

Atrial and Ventricular Deformation Analysis in Normal Fetal Hearts Using Two-Dimensional Speckle Tracking Echocardiography

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Keywords

Speckle tracking echocardiography · Atrial deformation · Atrial and ventricular strain · Myocardial function · Systolic strain

Abstract

Objective: Two-dimensional speckle tracking echocardiography (2D-STE)-based strain values of the left and the right ventricle have been established; however, less is known about atrial deformation. The aim of our study was to assess both atrial strain and ventricular strain using 2D-STE in a cardiac 4-chamber view and to investigate the effect of possible influencing factors such as gestational age. **Methods:** Fetal echocardiography was performed on a Toshiba Aplio 500 ultrasound system. Based on an apical or basal 4-chamber view of the fetal heart, left and right ventricular longitudinal peak systolic strain (LVLPSS and RVLPSS) as well as left and right atrial longitudinal peak systolic strain (LALPSS and RALPSS) were assessed by 2D-STE. **Results:** A total of 101 healthy fetuses were included. The mean gestational age (GA) was 26.0 ± 5.6 weeks. GA was significantly positively correlated ($p < 0.05$) with LVLPSS and RVLPSS and significantly negatively correlated ($p < 0.05$) with LALPSS and

RALPSS. The mean values for LVLPSS and RVLPSS were $-17.44 \pm 2.29\%$ and $-16.89 \pm 1.72\%$. The mean values for LALPSS and RALPSS were $34.09 \pm 4.17\%$ and $35.36 \pm 2.90\%$. **Conclusion:** Ventricular and atrial deformation analysis in 2D-STE was technically feasible and showed comparable values to current data. For future research on myocardial function (MF) of the fetus, considering GA as an influencing factor for deformation analysis seems to be adequate. Especially, atrial deformation analysis allows the assessment of diastolic myocardial function. Further research needs to clarify the clinical meaning of these myocardial deformation indices in fetuses at risk.

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Introduction

Two-dimensional speckle tracking echocardiography (2D-STE) is an angle-independent technique to quantify myocardial function (MF) of the fetus. 2D-STE has been applied in several pathological conditions such as twin-to-twin-transfusion syndrome, congenital diaphragmatic hernia, maternal diabetes, or congenital heart disease [1–4].

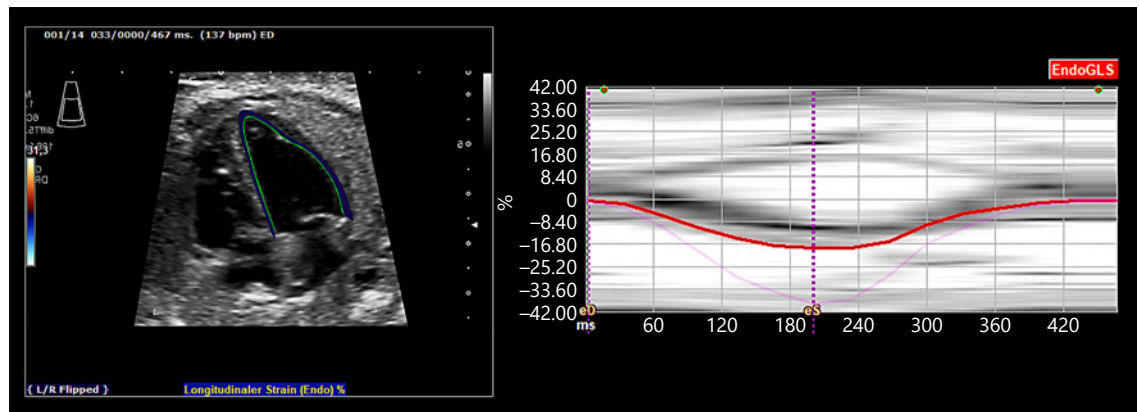


Fig. 1. Ventricular strain analysis. Left: 4CV of the fetal heart with myocardial border tracking of the left ventricle. Right: ventricular global longitudinal peak systolic strain measurement within 1 cardiac cycle. 4CV, 4-chamber view.

Recent evaluation of deformation values by 2D-STE has gained greater acceptance, as it has shown to be feasible and reproducible for the assessment of both right ventricular (RV) and left ventricular (LV) performance in the fetus [5–12]. However, reported ventricular strain values for mean LV and RV global longitudinal peak systolic strain (LPSS) show a widespread ranging [8, 10, 13–17]. Our own work revealed that the variability in image acquisition, optimal temporal resolution, and use of different ultrasound software packages are important influencing factors and possible reasons for this divergent strain values [10–12]. On the other hand, data on fetal myocardial deformation properties of the left atrium (LA) and right atrium (RA) are sparse [18, 19]. However, current data in adult cardiology shows feasibility and acceptable reproducibility of atrial 2D-STE. Furthermore, these data illustrate the potential of atrial deformation parameters, which may act as predictors for the necessity of therapeutic interventions in adult cardiology [20]. Besides already investigated potential function of 2D-STE to distinguish between healthy fetuses and fetuses with congenital heart diseases (CHD), the function of myocardial strain as a predictor for the success of cardiosurgical interventions may be a potential usage for 2D-STE [21, 22]. To enable future research in these areas, the aim of our study was to evaluate atrial and ventricular MF using 2D-STE in normal fetal cardiac 4-chamber view (4CV), which is a common standard in basic sonographic screening, and test reproducibility of our collected deformation values. In addition, the possible influence of gestational age (GA) and fetal heart rate (FHR) on atrial and ventricular LPSS analysis should be assessed. Especially, atrial defor-

mation analysis allows the assessment of diastolic MF and could give additional insights into the pathophysiology of CHD in this way.

Methods

Study Population

We retrospectively analyzed prospectively acquired data on healthy fetuses between the 16th and 39th week of gestation selected from women referred for fetal echocardiography from April 2014 to March 2016. Some of these fetuses were reported in previous studies [10–12].

All patients underwent a morphological examination of the fetal heart in order to exclude structural anomalies. Cases with the evidence of chromosomal anomalies, twin pregnancies, or other conditions with possible effect on fetal hemodynamics such as pre-eclampsia, preterm labor, or endocrine disorders (e.g., thyroid disease and maternal diabetes) were excluded from analysis. Postnatally, a complete physical examination was performed to assess the clinical status of the neonates. The institutional review board approved this study. Informed written consent was obtained from all participants.

Echocardiography

According to our previous studies [10, 12], fetal echocardiography was performed standardized by a highly experienced operator on a Toshiba Aplio 500 ultrasound system (Toshiba Medical Systems Corporation, Otawara, Tochigi, Japan) with a 1–5 MHz curved array probe (PVT 375 BT). Based on practical knowledge of previous data acquisitions, B-mode image depth was reduced, sector width was adjusted, and fetal as well as maternal movements were avoided to guarantee high-quality image acquisition with the aim to display every cardiac cavity in their full size. To perform offline strain analysis, a minimum of 3 cardiac cycles were recorded in preferably apical or basal 4CV. These B-mode cine loops were digitally stored in a standard format called Digital Imaging and Communications in Medicine (DICOM FR [60 fps]).

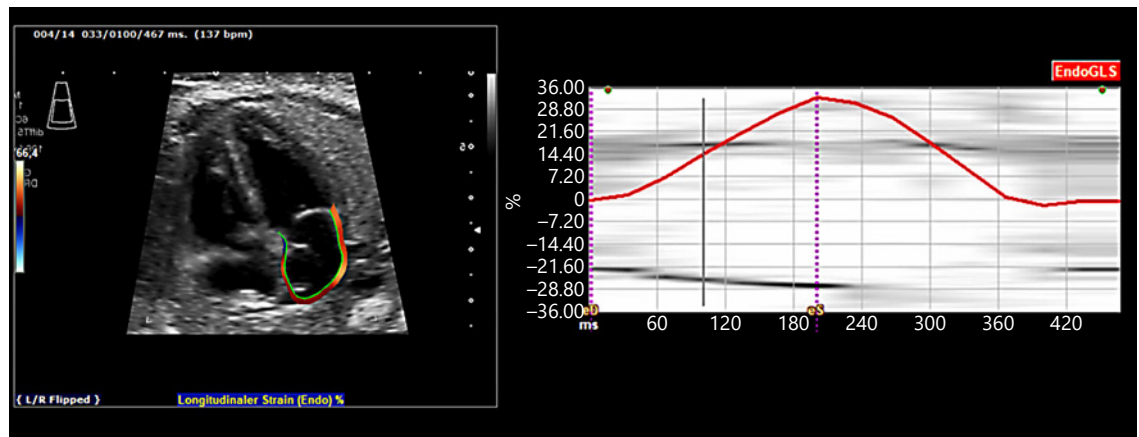


Fig. 2. Atrial strain analysis. Left: 4CV of the fetal heart with myocardial border tracking of the left atrium. Right: atrial global longitudinal peak systolic strain measurement within 1 cardiac cycle. 4CV, 4-chamber view.

Table 1. Study group with corresponding number of included 4CV, mean, standard deviation, minimum, maximum, and 95% confidence interval for mean of GA, FHR, and LPSS of all cardiac cavities and LV/RV ratio

	GA	FHR	LVL PSS	RVL PSS	LAL PSS	RAL PSS	LV/RV ratio
Total, <i>N</i>	101	101	101	101	101	101	101
Valid	101	101	101	101	86	94	100
Missing	0	0	0	0	15	7	1
Mean	26.00	143.80	-17.44	-16.89	34.09	35.36	1.03
SD	5.62	11.35	2.29	1.72	4.17	2.90	0.15
Minimum	16.29	112	-23.88	-21.38	24.13	30.12	0.76
Maximum	38.57	170	-12.28	-11.21	42.09	42.58	1.41
95% confidence interval for mean							
Lower bound	24.89	141.56	-17.90	-17.23	33.20	34.77	1.01
Upper bound	27.11	146.04	-16.99	-16.55	34.99	35.96	1.06

GA, gestational age; FHR, fetal heart rate; LV, left ventricular; RV, right ventricular; LA, left atrial; RA, left atrial; LPSS, global longitudinal peak systolic strain; LV/RV ratio, left and right ventricular LPSS ratio; 4CV, 4-chamber view.

Two-Dimensional Speckle Tracking Technology

Speckle tracking is an application of the 2D-Cardiac Performance Analysis[®] (2D-CPA) technology to ultrasound cine data to detect motion of the fetal heart. This method does not make use of Doppler information, so there is no Doppler angle dependency [12, 23].

Strain Analysis

Strain analysis was performed with the offline STE Software "TomTec Image Arena" (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) by 2 trained investigators. One fetal heart cycle was identified and selected by anatomical M-mode using the closure of the mitral and tricuspidal valve as orientation for determination of the end systole. Via three-point analysis, the operator set endocardial borders of every cardiac cavity. For this purpose, we set 1 point at each approach of the valves in the

chamber and 1 point at the top of the chamber to be analyzed. Atrial and ventricular strain analysis varies in the location of the apex point (Figs. 1, 2). Once the points are defined, the software is able to detect the borders of the selected heart chamber automatically and performs a complete strain analysis. This analysis is based on the 2D-CPA technology, which in turn is based on the hierarchical algorithm at multiple scales and 1D and 2D feature tracking. Left and right ventricular longitudinal peak systolic strain (LVL PSS and RVL PSS) as well as left and right atrial longitudinal peak systolic strain (LAL PSS and RAL PSS) are displayed graphically and numerically. In consequence of different contraction directions related to the valve level, atrial LPSS is positive and ventricular LPSS is negative. Absolute values reflect the magnitude of deformation irrespective of its direction. To detect possible differences in ventricular MF between the single ventricles, LV/RV ratio was formed [10–12]. The FHR was determined

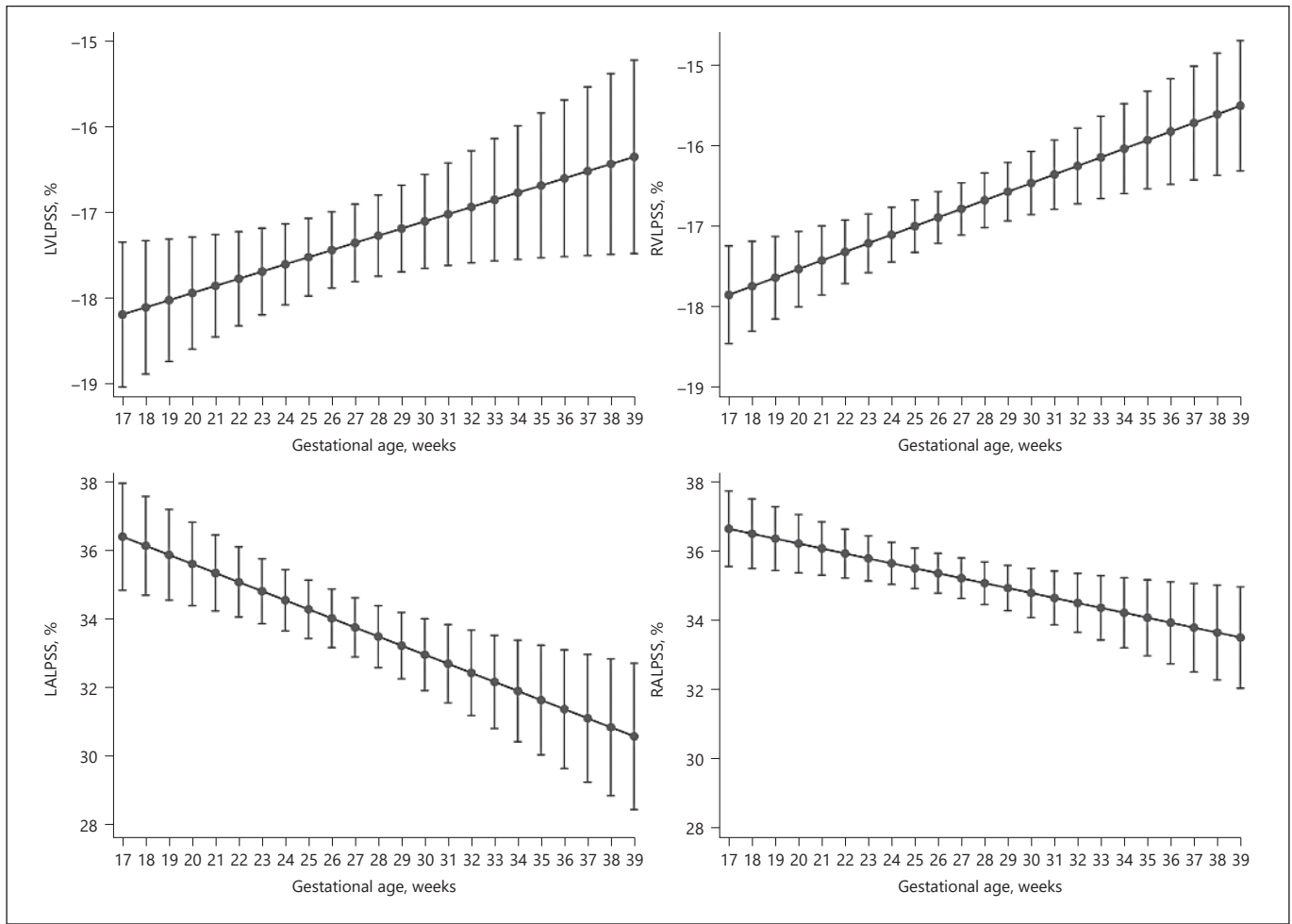


Fig. 3. Linear regression analysis of LPSS and GA with 95% confidence interval. LV, left ventricular; RV, right ventricular; LA, left atrial; RA, right atrial; LPSS, global longitudinal peak systolic strain; GA, gestational age.

on the basis of one heart cycle duration, and out of this, frames per cycle (fpc) were calculated. Tracking inaccuracy had to be corrected by the operator. How to perform a strain analysis in cardiac 4CV and handle tracking inaccuracies is shown in see online suppl. videoclip 1; for all online suppl. material, see www.karger.com/doi/10.1159/000508881. Nonsatisfactory strain analyses were excluded from final analysis, and the resulting dropout rate will be reported.

Statistical Analysis

IBM SPSS Statistics (Version 25.0 for Windows) and STATA (Version 15.1 for Windows) were used for statistical analysis. Using linear regression analysis, we observed the dependencies between the regressor $X = GA$ and the dependent variable $Y = LPSS$. Unstandardized regression coefficient b is reported. Following the suggestion of Alan C. Acock, observations with standardized residuals larger than $|2.58|$ can be expected in less than 1% of the observations by chance and are defined as outliers [24]. In the following evaluation, a model without outliers and resulting dropout rate is reported. In case of significant association between GA and

LPSS, GA-dependent marginal means for LPSS are reported. To allow the comparison of our data with future examined strain values, we show the regression formula for every correlation. Analogously to Kurmanavicius et al. [25], from out of here Z-scores can be calculated using the formula: $Z = [X - M(GA)]/SD(GA)$. To detect possible associations between the single LPSS values of different cardiac cavities, which may be used as indicators for more detailed clinical examination, Pearson correlation analysis was performed. Exemplary for LVLPPS, we analyzed the influence of the mediator variable $M = FHR$ on the dependency between $Y = LVLPPS$ and $X = GA$ through mediation analysis, using the PROCESS 3.1 module for SPSS by Hayes [26].

All accomplished statistical tests were performed with a significance level of 0.05. The data were validated by using double data entry. Descriptive statistics are presented as mean \pm 1 SD.

Twenty randomly chosen patients were used for calculating interrater reliability and 101 patients were used for calculating intrarater reliability with an interval longer than 8 weeks after the 1st measurement to limit recall bias. Reliability was examined with Bland-Altman analysis.

Table 2. Marginal mean values for LPSS of all cardiac cavities for the 20th, 26th, 32nd and 38th week of gestation with 95% confidence interval

GA, week	Marginal mean	95% confidence interval	
		lower bound	upper bound
LVL PSS, %			
20th	-17.95	-18.6	-17.29
26th	-17.44	-17.89	-16
32nd	-16.94	-17.6	-16.29
38th	-16.44	-17.5	-15.39
RVL PSS, %			
20th	-17.54	-18.01	-17.07
26th	-16.89	-17.21	-16.57
32nd	-16.25	-16.72	-15.78
38th	-15.61	-16.37	-14.85
LAL PSS, %			
20th	35.63	34.42	36.83
26th	34.05	33.21	34.89
32nd	32.48	31.25	33.72
38th	30.91	28.93	32.88
RAL PSS, %			
20th	36.21	35.37	37.05
26th	35.36	34.78	35.93
32nd	34.5	33.65	35.35
38th	33.64	32.27	35.01

GA, gestational age; LV, left ventricular; RV, right ventricular; LA, left atrial; RA, right atrial; LPSS, global longitudinal peak systolic strain.

Results

This study included 101 healthy fetuses. The mean GA was 26.0 ± 5.6 weeks (range 16.3–38.6 weeks). The mean FHR was 143.8 ± 11.3 beats per minute (bpm), and temporal resolution was 26 frames per cycle (fpc).

In consequence of an incomplete view on LA or RA in some 4CV, strain analysis was not feasible in 12 (11.9%) cases for LA and 3 (3.0%) cases for RA. As mentioned above, after inspection of model residuals, divergent cases were additionally excluded for strain analysis of LA in 3 (3.0%) cases, RA in 4 (4.0%) cases, and LV/RV ratio in 1 (1.0%) case (Table 1). Descriptive statistics for LPSS values are accessible in Table 1. The mean values for LVL PSS and RVL PSS were $-17.44 \pm 2.29\%$ and $-16.89 \pm 1.72\%$. The mean values for LAL PSS and RAL PSS were $34.09 \pm 4.17\%$ and $35.36 \pm 2.90\%$. The mean LV/RV ratio was 1.03 ± 0.15 .

Linear regression analysis revealed a significant association between GA and the LPSS for every cardiac cavity (Fig. 3). GA was positively correlated with LVL PSS ($b = 0.08$; $p < 0.05$) and RVL PSS ($b = 0.10$; $p < 0.05$) and nega-

Table 3. Regression formula for correlation between LPSS of respective cardiac cavity and gestational age. Z-scores can be calculated for every measured strain value following the formula: $Z = [X - M(GA)]/SD(GA)$

Regression formula	
LVL PSS	$M(GA) = -19.618317 + 0.083628 * GA(W)$ $SD(GA) = 2.246169$
RVL PSS	$M(GA) = -19.672545 + 0.106,851 * GA(W)$ $SD(GA) = 1.61462281$
LAL PSS	$M(GA) = 40.865495 - 0.262013 * GA(W)$ $SD(GA) = -11.334207 + 1.072556 * GA(W) - 0.017863 * GA(W)$
RAL PSS	$M(GA) = 39.066751 - 0.142695 * GA(W)$ $SD(GA) = 4.482349 - 0.067521 * GA(W)$

$M(GA)$, mean value for the appropriate gestational age; $GA(W)$, gestational age in exact weeks; $SD(GA)$, standard deviation for the appropriate gestational age; LV, left ventricular; RV, right ventricular; LA, left atrial; RA, right atrial; LPSS, global longitudinal peak systolic strain.

Table 4. Indirect, direct, and total effect of the FHR on the relationship between GA and LVL PSS with 95% confidence interval

	Coefficient	95% confidence interval	
		LLCI	ULCI
Total effect	0.084	0.0116	0.1557
Direct effect	0.110	0.0323	0.1867
Indirect effect	-0.030	-0.0578	-0.001

LVL PSS, left ventricular global longitudinal peak systolic strain; GA, gestational age; LLCI, lower level confidence interval; ULCI, upper level confidence interval.

tively correlated with LAL PSS ($b = -0.26$; $p < 0.05$) and RAL PSS ($b = -0.14$; $p < 0.05$). There was no relevant effect of GA on the LV/RV ratio. From the 17th to 38th week of gestation, this means an absolute increase in LVL PSS by 1.68% and an absolute increase in RVL PSS by 2.1%. Regarding atrial deformation, a total decrease in LAL PSS by 5.46% and RAL PSS by 2.94% was observed.

Marginal mean values for LPSS of every heart cavity for the 20th, 26th, 32nd, and 38th week of gestation are displayed in Table 2. The regression formula is shown in Table 3. Interactions between single LPSS values of different cardiac cavities did not correlate significantly.

Table 5. Numerical results of Bland-Altman analysis for intra- and interrater reliability with bias and lower and upper 95% limit of agreement

	Intraobserver reliability			Interobserver reliability		
	bias	LLoA	ULoA	bias	LLoA	ULoA
LVL PSS	-0.06	-1.36	1.23	-0.14	-1.24	0.96
RVL PSS	0.03	-1.27	1.34	-0.11	-1.39	1.18
LAL PSS	0.23	-2.1	2.57	0.24	-3.01	3.48
RAL PSS	0.21	-2.27	2.69	-0.11	-2.75	2.53

LLoA, lower 95% limit of agreement; ULoA, upper 95% limit of agreement; LV, left ventricular; RV, right ventricular; LA, left atrial; RA, right atrial; LPSS, global longitudinal peak systolic strain.

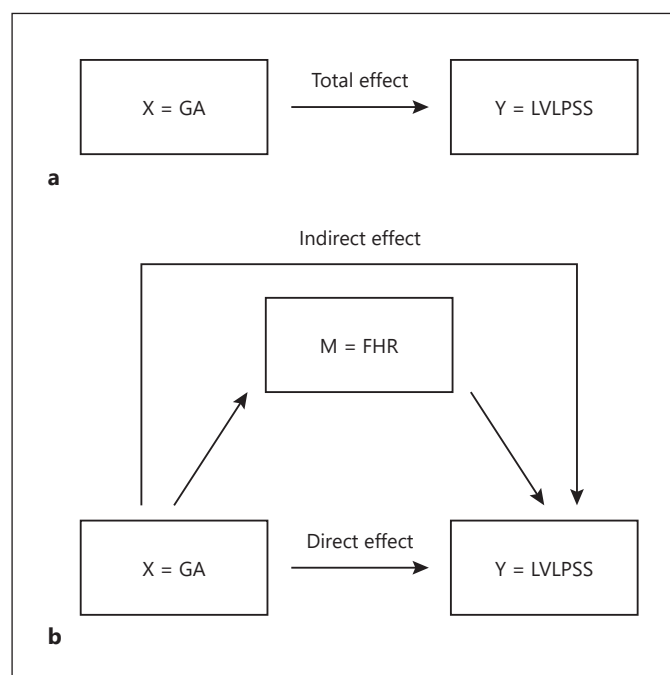


Fig. 4. Conceptual mediation model diagram for the relationship between LVL PSS, GA, and FHR: **a** Total effect of X = GA on Y = LVL PSS, which is equivalent to the regression coefficient of linear regression analysis. This total effect could be decomposed in direct and indirect effects. **b** Direct effect of GA on LVL PSS, which describe correlation between GA and LVL PSS without the influence of FHR, and indirect effect of FHR on the association between GA and LVL PSS. The numerical results of the mediation analysis are shown in Table 3. GA, gestational age; LVL PSS, left ventricular global longitudinal peak systolic strain; FHR, fetal heart rate.

The effect of FHR on the association between GA and LVL PSS is displayed schematically in a conceptual diagram (Fig. 4) and numerically in Table 4. Using mediator analysis, association between GA and LVL PSS can be decomposed in different effects.

Without controlling for FHR, the linear association between GA and LVL PSS is positive and significant ($b = 0.08$). When controlling for FHR, the association between GA and LVL PSS becomes stronger ($b = 0.11$). This can be explained by the mediating effect of the FHR: A higher GA leads to smaller FHR values. The FHR is associated positively with LVL PSS. Thus, it can be said that because GA is increasing and an increasing GA leads to decreasing FHR values, the LVL PSS values are decreasing with higher GA (indirect effect, $b = -0.03$). However, in addition to this negative effect of GA (via FHR) on LVL PSS, there is a stronger positive association between GA and LVL PSS, independent of the FHR ($b = 0.11$). Together, this negative indirect effect and the positive remaining association make the total effect between GA and LVL PSS ($b = 0.08$). From the 17th to 38th week of gestation, this means without the indirect effect of FHR, LVL PSS would absolutely increase by 2.31% instead of 1.68%. The 95% confidence interval (BcA, 1,000 bootstrap repetitions) did not include zero; thus, the indirect effect can be interpreted as statistically significant. For strain analysis, Bland-Altman plots for intrarater reliability and interrater reliability are displayed in Figures 5 and 6 and Table 5 with 95% limits of agreement.

Discussion

The objective of this study was to examine ventricular and atrial MF in fetal cardiac 4CV using 2D-STE. Investigation of atrial and ventricular LPSS was feasible, and a correlation between GA and LPSS for every cardiac cavity was detectable. The FHR turned out to be an effector for the association between GA and LPSS. This study is one of the 1st attempts to measure atrial LPSS.

Ventricular strain values are well established and reported with acceptable reproducibility [5–12]. However, small differences in ventricular LPSS values are notice-

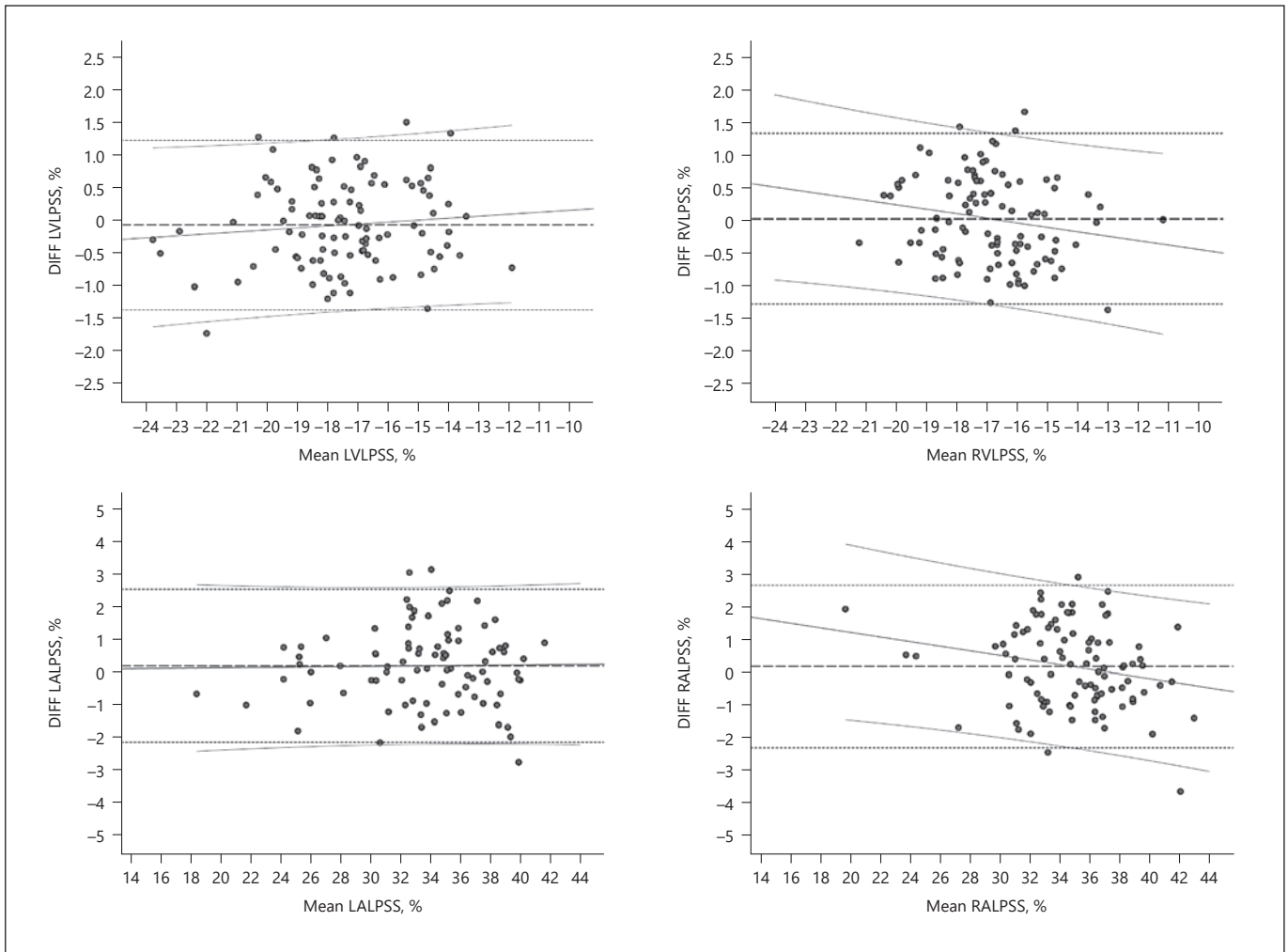


Fig. 5. Bland-Altman plots for intrarater reliability for measurements of every cardiac cavity with mean and 95% limits of agreement (dotted horizontal lines). In addition, regression of the differences of mean values with 95% confidence interval is shown (gray solid lines).

able compared with previous studies of Enzensberger et al. [10], what might be the result of different speckle tracking software packages [10–12]. Our own data revealed that the variability in image acquisition, the optimal temporal resolution, and the use of different ultrasound packages are important influencing factors [10–12]. Definitions for a common standard for 2D-STE were published to standardize deformation imaging in adult cardiology [27]. A widespread ranging between actual fetal global longitudinal strain values is still noticeable, which might be explained by different methods and technical conditions for 2D-STE (Tables 6, 7). Hence, more detailed standardization of image acquisition and 2D speckle tracking, especially for fetal echocardiography, seems to be more and more important for future research.

These technical challenges were even more important for atrial deformation analysis. In consequence of incomplete view on the left and right myocardium, strain analysis was not feasible in 12 (11.9%) cases for LA and 3 (3%) cases for RA. In order to further increase the feasibility, an adaption of the 4CV with regard to an optimized atrial view would be necessary. Maximal resolution during image acquisition was necessary to minimize this drop-out rate by displaying the thin atrial myocardium in full thickness. However, Bland-Altman analysis shows marginal bias and mean difference in intra- and interobserver reliability for every cardiac cavity.

Until now, only Dahlbäck et al. [18] performed atrial 2D-STE in normal fetal hearts and revealed a left atrial global longitudinal strain of $23.2 \pm 13.1\%$ and right atrial

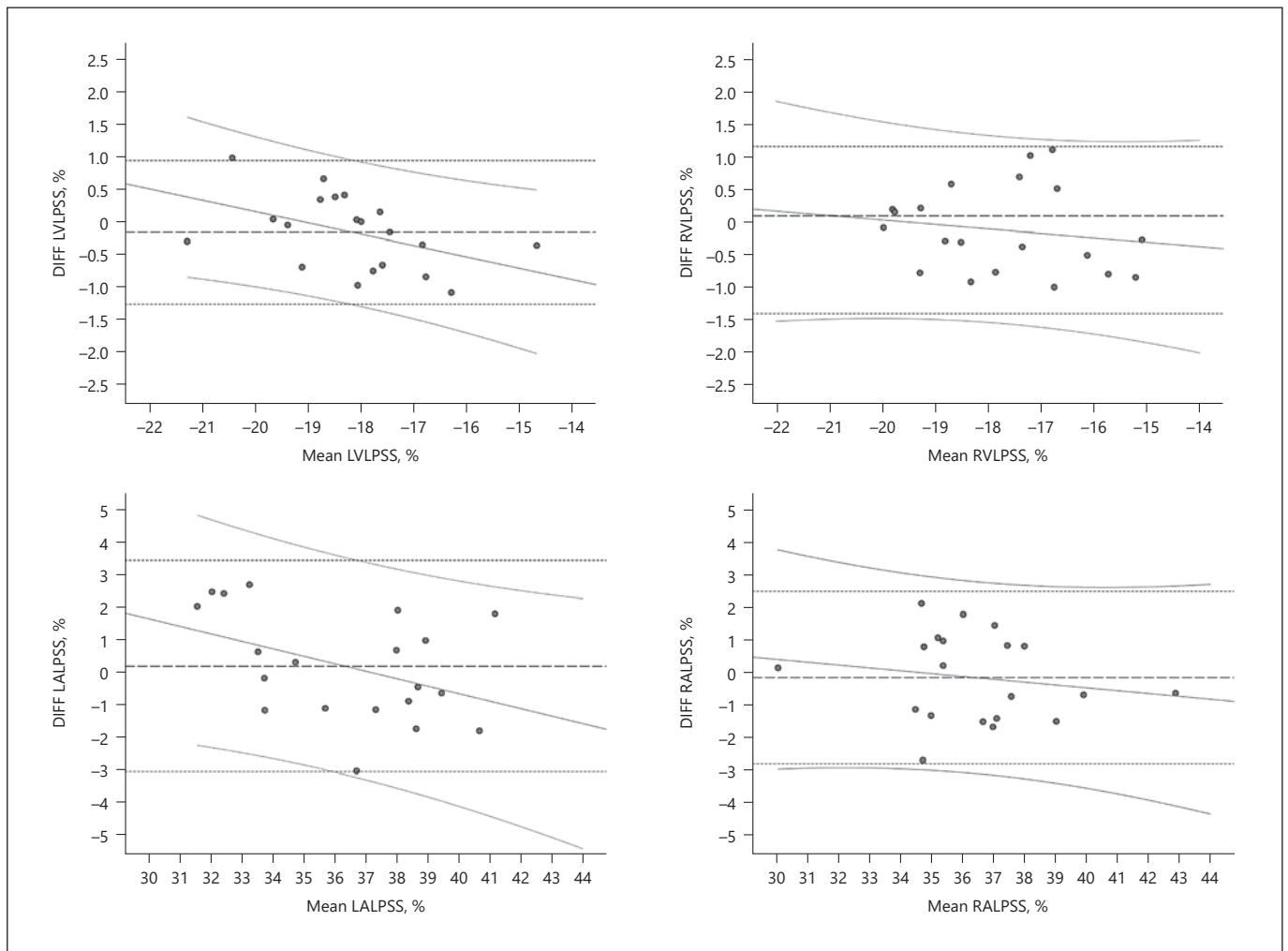


Fig. 6. Bland-Altman plots for interrater reliability for measurements of every cardiac cavity with mean and 95% limits of agreement (dotted horizontal lines). In addition, regression of the differences of mean values with 95% confidence interval is shown (gray solid lines).

global longitudinal strain of $33.6 \pm 19.7\%$. The authors used a different speckle tracking pattern, which exclude the interatrial septum from strain analysis. High variability and low ICC values for global longitudinal strain as well as the differences in LALPSS values might be caused by this different speckle tracking pattern. Steinhart et al. [19] recently reported atrial strain analysis using tissue Doppler imaging (TDI).

Our study has strengths and limitations. To perform atrial strain analysis, the use of an STE software package, which is also used in adult cardiology, was necessary. A possible influence of the used software package cannot be excluded. Also, the frame rate in STE is a part of discussion in the current research. For fetal STE, a frame rate of at least 80 fps is recommended by DeVore et al. [33],

which results in a temporal resolution of 40 fpc. However, a consensus about the optimal frame rate and temporal resolution is still missing. We generally agree that using high frame rates might have an influence on STE, especially regarding the exact definition of the end systole. However, further studies should consider a possible intervenditor variability in technical basics of different software packages. A detailed knowledge about the use of radiofrequency-STE and grayscale-STE in the respective software packages is needed to assess the influence of frame rate correctly. Also, the usage of the same frame rate in every clip could be an important factor for strain analysis. The use of 26 fpc in this study should be considered as strain values could be underestimated. Apart from these abovementioned technical challenges, other limita-

Table 6. Published global longitudinal peak systolic strain values for the left ventricle

Author	Year	Patients studied, <i>n</i>	Gestational age, weeks	Ultrasound system	LV strain values, %	SD
Patey et al. [13]	2017	108	39±1.5	Toshiba	-11.0	4.0
Ishii et al. [8]	2012	81	19–42	Siemens	-15.2	2.7
Miranda et al. [28]	2017	12	19–33	Toshiba	-16.7	NR
Enzensberger et al. [10]	2017	101	17–39	Toshiba	-17.5	NR
Barker et al. [17]	2009	33	17–38	Siemens	-17.7	6.4
Crispi et al. [29]	2014	37	32	GE	-18.2	4.4
Germanakis et al. [30]	2012	144	14–39	Siemens	-21.9	3.7
DeVore et al. [14]	2018	200	20–40	GE	-22.9	3.5
Kapusta et al. [15]	2013	44	30–34	GE	-24.7	4.8
Kapusta et al. [9]	2012	78	20–24	GE	-24.9	4.6
Di Salvo et al. [31]	2008	100	20–32	GE	-25.0	4.0
Willruth et al. [32]	2011	150	13–39	Siemens	-27.9	10.5

LV, left ventricular; SD, standard deviation; NR, not reported.

Table 7. Published global longitudinal peak systolic strain values for the right ventricle

Author	Year	Patient studied, <i>n</i>	Gestational age, weeks	Ultrasound system	RV strain values, %	SD
Patey et al. [13]	2017	108	39±1.5	Toshiba	-11.5	3.8
Miranda et al. [28]	2017	12	19–33	Toshiba	-13.4	NR
Ishii et al. [8]	2012	81	19–42	Siemens	-16.0	3.3
Enzensberger et al. [10]	2017	101	17–39	Toshiba	-16.5	NR
Crispi et al. [29]	2014	37	32	GE	-17.3	4.5
Barker et al. [17]	2009	33	17–38	Siemens	-17.4	6.3
Germanakis et al. [30]	2012	144	14–39	Siemens	-22.0	3.7
DeVore et al. [14]	2018	200	20–40	GE	-22.7	4.1
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Di Salvo et al. [31]	2008	100	20–32	GE	-24.0	4.0
Kapusta et al. [9]	2012	78	20–24	GE	-25.4	NR
Willruth et al. [16]	2011	150	13–39	Siemens	-35.9	11.2

RV, right ventricular; SD, standard deviation; NR, not reported.

tions should be emphasized. In accordance with Koca et al. [20], we include the interatrial septum for better orientation in strain analysis. From our point of view, using valve level as orientation in strain analysis is the best way to guarantee consistent results in 2D-STE. Also, technical conditions of 2D-CPA require clear orientation points like the mitral plane. The impact of open foramen ovale should be regarded at this point. By including the interatrial septum in the strain analysis, we accept a change of LPSS values for better reproducibility of 2D-STE, which is even reached with a bias of smaller than 1.0 in Bland-Altman analysis. Furthermore, a two-dimensional section of the atria at cardiac 4CV likely does not reflect the

maximum diameter of the fetal atria. To assess the true volume change, three-dimensional STE seems to be a solution. However, fetal cardiac 4CV is a part of the basic ultrasonic screening and might be more suitable for 2D-STE and a clinical implementation of it. A methodology for atrial strain analysis, which is applicable in clinical routine, was one of the major ideas of this study. This could be reached with a good reproducibility.

In addition, linear regression analysis revealed significant correlations between GA and LPSS for every cardiac cavity. Considering different contraction directions related to the valve level, atrial and ventricular LPSS have different algebraic signs. Consequently, absolute values of

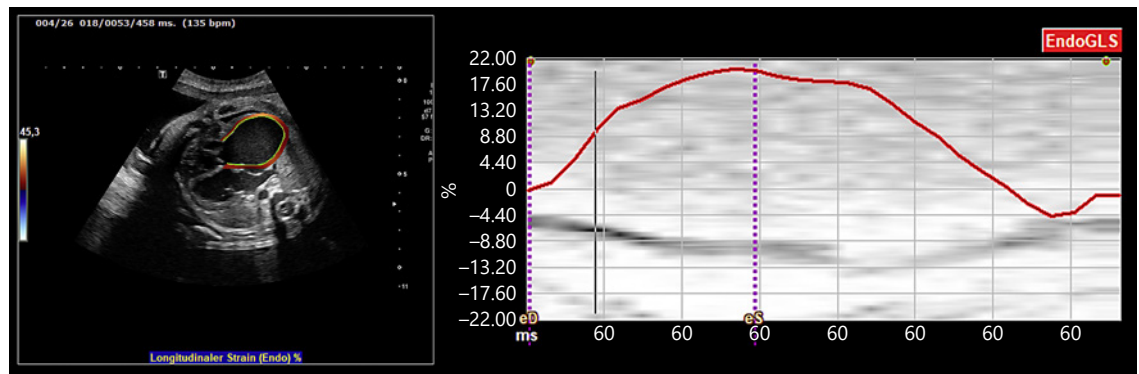


Fig. 7. Atrial strain analysis in a fetus with PAIVS. Left: 4CV of a fetus with PAIVS with myocardial border tracking of the right atrium. Right: atrial global longitudinal peak systolic strain measurement within 1 cardiac cycle. PAIVS, pulmonary atresia with intact ventricular septum; 4CV, 4-chamber view.

LPSS reflect the magnitude of deformation irrespective of its direction. This means that the positive correlations between GA and ventricular LPSS values as well as the negative correlations between GA and atrial LPSS can be interpreted as a phenomenological decrease in myocardial strain between the 17th and 38th week of gestation. As mentioned by Willruth et al. [16], a possible reason for this decrease in myocardial strain might be an increase in cardiac afterload caused by changes of placental resistance during gestation [16, 34, 35]. The meaning of GA as an influencing factor for strain analysis has to be examined in further prospective studies. Longitudinal examination of the same fetus in further studies seems to be adequate to confirm the results of linear regression analysis.

Interactions between single LPSS values of different cardiac cavities did not correlate significantly. However, this stands in contrast to actual MRI studies in pediatric population, which show an atrioventricular interaction [36]. Further studies need to verify this correlation, which might be the result of the relatively small study population.

To examine possible influencing factors for the result of linear regression analysis, we perform a mediator analysis exemplary for left ventricular strain values. Interpreting mediator analysis, we show a significantly indirect effect of FHR on the relationship between LVLPS and GA. A clearer decrease in myocardial strain during gestation can be assumed without the indirect effect of FHR. This result seems to be plausible because myocardial shortening will be more effective with decrease in FHR. Besides the changes of placental resistance as a possible reason for the dependency between LPSS and GA, a decrease in the FHR during gestation might partially

compensate the phenomenologically shrinking LPSS during gestation to guarantee cardiac output. High confidence intervals for indirect effect might be the result of relatively low numbers of incoming 4CV. Future studies should clarify this effect of the FHR for all cardiac cavities. Other influencing factors such as heart volume or stroke volume will be examined to explain the total effect of GA on LPSS, whose magnitude is mainly caused by the direct effect.

Finally, the potential and applicability of especially atrial strain measurements in fetuses at risk should be demonstrated. By performing atrial strain analysis in a fetal heart with pulmonary atresia with intact ventricular septum (PAIVS), we could reveal a strong reduction in RALPSS compared with our control group, reflecting reduced right ventricular MF in this case (Fig. 7). The RALPSS in the fetus with PAIVS was 20.65%. An evaluation of atrial deformation for fetuses at risk seems to be generally possible. It should be noticed that our method, which includes interatrial septum in strain analysis, seems to make atrial deformation analysis feasible. Furthermore, Koca et al. [20] demonstrated the potential of atrial strain analysis by using atrial LPSS as a predictor for the success of therapeutic interventions, which also may be applied in prenatal medicine.

In conclusion, quantification of MF using 2D-STE for both atrial and ventricular deformation analysis was feasible in cardiac 4CV. We present in this study atrial LPSS values, which enable further research about the relevance of the atriums for pathological conditions prenatally. Furthermore, GA-dependent LPSS values could be determined for every cardiac cavity. For future research on MF of the fetus, considering GA as an influencing factor for deformation analysis seems to be adequate.

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Statement of Ethics

This study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The institutional ethical review board of Justus Liebig University Giessen approved this study (ethical approval number: AZ 186/18). Informed written consent was obtained from all participants.

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