Quantitative analysis of left atrial myocardial function and compliance in patients with pre-eclampsia

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Abstract

Background: Pre-eclampsia (PE) is a severe obstetric complication associated with many cardiovascular disorders. Left atrial (LA) function and its relevance to the cardiovascular adaptation changes associated with PE have not been adequately addressed. The aim of this study was to quantify LA myocardial deformation characteristics in women with PE using speckle tracking echocardiography (STE).

Methods: Using STE, LA global longitudinal strain (LAGLS), phasic LA strain values and LASr/(E/e'), which was the value of LA reservoir strain (LASr) divided by the quotient of early mitral flow velocity (E) and diastolic mitral ring velocity (e'), were compared among nonpregnant controls (n=39), normotensive pregnant women (n=40), and PE (n=43) patients.

Results: LAGLS, LASr and LA conduit strain reduced in PE group in spite of no difference of LA contraction strain among the three groups. LASr/(E/e'), the surrogate of LA compliance, was decreased during PE pregnancy. The multivariate regression analyses showed LAGLS was independently correlated with LASr/(E/e'), left ventricular global longitudinal strain and LA maximum volume.

Conclusion: PE cases undergo impaired LA myocardial function and decreased atrial compliance. STE-derived LA strain may be a powerful diagnostic parameter to evaluate diastolic function with the progression of PE pregnancy.

Introduction

Pre-eclampsia (PE) is a serious obstetric complication characterized by severe hypertension during pregnancy and is associated with many cardiovascular disorders. In the short time of perinatal period, PE can lead to subsequent heart failure (HF), pulmonary edema, and stroke. After the troubled pregnancy, PE relates to a 2- to 7-fold increased cardiac disease risk including ischemic heart disease, arrhythmias, diastolic dysfunction, and HF[1–3]. Even before the cardiovascular events emerge, PE women have presented asymptomatic cardiac abnormalities.

During a PE pregnancy, the left ventricle (LV) undergoes concentric hypertrophy, ventricular dysfunction and myocardial damage occurs, particularly diastolic function[4, 5]. It is important to

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recognize the interplay existing between the atrial action and ventricular performance throughout the cardiac cycle. Multiple studies have demonstrated that left atrium (LA) structural and functional changes are indicators of LV dysfunction[5]. However, although there are many publications about maternal LV abnormalities, LA function and its relevance to the cardiovascular adaptation changes associated with PE have not been adequately addressed.

Many of the cardiac impairment in PE have been discovered by two-dimensional (2D) and tissue Doppler echocardiography. More recently, speckle tracking echocardiography (STE) has emerged as an especially valuable adjuvant modality to reveal myocardial dysfunction even when traditional echocardiographic measures are normal[6–8]. STE-derived parameters such as strain and strain rate are less load-dependent than the conventional echocardiographic markers[5] and STE-derived LA strain currently constitutes the best method to assess atrial function[9]. To date, atrial strain has been evaluated in multiple conditions, especially HF and atrial fibrillation [10–13].

However, there are few reports about the effects of PE on maternal LA mechanics though some studies described the STE-derived LA deformation parameters in normal pregnancy and the postpartum period[14, 15]. In the previous studies, using a real-time three-dimensional echocardiography, we identified the dilated atrial chamber and reduced volumetric action of LA occurring during the course of PE[16]. We hypothesized that LA myocardial function and compliance decrease associated with increased afterload during PE pregnancy. To test this hypothesis, we evaluated LA myocardial deformation characteristics in women with PE using STE in this study.

Methods

Study population

Singleton pregnancies diagnosed with PE for the first time in the antenatal clinic were recruited for this study. PE was identified according to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2014[17]. Pregnancies with medical conditions, including essential hypertension, renal or cardiovascular disorders etc., multiply pregnancy, and gestational diabetes mellitus or pregnancy-induced hypertension were ineligible. There was no difference in the age and gestational week between PE and normal pregnant women. Were considered as

complications: maternal or fetal death, emergency delivery, hospitalization of more than 7 days for the newborn due to tension disorder, birth weight < 2500 g and any eclampsia. In addition, 39 age-matched, healthy, nonpregnant women were enrolled as control subjects. Informed consent was obtained from all included subjects, which was approved by the institutional review board and ethics committee of the Affiliated Hospital of Qingdao University.

Conventional echocardiography

Echocardiographic studies were performed in all subjects using a commercially echocardiography system (EPIQ7C, Philips Healthcare) and a broad-band S5-1 probe (1.0–5.0 MHz). Connecting the electrocardiogram, all images were obtained from the standard views in the left lateral position at the end of inspiration. The frame rate was 52–76 frames/s. Measurements were performed for three consecutive cardiac cycles and averaged.

The interventricular septum (IVS), LV posterior wall (LVPW), LV end-systolic and end-diastolic diameters (LVDd) and LA dimension were measured in parasternal long axial view of LV according to the recommendation[18]. Relative wall thickness (RWT) was calculated following the previous description[19]. LV mass was calculated according to a necropsy validated formula of LV mass = 0.8 × (1.04 × ((IVS + LVDd + (LVPW)^3 − (LVDd)^3) + 0.6 and indexed to body surface area (BSA)[20]. LV ejection fraction was calculated by averaging measurements of end-diastolic and end-systolic volumes from apical views using the biplane Simpson's method. Diastolic parameters were measured from the apical four-chamber view using pulsed-wave Doppler at the level of the mitral orifice included early (E) and late (A) transmitral flow velocities, the ratio of early to late velocities (E/A). The average of peak early diastolic velocities at septal and lateral of mitral annular (e') assessed by pulsed-wave tissue Doppler, and the E/e' ratio to estimate LV filling pressure.

From apical views, LA volumes were calculated by the area–length method and averaged to calculate maximum (LAVmax) and minimal volumes. The LA emptying fraction (LAEF) was obtained from the relative difference between LA maximum and minimal volumes.

Analysis of the LA Strain by STE

Standard 2D images from the apical two-chamber view were recorded and the imaging data were

imported into the software of TomTec special for off-line analysis of LA. The three tracing points were placed in the IVS site and LV lateral wall site of the mitral annulus and LA apex. After tracing of the endocardial LA borders, the region of interest was automatically determined, and speckles were tracked frame by frame. In cases of insufficient tracking, manual adjustments were applied to optimize tracking quality. LA deformation is a cyclic process, which can be sub-divided into three phases including reservoir, conduit and contraction phase[21]. Different phases of LA global longitudinal strain (LAGLS) were identified from the plotted strain curve including LV systole (LA reservoir stage, LASr), LV early diastole (conduit phase, LAScd), and LV late diastole (LA contraction stage, LASct) (Fig. 1). In the study,the ventricular cycle was used and the zero reference of the strain curve was set at LV end-diastole. Then the phasic values of LA strain were calculated as follows (Fig. 2)[21]:

1. LASr = strain during reservoir phase, measured as the difference of the strain value at mitral valve opening minus ventricular end-diastole.

2. LAScd = strain during conduit phase, measured as the difference of the strain value at mitral valve opening minus the onset of atrial contraction.

3. LASct = strain during contraction phase, measured as the difference of the strain value at the onset of atrial contraction minus ventricular end-diastole.

In addition, LA compliance was estimated by the quotient of LASr and E/e'[5]. LV global longitudinal strain was analyzed as previously described[22].

Interobserver and intraobserver agreement

The imaging data was analyzed by one observer in random order. To assess interobserver variability, parameters were analyzed by a second observer who was blinded to the measurement of the first observer. To test intraobserver variability, a single observer analyzed the data twice on occasions separated by an interval of 1 month.

Statistical analysis

Statistical software package used was SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation for continuous variables. Differences among continuous

variables were tested using a one way analysis of variance. The chi-square test was used for comparison of data as appropriate. Pearson's coefficient was performed to determine the correlation between two variables. Multivariate regression analysis was used to eliminate the interaction among factors. The interobserver and intraobserver agreements were determined by evaluation of the intraclass correlation coefficients. P value < 0.05 was considered to indicate statistical significance. All measurements of strain were presented as its absolute value.

Results

Among the 132 subjects initially enrolled in the study, five PE cases (3 with poor quality images, 1 with pregnancy-related diabetes mellitus and 1 with pregnancy-related hyperthyroidism) and four normotensive pregnant participants (3 with poor quality images and 1 with diabetes mellitus) were rejected, meanwhile, one woman with poor quality images in the control group was excluded from the study. Finally, a total of 43 women with PE, 40 normotensive pregnancies and 39 healthy nonpregnant women were recruited in the analysis. All participants were Han Chinese.

Clinical characteristics

The detailed demographic and clinical characteristics of the three groups are presented in Table 1. Gestational ages were closely matched between normotensive pregnancy group and PE group. Among the three groups, BSA and body mass index were the highest in PE group. Meanwhile, systolic and diastolic blood pressure (SBP and DBP) dramatically increased in PE cases compared to the women of other two groups. Moreover, the incidence of complications was significantly higher while gestational ages of delivery, neonatal birth weight and neonatal Apgar scores were much lower in PE patients than the normotensive pregnant women.

Table 1

Clinical and hemodynamic characteristics in normotensive and pre-eclamptic pregnancy

Variable	Controls (n = 39)	Normotensive pregnancy (n = 40)	Pre-eclampsia (n = 43)
Age (y)	28.62 ± 4.09	30.30 ± 4.81	29.72 ± 4.60
GA (weeks)	-	30.39 ± 4.19	30.37 ± 4.56
BSA (m^2)	1.61 ± 0.08	1.77 ± 0.09*	1.86 ± 0.09$^{*\#}$
BMI (kg/ m^2)	22.43 ± 1.63	25.88 ± 1.78*	28.72 ± 1.56$^{*\#}$
HR (bpm)	76.76 ± 6.90	78.88 ± 8.92	80.95 ± 9.04
SBP (mmHg)	115.05 ± 10.60	117.63 ± 11.49	161.58 ± 12.42$^{*\#}$
DBP (mmHg)	73.00 ± 7.12	76.48 ± 7.47	113.07 ± 16.93$^{*\#}$
Pregnancy with complications (%)	-	5.0	67.4$^{\#}$
GA of delivery(weeks)	-	38.26 ± 1.29	33.14 ± 5.09$^{\#}$
Neonatal birthweight (g)	-	3229.25 ± 369.15	2292.56 ± 1096.99$^{\#}$
Neonatal Apgar score	-	9.85 ± 0.43	7.30 ± 4.11$^{\#}$
GA gestational age, BSA body surface area, BMI body mass index, HR heart rate, SBP systolic blood pressure, DBP diastolic blood pressure			
* $_P <$ 0.05 vs. controls, # $_P <$ 0.05 vs. normotensive pregnancy			
Data are given as mean ± SD			

Conventional echocardiographic parameters

The conventional echocardiographic data are demonstrated in Table 2. When compared to

normotensive pregnancy and control groups, we observed an enlarged LV chamber and increased

RWT during the PE pregnancy. The value of LV ejection fraction significantly decreased but still within

a normal range in the women with PE. Although mitral E/A ratio showed no difference among the

three groups, mitral E/e' ratio increased in PE cases. Meanwhile, maternal LA chamber was

significantly dilated and LAEF was remarkably reduced during the course of PE pregnancy.

Table 2

Conventional echocardiography parameters in normotensive and pre-eclamptic pregnancy

Variable	Controls (n = 39)	Normotensive pregnancy (n = 40)	Pre-eclampsia (n = 43)
IVSd (mm)	8.57 ± 0.68	8.65 ± 0.77	$10.28 \pm 1.20^{*\#}$
LVPWd (mm)	7.52 ± 0.51	7.63 ± 0.67	$9.53 \pm 1.01^{*\#}$
RWT	0.39 ± 0.04	0.38 ± 0.04	$0.43 \pm 0.05^{*\#}$
LVDd (mm)	41.81 ± 2.89	43.10 ± 3.00	$46.03 \pm 3.41^{*\#}$
LVDs (mm)	26.95 ± 2.44	27.18 ± 2.77	$31.19 \pm 3.19^{*\#}$
LVMI (g/ m^2)	63.15 ± 10.17	61.75 ± 11.04	$85.68 \pm 19.17^{*\#}$
LVEF (%)	64.14 ± 4.84	64.38 ± 5.29	$59.37 \pm 5.23^{*\#}$
Mitral e'(cm/s)	12.13 ± 1.98	11.62 ± 2.26	$9.11 \pm 2.41^{*\#}$
Mitral E/A ratio	1.43 ± 0.27	1.31 ± 0.32	1.28 ± 0.40
Mitral E/e' ratio	7.94 ± 1.26	8.16 ± 1.69	$9.68 \pm 2.48^{*\#}$
LAd (mm)	30.67 ± 2.92	31.33 ± 3.18	$34.79 \pm 4.14^{*\#}$
LAVmax (ml)	24.38 ± 5.73	$37.28 \pm 6.11^{*}$	$58.22 \pm 7.22^{*\#}$
LAVImax (ml/m^2)	15.22 ± 3.92	$21.26 \pm 3.38^{*}$	$31.66 \pm 3.71^{*\#}$
LAEF (%)	61.60 ± 5.15	$58.87 \pm 4.06^{*}$	$53.12 \pm 4.53^{*\#}$

IVSd interventricular septum diameter, LVPWd left ventricular posterior wall diameter, RWT relative wall thickness, LVDd left ventricular end-diastolic dimension, LVDs left ventricular end-systolic dimension, LVMI left ventricular mass index, LVEF left ventricular ejection fraction, E peak early diastole transmitral wave velocity, A peak late diastole transmitral wave velocity, e' the average of peak early diastolic velocities at septal and lateral of mitral annular, LAd left atrial maximal dimension, LAVmax left atrial maximum volume, LAVImax left atrial maximum volume index, LAEF left atrial ejection fraction

* $P < 0.05$ vs. controls, $^{\#}$ $P < 0.05$ vs. normotensive pregnancy

Data are given as mean ± SD

Measurements of LA myocardial deformation

The changes observed in LA myocardial deformation are reported in Table 3. When compared to nonpregnant controls, the lower values for LAGLS, LASr and LAScd were identified in the healthy pregnant women, while the lowest ones were founded in PE patients in spite of no difference of LASct among the three groups in the study (Fig. 3). Even adjusted for LAVmax, LASr remained significantly impaired in the patients suffering from PE. As for LA compliance, LASr/(E/e') was remarkably decreased during the PE pregnancy. In addition, LV global longitudinal strain declined dramatically in PE group in comparison with the other two groups.

Table 3

Measurements of the left atrial strain in normotensive and pre-eclamptic pregnancy

Variable	Controls (n = 39)	Normotensive pregnancy (n = 40)	Pre-eclampsia (n = 43)
LAGLS (%)	39.64 ± 6.03	35.87 ± 6.60*	31.87 ± 6.97*#
LASr (%)	46.03 ± 4.48	40.27 ± 6.09*	34.99 ± 6.81*#
LAScd(%)	32.88 ± 2.44	26.53 ± 3.55*	22.71 ± 5.72*#
LASct (%)	13.15 ± 3.07	13.74 ± 3.85	12.27 ± 4.08
LASr/(E/e')	5.92 ± 1.05	5.19 ± 1.51*	3.89 ± 1.31*#
LASr/LAVmax	1.86 ± 0.50	1.07 ± 0.24*	0.61 ± 0.14*#
LVGLS (%)	23.09 ± 3.43	20.41 ± 2.79*	17.45 ± 2.36*#

LAGLS left atrial global longitudinal strain, LASr left atrial strain of reservoir phase; LAScd left atrial strain of conduit phase, LASct left atrial strain of contraction phase, E peak early diastole transmitral wave velocity, e' the average of peak early diastolic velocities at septal and lateral of mitral annular, LAVmax left atrial maximum volume, LVGLS left ventricular global longitudinal strain

* $P < 0.05$ vs. controls, # $P < 0.05$ vs. normotensive pregnancy

Data are given as mean ± SD. All measurements of strain were presented as its absolute value

Correlation analysis

The correlation between clinical characteristics, echocardiographic indices and LAGLS was assessed in the study. To eliminate the interaction among factors, multivariate regression analyses were used. Finally, LAGLS was independently correlated with LASr/(E/e'), LV global longitudinal strain and LAVmax (Table 4).

Table 4

The multivariate regression analyses of clinical characteristics and echocardiographic indices with left atrial global longitudinal strain

	Coef.	Std. Error	β	t	P
LASr/(E/e')	2.760	0.539	0.517	5.121	< 0.001
LVGLS	1.029	0.299	0.350	3.447	0.001
LAVmax	0.001	0.094	-0.299	-3.070	0.004

Abbreviations as shown in Table 2 and 3

Reproducibility

Intraclass correlation coefficients for interobserver agreement of LAVmax, LAGLS and LASr were 0.939, 0.881, 0.905, respectively. Regarding intraobserver agreement, intraclass correlation coefficients for LAVmax, LAGLS and LASr were 0.927, 0.916, 0.934, respectively.

Discussion

LA makes a large contribution to LV filling and thus plays an important role in the pathophysiology and progression of cardiovascular disease[5]. Although some studies on maternal LA structure and performance during pregnancy, those reports just focused on the volumetric analysis[16, 14] or the adaptive changes during the healthy pregnancy rather than PE pregnant course[14, 15]. To the best

of our knowledge, this study is the first to demonstrate the LA myocardial deformation and atrial compliance by STE in the patients suffering from PE.

Despite the relatively thin wall and the heterogeneous distribution of myofibers, the myocardium component is responsible for the atrial expandability and performance[23, 24]. Recently, 2D-STE is emerging as a simple and attractive diagnostic imaging modality to assess intrinsic LA myocardial deformation directly by allowing measurement of atrial contractile and diastolic performance all from a single beat[25]. It has been demonstrated how LA function, assessed by STE, deteriorates even without chamber dilation[26]. Multiple studies have showed that LV diastolic dysfunction and impaired ventricle myocardial relaxation were highly prevalent in the women destined to develop PE (30% and 70%, respectively), accompanied by increased afterload and LV hypertrophy[27]. The LA cavity is exposed to LV pressures directly during every diastole phase when the mitral valve opens, so LA plays a key role in preserving cardiac diastolic function[9]. Thus, the alterations in LA size and action could represent a cumulative rise in LV filling pressure and the damaged cardiac relaxation. Indeed, enlarged LA chamber, declined atrial empty function and increased ventricular mass as well as higher ratio of E/e' process were detected in women with PE in this study. Our findings are consistent with those of the previous studies[28–30].

LA strain globally reflects atrial function, remodelling and distensibility components, which has been demonstrated to outperform other commonly echocardiographic criteria used in the evaluation of diastolic dysfunction and HF [31]. In the setting of continued volume and pressure overload in PE, the thin-walled atrium is sensitive to myocyte stretch. In this study, with the dilated chamber, both LA reservoir strain and conduit strain were significantly declined in the PE cases. However, LA strain in the atrial contraction phase showed a mild but not significant decrease in the patients suffering from PE. Furthermore, LA reservoir strain remained significantly impaired in PE patients even after adjusting for LAVmax. This finding is likely explained by the Frank-Starling mechanism: although initially acting as a compensatory mechanism in response to atrium dilation, it can also lead to a deterioration of LA function with time[32]. Additionally, as previously identified by others, a positive correlation between LA strain and LV longitudinal performance was found in our study, which

explained by the interaction existing between LV and LA[33]. Moreover, we found that LAGLS was independently associated with not only LAVmax but also the ratio of LASr/(E/e'),the surrogate of LA compliance, during the PE pregnancy.

In particular, LA compliance was quantified among PE and normotensive pregnant women in this study. LA compliance, as measured by indexing LA reservoir strain to estimated LA pressure (E/e'), has been reported to be superior to LA reservoir strain alone in diagnosing HF with preserved ejection fraction and may be the single best echocardiographic correlate of elevated filling pressures either at rest or exertion[5]. In the current study, a remarkably depressed LA compliance was detected in PE cases when compared to the healthy pregnancies, which further suggested a deteriorative diastolic function happening during the course of PE pregnancy.

Limitations

Firstly, the apical two-chamber view was obtained to assess the LA strain in our research since the pulmonary veins and LA appendage orifice are difficult to separate from the LA wall in the apical four-chamber view. However,measurement of LA strain in a single apical view was proved to be acceptable[34]. Secondly, the commercial-specific LA-dedicated software was used in the study, so our findings may not apply to analysis by different vender-independent software. Thirdly, although previous studies have shown the cardiovascular implication of PE do not end with the birth of the baby and placenta[28, 35], our study focuses on the acute cardiac impairment in PE during pregnancy rather than thereafter. Finally, our study reported the characteristics of LA deformation in women with PE and only covered a relatively small number in a single centre, further study is required to confirm whether LA dysfunction could be better examined with the separate aspects of LV dysfunction among PE patients.

Conclusions

The current findings reveal the damaged LA myocardial function and decreased atrial compliance in PE and suggest that STE-derived LA strain may be a powerful diagnostic parameter to quantify diastolic dysfunction with the progression of PE pregnancy.

Abbreviations

PE: Pre-eclampsia; HF: heart failure; LV: left ventricle; LA: left atrium; 2D: two-dimensional; STE: speckle tracking echocardiography; IVS: interventricular septum; LVPW: left ventricular posterior wall; LVDd: left ventricular end-diastolic diameter; RWT: relative wall thickness; LAVmax: left atrial maximum volume; LAEF: left atrial emptying fraction; LAGLS: left atrial global longitudinal strain; LASr: left atrial strain of reservoir phase; LAScd: left atrial strain of conduit phase; LASct: left atrial strain of contraction phase

Declarations

Availability of data and materials

The whole images or part of it, neither has been published and is not being considered for publication elsewhere in whole or part in any language.

Authors' contributions

All authors have substantially contributed to the paper. Planning and conducting the study: Juan Cong. Analyzing and interpreting data: Fei Sun. Acquiring imaging data: Yong Li, Rong Li, Xiangqin He. Providing cases: Lin Xu, Min Zhao. Writing the manuscript: Fei Sun, Wugang Wang. Revising the manuscript: Juan Cong.

Ethics approval and consent to participate

All patients had given informed consent, and the study design was approved by the institutional review board and ethics committee of the Affiliated Hospital of Qingdao University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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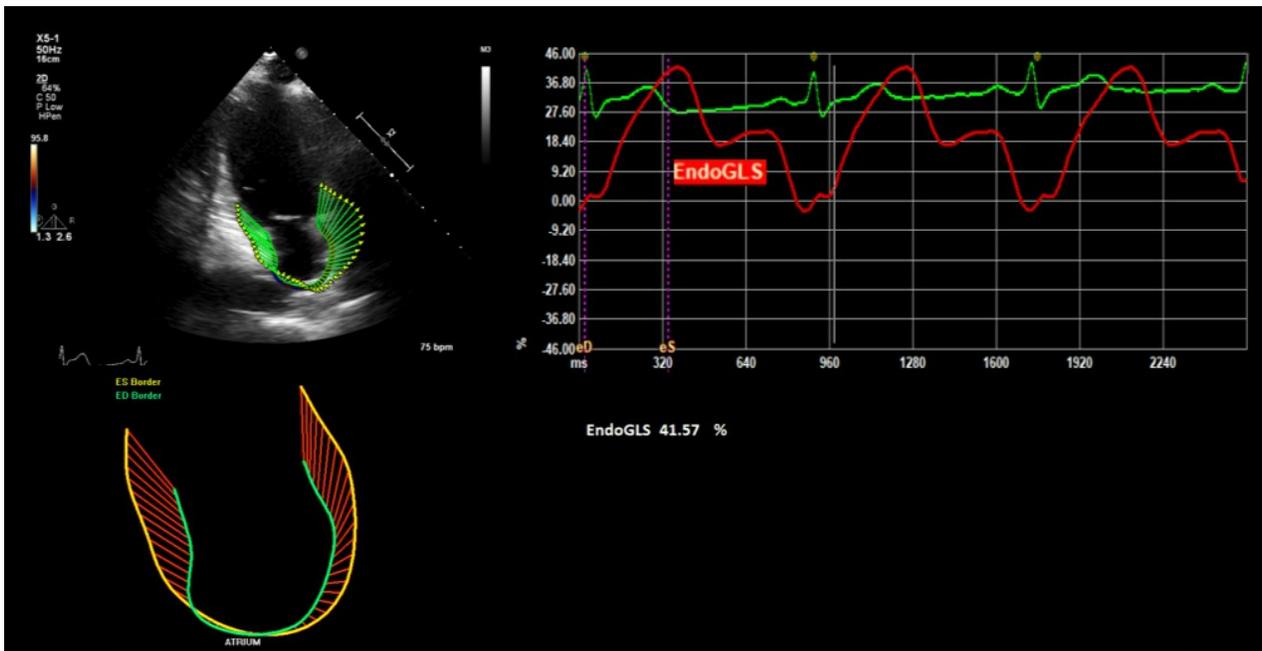
Figures

Figure 1

Pattern of left atrial strain curve obtained from the apical two-chamber view by speckle

tracking echocardiography (STE) in an example subject of our study population. The green

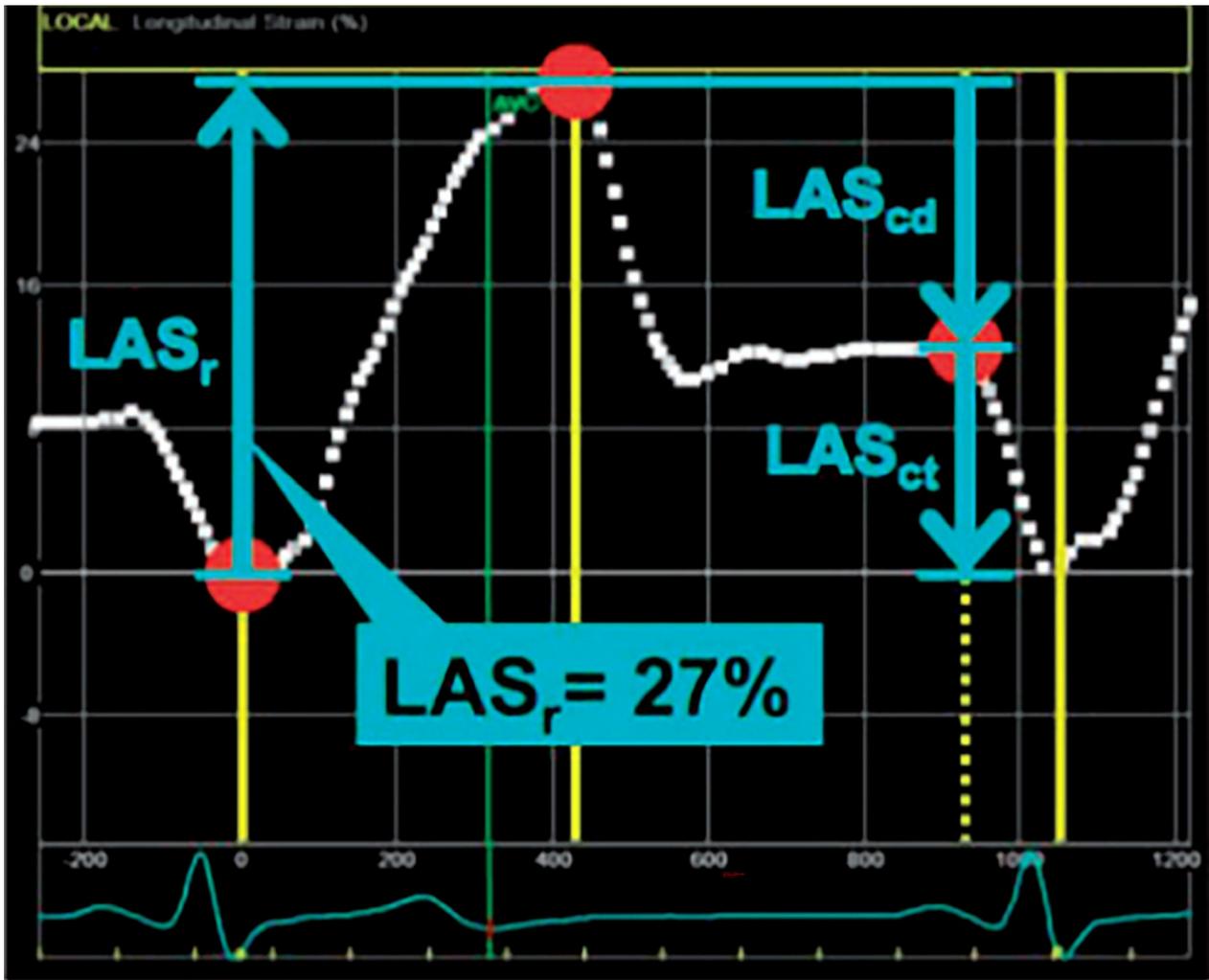arrows are the motion vectors of the left atrium

Figure 2

Schematic diagram of measurements of left atrial phasic strain from left atrial strain curve[19]. With the zero strain reference at left ventricular end-diastole, three measurement points (red dots) are needed to calculate the deformation during the three phases of the left atrial cycle. LASr, left atrial strain of reservoir phase; LAScd, left atrial strain of conduit phase; LASct, left atrial strain of contraction phase
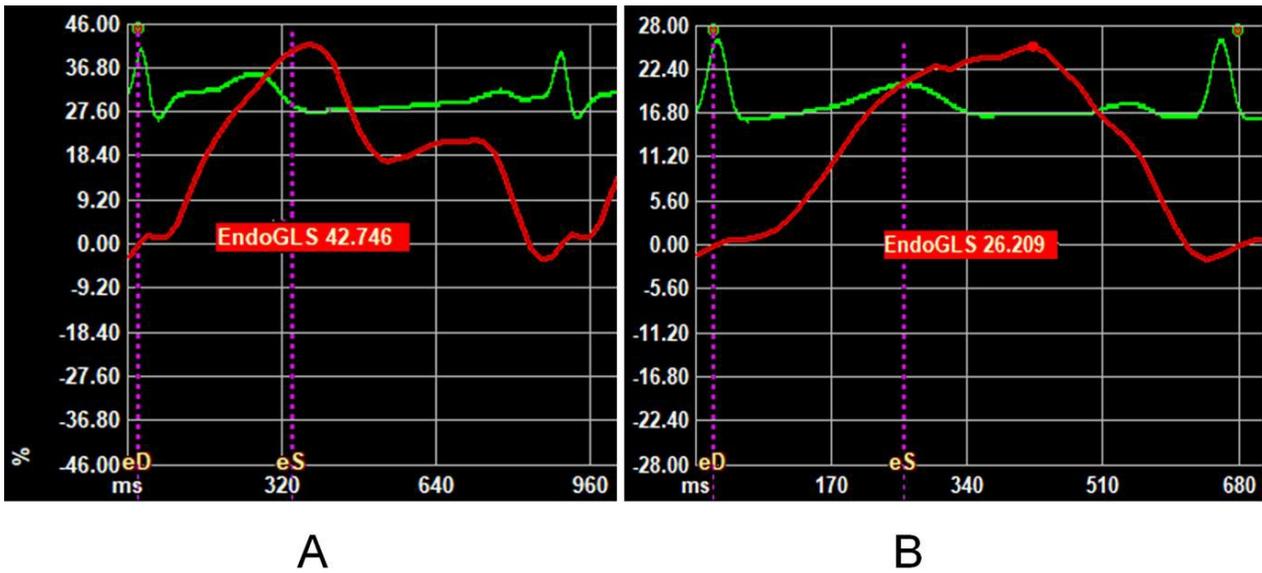
Figure 3

Representative examples of left atrial global longitudinal strain analysis acquired in a normotensive pregnant woman (panel A) and a patient undergoing pre-eclampsia (panel B): As shown, left atrial strain values are reduced in the patient with pre-eclampsia (LASr 42.75 %, LAScd 22.71 %, LASct 20.04 %) compared to the normotensive pregnant woman (LASr 26.21%, LAScd 14.02 %, LASct 12.19 %)