

## Clinical Research

## Diastolic function in patients with preeclampsia during pre- and post-partum period using tissue doppler imaging

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## ABSTRAK

**Latar belakang:** Penelitian sebelumnya telah menunjukkan bahwa terdapat peningkatan E/e' pada pasien dengan preeklampsia, tetapi belum terdapat data apakah peningkatan tersebut tetap terjadi setelah melahirkan. Tujuan penelitian ini adalah untuk membandingkan fungsi diastolik pada pasien preeklampsia saat prepartum dan postpartum dengan menggunakan parameter E/e'.

**Metode:** Penelitian ini merupakan penelitian kohort prospektif dari pasien dengan diagnosis preeklampsia yang dirawat untuk terminasi kehamilan. Karakteristik dasar diperoleh dari semua sampel. Pemeriksaan ekokardiografi dilakukan prepartum, 48-72 postpartum, dan 40-60 hari postpartum. Analisis post hoc dengan menggunakan metode least significant difference dilakukan untuk membandingkan hasil antar waktu pengukuran.

**Hasil:** Terdapat 30 sampel pada penelitian ini. Analisis E/e' menunjukkan adanya perbedaan bermakna antara prepartum E/e' dan 40 hari postpartum E/e' ( $11,87 \pm 3,184$  vs  $9,43 \pm 2,529$ ),  $p=0,001$ ,  $CI=1,23-3,751$ ), dan antara 48 jam postpartum dengan 40 hari postpartum ( $12,12 \pm 2,754$  vs  $9,43 \pm 2,529$ ),  $p<0,001$ ,  $CI=1,615-3,771$ ). Tidak terdapat perbedaan bermakna antara prepartum E/e' dan 48 jam postpartum E/e' ( $11,87 \pm 3,184$  vs  $12,12 \pm 2,754$ ),  $p=0,633$ ,  $CI=-1,345-0,832$ ).

**Kesimpulan:** Penelitian ini menunjukkan disfungsi diastolik pada pasien preeklampsia tetap terjadi sampai beberapa hari setelah melahirkan, tetapi membaik dalam waktu 40 hari setelah melahirkan yang ditunjukkan melalui tissue doppler imaging.

## ABSTRACT

**Background:** Prior studies have compared the E/e' elevation in preeclampsia patients to normal patients, however there are no data whether this elevation persists after birth. The aim of this study is to analyze diastolic function in preeclampsia patients during pre- and post-partum period using E/e' parameter measurement.

**Methods:** This is a prospective cohort study of pregnant women with preeclampsia who were hospitalized and planned for pregnancy termination. Basic clinical characteristics were obtained from all samples. Echocardiography was done prepartum, 48-72 hours after termination, and 40-60 days postpartum. Post hoc analysis using least significant difference method was used to compare the results between measurements.

**Results:** 30 subjects were enrolled in the study. Analysis on E/e' characteristics showed statistical difference between prepartum E/e' and 40 days postpartum E/e' ( $11.87 \pm 3.184$  vs  $9.43 \pm 2.529$ ,  $p=0.001$ ,  $CI=1.123-3.751$ ), as well as between 48 hours post-partum and 40 days post-partum period ( $12.12 \pm 2.754$  vs  $9.43 \pm 2.529$ ,  $p<0.001$ ,  $CI=1.615-3.771$ ). There were no statistical differences between pre-partum E/e' and 48 hours post-partum E/e' ( $11.87 \pm 3.184$  vs  $12.12 \pm 2.754$ ,  $p=0.633$ ,  $CI=-1.345-0.832$ ).

**Conclusion:** This study showed diastolic dysfunction in preeclampsia patients persists up until a few days after birth, but resolves in time (40 days after birth) as measured by tissue doppler imaging.

**Keywords:** diastolic dysfunction, postpartum, preeclampsia, prepartum

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Hypertension is one of pregnancy complications, and the leading cause of global maternal morbidity and mortality. This condition is commonly precipitated by preeclampsia and its comorbidities.<sup>1</sup> Preeclampsia occurs when there is overexpression of pro-inflammatory factors, anti-angiogenic factors, and angiogenic factors that cause systemic endothelial cell dysfunction with exaggerated inflammatory response and vasoconstriction.<sup>2</sup> Vasoactive hormones play an important role in the pathogenesis of preeclampsia; they are the primary link between placental hypoperfusion, hypertension, systemic complications, as well as proteinuria. In preeclampsia, vasoconstriction and fluid retention occur, thus diastolic dysfunction becomes a significant hemodynamic change in these patients.<sup>1</sup>

A study compared the diastolic functions in preeclampsia patients using tissue doppler imaging (TDI) parameter (E/e') in 115 women (first pregnancy) which comprised 52 preeclampsia patients and 63 normotensive patients. The result was an increase of E/e' value in preeclampsia patients compared to their normal counterpart. This study also found that plasma brain natriuretic peptide (BNP) elevation in preeclampsia patients reflected an increase in cardiac workload, confirmed by elevation in antepartum period and significant decrease in postpartum period.<sup>1</sup>

Prior studies have compared the E/e' elevation in preeclampsia patients to their normal cohort, however there are no data whether this elevation persists after birth. The aim of this study is to analyze diastolic function in preeclampsia patients during pre- and post-partum period using E/e' parameter measurement.

## METHODS

This was a prospective cohort study of pregnant women with preeclampsia who were hospitalized and planned for pregnancy termination. Subjects were taken consecutively from Harapan Kita Maternity Hospital and Budi Kemuliaan Maternity Hospital, Jakarta, Indonesia, from April until October 2015. The protocol of this study has been approved by The Committee on Institutional Review Board/Health Research Ethics of

national Cardiac Center "Harapan Kita" Hospital (No. LB.02.01/VII/087/KEP.015EV/2016). The exclusion criteria were refusing to participate in the trial after informed consent, prior history of hypertension, diabetes mellitus, smoking, immunological disorder, valvular heart disease or ejection fraction <50%, and/or kidney disease with glomerular filtration rate of <30 mL/min/1.73 m<sup>2</sup>. Preeclampsia was defined as *de novo* hypertension followed by significant proteinuria (new onset) of >0.3 g/24 hr. Edema was no longer included in diagnosis criteria, since edema occurs in 60% of normal pregnancy.<sup>3</sup>

Basic clinical characteristics were obtained from all samples. Echocardiography was done prepartum, 48–72 hours after termination, and 40–60 days postpartum. Echocardiography was performed by an experienced sonographer and validated by an echocardiography consultant. E/e' parameter was calculated from four chamber views according to American Society of Echocardiography (ASE) guideline.<sup>4</sup> Measurement was obtained with volume sample put right on or within 1 cm of mitral valve insertion for e' wave and adjusted as necessary to stay in the annulus when longitudinal excursion occurs during systolic and diastolic periods. For E wave measurement a 1-mm to 3-mm sample volume is placed between the mitral leaflet tips during diastole, and optimized according to ASE guideline.<sup>5</sup>

Normality test was done using Shapiro-Wilk test. Post-hoc analysis using least significant difference method was used to compare the results between measurements. Normal distribution data are presented in mean with standard deviation, whereas the abnormal distribution data are presented in median with maximum and minimum value. This study has been approved by the local Institutional Review Board/Health Research Ethics Committee No. LB.02.01/VII/087/KEP.015 EV/2016.

## RESULTS

Thirty subjects were enrolled in the study. Sample characteristics are presented in Table 1 and 2.

Table 2 shows the difference among characteristics from time to time, prepartum

period, 48 hours postpartum period, and 40 days post-partum period. Systolic and diastolic blood pressure as well as heart rate showed a decrease from prepartum period until 40 days postpartum period ( $p < 0.001$ ).

There was significant difference on ejection fraction between pre-partum and 48 hours postpartum period ( $p = 0.005$ ,  $CI = 0.708 - 3.692$ ), as well as pre-partum and 40 days postpartum period ( $p = 0.013$ ,  $CI = 0.591 - 4.609$ ). Tricuspid annular plane systolic excursion (TAPSE)

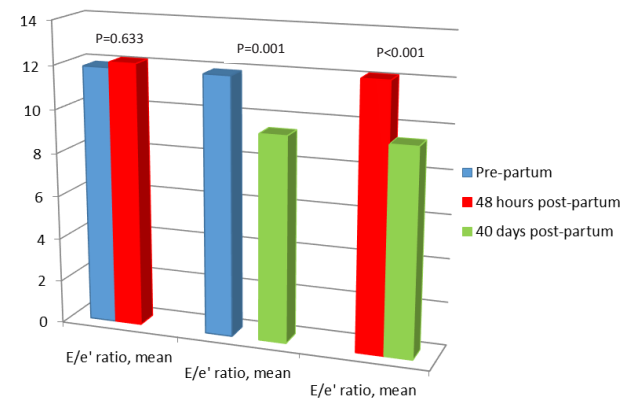
measurements showed no significant difference between each period. Analysis of stroke volume showed a statistical difference between pre-partum and 40 days post-partum period ( $p = 0.024$ ,  $CI = 0.502 - 6.565$ ) as well as between 46 hours post-partum and 40 days post-partum period ( $p = 0.019$ ,  $CI = 0.658 - 6.742$ ). There is no significant difference in mean pulmonary artery pressure (mPAP) value from time to time ( $p = 0.073$ ).

Normality test on E/e' data using Shapiro-Wilk's test showed a normal distribution data ( $p$  value of  $> 0.05$ ). Figure 1 provides the data for patients' diastolic function measured with TDI.

**Table 1.** Basic characteristics

Characteristics	Prepartum (n=30)
Age in years, mean + SD	28.53±6.42
Body mass index, mean + SD	27.43±5.68
Gestational age on delivery in weeks, median (min-max)	37 (20–40)
Edema, n (%)	
General	2 (6.7)
Peripheral	18 (60.0)
Lung edema, presence, n (%)	2 (6.7)
Parital status, primipara, n (%)	19 (63.3)
Prior history of preeclampsia, presence, n (%)	3 (10.0)
Familial history of preeclampsia, presence, n (%)	4 (13.3)
History of abortion, presence, n (%)	2 (6.7)
History of intrauterine fetal death, presence, n (%)	4 (13.3)
History of stillbirth, presence, n (%)	1 (3.3)

Analysis on E/e' characteristics showed statistical difference between pre-partum E/e' and 40 days post-partum E/e' ( $11.87 \pm 3.184$ ) vs  $9.43 \pm 2.529$ ,  $p = 0.001$ ,  $CI = 1.123 - 3.751$ ), as well as between 48 hours post-partum and 40 days post-partum period ( $12.12 \pm 2.754$  vs  $9.43 \pm 2.529$ ,

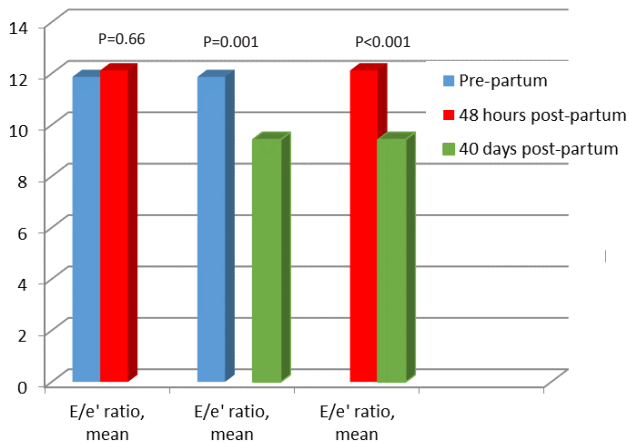


**Figure 1.** Diastolic function in preeclampsia patients. based on post-hoc analysis test

**Table 2.** Sample characteristics during pre-partum, 48 hours post-partum, and 40 days post-partum periods

Characteristics	Pre-partum n=30	48 hours post-partum n=30	40 days post-partum n=30	*
SBP (mmHg), median (range)	160 (135–205)	140 (120–170)	130 (115–180)	<0.001
DBP (mmHg), median (range)	100 (70–140)	90 (70–105)	85 (70–110)	<0.001
HR (bpm), median (range)	96 (68–130)	88 (67–104)	76.5 (62–99)	<0.001
Ejection fraction (%), mean + SD	67.37±6.00	65.17±4.84	64.77±5.82	0.007
TAPSE (cm), mean + SD	2.57±0.36	2.58±0.25	2.47±0.30	0.145
Stroke volume (mL), mean + SD	66.47±10.95	66.63±10.89	62.93±9.77	0.037
mPAP (mmHg), median (range)	15 (5–25)	10 (5–25)	10 (5–20)	0.073

\* based on repeated measured ANOVA analysis; TAPSE= tricuspid annular plane systolic excursion; mPAP= mean pulmonary artery pressure; SBP= systolic blood pressure; DBP= diastolic blood pressure; HR= heart rate



**Figure 2.** Diastolic function in preeclampsia patients adjusted to age, body mass index, edema, lung edema, and heart rate. based on analysis of covariant to compare differences between measurements

$p < 0.001$ ,  $CI = 1.615-3.771$ ). There were no statistical differences between pre-partum  $E/e'$  and 48 hours post-partum  $E/e'$  ( $11.87 \pm 3.184$  vs  $12.12 \pm 2.754$ ,  $p = 0.633$ ,  $CI = -1.345-0.832$ ).

After adjustment on age, body mass index, edema, lung edema, and heart rate parameters, a significant difference of  $E/e'$  ratio still persists between pre-partum period and 40 days post-partum period ( $11.87 \pm 3.184$  vs  $9.43 \pm 2.529$ ,  $p = 0.001$ ,  $CI = 1.048-3.825$ ), as well as 48 hours post-partum period and 40 days post-partum period ( $12.12 \pm 2.754$  vs  $9.43 \pm 2.529$ ,  $p < 0.001$ ,  $CI = 1.583-3.804$ ). There were no statistical differences between pre-partum  $E/e'$  and 48 hours post-partum  $E/e'$  ( $11.87 \pm 3.184$  vs  $12.12 \pm 2.754$ ,  $p = 0.66$ ,  $CI = -1.445-0.931$ ) (Figure 2).

## DISCUSSION

$E/e'$  measurement compared to strain rate examination was proven to have similar accuracy in diagnosing diastolic dysfunction in heart failure patients with normal ejection fraction.<sup>6</sup>

Normal  $E/e'$  value is influenced by age,  $e'$  value will increase in accordance with age. Normal septal  $e'$  value for 16-20 years of age is  $14.9 \pm 2.4$  cm/s, for 21-40 years is  $15.5 \pm 2.7$ , for 41-60 years is  $12.2 \pm 2.3$ , and for >60 years is  $10.4 \pm 2.1$ .<sup>5</sup> Aside from age, body mass index also influences diastolic function, overweight and obese patients independently have negative effects on

diastolic function as measured by tissue Doppler imaging.<sup>7</sup> Previous research also showed that  $E/e'$  parameter is influenced by preload, which in this research is showed by edema: peripheral, general, and lung edema.<sup>8</sup> Heart rate frequency also influences  $E$  and  $e'$  value.<sup>9</sup> Therefore, analysis of covariant was performed adjusted to age, body mass index, cardiac preload, as well as heart rate parameters.

Prior research showed physiologic remodelling during pregnancy such as an increase in left ventricular septal thickness, left ventricular posterior wall thickness, as well as heart chamber size and mass caused by the increase of blood volume during pregnancy (which will increase cardiac pre-load) while systolic and diastolic function measured by global longitudinal strain rate was still normal.<sup>10</sup>

However, this research showed the presence of diastolic dysfunction in preeclampsia patients during pregnancy, post-partum period, and follow-up period, as measured by  $E/e'$  parameter. This conclusion is supported by previous studies on pregnant women suffering from preeclampsia, where there is an increase of septal  $E/e'$  ratio and lateral  $E/e'$  ratio during pregnancy up until three to six months after delivery.<sup>11</sup>

These changes may be caused by several reasons. During a normal pregnancy, there is a physiologic remodeling by fetal syncytial trophoblasts which penetrate and remodel maternal arteries, causing them to dilate into large, flaccid vessels. This remodeling accommodates the increased maternal circulation needed for adequate placental perfusion during pregnancy. However in preeclampsia patients this remodeling is somehow prevented, which causes increased left ventricle (LV) wall thickness and mass more pronounced than in normal pregnancy, but less pronounced LV widening.<sup>12</sup> This concentric hypertrophy develops secondary to the increased LV workload that accompanies the elevated blood pressure.<sup>13</sup> Subsequently impaired diastolic function will occur as shown by increased  $E/e'$  ratio.

Generally once the placenta is delivered there will be a large shift of fluid, but women with severe and early onset of disease may worsen before getting better.<sup>12</sup> Even in normal pregnancy,

the increase of systolic and diastolic blood pressure still persisted in 48 hours postpartum, and start to return to the same values as those in 12 weeks of pregnancy, at two to six months after delivery.<sup>14</sup> This might explained the non-significant changes in diastolic function between pre partum and 48 hours postpartum, but there are significant changes between prepartum and 40 days postpartum, and between 48 hours and 40 days postpartum. Other study also showed that the physiologic changes of preeclampsia are completely reversible after delivery.<sup>12</sup>

In conclusion, this study showed diastolic dysfunction in preeclampsia patients persists up until a few days after birth, but resolves in time (40 days after birth) as measured by tissue doppler imaging.

### Conflicts of interest

The authors affirm no conflict of interest in this study

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