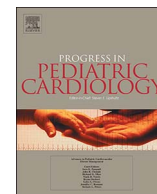




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Serial assessment of brain natriuretic peptide in single ventricle patients with a hybrid stage 1 palliation

Christina M. Phelps^{a,b}, Corey Stiver^{a,b}, Tracy Heard^b, Karen M. Texter^{a,b}, Andrew R. Yates^{a,b,c,*}

^a The Ohio State University, Department of Pediatrics, Nationwide Children's Hospital, United States

^b The Ohio State University, Section of Cardiology, Nationwide Children's Hospital, United States

^c The Ohio State University, Section of Critical Care, Nationwide Children's Hospital, United States

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ABSTRACT

Brain natriuretic peptide (BNP) has been used as a marker for heart failure. Cross-sectional studies have documented differences in BNP levels in patients with single ventricle physiology but the utility of longitudinal samples has not been established. We hypothesized that change in BNP would correlate with change in clinical status in single ventricle patients palliated with a hybrid stage 1 palliation. Retrospective Ross heart failure score, inotrope score, lactate, and creatinine were obtained at time of each BNP. Events requiring CPR or intubation were noted in relationship to BNP. Data was analyzed with non-parametric statistics with $p < 0.05$ considered significant.

14 patients (11 with serial values) had BNP values obtained primarily in the inpatient setting between 9/2010 and 9/2012. BNP values were obtained at a median age of 38 days (range 1–170 days) in patients with hypoplastic left heart palliated with a hybrid palliation. There was no correlation between BNP and inotrope score, age at time of BNP or systemic saturation. BNP correlated with lactate ($p = 0.002$, $r^2 = 0.12$) and Ross score ($p < 0.0001$, $r^2 = 0.25$). BNP values were greater in patients with an elevated lactate (median 3980 pg/ml, range 565–4500 vs. 1213 pg/ml, range 94–4500, $p = 0.0003$) or if related to an arrest or intubation (median 4500 pg/ml, 364–4500 vs. 1536 pg/ml, 94–4500, $p < 0.0001$). A change in BNP value was associated with a change in Ross score ($p < 0.0001$, $r^2 = 0.19$).

We conclude that serial measurements of BNP values may help to predict worsening heart failure in infants with single ventricle physiology palliated by a hybrid stage 1 procedure.

1. Introduction

Non-invasive assessment of cardiac function in single ventricle patients is limited by the challenges of quantification of right ventricular (RV) function with echocardiography. Cardiac Magnetic Resonance Imaging (cMR) can quantify RV function accurately, but often requires general anesthesia in the infant patient population [1,2]. Serum biomarkers, such as brain natriuretic peptide (BNP), while more invasive than echocardiography, may be useful to identify changes in cardiac volume and function and may help to guide therapies.

BNP is a hormone released in response to myocardial pressure overload, volume overload, and increased wall stress. In the adult population, BNP is an accepted part of heart failure diagnosis and management. The utilization of natriuretic peptides is a class 1A recommendation for both the diagnosis and prognosis of heart failure in the ambulatory setting in adults [3]. BNP is less well studied within the

pediatric population. The largest congenital heart disease populations where BNP studies are available are in adult survivors of tetralogy of Fallot, those patients with systemic right ventricle (i.e. after mustard repair) or in single ventricle patients with Fontan physiology [4–6]. There are very few reports of using BNP in infants with palliated single ventricle physiology where the systemic ventricle is volume loaded at baseline.

BNP and NT-BNP have been proposed as additions to heart failure classification guidelines given the correlation with clinical findings [7]. Nonetheless, none of these rating methodologies have taken into account the features of single ventricle patients and their palliation. Given that there is a relationship between clinical findings of heart failure in children and BNP levels, we hypothesized that a change in BNP would correlate with a change in clinical heart failure score in infants palliated with a Hybrid stage I procedure. Our secondary objective was to examine whether a significant clinical deterioration in patient status was

* Corresponding author at: The Heart Center, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, United States.

E-mail addresses: Christina.phelps@nationwidechildrens.org (C.M. Phelps), Corey.stiver@nationwidechildrens.org (C. Stiver), Tracy.heard@nationwidechildrens.org (T. Heard), Karen.Texter@nationwidechildrens.org (K.M. Texter), Andrew.yates@nationwidechildrens.org (A.R. Yates).

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related to BNP levels.

2. Methods

After IRB approval, we retrospectively reviewed all BNP values obtained in single ventricle patients palliated with a hybrid stage 1 procedure at our institution between 9/2010 and 9/2012. We identified patients palliated with hybrid stage 1 procedure from our cardiothoracic surgical database and queried the electronic medical record for all patients with BNP values. Additionally, we collected clinical data including demographic information, systemic saturation, vasoactive-inotrope score [8], serum lactate, and creatinine values at the time point closest to the BNP level. Serum lactate of < 2.2 pg/ml was considered normal with any value > 2.2 pg/ml was elevated.

Echocardiograms performed on the day a BNP value was drawn were evaluated for findings of decreased function or changes in volume load quantitatively via RV fractional area of change and RV end diastolic volume. Additionally, RV function and tricuspid valve regurgitation were qualitatively assessed per standard echocardiographic criteria. All measurements were performed in triplicate and averages utilized for analysis. The investigator reviewing echocardiographic data was blinded to the BNP values.

We retrospectively calculated a Ross heart failure score for infants using data extracted from clinical documentation [9]. Physiologic parameters were scored based upon the electronic medical record at the time closest to the obtained BNP sample. Physical exam findings were scored based on clinical documentation for the day by the attending cardiologist or cardiac intensivist depending on location of the patient. Our institutional practice in children who are ill with heart failure symptoms is to provide tube feedings for nutrition if tolerated and thus many of our patients lacked values for the feeding portion of the composite Ross score. Infants were classified as no heart failure (Ross score of ≤ 2), mild heart failure (Ross score 3–6), or moderate to severe heart failure (Ross score > 7).

The BNP was considered to be “linked” to a clinically significant decompensation if the BNP value was obtained within 24 h prior to or after that event. Clinically significant events were defined as either a cardiac arrest or an endotracheal intubation not related to a procedure.

All values were entered into Excel spreadsheet and analyzed with Prism 6 (Graphpad Software, San Diego, California). Associations between demographic variables and BNP levels were analyzed by linear regression. Comparisons between groups were performed with Mann-Whitney U test for non-parametric testing with $p < 0.05$ considered significant.

3. Results

A total of 90 BNP values were reviewed in 14 patients palliated with a hybrid stage 1. The maximum BNP value reported at our institution at the time of the study was 4500 (pg/ml). The median age of patients at the time of BNP sampling was 38 days (range 1–170 days). All patients had a systemic right ventricle with a diagnosis of hypoplastic left heart (5/14 with aortic and mitral atresia, 5/14 with aortic and mitral stenosis, 4/14 with mitral stenosis and aortic atresia).

BNP values were not related to age ($p = 0.45$), inotropic support ($p = 0.55$) or systemic saturation ($p = 0.33$). BNP weakly correlated with lactate ($p = 0.002$, $r^2 = 0.12$) and Ross score ($p < 0.0001$, $r^2 = 0.25$). There was a weak association between BNP value and serum creatinine value ($p = 0.01$, $r^2 = 0.09$) for the 69 paired samples able to be analyzed.

Echocardiographic measurements were available for 23 BNP values. There was no correlation between BNP and RV fractional area of change ($p = 0.94$), RV diastolic volume ($p = 0.54$), degree of Tricuspid valve regurgitation ($p = 0.99$), or qualitative assessment of RV function ($p = 0.54$).

BNP values were able to differentiate between those patients

BNP Stratified by Ross Score

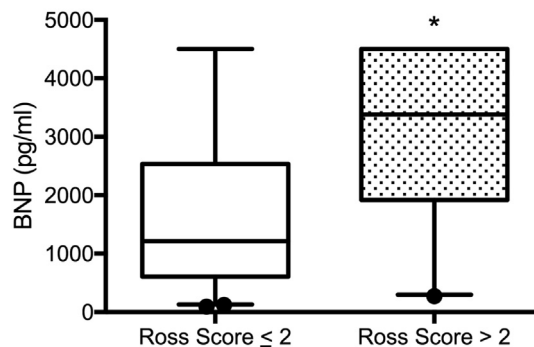


Fig. 1. BNP values in patients without heart failure symptoms (Ross score < 2) compared to those patients with heart failure symptoms (Ross score ≥ 2). *Indicates $p \leq 0.0001$.

without heart failure symptoms (Ross score ≤ 2) and those with heart failure symptoms (median 1213 pg/ml range 94–4500 vs. median 3379 pg/ml range 271–4500, $p < 0.0001$) (Fig. 1). In the setting of decompensated heart failure, anaerobic metabolism leads to lactic acidosis, and those patients with a lactate level greater than the upper limit of normal for our clinical assay (> 2.2 pg/ml) had a higher BNP level greater than those with a lactate value within the normal range (median 3980 pg/ml, range 565–4500 vs. 1213 pg/ml, range 94–4500, $p = 0.0003$) as demonstrated by Fig. 2. Similarly, BNP values obtained within 24 h of an adverse event (non-elective intubation or cardiac arrest) were higher than BNP values obtained at other times (median 4500 pg/ml, 364–4500 vs. 1536 pg/ml, 94–4500, $p < 0.0001$) as shown in Fig. 3.

11 patients had multiple BNP values obtained which allowed for evaluation of the change in BNP value compared to the change in Ross score. Fig. 4 demonstrates the associated change in BNP values with the change in Ross score ($p < 0.0001$, $r^2 = 0.19$). A decrease in the BNP was associated with a similar decrease in the Ross score as well as an increased BNP value was associated with worsening Ross score.

4. Discussion

BNP has been reported to differentiate a shock state in unrepaired patients with left sided obstructive lesions upon presentation (1–3 days of age) with patients in shock demonstrating a median BNP of 4100 pg/ml compared to a median of 656 pg/ml in those without shock [10]. Lowenthal and colleges assessed BNP and NT-BNP in a cross-sectional

Difference in BNP values based on Serum Lactate

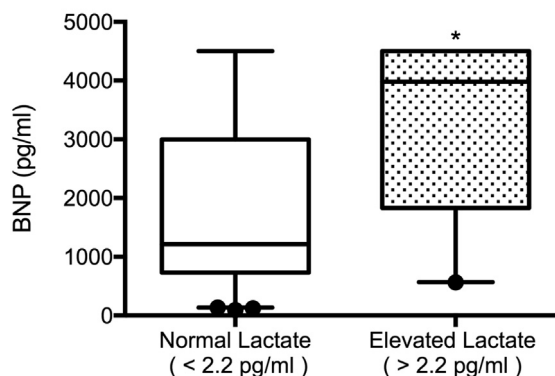


Fig. 2. BNP values in patients with and without elevated lactate (> 2.2 pg/ml). *Indicates $p = 0.0002$.

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