Assessment of strain and dyssynchrony in normal fetuses using speckle tracking echocardiography – comparison of three different ultrasound probes

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Abstract

Objective: To evaluate segmental left (LV-S) and right (RV-S) ventricular strain as well as longitudinal mechanical myocardial dyssynchrony as a time difference between peaks in strain of both ventricles in fetuses (two-chamber-dyssynchrony, 2C-DYS) using speckle tracking echocardiography (STE). The aim of our study was to evaluate the influence of data acquisition on the results of STE measurement using different ultrasound probes.

Methods: We prospectively recorded cardiac cycles of four-chamber views of 56 normal fetuses with three different ultrasound probes and analyzed them offline with speckle tracking imaging software. Furthermore, we looked at a possible influence of heartbeat variability (beat-to-beat variability).

Results: The evaluation of the parameters was feasible with all three probes in 53 cases. There was no influence of heartbeat variability and no noticeable differences in 2C-DYS, LV-S and RV-S in all cases and for all three probes determined.

Conclusion: Assessment of strain and dyssynchrony using STE with three different probes is comparable. Further research is needed to validate dyssynchrony as a predictor for fetal outcome.

Keywords: Dyssynchrony; fetal; myocardial deformation; strain; two-dimensional speckle-tracking echocardiography.

Introduction

Although fetal echocardiography was introduced into clinical practice to identify structural congenital heart disease, more recently functional assessment of the fetal heart became a field of interest to predict outcomes in cardiac and extracardiac pathologies. Echocardiography is usually performed by using M-mode, B-mode and Doppler ultrasound [1, 2]. Several studies tried to identify suitable, new deforming imaging parameters for the evaluation of fetal cardiac function, such as strain, strain rate and myocardial performance index [3, 4] assessed by tissue Doppler imaging (TDI), velocity vector imaging (VVI) [5, 6] and speckle tracking echocardiography (STE) [1, 7–15]. However, there are no established clinical standards for the assessment of fetal cardiac function by new deforming imaging parameter yet [2].

Two-dimensional (2D) STE is a non-Doppler technique based on B-mode image analysis. It is an innovative technique to study myocardial motion frame by frame as a surrogate for cardiac function. STE is able to quantify myocardial deformation by measuring strain or strain rate, and it provides regional and global information on myocardial contractility concerning the left and right heart [16]. Potential advantages include only a short extra scanning time and relative angle independence [11].

STE could be a promising tool in the functional assessment of the fetal heart, as it showed good feasibility and reproducibility of measurements in early clinical experiences [8, 14]. Nevertheless, it is still challenging due to the high fetal heart-rate, the small size of the fetal heart, the restricted physical access to the fetus and the impossibility of fetal ECG recording. In addition, the technique depends on different software tools and ultrasound equipment [1, 10, 17].

In adulthood, the main areas of application of STE are the detection of clinical and subclinical myocardial dysfunction, e.g. in hypertension, diabetes, coronary heart disease and cardiomyopathies [18]. Furthermore, mechanical dyssynchrony assessed by STE is a causal factor in left ventricle (LV) dysfunction [19], and it predicts the LV functional response to cardiac resynchronization therapy (CRT).
[20]. As far as we know, there is limited knowledge about the assessment of dyssynchrony in fetal echocardiography.

The aim of our study was to assess strain and dyssynchrony in normal fetal hearts by STE with three different ultrasound probes in order to evaluate the influence of data acquisition. Moreover, one observer analyzed the data of two cardiac cycles from each fetus and from each ultrasound probe to consider a possible influence of heartbeat variability (beat-to-beat variability) and to evaluate the intrastudy variability in image acquisition.

Materials and methods

Study population

We prospectively recorded four-chamber views of the heart in a cohort of unselected 56 fetuses from women with singleton pregnancies, who attended the Clinic of Obstetrics and Gynecology, University Hospital Muenster, from May 2015 to November 2015 for routine screening. The institutional review board approved this study, and informed consent was obtained from all patients for our records of B-Mode-video raw data clips during routine clinical visits. All scans were anonymized before analysis.

All fetuses were healthy, in sinus rhythm and had normal cardiac morphology. Gestational age was determined by the crown-rump length. We excluded those with multiple pregnancies, gestational age below 20 weeks, maternal age below 18 years, known maternal disease such as diabetes or fetuses with malformations, aneuploidy, intrauterine growth restriction or infections.

Fetal echocardiographic and speckle tracking recording and analysis

The 2D STE was performed with a commercially available EPIQ 7 ultrasound device (Philips Medical Systems, Andover, MA, USA), equipped with three different ultrasound probes [5 MHz Sector Array (S5-1), 8 MHz Sector Array (S8-3) and 5 MHz xMatrix Array (X5-1); Philips Medical Systems]. The data acquisition was performed by three experienced obstetricians who were specialists for fetal echocardiography (R.S., M.M. and K.H.). High-resolution, zoomed B-mode video raw data clips of oblique four-chamber views were acquired and stored for offline analysis. Only cases with clear delineation of the left and the right ventricular wall and the septum were included in the study. While recording the loop, the high-resolution zoom was used, and the sector width was narrowed as much as possible to achieve high frame rates. Scans were performed in the absence of maternal and fetal breathing and movements.

Because of the inability of ECG gating in fetal echocardiography, a dummy electrocardiographic signaling was used to enable offline analysis. With each of the three ultrasound probes, two data sets of cardiac cycles were recorded as raw-data clips, stored as standard DICOM files and transferred to a workstation. Further speckle tracking analysis was performed with QLab (QLab 10.4 software, Philips Medical Systems, Andover, MA, USA) with the original frame rate.

The following analysis procedure was performed equally on all six data sets by one investigator (D.R.): Initially, in each case, the myocardial borders of the right and left ventricle were identified on a single end-diastolic frame. The lateral atrioventricular valve annulus of both ventricles and the apex were manually marked to start the automatic placement of seven symmetric tracking segments. The segments covered the whole myocardium of the ventricular wall of the left and right ventricle. The tracking quality was verified for each segment, with subsequent manual adjustment of the segments if necessary. A myocardial longitudinal strain profile was obtained for all seven segments. While developing the analysis method, we chose to assess the whole myocardium because a possible interventricular dyssynchrony could only be obtained if the deformation of both lateral ventricular walls is measured simultaneously. Furthermore, as a consequence of a pilot investigation of our study group, we excluded the three apical and the two basal segments from further measurement because the expected strain values of the middle segments are higher than in the basal and apical segments. The aim of our study was to compare the measurement of strain and dyssynchrony with three different ultrasound probes. Therefore, we selected the mid segments of both lateral walls for further analysis because higher values are more suitable for the detection of possible measurement differences.

We measured the strain of the middle segments of the left (LV-S) and right ventricle (RV-S) as a difference of minimum and maximum peak strain. Two-chamber dyssynchrony (2C-DYS) was calculated as the absolute time difference between the peaks in LV-S and RV-S (Figures 1–3). To evaluate a possible influence of heartbeat variability (beat-to-beat variability), differences between the measurements of two different heartbeats (first beat, second beat) from each fetus and from each ultrasound probe were analyzed separately by one examiner (D.R.).

Statistical analysis

Statistical analysis was performed using the SPSS software (IBM Corporation, New York, NY, USA, version 23). Descriptive statistics were used to characterize the study population. The not normally distributed metric variables were univariate described by median and interquartile range (IQR). For 2C-DYS and frame-rate, range (difference between maximum and minimum) was given instead of IQR because the quartiles Q1, Q2 and Q3 coincided.

Wilcoxon signed-rank test was used to compare two related samples regarding a metric outcome. This was applied (i) to compare the different ultrasound probes (S5-1, S8-3, X5-1) regarding measurement of strain, dyssynchrony and frame-rate (outcome averaged over both heartbeats) and (ii) to analyze interbeat differences.

Analyses were regarded as explorative with P-values displayed for descriptive reasons in order to detect and study meaningful effects. In particular, no adjustment for multiple testing was performed and “significance” refers to local statistical significance defined as a local, unadjusted P-value below 0.05.

Results

Median maternal age was 31 (28, 33) years. Median gestational age was 27 (22, 30) weeks, and median BMI of the women was 23 (20, 25) kg/m².
It was possible to perform speckle tracking echocardiography and analysis of LV-S and RV-S as well as 2C-DYS in 53 of 56 included cases (95% feasibility) with all three ultrasound probes. We excluded three cases with low B-mode image quality and without a clear delineation of the lateral wall. The BMI of the excluded and included cases was comparable [21.6 (19.0, 21.6) vs. 22.0 (20.3, 25.0) kg/m², P = 0.748].

The findings of STE for all fetuses are shown in Table 1. No differences were obtained in LV-S (S5-1 vs. S8-3, P = 0.332; S5-1 vs. X5-1, P = 0.611; S8-3 vs. X5-1, P = 0.661) and RV-S (S5-1 vs. S8-3, P = 0.246; S5-1 vs. X5-1, P = 0.158; S8-3 vs. X5-1, P = 0.639) measured by the three different ultrasound probes.

In all measurements with the three ultrasound probes, we observed no noticeable 2C-DYS.

The frame rates of each individual ultrasound probes were comparable throughout the whole series of measurements. The S5-1 and S8-3 probe showed similar frame rates (P = 0.861). The recorded frame rates of the X5-1 probe were lower compared to the two other probes (S5-1 vs. X5-1, P < 0.001; S8-3 vs. X5-1, P < 0.001).

Table 2 reports results of the analysis of the beat-to-beat variability. There are no noticeable beat-to-beat differences recorded for 2C-DYS, frame rates and strain values in all tested probes.

**Discussion**

As far as we know, this is the first study that compares the impact of different ultrasound probes on the results of STE measurements. We did not find any indication that data acquisition by different probes influences the results of STE. The results of the LV-S, RV-S and 2C-DYS measurements are comparable among all tested probes.

Although structural evaluation of the fetal heart is well established, functional cardiac evaluation remains
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The range of ultrasound techniques applied for the evaluation of fetal cardiac function is as broad as the parameters suggested for its quantification. STE is a new technique for analyzing myocardial motion [21], and its major advantage over TDI cardiac function assessment is that the technology is relatively angle independent [22]. Therefore, recent studies in assessment of fetal cardiac function focus on strain-analysis with speckle-based technologies: First, Di Salvo et al. [8] demonstrated that STE is a feasible and reproducible approach to assess both left and right regional ventricular function in the normal fetal heart. Recent approaches in STE generated reference values for strain [12] and evaluated cardiac function in fetuses with congenital diaphragmatic hernia [7], fetal congenital heart disease [11] and fetuses affected by twin to twin transfusion syndrome [15]. They concluded that STE might be a useful tool to study the progress of myocardial function in affected fetuses [11]. However it remains unclear if assessment of strain by STE allows for better discrimination between healthy fetuses and fetuses with congenital heart disease [14].

The common techniques in fetal strain analysis track the ventricular lateral and septal walls of only one ventricle [1, 8, 15, 23]. In our study, the tracking segments cover the whole myocardium of the ventricular wall of the left and right ventricle. In this way, strain values for the left (LV-S) and right (RV-S) ventricle are achievable in one tracking algorithm. Only by this, it is possible to calculate the new parameter 2C-DYS as the absolute time difference between the peaks in LV-S and RV-S.

In adults, strain has demonstrated to be a very sensitive marker for cardiac dysfunction [24, 25]. The assessment of echocardiographic dyssynchrony is useful to predict CRT response and outcome and is a recent field of research in adults [20, 26, 27], but it does not play a role in fetal echocardiography yet.
In a study of our research group, we tested the reliability of dyssynchrony measurement assessed by STE. The intra- and interobserver variability was low with an excellent intraclass (>0.9) and interclass correlation coefficient (>0.9) [28].

In STE, it is important to differentiate between myocardial wall motion and wall deformation. We chose to analyze strain as deformation analysis, which offers the advantage of discriminating between active and passive myocardial tissue movement [18]. On top of that, it is possible to distinguish between Lagrangian and natural strain. Although Lagrangian strain describes the changes of tissue in relation to the initial length, natural strain expresses the deformation relative to the length at a particular reference point.

![Figure 3: Zoomed diastolic four-chamber view measured with X5-1 probe.](image)

Positioning of the segments for left (LV-S) and right (RV-S) ventricular strain and their corresponding curves. The red arrow shows that there is no longitudinal mechanical myocardial dyssynchrony as a time difference between peaks in strain of both ventricles (two-chamber-dyssynchrony, 2C-DYS) observed.

### Table 1: Outcomes (averaged over first and second beat) by ultrasound probe.

<table>
<thead>
<tr>
<th>Variable</th>
<th>S5-1</th>
<th>S8-3</th>
<th>X5-1</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-S (%)</td>
<td>28.3 (22.6, 33.9)</td>
<td>28.9 (25.0, 35.0)</td>
<td>28.4 (23.7, 33.9)</td>
<td>0.332</td>
<td>0.611</td>
<td>0.661</td>
</tr>
<tr>
<td>RV-S (%)</td>
<td>27.7 (23.2, 34.9)</td>
<td>29.7 (23.7, 36.2)</td>
<td>30.1 (25.0, 36.4)</td>
<td>0.246</td>
<td>0.158</td>
<td>0.639</td>
</tr>
<tr>
<td>2C-DYS*, Δt in ms</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Frame rate, frames/s</td>
<td>199 (169, 201)</td>
<td>199 (146, 201)</td>
<td>187 (151, 201)</td>
<td>0.861</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as medians together with the 25th and 75th percentiles for LV-S and RV-S and with range for 2C-DYS and frame rate. LV-S, segmental left ventricular strain; RV-S, segmental right ventricular strain; 2C-DYS, two-chamber-dyssynchrony.

P1 = S5-1 vs. S8-3; P2 = S5-1 vs. X5-1; P3 = S8-3 vs. X5-1.

P-values by Wilcoxon signed-rank test.

*No test was performed because outcome was identical in all probes.
previous time instance. In echocardiography, it is more appropriate to measure the natural strain, as used in our study, because the measured values are less dependent on the definition of the initial length [18, 29].

Frame rate is considered to be one of the most important aspects of echocardiographic image acquisition [30], but it is still unknown which frame rate should be favored in STE: It must be high enough so that the motion of specific speckle patterns is recognizable between frames and can be followed [31]. A recent study by Sanchez et al. [32] showed the highest reproducibility for right and left ventricular strain when frame rates above 110 frames/s were used in premature infants. D’hooge et al. [33] recommended a frame rate of 80 frames/s as a minimum to display all myocardial motion at normal adult heart rate. In addition, according to Asrar ul Haq et al. [34], for accurate speckle tracking, a high frame rate is important as it decreases the speckle change between frames, allowing better tracking.

By contrast, Dandel et al. [18] reported that the optimal frame rate for STE seems to be 50–70 frames per second, but they also discuss that using higher frame rates could reduce the undersampling problem. With recently developed ultrasound technology, as used in our study, high frame rates around 187 and 199 frames/s and remarkable spatial resolution could be obtained, even for fetal STE. High frame rate might be an important factor to detect changes in 2C-DYS in the millisecond range.

Despite its good feasibility in our study, STE still has several limitations when assessing the fetal heart. Challenging spatial resolution, the higher heart rate and the smaller size of the fetal heart complicate the exact placement of the segments. Nevertheless, our study shows that recent technology enables the reliable assessment of strain and dyssynchrony in fetal hearts. Manual adjustment is necessary to ensure sufficient tracking of the myocardial wall because so far the software is not customized for fetal echocardiography. However, for an experienced prenatal ultrasound observer, there is a short learning curve to obtain and analyze short cine-loop sequences of the fetal cardiac four-chamber view with STE.

In conclusion, the evaluation of LV-S, RV-S and 2C-DYS was feasible with all three probes in all included cases. Assessment of strain and dyssynchrony using STE with three different probes is comparable.

Further research is needed to validate dyssynchrony as a predictor for fetal outcome.

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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 subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

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Table 2: Beat-to-beat variability.

<table>
<thead>
<tr>
<th>Variable</th>
<th>First beat</th>
<th>Second beat</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-S, % (S5-1)</td>
<td>28.3 (21.8, 34.4)</td>
<td>29.5 (19.4, 36.1)</td>
<td>0.604</td>
</tr>
<tr>
<td>LV-S, % (S8-3)</td>
<td>28.7 (22.2, 36.9)</td>
<td>29.6 (25.1, 35.6)</td>
<td>0.989</td>
</tr>
<tr>
<td>LV-S, % (X5-1)</td>
<td>27.7 (22.5, 34.3)</td>
<td>30.0 (21.3, 35.3)</td>
<td>0.770</td>
</tr>
<tr>
<td>RV-S, % (S5-1)</td>
<td>27.2 (22.3, 34.0)</td>
<td>28.3 (23.0, 35.6)</td>
<td>0.346</td>
</tr>
<tr>
<td>RV-S, % (S8-3)</td>
<td>30.9 (24.9, 35.9)</td>
<td>30.4 (20.7, 37.0)</td>
<td>0.901</td>
</tr>
<tr>
<td>RV-S, % (X5-1)</td>
<td>29.9 (23.9, 36.4)</td>
<td>30.3 (23.9, 37.9)</td>
<td>0.501</td>
</tr>
<tr>
<td>2C-DYSa Δt (S5-1, S8-3, X5-1)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>–</td>
</tr>
<tr>
<td>Frame ratea, frames/s (S5-1)</td>
<td>199 (169, 201)</td>
<td>199 (169, 201)</td>
<td>–</td>
</tr>
<tr>
<td>Frame rate, frames/s (S8-3)</td>
<td>199 (146, 201)</td>
<td>199 (146, 201)</td>
<td>0.317</td>
</tr>
<tr>
<td>Frame rate, frames/s (X5-1)</td>
<td>187 (151, 201)</td>
<td>187 (151, 201)</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Data are presented as medians together with the 25th and 75th percentiles for LV-S and RV-S and with range for 2C-DYS and frame rate.

LV-S, segmental left ventricular strain; RV-S, segmental right ventricular strain; 2C-DYS, two-chamber-dyssynchrony.

P-values by Wilcoxon signed-rank test.

aNo test was performed because outcome was identical in all probes.
References


