using the DV spectrum, in addition to monitoring PIV, attention should be paid to the correlation between the “v” wave-related ratios and right ventricular function.

Previous studies noted that a decline in cardiac diastolic function is often observed as an increase in DV spectrum PIV, a decrease in “a”-wave velocity, and disappeared or reversed blood flow[22–23]. This may occur because subjects in previous studies were fetuses with significant changes in cardiac functions, including gestational hypertension, IUGR, and twin-to-twin transfusion syndrome[24–30]. In this study, all the fetal DV spectrum “a”-waves in the control group were forward and could be observed throughout the entire cardiac cycle, potentially because of the high resistance of the fetal DV venous system and the weak atrial systolic force. Consequently, the DV pressure in the entire cardiac cycle was always greater than the atrial pressure; thus, the blood was unable to flow in the reverse direction into the DV. In the isolated SUA group, however, the DV spectrum “a”-waves of two cases were backward, both of which were SGA fetuses. Reversal of the “a”-wave might indicate a decrease in ventricular compliance, which is caused by atrial systolic venous blood reflux resulting in increased atrial pressure²⁸. Therefore, close attention should be paid to whether the DV backward “a”-wave occurs; if so, maternal and fetal examinations should be enhanced and the pregnancy terminated if necessary. This study showed that the “a”-wave flow velocity was lower in fetuses with isolated SUA than in the controls. This might have occurred because fetuses with isolated SUA are more prone to low bodyweight at birth, resulting in decreased circulating blood volume and DV blood flow volume. Moreover, none of the DV blood flow parameters in the fetuses with isolated SUA changed significantly compared to the healthy controls. This might be explained as follows: although the fetuses with isolated SUA have dynamic changes in their blood flow in the absence of one umbilical artery, such changes are not enough to cause an insufficient blood supply, which can lead to increased right heart load and right atrial pressure and blocked DV reflux. In this study, one of the healthy controls (1/34) displayed TR, whereas five of the isolated SUA fetuses (5/34) had TR. Thus, the isolated SUA group had a slightly higher TR rate than the control group. Therefore, once isolated SUA is diagnosed, TR should be monitored to facilitate a preliminary determination of right ventricular function in the fetus.

Limitation

First, because atrial pressure is a major factor affecting the changes in DV blood flow, and both respiration and motion of the fetus can affect the DV spectrum, atrial pressure should preferably be measured with the fetus in a resting state. Second, mapping of the fetal DV spectrum can be easily affected by the adjacent blood vessels, particularly the vena cava. Because vena cava displays

continuous backward blood flow under normal circumstances of atrial systole, it can be easily misjudged as the DV spectrum.

Conclusion

Fetuses with isolated SUA are prone to low bodyweight at birth. Changes in the cardiac functions in fetuses with isolated SUA can be evaluated by the DV spectrum velocities and velocity ratios. When monitoring the DV spectrum, v/D and PIV can be used to earlier identify changes in the right ventricular function of isolated fetuses.

Declarations

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Availability of data and materials

The data and material in the current study are available from the corresponding author on reasonable request.

Authors' contributions

TL carried out image and participated in the design of the study and drafted the manuscript. FN participated in the design of the study. ZL conceived of the study and participated in its design, performed the statistical analysis. PQ participated in image acquisition and analysis. QL and YW participated in the design of the study and coordination. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethics Committee of Gansu Provincial Maternity and Child-care Hospital

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1 Comparison of the measured fetal DV blood flow velocities and velocity ratios between the two groups (\pm s)

	Isolated SUA group	Control group	<i>P</i> -value
S (cm/s)	32.8 \pm 14.0	34.9 \pm 14.3	0.552
v (cm/s)	22.6 \pm 9.4	24.1 \pm 9.8	0.508
D (cm/s)	26.7 \pm 12.0	28.2 \pm 11.6	0.600
a (cm/s)	13.0 \pm 7.1	17.5 \pm 7.4	0.013
PIV	0.81 \pm 0.33	0.73 \pm 0.34	0.310
S/v	1.48 \pm 0.30	1.47 \pm 0.30	0.816
S/D	1.26 \pm 0.20	1.24 \pm 0.15	0.778
S/a	2.37 \pm 0.79	2.13 \pm 0.77	.214
v/D	0.86 \pm 0.71	0.86 \pm 0.75	.921
v/a	1.61 \pm 0.48	1.44 \pm 0.41	.126
D/a	1.90 \pm 0.60	1.70 \pm 0.53	0.163
E/A	0.64 \pm 0.13	0.64 \pm 0.10	0.975

Abbreviations: SUA, single umbilical artery; PIV, particle image velocimetry

Table 2 Comparison of basic characteristics and clinical data between the two groups (\pm s)

	Isolated SUA group	Control group	<i>P</i> -value
Maternal weight (kg)	61.9 \pm 5.8	61.8 \pm 5.5	0.978
Body mass index (kg/m ²)	24.1 \pm 3.6	24.6 \pm 3.7	0.853
Maternal age (years)	27.7 \pm 5.2	27.5 \pm 4.5	0.382
Delivery at week	37.9 \pm 1.1	38.8 \pm 0.9	0.139
Birth weight (kg)	2.9 \pm 0.3	3.3 \pm 0.4	0.011
Placenta quality (kg)	461 \pm 59	523 \pm 62	0.000

Abbreviations: SUA, single umbilical artery

Figures

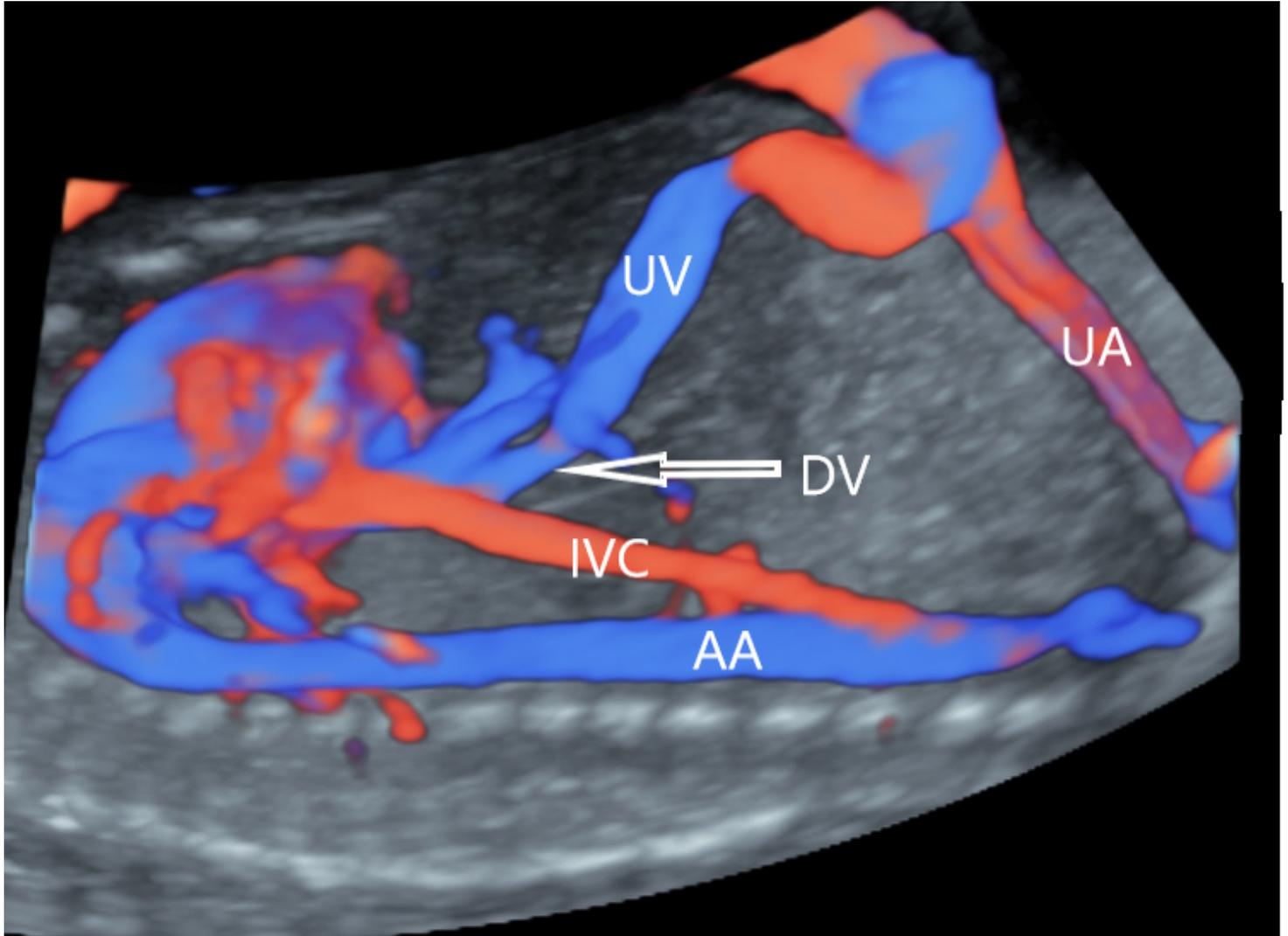


Figure 1

Sagittal view of the fetal chest and abdomen of a 28-week-old healthy fetus using color Doppler. The ductus venosus (DV) is directly connected to the umbilical vein and the inferior vena cava (IVC).

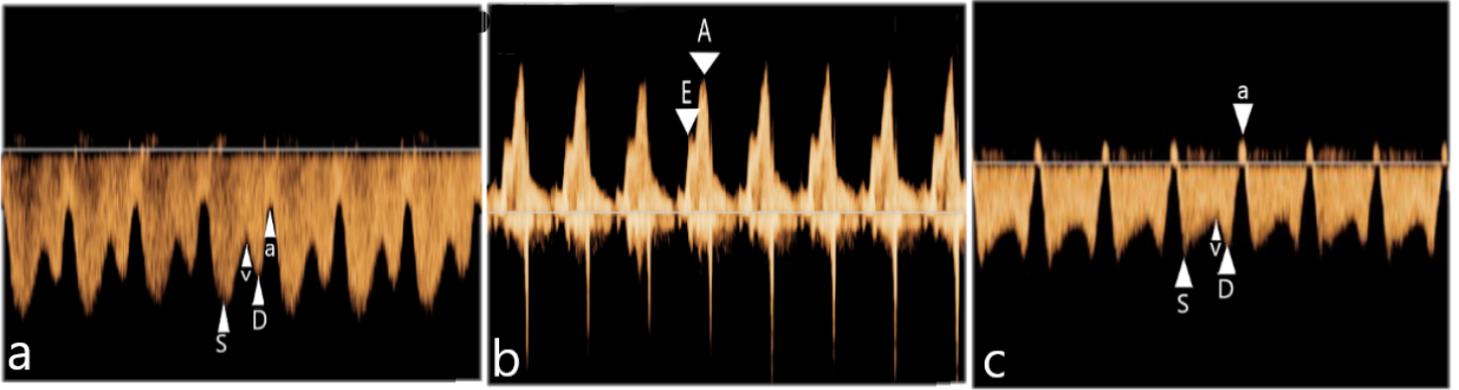


Figure 2

a Typical flow velocity waveform of the ductus venosus (DV). Including peak velocities during ventricular systole (S), end-systolic ventricular relaxation (v), early diastole (D), and atrial systole (a) were measured to calculate the velocity ratios. b From these waveforms, peak systolic velocity during early passive (E) and late active (A) ventricular filling was measured to calculate the E/A ratio for the tricuspid valve; c DV velocimetry of isolated SUA fetuses with SGA. The ductus venosus (DV) spectrum “a”-waves were backward.

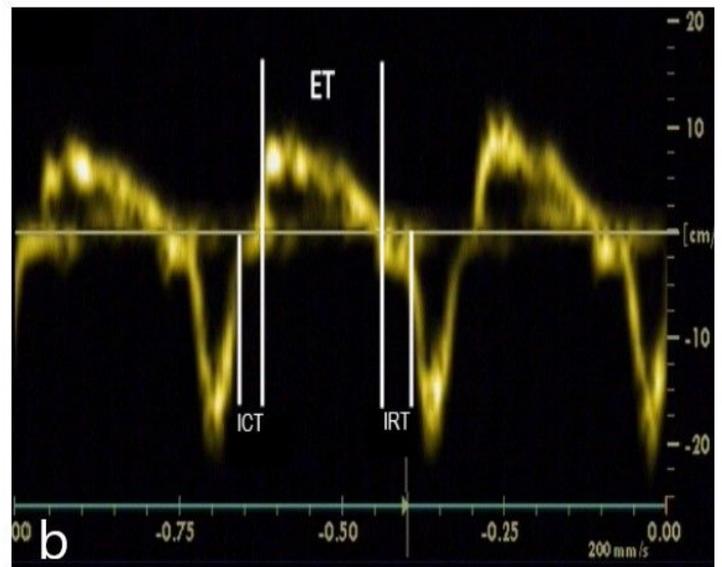
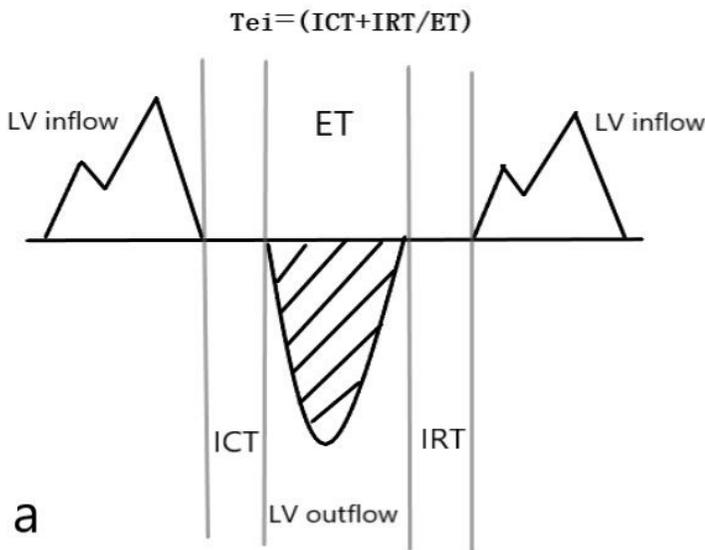


Figure 3

a Tissue Doppler Tei index measurement model of fetal left ventricular, isovolumetric contraction time (ICT), ejection time (ET) and isovolumetric relaxation time (IRT); b Doppler Tei index measurement of fetal left heart tissue, Tei index = (ICT + IRT / ET)

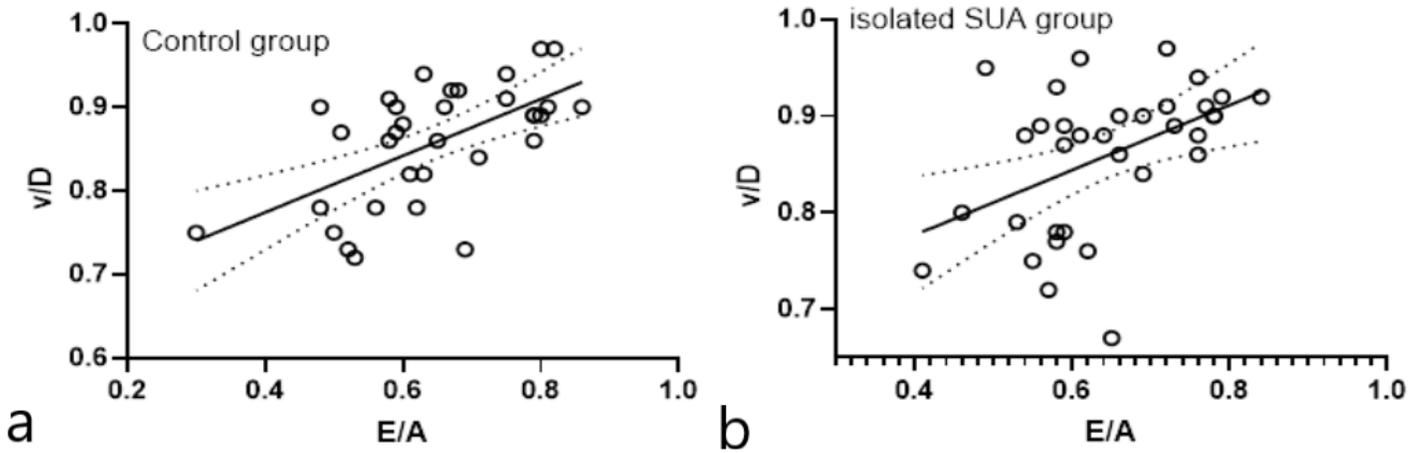


Figure 4

Scatterplots, with isolated SUA group and control group of the correlations between the v/D and the E/A ratio: (Control) ($R^2 = .358$); and (isolated SUA) ($R^2 = .520$)

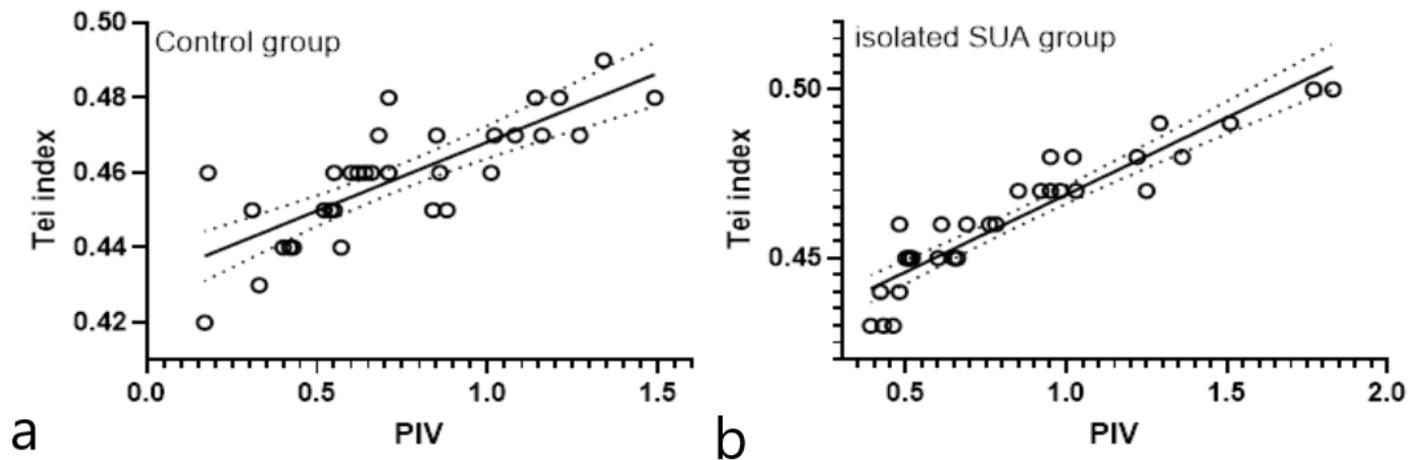


Figure 5

Scatterplots, with isolated SUA group and control group of the correlations between the PIV and the Tei Index: (Control) ($R^2 = .627$); and (isolated SUA) ($R^2 = .865$)

Supplementary Files

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