Fetal speckle-tracking echocardiography: a comparison between two-dimensional and electronic spatio-temporal image correlation (e-STIC) technique

# ABSTRACT

## Objectives

Speckle tracking technology has been applied to assess ventricular deformation throughout the cardiac cycle. Reproducibility is still a matter of concern because this technique mostly depends on the quality of acquisition. An electronic 4D probe that allows rapid acquisition of electronic spatio-temporal image correlation volumes (eSTIC) has been recently introduced. The aim of our study was to investigate whether e-STIC acquisition improves deformation analyses reproducibility.

## Methods

We recruited fetuses between 20 and 40 weeks of gestation. We obtained a 2D video clip and an e-STIC volume of a four-chamber view. An expert operator did the 2D and 4D measurements twice for each fetus. Other two operators, with a specific training on the software, made the 2D and 4D measurements once respectively. We focused on left ventricular global strain (LV-GS) and left ventricular ejection fraction (LV-FE). Intraobserver, interobserver and intermethod agreement were assessed by means of intraclass correlation coefficient (ICC) and illustrated by Bland-Altman plots. Systematic differences between measurements were assessed using a paired t-test.

## Results

The mean difference between LV-GS values obtained with e-STIC and 2D analysis was –0.10 (95% CI –2.28, 2.08). No systematic differences were found between the two techniques for LV-GS values (p-value = 0.927), the two methods agreed equally through the range of measurements. The mean difference between LV-FE values obtained with e-STIC and 2D analysis was 7.55 (95% CI 4.16, 10.95). This difference was statistically

significant (p-value < 0.001), indicating the presence of fixed bias between the two techniques. The inter-rater reliability of LV-GS was moderate-to-substantial for both e-STIC and 2D. On the contrary, the inter-rater reliability of LV-FE obtained via e-STIC was superior to that obtained via 2D analysis. The intra-rater reliability of LV-GS obtained with e-STIC was superior to that obtained with 2D analysis (ICC 0.857; 95% IC 0.761-0.917). Similarly, the intra-rater reliability of LV-FE obtained via e-STIC was superior to that obtained via 2D analysis (ICC 0.647; IC 0.51-0.783).

**Conclusion**

e-STIC has been proved to be a better technique than 2D analysis for intra-rater reliability of LV-GS. 2D-STE and e-STIC are not interchangeable when applied to measure LV-FE, given the presence of intermethod fixed bias. 4D acquisition might improve intrinsic limitations of STE.

## Introduction

Echocardiography has emerged as the mainstay of fetal cardiovascular assessment [1-3]. Primarily focused on identifying congenital heart defects, echocardiography has recently renewed by the increasing interest on fetal myocardial function [4]. However, objective methods to assess the presence and the degree of fetal cardiac dysfunction have not been thoroughly validated. Recently, 2-dimensional speckle tracking echocardiography, (STE) a technology based upon the principle of deformation (strain and strain rate) has been developed in order to obtain information regarding segmental and global cardiac function [5]. This approach is currently used in adults and children by cardiologists [6, 7] and it has recently been applied to the fetus [8-10], providing a non-invasive measure and representation of myocardial contractility in several pregnancy-related complications [11-15]. Deformation imaging directly measure the lengthening and shortening of the myocardium throughout the cardiac cycle [5, 16 17, 18]. Several issues limit its routinely use in fetal echocardiography. Spatial resolution, angle independence and the frame rate are questioned, and reproducibility is still a matter of concern because the technique mostly depends on the quality of acquisition [19, 20]. Moreover, several commercially available speckle-tracking software applications can reduce the comparing of analysis. Recently, three-dimensional (3D) STE has been introduced to adult and pediatric practice to overcome B-mode imaging limitations and there are only limited reports of its use in fetal cardiology. Previous studies have demonstrated that four-dimensional (4D) ultrasound technologies, such as spatiotemporal image correlation (STIC) [21], facilitate both examination and documentation of sonographic datasets [22]. However, acquisition of diagnostic volumes can be limited by fetal movements. With the standard mechanical probes available thus far, acquisition of a e-STIC volume of good quality requires 7.5-15

s. Recently, General Electric and Philips Ultrasound introduced an electronic 4D probe that allows acquisition of electronic STIC (e-STIC) volumes in a much shorter time. Our group has already proved that e-STIC volumes of good quality could be obtained in more than 90% of cases within the time frame of a standard examination of fetal anatomy [23]. The aim of our study was to investigate whether e-STIC acquisition improves deformation analyses reproducibility.

## Materials and methods

This observational cohort study included fetuses with accurate first and/or second-trimester dating ultrasound (US) scans, examined between 20- and 40-weeks' gestation, once during the study period. Fetuses were not at risk for congenital heart abnormalities or other fetal anomalies and the mothers did not have clinical conditions (diabetes mellitus, chronic hypertension, and preeclampsia).

*Image acquisition and analysis*

All measurements and acquisitions were performed by an expert examiner (G.P.). Two-dimensional images of the 4-chamber view were obtained with either an RM6C or EM6C transducer from a Voluson E10 US system (GE Healthcare, Milwaukee, WI).

The examiner identified the 4-chamber view within the chest, filling most of the ultrasound screen, with the apex perpendicular or tangential to the ultrasound beam. Images were optimized to enhance the borders between the blood pool and endocardium [24]. Three-second cine clips of the 4-chamber view were stored as Digital Imaging and Communications in Medicine files and exported to an offline cloud database. The Digital

Imaging and Communications in Medicine image frame rate was equivalent to the frame rate acquisition at the time of the examination.

Once a cine clip of the 2D image was saved, the examiner immediately activated the eSTIC sweep to acquire the volume.

E-STIC volumes were obtained using an electronic 4D probe, EM6C, using the option maximal quality, as we previously reported [23]. On the multiplanar display the examiner could manipulate the images to align the 4-chamber view in the optimal position and to mirror the 2D image previously acquired. The examiner compared each paired of datasets (2D image and eSTIC volume) before analysis to determine if the speckle tracking is altered by the type of image acquisition.

Once the 2D images and 4D e-STIC volumes of the 4-chamber view were obtained and stored in the Digital Imaging and Communications in Medicine format, they were examined using fetalHQ software (GE Healthcare; Zipf, Austria) using criteria that have been previously described [24]. Briefly, the endocardial border for each ventricle was traced from the base of the lateral wall to the apex and from the apex to the base of the septal wall at end diastole and end systole. After the tracing, automated analysis detected the endocardial borders during diastole and systole. An M-Mode derived from the 2-dimensional image of the four-chamber view was used to identify a single cardiac cycle (end-diastole, end-systole, end-diastole) used for speckle tracking analysis [24]. Following selection of one cardiac cycle, the automated software was activated to detect the endocardial border for each ventricle at end-systole and end-diastole. Adjustments were made to the end-systolic and end-diastolic contours, as needed, before the final analysis.

Using the equation of Hadlock et al [25, 26], the estimated fetal weight (computing the measurements of the biparietal diameter, head circumference, abdominal circumference, and femur length) was expressed using z-score [27].

The expert operator (G.P., operator 1) did the 2D and 4D measurements twice for each fetus. Other two operators (M.G.D. and E.M., operator 2 and 3), with a less expertise but with a specific training on the software made the 2D and 4D measurements once respectively.

Once the analysis was complete, the raw data were exported to a CSV file. This file was imported into an Excel® spreadsheet (Microsoft Corp., Redmond, WA, USA). In this study, we focused on left ventricular global strain (LV-GS) and left ventricular ejection fraction (LV-FE).

**Ethics**

The study protocol was approved by the local Ethics Committee of Sant' Orsola-Malpighi Hospital and a consent form signed at recruitment was obtained from each eligible patient (575/2018/Oss/AOUBo). The study protocol conforms to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008

**Statistical analyses**

Continuous variables were summarized as mean ± standard deviation; discrete and categorical variables were summarized as frequencies and percentages. Agreement between 2D and 4D measurements made by Operator 1 was assessed using a paired 2-

sample t-test, and illustrated using the Bland-Altman plot. Inter-rater reliability of measurements made by the 3 operators was assessed with intra-class correlation coefficient (ICC) estimates and 95% confidence intervals (CIs) based on a single-rating, absolute-agreement, 2-way random-effects model [28]. Intra-rater reliability of measurements made by Operator 1 was assessed with ICC estimates and 95% CIs based on a single-rating, absolute-agreement, two-way mixed-effects model. As a rule of thumb, values between 0.01 and 0.20 indicate “slight” agreement, values between 0.21 and 0.40 indicate “fair” agreement, values between 0.41 and 0.60 indicate “moderate” agreement, values between 0.61 and 0.80 indicate “substantial” agreement, and values between 0.81 and 1.00 indicate “almost perfect” agreement [28].

All data were analyzed using the Stata 15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

## Results

The study sample included 49 patients recruited between October 2018 and February 2019. Mean gestational age (GA) was 30±5 weeks (range: 19 to 36), mean z-score of estimated fetal weight (EFW) was 0.17±1.34, and mean z-score of abdominal circumferences (CA) was 0.45±1.16. One patient exhibited increased umbilical artery pulsatility index.

*Comparison between e-STIC and 2D*

The mean LV-GS values obtained with e-STIC and 2D analysis were –22.50±7.14 and –22.40±8.04, respectively. The mean difference between LV-GS values obtained with e-STIC and 2D analysis was –0.10 (95% CI –2.28, 2.08). Based on a paired 2-sample t-test, there were no systematic differences between the two techniques ($t = –0.09$, p-value = 0.927). As shown in Figure 1, there was no evidence of proportional bias, i.e., the two methods agreed equally through the range of measurements. The 95% limits of agreement illustrated in Figure 1, which are defined as the mean difference ±1.96 times the standard deviation of the differences and indicate how far apart measurements are likely to be for most individuals, were –14.98 (95% CI –18.71, –11.25) and 14.78 (95% CI 11.05, 18.51).

The mean LV-FE values obtained with e-STIC and 2D analysis were 60.65±10.34 and 53.10±8.41, respectively. The mean difference between LV-FE values obtained with e-STIC and 2D analysis was 7.55 (95% CI 4.16, 10.95). Based on a paired 2-sample t-test, this difference was significantly different from zero ($t = 4.47$, p-value < 0.001), indicating the presence of fixed bias between the two techniques (the e-STIC tends to give higher values). As shown in Figure 2, there was no evidence of proportional bias. The 95% limits of agreement illustrated in Figure 2 were –15.63 (95% CI –21.43, –9.83) and 30.73 (95% CI 24.93, 36.53).

*Inter-rater reliability*

Intra-class correlation coefficient (ICC) estimates and their 95% confidence intervals were calculated based on a single-rating ($k = 3$), absolute-agreement, two-way random-effects model [28]. Results are shown in Table 1. The inter-rater reliability of LV-GS was moderate-to-substantial for both e-STIC and 2D. On the contrary, the inter-rater reliability of LV-FE obtained via e-STIC was superior to that obtained via 2D analysis (moderate-to-substantial versus slight-to-fair).

*Intra-rater reliability*

ICC estimates and their 95% confidence intervals were calculated based on a single-rating (k = 2), absolute-agreement, two-way mixed-effects model [28]. Results are shown in Table 2. The intra-rater reliability of LV-GS obtained via e-STIC was superior to that obtained via 2D analysis (substantial-to-almost perfect versus fair-to-moderate). Similarly, the intra-rater reliability of LV-FE obtained via e-STIC was superior to that obtained via 2D analysis (moderate-to-substantial versus slight-to-fair).

## Discussion

We report the first observational study on 2D-STE and e-STIC for the evaluation of LV-GS and LV-FE parameters. Although these techniques are feasible, their reproducibility is limited.

STE is a semi-automated process, performed offline on previously acquired two-dimensional images, using small stable myocardial footprints, or speckles, generated by ultrasound-myocardial tissue interactions [29]. These bright myocardial areas can be tracked frame-by-frame using specific image-processing algorithm to measure strain and strain rate. The post processing software can automatically divide the myocardium into equal segments, giving also a quantification of regional strain [30].

Since first measures of myocardial strain in the healthy fetus were reported, many concerns remains about the reliability of these measurements [20]. Some studies have proved that calculation of strain parameters from bidimensional fetal images have good inter and intra-observer reproducibility [4, 31], partially as a consequence of the semi-automated nature of the technique. Some others have reported a lower interobserver variability at 24 weeks gestation compared to 20 [5, 19], but overall the agreement of 2D-STE appears to be good, and equal or superior to Doppler techniques [4, 19].

However, 2D imaging has several limitations [20]: fetal position can vary the orientation of four chamber view to the transducer; magnification and the foreshortening risk of the acquired images can affect the analysis. Moreover, myocardial function may be altered beat by beat during maternal breathing or fetal movements. The whole heart moves through the 2D plane of interest [32]. Therefore, 3D acquisitions have the potential to overcome the limitation of plane-dependency of 2D imaging. This has only recently experimented and there are limited reports of its use in fetal cardiology [33, 34]. Aiming to lower the times of acquisition, as fetal movements are a major limiting factor in these methods, we decided to apply e-STIC technique. The advantages of 4D over traditional 2-dimensional sonography of the fetal heart have been previously outlined [21-23]. In our study e-STIC has been proved to be a better technique than 2D analysis for intra-rater reliability of LV-GS. Similarly, the intra-rater reliability of LV-FE obtained via e-STIC was superior to that obtained via 2D analysis. Agreement between observers showed moderate-to-substantial for both e-STIC and 2D measurements of LV-GS. On the contrary, the inter-rater agreement of LV-FE obtained via e-STIC was superior to that obtained via 2D analysis.

According to these results, our study proved that 2D-STE and e-STIC cannot be interchangeably used, especially when used to measure LV-FE. Technical factors may account for this poor correlation. Cardiac volumes of optimal diagnostic quality are easily obtained with e-STIC because this approach is faster than 2D analysis [22, 23]. E-STIC acquisition stitches together sub-volumes and this results in a higher resolution real time image. Moreover, the multiplanar display allow the operator to improve the acquisition, manipulating it in A, B and C planes and observing corresponding changes in the perpendicular images before exporting the volume for initiating the strain software analysis [22, 24]. This advantage has already been outlined for STE compared to alternative methods of assessing fetal cardiac function, even if some studies still debate on it [20, 29, 35]. The multiplanar approach give a less angle dependent acquisition than conventional 2D method, allowing more flexibility.

The main strength of our study is that, for the first time, the performance of an electronic 4D probe was compared with 2-dimensional acquisition method for the myocardial deformation analyses. We do acknowledge some limitations. First, the small number of our cohort study composed by fetuses between second and third trimester of gestation. Second, we included fetuses of different estimated weight. Strain measurements vary through gestation [19] and SGA or IUGR fetuses could show altered myocardial deformation values [11, 15]. These factors could have been affected our results.

To conclude in our experience, speckle tracking made on 3D-STE volume showed a better reliability and this characteristic is crucial for a diagnostic tool. The main advantage of e-STIC analysis is the faster acquisition and the ability to modify the volumes, according to the desired plans of investigation, obtaining good analysis even in fetuses with non-optimal positions. Moreover, we observed that with the STIC technique the borders between the cavities of cardiac chambers and the endocardium are enhanced and this is fundamental for strain evaluation. One limitation for the wide spreading of this method is that e-STIC probe is quite expensive, but in a referral center with this tool available we recommend it to improve the reproducibility of the evaluations.

We believe that 4D acquisition might improve intrinsic limitations of STE. E-STIC acquisition need to be standardized and longitudinally experimented on a larger cohort of normal fetuses on both ventricles. Further studies are necessary also through gestational ages, relating to estimated fetal weight.

Supplementary material S1 contains video abstract illustrating fetal speckle-tracking technique and the main results of our study.

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**Table 1** Inter-rater reliability of e-STIC acquisition and 2D analysis for heart evaluation (LV-GS and LV-FE).

| Heart evaluation | Technique | ICC* | 95% confidence interval of ICC | |
|---|---|---|---|---|
| | | | Lower boundary | Upper boundary |
| LV-GS | e-STIC | 0.562 | 0.403 | 0.704 |
| | 2D | 0.581 | 0.424 | 0.718 |
| LV-FE | e-STIC | 0.544 | 0.382 | 0.689 |
| | 2D | 0.183 | 0.029 | 0.362 |

*ICC, intra-class correlation coefficient.

**Table 2** Intra-rater reliability of e-STIC acquisition and 2D analysis for heart evaluation (LV-GS and LV-FE)

| Heart evaluation | Technique | ICC* | 95% confidence interval of ICC | |
|---|---|---|---|---|
| | | | Lower boundary | Upper boundary |
| LV-GS | e-STIC | 0.857 | 0.761 | 0.917 |
| | 2D | 0.507 | 0.268 | 0.688 |
| LV-FE | e-STIC | 0.647 | 0.451 | 0.783 |
| | 2D | 0.114 | 0.000 | 0.359 |

*ICC, intra-class correlation coefficient.

**Figure 1** Bland-Altman plot of left ventricular global strain (LV-GS) measured with e-STIC acquisition versus 2D analysis. Short-dashed lines indicate the 95% confidence interval for the mean difference. Dotted lines indicate the 95% confidence intervals of the limits of agreement.

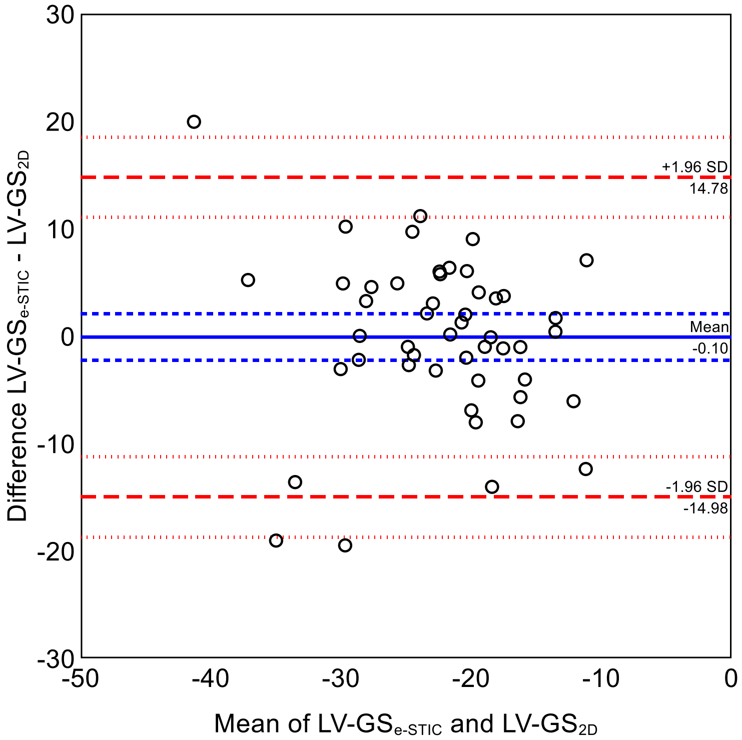
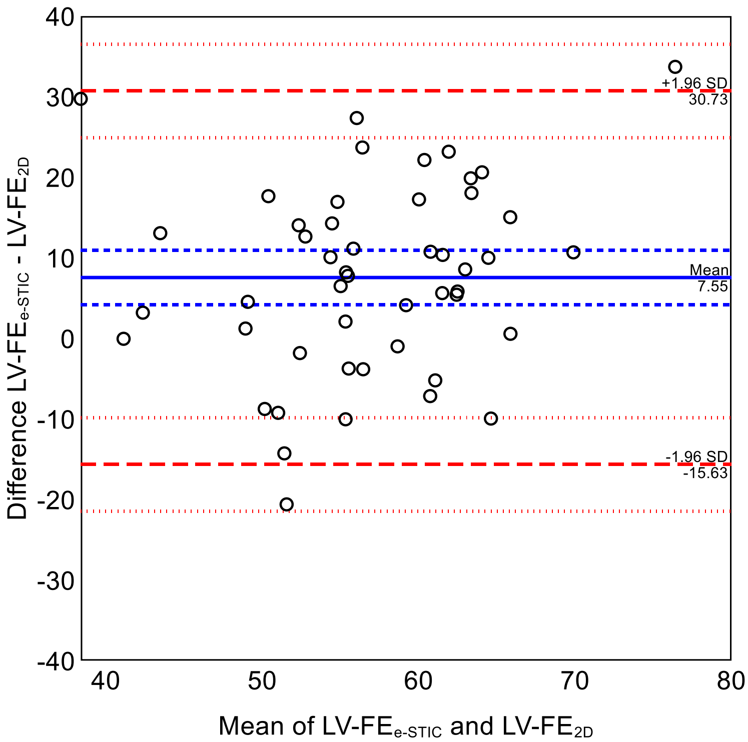


**Figure 2** Bland-Altman plot of LV-FE (%) measured with e-STIC acquisition versus 2D analysis. Short-dashed lines indicate the 95% confidence interval for the mean difference. Dotted lines indicate the 95% confidence intervals of the limits of agreement.




**Supplementary material S1** Video abstract illustrating fetal speckle-tracking technique and the main results of our study.