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Heart stroke volume and cardiac output by four-dimensional ultrasound in normal fetuses

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KEYWORDS: 4D ultrasound; fetal cardiac output; fetal stroke volume; STIC; VOCAL

ABSTRACT

Objective *To establish reference intervals for fetal heart stroke volume and cardiac output with gestation.*

Methods *Fetal heart ventricular volumes were measured using the four-dimensional (4D) spatiotemporal imaging correlation (STIC) ultrasound technique in 140 normal singleton pregnancies at 12–34 weeks' gestation. The Virtual Organ Computer-aided AnaLysis (VOCAL) technique was used to obtain a sequence of six sections of each ventricular volume in systole and diastole. Each volume was obtained after a 30° rotation from the previous one around a fixed axis extending from the apex of the heart to the point that divides symmetrically each atrioventricular valve. The contour of each ventricle was drawn manually and the 4D volumes of the left and right ventricle in systole and diastole were estimated. The stroke volume for each ventricle was then calculated by subtracting the one in systole from the one in diastole and the cardiac output was calculated by multiplying the stroke volume by the fetal heart rate. In 50 cases the stroke volumes were measured by the same sonographer twice and the intraobserver agreement of measurements was calculated.*

Results *The left and right stroke volume and cardiac output increased exponentially with gestation, from respective mean values of 0.02 mL, 0.01 mL, 2.39 mL/min and 1.80 mL/min at 12 weeks to 0.30 mL, 0.32 mL, 43.46 mL/min and 46.72 mL/min at 20 weeks, and 2.07 mL, 2.67 mL, 284.71 mL/min and 365.99 mL/min at 34 weeks. The ratio of right to left stroke volume increased significantly with gestation from about 0.97 at 12 weeks to 1.13 at 34 weeks. In the Bland–Altman test, the mean percentage difference and 95% limits of intraobserver agreement for left stroke volume and right stroke volume were −2.1 (−18.4, 14.2)% and −0.8 (−16.4, 18.0)%, respectively.*

Conclusions *In normal fetuses the stroke volume and cardiac output increase between 12 and 34 weeks' gestation. The extent to which, in pathological pregnancies, possible deviations in these measurements from normal prove to be useful in the prediction of outcome remains to be determined. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Assessment of fetal cardiac output has relied on the ultrasonographic measurement of ventricular dimensions during systole and diastole or measurement of the cross-sectional area of the outflow tracts and the flow velocity waveforms obtained by pulsed Doppler ultrasound across these vessels[1–3]. The ventricular volumes at the end of systole and the end of diastole were estimated from either the data obtained by M-mode echocardiography or the cross-sectional endocardiac perimeter in sections obtained by two-dimensional (2D) ultrasound at the level of the four-chamber projection of the fetal heart. These measurements were then used to estimate volumes with formulae that assume that the heart has the shape of an ellipsoid[1,2]. In the Doppler technique, the inner diameters in systole of the aortic valve annulus and pulmonary valve annulus are measured and the cross-sectional areas of the vessels are calculated. Doppler velocity waveforms are then obtained with the pulsed sample volume positioned just distal to the valve in the center of each vessel. The left and right stroke volumes are derived by multiplying the cross-sectional area of the aorta and pulmonary artery, respectively, by the time velocity integral of the Doppler waveform obtained from each vessel[3]. However, the validity of these estimates has been questioned because the repeatability of cross-sectional M-mode, B-mode and Doppler echocardiographic measurements is poor[4].

In adults quantitative three-dimensional (3D) echocardiography has been successfully used to measure ventricular volume and function. Comparative studies with

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cardiac magnetic resonance imaging, which is considered to be the gold standard for volume estimation, have shown that 3D echocardiography is more accurate than 2D echocardiography[5,6]. Similarly, in the fetus measurements of heart volume by 3D ultrasonography have been shown to be more reproducible than those estimated by 2D ultrasonography[7].

In two studies 3D ultrasound was used to measure ventricular function in fetuses by comparing the volume in systole with that in diastole[8,9]. In these studies, which were performed before the introduction of the spatiotemporal image correlation (STIC) technique, spatial orientation was provided by an electromagnetic position sensor attached to the ultrasound transducer. In the first study, the Doppler signals obtained from the outflow tracts were used to define the cardiac cycle and thereby select the appropriate images for the calculation of volume in systole and diastole, respectively. Meyer-Wittkopf *et al.* examined fetuses at 18–36 weeks' gestation and reported that in nine fetuses with cardiac defects characterized by inequality in ventricular size, such as hypoplastic left heart or tricuspid atresia, the combined stroke volume of both ventricles was significantly lower than in 29 normal fetuses and in 13 with cardiac defects that do not produce inequality in the ventricles, such as atrioventricular septal defects[8]. In the second study, a series of 3D images were obtained and offline analysis was used to examine the position of the ventricular walls and valves and thereby select the appropriate images corresponding to systole and diastole. The authors reported that in 25 fetuses examined at 16–26 weeks' gestation the end-diastolic volume and end-systolic volume of the ventricles increased with gestation[9].

The recent addition of time-domain STIC to 3D ultrasound has made it possible to obtain and display 3D cardiac data in real time, and many studies have reported on the use of the STIC technique to assess the anatomy of the fetal heart[10–12]. STIC has also been used to validate the results of an *in-vitro* study in which a balloon of known volume is inflated and deflated at regular intervals to simulate the cardiac cycle[13].

The aim of this study was to use four-dimensional (4D) ultrasound with STIC to establish reference intervals for the right and left fetal heart stroke volume and cardiac output between 12 and 32 weeks of gestation.

METHODS

Fetal heart ventricular volumes were measured using 4D ultrasound in 140 normal singleton pregnancies at 12–34 weeks' gestation. The inclusion criteria were uncomplicated singleton pregnancy with normal fetal anatomy and growth demonstrated by ultrasound examination, and gestational age defined by a known date of last menstrual period and confirmed by fetal crown–rump length at a first-trimester scan.

Several 4D volumes of the fetal heart were acquired by sonography using a motorized convex transabdominal transducer (RAB 4–8-MHz probe, Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA) and the data were processed by a sonography system capable of performing the STIC technique. First, the 2D settings were adjusted in order to obtain clear visualization of the internal limits of the heart. We aimed to acquire the volume when the fetus was not moving and the apex of the heart was towards the transducer, which was held over the transverse plane of the fetal heart at the level of the standard four-chamber view. The acquisition time was 7.5–12.5 s, depending on fetal motion, and the sweep angle varied according to the size of the fetal heart, from 20° in the first and second trimesters to 30° in the third trimester. The volumes with clear internal limits and no artifacts were then selected for further evaluation.

Virtual Organ Computer-aided AnaLysis (VOCAL) was used to obtain a sequence of six sections of each ventricular volume around a fixed axis in systole (minimum diameter of the ventricle when the atrioventricular valves are closed) and in diastole (maximum diameter of the ventricle when the atrioventricular valves are closed). The starting point of rotation was the four-chamber view of the heart, and each volume was obtained after a rotation of 30° from the previous one around a fixed axis extending from the apex of the heart to the point that divides symmetrically each atrioventricular valve.

The inner contour of each ventricle in each plane was drawn manually after appropriate post processing brightness/contrast adjustment, with the settings in gray chroma map number 2 (Voluson 730 Expert Operation Manual, GE Medical Systems, Milwaukee, WI, USA), and the 4D volumes of the left and right ventricle in systole and diastole were estimated (Figure 1). The stroke volume for each ventricle was then calculated by subtracting the one in systole from the one in diastole and the cardiac output was calculated by multiplying the stroke volume by the fetal heart rate. Every measurement was done offline after the scan by the same operator, and the average time needed to get the stroke volume in both ventricles was 15 min.

In 50 randomly selected cases (15 before 20 weeks, 20 at 20–25 weeks and 15 at 26–34 weeks), the stroke volume in both ventricles was measured by the same sonographer twice in order to compare the measurements and calculate intraobserver agreement.

Statistical analysis

Regression analysis was used to determine the significance of association of the right and left stroke volumes and cardiac output with gestational age. The best fit to the means of the natural logarithms of these parameters was calculated using cubic regression equations. The construction of normal ranges was done as previously described[14]. Briefly, the appropriate regression curve was calculated for the relationship of left stroke volume, right stroke volume and cardiac output with gestational age; the distribution of the scaled absolute residuals was examined and the standard deviations were calculated. The 5^{th} and 95^{th} centiles were calculated as mean $\pm$ 1.645 SD. To validate the model for each parameter, the values of volumes were expressed as Z-scores ((actual

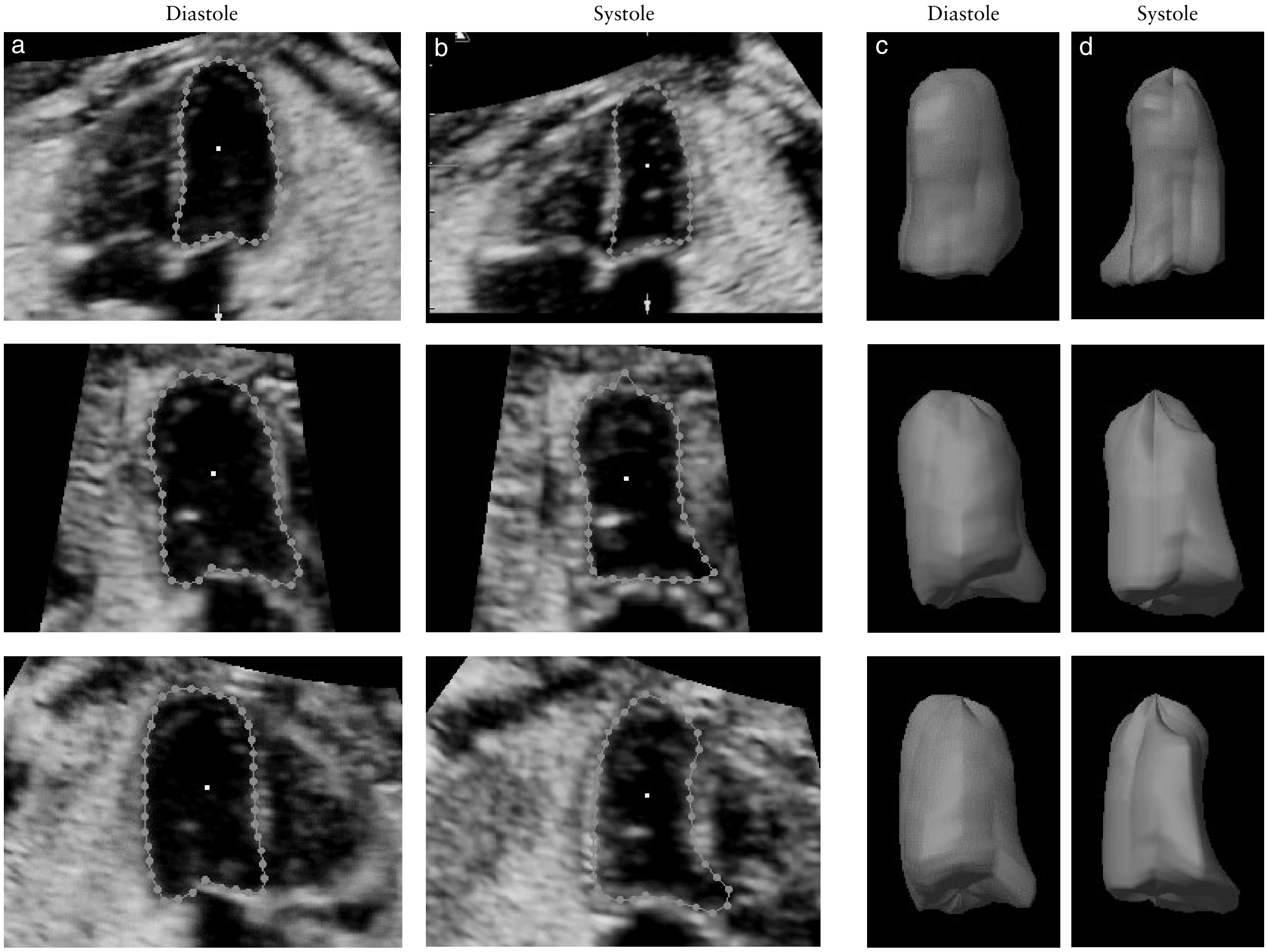

Figure 1 Three-dimensional ultrasound images of three different sections of the left ventricle in diastole (a) and systole (b) and the cardiac volumes deduced from them using VOCAL (Virtual Organ Computer-aided AnaLysis) (c and d, respectively).

value – estimated mean for gestation)/estimated SD for gestation). The Kolmogorov–Smirnov test confirmed a normal distribution of the *Z*-scores, and therefore the goodness of fit of each model. Bland–Altman analysis was used to compare the measurement agreement and bias for a single examiner[15]. The data were analyzed using the statistical software package SPSS 14.0 (SPSS Inc., Chicago, IL, USA) and Excel for Windows 2003 (Microsoft Corp., Redmond, WA, USA). A value of $P < 0.05$ was considered statistically significant.

RESULTS

The mean left and right stroke volume and cardiac output increased exponentially with gestation, from respective mean values of 0.02 mL, 0.01 mL, 2.39 mL/min and 1.80 mL/min at 12 weeks to 0.30 mL, 0.32 mL, 43.5 mL/min and 46.72 mL/min at 20 weeks, and 2.08 mL, 2.67 mL, 284.70 mL/min and 365.98 mL/min at 34 weeks. The ratio of right to left stroke volume increased significantly with gestation from about 0.97 at 12 weeks to 1.13 at 34 weeks (Figures 2 and 3; Table 1).

The natural logarithm of the left and right stroke volume, left and right cardiac output and total cardiac output were described by the equations:

$$\ln(\text{left stroke volume}) = -12.662 + (0.136 \times \text{GA}) - (4.715 \times 10^{-4} \times \text{GA}^2) - (5.597 \times 10^{-7} \times \text{GA}^3)$$

$(r = 0.966, P < 0.0001)$;

$$\ln(\text{right stroke volume}) = -15.980 + (0.199 \times \text{GA}) - (8.567 \times 10^{-4} \times \text{GA}^2) + (1.329 \times 10^{-6} \times \text{GA}^3)$$

$(r = 0.966, P < 0.0001)$;

$$\ln(\text{left cardiac output}) = -7.632 + (0.138 \times \text{GA}) - (4.860 \times 10^{-4} \times \text{GA}^2) + (5.936 \times 10^{-7} \times \text{GA}^3)$$

$(r = 0.964, P < 0.0001)$;

$$\ln(\text{right cardiac output}) = -10.950 + (0.201 \times \text{GA}) - (0.001 \times \text{GA}^2) + (1.363 \times 10^{-6} \times \text{GA}^3)$$

$(r = 0.964, P < 0.0001)$; and

$$\ln(\text{total cardiac output}) = -8.557 + (0.168 \times \text{GA}) - (6.768 \times 10^{-4} \times \text{GA}^2) + (9.763 \times 10^{-7} \times \text{GA}^3)$$

$(r = 0.969, P < 0.0001)$, where GA is gestational age in days.

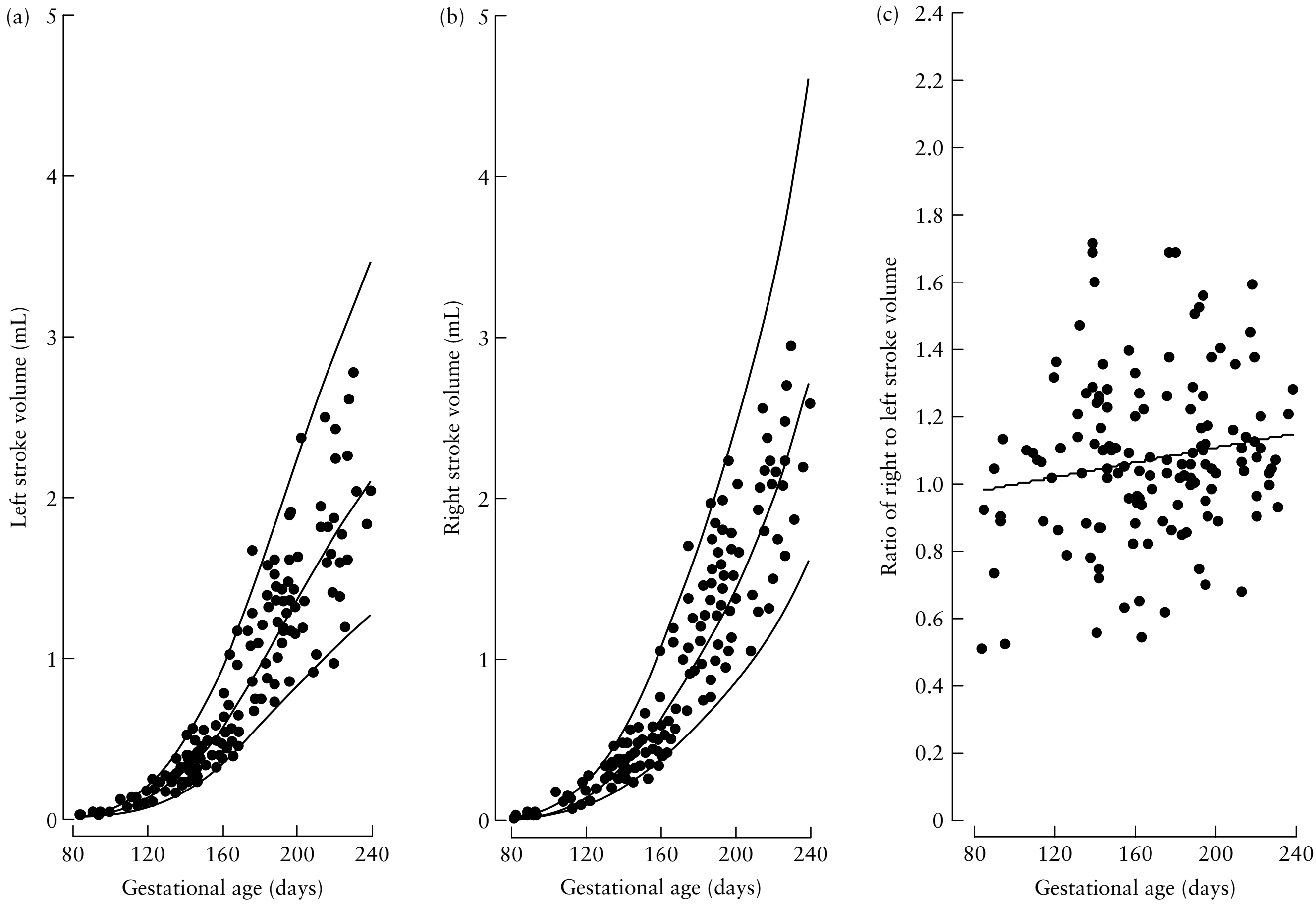

Figure 2 Mean and 90% reference intervals of left (a) and right (b) fetal ventricular stroke volume and the ratio of right to left stroke volume (c) with gestation.

Table 1 Mean (5th, 95th centiles) of left and right stroke volume and left and right cardiac output with gestation

Gestational age (weeks)	*Left stroke volume (mL)*	*Right stroke volume (mL)*	*Left cardiac output (mL/min)*	*Right cardiac output (mL/min)*
12	0.02 (0.01, 0.03)	0.01 (0.01, 0.02)	2.39 (1.45, 3.92)	1.80 (1.01, 3.21)
13	0.02 (0.02, 0.04)	0.02 (0.01, 0.03)	3.80 (2.31, 6.25)	3.15 (1.78, 5.58)
14	0.04 (0.02, 0.06)	0.03 (0.02, 0.06)	5.86 (3.57, 9.64)	5.24 (2.98, 9.22)
15	0.06 (0.04, 0.09)	0.05 (0.03, 0.09)	8.78 (5.34, 14.43)	8.33 (4.76, 14.56)
16	0.08 (0.05, 0.14)	0.08 (0.05, 0.14)	12.75 (7.76, 20.97)	12.68 (7.30, 22.02)
17	0.12 (0.07, 0.20)	0.12 (0.07, 0.21)	18.02 (10.96, 29.62)	18.54 (10.75, 31.98)
18	0.17 (0.10, 0.27)	0.18 (0.10, 0.30)	24.78 (15.08, 40.73)	26.10 (15.23, 44.72)
19	0.22 (0.14, 0.37)	0.24 (0.14, 0.40)	33.22 (20.21, 54.60)	35.48 (20.84, 60.41)
20	0.30 (0.18, 0.48)	0.32 (0.19, 0.54)	43.45 (26.44, 71.42)	46.72 (27.63, 79.02)
21	0.38 (0.23, 0.62)	0.41 (0.24, 0.69)	55.54 (33.79, 91.28)	59.75 (35.57, 100.38)
22	0.48 (0.29, 0.78)	0.51 (0.31, 0.87)	69.44 (42.25, 114.13)	74.42 (44.59, 124.19)
23	0.59 (0.36, 0.97)	0.63 (0.37, 1.06)	85.04 (51.74, 139.77)	90.52 (54.60, 150.06)
24	0.72 (0.44, 1.17)	0.76 (0.45, 1.27)	102.12 (62.13, 167.85)	107.83 (65.48, 177.59)
25	0.85 (0.52, 1.39)	0.89 (0.53, 1.50)	120.41 (73.26, 197.91)	126.16 (77.12, 206.40)
26	0.99 (0.61, 1.62)	1.03 (0.61, 1.74)	139.58 (84.92, 229.41)	145.38 (89.45, 236.27)
27	1.14 (0.69, 1.86)	1.18 (0.70, 1.99)	159.24 (96.89, 261.73)	165.46 (102.49, 267.13)
28	1.28 (0.79, 2.10)	1.34 (0.79, 2.25)	179.04 (108.93, 294.26)	186.51 (116.29, 299.13)
29	1.43 (0.88, 2.34)	1.50 (0.89, 2.53)	198.61 (120.84, 326.43)	208.82 (131.07, 332.69)
30	1.58 (0.96, 2.58)	1.69 (1.00, 2.84)	217.65 (132.42, 357.72)	232.86 (147.13, 368.55)
31	1.71 (1.05, 2.80)	1.88 (1.12, 3.17)	235.91 (143.53, 387.73)	259.37 (164.97, 407.79)
32	1.84 (1.13, 3.01)	2.11 (1.25, 3.55)	253.21 (154.06, 416.18)	289.36 (185.27, 451.93)
33	1.97 (1.20, 3.21)	2.37 (1.41, 3.98)	269.48 (163.96, 442.91)	324.25 (208.99, 503.08)
34	2.08 (1.27, 3.40)	2.67 (1.59, 4.50)	284.70 (173.22, 467.93)	365.98 (237.45, 564.09)

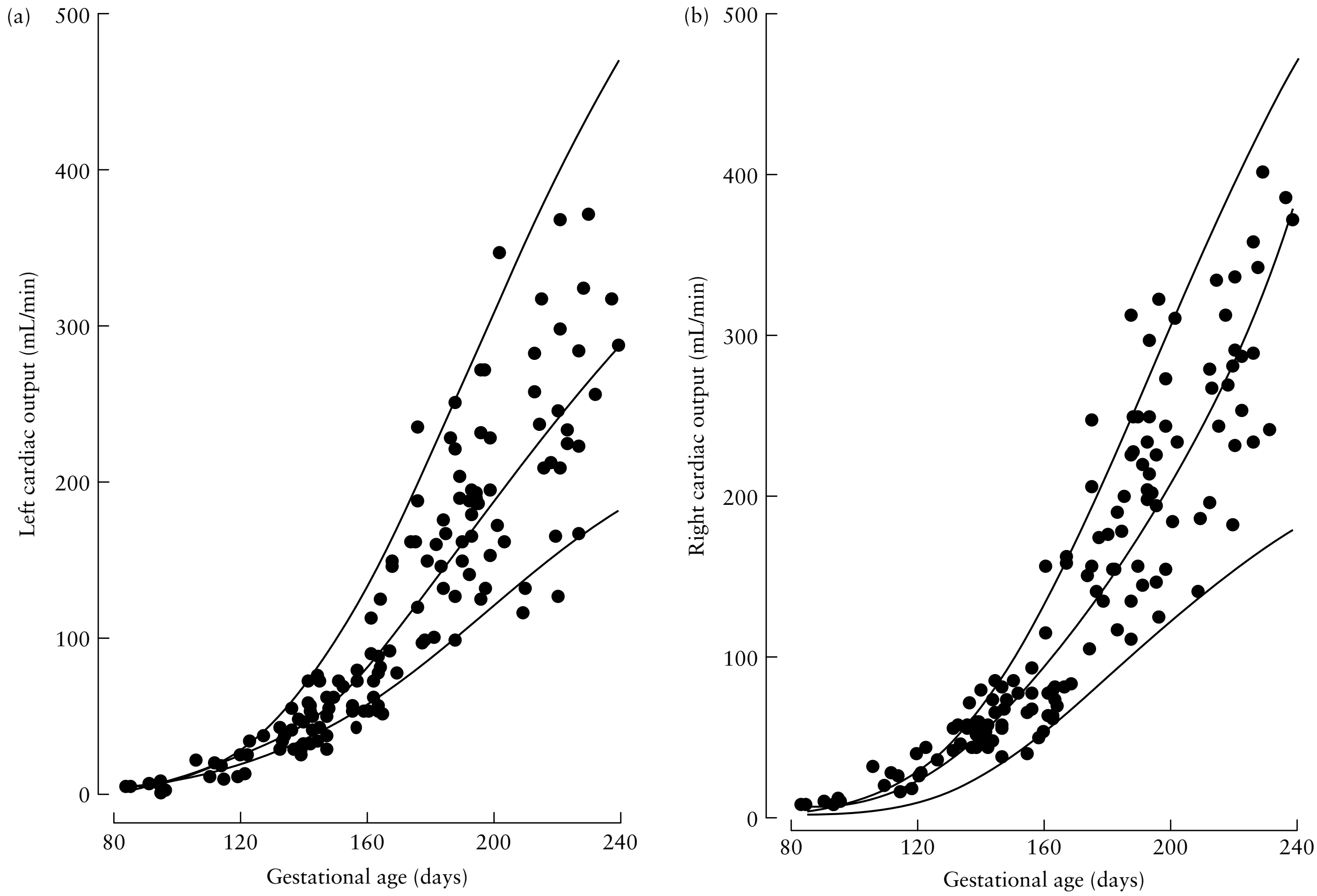

Figure 3 Mean and 90% reference intervals of left (a) and right (b) fetal cardiac output with gestation.

The scaled absolute residuals for the natural logarithms of the left and right stroke volume, left cardiac output and total cardiac output did not change significantly with gestational age and therefore the standard deviations of the corresponding residuals (0.299, 0.317, 0.302 and 0.284) were used to calculate the 5^{th} and 95^{th} centiles. The SD for the natural logarithm of the right cardiac output decreased with time according to the equation: SD = 0.491 − 0.001 × GA ($r = 0.190$, $P = 0.026$). The mean, 5^{th} and 95^{th} centiles for the actual measurements were calculated after exponentiation. The goodness-of-fit of the five models was validated after checking for normality of the corresponding standardized residuals (Kolmogorov–Smirnof test, $P = 0.920$ for left stroke volume, $P = 0.629$ for right stroke volume, $P = 0.678$ for left cardiac output, $P = 0.589$ for right cardiac output and $P = 0.687$ for total cardiac output). In the Bland–Altman plot the mean percentage difference and 95% limits of intraobserver agreement for left and right stroke volumes were −2.1 (−18.4, 14.2)% and −0.8 (−16.4, 18.0)%, respectively (Figure 4).

DISCUSSION

This study demonstrates the feasibility of utilizing 4D ultrasound with STIC to measure the volume of the left and right ventricles in systole and diastole and thereby estimate the fetal stroke volume and cardiac output. As already mentioned, we found that both left and right cardiac outputs increase with gestation from respective mean values of about 2.4 mL/min and 1.8 mL/min at 12 weeks to 285 mL/min and 366 mL/min at 34 weeks. The ratio of right to left cardiac output and stroke volume increased with gestation from about 0.97 at 12 weeks to 1.13 at 34 weeks.

The benefit of our method is that it avoids the geometric assumptions made in the 2D methods for estimating ventricular volume. The advantages of the VOCAL technique are firstly, during the drawing of the planes the whole ventricle is visualized simultaneously, and secondly, after the initial calculation of the ventricular volume it is possible to modify the contour in each plane so that we are able to adapt more accurately the drawn contour with the volume that we are measuring. The prerequisites for measuring stroke volume are acquisition of the volume with the fetus facing the transducer in the absence of fetal movements and accurate definition of each chamber when drawing the contours.

Limitations for the acquisition of the volumes are maternal obesity and breathing movements, fetal movements and fetal position. In addition, in the first trimester because of the small volume of the ventricles the reproducibility of the VOCAL technique was poor. In the third trimester the fetus is often in a spine-up position,

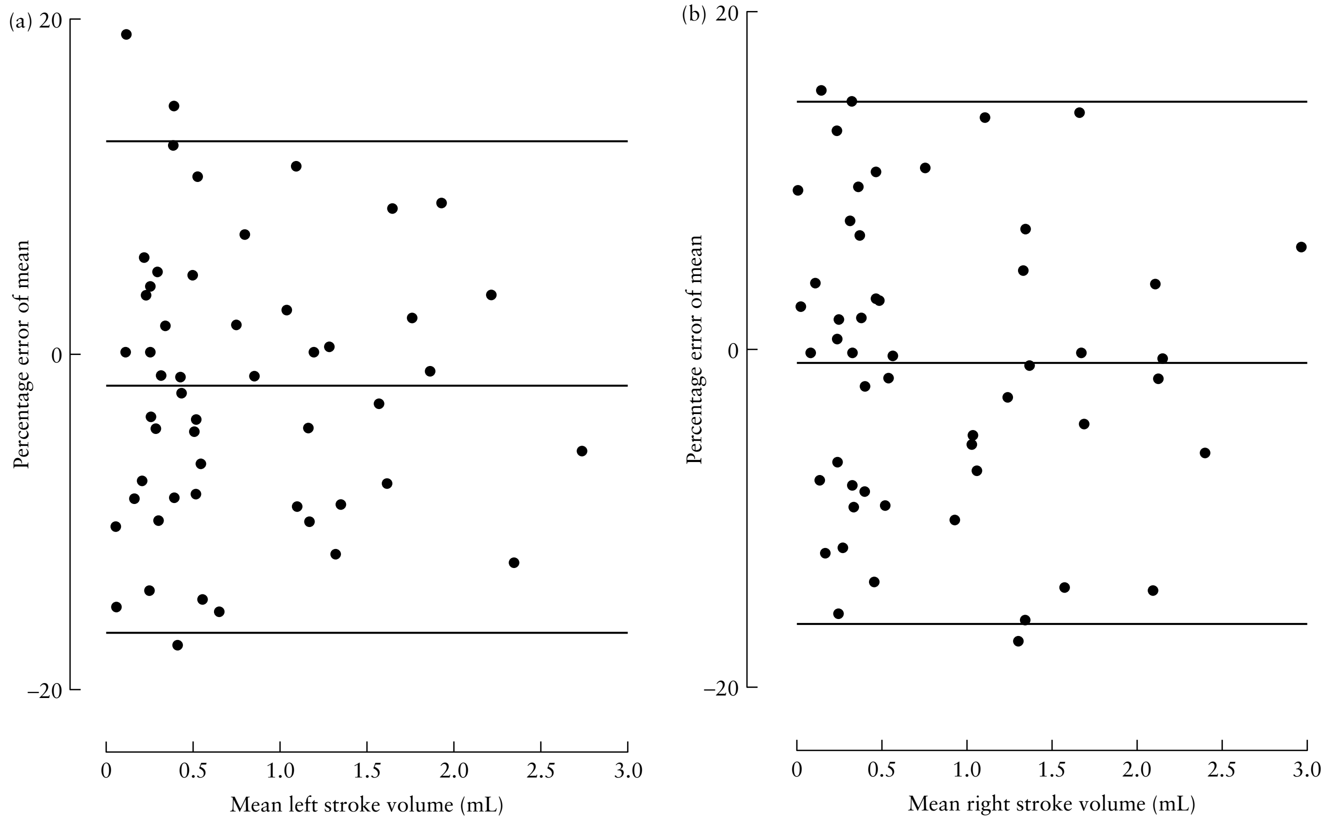

Figure 4 Bland–Altman plots of the mean percentage difference and 95% limits of agreement between paired measurements by the same sonographer of the left (a) and right (b) stroke volume.

Table 2 Fetal cardiac output in previous studies using two-dimensional ultrasound in comparison with the results of the present study

		Left cardiac output (mL/min)			*Right cardiac ouput (mL/min)*		
Reference	*Method of measurement*	*16 weeks*	*24 weeks*	*34 weeks*	*16 weeks*	*24 weeks*	*34 weeks*
Mielke & Benda (2001)[3]	Vessel area & TVI	20	125	380	30	175	575
Allan *et al*. (1987)[16]	Vessel area & TVI	33	127	409	44	171	547
De Smedt *et al*. (1987)[17]	AVV area & TVI	50	150	550	75	175	625
Kenny *et al*. (1986)[18]	Vessel area & TVI	83	167	400	116	226	518
Veille *et al*. (1990)[19]	M-mode echocardiography	48	142	362	55	166	433
Schmidt *et al*. (1995)[20]	Method of discs	23	102	367	34	133	423
Present study	4D ultrasound & VOCAL	13	102	285	13	108	366

4D, four-dimensional; AVV, atrioventricular valve; TVI, time velocity integral; VOCAL, Virtual Organ Computer-aided AnaLysis.

there are many fetal breathing movements and the ossified ribs and consequent shadows they produce obscure accurate definition of the limits of the ventricles. Problems regarding the anatomic accuracy of endocardial tracing also become progressively worse with advancing gestation because both the myocardium and the atrioventricular septa appear thicker and have lower resolution in the orthogonal plane than in the original data acquisition cross section. This finding might be related to spatial volume artifacts, slower frame rates, or erroneous rendering algorithms, as described by other authors[8]. Another limitation of this method is the long duration and extensive expertise required for data analysis.

In our study the values for right and left cardiac output are smaller than those in previous reports that estimated cardiac output from 2D sonographic assessment of ventricular dimensions or the measurement of the cross-sectional area of the outflow tracts and the flow velocity waveforms obtained by pulsed Doppler ultrasound across these vessels (Table 2)[3,16–20]. A comparative study reported that the heart volumes measured by 3D ultrasound were smaller than those measured by 2D ultrasound because in the estimation of volume by the latter it is assumed that the heart has an elliptical or spherical shape[7]. The results of the Doppler studies may be inaccurate because the myocardium in fetal life is greatly limited in its ability to contract when compared to the postnatal period, therefore the Frank–Starling law (on which the Doppler technique relies) applies in a different manner[21,22].

The findings of fetal cardiac output are not comparable with the results of postnatal Doppler studies because firstly, myocardial contractility is better and ventricular compliance greater in the neonatal period than in fetal life[21,22] and secondly, in the first hours after birth following closure of the ductus arteriosus and the foramen ovale there is a decrease in cardiac output. Winberg *et al.* measured cardiac output in normal newborn babies by Doppler ultrasound and demonstrated a decrease from about 240 mL/min/kg in the first 2 h to 190 mL/min/kg at 24 h[23].

This study has established reference ranges for the stroke volume of both ventricles between 12 and 34 weeks of gestation. The extent to which in pathological pregnancies possible deviations in these measurements from normal prove to be useful in the prediction of outcome remains to be determined.

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