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Circumferential and Longitudinal Ventricular Strain in the Normal Human Fetus

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Abstract

Background: Echocardiography with speckle-tracking (STE) analysis is a novel angle-independent technique for assessing global and regional cardiac function. Normal data on longitudinal strain have been reported for human fetuses. The aim of this study was to define circumferential LV strain in a normal fetal population.

Methods: Singleton fetuses between 17 and 42 weeks in gestational age (GA) with no adverse maternal health issues or fetal abnormalities were studied. Regional and averaged cardiac strain were measured using Syngo Velocity Vector Imaging (VVI) software.

Results: Data from 81 fetuses were analyzed (GA 29.2 ± 5.7 weeks). Overall, average mid-ventricular circumferential strain (LVCS) was 18.7 ± 3.3 , LV longitudinal strain (LVLS) was 15.2 ± 2.7 , and RV longitudinal strain (RVLS) was 16.0 ± 3.3 , with no correlation to GA.

Conclusion: This is the first study to report normal fetal LV circumferential strain. These data may be useful as a reference for assessing fetal cardiac function. The retrospective study design and relatively low frame rates used in this study were important limitations.

Keywords

fetus; echocardiography with speckle-tracking; circumferential strain

INTRODUCTION

Fetal cardiac function can be affected by a variety of conditions and prenatal interventions, including cardiac disease, twin-twin transfusion syndrome, thoracic anomalies, and procedures to treat them (1). Accurate assessment of fetal cardiac function may help improve the understanding of disease processes and prognosis, as well as the evaluation of

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prenatal interventions for conditions such as twin-twin transfusion syndrome or fetal cardiac diseases.

Echocardiography with speckle-tracking (STE) is a novel angle-independent technique for assessing global and regional cardiac function. STE makes it possible to assess not only the global condition of the fetal heart chambers but also segmental function, and the angle-independency broadens its potential application in the face of varying fetal positioning. Although STE allows for the assessment of longitudinal, circumferential and radial strain only data on longitudinal function have been reported for fetuses (2–9). However, some conditions, such as fetal aortic stenosis or consequent endocardial fibroelastosis, may have different effects on circumferential and longitudinal left ventricular (LV) contraction, and it may be important to assess cardiac function in different axes (10,11).

The aim of this study was to define circumferential strain values for the normal fetal population. In addition, to confirm the reliability of this study, we compare our findings to previously published studies. We also compared these values with strain measurement obtained from fetuses with aortic stenosis (AS) to assess the usefulness of circumferential strain among fetuses with possible cardiac dysfunction.

METHODS

Study Population

We retrospectively evaluated cardiac ultrasound studies on fetuses referred to Children's Hospital Boston for fetal echocardiography for a family history of congenital heart disease or suggested fetal arrhythmia from 2004 to 2010. From these, we identified singleton fetuses between 17 and 42 weeks in gestational age (GA) with no maternal disease, fetal structural disease, or arrhythmia. After review of the echocardiographic studies, those with images felt to be sufficiently clear for STE were sequentially selected and analyzed. About 20 studies were selected for each GA subgroup (24, 25-29+6/7, 30-34+6/7, 35), with the intent of selecting a balanced distribution of fetal GA.

We identified fetuses with AS and moderate or less LV dysfunction. The AS gradient (ASPG) was estimated using the modified Bernoulli equation and LV volumes and LV ejection fraction (LVEF) by the single plane area-length method. We selected 5 fetuses with AS to represent different physiologic states. Cases 1 and 2 had moderate LV dysfunction and substantial AS gradients; cases 3 and 4 had normal or mildly depressed LV function and substantial AS gradients; case 5 had normal LV function and a mild AS gradient. STE was performed retrospectively in these fetuses, and was not used to determine whether to perform fetal aortic valvuloplasty (fAVP) or to determine the timing of fAVP.

The study was performed in conjunction with a protocol that was approved by the Children's Hospital Committee for Clinical Investigations.

Image Acquisition

Images were acquired using Siemens Sequoia (Siemens Medical Solutions, Mountain View, CA), Phillips SONOS 5500, and Philips iE33 (Philips Medical Systems, Bothell, WA)

machines. Phased array sector or linear probes ranging from 4.0-7.0 Hz were used. The short-axis view was obtained by scanning perpendicular to the long axis of the heart (12). For circumferential strain, short-axis images containing some part of both papillary muscles without any mitral valve tissue through the whole cardiac cycle were selected as mid-papillary muscle level images; for longitudinal strain, 4-chamber views were selected. All the images were stored in DICOM format and analyzed offline. Fetal echocardiographic images were automatically stored at a frame rate of 30Hz.

Offline Analysis

Regional cardiac function was measured using Syngo Velocity Vector Imaging (VVI) software (Siemens Medical Solutions, Mountain View, CA). Among images stored as DICOM clips in routine screening, well visualized 4-chamber and short-axis views were selected. Images that were acquired by Phillips SONOS 5500 or Phillip iE33 machines were reformatted to be compatible with Syngo VVI software.

To define a fetal cardiac cycle, using superimposed M-mode tracings, end-diastole was defined as the point just before closure of the atrioventricular valve. For short axis, longest LV dimension was used to define end-diastole. After manually tracing the subendocardial surface of ventricle on the frame, VVI software calculated strain automatically using the feature-tracking algorithm (Figure 1). Feature-tracking accuracy was visually confirmed, and the tracing was corrected until consistent endocardial tracking was obtained. Only one cardiac cycle was used for analysis instead of averaging over multiple cardiac cycles, in order to avoid artifact by fetal movement or change of cardiac cycle. Analysis was performed by one examiner, who was blinded to outcomes and other echocardiographic parameters.

Because of the variable fetal cardiac location, some rearrangement was needed to match the actual segment of the fetal heart and the segment displayed on the screen. The segment consisting primarily of the septum and closest to the tricuspid valve (Figure 2) was defined as septal, and other segments were defined in order.

Longitudinal and circumferential negative peak strains were used for strain values. Longitudinal strains for all segments were averaged to express global strain.

Data Analysis

To assess intra- and interobserver variability, a randomly selected subset of 15 data sets, analyzed by two examiners who were blinded to each others measurements, was used. Bland-Altman analysis bias was calculated and presented with the standard deviation (SD). To assess the success rate of analysis, chi-square test was conducted and significance was set at $P < 0.05$. To assess relationships between gestational age and STE data, linear regression was performed. Data are presented as mean $\pm$ SD.

RESULTS

General Characteristics

Indication for fetal echocardiograms in the normal cohort included; sibling of child with congenital heart disease (CHD), possible fetal arrhythmias detected by primary obstetrician, and maternal CHD. From 150 sequential fetal studies mothers with CHD (except for one with a small ASD), significant fetal arrhythmia and fetus with any anomalies were excluded. Because a majority of fetuses were evaluated in the mid- second trimester, we selected 81 of those 150 fetuses with the intent of selecting a balanced distribution of fetal GA that met demographic and diagnostic inclusion criteria for analysis. At the time of the examination, there were no identified obstetrical abnormalities. GA at the time of echocardiogram ranged from 19 to 42 weeks (29.2 ± 5.7 weeks) and the average HR was 140 ± 9 per minute. Among 81 fetuses, strain analysis was performed successfully in 62 (77%) for LV longitudinal function, 64 (79%) for RV longitudinal function, and 49 (64%) for LV circumferential function (Table 1). The frequency of successful analysis was lower for LV circumferential analysis, especially in late gestation fetuses.

Longitudinal and Circumferential Strain

Global RV and LV longitudinal strains were 16.0 ± 3.3 and $15.2 \pm 2.7\%$ respectively, and average mid-LV circumferential strain was $18.7 \pm 3.3\%$. There were no correlations between GA and RV longitudinal strain LV longitudinal strain or LV circumferential strain (Figure 3). Values of segmental longitudinal and circumferential strain are shown in Table 2. Figure 4 is a representative strain curve for circumferential strain.

Fetuses with Aortic Stenosis

Five fetuses with AS and no other cardiac malformation including LV hypoplasia were selected for analysis. Cases 1 and 2 met criteria for fetal intervention (13) and underwent fetal aortovalvuloplasty (fAVP) for AS soon after the echocardiogram evaluation used in this study. Cases 3 and 4 did not meet criteria for intervention and underwent fAVP 2 and 3 weeks later respectively. Case 5 (still in utero) was observed without intervention for 3 months.

One fetus (Case 1) that had both longitudinal and circumferential strains more than 2 standard deviations below underwent immediate fAVP. The 2 fetuses (Cases 2 and 3) that had borderline low circumferential strain underwent intervention the next day ($n=1$) or after 2 weeks of observation ($n=1$). In the 2 AS fetuses that had average or above average circumferential strain (Cases 4 and 5), only the fetus that had borderline high circumferential strain underwent fAVP (Table 3).

Intra- and Interobserver Variability

Intraobserver and interobserver variability are shown in Table 4 and Figure 5.

DISCUSSION

General Characteristics

The success of short-axis view tracking in this study was lower than that for the long-axis (4-chamber) view, and the likelihood of successful STE analysis was also lower at older GA. Among the few studies reporting normal values for LV circumferential strain in children, one similarly found lower a likelihood of successful STE analysis for circumferential strain than for longitudinal strain (14). The reason for the lower likelihood of success in circumferential strain analysis could be related to the movement of the LV in directions other than radial or circumferential, as suggested by Bussadori et al (14). Another reason for the lower success could be that, in contrast to the 4-chamber view, short-axis views are more likely to be affected by costal shadowing, as the probe is oriented almost perpendicular to the ribs. This factor may also contribute to the lower success of STE analysis later in gestation, as ossification of the ribs increases shadowing.

Comparison of Longitudinal Strain with Prior Reports

Strain values in this study were generally similar to published data (Table 5) (2–9). In contrast to our report, many prior studies reported a stronger relationship between strain and GA, including an increase in strain with GA in one study (3) and a decrease with GA in two (2,9). One of those reports used manually calculated Lagrangian strain, instead of the “segmental natural strain” that VVI software estimates by averaging the sum of Lagrangian strains of multiple short segments, which may be an explanation for the difference. As fetal hemodynamics dramatically change through prenatal life and strain is affected both by preload and afterload (15), strain could depend on GA. Our finding of independence of strain from GA could be due to the low frame rate used for echocardiograms in this study.

Comparison of Circumferential Strain with Prior Reports

This is the first report of LV circumferential strain in the fetus. Because mid-papillary muscle level short axis cuts are one of our routine images of fetal screening, mid-level circumferential strain was analyzed. Only a few studies have reported reference values for circumferential strain in the pediatric population (14,16,17). Using 2D tissue tracking with a frame rate of 40–64 Hz, Bussadori et al. reported average mid-LV circumferential strain of $24 \pm 6\%$ in a cohort of 15 normal children (mean age 8 ± 2 years) (14). Pettersen et al. reported a normal value of $26.2 \pm 2.4\%$ for LV circumferential strain, using STE with a frame rate of 69–112 Hz, in a cohort of 22 children (mean age 12.7 ± 2.3 years) (16). In a cohort of children under 10 years of age undergoing MRI, Hor et al. reported a mean normal value of 19.3% for circumferential LV strain with a strain value $>16\%$ in all patients (17). The lower circumferential strain values in our series may be related to the lower frame rates used for image acquisition in this study and potentially to physiologic differences between the fetus and children or adults such as blood pressure or the circulatory configuration in the fetuses.

LV Circumferential and Longitudinal Strain in the Fetus with Aortic Stenosis

Carasso et al reported a circumferential compensatory mechanism in patients with severe AS and a normal LVEF. This relationship was also observed in the one fetus with AS that underwent delayed fAVP (Cases 4). Carasso et al also reported that this circumferential compensation was lost in severe AS patients with low LVEF, which we also observed in Cases 1 and 2. In Case 5, a fetus with normal LV function and mild AS, LV strain remained normal both circumferentially and longitudinally without fAVP. There was an interesting consistency with previous reports between strain measurements and clinical management or other conventional findings, albeit in a small number of fetuses (10). In case 3, despite the below borderline longitudinal strain and borderline low circumferential strain, clinical management and other findings suggested relatively preserved LV function. For a variety of reasons, including the relatively large biases of fetal LV strain measurements, further studies are necessary to assess the potential clinical utility of fetal STE findings, whether for planning fAVP or otherwise.

fAVP is a procedure aiming to alter the natural history of fetal AS with evolving hypoplastic left heart syndrome by relieving LV outflow obstruction and afterload, this promoting LV filling and reducing mural stress (13). At present, our ability to understand mid-gestation factors associated with progression from AS to HLHS is based on anatomic and some functional echocardiographic data in small series (18). If incorporation of STE evaluation could provide further insight into physiological compensation in fetuses with borderline hypoplastic left heart disease, this might advance our ability to select patients for fAVP.

Limitations

Only 70-79% of the echocardiograms in this series could be analyzed successfully for longitudinal strain, and 64% for circumferential strain, which were relatively low compared to most prior studies (Table 5). The relatively low rate of successful analysis was likely due to the fact that this was a retrospective analysis of normal fetal echocardiograms that were not obtained with the intention of performing STE analysis especially in terms of frame rate. Frame rates 30 Hz with the upper limit of 100 Hz were reported to be tolerable (19). However, higher frame rates improve accuracy of STE analysis, and a rate of 50-90 Hz was recommended for prospective STE analysis (20). Considering that higher frame rates are recommended, especially for fetuses with higher heart rates, the low frame rate used in this retrospective study was likely responsible for the lower success rate of analysis, as well as the relatively lower strain values.

Due to the small size of the fetal heart, there are spatial limitations in performing tissue tracking on fetal echocardiograms using VVI software to measure strain compared to Lagrangian strain obtained by manual calculation. The limited spatial discrimination in the small fetal heart could contribute to underestimation of strain (9). Although VVI assessed innermost myocardial function using 5-pixel bands, instead of averaging subendocardial and subepicardial motion, still there was an intrinsic limitation of the speckle tracking algorithm, averaging all speckles in the region of interest (21).

In this study, Siemens Sequoia, Phillips SONOS 5500, and Philips iE33 machines were used to acquire images. Through this process, without any compression, image quality was not affected. However, Koopman et al using Vivid7 (GE healthcare) and iE33 (Philips Medical System) reported that images from different systems can contribute to variability in STE findings, especially for circumferential strain (19). However, in contrast, Mehta et al reported minimal influence of vendor difference using VVI (22). Based on the somewhat conflicting findings of those two reports, it is unclear how important differences between machines are in obtaining reliable strain analysis within a single clinical cohort. Because of this factor, our findings may not be generalizable across sonography machines and software.

Other methodological differences between our study and others that may have implications for the accuracy and/or comparability of our findings include the region of interest (atrioventricular valve annulus in some studies) and averaging over multiple cardiac cycles, which we did not do in this study.

Despite the above mentioned limitations and relatively small number of patients in this cohort, and granting that a higher frame rate is optimal for analysis of strain measurement, these data should be useful as a reference for assessing fetal cardiac function and may facilitate further studies of fetal cardiac function in various clinical circumstances.

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Figure 1.

A still frame of the short axis of left ventricle with velocity vectors. The arrow represents magnitude of the tissue velocity, and the direction of movement of the myocardium.

Figure 2.

These short-axis echocardiographic images demonstrate the method of segmenting the left ventricle (LV) into 6 segments. Syngo software calculates the center of the gravity of the tracing circle automatically. Segment 1 is defined by the software as the 60° region centered on a vertical line drawn upward from the center of the gravity (30° to each side of the line). Moving clockwise around the wall of the LV, successive 60° segments are defined as segments 2-6. In the case depicted in the figure, the segment consisting primarily of the septum and closest to the tricuspid valve was segment 1. The liver was on the right, the stomach (S) was below the heart, and the head was to the left of the image. P1 indicates the posteromedial papillary muscle, and P2 indicates the anterolateral papillary muscle. Therefore the 6 segments were defined as: Anterior-5, Lateral-4, Posterior-3, Inferior-2, Septal-1, Anteroseptal-6.

Figure 3.

Peak negative global strain plotted against gestational age in RV longitudinal (A), LV longitudinal (B), and LV circumferential strain(C). RV, right ventricle; LV, left ventricle. In this figure, blue symbols indicate RV longitudinal strain; red symbols indicate LV longitudinal strain; black symbols indicate LV circumferential strain.

Figure 4.
Circumferential strain curves. Each curve represents each segmental strain and its average.

Figure 5.

Bland-Altman analysis of intraobserver variability for longitudinal strain (A) and circumferential strain (B), and interobserver variability for longitudinal strain (C) and circumferential strain (D). In this figure, blue symbols indicate RV longitudinal strain; red symbols indicate LV longitudinal strain; black symbols indicate LV circumferential strain.

Table 1.

Success Measuring Strain According to Gestational Age, Ventricle, and Strain Dimension

GA (weeks)	Longitudinal RV (%)	Longitudinal LV (%)	Circumferential LV (%)
24	16/21 (76)	17/21(81)	16/20 (80)
25-29 6/7	17/22 (77)	16/22 (72)	16/22 (72)
30-34 6/7	17/20 (85)	17/20 (85)	12/19 (63) ^{†‡}
35	12/18 (67)	12/18 (67)	5/16 (31) ^{†‡*}
Total	62/81 (77)	64/81 (79)	49/77 (64) ^{†‡}

GA, gestational age; LV, left ventricle; RV, right ventricle

[†] p<0.05 when compared to RV longitudinal strain in the same GA subgroup.[‡] p<0.05 when compared to LV longitudinal strain in the same GA subgroup.^{*} p<0.05 when compared to previous gestational age group in the same strain analysis subgroup.

Table 2.

Average and Segmental Longitudinal and Circumferential Strain

	Free Wall			Septum			Global Strain
	Basal	Mid	Apical	Basal	Mid	Apical	
RV Longitudinal Strain (%)	17.6 ± 5.6	17.7 ± 4.4	16.8 ± 5.0	15.4 ± 4.4	14.4 ± 4.6	14.3 ± 5.0	16.0 ± 3.3
LV Longitudinal Strain (%)	16.3 ± 4.5	15.9 ± 3.8	15.4 ± 4.8	14.2 ± 4.6	14.0 ± 4.0	15.2 ± 2.7	15.2 ± 2.7
	Anterior	Lateral	Posterior	Inferior	Septal	Ant Septal	Average Strain
Mid-LV Circumferential Strain (%)	19.9 ± 5.5	19.1 ± 5.7	17.5 ± 5.4	18.7 ± 5.8	19.1 ± 5.4	18.0 ± 5.4	18.7 ± 3.3

RV = right ventricle; LV = center ventricle; Ant Septal = anteroseptum

Table 3.

Profiles of Fetal Aortic Stenosis

Case	GA (weeks)	LV Strain (%)		LV Dysfunction	Peak ASPG (mmHg)	LVEF (%)	Outcome
		Global Long (SD)	Average Mid-Circ (SD)				
1	22	8.8 (−2.3)	8.4 (−3.1)	moderate	35	46	immediate fAVP
2	22	10.8 (−1.6)	12.8 (−1.8)	moderate	62	40	immediate fAVP
3	23	5.3 (−3.6)	12.6 (−1.8)	mild	63	55	2weeks to fAVP
4	23	11.5 (−1.3)	23.0 (1.3)	None-mild	28	N.A.	3 weeks to fAVP
5	23	13.2 (−0.7)	18.5 (−0.1)	None-mild	10	68	3 months observation (in utero)

GA, gestational age; SD, standard deviation; Long, longitudinal; Mid-Circ, Mid-circumferential; PGAS, pressure gradient of aortic stenosis; LVEF, center ventricle ejection fraction; fAVP, fetal aortoavtroplasty; N.A., not available

Table 4.

Intraobserver and Interobserver Agreement

	Intraobserver variability		Interobserver variability	
	Bias	SD of Bias	Bias	SD of Bias
Longitudinal Strain (%)	0.2	2.0	−0.1	2.4
Circumferential Strain (%)	−0.3	1.2	−0.7	2.1

SD, standard deviation

Table 5.

Values for Fetal LV and RV Longitudinal Strain and Strain Rate Reported in the Literature

Article	N	GA (wks)	Machine	Frame Rate (Hz)	Successful Strain Analysis	RV Average strain	LV Average Strain
Matsui (9)	124	14-39	Si	27.4-167.2 (High), 25 (Low)	86% (High) 76% (Low)	-22.3% (High) -23.2% (Low)	-21.6% (High) -19.6 % (Low)
Peng (4)	170	20-41	Si	30-40	87-89%	-23.4 to -24.8	-16.0 to -18.8
Pu (8)	170	20-41	Si	30-40	87-89%	-23.4 to -24.8	-16.0 to -18.8
Van Mieghem (7)	59	16-36	GE	60-110	83%	-18.5±6.8	-15.1±5.2
Barker (5)	33	17-38	Si	N/A	100%	-17.4±6.4	-17.7±6.4
Di Salvo (3)	100	20-32	GE	40-90	100%	-24±4	-25±4
Younoszai (6)	27	18-39	Si	30	89%	N.A.	N.A.
Ta-Shma (2)	28	20-38	GE	90-200	94%	21±5	18.9±5.7

N = number of patients; GA = gestational age; Si = Siemens; RV = right ventricle; LV = center ventricle; SRs = systolic strain rate; SRd = diastolic strain rate; N.A. = not available