Brain Natriuretic Peptide Levels in Managing Pediatric Patients With Pulmonary Arterial Hypertension*

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Background: **Pulmonary arterial hypertension (PAH) is an important determinant of morbidity and mortality in children. In this study, we aimed to investigate the value of brain natriuretic peptide (BNP) in a cohort of children with PAH, with respect to monitoring disease severity as assessed by hemodynamic and echocardiographic parameters.**

Methods: **We performed a prospective study to determine whether BNP varies over time in this population and whether these changes track with hemodynamic or echocardiographic parameters. The population included a group of 78 pediatric patients from January 2005 to April 2008. All patients had received a diagnosis of PAH and had serum BNP, catheterization, and echocardiographic variables collected longitudinally.**

Results: **The median BNP level, for all observations, was 36 pg/mL (interquartile range, 18 to 76 pg/mL). There was no strong correlation found between commonly used echocardiographic or hemodynamic data and BNP. However, using a bivariate model, the change in BNP measurements over time significantly correlated with the change in the hemodynamic and echocardiographic parameters. Patients with a BNP value > 180 pg/mL had a decreased survival rate.**

Conclusions: **BNP could be a useful marker to monitor disease severity in pediatric PAH. We show that simple correlations between variables and BNP are not likely to illustrate its usefulness due to variations in the normative levels. Instead, we propose that patient BNP levels should be monitored over time, as changes in BNP within a patient are likely to be more informative.**

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Key words: biomarkers; brain natriuretic peptide; longitudinal changes; pediatrics; pulmonary arterial hypertension

Abbreviations: BNP = brain natriuretic peptide; CI = cardiac index; FS = fractional shortening; IPAH = idiopathic pulmonary arterial hypertension; IQR = interquartile range; LVDd = left ventricular diastolic dimension; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; NTproBNP = N-terminal proBNP; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; ROC = receiver operating characteristic; RVDd = right ventricular diastolic dimension; SVR = systemic vascular resistance; TRp = tricuspid regurgitation pressure gradient; TRv = tricuspid regurgitation velocity

Pulmonary arterial hypertension (PAH) is an elevation in pulmonary artery pressure that is associated with a spectrum of diseases and causes. At this time, there is no cure for PAH and, without appropriate management, PAH is often progressive and fatal. It is an important determinant of morbidity and mortality in children and its clinical severity and presentation are widely varied, making the accurate assessment of prognosis in patients with PAH difficult.[1–4]

Currently, hemodynamic parameters are the basis for characterizing disease progression and prognosis in patients with PAH.[5,6] These measurements are obtained invasively by cardiac catheterization in pediatric patients and are associated with specific risks.[7] Additionally, echocardiography is helpful in the monitoring of disease severity in PAH, yet has its own inherent limitations. Therefore, alternative parameters that are noninvasive, reliable, and relatively quickly determined are needed in pediatric patients with PAH to monitor disease severity and prognosis.

The release of brain natriuretic peptide (BNP) results in improved myocardial relaxation and is

targeted at protecting the cardiovascular system from the effects of volume overload. The initiation of synthesis of proBNP results from wall stress caused by volume expansion or pressure overload. Subsequently, the peptide is cleaved to produce the biologically active hormone BNP and the inactive N-terminal proBNP (NTproBNP). Both BNP and NTproBNP can be detected and measured in the circulation. In general, these peptide levels are reasonably correlated, and either can be used in patient care, although the absolute levels are not interchangeable. Normal values vary depending on the assay method and the demographics of the patient.[8] Even though appropriate reference values are lacking in children, preliminary data suggest that BNP levels are useful in diagnosing and managing pediatric heart failure.[9–13]

Several studies have been performed in the adult population to determine if elevated serum levels of natriuretic peptides can be used as a prognostic indicator of disease severity in PAH.[14–19] In one study, survival was strikingly worse for patients with a supramedian value of BNP > 180 pg/mL than for those with an inframedian value.[17] However, related studies in pediatric PAH patients, specifically involving some form of BNP, are few. It is unknown whether BNP, specifically, can be used as a prognostic tool in children in the same way as in adults.

To investigate this topic, we performed a prospective study in children with PAH who presented to The Children's Hospital of Denver from January 2005 to May 2008. We aimed to determine the relation between serum levels of BNP and currently monitored hemodynamic and echocardiographic variables in PAH.

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Materials and Methods

Seventy-eight pediatric patients with PAH were subsequently enrolled in the institutional review board-approved Prospective Evaluation of Adolescents and Children with Pulmonary Arterial Hypertension study at our institution beginning January 2005. Of the 78 patients, 26 patients had idiopathic PAH (IPAH), and 52 patients had associated PAH; 42 patients were female. The median age at first sample was 9 years (range, 6 months to 22 years). IPAH and associated PAH were defined based on the

Table 1—*Patient Demographics and Baseline Clinical Measurements (n = 78)*

Variables	Data
Median age (range), yr	9.3 (5.2–14.2)
Female gender, No. (%)	42 (53.9)
IPAH, No. (%)	26 (33.3)
Associated PAH	
Congenital heart disease, No. (%)	41 (52.5)
Repaired/unrepaired, No.	
Ventricular septal defect	10/3
Atrial septal defect	6/2
Atrioventricular septal defect	6/2
Patent ductus arteriosus	2/1
Transposition of the great arteries	2/0
Double-outlet right ventricle	1/0
Total anomalous pulmonary venous return	2/0
Tetralogy of Fallot	1/0
"Absent pulmonary artery"	0/3
Portopulmonary hypertension, No. (%)	2 (2.5)
Connective tissue disease, No. (%)	3 (3.8)
Sickle-cell disease, No. (%)	1 (1.2)
Bronchopulmonary dysplasia, No. (%)	5 (6.4)
Baseline catheter measurements, median (IQR)	
Right atrial pressure, mm Hg	6 (4–8), n = 77
Pulmonary artery pressure, mm Hg	38 (29–59), n = 79
PCWP, mm Hg	9 (7–10), n = 73
CI, L/min/m^2	3.5 (2.8–4.4), n = 63
PVR index, Wood units/m^2	6.5 (4.7–14.7), n = 74
Systemic arterial pressure, mm Hg	64 (58–70), n = 78
SVR index , Wood units/m^2	14.8 (11.2–19.2), n = 72
PVR/SVR	0.5 (0.4–0.8), n = 72
Baseline echocardiographic measurements, median (IQR)	
RVDd, cm	2.7 (2.1–3.2), n = 47
LVDd, cm	3.6 (3.0–4.2), n = 70
FS of the left ventricle, %	40.0 (35.5–46.5), n = 69
TRv, m/s	4.2 (3.5–4.8), n = 64
TRp, mm Hg	70.1 (49.2–91.9), n = 64
Catheters per patient, range	0–8
Patients with one or no catheters, No.	41
Patients with two or more catheters, No.	37
Echocardiograms per patient, range	0–27
Patients with one or no echocardiograms, No.	7
Patients with two or more echocardiograms, No.	71