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Assessment of right ventricular global and regional longitudinal peak systolic strain, strain rate and velocity in healthy fetuses and impact of gestational age using a novel speckle/feature-tracking based algorithm

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KEYWORDS: feature tracking; fetus; strain; strain rate; velocity

ABSTRACT

Objective *To evaluate the correlation between feature tracking-derived measurements of the right ventricular myocardium and gestational age in healthy fetuses.*

Methods *Global and segmental longitudinal peak systolic strain, strain rate and velocity values of the right ventricular myocardium were assessed by a novel feature-tracking technique in 150 healthy fetuses at between 13 and 39 weeks' gestation. Reference ranges were constructed with respect to gestational age, and inter- and intraobserver variability was analyzed.*

Results *Strain, strain rate and velocity exhibited a segmental base to apex gradient (*$P < 0.001$*). Global longitudinal peak systolic velocities increased significantly across the gestational age range considered (*$P < 0.001$*), whereas global longitudinal peak systolic strain and strain rate (taken as absolute values) decreased significantly (*$P < 0.001$ *and* $P < 0.001$*). Inter- and intraobserver variability of global right ventricular peak systolic strain, strain rate and velocity was acceptable. The SDs of measurement error between the two observers were 5.9%, 0.7/s and 0.5 cm/s, respectively.*

Conclusions *Global myocardial peak systolic velocities of the right ventricle increase with gestational age whereas global myocardial peak absolute systolic strain and strain rate significantly decrease throughout gestation. This novel angle-independent technique offers a new non-invasive approach for quantifying and monitoring fetal myocardial function throughout gestation. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Global and segmental quantitative non-invasive assessment of right ventricular myocardial function has always been challenging due to the geometric shape of the ventricle. In 1999 Harada *et al.*[1] published the first data on myocardial tissue motion and velocities in normal fetuses. Since then several studies have been performed to assess regional myocardial properties and deformation based on two-dimensional (2D) and M-mode imaging. Normal global and segmental systolic and diastolic velocities, strain and strain rate values in adults and children have already been published using tissue Doppler imaging[2,3] or color Doppler myocardial imaging[4–6]. At present two methods, one based on tissue Doppler analysis and the other on gray-scale image tracking, are available for the assessment of fetal strain and strain rate[7]. The use of tissue Doppler imaging (TDI) to determine strain and strain rate is limited by the angle and signal noise dependence of this method[8,9]. The 'syngo Velocity Vector Imaging' (VVI) is an offline software package, based on a gray-scale image and feature-tracking technique, which provides 2D analysis of velocities and deformation in all myocardial segments, without the limitations of Doppler echocardiography[10,11]. The feasibility and reliability of this new technique for assessing regional myocardial function have been analyzed in an animal model[11] and several studies evaluating the adult heart[12–15]. The published data regarding the use of VVI in fetal hearts are sparse[10,16–18].

The aim of this study was to assess the effect of gestational age on VVI-derived measurements of regional and global right ventricular function in normal fetuses and to provide gestational age-adjusted reference values.

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METHODS

This was a prospective cross-sectional study in which a total of 150 fetuses (126 singletons and 24 dichorionic twins), with gestational ages ranging from 13 to 39 weeks, underwent 2D echocardiography at the Department of Obstetrics and Prenatal Medicine, University of Bonn. The local ethics committee approved the study protocol and informed consent was obtained from each mother.

All fetuses were healthy, in sinus rhythm and had normal cardiac morphology. Monochorionic twins and all fetuses with malformations, chromosomal abnormalities, cardiac defect or failure, arrhythmia or intrauterine growth restriction were excluded from the study. All women were selected according to a suitable maternal body habitus (body mass index < 30). An ACUSON S2000™ (Siemens Healthcare, Erlangen, Germany) ultrasound system equipped with a 2–6-MHz transducer and a 4–9-MHz linear transducer was used to acquire a high-resolution, zoomed B-Mode of the apical or basal four-chamber view. D'hooge *et al.*[19] recommended a frame rate of 80 frames/s as a minimum to display all myocardial motion at normal adult heart rates. Therefore, in our study on fetal hearts with normal heart rates depth was reduced and sector width was narrowed as much as possible to achieve high frame rates (≥ 100 frames/s). Preferentially, we obtained a slightly angled apical or basal four-chamber view so that the right ventricular free wall, the interventricular septum and the left ventricular wall were clearly delineated. All clips analyzed in our study used the acoustic capture option with the original frame rate that is displayed on the image (median 111 (range, 83–167) frames/s). For each fetus between one and four cardiac cycles were recorded as clips, stored as standard DICOM files and transferred without any loss of frame rate to a workstation (syngo US Workplace, Siemens Healthcare) for offline analysis. Due to the inability to record fetal electrophysiological signals a reconstructed M-mode tracing through the atrioventricular (AV) valve was used in the background to identify the beginning and end of a cardiac cycle, with end-diastole defined by the complete closure of the AV valve.

Initially, in each case the endocardial border of the right ventricle (RV) was identified and manually traced on one arbitrary frozen frame that provided the best resolution of endocardial border definition. The tracing started and ended at the tricuspid valve plane without involvement of the papillary muscles. In a second step the initial trace was manually postprocessed to provide a better landmark for the algorithm. In a third step the algorithm automatically tracked the endocardial border throughout the whole video sequence, based on a combination of feature tracking of the endocardial tissue, tricuspid annular motion, tissue border detection, periodicity of the cardiac cycle and spatial coherence using R–R intervals (Figure 1)[20]. Postprocessing and averaging over the acquired cardiac cycles resulted in improvement of the beat-to-beat reproducibility of velocity and strain-rate data. The resulting data allowed evaluation of all myocardial segments and global ventricular function without the limitations of tissue Doppler imaging[15]. Finally, the software automatically divided both the ventricular septum and free wall of the RV into three equally sized segments (basal, mid and apical). Right ventricular global and segmental longitudinal strain, strain rate and velocity were calculated from the entire stored video datasets (based on one to four cardiac cycles). The peak systolic values for velocity, strain and strain rate were evaluated from each cardiac cycle and subsequently averaged for the individual fetus.

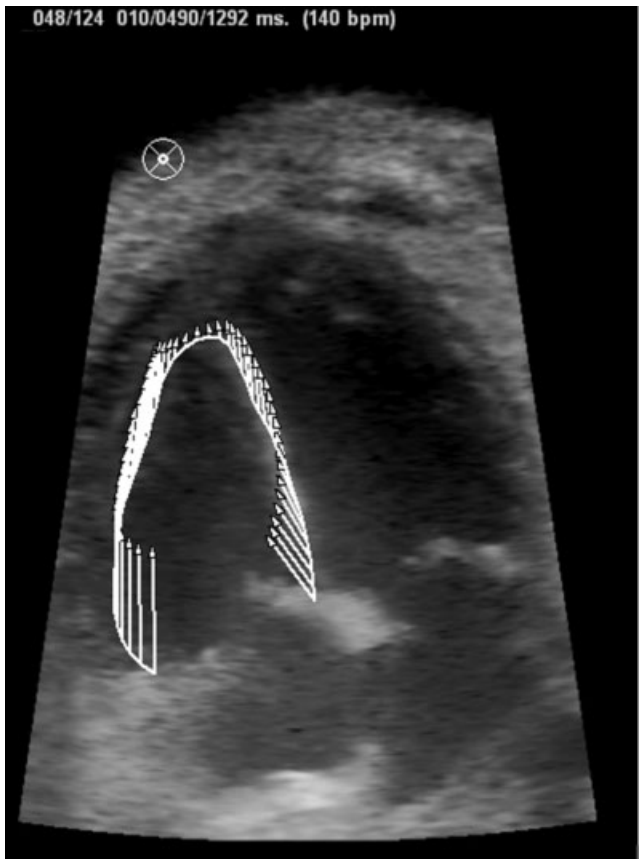

Figure 1 Systolic velocity vector tracking of the right ventricular endocardium in a healthy fetus at 24 weeks' gestation. The magnitude and direction of each vector reflect the corresponding myocardial motion towards the reference point.

By convention, strain (%) is defined as the instantaneous local border lengthening (positive value) or shortening (negative value) related to the initial muscle length commonly determined by the end of diastole[21]. Strain rate is by definition the temporal derivative of strain (1/s) and is also equivalent to the shortening velocity per fiber length[22].

Statistical analysis

Global and region-specific values for velocity, strain and strain rate were calculated as the maximum of velocity, strain and strain rate, respectively, over all measurements in the specific region and one cardiac cycle. Strain and strain rate were analyzed as absolute values in our

data analysis. If data for more than one cycle were recorded per fetus these values were averaged over all analyzed cycles. Mean peak systolic values from each of the six segments (basal, mid, apical segments of the ventricular septum and free wall of the RV) were identified and in a second step global mean peak values (velocity, strain and strain rate) were calculated from these six maximum segmental measurements. Repeated measurement analysis of variance was used to check for dependency on location. Linear regression analysis was used to estimate and test the dependency of the variables on gestational age. The 90% normal ranges for velocity, strain and strain rate depending on the gestational week were constructed following Royston and Wright[23], using fractional polynomials up to grade 2 for the mean curves and at most a linear function or a constant value for the SD. The variable strain was log-transformed before calculating the normal ranges. Inter- and intraobserver measurement errors were calculated as the SD of the difference between the measurements of two raters and the repeated measurement of one rater on the same subject, respectively[24]. Repeatability is calculated as $r = 2.77 \times \text{SD}$; the difference between two measurements for the same subject is expected to be less than this value for 95% of pairs of observations. Repeated measurements were performed on 10 randomly selected echocardiographic clips.

RESULTS

Longitudinal peak systolic strain, strain rate and velocity measurements could be obtained in 147 of 150 healthy fetuses (98.0%). The fetal heart could not be visualized in three cases because of difficulties related to fetal position. Overall, 882 cardiac segments in healthy fetuses were analyzed. The median gestational age was 22 (range, 13–39) weeks. All video clips were recorded with a median frame rate of 111 (range, 83–167) frames/s. In all cases cardiac imaging was performed in an apical or basal four-chamber view and a median of three cardiac cycles (range, 1–4 cycles) were stored for offline analysis. In 2% of analyzed fetuses we were able to record only one cardiac cycle because of unacceptable image quality due to fetal movement. The median fetal heart rate was 145 (range, 107–191) beats per minute. The derived formulae for reference values of right ventricular longitudinal global peak systolic velocity, strain and strain rate are provided in Table 1, with the values for each specific week of gestation available online in Table S1.

The mean global RV peak systolic velocity was 3.98 ± 1.47 cm/s with a median of 3.75 (range, 1.23–8.19) cm/s. The highest velocities were measured at the basal segments with a significant base to apex divide ($P < 0.001$). Furthermore, there was a strongly significant correlation (Figure 2a) between velocity and increasing gestational age ($P < 0.001$).

The mean global RV peak systolic strain was −35.88 ± 11.21% with a median of −33.87% (range, −18.33 to −75.81%). The highest strain values were detected in the two basal segments and the observed base to apex gradient also reached significance ($P < 0.01$). There was a significant inverse correlation (Figure 2b) between RV global longitudinal peak absolute systolic strain and gestational age ($P < 0.001$), whereas in the segmental RV free wall the correlation did not reach significance.

The mean global RV peak systolic strain rate was −5.43 ± 2.41/s with a median of −4.81 (range, −2.42 to −14.58)/s. Analyzing each segment separately showed the highest strain rate measurements in the basal segments, with a significant base to apex gradient ($P < 0.05$). The correlation between strain rate and gestational age in the RV free wall segments did not reach significance. However, the correlation between global longitudinal RV peak absolute systolic strain rate and increasing gestational age (Figure 2c) was also inverse and highly significant ($P < 0.001$).

The inter- and intraobserver variability – expressed as the SD of measurement error – and the repeatability are displayed in Table S2. The SDs of measurement error of global RV peak systolic strain, strain rate and velocity between the two observers were 5.9%, 0.7/s and 0.5 cm/s, respectively. The equivalent values for intraobserver variability were 6.96%, 1.4/s and 0.4 cm/s, respectively. The SD of measurement error was higher in segments with large alterations (base free wall, mid free wall) than in apical segments.

DISCUSSION

VVI is a new non-Doppler, angle-independent, echocardiographic technique that can be used to obtain quantitative information about 2D global and segmental myocardial wall velocities and deformation qualities. Myocardial velocity alone will include artifactual components from fetal motion, normal fetal cardiac translation, rotation or fetal motion induced by maternal aortic pulsation[25]. Therefore deformation indices like strain and strain rate

Table 1 Derived formulae for calculation of mean and 5th and 95th centiles of peak absolute longitudinal velocity, strain and strain rate of the right ventricle in 147 fetuses

Variable	*Mean curve*	*5th/95th centiles*
Velocity (cm/s)	$9.505 - 40.55 \times (\ln GA/GA)$	Mean ± $(0.0944 - 0.0643 \times GA)$
Ln(strain) (%)	$3.380 + 73.58/GA^2$	Mean ± 3.6138
Strain rate (1/s)	$3.747 + 798.5/GA^2$	Mean ± $(4.8419 - 0.06921 \times GA)$

GA, gestational age (in weeks).

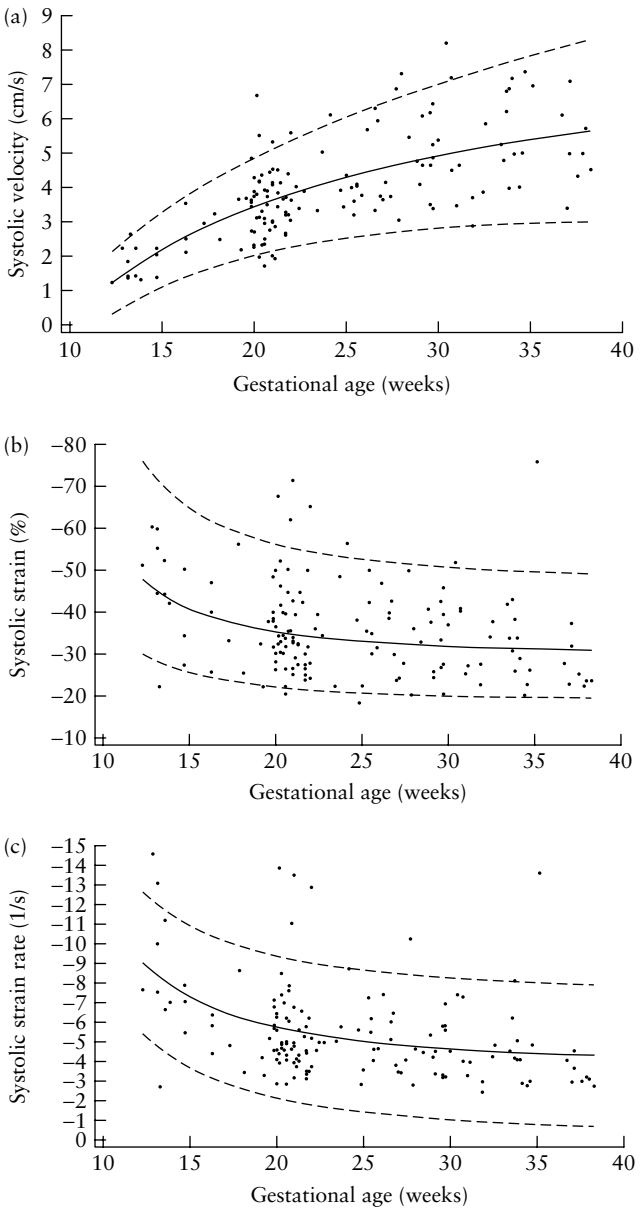

Figure 2 Global right ventricle myocardial longitudinal peak variables plotted against gestational age, showing the regression line and 90% confidence intervals: (a) systolic velocity; (b) systolic strain; and (c) systolic strain rate.

have turned out to be a quantitative technique for accurately estimating global and segmental myocardial function and contractility[21,26].

While there is general agreement over segmental and age-related distribution of velocity, there is much less agreement about strain and strain rate (Table 2). Consistent with the published VVI data for fetuses, children and adults, our longitudinal velocity profiles showed a gradient with the highest velocities at the base and the lowest at the apex[3,16–18,27,28]. Calculated myocardial velocities in our study were nearly twice as high as those reported by Barker *et al.*[16] in their preliminary study on 33 normal fetuses, but only half the values previously reported in 30 healthy children studied by Kutty *et al.*[27]. Fewer myocytes and the stiffer

Table 2 Summary of prenatal studies of longitudinal global and segmental peak systolic velocity, strain and strain rate using speckle tracking and color tissue Doppler imaging (C-TDI) techniques

				Relationship with gestational age			
Reference	*Method*	*Frame rate (frames/s)*	*Number of fetuses*	*Velocity*	*Strain*	*Strain rate*	*Further results*
Barker *et al.*[16]	VVI	Not stated	33	Not applicable	Not applicable	Not applicable	Velocity base–apex gradient of RV, LV and IVS
Younoszai *et al.*[10]	VVI	30	27	+ (RV, LV, IVS)	± (RV, LV, IVS)	± (RV, LV, IVS)	Positive correlation between strain rate and HR
Peng *et al.*[17]	VVI	30–40	151	+ (LV, IVS)	± (LV, IVS)	± (LV, IVS)	Velocity base–apex gradient of LV, IVS
Van Mieghem *et al.*[18]	VVI	60–110	59	+ (RV, LV, IVS)	± (LV, IVS)	± (LV, IVS) – (global RV)	Velocity base–apex gradient of RV, LV and IVS
Di Salvo *et al.*[31]	AFI	40–90	100	Not applicable	– (RV, LV, IVS)	Not applicable	—
Ta-Shma *et al.*[33]	AFI	90–200	28	+ (RV, LV)	± (RV, LV)	– (global RV, LV)	Velocity of RV > velocity of LV; strain rate of RV = strain rate of LV
Ta-Shma *et al.*[33]	C-TDI	72–220	28	Not applicable	Not applicable	Not applicable	Velocity of RV > velocity of LV; strain rate of RV = strain rate of LV
Perles *et al.*[34]	C-TDI	105–212	98	+ (RV, LV)	± (RV, LV)	± (RV, LV)	Velocity, strain and strain rate independent of HR
Di Salvo *et al.*[35]	C-TDI	145–175	75	+ (RV, LV, IVS)	+ (RV, LV, IVS)	+ (RV, LV, IVS)	Velocity of RV and LV > velocity of IVS; strain and strain rate of RV, LV and IVS are the same
Present study	VVI	83–167	150	+ (Global, RV, IVS)	– (Global, IVS) ± RV	– (Global, IVS) ± RV	Velocity base–apex gradient of RV and IVS

All studies were cross-sectional. +, Increase with gestational age; –, decrease with gestational age; ±, constant with gestational age; AFI, automatic functional imaging; Global, global right ventricular measurement; HR, heart rate; IVS, interventricular septum; LV, left ventricular free wall; RV, right ventricular free wall; VVI, velocity vector imaging.

fetal heart compared with neonatal and adult hearts may provide the main explanation for this large difference[29]. In addition, systolic velocities of all RV segments in our study increased significantly with gestational age. These findings are consistent with fetal somatic growth and the results of another recently published study using VVI to evaluate fetal myocardial function[18].

The heterogeneity in myocardial velocities between the segments is ascribed to variations in fiber orientation throughout the heart. The left ventricular (LV) wall consists of longitudinal and transverse fibers whereas the RV free wall has a predominance of longitudinal and oblique fibers[30]. RV contraction in healthy adults occurs principally in a longitudinal mode, whereas LV contraction exhibits a more prominent circumferential component of shortening[4,30]. Long-axis fibers are absent from the interventricular septum, which accounts for the lower velocities there[30].

At present the most conventional and evaluated deformation parameter used to analyze segmental and global myocardial contractility in healthy adults is longitudinal peak systolic strain[5,13]. Our global longitudinal peak systolic strain values of the RV are comparable with the results of Di Salvo *et al.*[31] from 100 fetuses and a recently published study investigating strain in 129 healthy children[32], but slightly higher than those of Barker *et al.*[16] in 33 fetuses. Peng *et al.*[17] analyzed the LV in 151 healthy fetuses and also detected lower strain values of the interventricular septum and LV free wall (Table 2). In our study, the correlation between longitudinal peak systolic strain and gestational age did not reach significance in the RV free wall, which is in line with published data using VVI on fetuses[10,33,34], whereas our strain values of the interventricular septum and global measurements decreased significantly with advancing gestational age.

In our study global and septal strain rate measurements behaved in a similar manner and decreased significantly with gestational age, which is in contrast to some of the previously published fetal data[10,35]. However, this observation is in agreement with data recently published by Ta-Shma *et al.*[33] and Van Mieghem *et al.*[18], and could be explained by the increasing afterload throughout gestation related to the increase in systolic blood pressure caused by a progressive increase in placental impedance associated with placental maturational changes[36,37]. A second possible explanation that has been suggested for the decrease in global peak systolic longitudinal strain and strain rate in early pregnancy and relatively stable values in the second and third trimesters – which is in contrast to the postnatal period when the deformation parameters distinctly decrease – is that the fetal heart mainly grows through myocyte hyperplasia rather than hypertrophy in early gestation[38], whereas in mid and late gestation, and especially in the postnatal period, cardiac growth is mainly characterized by progressive myocardial hypertrophy, where the myocytes do not divide any more[39,40]. Therefore the cardiac muscle consists of an increased number of myocytes, whereas the number of cardiomyocytes per volume remains stable with ongoing pregnancy[38]. This results in increasing velocities during cardiac contraction, but relatively constant strain (displacement from the initial corrected size) and strain rate[38].

Potential limitations of this study are the inclusion of only women with a suitable maternal body habitus and the evaluation of only longitudinal cardiac velocity, strain and strain rate. Radial deformation parameters were not examined because of the size of the fetal heart and the combined very thin layers, especially of the septum. In early pregnancy axial resolution may be compromised and measurement errors may have an impact on the final analysis, which is reflected in the wide confidence intervals of strain and strain rate in this study. Further limitations of our study are mostly related to the software used, and the offline analysis is based on 2D video sequences. The accuracy of VVI as a feature-tracking technique depends on image quality, suggesting that poor endocardial delineation is likely to result in inaccurate findings as a result of errors in endocardial tracking, especially at the start and endpoint of the tracking level with the AV valve. A gold standard for gray-scale tracking techniques for the evaluation of fetal cardiac function has not yet been determined, which makes it difficult to compare published data based on the different commercially available algorithms. At present all available software algorithms using feature tracking to analyze fetal myocardial function are based on results obtained from adult hearts.

In summary, global longitudinal peak systolic velocities in healthy fetuses increased significantly throughout gestation, whereas global peak systolic strain and strain rate decreased at a highly significant rate as pregnancy progressed. The highest segmental velocities, strain and strain rate measurements were detected at the base with a significant base to apex gradient. This new speckle-tracking technique is compatible with all available ultrasound systems and automatically generates parameters for assessing regional myocardial properties; it may therefore significantly contribute to the study of normal and pathological fetal cardiac function. Significant global cardiac disorders in the fetus may occur in anemia, twin-to-twin transfusion syndrome, fetal growth restriction, maternal diabetes mellitus, fetal inflammation and infection whereas regional cardiac dysfunctions (i.e. Ebstein's anomaly, pulmonary and aortic stenosis/atresia with intact interventricular septum, aortic coarctation) are rare conditions. This new angle-independent technique may have the potential to detect abnormalities of fetal cardiac function, in particular regional dysfunction, earlier than do other techniques for the assessment of fetal cardiac function such as M-mode, Doppler echocardiography and tissue Doppler imaging[41], but the clinical relevance of speckle tracking will have to be demonstrated in complicated pregnancies. However, the variation in measurement error limits the application of VVI outside a research setting. Further investigations on this topic are required before this new technique can be implemented in routine clinical practice.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Gestational age-adjusted reference values of peak absolute longitudinal velocity, strain and strain rate of the right ventricle.

Table S2 Interobserver and intraobserver variability of measurements of peak absolute longitudinal velocity, strain and strain rate of the right ventricle.

