B-Type Natriuretic Peptide in the Emergency Diagnosis of Critical Heart Disease in Children

Kevin O. Maher, MD, Heather Reed, BS, Angel Cuadrado, MD, Janet Simsic, MD, William T. Mahle, MD, Michael DeGuzman, MS, Traci Leong, PhD, Subhankar Bandyopadhyay, MD

OBJECTIVE. The initial presentation of congenital and acquired heart disease in children can present a diagnostic challenge. We sought to evaluate B-type natriuretic peptide as a marker of critical heart disease in children at presentation in the acute care setting.

METHODS. A cohort of 33 pediatric patients with newly diagnosed congenital or acquired heart disease had B-type natriuretic peptide levels obtained on hospital admission after evaluation in an acute care setting. Patients were admitted from March 2005 through February 2007. A noncardiac cohort of 70 pediatric patients who presented with respiratory or infectious complaints had B-type natriuretic peptide levels obtained during emergency department evaluation. A comparison of B-type natriuretic peptide results was performed.

RESULTS. Cardiac diagnoses included cardiomyopathy (14), left-sided obstructive lesions (12), anomalous left coronary artery from the pulmonary artery (4), total anomalous pulmonary venous return (2), and patent ductus arteriosus (1). Cardiac cohort mean age at presentation was 33.6 months. The 33 patients with new cardiac diagnoses had a mean B-type natriuretic peptide level of 3290 pg/mL (SD: ±1609; range: 521 to >5000 pg/mL). The 70 noncardiac patients’ mean age at presentation was 23.1 month, and mean B-type natriuretic peptide level was 17.4 pg/mL (SD: ±20; range: <5 to 174 pg/mL).

CONCLUSIONS. B-type natriuretic peptide levels were markedly elevated at presentation in the acute care setting for all patients in this cohort of children with newly diagnosed congenital or acquired heart disease. B-type natriuretic peptide levels from noncardiac patients were significantly lower, with no overlap to the cardiac disease group. B-type natriuretic peptide level can be useful as a diagnostic marker to aid in the recognition of pediatric critical heart disease in the acute care setting. Pediatrics 2008;121:e1484–e1488

Congenital and acquired heart disease contributes significantly to the disease-related morbidity and mortality in children, especially in the first year of life. The recognition of heart disease in children can be challenging, because children often have a limited repertoire of presenting signs and symptoms. Many cardiac disease states can mimic the more common illnesses of childhood, such as bronchiolitis, reactive airway disease, and sepsis. The diagnosis of heart disease can be especially difficult when children present at institutions that do not specialize in pediatric health care and are without ready access to pediatric echocardiography. In 2004, $1.73 billion was awarded in pediatric malpractice claims. The most common cause for litigation was failure to diagnose, followed by improper management and delay in diagnosis. Both pediatric patients and their health care practitioners would benefit from a sensitive marker to aid in the recognition of heart disease in children.

In the past 25 years, numerous investigations have evaluated the role of B-type natriuretic peptide (BNP) in heart disease. Increasing experience with BNP in pediatric heart disease has led to greater interest in this protein as a potential marker of heart disease in children. BNP is part of a family of natriuretic peptides that affect the cardiovascular system. The natriuretic peptides are produced primarily by myocardial tissue in response to wall stress, modifying vascular tone, and volume homeostasis. BNP activates the membrane-bound guanylate cyclase-A...
receptor, with resultant smooth muscle and cardiac myocyte relaxation properties. In adults, the use of BNP has been well demonstrated to be an accurate marker of cardiac disease and can be beneficial in differentiating pulmonary from cardiac disease in the acute care setting. Numerous studies showed elevated BNP and NT-pro BNP levels in many types of pediatric heart disease; however, no previous reports have evaluated BNP levels at initial presentation of pediatric critical heart disease in the emergency setting. We sought to evaluate BNP as a marker of pediatric critical heart disease in the acute care setting and to compare these BNP findings with noncardiac pediatric patients who also presented in the emergency care setting.

METHODS

Two cohorts of children were evaluated. The cardiac cohort consisted of children who presented to emergency departments (EDs) or PICUs and NICUs in the greater Atlanta, Georgia, area and were subsequently transferred to Children’s Healthcare of Atlanta for diagnosis and management of critical heart disease. None of the patients carried a diagnosis of heart disease before acute care presentation; heart disease was diagnosed in the acute care setting or on transfer to our institution. Patients were transferred to a dedicated pediatric cardiac ICU for evaluation and treatment of congenital and acquired heart disease. Nonsurgical indications for cardiac ICU admission included congenital and acquired heart disease with hemodynamic or respiratory instability. Patients received inotropic support, invasive monitoring, prostaglandin therapy, treatment of arrhythmias, and/or respiratory support on the basis of the diagnosis and condition. Critical heart disease was defined as patients who required intensive care admission for management of their disease. Patients who presented with cyanosis or heart murmur in isolation were excluded. BNP level, lactate, metabolic laboratory values, arterial blood gases, and complete blood counts were routinely obtained for new patients with cardiac compromise on admission to the cardiac unit. Diagnosis of heart disease was made by echocardiography in all cases, with additional imaging by cardiac catheterization in selected cases. Patients were admitted between March 2005 and February 2007.

The second cohort of children served as the noncardiac group. Investigators in the ED identified patients who presented with complaints that were respiratory or infectious in nature. A group of 70 prospectively enrolled patients had BNP levels drawn after informed consent was obtained. Patients were eligible for participation when blood was being drawn as part of the ED evaluation for respiratory or infectious disease and no previous diagnosis of heart or other chronic disease existed. BNP results were not reported to the ED clinicians and were not part of the medical chart. Patients were prospectively enrolled between April 2006 and April 2007.

Children’s Healthcare of Atlanta and Emory University institutional review boards’ approval was obtained before initiation of both the prospective and the retrospective parts of the study. Informed consent was obtained for the prospective component of the study. Dr Leong performed the statistical analysis.

BNP levels for all patients were run on the Triage Biosite rapid assay system (Biosite, San Diego, CA). The assay uses a fluorescent immunoassay for determination of BNP levels. Control standards are to test for accuracy of BNP results per manufacturer recommendations. Previous studies have demonstrated the accuracy and clinical characteristics of this assay. Blood samples were obtained in potassium-EDTA tubes and transported to the laboratory for testing. The assay range was 5 to 5000 pg/mL.

Statistical Analysis

The BNP assay is able to detect values between 5 and 5000 pg/mL. Any value of < 5 was recorded as “5” and any value > 5000 was recorded as “5000” for statistical evaluation. Because of the nonnormality of the distribution of BNP, the Mann-Whitney test was used to compare 2 patient groups with respect to the continuous end point, BNP level. For the 3-group comparison (acquired heart disease, congenital heart disease, nonheart disease), the Kruskal-Wallis test was used to compare BNP levels. P < .05 was considered statistically significant.

RESULTS

In the cardiac cohort, patients ranged in age from 2 days to 17.5 years. The mean BNP level was 3290 ± 1609 pg/mL for all cardiac patients. Fifty-seven percent (19 of 33) had congenital heart disease, and 43% (14 of 33) had acquired heart disease (cardiomyopathy; Table 1, Fig 1). Patients with congenital heart disease had a mean BNP level of 3624 ± 1512 pg/mL, and patients with acquired heart disease had a mean BNP level of 2837 ± 1681 pg/mL (Table 1, Fig 1). Patients with congenital heart disease were younger (mean age: 2.1 months; median: 0.33 months; range: 2 days to 25 months). Patients with acquired heart disease had a mean age of 76 months (median: 14.8 months; range: 3 days to 17.5 years).

Among the 33 patients in the heart disease cohort, there were numerous visits to health care providers in pediatric and adult EDs, pediatric inpatient wards, and outpatient offices in the weeks preceding cardiac diagnosis. Chief complaints included fussiness, fatigue, poor feeding, shortness of breath, swelling of the lower extremities, weakness, and “not looking well.” Initial noncardiac diagnoses for these health care visits included viral illness, nephrotic syndrome, colic, sepsis, and pneumonia. Two deaths occurred in the cardiac cohort, both patients having had recent evaluations before diagnosis and admission. One patient, a 2-year-old child with Down syndrome, presented with right heart failure, severe pulmonary hypertension, and a large patent ductus arteriosus (PDA). The second child, a 14-year-old boy, presented with cardiovascular instability secondary to a dilated cardiomyopathy. He had a rapid decline on admission and had cardiovascular collapse. Both patients had evidence of end-organ dysfunction at presentation with serum urea nitrogen levels of 34 and 90 mg/dL,
liver enzyme elevation aspartate aminotransferase levels of 1149 and 2995 U/L, lactic acid levels of 24 and 51 mg/dL, prothrombin times of 29 seconds and 25 seconds, international normalized ratios of 2.6 and 2.0, and creatinine levels of 2.0 and 2.7 mg/dL for the 2 patients, respectively.

In the noncardiac group, chief complaints included fever, cough, shortness of breath, congestion, fatigue, vomiting/diarrhea, dizziness, abdominal pain, and cold symptoms. Patients were evaluated and treated in the pediatric ED at Children’s Healthcare of Atlanta. There were no diagnoses of heart disease on discharge from the hospital or on most recent follow-up. Mean age was 23.1 ± 19 months (median: 20 months; range: 3 days to 72 months). Noncardiac patients had a mean BNP level of 17.4 pg/mL (range: <5 to 174 pg/mL; Table 1, Fig 1). One patient had a BNP level of >100 pg/mL. This patient was admitted to the PICU with reactive airway disease. Echocardiography demonstrated normal cardiac structure and function. Two patients were initially enrolled in

**TABLE 1**  Patients’ BNP Result by Cardiac Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Age</th>
<th>BNP, pg/mL</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarctation</td>
<td>7</td>
<td>9 d</td>
<td>10 d</td>
<td>2 to 16 d</td>
<td>3499</td>
<td>3499</td>
</tr>
<tr>
<td>ALCAPA</td>
<td>4</td>
<td>2 mo</td>
<td>4 mo</td>
<td>0.17 to 4.5 mo</td>
<td>3622</td>
<td>3335</td>
</tr>
<tr>
<td>Interrupted aortic arch</td>
<td>3</td>
<td>3 d</td>
<td>2 d</td>
<td>2 to 5 d</td>
<td>3730</td>
<td>3260</td>
</tr>
<tr>
<td>TAPVR</td>
<td>2</td>
<td>1.7 mo</td>
<td>1.7 mo</td>
<td>0.7 to 2.7 mo</td>
<td>2095</td>
<td>2095</td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>2</td>
<td>5 d</td>
<td>5 d</td>
<td>2 to 8 d</td>
<td>4920</td>
<td>4920</td>
</tr>
<tr>
<td>PDA/PH/cardiomyopathy *</td>
<td>1</td>
<td>25.5 mo</td>
<td>25.5 mo</td>
<td>25.5 mo</td>
<td>5000</td>
<td>5000</td>
</tr>
<tr>
<td>All congenital</td>
<td>19</td>
<td>2.1 mo</td>
<td>0.33</td>
<td>2 d to 25.5 mo</td>
<td>3624</td>
<td>4430</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>14</td>
<td>76 mo</td>
<td>6 mo</td>
<td>3 d to 17.5 y</td>
<td>2837</td>
<td>2360</td>
</tr>
<tr>
<td>All cardiac patients</td>
<td>33</td>
<td>33 mo</td>
<td>2.2 mo</td>
<td>2 d to 17.5 y</td>
<td>3290</td>
<td>3260</td>
</tr>
<tr>
<td>Noncardiac patients</td>
<td>70</td>
<td>23 mo</td>
<td>20 mo</td>
<td>3 d to 72 mo</td>
<td>17.4 ± 20.0</td>
<td>19</td>
</tr>
</tbody>
</table>

ALCAPA indicates anomalous left coronary artery from the pulmonary artery; TAPVR, total anomalous pulmonary venous return; PH, pulmonary hypertension.

* The BNP was level obtained on hospital day 3, not on admission.

**FIGURE 1**  BNP level (pg/mL) for the 3 patient groups. Boxes show interquartile ranges, and the I bars represent the highest and lowest values. BNP levels in the congenital heart disease and acquired heart disease cohorts are markedly elevated when compared with the noncardiac patients. There is no overlap in BNP values from the noncardiac patients to either cardiac cohort.
the ED as noncardiac cohort patients who were subsequently removed because of a diagnosis of chronic disease (dermatomyositis) for 1 patient (BNP: 223 pg/mL) and previously diagnosed congenital heart disease (PDA) for the other (BNP: 418 pg/mL). Using a cutoff BNP value of 100 pg/mL to identify heart disease, a sensitivity of 100% and specificity of 98% were present for these 2 cohorts of patients.

DISCUSSION
The normal BNP level varies with age, with the largest value of 100 pg/mL to identify heart disease, a sensitivity for the other (BNP: 418 pg/mL). Using a cutoff BNP levels have been demonstrated to be a sensitive and specific marker for PDA and pulmonary hypertension of BNP levels in patients with milder forms of heart disease, not before presentation; it was not used as a screening tool. The noncardiac cohort of patients were not as sick as the cardiac patients. A more critically ill control population may have a higher BNP level on admission, potentially decreasing specificity of BNP. Of note, a study by Fried et al31 of children who presented with severe sepsis versus heart disease had a 10 times higher BNP level in the cardiac group, and 2 studies of pediatric heart disease versus pneumonia24,25 also demonstrated a marked elevation in BNP levels for cardiac versus noncardiac pediatric patients.

Neonates in the first days of life can have elevated BNP levels that could decrease specificity of the assay for cardiac disease, especially in the first 24 hours of life. We have not proved that a normal BNP level rules out cardiac disease. The use of BNP in the newborn nursery to screen for heart disease was not studied. BNP for serial measurement to determine ongoing severity was also not evaluated in this study.

BNP levels in patients with milder forms of heart disease or earlier presentation of critical heart disease may not have a marked elevation of BNP. Patients with cyanotic lesions such as transposition of the great arteries were not evaluated, and BNP results at the presentation of these diseases are unknown.

CONCLUSIONS
The ability for physicians to recognize and treat cardiac disease promptly is of paramount importance in both
adults and children, with potential impact on the short- and long-term morbidity and mortality. This study, along with numerous other previously published reports, has demonstrated the elevation of B-type natriuretic peptide in many types of pediatric heart disease. In this cohort of pediatric patients with hemodynamically significant congenital and acquired heart disease, BNP was markedly elevated in all cardiac patients, with no overlap to the noncardiac BNP levels. BNP can be a useful marker to aid in the emergency diagnosis of pediatric critical heart disease in the acute care setting.

REFERENCES


Downloaded from http://pediatrics.aappublications.org/ by guest on October 30, 2017
B-Type Natriuretic Peptide in the Emergency Diagnosis of Critical Heart Disease in Children

Kevin O. Maher, Heather Reed, Angel Cuadrado, Janet Simsic, William T. Mahle, Michael DeGuzman, Traci Leong and Subhankar Bandyopadhyay

*Pediatrics* 2008;121:e1484
DOI: 10.1542/peds.2007-1856

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/121/6/e1484