MATERNAL HYPERTROPHY AND DIASTOLIC DISFUNCTION AND BRAIN NATRIURETIC PEPTIDE CONCENTRATION IN EARLY AND LATE PRE-ECLAMPSIA

Short title: BNP and pre- eclampsia

V.T.M.BORGES, MD, PhD[*]; S. G. ZANATI, MD, Phd[†]; M.T.S.PERAÇOLI, PhD[‡]; J.R.POIATI, MS[*], M.ROMÃO-VEIGA, MS[‡]; J.C.PERAÇOLI, MD, PhD[*]; B. THILAGANATHAN, MD, PhD, FRCOG[#]

[*]Department of Obstetrics and Gynaecology, Botucatu Medical School, São Paulo State University - UNESP, São Paulo, Brazil. [†]Department of Clinical, Botucatu Medical School, São Paulo State University - UNESP, São Paulo, Brazil. [‡] Institute of Biosciences- UNESP, Botucatu, São Paulo, Brazil. [#]Fetal Maternal Medicine Unit, St George's University of London, London, UK

***Correspondence to**:*

Vera Therezinha Medeiros Borges

Department of Obstetrics and Gynaecology, Botucatu Medical School, UNESP-Sao Paulo State University, Rubião Junior, Botucatu, São Paulo/ Brazil, ZIP:18618-970 - Phone +55 14 38116227, **Email: vborges@fmb.unesp.br**

The authors report no conflict of interest.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.17495

Keywords: brain natriuretic peptide, cardiac hypertrophy, diastolic function, early-onset pre-eclampsia, late-onset pre-eclampsia.

ABSTRACT

Objective: Pre-eclampsia is associated with maternal cardiac remodelling and diastolic dysfunction. The aim of this study was to assess and compare maternal left ventricular structure and diastolic function and Brain Natriuretic Peptide (BNP) levels in women with early-onset pre-eclampsia (<34 weeks of gestation) and late-onset pre-eclampsia (≥ 34weeks of gestation).

Methods: A prospective, cross-sectional observational study was performed in 30 women with early-onset pre-eclampsia, 32 with late-onset pre-eclampsia and 23 normotensive controls. Maternal cardiac structure and diastolic function as assessed by echocardiography and plasma levels of BNP were measured by enzyme immunoassay.

Results: Pre-eclampsia was associated with an increased left ventricular mass index and relative wall thickness in early-onset pre-eclampsia compared with late-onset pre-eclampsia and normotensive controls. The prevalence of concentric hypertrophy (40%) and diastolic dysfunction (23%) was also significantly higher in early-onset pre-eclampsia than in late-onset pre-eclampsia (16% for both, all $p<0.05$). Maternal serum BNP values were also significantly higher in early-onset pre-eclampsia ($p<0.05$) and correlated with relative wall thickness and left ventricular mass index.

Conclusions: Early-onset pre-eclampsia has more severe cardiac impairment than late-onset pre-eclampsia as evidenced by increased prevalence of concentric hypertrophy, diastolic dysfunction and high concentrations BNP. These findings suggest that early-onset pre-eclampsia causes greater

myocardial damage increasing the risk of both peripartum and postpartum cardiovascular morbidity. Although these cardiovascular effects are easily identified by echocardiographic parameters and measuring BNP, further studies are needed to assess their clinical utility.

INTRODUCTION

Pre-eclampsia (PE) is associated with significant maternal morbidity and mortality and affects 5% - 7% of pregnant patients worldwide. It is predominantly a disorder with cardiovascular manifestations, which is clinically identified by hypertension and proteinuria occurring after the 20th week of gestation[1].

Recent evidence indicates that there are two main time of onset of PE. Early-onset (before34 weeks' gestation) and late-onset (at or after 34 weeks' gestation),[3,4] suggesting that different pathophysiological mechanisms may contribute to the timing of PE onset[2]. PE is commonly associated with abnormal placental pathology and placenta mediated complications such as fetal growth restriction. Previous studies have shown that women with PE have an increased risk of developing cardiovascular disease in the future - the risk being much higher in those with early-onset and severe PE[5,6,7]. Recent investigations have also demonstrated that PE is associated with altered levels of angiogenic factors and abnormalities of cardiac function, namely impaired myocardial relaxation and diastolic dysfunction – which is more severe in early-onset PE[8].

Cardiac myocytes release B-type natriuretic peptide (BNP), and its inactive N-terminal fragment cleavage product N-terminal pro-BNP, into the blood in response to stress. Measurements of BNP have been shown to be sensitive markers for the detection of mild systolic or diastolic heart failure or asymptomatic left ventricular dysfunction[9], and for the diagnosis of congestive heart failure in patients with dyspnoea in an acute-care setting. Although, a few recent studies have suggested that BNP levels are elevated in pregnancy and PE, it is not known whether this biochemical response is non-specific or directly

related to the degree of diastolic dysfunction seen in pregnancy and PE[10,11]. The aim of this study is to assess and compare maternal left ventricular structure and diastolic function and Brain Natriuretic Peptide (BNP) levels in women with early-onset pre-eclampsia and late-onset pre-eclampsia.

METHODS

This was a prospective cross-sectional study carried out over a 3-year period from January 2009, in antenatal clinic at department of Obstetrics and Gynaecology, Botucatu Medical School, Brazil. All women with singleton pregnancy and PE were recruited after informed consent and with local institutional review committee approval. Only women without comorbidities, and before starting any medication, were asked to take part in the study. Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy guidelines[12]. The PE group was divided into two subgroups: early onset PE, which included those who developed PE at less than 34 gestational weeks and late onset PE, in those who developed PE at 34 gestational weeks at least[13]. Subjects were categorised as having severe PE according to the guidelines of the International Society for Study of Hypertension in Pregnancy (ISSHP)[12]. The control group was recruited and matched for gestational age with the preeclamptic groups at time of sampling. These women remained normotensive until the end of gestation. Body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured and a physical examination was performed. Maternal blood

pressure was measured manually from the brachial artery using a mercury sphygmomanometer according to the guidelines of the ISSHP[12].

BNP measurement

Blood sampling (10mL) was standardised without a tourniquet and all samples were centrifuged immediately twice, at 2000 rpm to separate plasma. Blood samples were collected at the time of the echocardiography examinations. Specimens were stored (- 80^{o}C) until analysis. BNP was measured using an ELISA method (Wuhan EIAab, Science Co., Ltd, China, cat no. E0541h). The limit of detection for the BNP method was 3.90pg/mL and the intra- and inter-assay precision was less than 10% and 15% respectively.

Echocardiography

Ultrasound examinations were performed with a Vivid S6 da GE (General Electric), by one expert investigator (S.G.Z.). The two-dimensional, M-mode and Doppler echocardiography were acquired according to the guidelines of the American Society of Echocardiography and stored digitally[14]. Standard echocardiographic measurements included LV end-diastolic dimensions (LVDd), end-diastolic wall thickness of the interventricular septum (IVSd) and left ventricular posterior wall (PWTd). The left ventricular mass (LVM) was calculated according to the Devereux and Reichek formula. The LV mass index (LVMi) was calculated by the indexation of LV mass by height$^{2.7}$.The relative wall thickness (RWT) was calculated according to the formula (RWT) = [(IVSd + PWTd)/2] / LVDd, where IVSd is the interventricular septum dimension, PWT is

the posterior wall thickness and LVDd is the left ventricular diastolic diameter. Left ventricular hypertrophy was defined as LVMi ≥ 45g/m^{2,7}, considered concentric hypertophy when RWT>0.42 and eccentric hypertrophy when RWT<0.42[15].Transmitral, pulmonary venous flow velocities were acquired with pulsed Doppler. The velocities of early transmitral diastolic flow velocity (E) and flow velocity during atrial contraction (A), its ratio (E/A), and deceleration time (DT) and isovolumic relaxation time (IVRT) were measured. Diastolic dysfunction was defined as ratio (E/A <1.0 and/or IVRT>100ms and DT>180cm/s). Doppler-derived indices were averaged from between three and five consecutive cardiac cycles.

Statistical methods

Data were analysed using INSTAT software (GraphPad, San Diego, USA, 2000). All variables were compared using Kruskal-Wallis test, followed by Dunn's multiple comparison test, except birth weight variable, which ANOVA test was used. The Spearman rank order correlation coefficient was used to measure the association between some of the variables. *P*<.05 was considered statistically significant. A sample size of 28 in each subgroup PE was calculated to observe a 75% difference in standard deviation of the BNP between cases and control subjects. A significance level of 5% (α= 0.05) and statistical power of 80% (β= 0.20) were considered.

RESULTS

The study group consisted of 30 women with early-onset PE, 32 with late-onset PE and 23 normotensive controls. The demographic and clinical

characteristics of the study participants are shown in Table 1. There were no differences in the maternal age and body mass index between the groups. Women with early onset PE had significantly higher systolic and diastolic blood pressure than those with late onset PE (*P*= .05).

Results of echocardiographic geometric patterns and diastolic function are presented in Table 2. Women with early onset PE had increased relative wall thickness and prevalence of concentric hypertrophy (0.43 and 40%, respectively) compared to those with late onset PE (0.38 and 16%, respectively; both *p*<.05). No significant difference in eccentric hypertrophy in both of groups (late onset PE= 31% vs early onset pre-eclampsia = 10%, *p*= 0.085). Seven women with early-onset PE (23%) and five with late-onset PE (16%) demonstrated diastolic dysfunction compared with none in the control group, (*p*<0.05). Other parameters of diastolic function were not different between groups.

There was a significant graded increase in median BNP levels between controls (43pg/mL), late onset PE (147pg/mL) and early onset PE (214pg/mL; *P*<.05; Figure 1). There were significant correlations between BNP and relative wall thickness and left ventricular mass index in women with PE (Table 3, Figures 2 and 3).

DISCUSSION

The present study demonstrates that women with early-onset PE exhibit more severe cardiovascular impairment compared to those with late onset PE –

and that the magnitude of cardiovascular dysfunction was correlated with a significant increase in plasma concentrations of BNP. Both groups of PE present a significant increases in left atrial diameter, relative wall thickness, left ventricular mass index, flow velocity during atrial contraction (A), lower E/A ratio and altered left ventricular geometry in comparison with normal pregnancy.

In normal pregnancy, left ventricular mass index increases without changes in the ratio of wall thickness to cavity dimensions, indicative of a preload-mediated heart remodelling[15,16]. In PE, is a state of arterial vasoconstriction leading to an increased afterload, with high total vascular resistance[17]. The maternal heart responds to the acute and transient increase in afterload, with a process of adaptation characterised by remodelling, and sometimes concentric hypertrophy, despite the brevity of exposure of the heart to hypertension[18,19]. Previous studies have demonstrated that the increased LVM is accompanied by an increase in cardiac work suggesting that heart remodelling in PE is a response to the increased systemic afterload in order to minimise myocardial oxygen demand and thus preserving left ventricular performance[20].

Valensise *et al.*[4] compared maternal cardiac function at 24 weeks gestation in a group of normotensive asymptomatic patients with the subsequent development of early and late-onset PE. In this study, pregnant women with early-onset PE showed increased relative wall thickness and smaller LV diameter compared to the control groups and late-onset PE. These results demonstrate concentric hypertrophy, suggesting significant pressure overload in early-onset PE. Conversely, late-onset PE showed greater LV diameter, with an intermediate value of the left relative thickness wall compared

with early-onset PE and the control group, featuring eccentric hypertrophy, characteristic of volume overload [20,21,22]. A recent study found progression towards severe left ventricular hypertrophy in association with advanced cardiac dysfunction in about 20% of preterm preeclamptic women. This indicates that although most women with PE undergo adaptive heart remodelling to increased afterload, a small subgroup demonstrate signs of overt decompensation[23].

Our echocardiographic findings are consistent with those of Valensise *et al.*[4] and Melchiorre *et al.*[23]. PE women had a higher incidence of concentric hypertrophy, especially in the early onset PE (40%). The relevance of this result is the evidence that concentric LVH is a risk marker for diastolic dysfunction, the abnormal accumulation of interstitial collagen in the myocardium and reduced coronary reserve. Our study did not include analyses to assess coronary flow reserve, or composition of the myocardium, but the echocardiographic exams showed that early-onset PE associated concentric hypertrophy had diastolic dysfunction, suggesting potential damage in the myocardium. The mechanisms of dysfunction may not completely understand the results obtained. However, it is possible to suggest that the ventricles of small cavities and thick walls are less compliant. Thus, normal or even reduced blood volumes could result in increased filling pressure, characterising diastolic dysfunction.

Cardiac dysfunction can be associated with increased concentrations of natriuretic peptides, since these neurohormones are produced by the heart in cases of cardiac overload[24]. Currently, the clinical use of natriuretic peptides for diagnosis and risk stratification in heart failure is well established[25]; however, there are conflicting results with regard to BNP levels during pregnancy[26,27]. In our study, early-onset PE showed significantly higher BNP levels than late-

onset PE group and normotensive women. In late-onset PE, BNP values were higher than in the control group. Furthermore, 97% of pregnant women with early-onset PE and 84.3% of women with late-onset PE showed mean concentrations of BNP above100 pg/mL, which is considered a threshold for the diagnosis of dyspnoea of cardiac etiologic in non-pregnant women. Natriuretic peptides are recognised in non-pregnant individuals as markers of myocardial hypertrophy associated with cardiac dysfunction. Our study found a strong positive correlation between the concentration of BNP, LVMi and relative wall thickness in women with PE.

Study limitations

Apart from the small numbers and cross-sectional of our study, it should be noted that values of BNP are variable in previous pregnancy studies. For example, in our study, the average value of BNP in normal pregnancy (43pg/mL) was higher than that reported in other studies (20 pg/dL).These results can be explained by the recognized differences in both population and assay techniques.

Conclusions

The increased BNP levels in PE confirm that the observed maternal echo indices represent overt maternal diastolic dysfunction rather than an extended physiological adaptation in pregnancy. Furthermore, early-onset PE is characterised by an increased prevalence of concentric hypertrophy and LV diastolic dysfunction and higher BNP levels compared to late-onset PE suggesting that this entity causes greater myocardial damage increasing the

risk of per partum and postpartum cardiovascular sequelae. Although these cardiovascular effects are easily identified by echocardiographic parameters and a high plasma concentration of BNP, further studies are needed to assess the clinical utility of such measures.

REFERENCES

1. Carty DM, Delles C, Dominiczak AF. Pre-eclampsia and future maternal health. J Hypertens. 2010; 28:1349-55.
2. Phillips JK, Janowiak M, Badger GJ, Bernstein IM. Evidence for distinct preterm and term phenotypes of pre-eclampsia. J Maternal-Fetal and Neonatal Medicine. 2010; 23(7): 622-6.
3. Raymond D, Peterson E: A critical review of early-onset and late-onset pre-eclampsia. Obstet Gynecol Surv 2011; 66 (8):497–506.
4. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late pre-eclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension 2008; 52:873–80.
5. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007; 335:974–7.
6. Wikstrom AK, Larsson A, Eriksson UJ, Nash P, Norden-Lindeberg S, Olovsson M. Placental growth factor and soluble FMS-like tyrosine kinase-1 in early-onset and late-onset pre-eclampsia. Obstet Gynecol 2007; 109:1368–74.
7. Staff AC, Redman CWG, Williams D, Leeson P, Moe K, Thilaganathan B , Magnus P, Steegers EAP, Tsigas EZ, Ness RB, Myatt L, Poston L, Roberts JM, for the Global Pregnancy Collaboration (CoLab). Pregnancy and long-term maternal cardiovascular health progress through harmonization of research cohorts and biobanks. Hypertension 2016; 67:251-60.

8. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in pre-eclampsia an overview. Circulation 2014; 130:703-14.

9. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161–7.

10. Hamad RR, Larsson A, Pernow J, Bremme K, Eriksson MJ. Assessment of left ventricular structure and function in pre-eclampsia by echocardiography and cardiovascular biomarkers. J Hypertension 2009; 27:2257–64

11. Hameed AB, Chan K, Ghamsary M, Elkayam U. Longitudinal changes in the B-type natriuretic peptide levels in normal pregnancy and postpartum. Clin Cardiol. 2009; 32:E60–2.

12. Magee LA, Pels A, Helewa M, Rey E, Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 2014; 4: 105–145.

13. Huppertz B. Placental origins of pre-eclampsia: challenging the current hypothesis. Hypertension 2008; 51:970–5.

14. Lang RM, Pridjian G, Feldman T, Neumann A, Lindheimer M, Borow KM. Recommendations for chamber quantification. Eur J Echocardiography 2006; 7:79–108.

15. Moran AM, Colan SD, Mauer MB, Geva T. Adaptive mechanisms of left ventricular diastolic function to the physiologic load of pregnancy. Clin Cardiol 2002; 25:124–31.

16. Melchiorre K, Sharma R, Khalil A, Thilaganathan B. Maternal Cardiovascular Function in Normal Pregnancy Evidence of Maladaptation to Chronic Volume Overload. Hypertension 2016; 67:754-62.

17. Lang RM, Pridjian G, Feldman T, Neumann A, Lindheimer M, Borow KM. Left ventricular mechanics in pre-eclampsia. Am Heart J 1991; 121(6 Pt1): 1768–75.

18. van Oppen AC, van der Tweel I, Alsbach GP, Heethaar RM, Bruinse HW. A longitudinal study of maternal hemodynamics during normal pregnancy. Obstet Gynecol. 1996; 88:40–6.

19. Valensise H, Novelli GP, Vasapollo B, Di Ruzza G, Romanini ME, Marchei M, Larciprete G, Manfellotto D, Romanini C, Galante A. Maternal diastolic dysfunction and left ventricular geometry in gestational hypertension. Hypertension. 2001; 37:1209–15.

20. Simmons LA, Gillin AG, Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. Am J Physiol Heart Circ Physiol. 2002; 283:H1627–H33

21. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with pre-eclampsia at term. Hypertension 2011; 57:85–93.

22. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. BJOG 2013;120:496–504

23. Melchiorre K, Sutherland GR, Watt-Coote I, Liberati M, Thilaganathan B. Severe Myocardial Impairment and Chamber Dysfunction in Preterm Pre-eclampsia. Hypertension in Pregnancy 2012; 31(4):454–71.

24. Yamaguchi H, Yoshida J, Yamamoto K, Sakata Y, Mano T, Akehi N, Hori M, Lim YJ, Mishima M, Masuyama T. Elevation of plasma brain natriuretic peptide is a hallmark of diastolic heart failure independent of ventricular hypertrophy. J Am Coll Cardiol. 2004; 43:55–60.

25. Mueller C1, Laule-Kilian K, Scholer A, Frana B, Rodriguez D, Schindler C, Marsch S, Perruchoud AP. Use of B-type natriuretic peptide for the management of women with dyspnea. Am J Cardiol. 2004; 94:1510–4.

26. Yoshimura T, Yoshimura M, Yasue H, Ito M, Okamura H, Mukoyama, M Nakao K. Plasma concentration of atrial natriuretic peptide and brain natriuretic peptide during normal human pregnancy and the postpartum period. J Endocrinol 1994; 140:393–7.

27. Resnik JL, Hong C, Resnik R, Kazanegra R, Beede J, Bhalla V, Maisel A.. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. Am J Obstet Gynecol 2005; 193:450–4.

TABLE 1 – Clinical characteristics in the control, late-onset PE and early-onset PE groups.

	Controls (n =23)	Late-onset PE (n=32)	Early-onset PE (n=30)
Maternal age (y)	27(22-33)	24(19-30)	25 (20-32)
BMI at assessment (Kg/m^2)	27.4 (26.0-29.7)	30.8 (27.4-36.0)	31.6 (26.5-33.9)
Gestational age at assessment (week)	34 (29-37)	37 (36-38)†	32 (23-33)*,†
Gestational age at delivery (week)	40 (39-40)	37 (37-38)†	32 (28-33)*,†
Birth weight (g)	3410 (426)	2976 (471)	1351 (557)*,†
Systolic pressure at diagnosis (mmHg)	110 (103-112)	150 (140-160)†	160 (150-170)*,†
Diastolic pressure at diagnosis (mmHg)	69(63-70)	100 (90-100)†	110 (102-120)*,†

BMI: body mass index. Data are expressed as median (interquartile) or as mean (± SD). $^{*}p< .05$ versus late-onset PE; $^{\dagger}p< .05$ versus controls by Kruskal-Wallis, followed by Dunn's multiple comparison test or by Anova (birth weight).

TABLE 2 – Echocardiographic geometric patterns and diastolic function in the control, late-onset PE and early-onset PE groups.

	Controls (n =23)	Late-onset PE (n=32)	Early-onset PE (n=30)
Cardiac geometry			
Left atrial diameter (mm)	37(36-37)	41(39-42)†	40 (37-42)†
LVDD (mm)	47(45-47)	46(45-48)*	46(45-48)*
LVSD (mm)	28(27-29)	29 (27-31)	27(24-28)*
Relative wall thickness	0.35(0.35-0.36)	0.38(0.36-0.44)†	0.43(0.40-0.47)*,†
LVM (g)	122(115-127)	158(152-170)†	152(132-185)†
LVMi (g/m$^{2.7}$)	35(32-38)	44(42-49)†	44 (36-52)†
LV eccentric hypertrophy	0	10 (31%)†	3 (10%)†
LV concentric hypertrophy	0	5 (16%)†	12 (40%)*, †
Diastolic function			
E/A ratio	1.7(1.5-1.9)	1.5(1.3-1.7)†	1.4(1.3-1.6)†
IVRT (ms)	81(81-89)	87(80-95)	88(81-96)
Deceleration time (ms)	194(185-200)	192 (187-206)	201(188-219)
Diastolic dysfunction#	0	5 (16%)	7 (23%)†

LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVM: left ventricular mass; LVMi: left ventricular mass index; E wave: early transmitral diastolic flow velocity; A wave: flow velocity during atrial contraction; IVRT: isovolumic relaxation time.

Data are expressed as median (interquartile) or as number (percentage). *p< .05 versus late-onset PE; †p< .05 versus controls by Kruskal-Wallis, followed by Dunn's multiple comparison test.

TABLE 3 – Spearman´s correlations between BNP and E/A, LAD, LVDD, PWT, RWT and LVMi in late-onset PE and early-onset PE groups.

	Late-onset PE vs BNP (pg/mL)		**Early-onset PE vs BNP (pg/mL)**	
	r	***p***	**r**	***p***
E/A ratio	- 0.3319	.0731	-0.2814	.1551
LAD (mm)	0.2094	.2666	0.5546	**.0027**
LVDD (mm)	-0.1331	0.4832	0.1725	0.3896
PWT (mm)	0.5003	**0.0049**	0.7011	**<0.001**
RWT	0.4787	**.0074**	0.5688	**.0020**
LVMi ($g/m^{2.7}$)	0.6596	**<.0001**	0.7132	**<.0001**

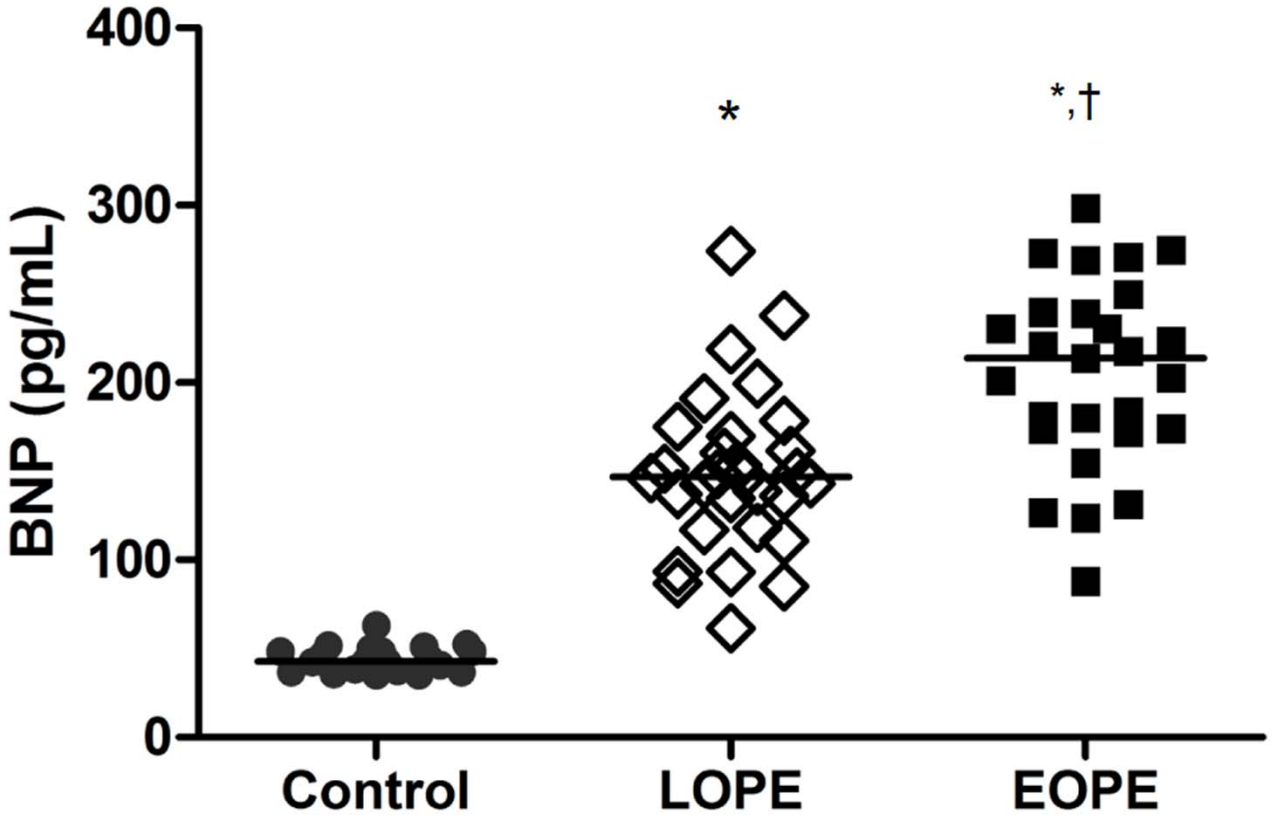
BNP: Brain Natriuretic Peptide; E wave: early transmitral diastolic flow velocity; A wave: flow velocity during atrial contraction; LAD: left atrial diameter; LVDD: left ventricular diastolic diameter; PWT: posterior wall thickness; RWT: relative wall thickness; LVMi: left ventricular mass index; r=Spearman's.

FIGURE LEGENDS

Figure 1: BNP level (pg/mL) in control, late-onset pre-eclampsia (LOPE) and early-onset pre-eclampsia (EOPE) groups.

Figure 2: Correlation between BNP level (pg/mL) and relative wall thickness (RWT) in control, late-onset pre-eclampsia (LOPE) and early-onset pre-eclampsia (EOPE) groups.

Figure 3: Correlation between BNP level (pg/mL) and left ventricular mass index (LVMi) in control, late-onset pre-eclampsia (LOPE) and early-onset pre-eclampsia (EOPE) groups.



*p< .05 versus late-onset PE; †p< .05 versus controls

Figure 1

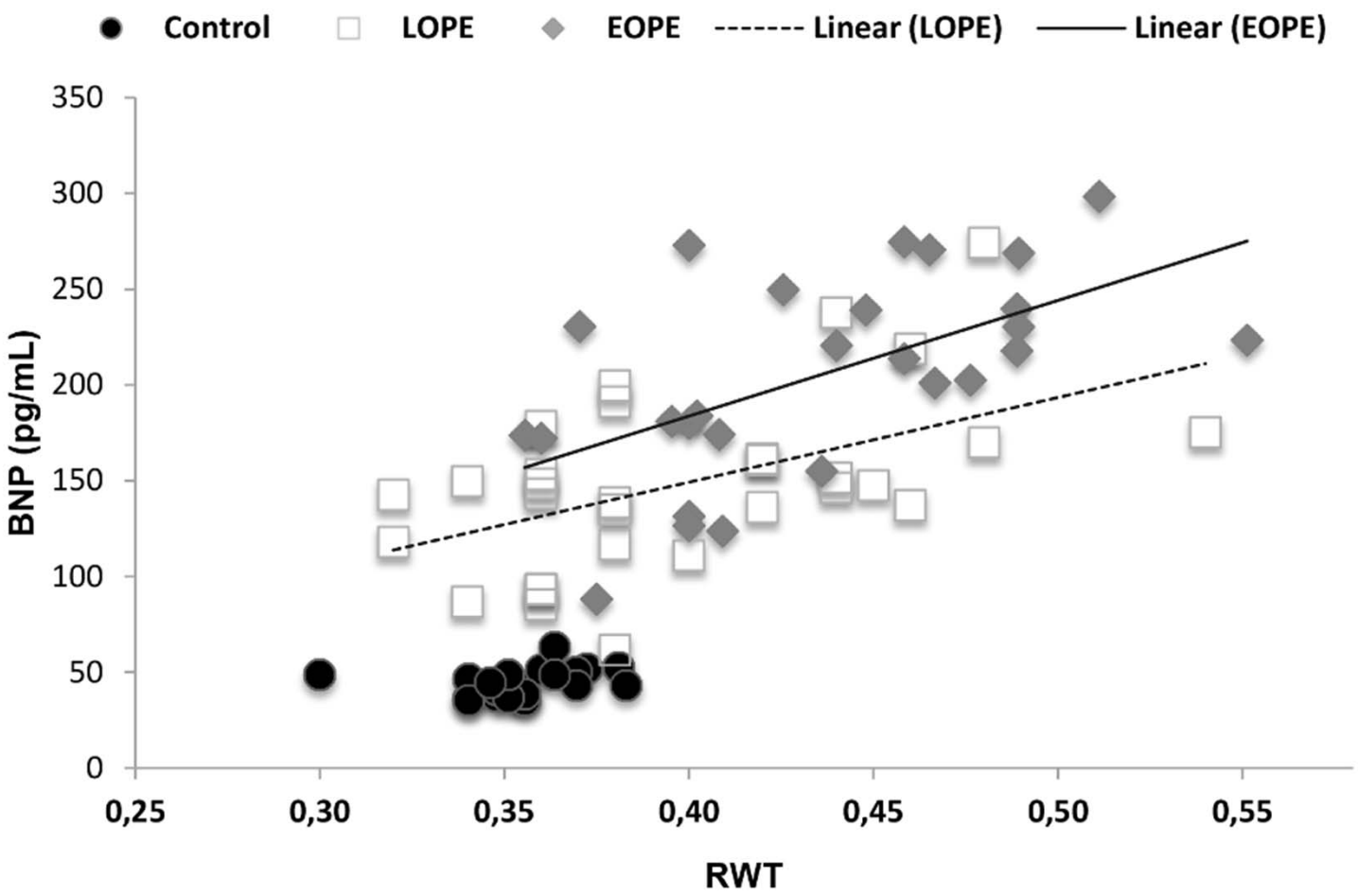


Figure 2

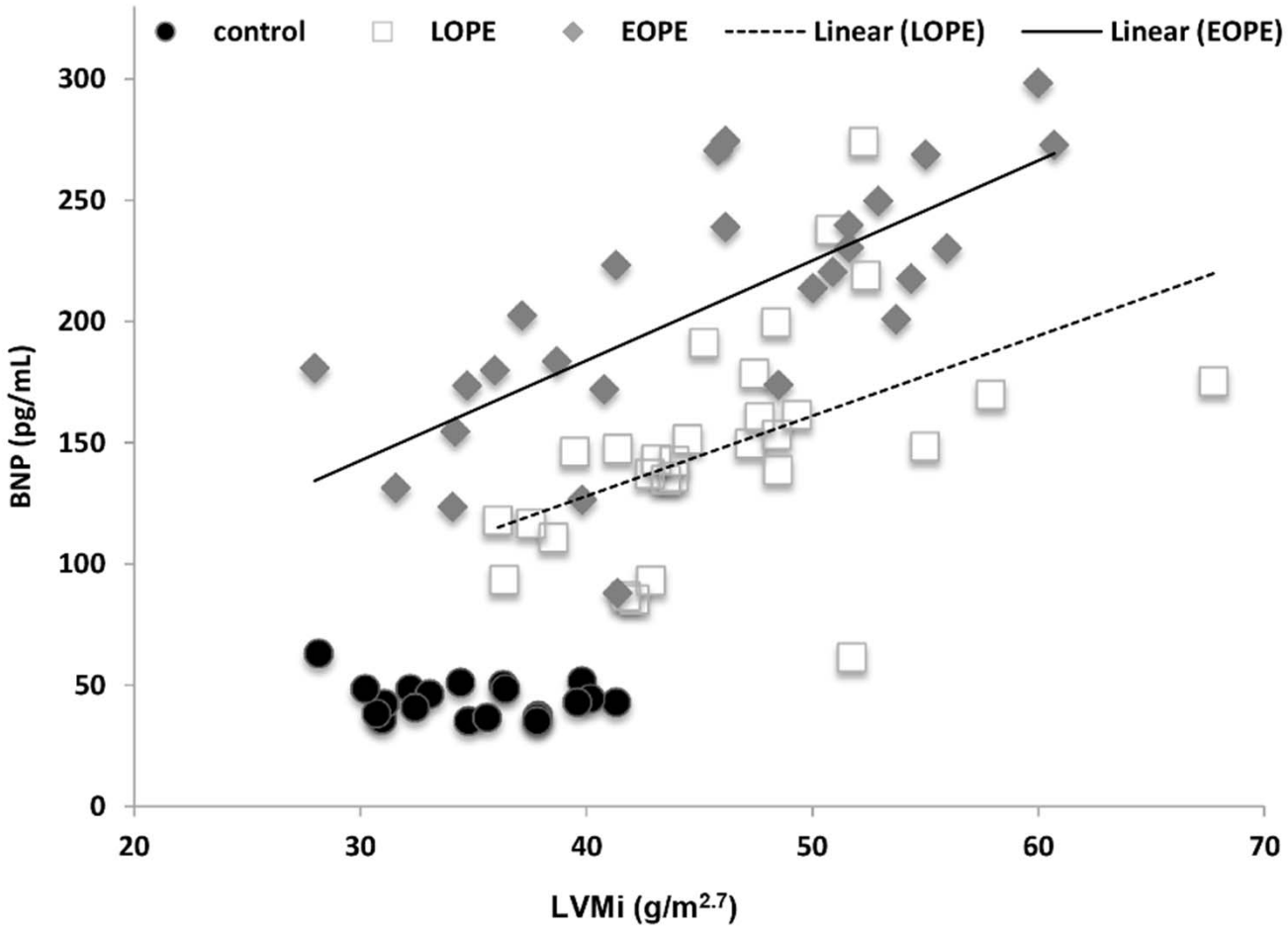


Figure 3