Thieme

Color Tissue Doppler to Analyze Fetal Cardiac Time Intervals: Normal Values and Influence of Sample Gate Size

Zeitintervallanalyse des fetalen Herzzyklus mittels farbkodiertem Gewebedoppler: Normwerte und Einfluss der Dopplergate-Größe

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Key words

cardiac, heart, ultrasound Doppler

received 07.06.2014
accepted 07.10.2015

Bibliography

DOI https://doi.org/10.1055/s-0041-107765
Published online: February 04, 2016 | Ultraschall in Med 2018; 39: 56–68 © Georg Thieme Verlag KG, Stuttgart · New York, ISSN 0172-4614

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ABSTRACT

Purpose To assess the time intervals of the cardiac cycle in healthy fetuses in the second and third trimester using color tissue Doppler imaging (cTDI) and to evaluate the influence of different sizes of sample gates on time interval values.

Materials and Methods Time intervals were measured from the cTDI-derived Doppler waveform using a small and large region of interest (ROI) in healthy fetuses.

Results 40 fetuses were included. The median gestational age at examination was 26 + 1 (range: 20 + 5 – 34 + 5) weeks. The median frame rate was 116/s (100 – 161/s) and the median heart rate 143 (range: 125 – 158) beats per minute (bpm). Using small and large ROIs, the second trimester right ventricular (RV) mean isovolumetric contraction times (ICTs) were 39.8 and 41.4 ms ($p = 0.17$), the mean ejection times (ETs) were 170.2 and 164.6 ms ($p < 0.001$), the mean isovolumetric relaxation times (IRTs) were 52.8 and 55.3 ms ($p = 0.08$), respectively. The left ventricular (LV) mean ICTs were 36.2 and 39.4 ms ($p = 0.05$), the mean ETs were 167.4 and 164.5 ms ($p = 0.013$), the mean IRTs were 53.9 and 57.1 ms ($p = 0.05$), respectively. The third trimester RV mean ICTs were 50.7 and 50.4 ms ($p = 0.75$), the mean ETs were 172.3 and 181.4 ms ($p = 0.49$), the mean IRTs were 50.2 and 54.6 ms ($p = 0.03$); the LV mean ICTs were 45.1 and 46.2 ms ($p = 0.35$), the mean ETs were 175.2 vs. 172.9 ms ($p = 0.29$), the mean IRTs were 47.1 and 50.0 ms ($p = 0.01$), respectively.

Conclusion Isovolumetric time intervals can be analyzed precisely and relatively independent of ROI size. In the near future, automatic time interval measurement using ultrasound systems will be feasible and the analysis of fetal myocardial function can become part of the clinical routine.

ZUSAMMENFASSUNG

Ziel Analyse der Zeitintervalle des fetalen Herzzyklus gesunder Feten im 2. und 3. Trimenon mittels farbkodiertem Gewebedoppler (color DTI) und Evaluation des Einflusses der ROI-Größe auf die jeweiligen Zeitintervalle.

Material und Methoden Die Zeitintervalle wurden anhand der cTDI ermittelten Gewebedopplerkurven gemessen, wobei jeweils eine kleine (3 mm durchmessend) und eine große Region of Interest (freie Wand des Ventrikel) betrachtet wurde.

Ergebnisse 40 Feten wurden untersucht. Im Median betrug das Schwangerschaftsalter 26 + 1 (20 + 5 – 34 + 5) Wochen,

die Bildwiederholrate 116/s (100 – 161/s) und die Herzfrequenz 143 (125 – 158) Schläge pro Minute. Im 2. Trimenon – jeweils mit kleiner und großer ROI gemessen – betrugen rechtsventrikulär die mittlere ICT 39,8 und 41,4 ms (p = 0,17), die mittlere ET 170,2 und 164,6 s (p < 0,001), die mittlere IRT 52,8 vs. 55,3 ms (p = 0,08). Linksventrikulär betrugen die mittlere ICT 36,2 vs. 39,4 ms (p = 0,05), die mittlere ET 167,4 und 164,5 ms (p = 0,013), die IRT 53,9 vs. 57,1 ms (p = 0,05). Im 3. Trimenon betrugen rechtsventrikulär die mittlere ICT 50,7 vs. 50,4 ms (p = 0,75), die mittlere ET 172,3 und 181,4 ms (p = 0,49), die mittlere IRT 50,2 und 54,6 ms (p = 0,03); linksventrikulär betrugen die mittlere ICT 45,1 und 46,2 ms (p = 0,35), die mittlere ET 175,2 und 172,9 ms (p = 0,29), die mittlere IRT 47,1 und 50,0 ms (p = 0,01).

Schlussfolgerung Isovolumetrische Zeitintervalle können präzise und relativ unabhängig der ROI-Größe analysiert werden. Zukünftig werden Ultraschallsysteme selbständig die Zeitintervalle des fetalen Herzzyklus messen können, so dass die Herzmuskelfunktionsanalyse somit zum Bestandteil der klinischen Routine werden könnte.

Introduction

Traditionally, cardiac function has been assessed by measuring blood flow via conventional spectral Doppler or cardiac morphometry in 2 D or M-mode [1 – 4]. In adult echocardiography, tissue Doppler imaging (TDI) has emerged as an adjunct to routine echocardiography that analyzes myocardial performance directly [5]. During pregnancy, TDI can detect alterations in maternal tissue velocities that reflect maturational myocardial changes [6] and is also useful in the early identification of subtle fetal cardiac dysfunction in preclinical stages [7]. TDI derives measurements of contraction and relaxation velocities from the fetal myocardium and can be used for the quantitative assessment of systolic and diastolic ventricular function [8]. Furthermore, the myocardial performance index (MPI, Tei index), which is based on the analysis of cardiac time intervals and is defined as the sum of the isovolumetric contraction time (ICT) and the isovolumetric relaxation time (IRT) divided by the ejection time (ET), can be determined as a global parameter of myocardial function [9]. The original method, as described by Tei et al. [9], which uses different cardiac cycles and different images to measure the time intervals, resulted in significant variability between studies [10]. After the spectral Doppler-based "valve click method" (modified MPI) was introduced into fetal echocardiography, the aortic and mitral Doppler valve clicks could be used to demarcate the time intervals in the same cardiac cycle, making the method more reliable and reproducible [11].

Color TDI (cTDI), in contrast to pulsed wave TDI (pwTDI), which evaluates only one area of interest in the myocardium, permits the analysis of multiple areas from a single cardiac cycle simultaneously [12]. PwTDI and cTDI are based on different post-processing methods, have different temporal resolution and therefore cannot be used interchangeably. A second reason for the differences between the two TDI methods is that pwTDI measures the maximum instantaneous myocardial velocity, whereas cTDI measures the regional mean velocities [12].

The MPI comprises both systolic (ICT, ET) and diastolic (IRT) components. The published normal ranges vary widely and this causes concerns about the validity of this technique [13]. The short time periods, particularly the IRT, become abnormal in the early stages of dysfunction, reflecting an increase in the time required to relax the myocardium fully [4].

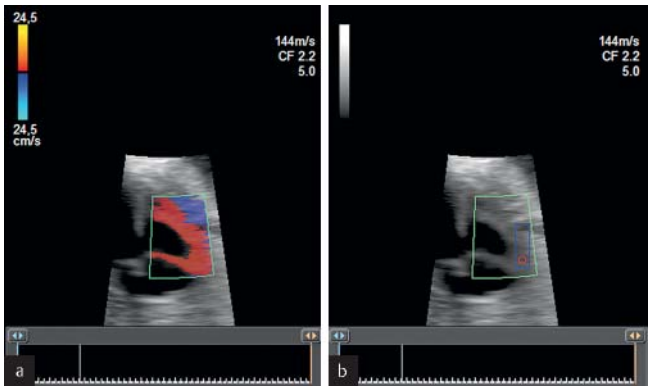
Compared to methods that analyze fetal myocardial function (2 D echocardiography, M-mode, blood flow pwDoppler, 3 D/4 D volumetry), TDI would appear more sensitive when it comes to detecting subtle cardiac dysfunction even in situations with normal umbilical artery Doppler parameters (i. e., in fetuses that are small for their gestational age) [12, 14] or in pregnancies with gestational diabetes [15].

Our objective was to determine the isovolumetric time intervals of cardiac cycle in healthy fetuses in the second and third trimester individually and to evaluate the influence of differently sized sample gates (regions of interest: ROIs) on time interval values using cTDI.

Methods

This is a prospective multicenter cross-sectional study between May 2011 and July 2013. The study protocol was approved by the ethics committee of the University of Bonn. Women with normal singleton pregnancies were eligible. The gestational age was calculated based on the first day of the last menstrual period confirmed by crown-rump length at the first trimester ultrasound scan. Patients were referred for a routine anomaly scan before 25 weeks of gestation or a growth scan during later gestation. After an assessment of normal fetal anatomy including B-mode and color Doppler echocardiography, in accordance with the recommendations of the German Society of Ultrasound in Medicine (Deutsche Gesellschaft für Ultraschall in der Medizin, DEGUM) [3, 16], patients were asked for their written informed consent.

Raw cTDI data with the original acoustical frame rate (the original frame rate of the raw ultrasound clip created) were acquired in each participating center using an Aplio XG (Toshiba Medical Systems Corporation, Otawa, Tochigi, Japan) equipped with a 1 – 5 MHz curved-array probe (PVT-375BT, Toshiba Medical Systems Corporation, Otawa, Tochigi, Japan). The optimum Doppler settings for the detection of myocardial tissue motion including pulse repetition frequency, gain, persistence, color priority, wall filter and line density were stored as presets for each center and were invoked at the beginning of every examination in the study. We chose a time limit of 15 – 20 minutes for the acquisition of the raw data sets as a feasible approach at an outpatient appointment.

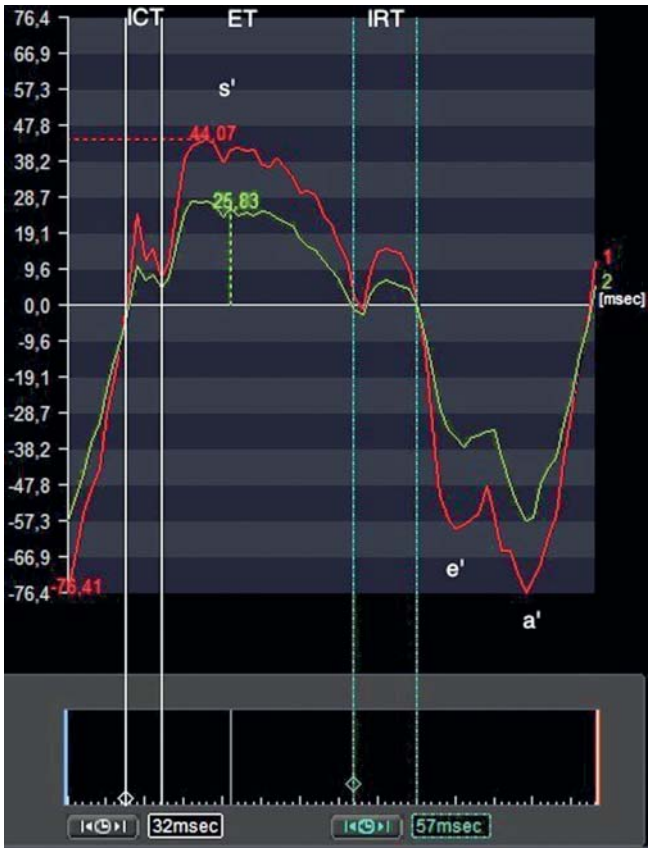


▶ **Fig. 1** **a** Still image of magnified right ventricle with overlying TDI color box of healthy fetus at 29 + 4 weeks. **b** Still image of magnified right ventricle (overlying TDI color box switched off) with small (red circle) and large ROI (blue rectangle) of healthy fetus at 29 + 4 weeks.

The fetal heart was magnified to occupy about 75 % of the screen in an apical or basal four-chamber view using high-resolution zoom. The angle of insonation relative to the long axis of the heart was kept as small as possible, but always below 15°. All recordings were obtained in the absence of fetal movements, and the 2 D scan area and overlying TDI color box were kept as small as possible to obtain the highest frame rate (▶ **Fig. 1a**). At least three cardiac cycles with a high frame rate (> 100 frames/s) were recorded and stored digitally. The scanning was performed by one of the authors (AW, JS, CE, RA, FB).

The offline analysis of TDI-derived parameters was performed in each center using the TDIQ software (Toshiba Medical Systems Corporation, Otawa, Tochigi, Japan) on a laptop. In the four-chamber view, firstly a small 3x3 mm-sized sample volume (ROI) was placed within the basal part of the right and left ventricular wall immediately distal to the atrioventricular valves in the region of maximum displacement; secondly, a large sample volume (large ROI) was recorded, covering the middle and basal sections of the right/left ventricular wall (▶ **Fig. 1b**). The cardiac time intervals were measured from the most appropriate cycle that clearly delineated the ICT (interval between atrioventricular valve closure and semilunar valve opening), the ET (interval between semilunar valve opening and closure) and the IRT (interval between semilunar valve closure and atrioventricular valve opening) (▶ **Fig. 2**). The positioning of the time calipers is defined firstly by the time of zero flow (first crossing of the x-axis) until the lowest reversal point (ICT), secondly from this point until the second crossing of the x-axis (ET) and finally from the second to the third crossing of the x-axis (IRT).

The maximum tissue velocities along the long axis at systole (s'), in the early filling phase of diastole (e') and during atrial contraction (a') were averaged from three consecutive cardiac cycles for the right and left ventricular free wall. During offline analysis, drifts, slight movements and minimal changes of the position of the small sample volume (3 mm ROI) in the myocardium at atrioventricular valve level resulted in widely varying peak tissue velocities, and we therefore averaged the peak velocities from three consecutive cardiac cycles. As the fetal heart



▶ **Fig. 2** Right ventricular isovolumetric time intervals (small ROI: red curve; large ROI: green curve) of healthy fetus at 29 + 4 weeks.

growth, the large ROI was adapted to the basal and middle sections of the ventricular free wall and therefore no constant size was used for the ROI.

Statistics

Differences between the small and large ROIs were tested with a paired t-test and the correlation between the measurements in these two ROIs was given with Pearson's correlation coefficient. Interobserver variability between two independent observers was given by the intraclass correlation coefficient ICC (A,1) and intraobserver variability between the measurements of one observer was given by the intraclass correlation coefficient ICC (C,1), as described by McGraw and Wong [17]. The values of reliability were characterized as suggested by Landis and Koch [18]: slight (0.0 – 0.20), fair (0.21 – 0.40), moderate (0.41 – 0.60), substantial (0.61 – 08.0) and almost perfect (0.81 – 1.0).

Results

The median gestational age at the time of examination was 26 + 1 (range: 20 + 5 – 34 + 5) weeks. Divided into two subgroups, 20 patients were in the second trimester (median: 21 + 4 weeks of gestation) and 20 patients were in the third trimester of pregnancy (median: 30 + 6 weeks of gestation). The median frame rate

was 116/s (range: 100 – 161/s) for the right ventricle and 114/s (range: 100 – 161/s) for the left ventricle. The median heart rate was 143 beats per minute (bpm) (range: 125 – 158 bpm). ▶ **Table 1** shows the time intervals and myocardial velocity values according to gestational age.

The regional myocardial velocities were significantly higher in the entire patient group when using the small ROI compared to the large ROI. This difference was also detected in the second and third trimester subgroups (▶ **Table 1**).

▶ **Fig. 3 – 6** show right and left ventricular scatter plots for isovolumetric time intervals (ICT, IRT), ejection time (ET) and myocardial peak systolic and diastolic tissue velocities, plotted against gestational age.

Comparing large and small ROI isovolumetric time interval measurements in the entire patient group revealed good correlations (Pearson correlation coefficient 0.77 – 0.94) without large differences in ROI size in the second and third trimesters (except the right and left ventricular IRT in the third trimester), whereas the diastolic and systolic myocardial velocities exhibited wider ranges and more moderate correlations (Pearson CC 0.47 – 0.74).

The intraobserver reliability for ICT and IRT indicated good agreement (ICC (C,1) 0.81 – 0.98), whereas the interobserver reliability (ICC (A,1)) was moderate for the small ROI and substantial for the large ROI (▶ **Table 2**). Bland-Altman plots of inter- and intraobserver variability are displayed in ▶ **Fig. 7 – 14**.

Discussion

Today, tissue Doppler myocardial imaging is an integrated part of evaluating cardiac function in adult cardiology in order to assess diastolic left ventricular function [19]. In the past, spectral TDI values could be recorded at higher frame rates (250 frames per second, fps) than color TDI (50 – 150 fps). With current echocardiographic ultrasound machines, temporal resolution is less of an issue because they can achieve up to 300 fps with color TDI [12]. The proper acquisition of tissue velocities and the short duration of myocardial tissue movements require a high frame rate in order to obtain an adequate temporal resolution [20]. This issue becomes even more important due to the high fetal heart rate [21]. There are published fetal reference values for spectral [22 – 24] and color-derived [12, 25] TDI velocities. As early as 2000, Paladini et al. [25] was one of the first to publish data on 89 healthy fetuses (17 – 37 weeks) with reference values for right and left ventricular myocardial tissue velocities in a transverse four-chamber view by cTDI (RV: s' 13.98 ± 5.55 cm/s, e' 22.78 cm/s, a' 26.12 cm/s; LV: s' 14.11 cm/s, e' 18.77 cm/s, a' 21.30 cm/s) using an ultrasound machine (Toshiba Powervision) with low frame rates (20 – 40 frames/s). Perles et al. [26] used a GE Vivid-7 echocardiography system (and offline analysis using EchoPAC; GE Medical Systems, Milwaukee, Wisconsin) with high frame rates (105 – 212 frames/s) to analyze myocardial velocities in 98 normal fetuses (13 – 40 weeks) at the level of the atrioventricular annulus (ROI size not specified) by cTDI. All maximum diastolic and systolic tissue velocities of both ventricles were clearly < 10 cm/s throughout gestation. This observation can be explained by the very different angle of insonation used by the study group. In our opinion, measurements of tissue velocities are highly dependent on the caliper placement (even close to the atrioventricular level), the basically undefined caliper size (in the literature this ranges between 1 and 3 mm) and the different ultrasound machines with postprocessing algorithms. We therefore believe that published tissue velocities vary markedly and cannot generally serve as standard values. We detected higher values in the right ventricular free wall compared to the left, and much higher values than published previously (▶ **Table 1**). Unsurprisingly, averaged tissue velocity values showed lower velocities using the large ROI compared to the respective values using the small ROI. This is firstly due to the fact that the highest tissue velocities are in the region of the atrioventricular valve, which are mainly captured by the small ROI, and secondly because of the averaging of all the values measured in each selected ROI.

Saini et al. [12] analyzed tissue Doppler velocities in 91 healthy fetuses in the second and third trimesters (mean gestational age 28.6 ± 6.6 weeks) using cTDI, and compared the values with spectral TDI. The main finding was that peak pwTDI-derived velocities were always higher than those derived by cTDI. The myocardial velocities measured by either technique increased with advancing pregnancy [12].

Meriki and Welsh [13] described the influence of the caliper position on time interval measurements in the same cardiac cycle using pwTDI. They concluded that the breadth of valve click will ultimately affect the value of the time intervals [13]. To overcome this potential inconsistency caused by the breadth of the clicks, they proposed using the peak of the valve click for both closure and opening [13]. We, however, believe that a thicker signal line would proportionately affect both the beginning of the first and the following signal, so that there should not be any major inaccuracy. Because of this, we strongly recommend using trailing edges to measure time intervals.

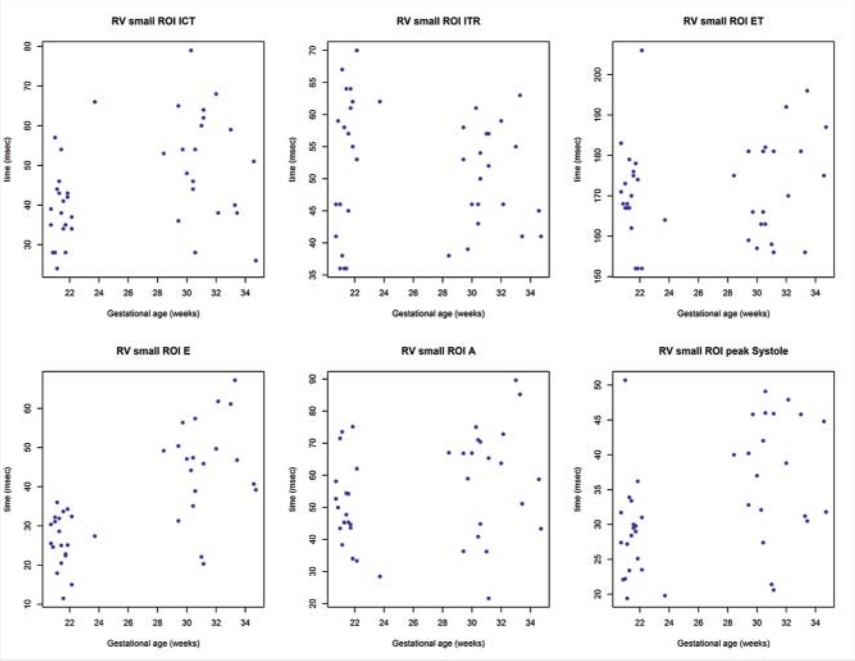
Using conventional pulsed wave blood flow Doppler, Friedman et al. [27] assessed the left ventricular time intervals on 74 healthy fetuses in the second and third trimester and revealed ICT (43 ± 14 ms), IRT (48 ± 13 ms) and ET (173 ± 16 ms) independent of gestational age (18 – 31 weeks), which was comparable with our values (ICT 40.6 ± 10.7 ms; IRT 50.5 ± 9.4 ms; ET 171.3 ± 13.0 ms).

Van Mieghem et al. [10] analyzed left ventricular myocardial function in 117 healthy fetuses and 14 fetuses with twin-twin transfusion syndrome (≥ 20 weeks) in the second and third trimesters (20 – 36 weeks) using "modified MPI" (pwTDI) as described by Hernandez-Andrade et al. [11]. They discovered that IRT increased with gestational age and found clearly altered cardiac function in TTTS recipients (ICT prolonged significantly; 38.8 ± 8.5 ms) compared to healthy controls (ICT 26.2 ± 6.7 ms). Degenhardt et al. [28] demonstrated short-time impact of laser therapy on altered myocardial function in TTTS recipients. Using pw TDI, they revealed shortened postoperative IRT intervals reflecting improved diastolic function. In their study of 557 normal fetuses (19 – 39 weeks) using pwTDI, Hernandez-Andrade et al. [29] revealed constant ICT, slightly increasing IRT and slightly decreasing ET throughout gestation. We cannot comment on the dependence of isovolumetric time intervals on gestational age because of the small sample size and the distribution of patients clustering around 21 and 31 weeks.

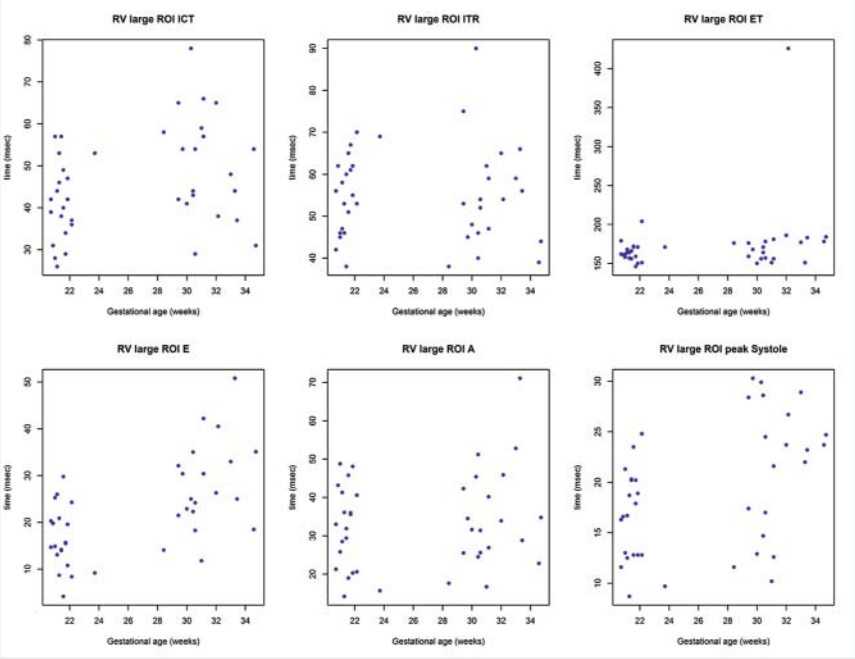
▶ **Table 1** Time interval and longitudinal myocardial velocity measurements.

			mean (95 % confidence interval)			
	ventricle	variable	3 mm ROI	large ROI	p-value	pearson correlation coefficient
all (n = 40)						
	RV	ICT (ms)	45.2 (41.0 – 49.5)	45.9 (42.1 – 49.7)	0.3831	0.94
		ET (ms)	171.2 (167.3 – 175.1)	173.0 (159.3 – 186.7)	0.7884	0.25
		IRT (ms)	51.5 (48.4 – 54.6)	55.0 (51.4 – 58.5)	0.004	0.77
		e' (mm/s)	36.0 (31.6 – 40.4)	22.2 (19.0 – 25.5)	< 0.0001	0.73
		a' (mm/s)	54.7 (49.5 – 59.8)	33.5 (29.6 – 37.4)	< 0.0001	0.64
		s' (mm/s)	33.1 (30.3 – 36.0)	19.1 (17.1 – 21.0)	< 0.0001	0.51
	LV	ICT (ms)	40.6 (37.2 – 44.1)	42.8 (38.9 – 46.6)	0.0291	0.87
		ET (ms)	171.3 (167.1 – 175.5)	168.7 (163.9 – 173.5)	0.0316	0.87
		IRT (ms)	50.5 (47.5 – 53.5)	53.5 (50.7 – 56.4)	0.0019	0.80
		e' (mm/s)	29.6 (25.3 – 33.9)	16.4 (14.1 – 18.7)	< 0.0001	0.74
		a' (mm/s)	41.2 (36.7 – 45.7)	20.4 (18.0 – 22.8)	< 0.0001	0.47
		s' (mm/s)	27.8 (24.2 – 31.5)	14.8 (12.6 – 17.0)	< 0.0001	0.71
2nd trimester (n = 20)						
	RV	ICT (ms)	39.8 (34.9 – 44.7)	41.4 (37.0 – 45.8)	0.1711	0.88
		ET (ms)	170.2 (164.5 – 175.9)	164.6 (158.8 – 170.4)	0.0004	0.89
		IRT (ms)	52.8 (47.5 – 58.1)	55.3 (51.0 – 59.7)	0.0793	0.85
		e' (mm/s)	26.4 (23.3 – 29.5)	16.5 (13.3 – 19.6)	< 0.0001	0.73
		a' (mm/s)	50.0 (43.9 – 56.1)	31.8 (26.7 – 36.9)	< 0.0001	0.49
		s' (mm/s)	28.7 (25.4 – 32.0)	16.5 (14.3 – 18.6)	< 0.0001	0.15
	LV	ICT (ms)	36.2 (32.3 – 40.0)	39.4 (34.7 – 44.0)	0.0483	0.74
		ET (ms)	167.4 (162.0 – 172.8)	164.5 (158.9 – 170.2)	0.0127	0.92
		IRT (ms)	53.9 (50.1 – 57.7)	57.1 (53.9 – 60.2)	0.0543	0.59
		e' (mm/s)	19.2 (16.9 – 21.5)	12.0 (10.0 – 14.0)	< 0.0001	0.57
		a' (mm/s)	34.0 (29.3 – 38.6)	18.4 (15.4 – 21.4)	< 0.0001	0.70
		s' (mm/s)	20.5 (17.9 – 23.1)	11.1 (9.7 – 12.4)	< 0.0001	0.57
3 rd trimester (n = 20)						
	RV	ICT (ms)	50.7 (44.2 – 57.1)	50.4 (44.4 – 56.3)	0.7511	0.95
		ET (ms)	172.3 (166.4 – 178.1)	181.4 (153.9 – 208.9)	0.4909	0.15
		IRT (ms)	50.2 (46.6 – 53.8)	54.6 (48.6 – 60.6)	0.0259	0.80
		e' (mm/s)	45.6 (39.8 – 51.4)	28.0 (23.4 – 32.5)	< 0.0001	0.51
		a' (mm/s)	59.3 (51.1 – 67.5)	35.2 (28.9 – 41.4)	< 0.0001	0.72
		s' (mm/s)	37.6 (33.5 – 41.6)	21.6 (18.6 – 24.7)	< 0.0001	0.51
	LV	ICT (ms)	45.1 (39.8 – 50.4)	46.2 (39.9 – 52.4)	0.3483	0.94
		ET (ms)	175.2 (168.9 – 181.5)	172.9 (165.0 – 180.7)	0.2854	0.82
		IRT (ms)	47.1 (42.6 – 51.5)	50.0 (45.6 – 54.4)	0.0109	0.88
		e' (mm/s)	40.0 (35.0 – 45.1)	20.8 (17.5 – 24.0)	< 0.0001	0.50
		a' (mm/s)	48.5 (42.0 – 54.9)	22.4 (18.6 – 26.2)	< 0.0001	0.22
		s' (mm/s)	35.2 (29.9 – 40.4)	18.6 (15.0 – 22.2)	< 0.0001	0.56

RV: right ventricle; LV: left ventricle; ROI: region of interest; ICT: isovolumetric contraction time; ET: ejection time; IRT: isovolumetric relaxation time; e': early diastolic myocardial peak velocity; a': late diastolic myocardial peak velocity; s': myocardial systolic peak velocity.

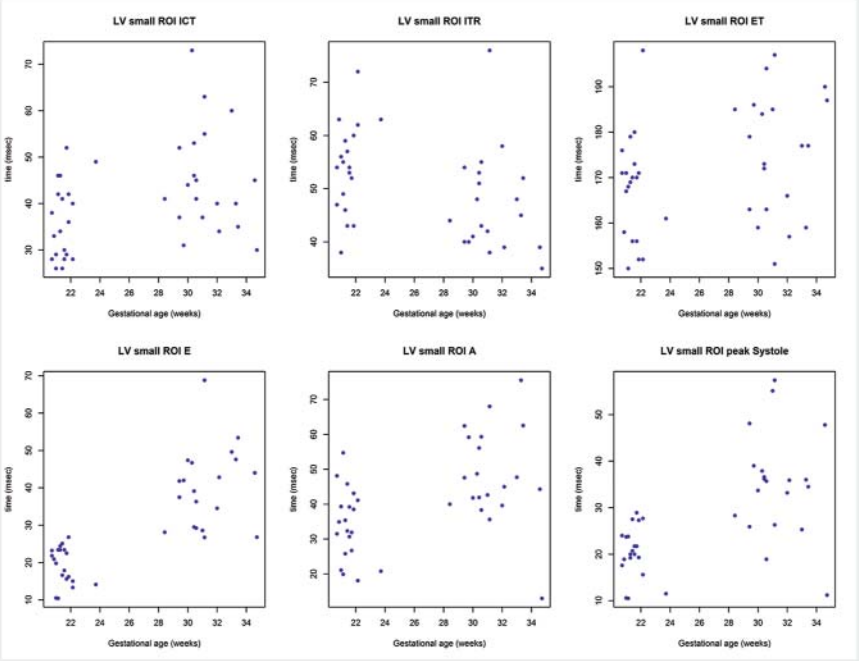


▶ **Fig. 3** Scatter plots of the small ROI of the RV plotted against gestational age. Measurements of right ventricular small ROI plotted against gestational age.

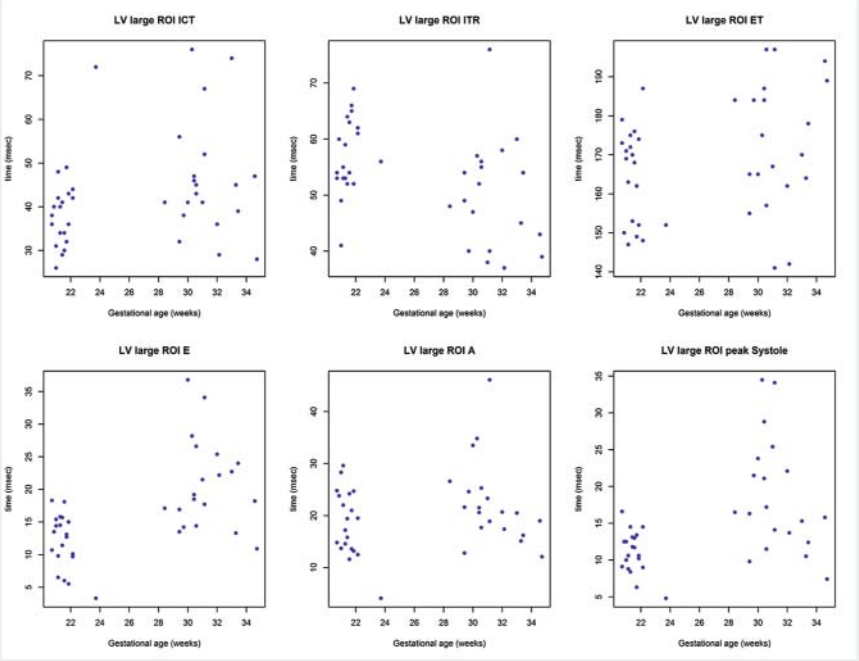


▶ **Fig. 4** Scatter plots of the large ROI of the RV plotted against gestational age. Measurements of right ventricular large ROI plotted against gestational age.

Nii et al. [30] assessed atrioventricular (AV) interval measurements (time interval between onset of atrial contraction and onset of isovolumetric contraction and time interval between onset of atrial contraction and onset of ventricular systole) in 110 healthy fetuses between 14 and 42 weeks gestation using cTDI and pwTDI and correlated the values determined with signal-averaged PR intervals on fetal electrocardiogram (ECG). They concluded firstly that it is feasible to measure AV intervals using TDI and secondly that TDI-derived time intervals track ECG PR intervals more closely than pw Doppler methods and TDI should therefore



▶ **Fig. 5** Scatter plots of the small ROI of the LV plotted against gestational age. Measurements of left ventricular small ROI plotted against gestational age.



▶ **Fig. 6** Scatter plots of the large ROI of the LV plotted against gestational age. Measurements of left ventricular large ROI plotted against gestational age.

be used as the ultrasound method to analyze fetal AV conduction time [30].

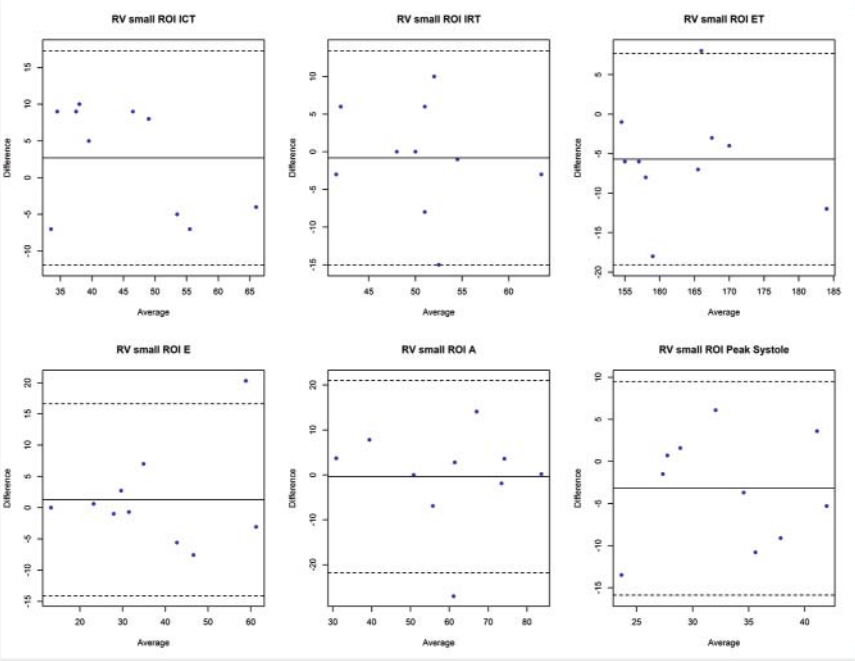
As far as we know, the present study is the first to assess fetal isovolumetric time intervals and the influence of ROI size using cTDI. In the second and third trimesters, the isovolumetric time intervals could be measured independently of ROI size (▶ **Table 1**), except IRT in the third trimester (RV p = 0.03 and LV 0.01).

In line with the reported reliabilities of left (ICC 0.78 – 0.86) and right MPI (ICC 0.70 – 0.76) [31, 32], our measurements of

▶ **Table 2** Intra- and interobserver reliability of time intervals and myocardial peak velocities.

	intraobserver reliability		interobserver reliability	
parameters	**small ROI**	**large ROI**	**small ROI**	**large ROI**
diastolic parameters				
right IRT	0.88 (0.6 – 0.97)	0.88 (0.6 – 0.97)	0.52 (0.48 – 0.82)	0.74 (0.67 – 0.91)
right e'	0.75 (0.27 – 0.93)	0.39 (0 – 0.81)	0.89 (0.84 – 0.96)	0.58 (0.52 – 0.85)
right a'	0.56 (0 – 0.87)	0.27 (0 – 0.75)	0.81 (0.75 – 0.94)	0.14 (0.25 – 0.63)
left IRT	0.84 (0.48 – 0.96)	0.81 (0.41 – 0.95)	0.00 (0 – 0.38)	0.42 (0.41 – 0.78)
left e'	0.90 (0.65 – 0.98)	0.42 (0 – 0.81)	0.92 (0.88 – 0.97)	0.76 (0.69 – 0.92)
left a'	0.86 (0.53 – 0.96)	0.09 (0 – 0.66)	0.90 (0.85 – 0.97)	0.58 (0.53 – 0.85)
systolic parameters				
right ICT	0.98 (0.93 – 1.0)	0.97 (0.87 – 0.99)	0.78 (0.69 – 0.92)	0.75 (0.58 – 0.91)
right ET	0.93 (0.75 – 0.98)	0.93 (0.74 – 0.98)	0.65 (0.39 – 0.88)	0.84 (0.78 – 0.95)
right s'	0.53 (0 – 0.86)	0.54 (0 – 0.86)	0.54 (0.44 – 0.82)	0.30 (0.34 – 0.72)
left ICT	0.94 (0.78 – 0.99)	0.93 (0.73 – 0.98)	0.54 (0.48 – 0.83)	0.73 (0.66 – 0.91)
left ET	0.95 (0.83 – 0.99)	0.96 (0.86 – 0.99)	0.36 (0.36 – 0.74)	0.88 (0.83 – 0.96)
left s'	0.85 (0.5 – 0.96)	0.72 (0.22 – 0.92)	0.95 (0.92 – 0.98)	0.64 (0.56 – 0.87)

Values as intraclass correlation coefficient (95 % confidence interval).

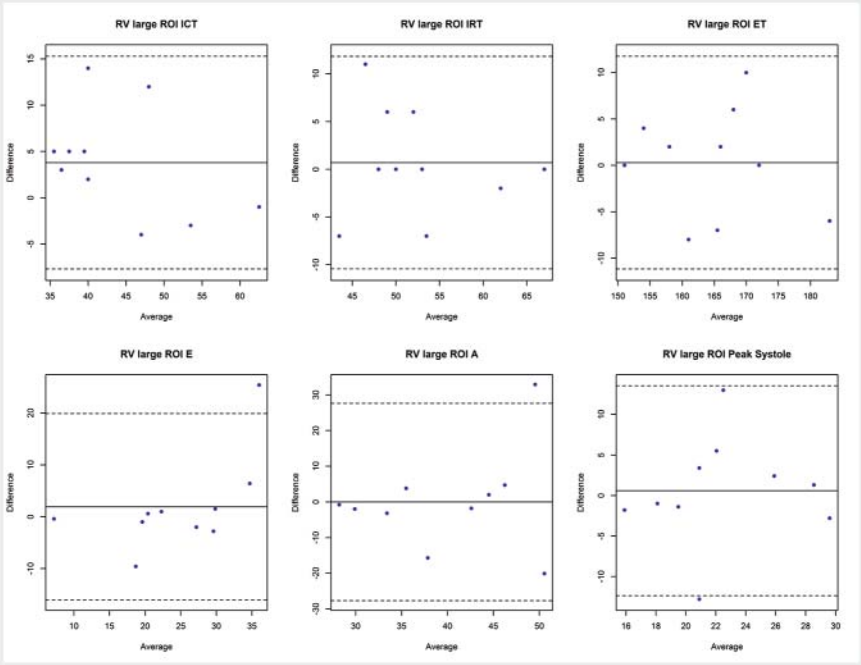


▶ **Fig. 7** Bland-Altman plots of interobserver variability of the small ROI of the RV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.

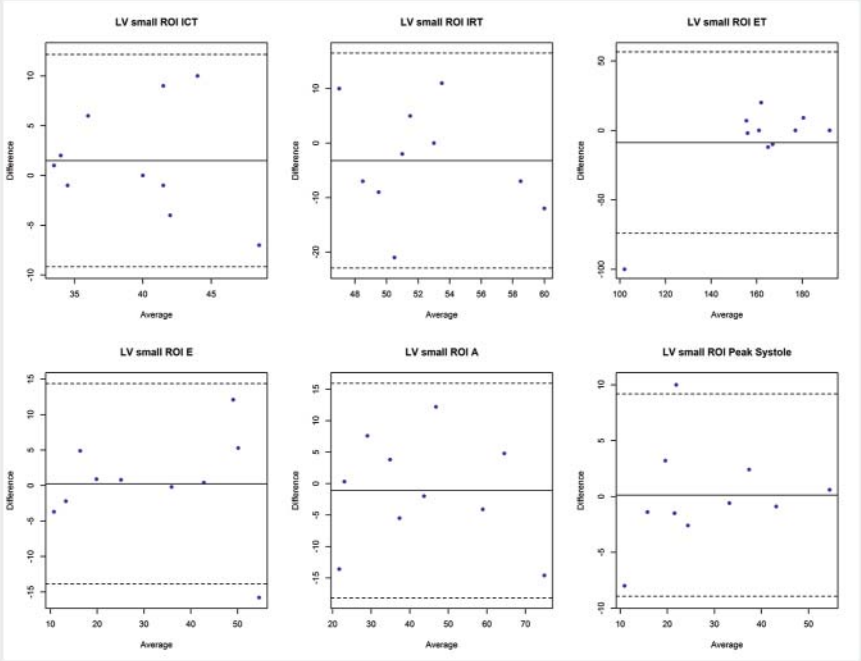
the isovolumetric time intervals revealed similar intraobserver reliabilities (ICC (C,1) 0.81 – 0.98), but unsatisfactory interobserver reliabilities (ICC (A,1) 0.0 – 0.75).

Limitations

The prenatal assessment of cardiac function remains challenging because of numerous fetal and pregnancy-associated conditions.

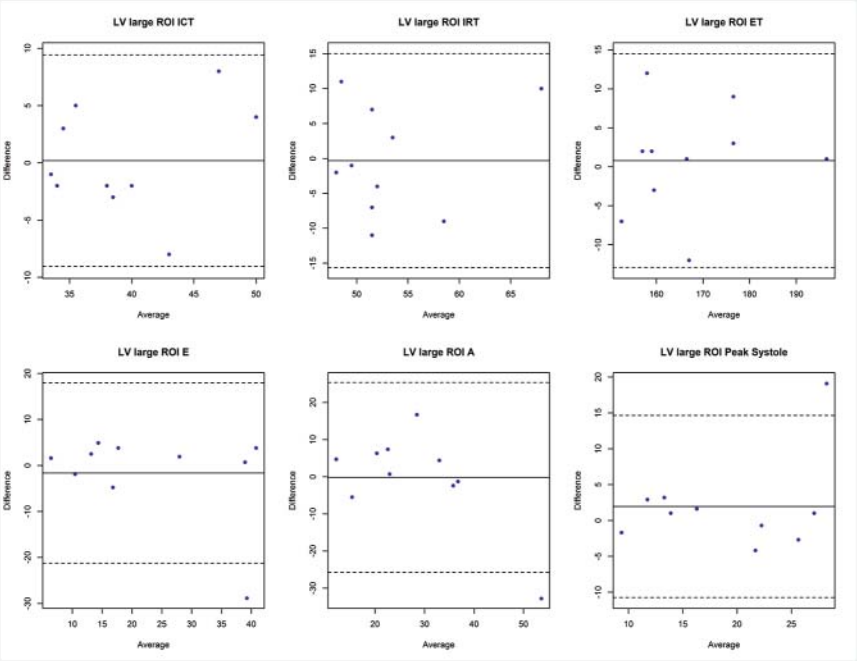


▶ **Fig. 8** Bland-Altman plots of the interobserver variability of the large ROI of the RV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.

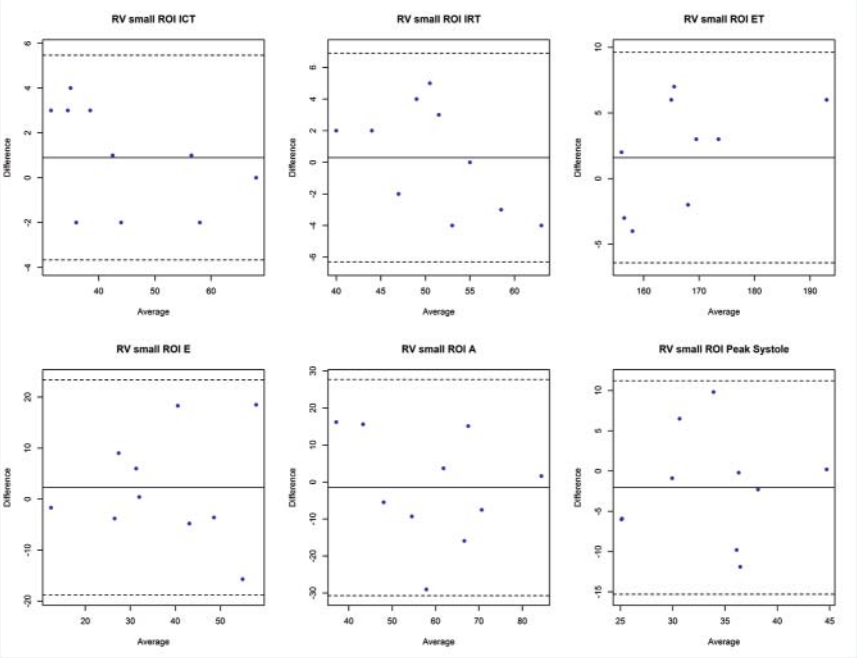


▶ **Fig. 9** Bland-Altman plots of the interobserver variability of the small ROI of the LV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.

We acknowledge that the small number of cases in this study means that it was rather limited. However, we do not consider this to be problematic in the context of the current research question because the main goal of the present study was simply to analyze fetal cardiac isovolumetric time intervals using different-sized ROIs. Of course, first the clinical value of cTDI-derived time interval measurements has to be assessed on a larger scale and secondly its additional benefit in pathological cases must be evaluated

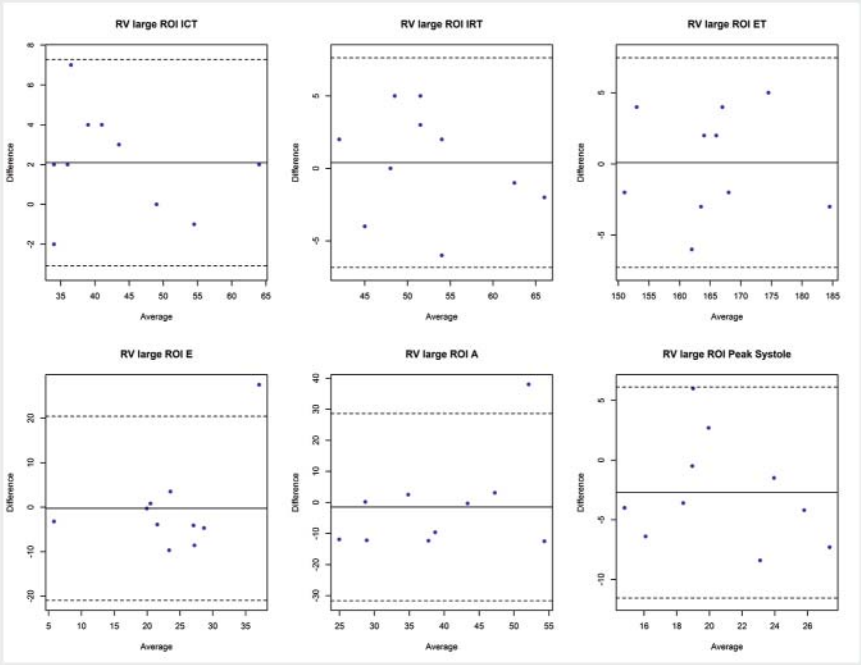


▶ **Fig. 10** Bland-Altman plots of the interobserver variability of the large ROI of the LV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.

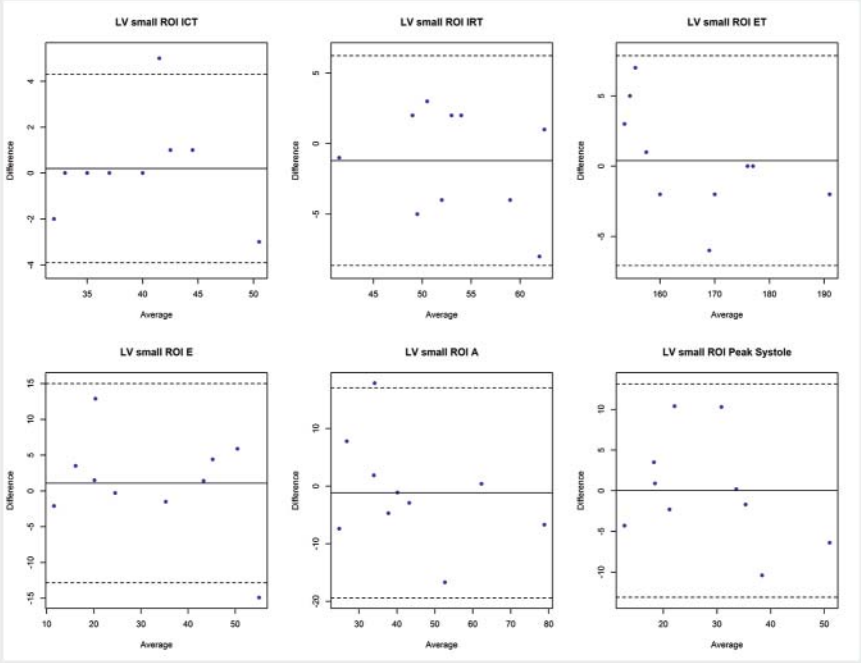


▶ **Fig. 11** Bland-Altman plots of the intraobserver variability of the small ROI of the RV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.

In conclusion, measurements of fetal cardiac isovolumetric time intervals using cTDI were feasible and relatively independent of ROI size. However, extensive training and time-consuming offline postprocessing are major limiting factors which impede the implementation of cTDI analysis for fetal cardiac function in the daily routine. Furthermore, the high interobserver variability suggests that this is a technique that is difficult to learn. The considerable interobserver variability may be explained by the beat-to-beat variability, the influence of caliper position on the time interval measurements in the same cardiac cycle (the



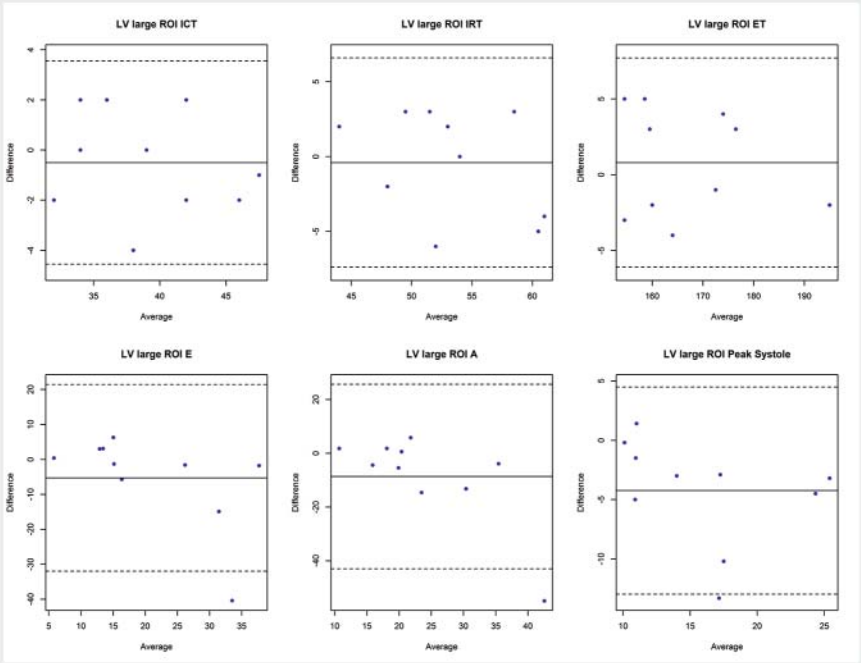
▶ **Fig. 12** Bland-Altman plots of the intraobserver variability of the large ROI of the RV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.



▶ **Fig. 13** Bland-Altman plots of the intraobserver variability of the small ROI of the LV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.

biggest contributor to variability was the caliper placement at the beginning and end of ET) and the subjective selection of the most appropriate cycle from all the video stored that clearly delineates the isovolumetric time intervals by different experts (▶ **Fig. 2**: slightly different zero crossings defining ICT and IRT comparing small and large ROIs).

We believe that in the near future, automatic time interval measurements using ultrasound systems (which automatically detect and use the whole ventricular free wall as the defined ROI)



▶ **Fig. 14** Bland-Altman plots of the intraobserver variability of the large ROI of the LV. Measurement differences are plotted against the mean of each pair of measurements. The mean deviation (solid line) and 95 % limits of agreement (dashed lines; mean ± 2 SD) are shown.

will become feasible and will neutralize many of the previously mentioned limitations. This next step towards automatic fetal myocardial functional imaging could significantly contribute to an objective, reproducible and robust method of analyzing myocardial function.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

This research study was funded in part by a grant from the German Society of Ultrasound in Medicine (Deutsche Gesellschaft für Ultraschall in der Medizin, DEGUM). Technical support was provided by Toshiba Medical Systems Corporation, Otawara-Shi, Tochigi, Japan.

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