Quantification of mechanical dyssynchrony in growth restricted fetuses and normal controls using speckle tracking echocardiography (STE)

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Abstract

Purpose: To evaluate longitudinal mechanical dyssynchrony in normally grown fetuses by speckle tracking echocardiography (STE) and to compare longitudinal mechanical dyssynchrony in fetal growth restriction (FGR) with normal controls.

Materials and methods: A prospective study was performed on 30 FGR and 62 normally grown fetuses, including 30 controls matched by gestational age, using STE and a transversal four-chamber view. Data analysis was carried out with a high frame rate of about 175 frames/s. Dyssynchrony was analyzed offline with QLab 9 (Philips Medical Systems, Andover, MA, USA) as time differences between peaks in strain of both ventricles and the septum. Inter- and intraventricular and intraseptal dyssynchrony were obtained and inter- and intraobserver reliability was analyzed.

Results: Longitudinal mechanical dyssynchrony was feasible in all cases, with high inter- and intraobserver reliability. Levels of inter- and intraventricular dyssynchrony were higher in the FGR than in the control group.

Conclusion: Speckle tracking echocardiography (STE) is a reliable technique for cardiac function assessment in the fetal heart. Interventricular dyssynchrony could be a potential parameter for early detection of subclinical myocardial dysfunction before other parameters demand intervention. The future clinical role of longitudinal mechanical dyssynchrony needs to be verified in larger studies and with a technique customized for prenatal echocardiography.

Keywords: Dyssynchrony; fetal growth restriction; speckle tracking echocardiography.

Introduction

Fetal growth restriction (FGR) is defined as an estimated fetal weight below the 10th percentile [1]. Up to 10% of all pregnancies are affected by FGR, which is associated with an increased risk for adverse short- and long-term outcomes [2]. The main reason for FGR is placental insufficiency, currently evaluated by umbilical artery (UA) Doppler [3]. However UA Doppler can be neither relied on for early identification of fetuses at risk [1] nor for perinatal management. Placental insufficiency induces a number of adaptive mechanisms in the fetus, leading to fetal programming and cardiovascular dysfunction [4]. Hence several studies focused on the evaluation of fetal cardiac function and tried to identify suitable parameters. So far there are no clinical standards for the assessment of fetal cardiac function [5, 6].

A recent approach to studying myocardial motion as a surrogate for cardiac function is the use of speckle tracking echocardiography (STE) [7]. It allows the quantification of myocardial deformation by providing regional information on myocardial contractility and interaction with neighboring segments and global circulation [8, 9].

Various studies reported the feasibility of STE in fetal echocardiography [8, 10, 11], although it is still limited. Applying apical four-chamber views, the authors examined segmental and global systolic and diastolic velocities, strain and strain rate values [12] as potential parameters for the assessment of fetal cardiac function.

In adults, STE is used for the quantification of mechanical dyssynchrony, an approved parameter for the evaluation of left ventricular (LV) function [13]. Its presence is a frequent and important manifestation in
heart failure, hypertension and diabetes mellitus [14]. The assessment of LV dyssynchrony is useful for the exploration of disease mechanisms, stratification of risks and the prediction of treatment response [15]. However, there is limited knowledge of the value of dyssynchrony in fetal echocardiography.

The aims of our study were to assess longitudinal mechanical dyssynchrony in normally grown fetuses by STE and to compare longitudinal mechanical dys-
synchrony in a cohort of growth restricted fetuses with normal controls.

Materials and methods

Study population

Between January 2013 and April 2014 we performed a prospective cross-sectional study at the Clinic of Obstetrics and Gynecology, University Hospital Münster.

The cases were recruited from the population of pregnant women who attended our clinic for second and third trimester ultrasound examinations. The study population consisted of 30 growth restricted FGR and 62 appropriate-for-gestational age (AGA) fetuses, including 30 controls individually matched with cases by gestational age at inclusion (± 1 week). FGR was defined as an estimated fetal weight below the 10th percentile. Exclusion criteria were congenital malformations, chromosomal abnormalities, fetal infections and confirmed birth weight above the 10th percentile.

Informed consent was obtained from all patients and the institutional review board approved the study protocol.

Ultrasound measurements

2D echocardiography was performed with an iU22 ultrasound system (Phillips Medical Systems, Andover, MA, USA) using a 5-MHz transducer (SS5-1, Philips Medical Systems). The same customized preset was used in all cases and the examining gynecologist was an experienced specialist for fetal echocardiography (R.S.). High-resolution, zoomed B-mode video raw data clips of the transversal four-chamber view were acquired and stored for off-line analysis. While recording the loop, the sector width was narrowed as much as possible in order to achieve high frame rates > 100 frames/s. Scans were performed in the absence of maternal and fetal breathing and movements.

Due to the lack of ECG gating in fetal echocardiography, a metronome was interposed to artificially generate simulated ECG spikes with a rate of 150 beats per minute, thus enabling the identification of the beginning and the end of a cardiac cycle. For each fetus, two metronome derived cycles were recorded as raw data clips, ensuring the inclusion of a whole fetal cardiac cycle. These clips were stored as uncompressed standard digital imaging and communication in medicine (DICOM) files and transferred to a workstation for off-line analysis.

The raw datasets, one per fetus, were evaluated with QLab 9 software [cardiac motion quantification (CMQ), Philips Medical Systems, Andover, MA, USA], following a standardized protocol.

Initially, in each case the endocardial borders of the right and the left ventricle and the borders of the septum were identified on one arbitrary frozen frame that provided the best resolution of endocardial border definition. Only raw data clips of cases with clear delineation of the left and the right ventricular wall and the septum were included in the study. The atroventricular valve plane and the apex were marked to start the automatical placement of the seven tracking segments. In order to provide a better landmark for the algorithm and to make sure that the whole myocardium wall was included, the initial tracing was manually adjusted. Next, the tracking algorithm was launched and visual control of tracking quality was performed throughout the whole video sequence. Following successful cardiac motion tracking, the software produced a profile of longitudinal strain for each segment. Previous studies showed that the highest values for shortening fraction were reached in the basal and mid segments [16]. The shortening fraction is defined as the difference in the end-systolic and the end-diastolic diameters as a ratio to the end-diastolic diameters, displaying the sections of the heart where most excursions take place. Hence we excluded the three apical segments from further investigation. Peaks in strain were identified for each of the four remaining segments. We assumed that the peaks in strain indicated a change in myocardial deformation, from shortening to lengthening and vice versa. Interventricular dyssynchrony was calculated as the absolute time difference between the two peaks in the strain obtained for the mid segments placed in both ventricles (DYS Interventricular) (Figure 1). The same procedure was performed for the left ventricle and the septum (DYS LV Septum) and the right ventricle and the septum (DYS RV Septum). Intra-
ventricular dyssynchrony was calculated as the absolute time difference between the two peaks in the strain obtained for the basal and the mid segment of the left ventricle (DYS intraventricular LV), of the right ventricle (intraventricular RV) and of the septum (DYS intraseptal). Finally, we calculated the mean peak strain value from the four segmental peak strain values as ‘four-segments peak strain’ (4S peak strain).

The intra- and interobserver reliability for the measurements of interventricular dyssynchrony were assessed in 10 patients by two independent observers.

Statistical analysis

Descriptive statistic was used to characterize the study population. The results are shown in mean ± standard deviation (SD). Strain and time difference were analyzed as absolute values in our data analysis. To compare the characteristics and the dyssynchrony parameters between the two study groups, Mann-Whitney U-tests were conducted. The Spearman correlation was chosen to assess the correlation between interventricular dyssynchrony and gestational age. The ROC was used to evaluate the parameter DYS interventricular as a potential classifier for FGR or AGA fetuses. Intra- and interobserver reliability of dyssynchrony measurements were determined using the intraclass correlation coefficient (ICC, one-way random model). Statistical analysis was performed by SPSS software (IBM Corporation, New York, NY, USA, version 22).
Results

A total of 92 fetuses were included in our study and radial mechanical myocardial dyssynchrony was feasible in all cases included.

Table 1A summarizes the characteristics of all AGA fetuses. The mean gestational age was 29 weeks of gestation (range 24–35) at raw data collection and 39 weeks of gestation (range 37–42) at delivery. The mean birth weight centile was the 53rd percentile (range 28–78) and a mean frame rate of 178 frames/s (range 158–199) was utilized.

The findings of STE in all AGA fetuses are shown in Table 1B. The lowest rate of dyssynchrony was observed for interventricular dyssynchrony. No association was observed between interventricular dyssynchrony and gestational age in the AGA group (P = 0.33) (Figure 2).

Table 2A reports the characteristics of AGA controls and growth restricted fetuses. As a result of our matched design, gestational age at ultrasound was equal in cases and controls. However, gestational age at delivery was significantly lower in the FGR group (35.5 vs. 38.9 weeks of gestation; P < 0.001).

The results of STE in AGA controls and growth restricted fetuses are visualized in Table 2B. Inter- and intraventricular dyssynchrony were significantly higher.

### Table 1: Appropriate-for-gestational-age (AGA) fetuses.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AGA group (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Characteristics of the study group</td>
<td></td>
</tr>
<tr>
<td>GA at ultrasound (weeks)</td>
<td>29.5 ± 5.5</td>
</tr>
<tr>
<td>GA at delivery (weeks)</td>
<td>39.3 ± 2.6</td>
</tr>
<tr>
<td>Birth weight centile</td>
<td>53.0 ± 24.8</td>
</tr>
<tr>
<td>Frame rate (1/s)</td>
<td>178.5 ± 20.6</td>
</tr>
<tr>
<td>Umbilical artery PI</td>
<td>1.01 ± 0.16</td>
</tr>
<tr>
<td>(B) Speckle tracking echocardiography</td>
<td></td>
</tr>
<tr>
<td>(STE) characteristics</td>
<td></td>
</tr>
<tr>
<td>DYS Intraventricular LV</td>
<td>34.3 ± 26.5</td>
</tr>
<tr>
<td>DYS Intraventricular RV</td>
<td>30.9 ± 25.1</td>
</tr>
<tr>
<td>DYS Intraseptal</td>
<td>29.3 ± 23.7</td>
</tr>
<tr>
<td>DYS Interventricular LV and RV</td>
<td>10.2 ± 12.6</td>
</tr>
<tr>
<td>DYS LV Septum</td>
<td>22.1 ± 22.5</td>
</tr>
<tr>
<td>DYS RV Septum</td>
<td>27.3 ± 21.6</td>
</tr>
<tr>
<td>4S Peak Strain</td>
<td>31.5 ± 17.9</td>
</tr>
</tbody>
</table>

Data is given as mean ± SD.

GA = gestational age, PI = pulsatility index, DYS = dyssynchrony in ms, LV = left ventricular free wall, RV = right ventricular free wall, 4S = four-segments.

### Figure 1: Interventricular dyssynchrony as a time difference in peaks of strain in a normally grown (A) and a growth restricted fetus (B).

### Figure 2: Appropriate-for-gestational age (AGA, n = 62) fetuses: Interventricular dyssynchrony plotted against gestational age (Spearman’s ρ = 0.125, P = 0.332).
in the FGR than in the AGA group. After offline analysis, an association between radial mechanical myocardial dyssynchrony and the two study groups (AGA or FGR) was found in all calculated dyssynchrony parameters. It is noteworthy that the highest difference in dyssynchrony was found for interventricular dyssynchrony (9.7 vs. 68.0 ms). Unlike longitudinal mechanical dyssynchrony as a time difference in peaks of strain, the 4S peak strain did not correlate with the two study groups (P = 0.74).

The comparison between interventricular dyssynchrony in AGA controls and growth restricted fetuses is displayed with a box-and-whisker plot (Figure 3).

Interventricular dyssynchrony was evaluated as a diagnostic test for the distinction between FGR and AGA fetuses. According to Figure 4, interventricular dyssynchrony shows high levels of sensitivity and specificity in order to distinguish between FGR and AGA fetuses. We identified cut off values of 30 ms for an indicative dyssynchrony (sensitivity 96.7%, specificity 89.7%). The AUC value was 0.991 (0.95 CI 0.976–1).

Table 2: Appropriate-for-gestational age (AGA) controls and growth restricted fetuses (FGR).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n = 30)</th>
<th>FGR group (n = 30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Characteristics of the study groups</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GA at ultrasound (weeks)</td>
<td>30.3 ± 4.8</td>
<td>30.4 ± 5.0</td>
<td>0.767</td>
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<tr>
<td>GA at delivery (weeks)</td>
<td>38.9 ± 1.5</td>
<td>35.5 ± 5.2</td>
<td>&lt;0.001</td>
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<td>Birth weight centile</td>
<td>47.7 ± 23.5</td>
<td>4.0 ± 7.7</td>
<td>&lt;0.001</td>
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<td>Frame rate (1/s)</td>
<td>170.0 ± 19.7</td>
<td>174.0 ± 22.9</td>
<td>0.450</td>
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<tr>
<td>Umbilical artery PI</td>
<td>1.02 ± 0.14</td>
<td>1.28 ± 1.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(B) Speckle tracking echocardiography (STE) characteristics</td>
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<td></td>
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<tr>
<td>DYS Intraventricular LV</td>
<td>40.2 ± 30.0</td>
<td>69.8 ± 37.0</td>
<td>0.002</td>
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<tr>
<td>DYS Intraventricular RV</td>
<td>27.2 ± 31.6</td>
<td>68.7 ± 30.8</td>
<td>&lt;0.001</td>
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<tr>
<td>DYS Intraseptal</td>
<td>29.1 ± 24.1</td>
<td>55.0 ± 45.2</td>
<td>0.021</td>
</tr>
<tr>
<td>DYS Interventricular LV and RV</td>
<td>9.7 ± 14.1</td>
<td>68.0 ± 30.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DYS LV Septum</td>
<td>13.9 ± 18.6</td>
<td>52.3 ± 47.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DYS RV Septum</td>
<td>21.1 ± 19.8</td>
<td>55.1 ± 30.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4S Peak Strain</td>
<td>28.6 ± 15.4</td>
<td>30.2 ± 16.8</td>
<td>0.741</td>
</tr>
</tbody>
</table>

Data is given as mean ± SD.
*Independent samples Mann-Whitney U-test.
GA = gestational age, PI = pulsatility index, DYS = dyssynchrony in ms, LV = left ventricular free wall, RV = right ventricular free wall, 4S = four-segments.

Figure 3: Study group, appropriate-for-gestational age (AGA) or fetal growth restriction (FGR), correlated with interventricular dyssynchrony (DYS interventricular) (Mann-Whitney U-test P < 0.001).

Figure 4: Receiver operating characteristic curve of interventricular dyssynchrony for the study groups appropriate-for-gestational age (AGA) or fetal growth restriction (FGR) (AUC = 0.991, 0.95 CI 0.976–1).
The intraclass and interclass correlation coefficients were 0.95 (95% CI 0.83–0.99) and 0.94 (95% CI 0.82–0.99) for interventricular dyssynchrony, respectively.

Discussion

This study shows that first, longitudinal mechanical dyssynchrony can be described in fetal hearts using STE; and second, pregnancies complicated by FGR recorded significantly higher degrees of inter- and intraventricular dyssynchrony than those of normal controls.

These findings are in line with previous studies in growth restricted fetuses, reporting reduced cardiac function and altered cardiac morphology in newborns and children along with increased cardiovascular mortality in adults born with FGR [17]. Being the main cause of FGR, placental insufficiency causes redistribution of arterial circulation [18], shows increased levels of biochemical markers of myocardial dysfunction and damage [19] and leads to fetal cardiac compromise. Crispi et al. [4] described cardiovascular remodeling in growth restricted fetuses, which is both the result and the cause of an altered fetal pathophysiology [20] and offers a possible explanation for cardiac dyssynchrony.

While structural evaluation of the fetal heart is well established, functional fetal cardiac evaluation remains challenging. The range of ultrasound (US) techniques applied for the evaluation of fetal cardiac function is as broad as the parameters suggested for its quantification. Hernandez-Andrade et al. [5] focused on the conventional Doppler parameters E/A ratios, outflow tracts and the myocardial performance index (MPI) and recommended MPI as an early and consistent marker of cardiac dysfunction. However, all available reports on these parameters derive from studies implementing an apical or basal four-chamber view. Their qualification for the assessment of data derived from transversal four-chamber view has not yet been investigated. While the MPI is a simple and reproducible means of assessing adult global ventricular function [21] there has been a disappointingly broad variety of normal ranges when applied to normal and complicated pregnancies [22]. Although the application of stringent measurement and acquisition criteria have improved MPI calculation and produced gestational age adjusted reference ranges, Meriki et al. reported that minor variations in caliper placement resulted in significantly different ranges [23].

Recently, several studies focussed on identifying parameters to differentiate fetuses that are simply small for gestational age from pathologically growth restricted fetuses. The PORTO Study [1] reports a strong association between fetuses with an estimated birth weight (EFW) < 3rd centile or with a combination of EFW < 10th centile and abnormal UA Doppler and adverse perinatal outcome, thereby questioning the current FGR definition used and its potential to predict adverse perinatal outcome. Our study introduced interventricular dyssynchrony as a new centile independent parameter, showing high levels of sensitivity and specificity in order to distinguish between FGR and AGA fetuses.

A second innovation of our study was the use of a transversal four-chamber view to evaluate fetal cardiac function. The recently available technology is designed to measure longitudinal strain from an apical four-chamber view. In comparison to the apical or basal four-chamber view, utilized by the vast majority of published data on the evaluation of fetal cardiac function, the transversal four-chamber view offers better delineation of the septum and the ventricular free walls due to the angle of insonation. Allan et al. [16] showed that the highest levels of myocardial movement and shortening fraction are achieved in the basal and mid segments of the heart which can be displayed best in transversal four-chamber view. Although the apical view offers better speckle appearance and resolution for the evaluation of longitudinal myocardial deformation [24] our study reported good feasibility and high reproducibility using a transversal four-chamber view. In daily clinical practice, it is not always possible to achieve the favored view of the fetal heart, whether this be an apical or a transversal view. Hence further investigations on the quantification of apical dyssynchrony might be of value.

In adults, strain and strain rate have been demonstrated to be very sensitive markers for cardiac dysfunction [8, 25]. However, our study showed a low correlation between 4S peak strain values and the two different study groups. The practicability of strain and strain rate for the assessment of fetal ventricular function is controversial. Recently, Willruth et al. [12] reported slightly higher global strain rate values in fetuses with congenital heart diseases compared to healthy controls. Yet, strain and strain rate values obtained from different ultrasound equipments or software may yield variable results, restricting direct comparison [26].

Despite its good feasibility and its high reproducibility we acknowledge that 2D STE still has several limitations when assessing the fetal heart. The STE software is not yet customized for fetal echocardiography. The lack of ECG gating in fetal echocardiography makes the identification of the beginning and the end of a cardiac cycle difficult. Visual control is required in order to ensure the inclusion of a whole fetal cardiac cycle. Low spatial resolution, the
high fetal heart rate and the small size of the fetal heart complicate the exact placement of the segments. Manual adjustment is necessary to make sure that the tracking of the myocardium wall is accurate.

As a consequence of these technical limitations our study did not include examinations in the first and early second trimester.

Although the frame rate is high using the 5S1 transducer, the image quality for fetal cardiac examination is improvable. Therefore studies utilising high frequency transducers to evaluate dysynchrony might be an interesting focus for future work. Furthermore fetal movement makes accurate positioning difficult, as it is not always possible to acquire a transversal view of the heart. An experienced specialist of gynecological ultrasound is needed to obtain convenient raw data files. As the software was designed for the adult heart, the tracking algorithm is susceptible to errors in fetal hearts.

Unlike 2D echocardiographic modalities, 3D techniques permit the assessment of fetal organ volumes and cardiac chamber size in fetal hearts [6]. Displaying the fetal heart cycle in a 3D data volume, this modality allows a reliable tracking of speckles even at low frame rates [10]. In adult echocardiography, several experimental studies and clinical investigations revealed the reliability and the feasibility of 3D STE derived data [27]. Although 3D STE is not yet suitable for clinical use, the implementation of 3D STE might improve the detection of dysynchrony in fetal hearts in the future.

Besides these limitations our study demonstrated that longitudinal mechanical dysynchrony, derived by STE measurement, shows high levels of reproducibility in normally grown as well as in growth restricted fetuses.

In conclusion, evaluation of longitudinal mechanical myocardial dysynchrony of the fetal heart is feasible by 2D STE using a transversal four-chamber view. Fetuses affected by FGR showed increased levels of interventricular dysynchrony in comparison to normal controls. Therefore interventricular dysynchrony may be a useful parameter to evaluate fetal cardiac function. However this was the first study to implement dysynchrony in the fetal heart as a time difference in peaks of strain. Further investigations are required to assess the potential role of longitudinal mechanical dys synchrony as a predictor of poor outcome and as a monitoring tool in pregnancies complicated by FGR.

Author Contribution

Author’s Statement

Conflict of interest: Authors state no conflict of interest.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been compiled with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

References


