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Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker of cardiac filling pressures in pre-eclampsia

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ABSTRACT

Objective: To evaluate if amino-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels reflect intracardiac filling pressures in pre-eclamptic patients.
Study design: In a cross-sectional study we investigated 22 untreated critically ill pre-eclamptic women between 22 and 34 weeks gestation. All patients underwent intra-arterial blood pressure and central hemodynamic measurements and NT-proBNP was determined in stored plasma. Baseline characteristics, plasma NT-proBNP concentrations and relevant laboratory variables were investigated for correlations with hemodynamic values using Spearman's rank correlation test.
Results: No significant correlations were demonstrated between NT-proBNP concentrations and variables associated with the severity of the pre-eclampsia. We found significant positive correlations between NT-proBNP and diastolic pulmonary pressure ($r = 0.59$; $p = 0.005$) and pulmonary capillary wedge pressure (PCWP) ($r = 0.51$; $p = 0.015$). Multiple linear regression analysis showed that the association between NT-proBNP and PCWP was not affected by creatinine level.
Conclusion: NT-proBNP is a biomarker of left ventricular cardiac filling pressures in untreated pre-eclamptic patients.

1. Introduction

Antihypertensive treatment to prevent further vascular and circulatory damage forms a mainstay of clinical management of pre-eclampsia [1]. The elevated arterial blood pressure is associated with vasoconstriction and increased left ventricular afterload, reduced cardiac output, hypovolemia and low to normal, or slightly increased, cardiac filling pressures [2,3]. This makes vasodilators the drugs of choice for antihypertensive treatment, but the expansion of vascular space may induce hypotension and a further reduction of cardiac output with adverse effects on perfusion of maternal organs, including the kidney and the uteroplacental unit [1,4]. For that reason plasma volume expansion prior to vasodilating antihypertensive treatment has been recommended, in particular with the use of fast-acting intravenous medication [4,5].

Such hemodynamic treatment in critically ill pre-eclamptic patients requires assessment of cardiovascular risk and monitoring of hemodynamic responses. Central hemodynamic monitoring using flow-directed balloon-tipped pulmonary artery (Swan-Ganz) catheterization provides the most reliable means of assessing cardiac afterload and filling pressures, but it carries significant risks and should be reserved for critically ill patients [6]. Because non-invasive methods for cardiac monitoring have limitations, in particular with regard to measurement of left cardiac filling pressures [7], there is a need for reliable biomarkers of cardiac function and risk assessment.

In non-pregnant patients with a wide range of hemodynamic disturbances, circulating levels of atrial natriuretic peptides, in particular amino-terminal pro-brain natriuretic peptide (NT-proBNP), were shown to be independently associated with cardiac stress and risk of progressive heart failure and death [8,9]. Results of most studies indicate that circulating levels of atrial natriuretic peptides, including NT-proBNP, are increased in healthy pregnancies compared with non-pregnant controls and are higher in pre-eclampsia than in normotensive pregnancies, although not all studies agree [10–13].

We hypothesized that NT-proBNP could reflect the impaired hemodynamics associated with pre-eclampsia, which could make

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it a potential biomarker for cardiac risk. In order to test the hypothesis we assessed the association between maternal plasma NT-proBNP and hemodynamic variables in untreated critically ill pre-eclamptic women managed under a protocol of central hemodynamic monitoring with the use of a balloon-tipped pulmonary artery catheter.

2. Materials and methods

2.1. Subjects and study design

We selected 22 critically ill pre-eclamptic women between 24 and 34 weeks of gestation who were admitted to our obstetric high care unit. They had not yet received any treatment, and they were not in labor. All women were known to have been normotensive and nonproteinuric before 20 weeks gestation without evidence of chronic hypertension, cardiovascular or renal disease, or diabetes. The patients underwent invasive hemodynamic monitoring by means of an intra-arterial catheter and a flow-directed thermistor-tipped (Swan-Ganz) pulmonary artery catheter. We applied a standardized protocol for catheterization, calculation and interpretation of variables that was previously reported in detail [2,3,14]. Blood samples were drawn and measurements were started at least 1 h after catheterization, when heart rate and systemic arterial blood pressure had reached a steady state, before the start of pharmacologic treatment and administration of intravenous fluids. The following laboratory tests were carried out after admission: full blood cell count including platelets, liver enzymes, uric acid and creatinine.

Informed consent was obtained from all patients. The study formed part of a clinical scientific project to assess the efficacy of temporising hemodynamic treatment of severe pre-eclampsia approved by the University and Hospital Ethics Committee.

Pre-eclampsia was defined as the occurrence of a repetitive diastolic pressure $\geq$110 mm Hg (cuff measurement, Korotkoff V) at least 6 h apart and proteinuria $\geq$0.3 g in a 24-h urine collection, or the occurrence of repetitive diastolic blood pressures $\geq$90 mm Hg in combination with the HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) after 20 weeks gestation. HELLP syndrome was defined as the simultaneous occurrence of serum alanine amino transferase and serum aspartate amino transferase concentrations >30 U/l (2SD above the mean in our hospital), a platelet count $< 100 \times 10^9$/l, and hemolysis defined by abnormal peripheral smear.

2.2. Laboratory analysis

A blood sample was drawn from the radial artery catheter inserted for arterial pressure measurement and collected in chilled plastic tubes containing EDTA and aprotinin. Samples were immediately centrifuged at 4 °C for 10 min at $3000 \times g$, and plasma remained stored at −80 °C until assayed. We measured plasma NT-proBNP levels using a validated electrochemiluminescence immunoassay (Elecsys proBNP, F. Hoffman-La Roche Ltd., Basel, Switzerland) on an Elecsys 2010 analyzer [15]. Determinations were performed in duplicate in a single batch. The lower limit of detection was 17 pg/ml, within-assay variability was 6% and between-assay variability was 15%. Other biochemical tests were performed using routine laboratory techniques.

2.3. Statistical analysis

The association between different continuous variables was analyzed using Spearman's rank correlation tests. The Mann–Whitney test was used in the comparison of groups. The association between pulmonary capillary wedge pressure and NT-proBNP adjusting for creatinine level was assessed using linear multiple regression analysis. NT-proBNP concentrations were logarithmically transformed in this analysis in order to get an approximately normal distribution. The statistical analysis was performed using SPSS/PC (version 15.0, SPSS Inc., Chicago, IL). A two-sided p-value < 0.05 was considered to indicate statistical significance.

Table 1
Baseline characteristics on admission[a].

Characteristics	$N = 22$
Age (years)	25 (20–41)
Gestational age (weeks)	29 (24–34)
Nulliparous women	17 (77)
HELLP	6 (27)
Systolic blood pressure (mm Hg)	170 (135–214)
Diastolic blood pressure (mm Hg)	105 (95–120)
Hemoglobin (mmol/l)	7.4 (5.3–9.2)
Platelet count (10^9/l)	183 (20–395)
Uric acid (mmol/l)	0.39 (0.24–0.62)
Creatinine (μmol/l)	72 (47–95)
Albumin (g/l)	30 (26–39)
Urea (mmol/l)	4.8 (2.7–10.4)
ASAT (U/l)	26 (13–373)
ALAT (U/l)	17 (8–245)
LD (U/l)	354 (212–1120)
NT-proBNP (pg/ml)	100 (23–2419)
Proteinuria (g/24 h)	3.0 (0.6–15.5)

[a] Values shown represent median (range) or numbers of patients (%).

3. Results

3.1. Baseline characteristics

The baseline clinical and biochemical characteristics of the pre-eclamptic patients are presented in Table 1. HELLP syndrome was present in six women. The distribution of NT-proBNP concentrations was markedly skewed towards the right, but logarithmic transformation resulted in an approximately normal distribution. No significant correlations were found between NT-proBNP concentrations and maternal age, gestational age, peripheral blood pressures, serum concentration of creatinine, albumin and proteinuria. NT-proBNP concentrations in the six patients with the HELLP syndrome were not significantly different from those in the other 16 pre-eclamptic patients.

3.2. Hemodynamic variables and correlations

Hemodynamic variables and correlations with logarithmically transformed values of NT-proBNP are presented in Table 2. The intra-arterial diastolic blood pressures were 5–10 mm Hg lower than the indirectly measured pressures. We found significant positive correlations between NT-proBNP and diastolic pulmonary pressure ($p = 0.005$) and pulmonary capillary wedge pressure ($p = 0.015$) as shown in Fig. 1. Multiple linear regression analysis showed that the association between NT-proBNP and pulmonary capillary wedge pressure (PCWP) was not affected by the creatinine level. An increase in PCWP with 1 mm Hg was associated with an increase of NT-proBNP with 12% (95% CI: 2–24%; $p = 0.001$) adjusted for creatinine concentration.

4. Comments

The hemodynamic disturbances in critically ill pre-eclamptic women require hemodynamic monitoring to titrate pharmacologic and fluid management and assess its responses. Measurements with the pulmonary artery catheter, used in our study, are still acknowledged as the gold standard, but the ongoing debate over its