B-type Natriuretic Peptide: Perioperative Patterns in Congenital Heart Disease

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ABSTRACT

Objective. B-type natriuretic peptide (BNP) has diagnostic, prognostic, and therapeutic roles in adults with heart failure. BNP levels in children undergoing surgical repair of congenital heart disease (CHD) were characterized broadly, and distinguishable subgroup patterns delineated.

Design. Prospective, blinded, observational case series.

Setting. Academic, tertiary care, free-standing pediatric hospital.

Patients. Children with CHD; controls without cardiopulmonary disease.

Interventions. None.

Measurements. Preoperative cardiac medications/doses, CHD lesion types, perioperative BNP levels, intraoperative variables (lengths of surgery, bypass, cross-clamp), postoperative outcomes (lengths of ventilation, hospitalization, open chest; averages of inotropic support, central venous pressure, perfusion, urine output; death, low cardiac output syndrome (LCOS), cardiac arrest; readmission; and discharge medications).

Results. Median BNP levels for 102 neonatal and non-neonatal controls were 27 and 7 pg/mL, respectively. Serial BNP measures from 105 patients undergoing CHD repair demonstrated a median postoperative peak at 12 hours. The median and interquartile postoperative 24-hour average BNP levels for neonates were 1506 (782–3784) pg/mL vs. 286 (169–578) pg/mL for non-neonates ($P < 0.001$). Postoperative BNP correlated with inotropic requirement, durations of open chest, ventilation, intensive care unit stay, and hospitalization ($r = 0.33$–0.65, all $P < 0.001$). Compared with biventricular CHD, Fontan palliations demonstrated lower postoperative BNP (median 150 vs. 306 pg/mL, $P < 0.001$), a 3-fold higher incidence of LCOS ($P < 0.01$), and longer length of hospitalization (median 6.0 vs. 4.5 days, $P = 0.01$).

Conclusions. Perioperative BNP correlates to severity of illness and lengths of therapy in the CHD population, overall. Substantial variation in BNP across time as well as within and between CHD lesions limits its practical utility as an isolated point-of-care measure. BNP commonly peaks 6–12 hours postoperatively, but the timing and magnitude of BNP elevation demonstrates notable age-dependency, peaking earlier and rising an order of magnitude higher in neonates. In spite of higher clinical acuity, non-neonatal univentricular CHD paradoxically demonstrates lower BNP levels compared with biventricular physiologies.

Key Words. Natriuretic Peptides; Congenital Heart Defects; Congestive Heart Failure; Low Cardiac Output; Perioperative Care; Nesiritide

Introduction

As a diagnostic test, B-type natriuretic peptide (BNP) levels are sensitive and specific for the presence and magnitude of congestive heart failure (CHF) in adults and children, being elevated in settings of systolic and diastolic dysfunction, both acute and chronic.[1,2] BNP is a prognostic marker for common endpoints in adult and pediatric CHF—including readmission rates, lengths of stay, mortality, and other untoward outcomes.[3–9] The

recent availability of point-of-care BNP assays and therapeutic BNP (nesiritide) has stimulated a great deal of contemporary research. Several reviews have recently been undertaken in pediatrics that acknowledge that perturbations of the natriuretic hormone system are common in the settings of critical illness and congenital heart disease (CHD) but assert that further investigation is needed before this measure is of practical utility in these populations.[10–16]

As a therapeutic agent, human recombinant BNP (hrBNP) has been used to treat adults and children with decompensated CHF, demonstrating some improvements in cardiac performance.[17–19] While garnering early enthusiasm, several studies subsequent to Food and Drug Administration approval have questioned the safety of therapeutic hrBNP, noting possible increased risks of renal dysfunction and mortality.[20–22] A prospective study of hrBNP in adults is expected to be completed in 2010 and should inform current safety concerns.[23]

While extrapolations might be reasonably made from adult CHF populations to children with anatomically normal but failing hearts, less is known about the utility of BNP in the perioperative management of children undergoing repair of CHD. Because of the numerous congenital cardiac defects, intracardiac shunting, complex pressure-volume loading, as well as the marked physiologic elevation in the neonatal period, BNP may well have conditional validity and variable cutoffs as a marker for cardiac function in specific types of CHD.[8,9,11,24–29]

The literature regarding BNP in CHD has largely been descriptive, demonstrating broad correlations to severity of illness and adverse clinical outcomes, and also suggesting possible cutoff points for risk stratification. However, there remains little data to suggest how measuring BNP levels could guide perioperative decision making or therapy in any practical sense.[13,14,24,30–34] Therefore, we sought to look at similar perioperative CHD BNP data from a different vantage point. Beyond further characterization of perioperative BNP levels generally, our efforts were aimed at identifying circumstances where BNP levels appeared disproportionately low relative to the clinical severity of CHF compared with other CHD patients. Such subpopulations might theoretically benefit from administration of hrBNP based on a theragnostic rationale, possibly giving BNP a more practical role in the perioperative management of CHD.[35]

Methods

Study Design

This study was approved by an institutional review board (IRB) and was conducted at Rady Children's Hospital in San Diego, California. All the subjects' legal guardians signed a written consent. Where possible, developmentally appropriate subjects signed a written assent.

This prospective observational study enrolled subjects from birth through 22 years of age with any congenital heart lesion undergoing open surgical repair. For a normative control group, a convenience blood sample was obtained and BNP measured in children without cardiopulmonary disease who were undergoing sedation or general anesthesia for minor procedures or imaging. For a surgical stress control group, BNP was measured before and after prolonged, intensive surgeries in children without cardiopulmonary disease. Patients, surgeons, and anesthesiologists were blinded to the measured BNP values of all the subjects and the controls. Operative variables were obtained, including cardiac lesion(s), surgical correction(s), and durations of surgery, cardiopulmonary bypass, and aortic cross-clamp. These subjects were comanaged postoperatively in two separate care units—the Pediatric Intensive Care Unit (PICU) and the Neonatal Intensive Care Unit (NICU)—based on age. Cardiology and cardiothoracic surgical teams were the same, but intensivists and support staff differed in these ICUs.

Blood samples were analyzed for BNP using the Triage Meter (Biosite, Inc., San Diego, CA, USA) in accordance with the product insert. In the main study group, BNP was measured at the following times: preoperatively, on arrival to the intensive care unit postoperatively, every 6 hours for 24 hours, daily through postoperative day number 5, before and after specified events (e.g., extubation, extra-corporeal membrane oxygenation (ECMO) initiation, chest closure, operative revisions), and upon exiting the ICU or becoming non-ICU status. Samples were no longer obtained after the patients left the ICU, even if this occurred before postoperative day number 5. For comparative and statistical purposes, the following isolated and composite BNP measures were established for each patient: preoperative BNP, peak BNP postoperatively, 24-hour average BNP postoperatively, and maximum positive change in BNP over 6 hours during the first postoperative day.

Clinical data were obtained with each postoperative BNP sample, including urine output, central venous pressure (CVP), clinical perfusion assessment by nursing, and cardiovascular medications with doses. Composite scores were created from serial data obtained on postoperative day 1. These composite postoperative outcome measures included daily averages of clinical perfusion, inotropic support, and CVP. Perfusion was scored 0–4 points for each of three aspects routinely charted by the bedside nurse in all cardiac patients— capillary refill, peripheral pulses, and extremity temperature—for a total range of 0–12. An inotropic score with a potential range of 0–8 was devised based on the number of four agents commonly used and on dose ranges reflective of local titration practice patterns (0 points if inotropic agent absent; +1 point if dopamine <5 mcg/kg/m, epinephrine <0.05 mcg/kg/m, dobutamine <5 mcg/kg/m, or milrinone ≤1 mcg/kg/m; +2 points if dopamine ≥5 mcg/kg/m, epinephrine ≥0.05 mcg/kg/m, dobutamine ≥5 mcg/kg/m, milrinone >1 mcg/kg/m). All composite scores described herein were devised strictly for analysis in this study. Low cardiac output syndrome (LCOS) was prospectively defined as 2 or more of the following clinical signs or symptoms— specifically oliguria (<0.5 mL/kg/hour), perfusion impairment (perfusion score <5), or hemodynamic impairment (CVP >15 mm Hg)—without consideration of laboratory findings.[36] Finally, open chest status, as well as lengths of mechanical ventilation, critical care status, and hospitalization, were recorded.

Between November 2003 and May 2005, a total of 221 patients were enrolled—102 normative controls, 13 surgical stress controls, and 106 congenital heart lesion repairs. One of the CHD patients was transferred to another ICU after surgery and was unable to be followed up.

Statistical Analysis

This sample was analyzed as a group and by subsets based on age, care unit, cardiac lesion, surgical repair, and final cardiac physiology. Distributions and time-vs.-BNP curves were plotted to characterize aggregate and subset samples. The distributions of BNP values were consistently asymmetric (medians lower than means) and CHD-specific subsets of the sample were relatively small. Therefore, nonparametric statistical tests were generally preferred, and data were not transformed except for graphical display. The Mann–Whitney rank-sum test was used for two sample comparisons and Wilcoxon's signed-rank test for matched pairs. Fisher's exact test was used for 2-by-2 nominal comparisons of groups. Specific associations between BNP measures, operative variables, and postoperative outcomes were prospectively sought, and where additional patterns emerged, these were explored on a post hoc basis. Corrections of *P* values were not made for multiple simultaneous tests, given the exploratory nature of the post hoc analyses. For BNP assay results outside the range of the BNP meter, the range limit was used for statistical calculations.

Results

Normative BNP levels obtained from 102 subjects from adjusted gestational age of 30 weeks through 22 years sorted clearly into two populations: neonates and preterm infants <44 weeks adjusted gestational age, and infants >4 weeks of age and older children. The difference in medians between the neonates plus preterm infants vs. all the older children was 27 vs. 7 pg/mL, respectively (*P* < 0.001). The BNP levels in non-neonatal children are low and narrowly distributed (median of 6.9 pg/mL, interquartile range of 5–13.3 pg/mL, and a maximum of 52.1 pg/mL).

Thirteen surgical stress controls ages 0.4–17 years (median 9.4 years) underwent prolonged invasive surgeries (the majority were anterior– posterior spinal fusions) with a median intraoperative duration of 3.8 hours (range 2.3–5.3 hours) and volume administration of 30 mL/kg (range 12–92 mL/kg). Median preoperative and postoperative BNP were both 6.9 pg/mL, with maximal changes of +1.3 and –6.6 pg/mL. Changes did not correlate to surgical duration or administration of volume.

Serial BNP measurements were obtained from 105 children undergoing repair of CHD. Table 1 summarizes the characteristics of this surgical cohort. The majority of the patients were cared for in the PICU (n = 91) and a minority in the NICU (n = 14). Because of the striking difference in neonatal BNP levels (not unlike the neonatal controls), statistical analyses were segregated by neonatal vs. non-neonatal status, except when comparing these two groups.

Median preoperative and postoperative BNP levels in non-neonatal CHD were 22 and 41 pg/mL (median change of +19 pg/mL, *P* < 0.001), and neonatal CHD repairs demonstrated respective levels of 2370 and 2140 pg/mL (median change of –230 pg/mL, *P* = 0.9). Age was plotted

Table 1. Descriptive Statistics of Congenital Heart Disease Subjects

Demographics	Values
Age, in years, median (range)	1.0 (0–17)
Weight, in kg, median (range)	8.4 (1.9–85)
Male : female, n (%)	64:41 (61:39)
Pediatric : neonatal intensive care unit, n (%)	91:14 (87:13)
Lesions, n (%)	105 (100)
Ventricular septal defect (VSD)	13 (12)
Tetralogy of Fallot (TOF)	12 (11)
Hypoplastic left heart syndrome (HLHS)	11 (11)
Atrio-ventricular canal (AVC)	10 (9.5)
Complex single ventricle (CSV)	8 (7.6)
Atrial septal defect (ASD)	8 (7.6)
Transposition of the great arteries (TGA)	6 (5.7)
Double-outlet right ventricle (DORV)	5 (4.8)
Tetrology of Fallot, repaired (TOF-R)	5 (4.8)
Pulmonary atresia + VSD (PA-VSD)	5 (4.8)
PA + intact ventricular septum (PA-IVS)	3 (2.9)
Atrio-ventricular canal, unbalanced (AVC-UN)	3 (2.9)
Tricuspid atresia (TA)	3 (2.9)
Others (if fewer than 3 of a lesion type)	14 (13)
Repairs, n (%)	105 (100)
Complete repair (CR)	58 (55)
Total-cavo-pulmonary anastomosis (T-CPA), all fenestrated Fontans	16 (15)
Superior-CPA (S-CPA), mainly bidirectional Glenns	7 (6.7)
Stage-1 palliation (S1P), mainly Norwoods	7 (6.7)
Arterial switch	6 (5.7)
Right ventricular outflow tract revision (RVOT-R)	5 (4.8)
Valve repair / replacement	4 (3.8)
Pulmonary arterioplasty and BT-shunt (PAP-BTS)	3 (2.9)
Outcomes	
Length of surgery, in minutes, median (range)	248 (114–807)
Length of bypass, in minutes, median (range)	119 (0–346)
Length of cross-clamp, in minutes, median (range)	51 (0–164)
Length of ventilator, in days, median (range)	1.35 (0.5–59)
Length of intensive Care, in days, median (range)	2 (1–59)
Length of hospitalization, in days, median (range)	5 (2–64)
Low cardiac output syndrome (%)	29 (28)
Extra-corporeal membrane oxygenation, n (%)	3 (2.9)
Deaths, n (%)	3 (2.9)

against 24-hour avg BNP in the CHD population, irrespective of cardiac lesion (Figure 1). BNP levels were higher in younger children, both within and between preoperative diagnostic categories, with a more marked and prolonged inverse age-dependence in CHD patients than in controls.

Of the composite BNP scores devised, the postoperative 24-hour average BNP (24-hour avg BNP) had the highest overall correlation to postoperative outcomes and was therefore the preferred BNP measure for further analysis (Table 2). The weakest correlations were between postoperative BNP and intraoperative variables, although length of surgery was significant where the durations of cardiopulmonary bypass and aortic cross-clamp were not. The postoperative peak BNP and 24-hour avg BNP both correlated significantly with all postoperative outcomes noted in Table 2, most notably, durations of open chest, ventilation, ICU stay, and hospitalization (r = 0.51–0.65, all $P < 0.001$). Preoperative BNP correlated with 24-hour avg BNP (r = 0.64, $P < 0.001$), but was a weak predictor of intraoperative and postoperative measures (r all < 0.31, where significant).

Neonates and non non-neonates demonstrated significantly different BNP levels at all points in the time measured (Figure 2). The highest postoperative BNP occurred during postoperative day 1 in 92% of the patients, but the distribution was generally a right-skewed curve, with the mode occurring at 12 hours in 48% of the non-neonates and at 6 hours in 62% of the neonates (difference in time to peak $P < 0.001$). After postoperative day 1, the neonates most commonly demonstrated BNP levels lower than their preoperative levels—a pattern opposite to the non-neonates. Peak and 24-hour avg BNP were significantly higher in the non-neonatal CHD repairs with longer ICU and hospital stays. For the entire sample, mean BNP levels tended to be approximately twice the median value, and the peak BNP on postoperative day 1 was roughly twice the postoperative 24-hour average.

The median increase in BNP from preoperative BNP to postoperative 24-hour avg BNP in the non-neonatal populations was 251 pg/mL ($P < 0.001$). Corresponding BNP levels in the neonatal CHD population were substantially higher (>1000 pg/mL difference, $P < 0.001$). The majority of BNP measurements that were in excess of the assay's upper limit (>5000 pg/mL) occurred in the postoperative neonates with CHD, decreasing sensitivity to any upward trends in this subset. Only 1 of 92 (1%) non-neonates had a peak BNP that was lower than the preoperative BNP (72 vs. 101 pg/mL, diagnosis of pulmonary atresia with ventriculoseptal defect). However, 2 of 10 (20%) neonates had a preoperative BNP greater than their postoperative peak.

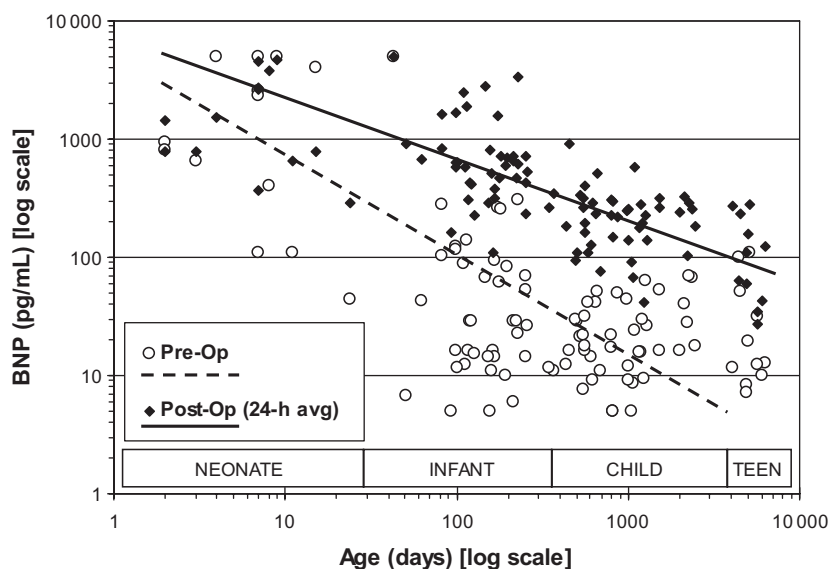Patterns of perioperative BNP expression had great variability between and within CHD lesions

Figure 1. Preoperative and postoperative 24-hour average B-type natriuretic peptide (BNP) levels vs. patient age in congenital heart disease (CHD) patients. Children of younger age demonstrate higher BNP levels. Distinct from normative controls, this age-dependence in CHD persists years into childhood, and it appears to be most pronounced in postoperative BNP levels. When analyzed within different preoperative CHD diagnostic categories, this trend persists in 10 of 13 categories preoperatively and 13 of 13 postoperatively.

Table 2. Significant Correlations between B-Type Natriuretic Peptide Measures and Other Clinical Measures in Non-Neonatal Congenital Heart Disease Subjects

B-Type Natriuretic Peptide (BNP)	Pre-Op (r)	Postoperative 24-hour Average (r)		
Non-Neonatal Population (n)	All (92)	All (92)	Biventricular (66)	Fontan (16)
Length of aortic cross-clamp	—	—	—	—
Length of cardiopulmonary bypass	—	—	—	—
Length of surgery	0.21*	0.28**	0.23*	—
POD 1 urine output	—	—	—	—
POD 1 perfusion score impairment	—	0.28*	0.37**	—
POD 1 central venous pressure	—	0.27**	0.38***	—
POD 1 inotropic support score	0.26*	0.33***	0.46***	—
Length of chest open	—	0.61***	0.55***	—
Length of ventilation	0.22*	0.51***	0.54***	—
Length of intensive care	0.29**	0.53***	0.53***	0.52*
Length of hospitalization	0.31**	0.65***	0.52***	0.51*
Discharge diuretic dose	—	0.33***	0.26*	—
Discharge ACE inhibitor dose	—	0.20*	0.32*	—

*$P < 0.04$; **$P < 0.01$; ***$P < 0.001$.
POD, postoperative day; ACE, angiotensin-converting enzyme.

(Figure 3), and BNP receiver–operator characteristic (ROC) curves were generally of weak discriminatory performance in our sample. The area under the curve (AUC) for the 24-hour avg BNP to detect LCOS was 0.61 in aggregate, 0.77 in neonates, and 0.56 in non-neonates.

Lesion-specific subsets were generally too small to perform meaningful statistical analyses. When aggregated into larger subsample categories based on stage of univentricular palliation vs. complete biventricular repairs (Figure 4),

univentricular patients demonstrated a sequential decrease in BNP levels at each stage. Median postoperative 24-hour avg BNP for univentricular patients—Stage 1 Palliations, bidirectional Glenn anastamoses, and fenestrated fontans— were, respectively, 778, 415, and 150 pg/mL, whereas the biventricular CHD repairs had a median postoperative 24-hour avg BNP of 318 pg/mL.

A post hoc comparison was made between the Fontans and the non-neonatal biventricular sub-
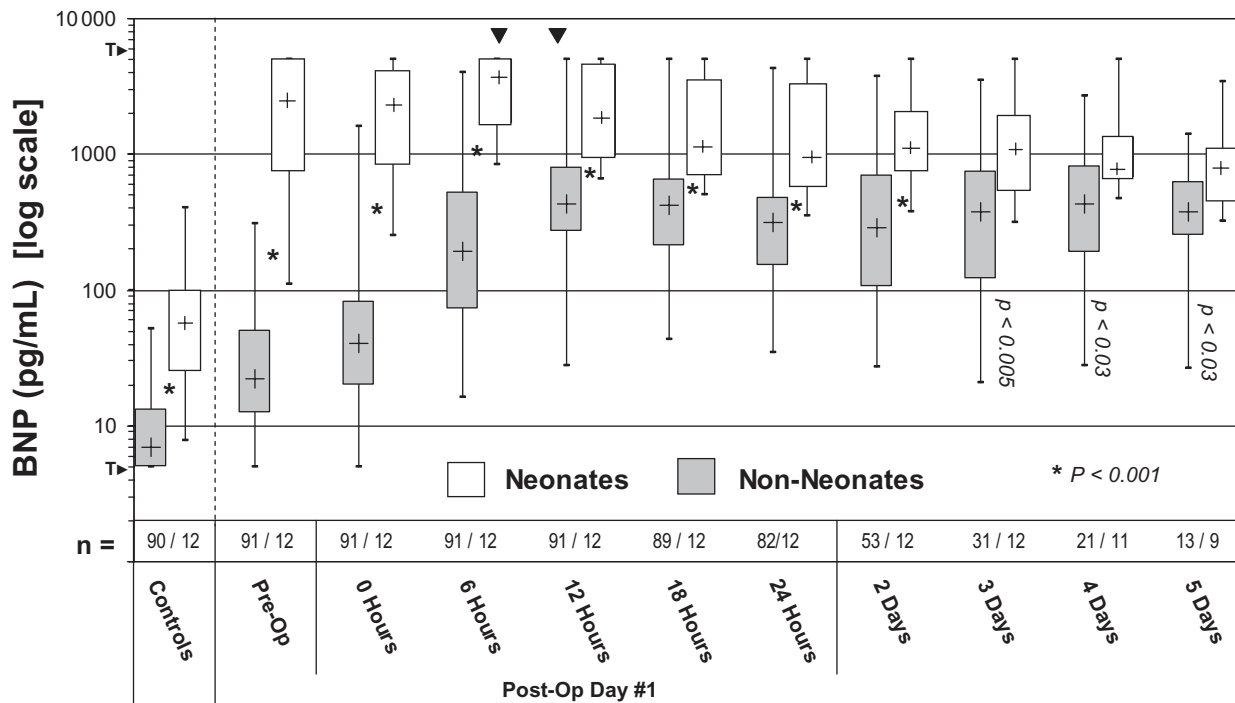
Figure 2. B-type natriuretic peptide (BNP) values across time: neonatal vs. non-neonatal congenital heart disease repairs. Neonatal and non-neonatal BNP values were distinct, both in timing of the peak and magnitude at each time point (*P* values all significant). In non-neonates, BNP levels were consistently higher in children with longer lengths of ventilation, intensive care unit (ICU) stay, and hospitalization. Later time points partly reflect patient attrition from the ICU and should not be misconstrued to represent typical individual curves, which generally demonstrated gradual reduction in BNP after the peak on postoperative day 1. The highest postoperative BNP occurred on postoperative day 1 in 92% of the patients, and the distribution was somewhat right-skewed with the mode (dark triangles) occurring at 12 hours in the pediatric ICU (48% of patients) and at 6 hours (62% of patients) in the neonatal ICU. This difference in time to peak was significant (*P* < 0.001). The two T's on the y-axis designate the upper and lower thresholds of the BNP assay.

jects (Table 3). Compared with the biventricular repairs, the Fontans demonstrated similar demographics but numerous measures of higher clinical acuity throughout the perioperative sequence—including higher doses of cardiovascular medications at admission and discharge, longer surgical time, higher inotropic requirements postoperatively, longer length of intensive care and hospitalization, and increased incidence of LCOS. The Fontan palliations demonstrated lower perioperative BNP measures than biventricular repairs—including preoperative BNP (16 vs. 23 pg/mL, *P* = 0.09), peak BNP (266 vs. 592 pg/mL, *P* < 0.001), maximal rate of rise (24 vs. 60 pg/mL/hour, *P* = 0.001), and 24-hour postoperative average (150 vs. 306 pg/mL, *P* < 0.001). The non-neonatal CHD sample demonstrated a positive and significant correlation between the postoperative 24-hour avg BNP and numerous clinical measures of acuity (Table 2), and while the biventricular CHD correlations were generally stronger, the Fontan sub-

group demonstrated weakly negative, statistically nonsignificant correlations to most of these same measures.

To assess the impact of cardiopulmonary bypass on very high BNP levels, the patients with preoperative BNP >1000 pg/mL had two additional intraoperative BNP samples: ~5 minutes after beginning cardiopulmonary bypass and ~5 minutes prior to unclamping the aorta. Of the 7 subjects with preoperative BNP levels >1000 pg/mL (all neonates), 5 were captured for this analysis. BNP levels uniformly dropped to a nadir at the end of aortic cross-clamp, rising again postoperatively to near-preoperative levels (Figure 5). The mean difference in BNP between preoperative (3926 pg/mL) and end of the cross-clamp (822 pg/mL) was 3104 pg/mL (*P* < 0.07).

Three subjects died, including one neonate (hypoplastic left heart syndrome [HLHS] undergoing Norwood palliation) and two non-neonates (HLHS undergoing a bidirectional Glenn proce-
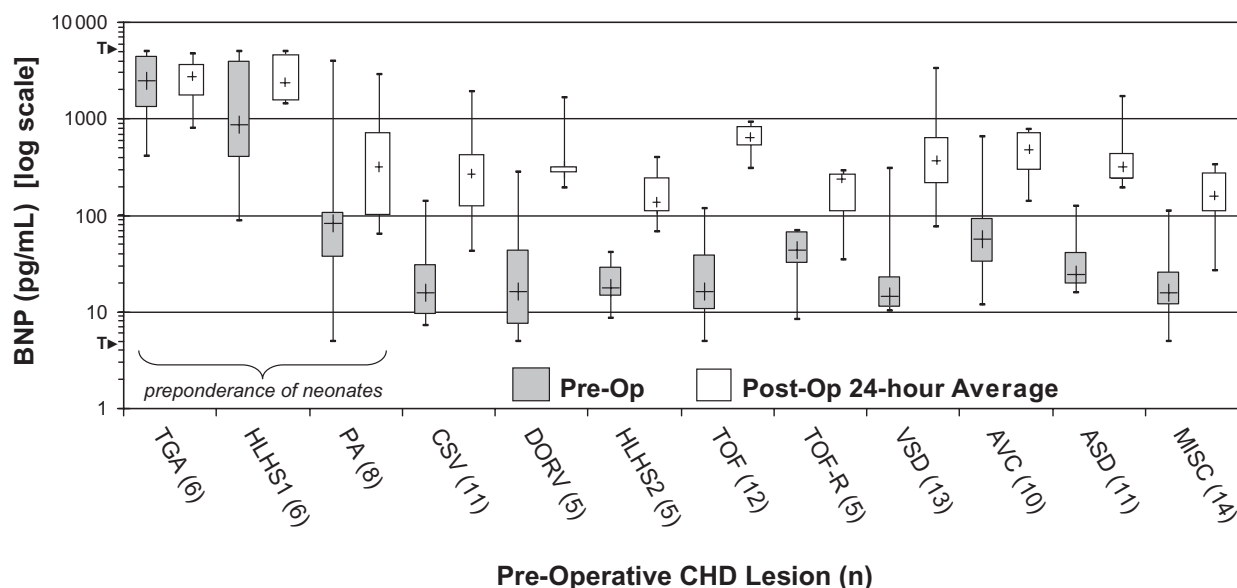
Figure 3. Preoperative B-type natriuretic peptide (BNP) and postoperative 24-hour average BNP in selected congenital heart disease lesions. Significant interindividual, interlesional, and age-dependent variability exists in BNP expression. TGA, transposition of the great arteries; HLHS1/2, hypoplastic left heart syndrome, Stage 1/2; PA, pulmonary atresia; CSV, complex single ventricle; DORV, double outlet right ventricle; TOF(-R), tetrology of Fallot (repaired); VSD, ventricular septal defect; AVC, atrio-ventricular canal; ASD, atrial septal defect; MISC, miscellaneous lesions (for which n < 5 for that lesion type). The two T's on the y-axis designate the upper and lower thresholds of the BNP assay.

dure, and a pulmonary atresia-ventricular septal defect undergoing an attempted biventricular repair). Within the non-neonatal cohort, the two nonsurvivors demonstrated preoperative BNP levels in the 83rd–88th percentile (67–88 pg/mL) and postoperative 24-hour average BNP in the 98–99th percentile (2492–2831 pg/mL). In contrast, the neonatal nonsurvivor's BNP was <50th percentile both preoperatively and postoperatively. If a composite measure of "adverse outcomes" is defined as death, cardiac arrest, or ICU length of stay >28d, a group of 5 non-neonatal patients were identified that demonstrated a preoperative BNP ROC AUC of 0.83 (BNP of >64 pg/mL yields 80% sensitivity and 85% specificity), while the 24-hour avg BNP ROC AUC is 0.96 (24-hour avg BNP of >721 pg/mL yields 80% sensitivity and 92% specificity).

Discussion

Normative pediatric BNP levels in children are lower and more narrowly distributed than in adults—with the notable exception of newborns and preterm infants who may exhibit high, widely distributed BNP levels during their circulatory transition.[37] Our data suggest a nadir in the first year of life, after which, a gradual rise in BNP

appears to take place. No straightforward surgical control group exists for CHD repairs, but in an effort to compare with some kind of relatable surgical stress, we selected a small sample of noncardiac surgeries expected to be several hours in duration with significant intraoperative blood loss and volume resuscitation. These controls demonstrated normal preoperative and postoperative BNP levels unaffected by intraoperative variables. In contrast, the non-neonatal CHD patients' postoperative BNP levels rose significantly by several orders of magnitude. This suggests that rising BNP levels in the CHD repairs are not likely relatable to nonspecific surgical stresses, anesthetic exposure, or routine intraoperative volume management for blood loss.

The vast majority of preoperative BNP levels in non-neonatal CHD were within the commonly accepted normative range for this assay (<100 pg/mL), likely reflecting a state of compensated CHF. Composite and isolated postoperative BNP levels correlated with numerous aspects of CHF in CHD repairs—including the timing and severity of LCOS, duration of ICU support, discharge medication doses, and a composite of adverse outcomes. Because BNP usually peaked on postoperative day 1, and because the time to peak varied, averaging BNP values over the first 24 hours to
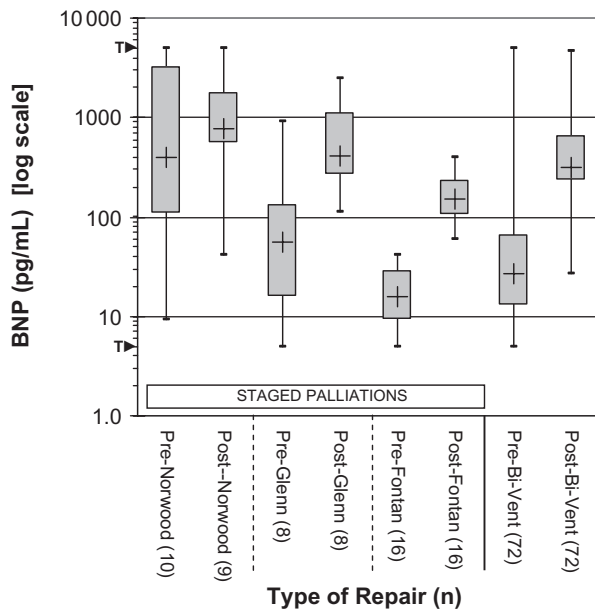
Figure 4. Preoperative and 24-hour average postoperative B-type natriuretic peptide (BNP) levels in staged univentricular palliations vs. complete biventricular repairs. Early postoperative BNP expression is higher in all groups of congenital heart disease repairs shown. In univentricular repairs, BNP trends downward with advancing stage and age. Pre, preoperative; Post, postoperative; Norwood, predominantly Norwoods plus similar stage-1 palliations; Glenn, predominantly bidirectional Glenns plus similar superior cavopulmonary anastamoses; Fontan, fenestrated Fontans; Bi-Vent, complete biventricular repairs. The two T's on the y-axis designate the upper and lower thresholds of the BNP assay.

estimate an AUC resulted in the composite measure that best correlated to clinical measures—and was the measure felt to be most reflective of overall physiologic BNP response. BNP levels appeared to behave as one might expect to common perioperative maneuvers—rising transiently after sternal closure and after discontinuing positive pressure ventilation (data not shown)—and generally trended down after a peak on postoperative day 1 as the patients convalesced.

When assessed in aggregate or by CHD lesion, BNP levels fell logarithmically with age, both preoperatively and postoperatively (Figure 1)—in contrast to the normative controls that trended upward after the neonatal period. In contrast to neonatal controls, this inverse age-dependence of BNP levels in CHD persisted years into life—not merely during the period of transitional circulation. While BNP trends might be influenced by different cardiac lesions being repaired at different ages, when analyzed within a dozen different pre-

operative diagnostic categories, this BNP-vs.-age relationship persisted universally in postoperative BNP and was re-demonstrated with preoperative BNP in the vast majority of categories.

Others have reported point-in-time cutoff values for BNP as a risk stratifier or predictor of outcomes in CHD, and similar analyses of our data are consistent with many of these findings.[7–9,14,27–29,33,34] Therefore, we looked at our perioperative BNP data from a slightly different perspective—seeking situations where BNP levels and severity of illness appeared discordant. Two such populations stood out: Fontans in general and neonates intraoperatively.

In a small sample of non-neonatal CHD repairs, Ationu found that preoperative BNP was within normal limits and only trivially reduced intraoperatively at various stages during CPB[38]—much as our CHD and surgical control data show. However, since BNP is rapidly liberated and has a half-life of approximately 22 minutes, intraoperative reductions may not be apparent in patients with normal preoperative BNP concentrations. Therefore, we selected CHD subjects with preoperative BNP greater than 1000 pg/mL for additional intraoperative BNP sampling (only neonates had preoperative levels this high). While a small sample, all five cases demonstrated the same pattern: BNP levels dropped dramatically while on cardiopulmonary bypass and reached a nadir at the end of aortic cross-clamp. Possible mechanisms include dilution from the proportionally larger bypass circuit prime in neonates, exclusion of the ramped up BNP-producing myocardium from the circulating blood volume, increased elimination efficiency by ultrafiltration, or upregulated peripheral metabolism of BNP. These remarkably high levels of BNP preoperatively may be physiologic and adaptive in neonatal CHD, and iatrogenic reductions intraoperatively could theoretically contribute to impaired physiologic homeostasis postoperatively.

In our comparison of biventricular repairs and Fontan palliations (Tables 2 and 3), the univentricular patients demonstrated higher clinical acuity yet significantly lower BNP measures—less than half the average amount of BNP on postoperative day 1. The Fontan patients required more cardiac medication, had longer lengths of stay, were readmitted more often, and showed an almost 3-fold increase in LCOS (in spite of similar CBP run lengths). In stark contrast to biventricular CHD, the Fontan palliations paradoxically demonstrated weak inverse correlations between

Table 3. Comparison of Perioperative Measures between Fontan Palliations and Non-Neonatal Complete Biventricular Congenital Heart Disease Repairs

Type of Surgical Repair/Palliation	Complete (Biventricular)	Fontan (Univentricular)	*P*
Demographics			
Sample Size (n)	66	16	
Age (in years, median/IQR)	1.2 (0.4–4.2)	1.7 (1.5–2.8)	—
Weight (in kg, median/IQR)	9.0 (5.5–16)	10.5 (9.5–12.4)	—
Admission measures (median/IQR)			
Number of cardiovascular medications	0.5 (0–2)	1 (1–2)	—
Furosemide/equivalent dose (mg/kg/d)	0 (0–1.2)	0.3 (0–1.2)	—
Captopril/equivalent dose (mg/kg/d)	0 (0–0)	0.3 (0.05–0.6)	<0.001
BNP measures (median/IQR)			
BNP, preoperative (pg/mL)	23 (12–53)	16 (9–30)	0.09
BNP, peak postoperative (pg/mL)	592 (432–1150)	266 (178–442)	<0.001
BNP, 24-h postoperative average (pg/mL)	306 (226–604)	150 (102–244)	<0.001
BNP, maximum rate of increase (pg/mL/h)	60 (31–108)	24 (19–49)	0.001
Intraoperative measures (median/IQR)			
Length of aortic cross-clamp (min)	56 (42–87)	52 (39–59)	—
Length of cardiopulmonary bypass (min)	119 (88–160)	119 (105–139)	—
Length of surgery (hours)	3.8 (2.9–4.7)	4.8 (4.2–5.8)	0.001
Clinical post-op measures (median/IQR)			
POD 1 central venous pressure (mm Hg)*	9.8 (7.8–13.2)	13.5 (11.5–15.3)	<0.001
POD 1 perfusion score impairment (0–12)	1.6 (1.1–2.2)	2.2 (1.2–2.9)	—
POD 1 inotropic support score (0–8)	2 (1.2–2.4)	2.4 (1.8–2.8)	0.04
POD 1 urine output (mL/kg/hr)	2.3 (1.7–3.2)	1.9 (1.5–2.7)	—
Duration post-op measures (median/IQR)			
Length of ventilation (days)	1.3 (0.8–2.6)	1.1 (0.9–1.5)	—
Length of intensive care (days)	2.0 (1–4)	3.0 (2–3.5)	0.08
Length of hospitalization (days)	4.5 (3–7)	6.0 (5.5–7.5)	0.01
Discharge measures (median/IQR)			
Number of cardiovascular medications	2 (1–3)	3 (3–3)	0.001
Furosemide/equivalent dose (mg/kg/day)	2.6 (1.3–3.0)	2.9 (2.6–3.1)	0.09
Captopril/equivalent dose (mg/kg/day)	0 (0–0.5)	0.7 (0.5–1)	<0.001
Binary outcomes			
Low cardiac output syndrome (n, %)	13 (20)	9 (56)	<0.01
Open chest postoperatively (n, %)	4 (6.1)	0 (0)	—
Deaths (n, %)	1 (1.5)	0 (0)	—
Readmission <6 weeks from discharge (n, %)	2 (3.0)	2 (12)	—

*Represents pulmonary artery pressure for Fontan physiology.
BNP, B-type natriuretic peptide; IQR, interquartile range; POD, postoperative day.

BNP and both CVP as well as inotrope score. With only 6 bidirectional Glenn anastamoses, analyses of this univentricular stage were quite limited statistically, but in general, these patients demonstrated similar BNP measures but worse clinical outcomes than the biventricular repairs—also suggesting a degree of discord between BNP and outcomes in this univentricular population. These findings supplement previous reports by others citing progressively lower BNP expression in staged univentricular CHD repairs—perhaps because of isolated cavopulmonary failure or impaired perioperative expression of natriuretic peptides.[24,26,28] These data also give us cause to consider whether BNP levels are mal-aligned with the clinical severity of CHF in these populations. While speculative, impairment of an otherwise adaptive BNP response in this population could conceivably contribute to the tendency of univentricular patients to require greater medical support and exhibit longer lengths of stay.

Measured BNP levels clearly reflect an equilibrium between many variables: production, degradation, endocytosis, excretion, and dilution. This can seriously confound the interpretation of BNP in perioperative CHD when many of these variables are not in a predictable steady state. Yet, with the exception of overt renal dysfunction, measured BNP levels appear to predominantly reflect production by the ventricular myocardium.[39,40] However, while BNP correlates to clinical measures and predicts poor outcomes (similar to many biomarkers), it does not reveal much that is not already apparent to clinicians—that sicker patients require more support for a longer time and tend to do worse. Indeed, the existing literature on BNP in perioperative CHD does not meaningfully guide therapy, and BNP risk stratification has not translated into differing management algorithms.[14,37,38,41–45]

Questions clearly remain regarding the appropriateness and effectiveness of endogenous
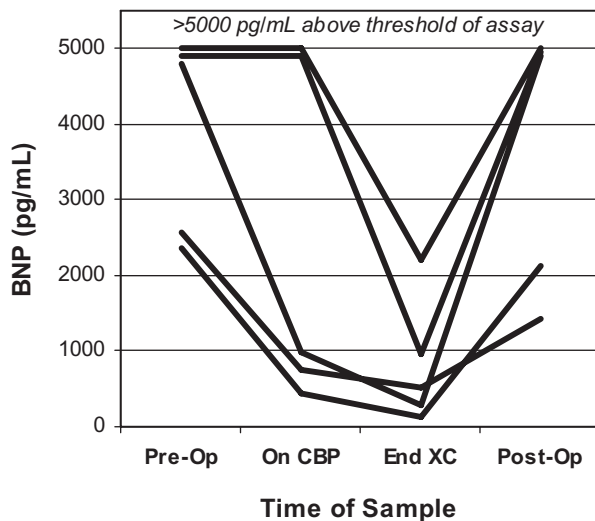
Figure 5. Intraoperative B-type natriuretic peptide (BNP) levels in five congenital heart disease repairs exhibiting markedly high preoperative BNP levels. In patients with very high levels of BNP preoperatively (all neonates), cardiopulmonary bypass and circulatory arrest consistently lowered serum BNP concentrations by thousands of pg/mL, which rose quickly postoperatively to near-preoperative levels. Pre-Op, preoperative; On CBP, ~5 minutes into cardiopulmonary bypass; End XC, ~5 minutes prior to unclamping aorta; Post-Op, upon arrival to the intensive care unit (ICU) postoperatively (hour 0 of BNP series in ICU).

BNP levels after CHD repair. In contrast to cardiomyopathies, CHD can have unique ventricular pressure-volume loading states because of parallel circulation, intracardiac shunting, single ventricle physiologies, ventricular reversals, and complex surgical reconfigurations. Univentricular CHD may have relatively less BNP-producing myocardium. Certainly, the myocardium is not able to effectively liberate BNP during asystole following cardioplegia. It may be that such aspects of CHD could alter the normal adaptive function of this important counter-regulatory signal, resulting in BNP responses that are inappropriately low or high relative to the clinical magnitude of heart failure.

The off-label use of hrBNP in children undergoing CHD repair has been undertaken—with retrospective analyses and case series suggesting improved surrogate endpoints and an absence of obvious complications.[19,23,46-49] However, clear indications, proven efficacy, and convincing safety have not been demonstrated. Exogenous BNP has several theoretically desirable features in the care of postoperative CHD patients, including vasodilitation, diuresis, and lusitropy. Yet, meta-analyses of adult trials with hrBNP have raised

concerns about increased renal dysfunction and mortality—so any therapeutic manipulations of the BNP axis ought not be applied indiscriminately without further guiding evidence.[21,22] The prospect of perioperative BNP elevations insufficient for optimal adaptation would provide a tempting mechanistic rationale for considering exogenous BNP in targeted CHD populations. Because nesiritide is a recombinant form of a human protein naturally found highly concentrated in children with heart failure, the drug may prove to be a safe and effective therapy in situations of relative deficiency—in contrast to creating supraphysiologic levels beyond the expected adaptive response in cardiomyopathy.

While our data do not definitively identify states of relative BNP insufficiency, it will remain challenging to tease out such a condition given the enormous variability in BNP responses superimposed on the clinical complexity of perioperative CHD. In this confounded and heterogeneous clinical setting, a theragnostic approach may be productive—using a biomarker to identify which patients are most likely to benefit from a specific drug therapy.[35] Therefore, we suggest that a rationale exists for further research into targeted administration of hrBNP in some circumstances encountered in the perioperative management of CHD. These include: patients undergoing cardiopulmonary bypass with very high BNP levels preoperatively (in an effort to replace any iatrogenic decrement in an adaptive hormone) and postoperatively to univentricular palliations (where our data show relatively low BNP levels compared with clinical acuity). Clinical trials assessing the safety and efficacy of hrBNP in such circumstances should be undertaken, and our data provides a starting point for mechanistically guided use in future research.

There are significant limitations to our data limiting generalizability. The heterogeneous sample unevenly distributed among numerous small CHD subsets makes our aggregate analyses difficult to extrapolate to individual CHD lesions. In particular, the NICU subjects were only enrolled in the last third of the study window after an IRB amendment, resulting in a particularly small neonatal subsample. There was also a paucity of hemi-Fontans, further limiting the kinds of univentricular subgroup analyses that could be made. As a matter of feasibility and convenience in this unfunded study, a perfusion score was devised based on routine nursing assessments, rather than formal core-vs.-peripheral tempera-

ture differentials. Also, an inotropic score was devised that weighted low, moderate, and high dosing levels in a manner that was felt to reflect local titration patterns. Because it used collapsed dose ranges rather than linear conversions, it is presumably less sensitive than other tools. While neither of these scales devised for this study are validated measures, they did both correlate as expected with other objective measures of clinical acuity and with each other. Apart from urine output, renal function was not measured, but since impaired renal function can result in elevated BNP levels, this is a potential confounder. However, BNP and UO did not correlate positively or negatively on postoperative day 1. Another limitation is the management of CHD by two different ICUs and intensivists groups within our institution, potentially introducing systematic differences in the assessment and management. However, the cardiothoracic surgeons and cardiologists were the same, and the strikingly higher levels of BNP in the neonatal population (controls and CHD) suggests that this group needs to be analyzed separately from older infants and children regardless. Because perioperative BNP levels in the NICU population were frequently above the upper limit of measurability, the upper range limit of the meter was used in calculations, likely blunting the sensitivity of this measure in our analyses. Future research including neonates should consider more accurate methods of measuring very high BNP, such as through dilutional techniques or alternative assays. Finally, corrections of *P* values were not made for multiple simultaneous tests, given the exploratory nature of the post hoc analyses, so marginally significant values should be treated with caution.

Conclusions

BNP is a valid biomarker for CHF in the CHD population during the perioperative period. Levels correlate to clinical severity of heart failure, lengths of therapy, and adverse outcomes. Peak BNP levels most often occurred 6–12 hours postoperatively, mirroring the classic period of the LCOS. However, the clinical utility of BNP as a rapid point-of-care diagnostic assay is limited after CHD repair because of the highly variable responses between and within CHD lesions as well as age-dependency. Randomly obtained BNP levels will remain difficult to interpret without other points on the BNP-vs.-time curve of an individual patient. Despite having greater

clinical acuity and resource utilization, Fontan palliations paradoxically exhibited lower BNP expression preoperatively and postoperatively compared with biventricular CHD. This pattern of potential BNP insufficiency, as well as others described here, suggest rational targets for investigating therapeutic administration of hrBNP perioperatively.

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