N-terminal B-type natriuretic peptide levels in pediatric patients with congestive heart failure undergoing cardiac surgery

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Objectives: The objectives of this study were to measure circulating N-terminal B-type natriuretic peptide levels in pediatric patients undergoing surgical repair of congenital heart lesions with left ventricular volume overload and to determine whether presurgical and immediate postoperative N-terminal B-type natriuretic peptide levels could predict patient outcomes after surgical intervention.

Methods: Thirty-eight children aged 1 to 36 months undergoing surgical repair of cardiac lesions with left ventricular volume overload were studied. Plasma N-terminal B-type natriuretic peptide levels were measured preoperatively and at 2, 12, 24, 48, and 72 hours after surgical intervention and were assessed for their predictive value of postoperative outcomes. Plasma N-terminal B-type natriuretic peptide levels were also measured in 34 similarly aged healthy children.

Results: Patient preoperative N-terminal B-type natriuretic peptide levels were significantly higher than those of healthy control subjects (3085 ± 4046 vs 105 ± 78 pg/mL). Preoperative N-terminal B-type natriuretic peptide levels correlated with the complexity of surgical repair, as measured by cardiopulmonary bypass time ($r = 0.529$, $P < .001$), and with postoperative measures, including fractional inhaled oxygen requirements registered at 12 hours ($r = 0.443$, $P = .005$) and duration of mechanical ventilation ($r = 0.445$, $P = .005$). Plasma N-terminal B-type natriuretic peptide levels increased 5-fold within 12 hours after cardiopulmonary bypass (14,685 ± 14,317 pg/mL). Multivariable regression analysis showed that the preoperative N-terminal B-type natriuretic peptide level was a significant predictor of duration of intensive care unit stay ($P = .02$) and that the peak postoperative N-terminal B-type natriuretic peptide level was a significant predictor of the intensity of overall medical management, as assessed by using the therapeutic intervention scoring system ($P = .01$).

Conclusion: Plasma N-terminal B-type natriuretic peptide levels measured preoperatively and postoperatively can be a prognostic indicator in the management of the pediatric patient after surgical intervention for congenital heart repair.

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The natriuretic peptides, of which atrial natriuretic peptides and brain or B-type natriuretic peptide (BNP) are of myocardial cell origin, play a significant role in the control of volume homeostasis and regulation of blood pressure.[1-3] Plasma levels of the cardiac natriuretic peptides have been shown to increase with congestive heart failure in adults and to correlate with the severity of disease, thus providing an indirect measure of left ventricular (LV) function.[4-6] The biologically inactive prohormone of BNP (proBNP), is secreted by cardiac ventricular myocytes in response to volume and pressure overload[7] and is enzymatically cleaved to the physiologically active form, BNP, and the inactive N-terminal fragment, NT-pro-BNP or N-BNP, in a one-to-one ratio.[8-10] Circulating levels of

Abbreviations and Acronyms

BNP	= B-type natriuretic peptide
CCAVC	= complete common atrioventricular canal
CPB	= cardiopulmonary bypass
LV	= left ventricle
N-BNP	= N-terminal B-type natriuretic peptide
PICU	= pediatric intensive care unit
TISS	= Therapeutic Intervention Scoring System
VSD	= ventricular septal defect

both BNP and N-BNP have been shown to be increased in early cardiac dysfunction in adults, making it a useful predictor of congestive heart failure in hypertrophic or dilated cardiomyopathy[4,5,11-14] and a prognostic indicator of outcome in congestive heart failure.[15-18] The recent commercial development of a diagnostic N-BNP assay was based on the greater in vitro stability of this moiety compared with that of BNP and with the longer half-life of circulating N-BNP, making it a reliable marker of cardiac function.[19,20]

Recently, measurements of either BNP or N-BNP as perioperative markers of ventricular function or as prognostic indicators of postoperative outcomes in pediatric patients with congenital heart disease have been explored.[21-24] However, only limited data exist regarding the effects of LV volume overload on the circulating levels of N-BNP in pediatric patients with congenital heart disease. Therefore, the primary goal of this study was to measure circulating levels of N-BNP in pediatric patients with LV volume overload who were undergoing cardiac surgery with cardiopulmonary bypass (CBP) and to correlate preoperative and postoperative N-BNP levels with outcome measures to assess the utility of N-BNP as a reliable marker of postoperative clinical status of the pediatric cardiac patient.

Materials and Methods

Study Inclusion Criteria and Diagnostic Classifications

This prospective study was conducted at Schneider Children's Hospital and was approved by the institutional review board of the North Shore Long Island Jewish Health System. Written informed consent was obtained from parents or guardians before recruitment into the study. Sixty-seven pediatric patients with congenital heart defects known to cause LV volume overload scheduled for complete surgical repair were identified between September 2004 and November 2005 as eligible for enrollment into this study. Thirty-eight of these patients who are included in the present analysis were 3 years of age and younger and had lesions including ventricular septal defect (VSD) and complete common atrioventricular canal (CCAVC). Patients with single-ventricle physiology and obstructive lesions, such as aortic stenosis or coarctation of the aorta, were excluded from the study. Evidence of preoperative renal insufficiency, as indicated by measures of blood urea nitrogen and creatinine, precluded participation.

Control subjects were recruited from healthy patients evaluated during well-care visits to the pediatric clinic at Schneider Children's Hospital. Written informed consent was obtained before enrollment in this study. A history of acute or chronic illness, any prior cardiac disease, or both precluded participation. All subjects had normal physical evaluations and no clinical evidence of congenital heart disease. Blood samples were drawn after the clinical evaluation for subsequent analysis of N-BNP levels.

Data Collection

Clinical data were prospectively collected on intraoperative parameters and postoperative outcomes. Surgical procedures, including CPB and anesthesia, followed standard practices, and postoperative patient management in the pediatric intensive care unit (PICU) were based on standard institutional protocol without knowledge of patient N-BNP test values. Presurgical blood samples were obtained from enrolled patients during outpatient presurgical routine blood analysis. After surgical intervention, patients were admitted to the PICU, with the majority of patients receiving mechanical ventilator support. Blood samples were drawn from central intravenous catheters at 2, 12, 24, 48, and 72 hours after termination of CPB or until the catheters were removed. Therefore, N-BNP analysis at later time points was not obtained on all patients because of the removal of central intravenous lines. Blood samples were processed immediately, and the plasma was stored at $-20°C$ until all samples could be analyzed. Plasma N-BNP levels were measured with a commercially available electrochemiluminescence immunoassay kit (Elecsys proBNP, Roche Diagnostics, NJ).

Patients were continuously monitored in the PICU, and clinical data, including quantities of vasodilator and inotropic drugs, blood gas and lactate analyses, oxygen requirement, urine output, blood pressures, cardiac rhythm, and heart rate, were recorded daily. These values were among 76 different therapeutic and monitoring procedures used to assess the overall degree of postoperative care, as calculated by using the Therapeutic Intervention Scoring System (TISS).[25] TISS scores were derived over a 24-hour period and reflected the invasiveness, intensity, and complexity of care rendered to the patient in the PICU. Inotropic scores were obtained at 24, 48, and 72 hours after CPB by using a modification of the calculation described by Wernovsky and colleagues[26]: Dopamine + Dobutamine + ([Epinephrine + Norepinephrine]) $\times$ 100. The daily inotropic score was calculated by obtaining the total amount of inotropic drug administered in a 24-hour period and expressed as micrograms per kilogram per minute.

Statistical Analysis

Plasma N-BNP values were compared between the healthy control group and the presurgical values of the study patients by using *t* tests. A repeated-measures analysis of variance was carried out to compare N-BNP values collected over time (preoperatively and postoperatively at 2, 12, 24, 48, and 72 hours) for the surgical patients. Tukey-adjusted pairwise comparisons were carried out to determine which time points significantly differed from one another. Because age was considered as a potential confounder, all analyses made an adjustment for age by using age as a covariate. It was determined that a log transformation of the data conformed to the standard ANOVA assumptions. Accordingly, all analyses

TABLE 1. Study subject demographics and characteristics

Healthy subjects (n)	34
Age (mo)	19.6 ± 9.1 (24; 2.4–36)*
Sex	Female, 44%; male, 56%
Surgical patients (n)	38
Age (mo)	7.1 ± 8.3 (4.0; 1–36)*
Sex	Female, 47%; male, 53%
Weight (kg)	6.3 ± 4.9 (4.4; 2.5–26.5)*
Anatomic defects (n)	
VSD	30
CCAVC	8

VSD, Ventricular septal defect; *CCAVC*, complete common atrioventricular canal. *Mean ± SD (median; minimum-maximum).

were conducted with the log-transformed data, but summaries and graphs are presented in the original untransformed units of measurement to facilitate interpretation. Correlation coefficients between the highest or peak N-BNP plasma level and each of the postoperative clinical measures were calculated by using Spearman correlation.

A multivariate regression analysis with a backward elimination algorithm was used to determine the best predictor or predictors separately for days in the PICU, ventilation time, and cumulative TISS score. Two sets of candidate variables were used: the first set included only variables known before surgical intervention, including age, lesion type, and preoperative N-BNP value, and the second set included variables known before surgical intervention and variables known by the second postoperative day, including age, lesion type, preoperative N-BNP value, CPB time, and peak postoperative N-BNP value.

Results

Study Group Characteristics and Study Outcomes

Table 1 shows the types of congenital heart lesions of the 38 patients enrolled in the study, with the majority (79%) having VSD and 21% having CCAVC. There was no difference in the mean age of the patient groups between the 2 types of lesions, but the mean body weight of the CCAVC group was lower than that of the VSD group (4.2 ± 2.0 vs 6.9 ± 5.3 kg, $P < .05$). The weight-for-age percentiles of 29 (76%) of the 38 patients were less than the 10th percentile, with none greater than the 50th percentile, a criterion indicative of significant heart failure. The healthy control subjects were similarly 3 years of age and younger; however, the healthy group was significantly older than the surgical patient group (19.6 ± 9.1 vs 7.1 ± 8.3 months, respectively; $P < .001$). Sex distribution was not different between the groups.

Table 2 lists intraoperative and postoperative outcomes data grouped by the type of cardiac lesion. Significant differences were found between the 2 lesion types, with longer CPB and crossclamp times recorded for the CCAVC group. Although both preoperative and peak postoperative plasma N-BNP levels were not significantly different between groups, both values tended to be higher in the patients with CCAVC. Significantly longer mechanical ventilation time, hospital stays, inotropic scores, and TISS scores were recorded for patients with CCAVC lesions.

Preoperative Plasma N-BNP Levels and Response to Surgical Intervention

Healthy subjects had a mean plasma N-BNP value of 105 ± 78 pg/mL, whereas the 38 patients with LV volume overload had a significantly higher mean presurgical N-BNP value of 3085 ± 4046 pg/mL ($P < .001$) (Figure 1; Table 3). The presurgical N-BNP values did not differ significantly with lesion type (Table 2) and were inversely correlated with patient age ($r = -0.672$, $P < .0001$), indicating that younger patients with heart failure had higher circulating levels of N-BNP before corrective operations.

In response to surgical intervention, circulating N-BNP levels did not increase immediately after discontinuation of

TABLE 2. Intraoperative and postoperative parameters

	VSD (n = 30)	CCAVC (n = 8)	*P* value
Intraoperative data*			
CPB time (min)	84 ± 29	134 ± 29	<.01
Crossclamp time (min)	48 ± 19	97 ± 28	<.01
Postoperative outcomes*			
Intensive care unit stay (d)	4.0 ± 2.0	6.3 ± 5.0	NS
Mechanical ventilation (h)	14.3 ± 11.7	50.3 ± 35	<.01
Hospital stay (d)	5.6 ± 3.5	18.8 ± 29.1	<.01
TISS (cumulative POD 1-3)	66.3 ± 19.1	90.5 ± 14.7	<.01
IS (cumulative POD 1-3)	2.9 ± 3.5	13.2 ± 9.3	<.01
FIO_2 at 2 h	58 ± 23	70 ± 26	NS
Preoperative N-BNP (pg/mL)	2739 ± 4084	4382 ± 3873	NS
Peak N-BNP (pg/mL)	14,845 ± 14,800	20,482 ± 12,879	NS

*Mean ± standard deviation. ns = not significant. *VSD*, Ventricular septal defect; *CCAVC*, complete common atrioventricular canal; CPB, cardiopulmonary bypass; *TISS*, Therapeutic Intervention Scoring System; *POD 1-3*, postoperative days 1 to 3; *IS*, inotropic score; FIO_2, fraction of inhaled oxygen.

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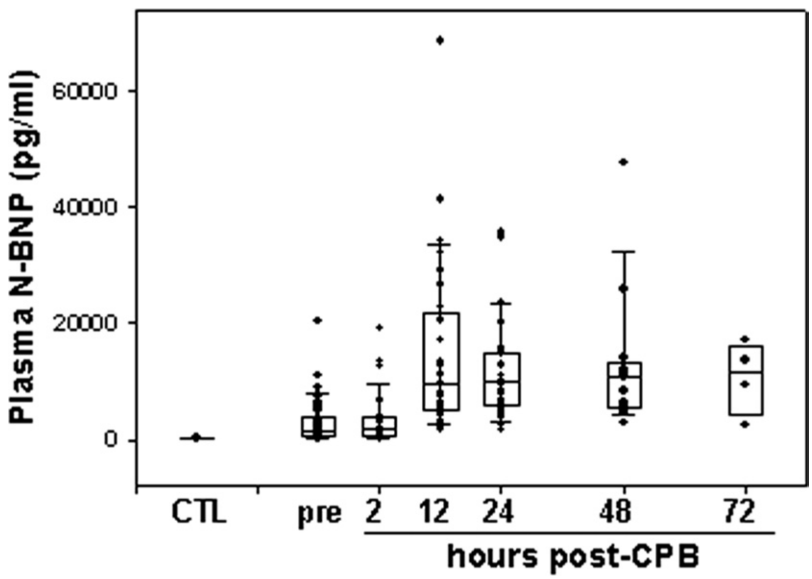

Figure 1. Circulating N-terminal B-type natriuretic peptide (*N-BNP*; in picograms per milliliter) in control *(CTL)* healthy children and in pediatric patients before and after cardiopulmonary bypass *(CPB)* surgery. The *box plot* encompasses the 25th to 75th percentiles, the *horizontal line* is the median value, and the *caps* represent the 10th and 90th percentiles.

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TABLE 3. Plasma N-terminal B-type natriuretic peptide levels

Time point	n	Mean ± SD (pg/ml)
CTL	34	105 ± 78
Patients		
Pre	38	3085 ± 4046*
2 h	34	3178 ± 4366
12 h	33	14685 ± 14317†
24 h	29	11891 ± 8582†
48 h	16	12331 ± 10960†
72 h	4	10645 ± 6296‡

*p $<$ 0.001 vs CTL. †p $<$ 0.0001 vs Pre and 2 h. ‡p $<$ 0.005 vs Pre and 2 h.

CPB (2 hours; 3178 ± 4366 pg/mL) but did increase significantly when measured at 12 hours after CPB (14,685 ± 14,317 vs preoperative value of 3085 ± 4046 pg/mL, $P < .0001$) and remained significantly higher at 24 and 48 hours ($P < .0001$) and at 72 hours ($P < .005$, Figure 1; Table 3). The plasma N-BNP levels in each patient reached a maximum value at either 12 or 24 hours after surgical intervention, and these peak N-BNP values correlated significantly with CPB time ($r = 0.400$, $P = .01$), suggesting that the complexity and duration of the surgical repair procedure, as reflected by CPB time, might have been determining factors in the magnitude of the induction of N-BNP synthesis and release.

Preoperative N-BNP and Peak N-BNP Values as Predictors of Clinical Outcomes

Correlation analysis between clinical outcomes and preoperative or peak N-BNP values showed that results using all 38 patients were similar to results from the 30 patients with VSDs; therefore we present only the data from the combined patient groups.

The preoperative N-BNP values correlated significantly with CPB time ($r = 0.529$, $P = .0006$), suggesting that the severity of the lesion or volume overload, as measured on the basis of increased circulating preoperative N-BNP levels, reflected the complexity of the surgical repair procedure. Preoperative N-BNP levels correlated with several outcome measures, including length of time supported by mechanical ventilation ($r = 0.445$, $P = .005$), fraction of inspired oxygen registered at 12 hours ($r = 0.445$, $P = .005$), length of hospital stay ($r = 0.487$, $P = .002$), and days in the PICU ($r = 0.435$, $P = .006$; Figure 2, *A*). The cumulative TISS score, reported as the sum of 24-hour scores recorded during the first 72 hours after surgical intervention, correlated positively with circulating preoperative N-BNP levels ($r = 0.412$, $P = .01$).

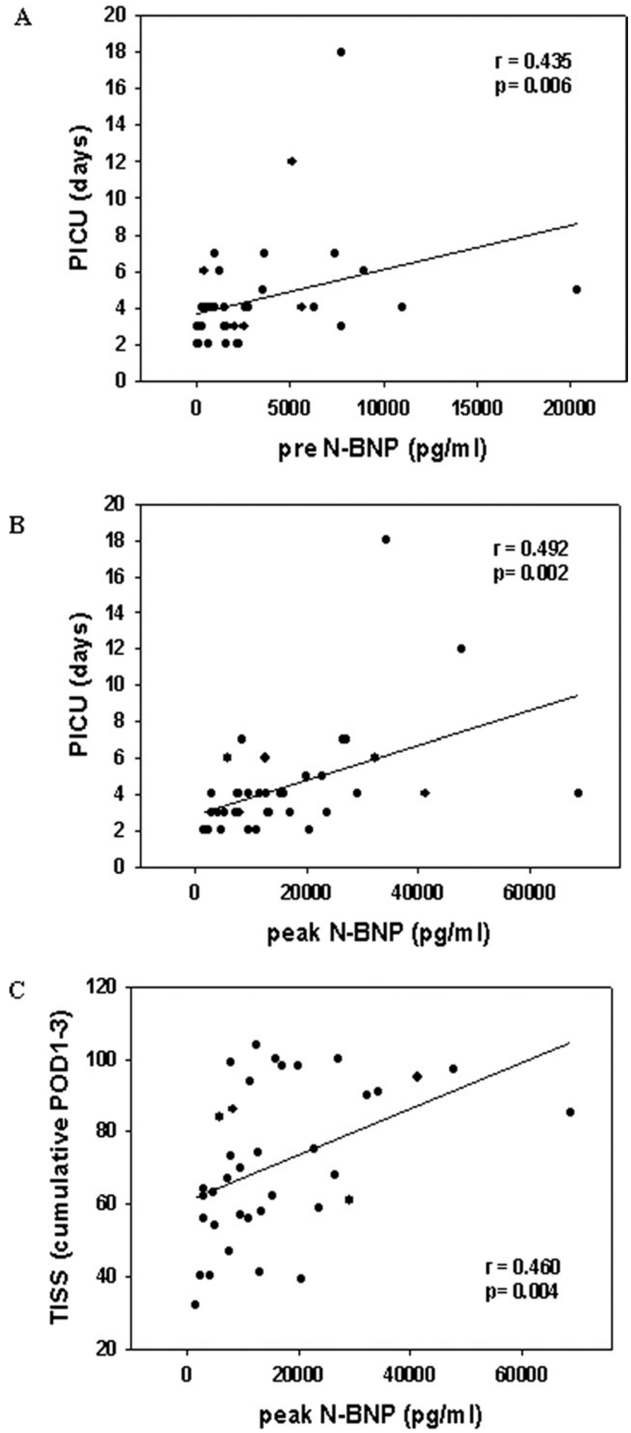

Figure 2. Preoperative and postoperative plasma N-terminal B-type natriuretic peptide *(N-BNP)* levels predict postoperative outcomes. Preoperative N-terminal B-type natriuretic peptide levels showed significant positive correlation with days spent in the pediatric intensive care unit (*PICU*; A). Peak postoperative N-terminal B-type natriuretic peptide levels showed significant correlation with PICU days (B) and with the TISS score summed from postoperative days 1 to 3 (*cumulative POD1-3*; C). The *line* represents the best-fit linear regression curve.

Multivariable regression analysis with variables known only before surgical intervention, including preoperative N-BNP values, age in months, and lesion type, showed that the preoperative N-BNP value was a moderate predictor of the number of days spent in the PICU (P = .02), regardless of lesion type. Type of lesion (VSD or CCAVC), however, was a highly significant predictor of cumulative TISS score (P = .002) and days of mechanical ventilation (P = .0008).

In support of the hypothesis that the N-BNP response to surgical intervention can predict clinical outcomes, significant positive correlations were observed between peak N-BNP values and the total time required for mechanical ventilator support (r = 0.454, P < .004), length of hospital stay (r = 0.571, P = .0002), and days in the PICU (r = 0.492, P = .002; Figure 2, *B*). Furthermore, the peak N-BNP value correlated with the intensity of overall medical management in the postoperative period, as assessed by using the cumulative TISS score (r = 0.460, P = .004; Figure 2, *C*). Multivariable regression analysis with variables known before surgical intervention, as described above, and variables known within 24 hours after surgical intervention, including peak N-BNP value and CPB time, showed that peak N-BNP value was a significant predictor of days in the PICU (P = .01) and the cumulative TISS score (P = .01).

Discussion

In this study we used a commercially available N-BNP assay to assess outcomes of pediatric patients undergoing surgical repair of cardiac lesions involving LV volume overload. The salient observations of the present study are as follows: (1) preoperative circulating levels of N-BNP were significantly increased in pediatric patients with lesions producing LV volume overload compared with those seen in healthy children; (2) preoperative N-BNP levels correlated with the complexity of surgical repair, as assessed by using intraoperative variables, including CPB time; (3) multivariable regression analysis with variables known before surgical intervention showed that the preoperative N-BNP level was a significant predictor of length of stay in the PICU; and (4) multivariable regression analysis with variables known preoperatively and within 24 hours postoperatively showed that the postoperative peak N-BNP level was predictive of TISS scores. This study also established a range of normal values for N-BNP in a cohort of healthy children of similar age, with a mean value of 105 ± 78 pg/mL, which is similar to that previously published.[27]

Kunii and associates[28] investigated the relationship between circulating BNP levels and LV volume overload lesions. They reported a significant correlation between BNP levels and the severity of disease and addressed the utility of BNP measurements in evaluating surgical indications. In the present study we focused our study on lesions causing LV volume overload, specifically VSD and CCAVC. All of these patients were well below the normal weight-for-age percentile, with the patients with CCAVC below the fifth percentile, indicating significant heart failure. Even within this homogeneous group of lesion types, the patients with CCAVC exhibited higher preoperative N-BNP levels and higher postoperative peak N-BNP that correlated with longer CPB times, perhaps reflecting more complicated surgical repairs. These patients required significantly greater postoperative medical care, as reflected in higher TISS scores, increased inotropic requirements, and longer duration of mechanical ventilation.

To determine which variables were the best predictors of outcomes, we tested 2 types of multivariable regression models: (1) a model using only variables known before surgical intervention (lesion type, age, and preoperative N-BNP level) and (2) a model using variables known before surgical intervention and at 24 hours after surgical intervention, including CPB time and peak postoperative N-BNP level. By using multivariable regression analysis with days in the PICU, cumulative TISS score, and duration of mechanical ventilation as the dependent variables, only the lesion type was a significant predictor of duration of mechanical ventilation ($P = .001$) and cumulative TISS score ($P = .002$) in both models. The preoperative N-BNP level was a significant predictor of length of stay in the PICU, whereas the postoperative peak N-BNP level was a significant predictor of days in the PICU and cumulative TISS score. When lesion type was eliminated from the equation by examining only the VSD group, the results were similar, with the peak N-BNP level remaining a significant predictor of TISS score and PICU days, whereas the preoperative N-BNP level remained in the model for predicting length of stay in the PICU. Absolute values of presurgical and postoperative peak N-BNP that could potentially be used to identify those patients at risk will require analysis of a much larger data set. However, data from this study and several other recently published reports support the potential predictive value of perioperative BNP and N-BNP measurements in determining the intensity of postoperative medical management, including inotrope requirements,[24] vasodilator support,[22] and duration of mechanical ventilation time.[21]

Increases in circulating N-BNP levels after CPB were anticipated, with peak postoperative N-BNP levels correlating with CPB duration ($r = 0.400$, $P = .01$). Cardiac surgery involving CPB triggers a systemic inflammatory response that involves the activation of lymphocytes, monocytes, endothelial cells, and cardiac myocytes that can produce many proinflammatory cytokines.[29,30] Whether myocardial secretion of BNP is also a response to inflammation is not known; however, inflammation-mediated changes in pulmonary and systemic vascular pressures that occur after CPB[26,31] can result in increased myocardial BNP production and secretion. Proinflammatory cytokines have been shown to upregulate cardiac-derived BNP,[32,33] and as we have previously published, pediatric cardiac surgery with CPB activates numerous proinflammatory cytokines.[34] Furthermore, CPB in infants with congestive heart failure has been reported to alter the biologic activity of the natriuretic hormones, but the underlying mechanism for this phenomenon remains unknown.[35]

Although the duration of CPB is a risk factor for morbidity after pediatric cardiac surgery, understanding of the complex pathophysiology of pulmonary dysfunction after CPB continues to be incomplete. Large intracardiac shunts with increased pulmonary blood flow will produce larger LV volume overload. In a previous report BNP levels were positively correlated with high Qp/Qs ratios in patients with VSD combined with patent ductus arteriosus.[28] Thus in the present study patients with high preoperative N-BNP levels and subsequent high postoperative N-BNP levels, potentially because of complicated surgical repairs and long CPB times, had ensuing pulmonary dysfunction with longer ventilator requirements.

Circulating N-BNP levels increase on the first day of life in neonates, potentially related to increased systemic vascular resistance and pulmonary blood flow after birth[36] and increased pulmonary artery pressures among premature infants.[37] Higher levels of BNP and N-BNP have been reported in the neonatal population when compared with older children.[22,28,36] The median age of patients in the present study was 4 months, with a range of 1 to 36 months. Because age was considered a potential confounder, all analyses made an adjustment for age by using age as a covariate. Patient age was not significantly different between the VSD and CCAVC groups; however, many postoperative outcome variables were significantly different, indicating that age per se was not predictive of surgical outcomes but that the pathophysiology of the cardiac lesion was a confounding factor.

There are several limitations in the present study, including the use of therapeutic indexes and clinical scoring systems to assess cardiovascular and pulmonary functions immediately after surgical intervention because access for direct measurement of cardiac output is limited in very young patients. Furthermore, studies involving larger numbers of patients will likely be necessary to generate absolute values of circulating N-BNP to identify at-risk patients and to determine timing for surgical intervention. Our analyses have led to the overall conclusion that high circulating N-BNP levels before surgical intervention reflect the extent of volume overload, ventricular distention, and cardiac stress and that the postoperative N-BNP levels are in response to CPB times and the complexity of surgical procedures necessitated by the nature of the congenital heart defect. Because plasma BNP levels have been correlated to

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shunt volume in children with congenital septal defects,[38] we anticipate that BNP levels would return to normal values after remodeling of the myocardium after surgical repair that would occur after several weeks or months.

In conclusion, the present study confirms the findings of recent investigations[21-24] supporting the potential prognostic utility of preoperative and postoperative BNP or N-BNP measurements in determining surgical risk and postoperative outcomes in pediatric patients.

References

1. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med.* 1998;339:321-8.
2. Dhingra H, Roongsritong C, Kurtzman NA. Brain natriuretic peptide: role in cardiovascular and volume homeostasis. *Semin Nephrol.* 2002; 22:423-37.
3. Mair J, Friedl W, Thomas S, Puschendorf B. Natriuretic peptides in assessment of left-ventricular dysfunction. *Scand J Clin Lab Invest Suppl.* 1999;230:132-42.
4. Shapiro BP, Chen HH, Burnett JC Jr, Redfield MM. Use of plasma brain natriuretic peptide concentration to aid in the diagnosis of heart failure. *Mayo Clin Proc.* 2003;78:481-6.
5. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. *BMJ.* 2002;324:1498-503.
6. Groenning BA, Nilsson JC, Sondergaard L, Pedersen F, Trawinski J, Baumann M, et al. Detection of left ventricular enlargement and impaired systolic function with plasma N-terminal pro brain natriuretic peptide concentrations. *Am Heart J.* 2002;143:923-9.
7. Yoshimura M, Yasue H, Okamura K, Ogawa H, Jougasaki M, Mukoyama M, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation.* 1993;87:464-9.
8. Cowie M, Mendez G. BNP and congestive heart failure. *Prog Cardiovasc Dis.* 2002;44:293-321.
9. Mukoyama M, Nakao K, Hosada K, Suga S, Saito Y, Ogawa Y, et al. Brain natriuretic peptide as a novel cardiac hormone in humans: evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest.* 1991;87: 1402-12.
10. Saito Y, Nakao K, Itoh H, Yamada T, Mukoyama M, Arai H, et al. Brain natriuretic peptide is a novel cardiac hormone. *Biochem Biophys Res Commun.* 1989;158:360-8.
11. Mizuno Y, Yoshimura M, Harada E, Nakayama M, Sakamoto T, Shimasaki Y, et al. Plasma levels of A- and B-type natriuretic peptide in patients with hypertrophic cardiomyopathy or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 2000;86:1036-40.
12. Fruhwald FM, Fahrleitner A, Watzinger N, Fruhwald S, Dobnig H, Schumacher M, et al. Natriuretic peptides in patients with diastolic dysfunction due to idiopathic dilated cardiomyopathy. *Eur Heart J.* 1999;20:1415-23.
13. Bay M, Kirk V, Parner J, Hassager C, Nielsen H, Krogsgaard K, et al. NT-proBNP: a new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function. *Heart.* 2003;89:150-4.
14. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-Type Natriuretic Peptide in the emergency diagnosis of heart failure. *N Engl J Med.* 2002;347:161-7.
15. Collins SP, Ronan-Bentle S, Storrow AB. Diagnosis and prognostic usefulness of natriuretic peptides in emergency department patients with dyspnea. *Ann Emerg Med.* 2003;41:532-45.
16. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med.* 2004;350:655-63.
17. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease. *Circulation.* 2003;108:275-81.
18. Silver MA, Maisel A, Yancy CW, McCullough PA, Burnett JC Jr, Francis GS, et al. BNP consensus panel 2004: a clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. *Congest Heart Fail.* 2004;10:1-30.
19. Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-proBNP): a new marker of cardiac impairment. *Clin Endocrinol.* 1997;47:287-96.
20. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Comparison of the Biomedica NT-proBNP enzyme immunoassay and the Roche NT-proBNP chemiluminescence immunoassay: implications for the prediction of symptomatic and asymptomatic structural heart disease. *Clin Chem.* 2003;49:976-9.
21. Shih CY, Sapru A, Oishi P, Azakie A, Karl TR, Harmon C, et al. Alteration in plasma B-type natriuretic peptide levels after repair of congenital heart defects: a potential perioperative marker. *J Thorac Cardiovasc Surg.* 2006;131:632-8.
22. Mir TS, Haun C, Lilje C, Laer S, Weil J. Utility of N-terminal brain natriuretic peptide plasma concentrations in comparison to lactate and troponin in children with congenital heart disease following open-heart surgery. *Pediatr Cardiol.* 2006;27:209-16.
23. Koch A, Kitzsteiner T, Zink S, Cesnjevar R, Singer H. Impact of cardiac surgery on plasma levels of B-type natriuretic peptide in children with congenital heart disease. *Int J Cardiol.* 2007;114:339-44.
24. Gessler P, Knirsch W, Schmitt B, Rousson V, von Eckardstein A. Prognostic value of plasma n-terminal pro-brain natriuretic peptide in children with congenital heart defects and open-heart surgery. *J Pediatr.* 2006;148:372-6.
25. Keene AR, Cullen DJ. Therapeutic Intervention Scoring System: update 1983. *Crit Care Med.* 1983;11:1-3.
26. Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR, et al. Post-operative course and hemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardio-pulmonary bypass and circulatory arrest. *Circulation.* 1995;92:2226-35.
27. Mir TS, Marohn S, Laer S, Eiselt M, Grollmus O, Weil J. Plasma concentrations of N-Terminal pro-brain natriuretic peptide in control children from the neonatal to adolescent period and in children with congestive heart failure. *Pediatrics.* 2002;110:e76.
28. Kunii Y, Kamada M, Ohtsuki S, Araki T, Kataoka K, Kageyama M, et al. Plasma brain natriuretic peptide and the evaluation of volume overload in infants and children with congenital heart disease. *Acta Med Okayama.* 2003;57:191-7.
29. Tarnok A, Hambsch J, Emmrich R. Complement activation, cytokines, and adhesion molecules in children undergoing cardiac surgery with or without cardiopulmonary bypass. *Pediatr Cardiol.* 1999;20:113-25.
30. Wan S, DeSmet JM, Barvais L. Myocardium is a major source of proinflammatory cytokines in patients undergoing cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1996;112:806-11.
31. Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation.* 1993;88:2128-38.
32. Kerbaul F, Giorgi R, Oddozc C, Collart F, Guidon C, Lejeune PJ, et al. High concentrations of N-BNP are related to non-infectious SIRS associated with cardiovascular dysfunction occurring after off-pump coronary artery surgery. *Br J Anaesth.* 2004;93:639-44.
33. Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. *J Mol Cell Cardiol.* 2004;36:505-13.
34. Madhok AB, Ojamaa K, Haridas V, Parnell VA, Pahwa S, Chowdhury D. Cytokine response in children undergoing surgery for congenital heart disease. *Pediatr Cardiol.* 2006;27:408-13.
35. Costello JM, Backer CL, Checchia PA, Mavroudis C, Seipelt RG, Goodman DM. Alterations in the natriuretic hormone system related to

cardiopulmonary bypass in infants with congestive heart failure. *Pediatr Cardiol.* 2004;25:347-53.
36. Mir TS, Laux R, Hellwege HH, Liedke B, Heinze C, von Buelow H, et al. Plasma concentrations of aminoterminal pro atrial natriuretic peptide and aminoterminal pro brain natriuretic peptide in healthy neonates: marked and rapid increase after birth. *Pediatrics.* 2003;112:896-9.
37. Holmstrom H, Hall C, Thaulow E. Plasma levels of natriuretic peptides and hemodynamic assessment of patent ductus arteriosus in preterm infants. *Acta Pediatr.* 2001;90:184-91.
38. Suda K, Matsumura M, Matsumoto M. Clinical implication of plasma natriuretic peptides in children with ventricular septal defect. *Pediatr Int.* 2003;45:249-54.