**INTER-VENDOR DISCORDANCE OF FETAL AND NEONATAL MYOCARDIAL TISSUE DOPPLER AND SPECKLE TRACKING MEASUREMENTS**

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**Abbreviations:** IVS=inter-ventricular septal; LV=left ventricular; RV=right ventricular; STE=speckle tracking echocardiography; TDI=pulsed waved tissue Doppler imaging.

**ABSTRACT**

**Background:** Fetal and neonatal studies report a wide range of cardiac parameters derived by pulsed-wave tissue Doppler imaging (TDI) and 2D speckle tracking echocardiography (STE). The use of different ultrasound systems and their vendor-specific software compromise the ability to compare echocardiographic findings between various studies. The aim of this study was to evaluate inter-vendor reproducibility as well as intra- and inter-observer repeatability of TDI and STE measurements in normal term fetuses and neonates.

**Methods:** Prospective study of term fetuses (n=196) from uncomplicated pregnancies assessed days before the onset of labor and a few hours after birth. Fetal and neonatal TDI and STE parameters were obtained and analyzed using vendor-specific software on three ultrasound systems: Toshiba Aplio MX vs. GE Vivid E9, and GE Vivid E9 vs. Philips EPIQ. Reproducibility study in fetuses and neonates (n=118) was performed by systematic scanning with head-to-head comparison.

**Results:** TDI reproducibility showed moderate to good correlation with good agreement for fetuses and neonates on Toshiba vs. GE (ICC=0.4-0.8). Correlation of TDI measurements on GE vs. Philips was poor to moderate for fetuses (ICC=0.1-0.6) and moderate to good for neonates (ICC=0.5-0.8) with wider limits of agreement. Fetal and neonatal STE parameters revealed very poor correlation (ICC =0.1-0.3) and agreement between ultrasound vendors. Intra- and inter-observer repeatability demonstrated good to excellent correlation of all fetal and neonatal TDI and STE measurements with good agreement irrespective of the ultrasound platform used.

**Conclusion:** Our findings demonstrate reliable assessment of fetal and neonatal TDI and STE measurements when performed on the same ultrasound platform, whereas different vendor ultrasound machines and software give significantly divergent estimates of TDI and STE parameters in fetuses and neonates. These inter-vendor discrepancies have significant clinical and research implications and should be considered when interpreting and comparing study findings, establishing reference standards, or performing systematic reviews.

**Key Words:** fetal heart; fetal echocardiography; LV torsion; myocardial deformation; neonatal echocardiography; repeatability and reproducibility; speckle tracking; tissue Doppler imaging.

**INTRODUCTION**

Measurement of fetal and neonatal cardiac functional parameters can aid diagnosis, assess disease severity, predict prognosis and direct management strategies. Increasingly, more recent ultrasound technologies such as spectral or pulsed wave tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) are being used to undertake functional cardiac assessments in fetuses and neonates. However, echocardiographic measurements, especially in fetuses, tend to produce various sorts of errors causing the measured value to differ from the true value (1). Adult and pediatric studies reported a high inter-vendor variability of modern ultrasound technologies and recommended further evaluation of these techniques before adoption for clinical and research use (2-7). Previous work in fetuses and neonates has provided a wide range of myocardial functional and deformational values derived from different ultrasound vendors, precluding accurate comparisons between studies (8, 9). There are few studies assessing reliability and agreement of STE indices in perinatal life, but these have all been performed using the same ultrasound system (10-16). Accurate assessment of functional cardiac indices term fetuses and neonates may improve knowledge of fetal perinatal adaptation in normal and compromised pregnancies to facilitate the delivery of treatment strategies to prevent adverse pregnancy outcome and reduce the long-term risk of cardiovascular pathology in later life. An appropriately conducted repeatability and reproducibility study reporting both intra-class correlation coefficient and limits of agreement between operators and vendors would provide important information on precision and reliability of perinatal cardiac functional assessment and ensure clinical relevance of study findings. The main objectives of this study were to evaluate inter-vendor reproducibility as well as intra- and inter-observer repeatability of TDI and STE measurements in normal term fetuses and neonates.

**METHODS**

This was a prospective longitudinal study involving 196 fetuses of healthy women with singleton uncomplicated naturally conceived pregnancies at the gestational age >37weeks and their newly born babies. Pregnant women attending for routine antenatal care at St. George’s University Hospital were recruited if the pregnancies were assessed as normal and fetuses had structurally normal hearts. Exclusion criteria were *in vitro* fertilisation (IVF) and multiple pregnancies, fetal structural and chromosomal abnormality, impaired fetal growth, fetal prematurity (<37weeks at birth), any maternal pre-pregnancy or pregnancy-related co-morbidity, and pregnant women in labor. All participants gave written consent for fetal and neonatal echocardiogram. The Ethics Committee of NRES Committee London-Surrey Borders approved the study protocol (Reference -12/LO/0945).

**Echocardiography**

Fetal spectral pulsed wave (PW) tissue Doppler imaging (TDI) and 2D speckle tracking echocardiography (STE) were performed a few days before birth. The neonatal cardiac assessment was done a few hours after birth. It was conducted intentionally on three different ultrasound platforms - Toshiba Aplio MX (Toshiba Medical Systems, Japan) [n=108], GE Vivid E9 (General Electric Healthcare, Norway) [n=54], and Philips EPIQ (Philips Medical System, USA) [n=34] from September 2012 to June 2015 with each machine used over a given time period. One investigator (OP) performed all ultrasound examinations using three different ultrasound machines for obtaining the paired fetal and neonatal echocardiographic data in all 196 pregnant women. When two ultrasound systems were available at the same time, the inter-vendor reproducibility study was carried out (Supplemental Figure S1).

In randomly selected 120 fetal and 120 neonatal echocardiograms, intra- and inter-observer repeatability of measurements in the same and different cardiac cycles was performed within all ultrasound platforms. In 59 patients, fetal and neonatal TDI and STE indices were obtained on different ultrasound platforms - Toshiba vs. GE (25 fetal and 25 neonatal scans) and GE vs. Philips (34 fetal and 34 neonatal scans) - by systematic scanning with the head to head comparison (scanning the same fetus or neonate on two different ultrasound machines performed consequently and a few minutes apart between scans with two ultrasound machines set by the both bedsides in the same scanning room). Using Toshiba Aplio MX ultrasound system, fetal and neonatal TDI curves and 2D images for STE analysis were obtained and recorded with the multi-sector tissue harmonic (TH) transducer PST-30 BT (3MHz) with TDI mode activated. On GE Vivid E9 ultrasound system, these data were obtained and recorded with the adult matrix phased array sector transducer M5S, while the adult matrix array sector transducer with pure wave crystal technology X5-1 was used on Philips EPIQ platform. Within the same platform, TDI curves and 2D images for STE analysis were obtained and recorded in the same manner and with the same ultrasound transducer in both fetal and neonatal groups. The narrowest possible ultrasound field and a single focal zone were used during STE image acquisition to obtain the frame rates *greater than 100 frames per second (fps)*. These settings provided an acceptable combination of high temporal resolution with spatial definition to enhance the feasibility of the frame-by-frame tracking technique. Additionally, we calculated the frame rate to heart rate (FR/HR) ratio in all fetuses and neonates as an index that has been closely linked to enhanced reproducibility (17). All neonatal examinations were recorded with a simultaneous electrocardiogram (ECG). In the absence of a fetal ECG, the cardiac cycle was determined from a dummy ECG device (Lionheart2 BIO-TEK® Multiparameter Simulator, BIO-TEK Instruments, Inc., Winooski, VT) as previously described (18-21). Three different vendor-specific software - Advanced Cardiac Package [ACP] (Toshiba), EchoPAC version 113 (General Electric), QLAB version 8 (Philips) - were used for TDI and STE analysis of the data obtained on Aplio MX, Vivid E9 and EPIQ ultrasound systems, respectively.

Fetal and neonatal LV and RV systolic and diastolic myocardial velocities and myocardial time intervals derived by PW-TDI and longitudinal myocardial deformation indices obtained by STE were assessed on all ultrasound vendors. Besides, GE ultrasound system allowed assessment of all aspects of global and regional myocardial deformation: longitudinal, circumferential, radial and rotational, whereas Toshiba had an option to evaluate transversal strain and systolic strain rate in both fetus and neonate. All TDI and STE indices were utilized for feasibility and intra- and inter-observer repeatability study within each ultrasound platform. All TDI parameters were also compared between different ultrasound vendors for reproducibility study. The reproducibility study of STE parameters on Toshiba vs. GE utilized LV and RV global longitudinal and regional strain and global strain rate , whereas LV and RV global and regional longitudinal strain measurements were compared between GE and Philips systems (Supplemental data). Image acquisition and data analysis were conducted according to the study protocol (Supplemental data) and with regards to previously published methodology (18-21). All collected data were exported to Excel spreadsheet for statistical analysis. Study terminology (concepts of feasibility, repeatability and reproducibility) is outlined in Supplemental data.

***Intra- and inter-observer repeatability***

TDI and STE measurements of 25 fetal and 25 neonatal echocardiograms were repeated by the same observer (OP) on a Toshiba Aplio MX ultrasoundmachine in the same cardiac cycle for calculation of the measurement errors, and in different cardiac cycles for calculation of the overall errors (combined acquisition and measurement errors). In 10 fetal and 10 neonatal echocardiograms on Toshiba Aplio MX, these measurements were repeated by different observers (MB, VDZ, and BS)in the same cardiac cycle and then in a different cardiac cycle. The intra- and interobserver overall errors of TDI and STE indices were also investigated in 20 fetuses and 20 neonates within Vivid E9 and Philips EPIQ platforms and their vendor-specific software. Additionally, intra- and inter-observer repeated measurements of *regional* longitudinal strain were analyzed in 10 fetuses and 10 neonates within all ultrasound machines. The fetal and neonatal echocardiograms were randomly selected. All observers were blinded to one another’s results, and the repeated measurements were performed 2-3 months apart from baseline fetal/neonatal measurements.

***Inter-vendor reproducibility***

The vendor-specific software allowed comparison of only longitudinal strain between the different ultrasound platforms. TDI indices and longitudinal strain (global and regional) were compared in 25 fetuses and 25 neonates between Toshiba vs. GE. The same parameters (Supplemental data) were analyzed and compared in 34 fetuses and 34 neonates between GE vs. Philips.

***Feasibility / Image quality***

The 2D image quality was assessed and graded as previously published (13, 22): [4] good – very clear myocardial definition, [3] adequate – all myocardial segments could be defined, [2] limited – the myocardial borders are not clearly defined in 1-2 segments, [1] poor – more than 2 segments are not well defined, [0] - unsuitable.

**Statistical analysis**

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk and Kolmogorov-Smirnov tests for normality were performed on all data sets to assess distribution. The continuous data were expressed as mean ± standard deviation (SD) or median and interquartile range according to the data distribution. To compare continuous data between three different ultrasound systems, one-way ANOVA test was performed for normally distributed data, and Kruskal-Wallis test was used for skewed data, as appropriate. The categorical data were compared between ultrasound machines using Pearson’s χ2 test.The differences between groups were deemed as significant only if the 2-tailed p-values were less than 0.01 (Bonferroni correction for type 1 error or false positive results of multiple measurements).

For repeatability and reproducibility, limits of agreement (LoA) with Bland-Altman graphs and Pitman’s test of difference in variance, and intra-class correlation coefficient (ICC) with 95% confidence intervals were calculated for each measurement (23, 24). A two-way mixed effect model was used when calculating the intra-class correlation coefficients. The accuracy and precision statistics provided included bias (the mean difference between two methods), precision (the standard deviation [SD] of differences), and 95% limits of agreement (bias±1.96 SD). ICC was interpreted as follows: > 0.80 as excellent, 0.70 ≤ ICC ≤ 0.80 as good, 0.40 ≤ ICC < 0.70 as moderate, ICC < 0.40 as poor (25). Additionally, the coefficient of variation (CV) was calculated as (SD/mean value)x100%; CV <15% was reported as a measure of minimal variability and positive reproducibility (13).

**RESULTS**

Demographic characteristics and baseline scan details of pregnancies enrolled in the study are summarized in Table 1. There were no cases of postnatal admission to the neonatal intensive care unit or adverse perinatal outcomes. Structurally and functionally normal hearts were confirmed by echocardiography in all newborns.

***Frame rate, image quality and feasibility***

There were no significant differences in fetal LV and RV frame rates between different ultrasound machines. The mean frame rates in apical/basal view were as followed: for fetuses, Toshiba, 135±14fps vs. GE, 135±14fps vs. Philips, 144±10fps (p=0.630); for neonates: Toshiba, 128±11fps vs. GE, 123±11fps vs. Philips, 136±13fps (p=0.271). Additionally, frame rates of LV short axis views at both apical and basal levels obtained on GE machine was 125±10 fps for the fetal heart and 120±11 fps for the neonatal heart. There were similar results when the frame rate to heart rate (FR/HR) ratios were compared between machines: for fetuses, Toshiba, 0.98 vs. GE, 0.99 vs. Philips, 1.04 (p=0.312); for neonates: Toshiba, 1.07 vs. GE, 1.06 vs. Philips, 1.15 (p=0.118). The quality of fetal images was significantly better on Philips and GE platforms (the mean image quality scores: Toshiba, 2.3±0.7 vs. GE, 3.1±0.8 vs. Philips, 3.6±0.5; p<0.0001), whereas neonatal images had significantly better quality on Toshiba and GE ultrasound systems (the mean image quality scores: Toshiba, 3.9±0.4 vs. GE, 3.6±0.6 vs. Philips, 3.3±0.8, p<0.01) (Figure 1 A). There was no significant difference infeasibility of both TDI and STI measurements between all ultrasound platforms (Figure 1 B and C) – with rates over 80% in fetuses and 95% in neonates.

***Inter-vendor reproducibility***

Reproducibility of spectral TDI indices on Toshiba vs. GE in both fetus and neonate demonstrated a moderate correlation with a good agreement (fetal RV S’ 5.2cm/s vs. 4.8cm/s, ICC=0.5 and LV S’ 5.1cm/s vs. 4.7cm/s, ICC=0.6; neonatal RV S’ 6.4cm/s vs. 6.0cm/s, ICC=0.7 and LV S’ 5.2cm/s vs. 4.7cm/s, ICC=0.5) (Figure 2, Tables 2 and S1). As for GE vs. Philips, there were a very poor correlation and a moderate agreement of spectral TDI parameters in fetuses (RV S’ 7.0cm/s vs. 6.2cm/s, ICC=0.3; LV S’ 5.0cm/s vs. 6.4cm/s, ICC=0.1), and a moderate to good correlation and a good agreement in neonates (RV S’ 7.0cm/s vs. 6.9cm/s, ICC=0.8; LV S’ 5.0cm/s vs. 5.3cm/s ICC=0.7) (Figure 2, Tables 2 and S2). The comparison of STE parameters on Toshiba vs. GE and GE vs. Philips systems demonstrated the very poor correlation and agreement in global and segmental values of longitudinal strain in both fetus and neonate (*Toshiba vs. GE*: fetal RV L-S -8.0% vs. -13%, ICC=0.1 and fetal LV S-L -10% vs. -14%, ICC=0.1; neonatal RV L-S -7% vs. -11%, ICC=0.2 and neonatal LV S-L -9% vs. -13%, ICC=0.1; *GE vs. Philips*: fetal RV L-S -15.0% vs. -22%, ICC=0.1 and fetal LV S-L -15% vs. -25%, ICC=0.1; neonatal RV L-S -12% vs. -20%, ICC=0.04 and neonatal LV S-L -13% vs. -22%, ICC=0.01; (Figures 3 and 4, Tables 2, S3 and S4). When compared base-to-apex deformational changes between different vendors in the fetus and neonate, LV and RV longitudinal strain gradient showed a decrease on Toshiba platform, while in contrast, this gradient was increased on Philips and GE platforms (Tables S3 and S4).

***Intra- and inter-observer repeatability***

Repeated by the same observer TDI and STE indices on Toshiba, GE and Philips machines showed an excellent correlation in the same frame, and good to excellent correlation in a different frame (Toshiba vs. GE vs. Philips: ICC >0.7 in 100% vs. 100% vs. 85% of fetal TDI measurements; 75% vs. 71% vs.100% of fetal STE indices; 92% vs. 100% vs. 85% of neonatal TDI parameters; 75% vs. 83% vs. 50% of neonatal STE indices, respectively) with excellent agreement for all measurements in both fetus and neonate (Tables 2 and S5 – S7). Segmental analysis of repeated measurements of fetal and neonatal longitudinal strain performed by the same observer within all vendors had the good correlation and agreement on both Toshiba and GE machines, and moderate correlation and agreement on Philips system (Tables S8 – S10). Within all ultrasound machines, inter-observer repeatability determined good to excellent correlation and agreement of fetal and neonatal TDI indices, and global and regional neonatal STE indices (Toshiba vs. GE vs. Philips: ICC >0.7 in 83% vs. 100% vs. 75% of fetal TDI parameters; 100% vs. 100% vs. 75% of neonatal TDI indices; 83% vs. 88% vs. 100% of neonatal STE measurements, respectively). Inter-observer repeated fetal STE global deformational measurements on GE system revealed a variation in correlation and agreement from moderate to excellent with the highest correlation of longitudinal deformation and the lowest inter-observer reliability and agreement of radial deformation. Both intra-vendor correlation and agreement of fetal global STE indices were better on Toshiba and GE ultrasound platforms than on Philips system (Toshiba vs. GE vs. Philips: ICC >0.7 in 75% vs. 66% vs. 50% of fetal STE indices). (Tables 2 and S11- S13). Furthermore, inter-observer repeatability of fetal STE parameters had an excellent correlation in the same cardiac cycle and showed moderate to good correlation when measurements were repeated in a different cardiac cycle.Fetal regional longitudinal strain analysis repeated by the different observer and performed within all vendors had a moderate to good correlation with a good agreement on both Toshiba and GE machines, and poor to moderate correlation and moderate agreement on Philips ultrasound system (Tables S8 - S10).

**DISCUSSION**

This study assesses repeatability and reproducibility of TDI and STE fetal and neonatal functional parameters on three different ultrasound vendors. Our results demonstrate that the inter-vendor correlation/agreement of TDI indices varied from poor to good depending on ultrasound system compared, whereas comparison of STE parameters on different vendors revealed a very poor correlation/agreement in both fetus and neonate. In contrast, there was good intra- and inter-observer reliability and agreement of fetal and neonatal novel indices performed on the same ultrasound platform.

**Inter-vendor TDI and STE measurement comparisons**

Feasibility of TDI and STE measurements was similar between all ultrasound platforms in our study and showed higher rates in neonates (95%) than in term fetuses (80% ). Ultrasound assessment of fetal cardiac function remains a challenging task due to fetal (size of the fetal heart, fetal position, fetal movements, high heart rate, maturational changes in the heart and distance from the ultrasound probe) as well as maternal factors such as increased body mass index, and technical difficulties related to different echocardiographic techniques limiting its feasibility in fetus (1, 11, 26). In general, feasibility studies that demonstrate > 80% are considered to be good (26), consistent with our study findings.

When TDI indices were compared between different ultrasound platforms, Toshiba vs. GE showed a moderate to good correlation with good agreement in both fetus and neonate. In contrast, there was a significant discordance of TDI parameters between GE and Philips for the measurement error of systolic and diastolic myocardial velocities and time intervals. The variations of time intervals and myocardial tissue velocities are likely to be the result of intrinsic algorithmic differences between GE and Philips ultrasound systems. Moreover, the angle dependencyof the TDI technique could also have contributed to inter-vendor acquisition errors in fetuses due to inevitable changes in the fetal position between scans resulting in slightly different acquisition angles of TDI velocities on different ultrasound platforms. Our results of inter-vendor discordance of fetal TDI indices are in an agreement with recent studies (8, 9).

Variability of fetal and neonatal STE indices introduced by a change in the ultrasound platform has not been well defined. The study data demonstrate a very poor correlation/agreement between the different ultrasound platforms for global and regional longitudinal strain values. Toshiba and GE software tended to produce consistently lower longitudinal deformational indices compared to the Philips software. The same trend for GE ultrasound systems was previously observed in the adult heart (27). Moreover, there were significant differences in the regional longitudinal strain across all segments between three vendors. Possible explanations include different requirements of frame rate depending on the vendor-specific method of speckle tracking by a particular vendor – such as block-matching, optical flow and combined (block-matching-optical) methods (28). It has been reported that optical flow method is more robust to noise and does not necessarily perform well on high frame rates as between-frame motion is simply too small to be detected accurately, and estimation error accumulates over the cardiac cycle. In contrast, block-matching is more sensitive to noise, and speckle tracking requires data to be acquired at higher frame rates. Additional vendor-specific differences include aspects of the analysis technique such as image format, numerical filters, processing algorithms, differences in tracking and boundary tracing. Another factor that could have influenced STI inter-vendor discordance is the way the fetal dummy ECG was used. In our study, the ECG gating for fetal image acquisition was used on all ultrasound platforms. However, the Philips platform permitted only approximation of a fetal cardiac cycle determination, contributing to a greater variation of deformational parameters.

There were also significant differences in the regional longitudinal strain across all segments between vendors with a tendency for LV and IVS regional longitudinal strain to increase towards the apex observed on both GE and Philips systems (29, 30). In contrast, Toshiba had a decreased trend of LV longitudinal deformation from base to the apex. Furthermore, RV base-to-apex gradient was decreased on GE and Toshiba as previously reported (29, 31-33), but again increased on the Philips platform. The deformational heterogeneity at the apical level may be explained by the differences in methodology of generating this strain measure (33). Decreased image quality at the apex or chamber foreshortening could also result in apical deformation value under- or over-estimation, respectively (34). Image artefacts such as reverberation can also reduce the inter-frame correlation between speckle patterns and influence regional myocardial values, particularly at the basal segments. Finally, different vendor-specific segmental models were implemented for strain and strain rate analysis - Philips had a seven-segmental model, whereas GE and Toshiba software employed a six-segmental model for the apical/basal four-chamber view.

**Intra-vendor TDI and STI measurement comparisons**

Intra- and inter-observer repeatability of all TDI indices performed separately on Toshiba and GE platforms demonstrated excellent correlation and limits of agreement in the same cardiac cycle and a different cardiac cycle in fetus and neonate. Some fetal indices, principally myocardial time intervals on the Philips, and LV and IVS E’/A’ ratios on Toshiba - had a significant overall error when repeated by a different observer. The latter findings could be explained by a known variation of fetal myocardial diastolic velocities due to fetal breathing movements or changes in heart rate from frame to frame influencing the diastolic ratio results (35, 36).

Our results showed good intra- and inter-observer repeatability of global myocardial deformational parameters within the same ultrasound platform with small acquisition errors – consistent with previous fetal and neonatal STE studies (11, 15, 16). It is fundamental for speckle tracking methodology that speckle patterns are preserved between image frames. However, speckle patterns are temporally unstable not only due to speckle decorrelation (out of plane motion) but also due to physiological changes of living tissue structures and modifications of interrogation angles between moving tissue and ultrasonic beam. The accumulation of small random errors in detection of speckled patterns along the tracking process can lead to inaccurate tracking results (37, 38). Moreover, it was reported that the high heart rate at a regular frame rate of 35fps resulted in more speckle decorrelation between frames, thus underestimating the global longitudinal strain (39). Speckle decorrelation could be limited by acquiring the data at sufficiently high frame rates although this would come at the expense of spatial resolution and signal-to-noise ratio of the image (13, 40, 41). On the other hand, the speckle distribution might be misleading when the frame rates are too high. Specifically, high frame rates can result in smoothing that may register the strain values where there is no deformation exists. In the current study, an average frame rate of 100-130fps was used for all acquisitions, low enough to allow measurement precision, but not so high as to compromise spatial resolution.

High-quality image data set will remain a prerequisite for high repeatability and reproducibility of the STE technique. The Philips system had the highest image quality score but demonstrated the poorest repeatability assessment for the global and regional longitudinal strain. This finding could be explained by the inability to precisely define the fetal cardiac cycle according to the movements of atrioventricular valves either during acquisition or post-processing.

The intra- and inter-observer repeatability analysis of all aspects on myocardial deformation was possible to perform on GE ultrasound system and demonstrated more obvious measurement error in fetal global radial strain and strain rate compared to longitudinal, circumferential and rotational deformation that was in concordance with adult studies (4, 42, 43). Toshiba system had similar findings of a weaker correlation of transversal strain and strain rate compared to longitudinal deformation. Tracking in the lateral direction is mainly dependent on lateral resolution, and considerable out-of-plane motion of acoustic markers in short-axis views could also represent a limitation for the consistency of findings when transversal/radial motion is analyzed (42).

**Strength and limitations**

This is a first study exploring inter-vendor reproducibility of STE in fetuses and neonate. The strength of our study is a prospective follow up design with the inclusion of a healthy population and application of three ultrasound systems from different manufacturers with their vendor-specific software. The limitation of our study was that we could not directly compare fetal and neonatal TDI and STE parameters obtained on Toshiba vs. Philips ultrasound platforms due to the unavailability of these two research machines at the same time.

**Clinical implications**

The inter-vendor discrepancies of fetal and neonatal TDI and STE parameters have significant clinical and research implications and should be considered when performing serial assessments, interpreting results, establishing reference standards, comparing study findings conducted on different ultrasound equipment, or performing systematic reviews. Our findings facilitate the ongoing efforts for standardization of software algorithm across different manufacturers.

**Conclusions**

Our findings demonstrate reliable assessment of spectral tissue Doppler and speckle tracking imaging measurements when performed on the on the same ultrasound platform. However, TDI and STE deformation parameters were highly vendor dependent, and discordance levels were beyond intrinsic measurement variability of any of the tested combinations of ultrasound platforms and their vendor-specific software.

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**CONFLICT OF INTERESTS**

None declared.

**REFERENCES**

1. Crispi F, Gratacos E. Fetal cardiac function: technical considerations and potential research and clinical applications. *Fetal Diagn Ther* 2012;32:47-64.

2. Koopman LP, Slorach C, Hui W, Manlhiot C, McCrindle BW, Friedberg MK, et al. Comparison between different speckle tracking and color tissue Doppler techniques to measure global and regional myocardial deformation in children. *J Am Soc Echocardiogr* 2010;23:919-28.

3. Nelson MR, Hurst RT, Raslan SF, Cha S, Wilansky S, Lester SJ. Echocardiographic measures of myocardial deformation by speckle-tracking technologies: the need for standardization? *J Am Soc Echocardiogr* 2012;25:1189-94.

4. Takigiku K, Takeuchi M, Izumi C, Yuda S, Sakata K, Ohte N, et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. *Circ J* 2012;76:2623-32.

5. Negishi K, Lucas S, Negishi T, Hamilton J, Marwick TH. What is the primary source of discordance in strain measurement between vendors: imaging or analysis? *Ultrasound Med Biol* 2013;39:714-20.

6. Park CM, March K, Williams S, Kukadia S, Ghosh AK, Jones S, et al. Feasibility and reproducibility of left ventricular rotation by speckle tracking echocardiography in elderly individuals and the impact of different software. *PLoS One* 2013;8.

7. Nagata Y, Takeuchi M, Mizukoshi K, Wu VC, Lin FC, Negishi K, et al. Intervendor variability of two-dimensional strain using vendor-specific and vendor-independent software. *J Am Soc Echocardiogr* 2015;28:630-41.

8. Lobmaier SM, Cruz-Lemini M, Valenzuela-Alcaraz B, Ortiz JU, Martinez JM, Gratacos E, et al. Influence of equipment and settings on myocardial performance index repeatability and definition of settings to achieve optimal reproducibility. *Ultrasound Obstet Gynecol* 2014;43:632-9.

9. Cruz-Lemini M, Valenzuela-Alcaraz B, Figueras F, Sitges M, Gomez O, Martinez JM, et al. Comparison of Two Different Ultrasound Systems for the Evaluation of Tissue Doppler Velocities in Fetuses. *Fetal Diagn Ther* 2016;40:35-40.

10. Pena JL, da Silva MG, Faria SC, Salemi VM, Mady C, Baltabaeva A, et al. Quantification of regional left and right ventricular deformation indices in healthy neonates by using strain rate and strain imaging. *J Am Soc Echocardiogr* 2009;22:369-75.

11. Crispi F, Sepulveda-Swatson E, Cruz-Lemini M, Rojas-Benavente J, Garcia-Posada R, Dominguez JM, et al. Feasibility and Reproducibility of a Standard Protocol for 2D Speckle Tracking and Tissue Doppler-Based Strain and Strain Rate Analysis of the Fetal Heart. *Fetal Diagn Ther* 2012;32:96-108.

12. Onugoren O, Gottschalk E, Dudenhausen JW, Henrich W. Assessment of long-axis ventricular function in the fetal heart with a tissue-tracking algorithm. *J Perinat Med* 2012;40:297-305.

13. Levy PT, Holland MR, Sekarski TJ, Hamvas A, Singh GK. Feasibility and reproducibility of systolic right ventricular strain measurement by speckle-tracking echocardiography in premature infants. *J Am Soc Echocardiogr* 2013;26:1201-13.

14. Ingul CB, Loras L, Tegnander E, Eik-Nes SH, Brantberg A. Maternal obesity affects fetal myocardial function as early as in the first trimester. *Ultrasound Obstet Gynecol* 2016;47:433-42.

15. Maskatia SA, Pignatelli RH, Ayres NA, Altman CA, Sangi-Haghpeykar H, Lee W. Longitudinal Changes and Interobserver Variability of Systolic Myocardial Deformation Values in a Prospective Cohort of Healthy Fetuses across Gestation and after Delivery. *J Am Soc Echocardiogr* 2016;29:341-9.

16. Enzensberger C, Achterberg F, Degenhardt J, Wolter A, Graupner O, Herrmann J, et al. Feasibility and Reproducibility of Two-Dimensional Wall Motion Tracking (WMT) in Fetal Echocardiography. *Ultrasound Int Open* 2017;3:E26-e33.

17. Ferferieva VVdBAC, P.; Jasaityte, R.; La Gerche, A.; Rademakers, F.; Herijgers, P.; D’hooge, J. Assessment of strain and strain rate by twodimensional speckle tracking in mice: comparison with tissue Doppler echocardiography and conductance catheter measurements. *Eur Heart J Cardiovasc Imaging* 2013;14:765-73.

18. Patey O, Carvalho, J.S., Thilaganathan, B. Perinatal changes in fetal cardiac geometry and function in gestational diabetic pregnancies at term. *Ultrasound Obstet Gynecol* 2018 doi: 10.1002/uog.20187 (in press).

19. Patey O, Carvalho, J.S., Thilaganathan, B. Perinatal changes in cardiac geometry and function in growth restricted fetuses at term. *Ultrasound Obstet Gynecol* 2018 doi: 10.1002/uog.19193 (in press)

20. Patey O, Gatzoulis MA, Thilaganathan B, Carvalho JS. Perinatal Changes in Fetal Ventricular Geometry, Myocardial Performance, and Cardiac Function in Normal Term Pregnancies. *J Am Soc Echocardiogr* 2017;30:485-92.e5.

21. Patey OC, J.S.; Thilaganathan, B. Left ventricular torsional mechanics in term fetuses and neonates *Ultrasound Obstet Gynecol* 2018 doi: 10.1002/uog.20261 (in press).

22. Colan SDS, G.; Margossian, R.; Gallagher, D.; Altmann; Canter, C. . The Ventricular Volume Variability Study of the Pediatric Heart Network: Study Design and Impact of Beat Averaging and Variable Type on the Reproducibility of Echocardiographic Measurements in Children with Chronic Dilated Cardiomyopathy. *J Am Soc Echocardiography* 2012;25:842-54.

23. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-10.

24. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. *Ultrasound Obstet Gynecol* 2003;22:85-93.

25. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016;15:155-63.

26. Erickson CTL, P.T.; Craft, M.; Li, L.; Danford, D.A.; Kutty, S. Maturational patterns in right ventricular strain mechanics from the fetus to the young infant. *Early Hum Dev* 2019;129:23-32.

27. Sun JP, Lee AP, Wu C, Lam YY, Hung MJ, Chen L, et al. Quantification of left ventricular regional myocardial function using two-dimensional speckle tracking echocardiography in healthy volunteers--a multi-center study. *Int J Cardiol* 2013;167:495-501.

28. Alessandrini M, Heyde B, Queiros S, Cygan S, Zontak M, Somphone O, et al. Detailed Evaluation of Five 3D Speckle Tracking Algorithms using Synthetic Echocardiographic Recordings. *IEEE Trans Med Imaging* 2016;35:1915-26.

29. Barker PC, Houle H, Li JS, Miller S, Herlong JR, Camitta MG. Global longitudinal cardiac strain and strain rate for assessment of fetal cardiac function: novel experience with velocity vector imaging. *Echocardiography* 2009;26:28-36.

30. Jashari H, Rydberg A, Ibrahimi P, Bajraktari G, Kryeziu L, Jashari F, et al. Normal ranges of left ventricular strain in children: a meta-analysis. *Cardiovasc Ultrasound* 2015;13:37.

31. Willruth AM, Geipel AK, Fimmers R, Gembruch UG. 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. *Ultrasound Obstet Gynecol* 2011;37:143-9.

32. Schubert U, Muller M, Norman M, Abdul-Khaliq H. Transition from fetal to neonatal life: Changes in cardiac function assessed by speckle-tracking echocardiography. *Early Hum Dev* 2013;89:803-8.

33. Levy PT, Sanchez Mejia AA, Machefsky A, Fowler S, Holland MR, Singh GK. Normal ranges of right ventricular systolic and diastolic strain measures in children: a systematic review and meta-analysis. *J Am Soc Echocardiogr* 2014;27:549-60, e3.

34. Germanakis I, Gardiner H. Assessment of fetal myocardial deformation using speckle tracking techniques. *Fetal Diagn Ther* 2012;32:39-46.

35. van der Mooren K, Wladimiroff JW, Stijnen T. Effect of fetal breathing movements on fetal cardiac hemodynamics. *Ultrasound Med Biol* 1991;17:787-90.

36. Miyague NI, Ghidini A, Miyague LL. Fetal breathing movements are associated with changes in compliance of the left ventricle. *Fetal Diagn Ther* 1997;12:72-5.

37. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *J Am Soc Echocardiogr* 2015;28:183-93.

38. Simpson J. Speckle tracking for the assessment of fetal cardiac function. *Ultrasound Obstet Gynecol* 2011;37:133-4.

39. Matsui H, Germanakis I, Kulinskaya E, Gardiner HM. Temporal and spatial performance of vector velocity imaging in the human fetal heart. *Ultrasound Obstet Gynecol* 2011;37:150-7.

40. Bansal M, Cho GY, Chan J, Leano R, Haluska BA, Marwick TH. Feasibility and accuracy of different techniques of two-dimensional speckle based strain and validation with harmonic phase magnetic resonance imaging. *J Am Soc Echocardiogr* 2008;21:1318-25.

41. D'Hooge J, Barbosa D, Gao H, Claus P, Prater D, Hamilton J, et al. Two-dimensional speckle tracking echocardiography: standardization efforts based on synthetic ultrasound data. *Eur Heart J Cardiovasc Imaging* 2016;17:693-701.

42. Manovel A, Dawson D, Smith B, Nihoyannopoulos P. Assessment of left ventricular function by different speckle-tracking software. *Eur J Echocardiogr* 2010;11:417-21.

43. Risum N, Ali S, Olsen NT, Jons C, Khouri MG, Lauridsen TK, et al. Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. *J Am Soc Echocardiogr* 2012;25:1195-203.

**FIGURE TITLES AND LEGENDS**

**Figure 1 Comparison of image quality and feasibility of TDI and STE techniques between different ultrasound vendors in term fetuses and neonates.** Bar charts demonstrate (A) significant differences in image quality of the fetal *(in blue)* and neonatal *(in pink)* hearts between Toshiba, GE and Philips ultrasound systems [p<0.0001 for fetal heart; p=0.01 for neonatal heart], and no significant differences in feasibility of (B) TDI and (C) STE techniques in fetuses and neonates between these ultrasound platforms.

**Figure 2 LV and RV myocardial systolic velocities S’ obtained by PW-TDI on Toshiba vs. GE and GE vs. Philips in fetuses and neonates.** Bland-Altman plots comparing limits of agreement on Toshiba vs. GE, and GE vs. Philips ultrasound vendors for measurements of (A, B) LV and (C, D) RV myocardial systolic velocities [S’] in fetuses, and (E, F) LV and (G, H) RV S’ in neonates.

**Figure 3 LV and RV longitudinal strain derived by STE on Toshiba vs. GE and GE vs. Philips in fetuses and neonates.** Bland-Altman plots comparing limits of agreement on Toshiba vs. GE and GE vs. Philips ultrasound vendors for measurements of (A, B) LV and (C, D) RV global longitudinal strain [L-S] in fetuses, and (E, F) LV and (G, H) RV L-S in neonates.

**Figure 4 STE images showing tracing of RV global longitudinal strain [L-S] with peak systolic values obtained by scanning with a head-to-head comparison on (A) Toshiba Aplio MX vs. GE Vivid E9 from the same fetus, and (B) GE Vivid E9 vs. Philips EPIQ from another fetus.** There is a significant inter-vendor discordance in RV L-S global peak systolic values: Toshiba [-13%] vs. GE [-19%], and GE [-18%] vs. Philips [-25% ] (p<0.001 for both).

**TABLES**

**Table 1.** Demographic characteristic of the study population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameters | Toshiba (N=108) | GE (N=54) | Philips (N=34) | P value |
| **Maternal characteristics**  |  |
| Maternal age (years) | 34 ± 5 | 33 ± 5 | 32 ± 6 | 0.264 |
| Ethnicity (number): |  |
|  Caucasian | 80 (74%) | 35 (65%) | 20 (58%) | 0.619 |
|  Asian | 21 (19%) | 15 (28%) | 8 (24%) | 0.424 |
|  Afro-Caribbean | 7 (7%) | 4 (7%) | 6 (18%) | 0.092 |
| Delivery mode (number): |  |
|  Caesarean section | 34 (32%) | 14 (26%) | 6 (18%) | 0.210 |
| **Fetal cardiac assessment**  |  |
| Gestational age (weeks) | 39 ± 1.5 | 39 ± 1.6 | 38 ± 2.0 | 0.783 |
| Time gap between the fetal scan and birth (days) | 8 (10) | 9 (7) | 13 (4) | 0.490 |
| **Neonatal cardiac assessment**  |  |
| Neonate’s age at the time of the scan (hours) | 13 (16) | 19 (15) | 14 (8) | 0.083 |
| Neonate’s sex male (number) | 58 (54%) | 32 (59%) | 15 (44%) | 0.175 |
| Neonate’s weight (kg) | 3.5 ± 0.5 | 3.5 ± 0.4 | 3.3 ± 0.5 | 0.649 |
| Neonate’s length (cm) | 52.0 ± 3.7 | 53.0 ± 3.7 | 52.0 ± 4.8 | 0.812 |

Values are mean ± SD, median (interquartile range), or n (%). N, the number of patients.

**Table 2.** Intra- and inter-observer TDI and STI errors on Toshiba, GE and Philips ultrasound systems

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Error |  N | Method | Fetal | Neonatal |
| CV <15% | ICC>0.7 | LoA/Pitman’s test p>0.05 | CV<15% | ICC>0.7 | LoA/Pitman’s test p>0.05 |
| **Toshiba (Aplio MX)** |
| Intra-observer measurement error (same cc) | 50 | TDI | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) |
| STE | 12/12 (100%) | 11/12 (92%) | 11/12 (92%) | 12/12 (100%) | 11/12 (92%) | 10/12 (83%) |
| Intra-observer overall error (different cc) | 50 | TDI | 12/12 (100%) | 12/12 (100%) | 11/12 (92%) | 12/12 (100%) | 11/12 (92%) | 11/12 (92%) |
| STE | 8/12 (67%) | 9/12 (75%) | 11/12 (92%) | 8/12 (67%) | 9/12 (75%) | 11/12 (92%) |
| INTER-observer measurement error (same cc) | 20 | TDI | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) |
| STE | 5/8 (63%) | 10/12 (83%) | 11/12 (92%) | 5/8 (63%) | 9/12 (75%) | 10/12 (94%) |
| INTER-observer overall error (different cc) | 20 | TDI | 11/12 (92%) | 10/12 (83%) | 11/12 (92%) | 10/12 (83%) | 12/12 (100%) | 12/12 (100%) |
| STE | 6/8 (75%) | 9/12 (75%) | 12/12 (100%) | 7/8 (88%) | 10/12 (83%) | 12/12 (100%) |
| **GE (Vivid E)** |  |
| Intra-observer overall error (different cc) | 20 | TDI | 12/12 (100%) | 12/12 (100%) | 12/12 (100%) | 11/12 (92%) | 12/12 (100%) | 12/12 (100%) |
| STE | 19/24 (79%) | 17/24 (71%) | 23/24 (96%) | 21/24 (88%) | 20/24 (83%) | 24/24 (100%) |
| INTER-observer overall error (different cc) | 20 | TDI | 12/12 (100%) | 12/12 (100%) | 11/12 (92%) | 12/12 (100%) | 12/12 (100%) | 11/12 (92%) |
| STE | 19/24 (79%) | 16/24 (66%) | 21/24 (88%) | 18/24 (75%) | 21/24 (88%) | 19/24 (79%) |
| **Philips (EPIQ)** |  |
| Intra-observer overall error (different cc) | 20 | TDI | 20/20/ (100%) | 15/20 (85%) | 20/20 (100%) | 20/20/ (100%) | 17/20 (85%) | 17/20 (85%) |
| STE | 2/2 (100%) | 2/2 (100%) | 1/2 (50%) | 2/2 (100%) | 1/2 (50%) | 2/2 (100%) |
| INTER-observer overall error (different cc) | 20 | TDI | 17/20 (85%) | 15/20 (75%) | 18/20 (90%) | 15/20 (75%) | 15/20 (75%) | 16/20 (80%) |
| STE | 1/2 (50%)  | 1/2 (50%) | 1/2 (50%) | 1/2 (50%) | 2/2 (100%) | 2/2 (100%) |
| **Toshiba (Aplio MX) vs. GE (VividE9)** |
| Intra-observer overall error  | 50 | TDI | 12/12 (100%) | 5/12 (42%) | 12/12 (100%) | 12/12 (100%) | 6/12 (50%) | 11/12 (92%) |
| STE | 0/4 (0%) | 0/4 (0%) | 0/4 (0%) | 0/4 (0%) | 0/4 (0%) | 2/4 (50%) |
| **GE (VividE9) vs. Philips (EPIQ)** |  |
| Intra-observer overall error  | 68 | TDI | 4/22 (18%) | 1/22 (5%) | 15/22 (68%) | 3/22 (14%) | 11/22 (50%) | 18/22 (82%) |
| STE | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) |

Data is presented as n/n’, where n is the number of cardiac indices with ICC>0.7 or Pitman’s test>0.05 or CV <15%, and n’ is the overall number of cardiac indices measured in each patient. N, the number of patients; CV, coefficient of variation; ICC, interclass correlation coefficient; LoA, limits of agreement; TDI, spectral or pulsed wave tissue Doppler imaging; STE, 2D speckle tracking echocardiography; cc, cardiac cycle; US, ultrasound.