Pregnancy Hypertension 17 (2019) 172–177

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Layer-specific longitudinal strain analysis by speckle tracking echocardiography in women with early and late onset preeclampsia

Weinai Liu, Yong Li, Wugang Wang, Junfang Li, Juan Cong*,[1]

Department of Echocardiography, The Affiliated Hospital of Qingdao University, Qingdao, Shandong Province, China

1. Introduction

Preeclampsia is a disease of multiple organ systems that is unique to pregnancy, occurring in 5% to 10% of the first pregnant women [1]. According to the timing of disease onset, it is divided into early-onset and late-onset preeclampsia: early-onset preeclampsia (EO-PE) occurring before or at 33 weeks of gestation and late-onset preeclampsia (LO-PE) that occurs at 34 weeks of gestation or later [2]. Growing evidence shows that EO-PE and LO-PE have different etiologies and distinct pathophysiological specific features [3].

Appropriate therapeutic management of preeclampsia patients request accurate evaluation of the changes in maternal cardiovascular system. Of the conventional echocardiographic parameters, ejection fraction remains relatively preserved until later in the course of the disease process, making it less useful as a screening tool to follow patients over time [4]. For this reason, the myocardial function based on speckle tracking echocardiography (STE) is developed recently, which is angle independent and is less prone to operator-related measurement errors. The myocardial strain, a parameter representing myocardial deformation, have been demonstrated to be more sensitive and more accurate than the conventional echocardiographic indices in detecting cardiac dysfunction [5]. Previous studies have showed there were a more decreased myocardial strain in EO-PE cases than either LO-PE or the normotensive pregnant women [6].

However, the myocardial wall of the left ventricle (LV) is not homogenous, which is a complex, multilayered structure [7]. Furthermore, histologic analysis have shown that different diseases could cause myocardial damage either across the ventricular wall or in specific layers predominantly [8]. Previous reports just focus on the complete myocardial wall thickness in the analysis of myocardial function rather than further distinction between different layers of the myocardium ranging from endocardium to epicardium.

Recent improvements in the STE have allowed separate quantification of deformation for the endocardial, mid-myocardial, and epicardial layers of the myocardium [9]. In this study, we aimed to assess the layer-specific longitudinal strain (LS) using the advanced STE in women with EO-PE or LO-PE. We hypothesized that longitudinal myocardial dysfunction in the special layers would be more severe in women with EO-PE compared to those with LO-PE and healthy pregnant controls.

2. Methods

This cross sectional study with the comparator group was carried out at a single tertiary center between January 2016 and December 2018. The Affiliated Hospital of Qingdao University Ethics Committee approved the study protocol before patient enrolment. All women included in this study were recruited after informed consent.

2.1. Study population

Consecutive patients with a singleton pregnancy complicated by PE were recruited in the study. PE was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy [10]: new-onset hypertension after gestational 20 weeks, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and proteinuria exceeding 300 mg/24 h, as well as normalization of blood pressure within 3 months postpartum. Then PE was classified as early (gestational age < 34 weeks at clinical onset) or late (≥34 weeks) [2]. None of the patients received antihypertensive therapy at least 3 days preceding the study. Normotensive healthy pregnant women matched for maternal age, gestational weeks and ethnicity were enrolled as control subjects from the routine antenatal clinic during the same period (N1 v.s. EO-PE, gestational age before or at 33 weeks, and N2 v.s. LO-PE group, gestational age of 34 weeks or later, respectively). The excluded criteria was poor quality images, multiple pregnancies, smoking history, obstetric complications or any preexisting medical conditions. Systolic blood pressure and diastolic blood pressure were measured. Mean arterial pressure (MAP) was calculated as [systolic blood pressure + (2 diastolic blood pressure)]/3.

Abbreviations: PE, preeclampsia; EO-PE, early-onset preeclampsia; LO-PE, late-onset preeclampsia; STE, speckle-tracking echocardiography; LV, left ventricle; LS, longitudinal strain; GLS, global longitudinal strain

* Corresponding author.
E-mail address: congjuan0725@163.com (J. Cong).
[1] Postal address: Department of Echocardiography, The Affiliated Hospital of Qingdao University, 16 Jiangsu St, Qingdao, Shandong Province 266003, China.

https://doi.org/10.1016/j.preghy.2019.06.001
Received 15 January 2019; Received in revised form 27 May 2019; Accepted 10 June 2019
Available online 11 June 2019

2.2. Echocardiography examination

Using a Vivid E9 ultrasound machine (GE Healthcare, Horten, Norway) equipped with a M5S transducer, participants were scanned in a left decubitus position from the parasternal and apical window.

The dimension of interventricular septum (IVSd), posterior wall (PWd), left ventricular end-diastolic (LVEDd) and end-systolic diameters was acquired by M-Mode in the parasternal long-axis view as previously described. Relative wall thickness (RWT) was determined as (IVSd + PWd)/LVEDd. LV ejection fraction and LV mass were calculated according to current guidelines [11]. Cardiac indices were normalized for body surface area. The stroke work index was calculated as (MAP × SV)/EDV, where SV was stroke volume, EDV was end-diastolic ventricular volume.

Three apical long-axis scans were obtained at the apical four-chamber, two-chamber, and long-axis planes. Moreover, the peak early (E) and late (A) diastole transmitral wave velocity were acquired by blood pulsed wave Doppler. Tissue pulsed Doppler was recorded in the apical four- and two-chamber view. The average of peak systolic velocities (Sm), early diastolic velocities (Em), and late diastolic velocities (Am) at the septal, lateral, anterior, and inferior at mitral annulus were computed. The LV was divided into 18 cardiac segments: 6 segments (anterior, anteroseptal, inferior, lateral, posterior, and septal) at 3 levels (basal, mid, and apical). The frame rate was 52–92 frames/s.

All image acquisitions were performed throughout three consecutive cardiac cycles during breath-holds. Standard echocardiograms were recorded to obtain morphological and traditional parameters and image loops were stored in the hard disk of the ultrasound machine as a standard DICOM format.

2.3. Layer-specific speckle tracking analysis

All grayscale images of the three apical long-axis 2D echocardiography were analyzed frame by frame using an offline software package (EchoPAC, PC version 113.1). The commercial analysis package measured the endocardial strain with the average strain across the myocardial wall and involved automatic grading of each segment on the basis of the tracking quality on a scale. For the assessment of layer-specific myocardial deformation, the myocardium across the whole ventricular wall was automatically divided into three layers of similar thickness, an endocardial, mid-myocardial, and epicardial layer. From the three acquired apical long-axis slices (long-axis, two-chamber and four-chamber views), peak systolic LS in three myocardial layers was obtained for each segment in the 18 segment LV model.

The new, modified strain speckle tracking started by delineating the endocardial borders in the end-systolic frame of the images at the three apical views. Subsequently, the myocardial wall was automatically defined with multiple chains of nodes and was divided into three separate myocardial layers of similar thickness automatically, allowing assessment of longitudinal endocardial, mid-myocardial and epicardial strains (Fig. 1). Then, quantitative myocardial parameters for each segment were evaluated in an 18 segment LV model (six segments at each level) at all three acquired apical long-axis views. Deformation parameters were determined as average of the three consecutive beats. The myocardial deformation at the basal, mid-ventricular and apical levels were averaged to global longitudinal strain (GLS) in the endocardial layer (GLS-endo), in the mid-myocardial layer (GLS-mid) and in the epicardial layer (GLS-epi), respectively. All segmental values were averaged to ventricular GLS. Additionally, the endocardial-to-epicardial gradient was calculated as [(endocardial LS − epicardial LS)/endocardial LS] × 100%.

2.4. Intraobserver and interobserver agreement

All imaging data was analyzed by one observer in random order. To test intraobserver variability, a single observer analyzed the data twice on occasions separated by an interval of 1 month. To test interobserver variability, a second observer analyzed the data without knowledge of the measurements of the first observer.

2.5. Statistical analysis

Statistical analysis was conducted with SPSS (version 19.0). Data were shown as mean ± SD. LS was presented in its absolute value. Normal distribution of the data was confirmed using Shapiro-Wilk test. Differences between groups for parametric variables were compared using independent sample *t* tests. ANOVA with Bonferroni correction was performed to compared the values of strain between each layer of myocardium and among ventricular levels. Reproducibility was assessed by the inter-class coefficient. $P < 0.05$ was considered to indicate statistical significance.

3. Results

From the initially enrolled 98 PE patients, 5 participants with poor quality images and 4 patients with pregnancy-related diabetes mellitus were excluded from the analysis. Meanwhile, those with poor quality images (3 pregnant women) and pregnancy-related pathology (2 diabetes mellitus, 1 systemic lupus erythematosus and 1 late miscarriage) in control group were rejected from the study. There was no refusal to participate in the study. Finally, a total of 89 women with preeclampsia (45 with EO-PE and 44 with LO-PE, respectively) and 86 women with normotensive pregnancy (44 with N1 group, gestational age before or at 33 weeks, and 42 with N2 group, gestational age of 34 weeks or later, respectively) were recruited in the analysis. All participants were Han Chinese. All chambers were analyzed for all participants.

3.1. Clinical and hemodynamic characteristics

Table 1 shows the clinical and hemodynamic characteristics of the both groups. There were closely matched for age and gestational weeks in EO-PE versus N1, and LO-PE versus N2 group respectively, while the age of pregnant women was similar between EO-PE and LO-PE. Although the values of BMI, DBP and CO index were similar between EO-PE and LO-PE group, the SV index and SBP in EO-PE women were higher than in LO-PE cases.

3.2. LV remodeling and functional characteristics

Table 2 demonstrates that the indices of LV volume and LV mass were detected significantly higher in EO-PE than in LO-PE group, despite similar LV dimension, RWT and the sphericity index between them. Regarding the LV function, the LV ejection fraction showed relatively declined in EO-PE cases than in control subjects, while there were no difference in EO-PE versus LO-PE group. Meanwhile, the value of E/e in mitral valve was increased prominently more in EO-PE than in LO-PE cases.

3.3. LV Three-layer longitudinal strain

The layer-specific LS values evaluated on a segmental basis are shown in Table 3. There were 1448 (90.27%) among 1604 segments with PE were successfully analyzed while 1451 (93.73%) out of 1548 segments with normal pregnancy were assessed using modified speckle-tracking imaging. Considering a longitudinal layer-specific analysis of myocardial deformation in preeclamptic pregnancy, the strain value showed a decreasing tendency from endocardial layer to epicardial layer, which was the highest at endocardium, lower at mid-myocardium, and the lowest at epicardium. The GLS of all three-myocardial layers showed reduced significantly in PE groups versus normotensive pregnant women. And the layer-specific LS worsened more in EO-PE cases, the value of GLS-endo, GLS-mid, GLS-epi and the average of GLS

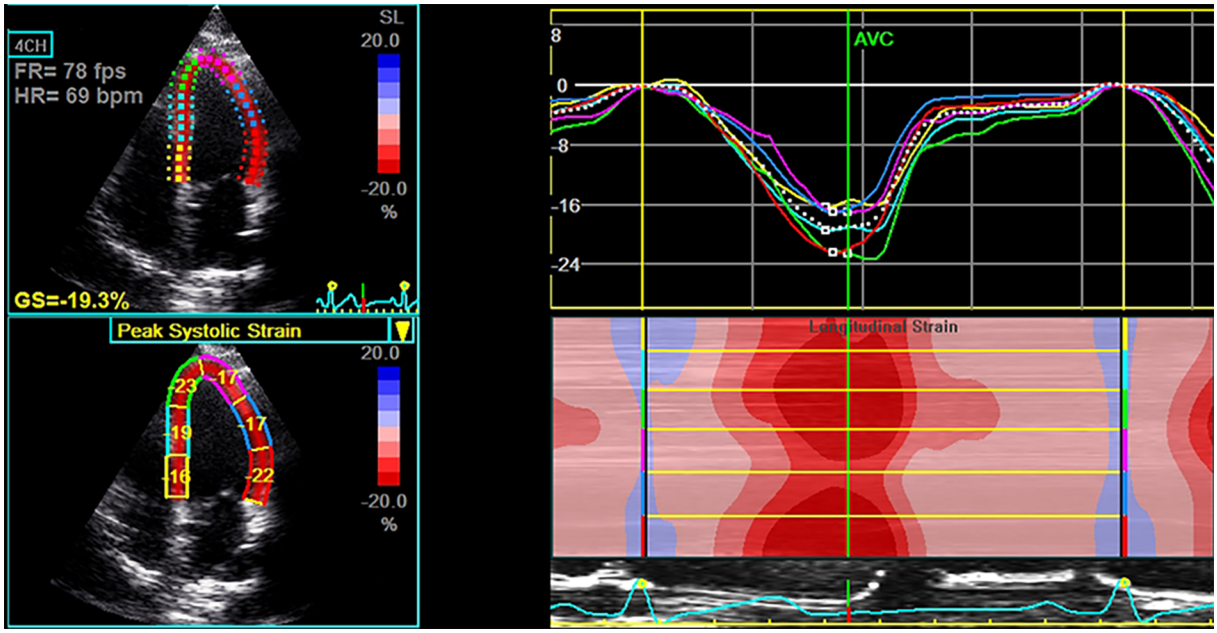

Fig. 1. The longitudinal strain in three myocardial layers at the apical four-chamber plane. The myocardial wall is defined with multiple chains of nodes for allowing assessment of longitudinal endocardial, mid-myocardial and epicardial strains in the end-systolic frame of the image (left panel). The related strain curves for the six segments and color-coded strain image within the longitudinal-axis view are given in the right panel. Color lines indicate regional strain; white dotted line means global (average) strain.

was reduced by 11.81%, 19.72%, 21.36% and 17.37% in the women with EO-PE when compared with the LO-PE patients, respectively.

Table 4 summarizes the parameters of layer-specific myocardial deformation at the three ventricle levels. During normotensive and preeclamptic pregnancy, all of the peak systolic LS in the endocardium, mid-myocardium and epicardium were gradually increased from the base to the apex, the greatest in the apical level and the lowest in the base. Except for its value in the mid- and outer layers at apical level in the LO-PE women, the peak systolic LS was significantly lower in the ventricular segments of the PE patients than the corresponding ones of the normotensive controls in all the three myocardial layers at each ventricular level. The peak systolic LS at the three ventricle levels was impaired prominently in EO-PE cases, relative to both LO-PE patients and the normotensive controls.

Focusing on the endocardial-to-epicardial gradient of LS, PE cases showed a higher gradient of LS at the three ventricular levels and among the global ventricle than did the normotensive pregnant women, despite having some lower values at the mid- and apical level in the LO-PE group, as shown in Table 5. Compared to the women with LO-PE, the endocardial-to-epicardial gradient was increased significantly more in EO-PE patients from the mid-ventricular level to the apical level.

3.4. Reproducibility

To assess the intraobserver and interobserver variability, the inter-class coefficients of the layer-specific peak systolic LS for the endocardial, mid-myocardial, and epicardial layers were 0.917, 0.902, 0.895, respectively, and 0.903, 0.895, 0.854, respectively.

4. Discussion

To the best of our knowledge, this is the first presentation of a cross-sectional study on the layer-specific myocardial function along the longitudinal direction between EO-PE and LO-PE women with the comparative group. For avoiding the possible selection bias, the control subjects were strictly required to match for the PE group (EO-PE v.s. N1, and LO-PE v.s. N2 group respectively) in maternal age, gestational weeks and ethnicity. The major findings of the present study are summarized as follows: although the strain value is lower in both EO-PE and LO-PE cases than in the normotensive controls, more worsened

Table 1
Clinical and hemodynamic characteristics in early and late onset preeclampsia.

Variable	Normotensive		Preeclampsia		*P* value		
	N1 (n = 44)	N2 (n = 42)	EO-PE (n = 45)	LO-PE (n = 44)	N1 vs. EO-PE	N2 vs. LO-PE	EO-PE vs. LO-PE
Age (y)	29.90 ± 6.15	31.03 ± 5.56	32.05 ± 6.42	31.88 ± 5.71	0.106	0.096	0.104
GA (w)	28.20 ± 3.93	37.39 ± 2.89	28.94 ± 3.66	36.43 ± 2.23	0.237	0.398	0.000
BMI (kg/m^2)	23.57 ± 2.26	25.36 ± 2.15	28.01 ± 3.95	30.13 ± 3.20	0.000	0.000	0.064
HR (bpm)	89.79 ± 10.89	83.62 ± 13.56	75.25 ± 12.35	82.70 ± 10.95	0.000	0.698	0.228
SBP (mmHg)	104.12 ± 6.62	106.20 ± 7.94	152.81 ± 16.05	144.83 ± 13.53	0.000	0.000	0.000
DBP (mmHg)	68.17 ± 7.15	71.08 ± 6.81	102.44 ± 13.67	98.59 ± 12.79	0.000	0.000	0.297
MBP (mmHg)	80.49 ± 6.40	83.12 ± 7.09	119.23 ± 12.35	114.09 ± 11.70	0.003	0.000	0.222
CI ($l{\cdot}min^{-1}{\cdot}m^{-2}$)	3.45 ± 0.62	3.59 ± 0.70	3.04 ± 0.52	2.96 ± 0.53	0.007	0.029	0.613
SVI (ml/m^2)	37.62 ± 6.75	36.41 ± 7.15	39.83 ± 9.09	36.22 ± 8.32	0.278	0.628	0.035

Data are given as mean ± SD. EO-PE indicates early-onset preeclampsia; LO-PE, late-onset preeclampsia; GA, gestational age; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; CI, cardiac index; SVI, stroke volume index.

Table 2
Remodeling and functional parameters of the left ventricle in early and late onset preeclampsia.

Variable	Normotensive		Preeclampsia		*P* value		
	N1 (n = 44)	N2 (n = 42)	EO-PE (n = 45)	LO-PE (n = 44)	N1 vs. EO-PE	N2 vs. LO-PE	EO-PE vs. LO-PE
LVd (mm)	46.34 ± 3.07	45.63 ± 3.02	49.29 ± 5.42	47.47 ± 4.91	0.020	0.048	0.228
LVs (mm)	30.17 ± 2.48	29.40 ± 2.94	31.69 ± 3.52	31.32 ± 3.70	0.042	0.013	0.762
IVSd (mm)	6.84 ± 0.71	6.91 ± 0.73	9.23 ± 1.76	9.04 ± 1.46	0.000	0.000	0.831
PWd (mm)	6.87 ± 0.79	7.06 ± 0.60	9.52 ± 1.58	9.21 ± 1.61	0.000	0.000	0.843
RWT	0.30 ± 0.03	0.31 ± 0.03	0.39 ± 0.08	0.39 ± 0.09	0.000	0.000	0.477
EDVi (ml/m^2)	49.89 ± 9.61	49.27 ± 8.65	60.34 ± 11.31	53.80 ± 8.34	0.000	0.035	0.000
LVMi (ml/m^2)	62.31 ± 8.70	65.42 ± 7.62	84.09 ± 10.24	75.29 ± 10.13	0.000	0.000	0.012
SpI	0.28 ± 0.04	0.28 ± 0.08	0.38 ± 0.06	0.37 ± 0.10	0.000	0.000	0.910
EF (%)	65.54 ± 4.32	64.78 ± 4.62	61.64 ± 5.54	63.77 ± 4.76	0.039	0.323	0.137
FS (%)	36.71 ± 2.36	35.54 ± 3.75	33.82 ± 3.07	33.10 ± 3.14	0.037	0.017	0.773
Lad (mm)	25.27 ± 5.72	26.54 ± 6.19	33.90 ± 5.86	31.59 ± 6.41	0.008	0.021	0.317
E/e	0.12 ± 0.03	0.12 ± 0.06	0.19 ± 0.05	0.16 ± 0.10	0.011	0.027	0.034

Data are given as mean ± SD. LVd indicates left ventricular end-diastolic dimension; LVs, left ventricular end-systolic dimension; IVSd, interventricular septum diameter; PWd, posterior wall diameter; RWT, relative wall thickness; EDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; SpI, Sphericity index; EF, ejection fraction; FS, fractional shortening; LAd, left atrial maximal dimension; E, peak early diastole transmitral wave velocity; e, the average of peak early diastolic velocities.

Table 3
Three-layer longitudinal strain of the left ventricle in early and late onset preeclampsia.

Longitudinal Strain (%)	Normotensive		Preeclampsia		*P* value		
	N1 (n = 44)	N2 (n = 42)	EO-PE (n = 45)	LO-PE (n = 44)	N1 vs. EO-PE	N2 vs. LO-PE	EO-PE vs. LO-PE
GLS-endo	23.97 ± 2.98	22.09 ± 2.16	16.60 ± 2.40	18.56 ± 3.20	0.000	0.000	0.013
GLS-mid	21.03 ± 2.81	18.94 ± 2.77	14.25 ± 3.01	17.06 ± 2.80	0.000	0.006	0.000
GLS-epi	18.61 ± 2.83	16.51 ± 2.57	12.31 ± 2.45	14.94 ± 2.47	0.000	0.008	0.000
GLS-Avg	21.21 ± 2.80	19.18 ± 2.81	14.39 ± 2.92	16.89 ± 2.63	0.000	0.000	0.004
P value (between layers)	0.000	0.000	0.000	0.004			

Data are given as mean ± SD in absolute values. GLS indicates the global longitudinal strain; GLS-endo, the average value of global longitudinal strain in the endocardial layer at the basal, mid-ventricular and apical levels; GLS-mid, the average value of global longitudinal strain in the mid-myocardial layer at the three levels; GLS-epi, the average value of global longitudinal strain in the epicardial layer at the three levels; GLS-Avg, the average value of GLS-endo, GLS-mid and GLS-epi.

Table 4
Three-layer longitudinal strain at the left ventricular three levels in early and late onset preeclampsia.

Longitudinal Strain (%)	Normotensive		Preeclampsia		*P* value		
	N1 (n = 44)	N2 (n = 42)	EO-PE (n = 45)	LO-PE (n = 44)	N1 vs. EO-PE	N2 vs. LO-PE	EO-PE vs. LO-PE
Basal level	18.38 ± 3.18	16.12 ± 2.63	12.36 ± 3.29	14.56 ± 2.14	0.000	0.006	0.003
Endocardial layer	18.91 ± 2.35	16.83 ± 2.91	13.12 ± 3.13	15.43 ± 2.59	0.000	0.032	0.007
Mid-myocardial layer	18.59 ± 2.67	16.13 ± 2.57	12.39 ± 3.05	14.47 ± 3.13	0.000	0.006	0.004
Epicardial layer	17.65 ± 4.70	15.57 ± 4.36	11.59 ± 4.42	13.77 ± 4.02	0.000	0.007	0.022
Mid-ventricular level	20.68 ± 3.03	18.41 ± 2.72	14.01 ± 2.93	16.21 ± 2.36	0.000	0.003	0.004
Endocardial layer	22.64 ± 2.11	20.00 ± 3.31	15.47 ± 4.18	17.33 ± 2.36	0.000	0.001	0.007
Mid-myocardial layer	20.57 ± 4.29	18.30 ± 3.80	14.13 ± 3.79	16.22 ± 4.05	0.000	0.008	0.036
Epicardial layer	18.83 ± 3.70	16.86 ± 3.61	12.72 ± 4.55	14.91 ± 3.56	0.000	0.004	0.040
Apical level	24.58 ± 3.76	21.66 ± 3.46	16.72 ± 2.88	19.90 ± 3.44	0.000	0.026	0.004
Endocardial layer	30.36 ± 3.44	27.47 ± 2.97	21.31 ± 3.25	23.16 ± 3.49	0.000	0.001	0.017
Mid-myocardial layer	23.90 ± 3.06	21.00 ± 3.47	16.23 ± 3.69	20.51 ± 3.47	0.000	0.346	0.002
Epicardial layer	19.35 ± 4.30	16.20 ± 3.97	12.61 ± 2.03	15.83 ± 3.28	0.000	0.416	0.004
P value (between levels)	0.000	0.000	0.000	0.027			

Data are given as mean ± SD in absolute values.

longitudinal myocardial deformation ranging from endocardial, mid-myocardial to epicardial layers is present in EO-PE cases when compared with the LO-PE patients. Moreover, EO-PE patients show a higher endocardial-to-epicardial gradient of LS at the mid-ventricular and apical level and among the global ventricle than do LO-PE women.

The cause and pathological mechanisms of preeclampsia are not fully understood and the underlying hemodynamic explanation still remains controversial. Clinically, preeclampsia can be classified as mild and severe preeclampsia depending on the severity of hypertension and proteinuria and also be divided into early- and late-onset depending on the gestational week of onset [12]. Dissimilar demographic characteristics and hemodynamic states have been reported between EO-PE and LO-PE [3]. Recently, some scientific reviews based on compelling studies confirm the need to regard preeclampsia as two distinct diseases, the early and the late form, rather than a single pregnancy complication, and even assume the possibility of this multisystem disorder being

Table 5
The endocardial-to-epicardial gradient of longitudinal strain in early and late onset preeclampsia Data are given as mean ± SD in absolute values. GLS indicates the global longitudinal strain.

Endocardial-to-epicardial gradient (%)	Normotensive		Preeclampsia		*P* value		
	N1 (n = 44)	N2 (n = 42)	EO-PE (n = 45)	LO-PE (n = 44)	N1 vs. EO-PE	N2 vs. LO-PE	EO-PE vs. LO-PE
GLS	11.51 ± 3.13	13.17 ± 2.54	25.84 ± 2.97	19.50 ± 2.55	0.000	0.002	0.000
Basal level	6.66 ± 1.57	7.49 ± 2.02	11.66 ± 2.18	10.76 ± 3.17	0.000	0.011	0.164
Mid-ventricular level	16.83 ± 2.40	15.70 ± 2.76	18.78 ± 2.58	13.96 ± 2.80	0.038	0.022	0.017
Apical level	36.26 ± 3.28	41.03 ± 3.30	40.83 ± 2.76	31.65 ± 3.02	0.009	0.000	0.000

independent of the gestational process [13,14].

Patients with EO-PE have been reported to have low cardiac output with high total vascular resistance whereas those developing LO-PE have a high cardiac output with low total vascular resistance [15]. In the present study, the indexes of SV, LV volume and LV mass were detected significantly higher in EO-PE than in LO-PE group. Meanwhile, LV diastolic function was reduced significantly more and LV filling pressure was elevated markedly more in EO-PE group than in LO-PE, as evidenced by a higher E/e in mitral valve in EO-PE (18.45 ± 5.33 vs 16.78 ± 4.25). These findings were consistent with the results of previous studies [6,15].

With regard to the myocardial deformation across the whole wall thickness, a lower magnitude of global strain had been detected in the EO-PE group than in LO-PE cases along with similar value of LV ejection fraction [6]. In the present study, considering a separate analysis of myocardial shortening in the three layer myocardium, the highest LS existed in the endocardial layer and the lowest in the epicardial layer, while the highest at the apex and the lowest at the base in both EO-PE and LO-PE cases, similarly to the phenomenon of the normotensive healthy pregnant women. We consider that this results is because of the contractile sequence of the ventricular myocardial fibers during the cardiac cycle, which is endocardial and epicardial longitudinally whereas the middle layer circumferentially oriented. Furthermore, the myocardial shortening worsened more in EO-PE when compared with the LO-PE patients in the three myocardial layers. Of note, EO-PE patients showed a higher endocardial-to-epicardial gradient of LS at the mid-ventricular and apical level and among the global ventricle than did LO-PE women.

We reasoned that the myocardial dysfunction in the specific layer between EO-PE and LO-PE could be due to an imbalance of pro-angiogenic and anti-angiogenic cytokines. Previous work has shown that women with PE have an angiogenic imbalance with high circulating levels of antiangiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt1) and low levels of proangiogenic proteins such as placenta growth factor (PlGF) [19,20]. The key effectors of biochemical perturbations is likely sFlt-1, which have been demonstrated to cause systemic vasoconstriction and intense small vessel myocardial vasoconstriction, leading to subendocardial microvascular ischemia and fibrosis. This would explain why the damage happens more in the endocardial layer than globally in the women with PE. Furthermore, EO-PE is to be shown more dramatic increases in sFlt-1, more reduced in PlGF and higher sFlt-1/PlGF ratios when compare to the women who develop LO-PE later [16–18]. Thus, the more serious biochemical perturbations, combined with a higher end systolic wall stress from an increased afterload, result in more longitudinal myocardium dysfunction significantly in EO-PE versus LO-PE. The decrease in LS could represent attenuation of early longitudinal muscle relaxation leading to elevation in ventricular filling pressures and diastolic dysfunction between EO-PE and LO-PE cases. Similarly, although the reduction of LS existing in all the three layers, the women with EO-PE may undergo more aggravated endocardial ischemia and therefore have a higher endocardial-to-epicardial gradient of LS when compared to the women with LO-PE.

There are some limitations of the study as follows. Firstly, sequential shortening and lengthening of myocardial band from the base to the apex is the principal movement of the ventricle [21], therefore longitudinal strain rather than circumferential and radial direction was assessed in the present study. Secondly, due to successive fiber in layers, thus the deformation of each myocardium could be a sum of an active movement within the layer and the passive traction of the neighboring layer.

The strengths of the present study were observed included: using the advanced STE, more severe myocardial dysfunction in each of the three layers was detected in women with EO-PE than LO-PE cases. And the prominent decrease in myocardial function occurred in the endocardium which contributed to the increased endocardial-to-epicardial LS gradient in EO-PE compared with LO-PE patients.

In summary, the study showed that the EO-PE underwent more damage in each of the three myocardial layers when compared to LO-PE cases. The layer-specific myocardial deformation analysis is likely to improve the pathophysiologic understanding of cardiovascular impairment. Using STE, layer-specific assessment of LS may help detect early subclinical cardiac dysfunction between EO-PE and LO-PE. How this knowledge can translate to the risk stratification and clinic management in patient with PE needs to be evaluated in the future.

Acknowledgment

This research was supported by the “Double First Class fund” of Shandong Province in China.

Declaration of Competing Interest

The authors state no conflict of interest.

Contributions

All authors have substantially contributed to the paper. Planning and conducting the study: Juan Cong. Acquiring imaging data: Yong Li, Junfang Li. Analyzing and interpreting data: Weinai Liu. Writing the manuscript: Weinai Liu, Wugang Wang.

References

[1] B. Sibai, G. Dekker, M. Kupferminc, Preeclampsia, Lancet 365 (9461) (2005) 785–799.
[2] A.L. Tranquilli, Early and late-onset preeclampsia, Pregnancy Hypertens. 4 (3) (2014) 241.
[3] P. Von Dadelszen, L.A. Magee, J.M. Roberts, Subclassification of preeclampsia, Hypertens. Pregnancy 22 (2) (2003) 143–148.
[4] K. Melchiorre, G.R. Sutherland, A. Baltabaeva, M. Liberati, B. Thilaganathan, Maternal cardiac dysfunction and remodeling in women with preeclampsia at term, Hypertension 57 (1) (2011) 85–93.
[5] S.A. Kleijn, M.F. Aly, C.B. Terwee, A.C. van Rossum, O. Kamp, Three-dimensional speckle tracking echocardiography for automatic assessment of global and regional left ventricular function based on area strain, J. Am. Soc. Echocardiogr. 24 (3) (2011) 314–321.
[6] J. Cong, T. Fan, X. Yang, J. Shen, G. Cheng, Z. Zhang, Maternal cardiac remodeling and dysfunction in preeclampsia: a three-dimensional speckle-tracking echocardiography study, Int. J. Cardiovasc. Imaging 31 (7) (2015) 1361–1368.

[7] F. Torrent-Guasp, M. Ballester, G.D. Buckberg, F. Carreras, A. Flotats, I. Carrio, et al., Spatial orientation of the ventricular muscle band: physiologic contribution and surgical implications, J. Thorac. Cardiovasc. Surg. 122 (2) (2001) 389–392.
[8] S.I. Sarvari, K.H. Haugaa, W. Zahid, B. Bendz, S. Aakhus, L. Aaberge, et al., Layer-specific quantification of myocardial deformation by strain echocardiography may reveal significant CAD in patients with non-ST-segment elevation acute coronary syndrome, JACC Cardiovasc. Imaging 6 (5) (2013) 535–544.
[9] U. Adamu, F. Schmitz, M. Becker, M. Kelm, R. Hoffmann, Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters, Eur. J. Echocardiogr. 10 (2) (2009) 303–308.
[10] M.A. Brown, M.D. Lindheimer, M. de Swiet, A. Van Assche, J.M. Moutquin, The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP), Hypertens. Pregnancy 20 (1) (2001) IX–XIV.
[11] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (1) (2015) 1–39 e14.
[12] A.L. Tranquilli, M.A. Brown, G.G. Zeeman, G. Dekker, B.M. Sibai, The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP), Pregnancy Hypertens. 3 (1) (2013) 44–47.
[13] M. Liang, J. Niu, L. Zhang, H. Deng, J. Ma, W. Zhou, et al., Gene expression profiling reveals different molecular patterns in G-protein coupled receptor signaling pathways between early- and late-onset preeclampsia, Placenta 40 (2016) 52–59.
[14] J. Sonek, D. Krantz, J. Carmichael, C. Downing, K. Jessup, Z. Haidar, S. Ho, T. Hallahan, H.J. Kliman, D. McKenna, First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume, 126.e1–126.e13, Am. J. Obstetrics Gynecol. 218 (1) (2018), https://doi.org/10.1016/j.ajog.2017.10.024.
[15] S. Vaddamani, A. Keepanasseril, A.A. Pillai, B. Kumar, Maternal cardiovascular dysfunction in women with early onset preeclampsia and late onset preeclampsia: a cross-sectional study, Pregnancy Hypertens. 10 (2017) 247–250.
[16] A.M. Yusuf, A. Kahane, J.G. Ray, First and second trimester serum sFlt-1/PlGF ratio and subsequent preeclampsia: a systematic review, J. Obstet. Gynaecol. Can. 40 (5) (2018) 618–626.
[17] S. Verlohren, A. Galindo, D. Schlembach, H. Zeisler, I. Herraiz, M.G. Moertl, J. Pape, J.W. Dudenhausen, B. Denk, H. Stepan, An automated method for the determination of the sFlt-1/PIGF ratio in the assessment of preeclampsia, 161.e1–161.e11, Am. J. Obstetrics Gynecol. 202 (2) (2010), https://doi.org/10.1016/j.ajog.2009.09.016.
[18] A. Perales, J.L. Delgado, M. de la Calle, J.A. Garcia-Hernandez, A.I. Escudero, J.M. Campillos, et al., sFlt-1/PlGF for prediction of early-onset Preeclampsia: STEPS (Study of Early Preeclampsia in Spain), Ultrasound Obstet. Gynecol. 50 (3) (2017) 373–382.
[19] S. Shahul, J. Rhee, M.R. Hacker, G. Gulati, J.D. Mitchell, P. Hess, et al., Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: a 2D speckle-tracking imaging study, Circ. Cardiovasc. Imaging 5 (6) (2012) 734–739.
[20] K. Baltajian, S. Bajracharya, S. Salahuddin, A.H. Berg, C. Geahchan, J.B. Wenger, R. Thadhani, S.A. Karumanchi, S. Rana, Sequential plasma angiogenic factors levels in women with suspected preeclampsia, Am. J. Obstetrics Gynecol. 215 (1) (2016) 89.e1–89.e10, https://doi.org/10.1016/j.ajog.2016.01.168.
[21] S.A. Reisner, P. Lysyansky, Y. Agmon, D. Mutlak, J. Lessick, Z. Friedman, Global longitudinal strain: a novel index of left ventricular systolic function, J. Am. Soc. Echocardiogr. 17 (6) (2004) 630–633.