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Early Elevations in B-Type Natriuretic Peptide Levels Are Associated With Poor Clinical Outcomes in Pediatric Acute Lung Injury

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Summary

Objectives—To determine B-type natriuretic peptide (BNP) levels in infants and children with acute lung injury (ALI), and to investigate associations between BNP levels and clinical outcome.

Design—Prospective observational study.

Subjects—After informed consent, plasma was collected from 48 pediatric patients on day 1 of ALI.

Methodology—Plasma BNP levels were measured by immunoassay on day 1 of ALI in 48 pediatric patients. Associations between BNP levels and outcome were determined.

Results—The mean PaO_2/FiO_2 at the onset of ALI was 155 (±74) and BNP values ranged from 5 to 2,060 pg/ml with a mean of 109 (±311). BNP levels were inversely correlated with ventilator-free days (Spearman rho −0.30, P =0.04), and positively correlated with exhaled tidal volume (Spearman rho 0.44, P =0.02). BNP levels were higher in patients receiving inotropic support (n =12) than patients not receiving inotropic support (n =33, P =0.02). BNP levels were correlated with PRISM III scores (Spearman rho 0.55, P <0.001) and PELOD scores (Spearman rho 0.4, P =0.006). Mortality for the cohort was 15%. BNP levels were higher in non-survivors (n =7) than survivors (n =41, P =0.055).

Conclusions—BNP levels are elevated in children with ALI/ARDS early in the disease course, and increased levels are associated with worse clinical outcome.

Keywords

pediatric acute lung injury (ALI); acute respiratory distress syndrome (ARDS); B-type natriuretic peptide (BNP); mechanical ventilation; mortality; biological markers

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INTRODUCTION

Acute lung injury (ALI0) and the acute respiratory distress syndrome (ARDS) cause significant morbidity and mortality in children.[1] Multi-system organ dysfunction develops often, indicating that the pathophysiology of ALI/ARDS is not limited to the lungs.[1,2] Our recent study found that in addition to the initial severity of oxygenation defect, the existence of non-pulmonary and non-central nervous system (CNS) organ dysfunction, and CNS dysfunction independently predicted mortality in a large cohort of children with ALI/ARDS.[1] Although the precise mechanisms of disease are incompletely understood, several lines of evidence support a potential role for cardiopulmonary interactions in the pathophysiology. For example, increased pulmonary artery pressure and pulmonary dead-space fraction were associated with worse clinical outcome in studies of adults and children. Further, low tidal volume ventilation, that would tend to reduce right ventricular afterload compared to high tidal volumes, improved outcome in adult patients with ALI/ARDS.[3–5] \

Given these data, subsets of pediatric patients with ALI/ ARDS may suffer from impaired cardiac performance, owing to adverse cardiopulmonary interactions. However, direct measurements of hemodynamic indices such as cardiac output and pulmonary artery pressure are often not possible in these patients, owing to size limitations and a lack of evidence that supports such invasive monitoring. Thus, novel biomarkers of cardiac performance in the setting of pediatric ALI/ARDS may be beneficial. B-type natriuretic peptide (BNP) is a 32 amino acid polypeptide hormone produced by the cardiac ventricles in response to myocyte stretch, with diuretic, natriuretic and vasoactive properties, which is used as a biomarker for the management of cardiac disease in both adult and pediatric patients.[6–8] BNP measurements were useful in distinguishing between cardiac and pulmonary etiologies in several studies of adult and pediatric patients with acute respiratory failure.[9–14] However, whether BNP is altered in pediatric patients with ALI/ARDS has not been studied.

In this pilot study, we hypothesized that elevated BNP levels would be associated with worse clinical outcome in a cohort of pediatric patients with ALI/ARDS. Therefore, the objectives of this study were: (1) to determine BNP levels in infants and children with ALI/ARDS, and (2) to investigate associations between BNP levels and clinical outcome.

MATERIALS AND METHODS

A prospective cohort study enrolling children with ALI was conducted on the Pediatric Intensive Care Unit (PICU) at the Children's Hospital and Research Center Oakland between August 2002 and January 2005. Written informed consent was obtained from the patients' parents or guardians prior to enrollment in the study. The Institutional Review Board at Children's Hospital and Research Center Oakland approved this study. Blood samples were available from all patients for analysis of BNP levels. In addition, blood samples were available from an additional six patients enrolled in the previous Prone Positioning in Pediatric Acute Lung Injury Study, which had identical enrollment criteria.[15] Thus, in order to increase the sample size, these patients were included in the analysis. The Institutional Review Boards at Children's Hospital and Research Center Oakland and the

centers enrolling patients in the Prone Positioning in Pediatric Acute Lung Injury Study approved the study of these patients.

Patients were eligible if they met the 1994 American European Consensus Committee definition of ALI (partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio <300, with acute onset of bilateral infiltrates on chest radiograph, and no evidence of left atrial hypertension). Patients were excluded if they were <36 weeks corrected gestational age or more than 18 years of age at the onset of ALI, had evidence of left atrial hypertension either clinically or by echocardiogram, or had echocardiographic evidence of intracardiac shunt.

All patients had at least one arterial blood gas supporting the PaO_2/FiO_2 <300 requirement. Arterial blood gases were obtained as a part of standard patient care except for six patients who were also enrolled in the Prone Positioning in Pediatric ALI trial.[15] Per study protocol, these patients had additional blood drawn specifically for research purposes. Patients received echocardiograms at the discretion of the intensive care team based on clinical need. All echocardiograms were interpreted by attending cardiologists on staff at each institution who were blinded to the study. Patients with evidence of moderate to severe left ventricular dysfunction and/or left atrial hypertension based on independent attending cardiologist interpretation were excluded from the study. Radiographic interpretation was confirmed by independent readings from attending radiologists at each institution who were blinded to the study. For patients who were not mechanically ventilated, the FiO_2 was calculated according to the American Association of Respiratory Care guidelines.[16] The medical management followed standard institutional practices. An on service team, blinded to the BNP values, made all patient management decisions.

Sample and Data Collection

A group of 48 patients with ALI/ARDS had plasma samples drawn or discarded plasma retrieved from the laboratory at their respective institutions within the first 24 hr of ALI. Separated plasma was stored at minus 70°C. For BNP determinations, the plasma was thawed to room temperature and BNP levels were measured using a commercially available fluorescence immunoassay (Triage® Meter Plus, Biosite® Diagnostic, San Diego, CA). The measurable range of BNP on this device is between 5 and 5,000 pg/ml. The estimated coefficient of variation for the assay is 9.2–11.4%.

Clinical data were collected from the medical record by an observer blinded to the BNP data and included in a relational Access database. Clinical data included the presence of inotropic support, the need for mechanical ventilation, peak inspiratory pressure, peak end expiratory pressure, exhaled tidal volume, central venous pressures, and arterial blood gas values. Severity of illness was measured using the adjusted Pediatric Risk of Mortality (PRISM) III scores and multi-system organ failure was measured using Pediatric Logistic Organ Dysfunction (PELOD) scores for the first day of ICU admission.[17–19]

Outcome Measures

The primary outcome measure was the number of ventilator-free days, defined as the number of days the patient was alive and not mechanically ventilated in the 28 days after onset of ALI. The secondary outcome was mortality in the PICU.

Data Analysis

Descriptive statistics were computed for each of the variables, including means, medians, standard deviations, and interquartile ranges. Correlations were used to examine the association between each pair of continuous measures. To compare differences between any two groups the non-parametric Mann–Whitney test was applied. A significance level of 0.05 was used for all statistical tests. Statistical analyses were performed with the use of Stata 6.0 (Stata Corp., College Station, Texas) and graphs created with the use of Prism 4.0 (GraphPad Software, Inc., San Diego, CA).

RESULTS

A total of 48 patients were enrolled. Patient characteristics for the entire cohort are shown in Table 1. The median age was 4.2 (range 0–18) years. The primary diagnoses associated with ALI were pneumonia 21 (44%), aspiration 4 (8%), trauma 6 (11%), cardiac disease 4 (8%), sepsis 3 (6%), and other 10 (19%). The diagnoses of the four patients with cardiac disease were: transposition of the great arteries, Tetralogy of Fallot, supracardiac total anomalous pulmonary venous return, and atrial and ventricular septal defect. All of the patients met criteria for enrollment after complete surgical repair, and none had residual intracardiac shunts.

The mean PaO_2/FiO_2 at the onset of ALI was 155 ± 74. All patients were treated with lung protective ventilation strategies (mean exhaled tidal volume 7.4 ±2.7 cc/kg). There were three (6%) patients who did not require tracheal intubation and mechanical ventilation at the time that they met criteria for ALI. Of these, one received supplemental oxygen by mask and two by nasal cannula. BNP levels were not different between patients receiving (n =45) and not receiving (n =3) mechanical ventilation at the onset of ALI. The medical team obtained an echocardiogram on four patients on the initial day of ALI.

BNP values ranged from 5 to 2,060 with a mean value of 109 ±311. Mean ventilator-free days for the cohort were 18 ±9.5. BNP levels were inversely correlated with ventilator-free days (Spearman rho −0.30, P =0.04), and positively correlated with exhaled tidal volume (Spearman rho 0.44, P =0.02, Fig. 1). There was no correlation between BNP levels and peak inspiratory pressures, peak end expiratory pressures, or the PaO_2/FiO_2 ratios. There was no correlation between BNP levels and central venous pressure (17 observations). Mortality for the cohort was 15%. BNP levels were higher in non-survivors (n =7) than survivors (n =41, P =0.055, Fig. 2).

In addition, BNP levels were higher in patients receiving inotropic support (n =12) than patients not receiving inotropic support (n =33, P =0.02, Fig. 3). BNP levels were correlated with PRISM III scores (Spearman rho 0.55, P <0.001, Fig. 4A) and PELOD scores (Spearman rho 0.4, P =0.006, Fig. 4B) calculated on the first day of admission to the ICU.

BNP levels were similar between the primary diagnoses of pneumonia, aspiration, trauma, and cardiac disease. Since BNP levels have been reported to increase in children after cardiac surgery with cardiopulmonary bypass we further analyzed the cohort with the four cardiac patients excluded. The relationship of BNP to all of the clinical outcomes was the same whether the cardiac patients were included or excluded from the analysis. Further, BNP levels were not different between patients with cardiac disease as compared to the remainder of the cohort (data not shown). BNP levels in patients with sepsis (n =3) were higher than patients without sepsis (n =45, P <0.001). In addition, BNP levels were higher in patients with indirect lung injury (sepsis, trauma, cardiac disease, other, n =27) than patients with direct lung injury (pneumonia, aspiration, near drowning, n =20, rho =0.39, P <0.01). BNP levels were not correlated with age, gender, pH, BUN, creatinine, or arterial blood gas values.

DISCUSSION

In this cohort of children with ALI/ARDS, elevated BNP levels early in the disease course were associated with worse clinical outcome. Specifically, we found that BNP levels obtained during the first day of diagnosis were correlated with the duration of mechanical ventilation. In addition, we found that BNP levels were correlated with tidal volumes while on mechanical ventilation, an indication of volutrauma, the degree of organ dysfunction as measured by PELOD score, and severity of illness, as measured by PRISM III score. As expected, elevated BNP levels also correlated with the need for inotropic support, and there was a suggestion of a correlation with mortality. As increased ventricular myocyte stretch is the primary stimulus for BNP release, the data from this pilot study suggest that altered cardiopulmonary interactions leading to increased ventricular volume or pressure may influence outcome in subsets of pediatric patients with ALI/ARDS.

The rationale for studying BNP in pediatric ALI is based upon the notion that abnormal cardiopulmonary interactions may accompany ALI/ARDS in a manner that relates to disease severity. The pathophysiology of ALI/ ARDS involves injury to both the alveolar epithelium and pulmonary vascular endothelium.[2] Injury to the vascular endothelium can result in diffuse vascular obstruction, owing to intravascular thrombi, segmental atelectasis, and/or increased hypoxic pulmonary vasoconstriction with resultant metabolic and respiratory acidosis.[2,20] In fact, impaired pulmonary blood flow can progress to pulmonary hypertension and right ventricular failure.[2,20–22] In a cohort of 23 children with ALI, Katz et al.[4] found that pulmonary artery pressures, pulmonary vascular resistance, and intrapulmonary shunt fractions were higher in non-survivors than in survivors. In a large cohort of adult patients with ARDS, Nuckton et al.[5] reported that the pulmonary dead-space fraction, an indication of dysregulated coagulation and pulmonary intravascular thrombosis, was an independent predictor of death. Therefore, we hypothesized that BNP levels would be elevated in children with ALI/ARDS, and that BNP levels would be associated with outcome.

We speculated that BNP levels would relate to outcome through the identification of a subset of patients with unfavorable cardiopulmonary interactions. However, one major limitation of this study was that we could not interrogate patients' cardiac function

prospectively with diagnostic modalities, such as echocardiography or pulmonary artery catheterization. In addition, only a small number of patients had echocardiograms performed within the first 24 hr of ALI. Thus, the present data are not sufficient to prove a causal link between cardiac function and outcome in this cohort, nor are they sufficient to identify the particular hemodynamic abnormality linking BNP levels with the severity of ALI/ARDS. Despite this limitation, several recent studies of BNP in infants and children with cardiac disease found that BNP levels were more sensitive predictors of outcome than echocardiography or cardiac catheterisation.[23–25] Thus, there is some evidence in pediatric patients indicating that BNP levels may capture impaired cardiac function in a manner not detected by other diagnostic modalities.

Interpretations of the present results must consider a recent large clinical trial in adult patients with ALI/ARDS that found no benefit to management guided by pulmonary artery catheters as compared to central venous catheters.[26] Interestingly, a recent study in adult patients with ALI found that BNP levels did not correlate reliably with measured pulmonary artery occlusion pressures.[14] Therefore, it is possible that BNP levels reflect cardiac function and/or cardiopulmonary interactions differently than measured cardiac index and pulmonary artery occlusion pressure. Furthermore, generalization from adult to pediatric populations may be inaccurate, particularly with respect to cardiopulmonary hemodynamics.

Limited studies have examined BNP levels in adult patients with ALI/ARDS.[9–11,14] Mitaka et al.[10] reported BNP levels above normal that were positively correlated with systemic and pulmonary vascular resistance, and negatively correlated with cardiac index in 10 patients with ALI. Three larger studies, demonstrated that low BNP levels were specific for ALI/ARDS, whereas high BNP levels were specific for cardiogenic pulmonary edema in adults presenting with acute hypoxemic respiratory failure.[9,11,14] In the largest of the studies, BNP levels were associated with in-hospital mortality irrespective of the final diagnosis.[11] In addition, recent studies found that BNP levels were useful in predicting successful weaning from mechanical ventilation in adult patients with ALI, which supports the importance of cardiopulmonary interactions.[27,28] However, to our knowledge the present study is the first to examine associations between BNP and clinical outcomes in a pediatric cohort with ALI/ARDS.

Another limitation of this study is that we did not measure BNP levels from a healthy group of children. However, several studies have documented BNP levels at different ages in normal subjects.[29,30] In these studies, mean BNP levels were highest at birth falling to ~10 pg/ ml in children >2 weeks of age, clearly lower than the mean of 109 pg/ml for children with ALI/ARDS in our study.[29,30] Our study did include three patients <28 days of age. BNP levels were not different between patients less than and greater than 28 days of age (P =0.96), and there was no correlation between age and BNP levels.

BNP levels were measured at only one point in the present study. In addition, the present pilot study did not have a sufficient sample size to establish clear cut-off values to predict the various clinical endpoints. Thus, a larger prospective study is necessary in order to establish the prognostic value of a single BNP level in a given patient. Indeed, it would be

useful in future investigations to measure BNP levels over time in ALI patients in order to track the correlation of BNP with clinical improvement or deterioration.

In the present study, BNP levels were highest in patients with sepsis associated ALI/ARDS. This finding is consistent with other studies that reported markedly elevated BNP and NT-BNP levels in patients with sepsis, including children.[31–34] Importantly, the associations with outcome for the cohort remained significant when these patients were removed from the analysis (data not shown). Furthermore, BNP levels were higher in patients with indirect lung injury compared to patients with direct lung injury, which included pneumonia, aspiration, and near drowning. While the data do not provide the mechanisms responsible for this difference, it is interesting to speculate that indirect lung injury is accompanied by more global organ dysfunction, including cardiac involvement that results in increased BNP levels.

The results of this study add to a growing literature on biological markers for prognosis in ALI/ARDS. A recent study found that elevated plasma von Willebrand factor antigen levels predicted mortality and prolonged mechanical ventilation in children with ALI/ARDS.[35] Other biomarkers with potential value include intercellular adhesion molecule-1, inflammatory cytokines such as interleukin-1 and -8, as well as markers involved in coagulation and fibrinolysis, such as protein C, plasminogen-activation inhibitor-1, and procollagen peptide III.[15,36–44] In fact, a combination of several biomarkers with other clinical predictors may prove to have superior prognostic value compared to single indicators. However, we believe that BNP is unique since it is so directly related to cardiac function and has a relatively short half-life, qualities that may permit the use of BNP for targeted therapy.

CONCLUSIONS

In this pilot study, BNP levels were elevated in children with ALI/ARDS early in the disease course, and were associated with worse clinical outcome. We believe that these data warrant a larger prospective study to confirm these findings, ultimately in order to determine whether point-of-care BNP measurements might allow clinicians to identify and treat patients particularly affected by adverse cardiopulmonary interactions.

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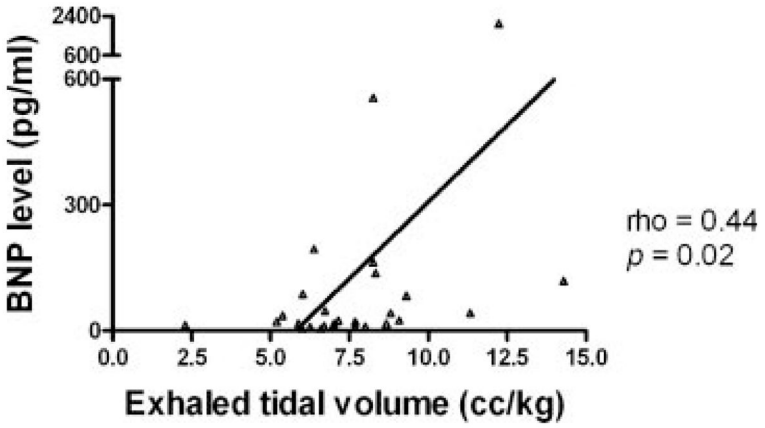

Fig. 1.

Scatter plot showing the relationship between BNP levels and exhaled tidal volume. Higher BNP levels were associated with higher exhaled tidal volumes.

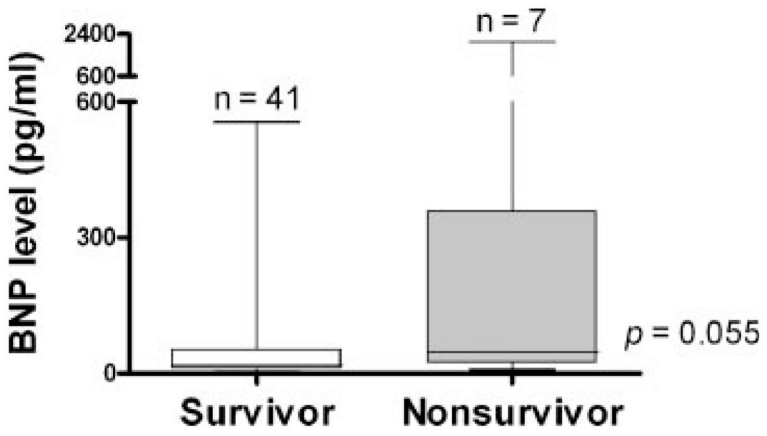

Fig. 2.

Box plots showing the relationship of BNP to 28-day mortality. Boxes represent 25th to 75th percentile range, with the midline indicating the median; I-bars represent the highest and lowest values.

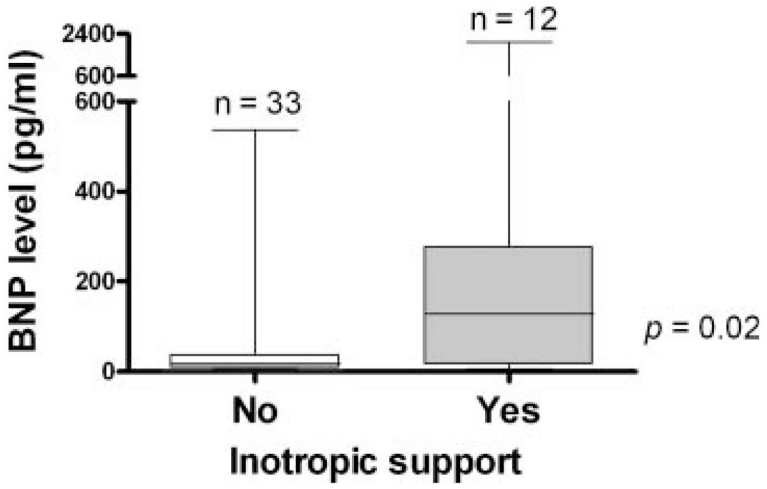

Fig. 3.

Box plots showing the relationship of BNP to the need for inotropic support. BNP levels were higher in patients who required inotropic support. Boxes represent 25th to 75th percentile range, with the midline indicating the median; I-bars represent the highest and lowest values.

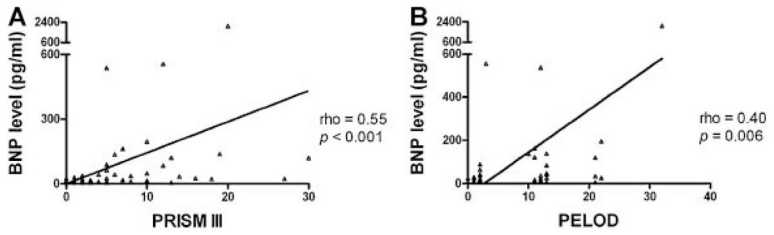

Fig. 4.

Scatter plots showing the relationship between BNP levels and PRISM III scores (A) and PELOD scores (B). Higher BNP levels were associated with higher PRISM III and PELOD scores.

TABLE 1

Characteristics of Pediatric Patients With ALI

No. Admissions with ALI	**48**
Median age, years (range)	4.2 (0–18)
Male, n (%)	22 (46%)
Ethnicities, n (%)	
Caucasian	21 (44%)
African American	8 (17%)
Hispanic/Latino	13 (27%)
Asian	4 (8%)
Other	2 (4%)
PaO_2/FIO_2 at ALI onset, mean ± SD	155 ±74
Peak inspiratory pressure, cmH_2O, mean ± SD	28.1 ±9.4
Peak end expiratory pressure, cmH_2O, mean ± SD	6.5 ±2.8
Adjusted exhaled tidal volume, cc/kg, mean ±SD	7.4 ±2.7
Need for inotropic support	12 (24%)
PRISM III score, mean ±SD	7.2 ±7.1
PELOD score, mean ±SD	8 ±7.7
Ventilator-free day, mean ±SD	18.4 ±9.5
PICU mortality	7 (15%)