

# Serum NT-proBNP levels as a marker for cardiopulmonary function in preeclampsia

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## Summary

**Purpose:** This study evaluated serum amino-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and echocardiography to determine their efficacy as markers for predicting postpartum pulmonary edema in patients with severe preeclampsia. **Methods:** We evaluated the NT-proBNP levels and echocardiographic results of 124 preeclamptic women (gestation preeclampsia (GPE) group, n = 77; superimposed preeclampsia on underlying hypertension (SPE) group n = 47). Patients were also divided into postpartum pulmonary edema (PPE, n = 28) and non-pulmonary edema (NPE, n = 96) groups. NT-proBNP levels and echocardiographic parameters were compared between groups, and their correlations were also evaluated. Statistical analysis was carried out using variance analysis, and significance was set at  $p < 0.05$ . **Results:** The SPE group had significantly higher NT-proBNP levels than the GPE group. They were also more likely to have PPE, but this was not significant. Echocardiography showed no significant differences in the left ventricular (LV) ejection fraction (LVEF) of the two groups, but a mild LV diastolic dysfunction was noted in the SPE group. The PPE group had significantly higher serum NT-proBNP levels and lower LVEF than the NPE group. There were no significant differences in the echocardiographic parameters of diastolic cardiac dysfunction in the two groups. The serum NT-proBNP levels were significantly negatively correlated with LVEF. **Conclusions:** PPE in patients with severe preeclampsia was associated with impaired cardiac function, especially LV systolic dysfunction. Serum NT-proBNP levels and echocardiography may be useful predictive markers for postpartum pulmonary edema in women with severe preeclampsia.

**Key words:** NT-proBNP; Preeclampsia; Echocardiography; Pulmonary edema; Cardiac function.

## Introduction

Preeclampsia (PE) and its related complications during pregnancy can result in serious maternal morbidity and mortality. Pulmonary edema is the most common cardiopulmonary complication of PE, which has been reported in about 3% of preeclamptic patients and up to 6% of severe preeclamptic patients [1]. Pulmonary edema mostly develops peripartum, and, especially if it occurs postpartum, it can be life-threatening; oftentimes, patients need be transferred to a tertiary center for ventilatory support.

Restricting the amount of peripartum intravenous fluid administration for prevention of postpartum pulmonary is necessary. However, as a result of an effort to maintain blood supply to maternal vital organs and the fetus, additionally to maintaining adequate urinary output, PPE is often aggravated by unintended volume overload [2]. Furthermore, despite proper restriction of intravascular fluid infusion, some patients with obesity, twin pregnancy, peripheral edema, or preexisting hypertensive cardiac disorders readily develop PPE. Hence, predicting the occurrence of PPE in patients with PE is very important but also difficult.

Amino-terminal pro-B-type natriuretic peptide (NT-proBNP; 76 amino acids), which is BNP in its inactive form, is secreted from the ventricular myocytes in response

to ventricular volume expansion and pressure overload [3]. It has been used as a sensitive marker of cardiac dysfunction. Recently, it has also been determined to have a role in the separation of pulmonary edema from other causes of acute dyspnea.

It is known that about 25% of preeclamptic patients with pulmonary edema display impaired left ventricular systolic function [4]. Although left ventricular remodeling during pregnancy is known to be consistent with underlying chronic hypertension (uHTN), the exact echocardiographic differences among preeclamptic women according to the presence of uHTN have rarely been reported.

We performed this study to investigate whether PPE is more prevalent in patients with uHTN and if it can be predicted before delivery based on serum NT-proBNP levels or echocardiographic examination.

## Materials and Methods

### Study subjects

A total of 124 severe preeclamptic women of 22 weeks of gestation or after presenting with gestational PE without uHTN (GPE group, N = 77) or superimposed PE on uHTN (SPE group, N = 47) from March 2006 to April 2015 in the Kyungpook National University Hospital were enrolled in this retrospective study. They were all admitted to the hos-

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Table 1. — Comparison of baseline characteristics according to the presence of uHTN.

	SPE	GPE	<i>p</i> value
Patients No.	47	77	
Age (y)	33.7 ± 5.0	32.6 ± 4.2	0.169
BMI (kg/m <sup>2</sup> )	30.2 ± 6.4	27.5 ± 4.8	0.026
Nulliparity	25(53%)	42(55%)	0.883
Pulmonary edema	13(28%)	15(19%)	0.291
Gestational age at delivery (days)	229.6 ± 32.1	234.8 ± 26.0	0.35
Birth weight (g)	1751.4 ± 839.8	1763.2 ± 662.6	0.937
SBP (mmHg)	160.4 ± 20.1	159.5 ± 19.9	0.809
DBP (mmHg)	100.7 ± 14.7	100.1 ± 14.8	0.822

Table 2. — NT-proBNP and echocardiographic parameters according to the presence of uHTN.

	SPE	GPE	<i>p</i> value
NT-proBNP (pg/mL)	1781.8 ± 4278.7	546.3 ± 1223.1	0.022
LVEF(%)	56.7 ± 8.8	57.9 ± 5.6	0.346
LVEDV(mL)	94.5 ± 27.5	90.9 ± 23.0	0.449
LVESV(mL)	42.9 ± 21.7	38.5 ± 13.5	0.237
IVS (cm)	0.95 ± 0.14	0.89 ± 0.13	0.016
LVPW (cm)	1.00 ± 0.12	0.93 ± 0.11	0.001
MVDT (ms)	197.8 ± 48.4	178.9 ± 41.8	0.03
MV E/A	1.00 ± 0.26	1.20 ± 0.35	0.001
E/E' (m/sec)	11.6 ± 2.6	10.6 ± 2.8	0.066

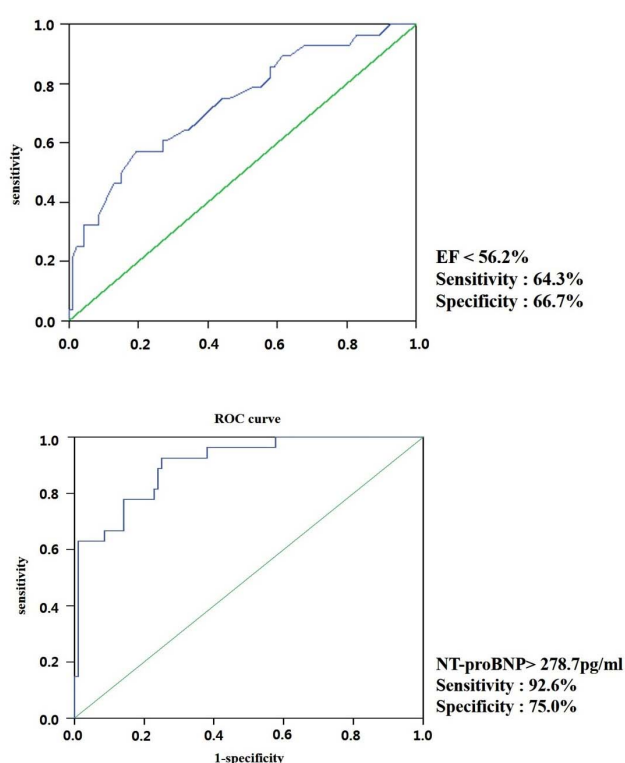


Figure 1. — ROC curve for the prediction of PPE.

pital for delivery due to aggravating maternal preeclamptic condition or fetal indication of delivery. Their medical records were thoroughly reviewed by two clinicians, and thereafter we classified them as having severe PE and enrolled them into the SPE or GPE group according to the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy guidelines [5].

During admission, we obtained maternal serum to examine NT-proBNP levels, and results of transthoracic two-dimensional (2D) echocardiography were examined by a cardiologic specialist. Left ventricular systolic function was evaluated according to left ventricular ejection fraction (LVEF) and diastolic function was measured using mitral valve deceleration time (MVDT), mitral valve E/A ratio (MV E/A), and a ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus (E/E').

The blood samples were collected in Vacutainers (serum REF 367820) and separated into clot and serum. Immediately, the serum was frozen at  $-20^{\circ}\text{C}$  and thawed. Electrochemiluminescence immunoassay was performed.

In our institution, 2D echocardiography has been performed for every severe preeclamptic woman exhibiting at least one sign or symptom, such as high blood pressure (systolic  $\geq 160$  mmHg or diastolic  $\geq 110$  mmHg), marked proteinuria over 2g/24 hours, low platelet counts, elevated liver enzymes, pulmonary edema on chest radiograph, oliguria, headache, visual disturbance, or epigastric pain. Twin

Table 3. — Comparison of baseline characteristics according to the presence of PPE.

	PPE	NPE	p value
Patients No.	28	96	
Age (y)	32.1 ± 4.8	33.3 ± 4.4	0.214
BMI (kg/m <sup>2</sup> )	27.3 ± 4.2	28.8 ± 5.8	0.3
Nulliparity	19(68%)	48(50%)	0.095
uHTN	13(46%)	34(35%)	0.291
Gestational age at delivery (days)	221.6 ± 31.6	235.9 ± 26.9	0.02
Birth weight (g)	1411.3 ± 636.4	1853.3 ± 733.0	0.008
SBP (mmHg)	162.0 ± 16.8	159.3 ± 20.7	0.521
DBP (mmHg)	99.8 ± 13.0	100.5 ± 15.2	0.824

Table 4. — NT-proBNP and echocardiographic parameters according to the presence of PPE.

	PPE	NPE	p value
NT-proBNP (pg/mL)	3473.4 ± 5119.7	305.1 ± 958.2	0.004
LVEF(%)	52.8 ± 9.1	58.8 ± 5.5	0.001
LVEDV(mL)	101.1 ± 27.9	89.7 ± 23.2	0.033
LVESV(mL)	49.6 ± 24.8	37.3 ± 12.9	0.019
IVS (cm)	0.95 ± 0.14	0.90 ± 0.13	0.102
LVPW (cm)	0.98 ± 0.13	0.95 ± 0.11	0.24
MVDT (ms)	175.7 ± 38.3	188.8 ± 46.6	0.202
MV E/A	1.16 ± 0.32	1.11 ± 0.33	0.555
E/E'(m/sec)	11.8 ± 2.1	10.8 ± 2.9	0.109

Table 5. — Correlation between NT-proBNP levels and echocardiographic parameters.

	LVEF	LVPWT	LVEDV	LVESV
NT-proBNP	-.222*	.200*	.236*	.303*

\*  $p < 0.05$ 

pregnancies, patients with diseases such as diabetes mellitus and systemic lupus erythematosus (SLE), or those who already had mild pulmonary edema on chest radiograph prior to delivery were included. However, patients with preexisting heart or kidney disease, moderate or severe pulmonary edema, or clinical heart failure before delivery were excluded. All enrolled patients underwent chest radiography within 2 days after delivery.

Pulmonary edema was defined as a definite evidence of pulmonary congestion on chest radiography together with PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 300 mmHg. Patients were also divided into PPE (N = 28) and non-pulmonary edema (NPE, N = 96) groups according to the presence of pulmonary edema after delivery.

We initially compared serum NT-proBNP levels, echocardiographic parameters, and the prevalence of pulmonary edema between the SPE and GPE groups and then we compared the same parameters between the PPE and NPE groups. The correlations between serum NT-proBNP levels and echocardiographic parameters were also evaluated.

#### Statistical analysis

Data analysis was carried out with SPSS Statistics, version 12.0. Student's *t*-test was used to compare mean values, and Pearson's correlation coefficient for analysis of the correlations between serum NT-proBNP levels and echocardiographic parameters.

#### Results

##### Comparison of baseline characteristics according to the presence of uHTN

There was no significant difference in age, nulliparity, gestational age at the time of delivery, birth weight, or blood pressure between the SPE and GPE groups. Body mass index (BMI) was significantly higher in the SPE group.

Although PPE was more frequent in the SPE group, it was not statistically significant (28% vs. 19%,  $p = 0.291$ ) (Table 1).

##### NT-proBNP and echocardiographic parameters according to the presence of uHTN

Serum NT-proBNP levels in the SPE group were significantly higher than those in the GPE group ( $1781.8 \pm 4278.7$  vs.  $546.3 \pm 1223.1$  pg/mL,  $p = 0.022$ ). No significant differences were noted in LVEF, left ventricular end diastolic volume (LVEDV), or left ventricular end systolic volume (LVESV). Compared to the GPE group, the SPE group showed significantly thicker interventricular septum (IVS) and left ventricular posterior wall (LVPW), longer MVDT and lower MV E/A, and higher E/E', though it showed only borderline significance ( $p = 0.066$ ) (Table 2).

### *Comparison of baseline characteristics according to the presence of PPE*

There was no significant difference in age, nulliparity, BMI, or blood pressure between the PPE and NPE groups. The prevalence of uHTN was also similar. The patients in the PPE group showed significantly shorter gestation age at the time of delivery and lower birth weight than those in the NPE group ( $221.6 \pm 31.6$  vs.  $235.9 \pm 26.9$  days, respectively,  $p = 0.020$ ;  $1411.3 \pm 636.4$  vs.  $1853.3 \pm 733.0$  g,  $p = 0.008$ ) (Table 3).

### *NT-proBNP and echocardiographic parameters according to the presence of PPE*

Serum NT-proBNP levels were significantly higher in the PPE group than in the NPE group ( $3473.4 \pm 5119.7$  vs.  $305.1 \pm 958.2$  pg/mL,  $p = 0.04$ ). They also showed significantly lower LVEF ( $52.8 \pm 9.1$  vs.  $58.8 \pm 5.5\%$ ,  $p = 0.001$ ) and higher LVEDV ( $101.1 \pm 27.9$  vs.  $89.7 \pm 23.2$  mL,  $p = 0.033$ ) and LVESV ( $49.6 \pm 24.8$  vs.  $37.3 \pm 12.9$  mL,  $p = 0.019$ ) (Table 4).

### *Prediction of PPE*

Receiver-operator characteristic curves were used to evaluate the role of LVEF and serum NT-proBNP for the prediction of PPE (Figure 1). A cutoff value of  $< 56.2\%$  showed a sensitivity of 64.3% and a specificity of 66.7% (area under the curve [AUC] = 0.734,  $p < 0.0001$ ) when using LVEF to predict PPE. For NT-proBNP, a cutoff value of  $> 278.7$  pg/mL had a sensitivity of 92.6% and a specificity of 75.0% (AUC = 0.905,  $p < 0.0001$ ) (Figure 1).

### *Correlation coefficients*

Serum NT-proBNP levels showed significant negative correlation with LVEF and positive correlation with LVPW thickness, LVEDV, and LVESV (Table 5).

## **Discussion**

Pulmonary edema in pregnant women can be caused by cardiogenic and non-cardiogenic factors. Peripartum cardiogenic pulmonary edema develops in patients with cardiomyopathy or hypertensive heart failure, while non-cardiogenic pulmonary edema results from excessive volume overload, deteriorated vascular permeability in patients with PE, or administration of drugs such as  $\beta$ -mimetics [6]. Because we always tried to avoid volume overload and control the infusion rate of intravenous fluids to at most 60-125 mL/hour, keeping peripartum urinary output just over 30 mL/hour, cardiac dysfunction in PE can be considered as a main causative factor for PPE [7].

Recently, the role of echocardiography in the management of women with PE has been emphasized. However, hemodynamic studies of PE demonstrated diastolic dysfunction and preserved LVEF [8]. This means that diastolic dysfunction is observed frequently in PE and usually precedes systolic dysfunction [9, 10]. Left ventricular remodeling, which occurs during normal pregnancy, is more apparent in PE. Increased left ventricular mass index and LVPW and IVS thickness are common findings in PE [11,

12]. This is an adaptive change to maintain myocardial contractility in response to both increased afterload and decreased preload.

In our study, left ventricular remodeling was more evident in the SPE group than in the GPE group. We also found a more impaired diastolic function in the SPE group than in the GPE group, although the difference may not be clinically significant. Both MVDT and MV E/A in the SPE group were close to Grade 1 diastolic dysfunction [13]. However, there was no difference in systolic function between the two groups, which may explain why there was no difference in PPE between the two groups. The pathogenesis of acute pulmonary edema is often explained by diastolic dysfunction in patients with old age and hypertensive disorder or those who have undergone renal transplantation [14, 15]. However, we did not find any difference in diastolic function between the PPE and NPE groups. LVEF was significantly lower in the PPE group, although it was mostly within the subclinical range. In women with PE, the failure to increase stroke volume at the moment of delivery may suggest dysfunction of the left ventricle to adapt to the volume load caused by delivery, prompting concern for the increased risk of PPE. Two main causes of volume load are crystalloid infusion during delivery and fluid re-shift from the third space. Once left ventricular systolic function is impaired, redistribution of increased intravascular volume to systemic circulation is restricted, causing the accumulation of fluid in the third space. Although LVEF is within normal range, subclinical impairment in the left ventricular systole can explain the increased risk of PPE [16].

In a previous study including 40 preeclamptic women, serum NT-proBNP was correlated with LVEF, LVEDV, and LVESV [17]. This finding was validated in our study in patients with severe PE. We also found that serum NT-proBNP and LVEF can be used as markers for PPE. To the best of our knowledge, there has been little investigation about echocardiography in patients with severe PE based on the history of uHTN. We have previously reported that the serum NT-proBNP level is elevated in preeclamptic patients as compared to controls [18]. A recent study also revealed that NT-proBNP levels in gravida with SPE were higher than in gravida with chronic hypertension [19]. In this study, we found that NT-proBNP levels are dependent on the history of uHTN in preeclamptic patients. This means that the preexisting cardiac burden can be worsened by increased afterload aggravating cardiac strain in patients with PE.

The strength of our study is that we enrolled a relatively large number of severe preeclamptic patients who underwent echocardiography before delivery and development of PPE. This is mainly because we have thought there was an association of impaired cardiac function before delivery and PPE. Five of 28 patients with PPE went on ventilator support after delivery and all recovered.

There are also some limitations in this study. First, we included twin pregnancies and patients with preexisting

medical diseases such as SLE, which might have different pathogenesis for the development of PPE. Second, some patients already had mild pulmonary edema before delivery, which may weaken the role of NT-proBNP and LVEF for the prediction of PPE.

## Conclusion

In conclusion, subclinical systolic cardiac dysfunction before delivery was associated with the risk of PPE in patients with severe PE, and both high NT-proBNP level and low LVEF can be used as predictive markers for the development of PPE. Though SPE suggests preexisting cardiovascular burden and the adaptation comprising left ventricular remodeling and subclinical diastolic dysfunction, left ventricular systolic function is preserved in most cases.

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## Conflict of Interest

The authors declare no conflict of interest.

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