B-Type Natriuretic Peptide and Rebound during Treatment for Persistent Pulmonary Hypertension

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Objective To investigate whether serum B-type natriuretic peptide (BNP) is a useful biomarker in evaluating the course of persistent pulmonary hypertension of the newborn (PPHN) and the effectiveness of treatment.

Study design Prospective follow-up study of infants with clinical and echocardiographic signs of PPHN, who were treated with inhaled nitric oxide (iNO). Of 24 patients with PPHN who were treated, serum BNP levels were determined longitudinally in 21. BNP levels were compared between infants with (n = 6) and without rebound PPHN (n = 15).

Results BNP levels in all infants with PPHN were not significantly different at the initial start of iNO. BNP levels decreased in both groups during iNO treatment. In the infants in whom rebound PPHN developed after weaning from iNO, a significantly higher increase was found in BNP (283 pmol/L to 1232 pmol/L) compared with that in infants without rebound (98 pmol/L to 159 pmol/L). This occurred before the onset of clinical deterioration. BNP again decreased significantly after iNO treatment was restarted.

Conclusions BNP, a biomarker of cardiac ventricular strain, proved to be useful in evaluating the efficacy of PPHN treatment, and moreover, BNP helps to predict a rebound of PPHN. *(J Pediatr 2012;160:111-5)*.

Persistent pulmonary hypertension of the newborn (PPHN) occurs when pulmonary vascular resistance fails to decrease after birth.[1] When the respiratory distress is complicated by oxygenation problems and low saturations, PPHN should be suspected. Because most diseases of the newborn start with respiratory problems, PPHN is often difficult to diagnose.[2]

B-type natriuretic peptide (BNP) is an endogenous peptide hormone, secreted by cardiac ventricles in response to an increased wall stress and ventricular filling pressure. BNP causes vasodilatation and has a diuretic and natriuretic effect. It has been used in infants and children to provide information on ventricular function and to diagnose significant cardiovascular disease.[3,4] BNP concentrations in plasma correspond well with echocardiographic findings of ventricular strain.[5,6] Reynolds et al suggested BNP as an early indicator of PPNH in the presence of respiratory illness in the newborn in the absence of congenital heart disease (CHD).[4]

When PPHN is suspected, echocardiographic evaluation is necessary to exclude CHD and to confirm signs of elevated pulmonary pressure.[7] Treatment is directed to improvement of oxygenation (surfactant replacement), pulmonary vascular dilatation (inhaled nitric oxide [iNO]) and to maintain adequate blood pressure (fluid replacement, inotropic support).[1,8] The decision how long iNO treatment should be continued is often difficult. After exposure to iNO, the pulmonary circulation can be sensitized for vasoconstriction, possibly because of suppression of endogenous nitric oxide production. Even when careful weaning is used, some infants will have a rebound of PPHN.[9] The objective of this study was to investigate whether BNP is a useful biomarker to evaluate the course of PPHN and the effectiveness of treatment.

Methods

In a prospective follow-up study, all infants with clinical and echocardiographic signs of PPHN who were treated with iNO and admitted to the University Medical Center Utrecht neonatal intensive care unit (NICU) from January 2009 until December 2009 were included in the study. Exclusion criteria were major congenital malformations including cardiac malformations, chromosomal abnormalities, and the need for extra-corporal membrane oxygenation, because then referral to another

AaDO2	Alveolar/arterial oxygen gradient
BNP	B-type natriuretic peptide
CHD	Congenital heart disease
FiO_2	Fraction of inspired oxygen
iNO	Inhaled nitric oxide
NICU	Neonatal intensive care unit
OI	Oxygenation index
PH	Pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn
TR	Tricuspid regugitation

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NICU was necessary. Because of the observational nature of the study approval from the medical ethics commission was not required. Parental consent for the anonymous processing of patient data was obtained in all cases. BNP blood samples were collected at admission and then daily during iNO treatment and at least once after completion of iNO treatment. In case of signs of rebound and reinstitution of iNO, daily determinations were continued. Echocardiography was routinely performed by an experienced pediatric cardiologist on suspicion of PPHN to confirm the diagnosis and to exclude CHD.

PPHN was defined as hypoxemia with echocardiographic findings of elevated pulmonary artery pressure, right-to-left shunting through a patent foramen ovale or the patent ductus arteriosus, or both. Rebound was defined as the reoccurrence of clinical signs of PPHN after decreasing or discontinuing the iNO treatment. Clinical signs were hypoxemia, decrease of "post-ductal" saturation, and lower partial pressure of oxygen levels, as a result of right-to-left shunting, which prompted the attending clinician to reinstitute iNO treatment and increase the fraction of inspired oxygen (FiO_2). This rebound was confirmed by using echocardiography with the known measures of increased tricuspid regurgitation as an estimate of elevated right ventricular pressure and by identifying the presence of right-to-left shunting at that moment.

The demographic data collected were gestational age at birth, birth weight, sex, prenatal and perinatal history, and associated illness. When each blood sample for BNP was taken, blood gas analysis was performed. The oxygenation index (OI) and alveolar/arterial oxygen gradient (AaDO2) as indicators of disease severity were calculated.[10,11] The iNO requirement at that point was registered.

To assess the intensity of blood pressure support, a blood pressure support scoring system was used, depending on the intensity of the treatment necessary (score 0, no treatment; score 1, volume expansion and/or dopamine ≤5 μg/ kg/ min; score 2, dopamine >5 and ≤10 μg/kg/min; score 3, dopamine >10 μg/kg/min or dopamine + dobutamine ≤10 μg/ kg/min; score 4, dopamine + dobutamine >10 μg/kg/min; score 5, additional adrenaline and/or corticosteroids).[12]

BNP measurements are standard clinical practice in our department and were done daily or more when required. Blood samples were collected from an arterial catheter or with capillary samples (heel stick) in a standard collection vial with ethyl-enediamine tetra acetic acid (Capijet, VWR, West Chester, Pennsylvania). BNP was analyzed on a DxI 800 immunochemistry system (Beckman Coulter Diagnostics, Brea, California).

Statistics

Descriptive data are presented as median and ranges. Comparison of BNP levels in time was done by using non-parametric statistical analysis with the Mann-Whitney *U* test, because the dataset had a non-parametric distribution. The Spearman rank-sum test was used to correlate BNP to associated variables. A *P* value <.05 was considered to be significant. For the statistical analysis, SPSS software version 15.0 (SPSS, Chicago, Illinois) was used.

Results

Twenty-four patients were admitted to the NICU for PPHN treatment with iNO. Three patients were referred for extracorporal membrane oxygenation treatment and were subsequentially excluded from the study. Of the 21 infants included in this study, 6 had rebound as defined in the Methods section, and 15 did not. The etiology of the PPHN in the rebound group was meconium aspiration syndrome (n = 2), meconium aspiration syndrome and perinatal asphyxia (n = 1), and perinatal asphyxia (n = 3). In the non-rebound group, the etiology was sepsis (n = 5), meconium aspiration syndrome (n = 5), sepsis and perinatal asphyxia (n = 1), perinatal asphyxia (n = 1), "dry lung" after premature rupture of membranes (n = 1), pneumothorax (n = 1), and pulmonary hypoplasia (n = 1).

The patient characteristics of the groups are shown in the Table. No significant differences were found between the rebound and non-rebound groups for birth weight, gestational age, sex, number of days of iNO treatment, Apgar score at 1 minute, Apgar score 5 minutes, or inotropic support.

The first BNP level was obtained just before the start of iNO treatment. The mean levels for the 21 infants were mean 361 ± 499 pmol/L (median, 155 pmol/L; range, 9-1838 pmol/L). In the rebound PPHN group the BNP levels were initially higher (median, 289 pmol/L; range, 9-1838 pmol/L) than in the non-rebound group (median, 147 pmol/L; range, 54-649 pmol/L); However this difference was not statistically significant. After the initiation of iNO treatment, BNP levels decreased, as shown in Figure 1, which shows a non-chronological interval because treatment duration was not identical for all patients. At the specified points during PPHN treatment, a BNP measurement was performed in all patients. After weaning and subsequent cessation of iNO treatment, a non-significant rise in BNP was seen in the non-rebound group, from a median of 98 pmol/L (range, 44-144 pmol/L) to 159 pmol/L (range, 7-448 pmol/L; *P* = .07). The rebound group showed a much greater rise in BNP plasma levels, from a median of 283 pmol/L (range, 49-341 pmol/L) to 1232 pmol/L (range, 430-2339 pmol/L; *P* = .004). This

Table. Characteristics of patients treated for PPHN

	Rebound (n = 6)	No rebound (n = 15)	*P* value
Birth weight, g	3390 (2100-4920)	3436 (1475-4790)	.74
Gestational age, weeks	390/7 (32-41 3/7)	392/7 (30-42 1/7)	.51
Male, %	67	60	.94
1-minute Apgar score, median	5	5	.97
5-minute Apgar score, median	6	7	.64
Total iNO, days	9 (5-14)	5 (1-11)	.11
Inotropic support	4.2 (2-5)	4.2 (2.5)	.78