Predictive Value of B-type Natriuretic Peptide Level on the Postoperative Course of Infants with Congenital Heart Disease

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ABSTRACT: **Background:** B-type natriuretic peptide (BNP) has been shown to have prognostic value for morbidity and mortality after cardiac surgery. Less is known about its prognostic value in infants.

Objectives: To investigate the predictive value of BNP levels regarding the severity of the postoperative course in infants undergoing surgical repair of congenital heart disease.

Methods: We conducted a prospective comparative study. Plasma BNP levels in infants aged 1–12 months with congenital heart disease undergoing complete repair were measured preoperatively and 8, 24 and 48 hours postoperatively. Demographic and clinical data included postoperative inotropic support and lactate level, duration of mechanical ventilation, intensive care unit (ICU) and hospitalization stay.

Results: Cardiac surgery was performed in 19 infants aged 1–12 months. Preoperative BNP level above 170 pg/ml had a positive predictive value of 100% for inotropic score ≥ 7.5 at 24 hours (specificity 100%, sensitivity 57%) and 48 hours (specificity 100%, sensitivity 100%), and was associated with longer ICU stay ($P = 0.05$) and a trend for longer mechanical ventilation ($P = 0.12$). Similar findings were found for 8 hours postoperative BNP above 1720 pg/ml. BNP level did not correlate with measured fractional shortening.

Conclusions: In infants undergoing heart surgery, preoperative and 8 hour BNP levels were predictive of inotropic support and longer ICU stay. These findings may have implications for preplanning ICU loads in clinical practice. Further studies with larger samples are needed.

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KEY WORDS: B-type natriuretic peptide (BNP), infants, cardiac surgery, congenital heart disease

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B-type natriuretic peptide is a hormone with diuretic, natriuretic and vasodilatory properties [1,2] that was first identified in 1988 by Sudoh et al. [3]. In humans, BNP is produced and secreted mainly by cardiac ventricular myocytes in response to wall stress due to excessive volume or pressure loading of the heart [4]. The level of BNP has been shown to have prognostic value in adults with congestive heart failure and myocardial infarction [5-8], and to predict morbidity and mortality after cardiac surgery [9-12]. Data for the pediatric population, however, are still unclear. In a study of 23 children after surgery for single-ventricle congenital heart disease, Berry et al. [13] found that early postoperative BNP levels were predictive of the need for inotropic support and of length of hospitalization. Niedner and co-authors [14] reported similar results in children. In a study on 36 neonates of whom 16 underwent a palliative procedure and 20 a biventricular repair, Hsu and colleagues [15] reported post/preoperative BNP levels above 1 that were associated with an increased incidence of low cardiac output syndrome and fewer ventilator-free days. However, the studies of Mir et al. [16] and Koch et al. [17] failed to support these findings. To our knowledge, the association of perioperative BNP levels with the postoperative course has not yet been investigated in infants, 1 month to 1 year old as a single age group.

The aim of the present study was to test the hypothesis, based on findings in adults and children, that high preoperative BNP levels in infants undergoing biventricular repair may serve as a prognostic factor for a complicated postoperative course and decreased left ventricular function on echocardiography.

BNP = B-type natriuretic peptide

PATIENTS AND METHODS

A prospective cohort study was conducted in the cardiac intensive care unit of a major tertiary pediatric medical center over 6 months. The protocol was approved by the institutional review board, and informed consent was obtained from the patients' parents or legal guardians.

The parents or guardians of infants who were scheduled for open heart surgery were approached to participate in the study. Infants aged 1–12 months with congenital heart disease who underwent complete surgical repair were eligible for the study. Infants who had preoperative liver or renal failure or who could not be separated from cardiopulmonary bypass were excluded.

SURGICAL PROCEDURE

All participating children underwent open heart surgery for biventricular complete repair with cardiopulmonary bypass under total intravenous anesthesia. The priming solution consisted of Ringer's lactate, packed red blood cells, mannitol, and methyl prednisolone. Moderate hypothermia was used, and ultrafiltration was performed during rewarming. Postoperatively, patients received 60% maintenance intravenous fluids, were placed on mechanical ventilation and then weaned according to their clinical progress. Inotropic support was administered as clinically indicated, preferably with dopamine and milrinone as the first drugs of choice, targeting capillary refill > 3 seconds, urine output ≥ 0.5 ml/kg/hour and normal blood lactate levels.

BACKGROUND AND OPERATIVE DATA

Demographic, diagnostic, and operative data (bypass time, aortic cross-clamp time, core temperature, etc.) were collected for all patients. Inotropic score was calculated at 8, 24 and 48 hours postoperatively according to the following formula: dopamine (dose in μg/kg/min) plus dobutamine (μg/kg/min) plus epinephrine (μg/kg/min) multiplied by 100 [18]. All patients underwent echocardiographic measurements of left ventricle fractional shortening at 8 and 24 hours post-surgery.

BNP AND LACTATE MEASUREMENT

Samples for measurements of BNP were obtained 1 day before surgery and 8, 24 and 48 hours after. Blood was collected into tubes containing potassium EDTA (ethylene diamine tetra-acetic acid), and BNP was measured on site by a sandwich immunoassay (Triage BNP assay, Biosite® Diagnostics Inc., San Diego, CA, USA). Lactate levels were measured at the same time using a blood gas analyzer (ABL 725, Radiometer, Copenhagen, Denmark).

STATISTICAL ANALYSIS

Standard *t*-test was used to analyze continuous variables (e.g., patient age, level of inotropic support, duration of stay in ICU) by BNP level. The ANOVA test was used for comparison between means of multiple groups. The negative predictive value of each assay was computed on the basis of these curves. For all tests, P values < 0.05 were considered statistically significant. Pearson coefficient correlation was used for analyzing linear correlation between two variables.

RESULTS

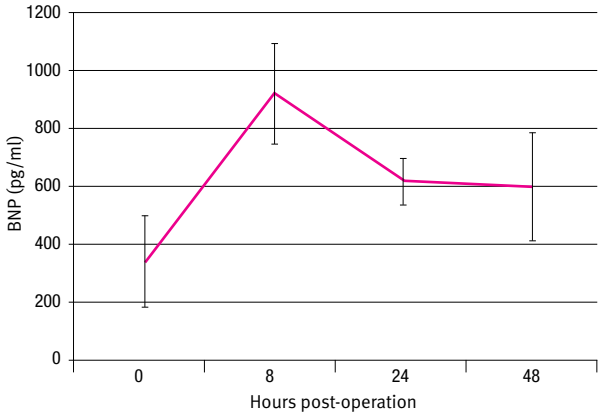
The study group included 19 patients, 11 males and 8 females, age 35 to 354 days (median 157 days) at surgery. The background data and distribution of the types of heart disease are shown in Table 1. Biventricular repair was performed in all patients.

ICU = intensive care unit

Table 1. Demographic and operative data in infants with congenital heart disease

Demographics	
No. of patients	19
Male	11
Female	8
Age at surgery (mean ± SD)	166 ± 126 days
Weight at surgery (mean ± SD)	5.3 ± 1.9 kg
Congenital defects (n)	
Ventricular septal defect	7
Atrioventricular canal	5
Tetralogy of Fallot	4
Transposition of the great arteries	2
Total anomalous pulmonary venous return	1
Perioperative data (mean ± SD)	
Cardiopulmonary bypass time	115.4 ± 36.8 min
Cross aortic clamp time	86.1 ± 31.5 min
Maximal lactate during cardiopulmonary bypass	38.6 ± 27.0 mg/dl
Time in intensive care unit	2.12 ± 1.44 days
Duration of hospitalization	8.58 ± 4.35 days
Exitus	0

Figure 1. B-type natriuretic peptide kinetics before and 48 hours after surgery



BNP KINETICS

The mean BNP levels for the whole study group at the various time points were as follows: preoperative, 313 ± 658 pg/ml (median 40 pg/ml, 25/75 percentiles 24 pg/ml and 160 pg/ml, respectively); 8 hours postoperative, 907 ± 762 pg/ml (median 480 pg/ml, 25/75 percentiles 313 pg/ml and 1620 pg/ml, respectively); 24 hours postoperative, 601 ± 324 pg/ml (median 570 pg/ml, 25/75 percentiles 275 pg/ml and 683 pg/ml, respectively); and 48 hours postoperative, 583 ± 530 pg/ml (median 417 pg/ml, 25/75 percentiles 318 pg/ml and 578 pg/ml, respectively) [Figure 1]. The differences between the preoperative and 8 hour postoperative values ($P < 0.001$), and between the 8 hour and 24 hour postoperative values ($P = 0.03$) were statistically significant. There was no significant difference between the preoperative and 24 hour postoperative values ($P = 0.74$) or between the 24 hour and 48 hour postoperative values ($P = 0.58$). There was no significant correlation between BNP and patient age, bypass and aortic cross-clamp time.

Table 2. Analysis of postoperative inotropic score by B-type natriuretic peptide levels

B-type natriuretic peptide cutoff	8 hour inotropic score (mean ± SD)	24 hour inotropic score (mean ± SD)	48 hour inotropic score (mean ± SD)
Preoperative			
≤ 170 pg/ml (n=14)	8.2 ± 6.5	5.0 ± 6.2	0.8 ± 1.2
> 170 pg/ml (n=5)	20.9 ± 5.4	21.8 ± 9.1	13.1 ± 5.2
P value	0.003	0.001	< 0.001
8 hours postoperative			
≤ 1720 pg/ml (n=14)	8.0 ± 6.3	4.7 ± 6.1	0.7 ± 1.2
> 1720 pg/ml (n=5)	20.9 ± 5.4	21.8 ± 9.1	13.1 ± 5.2
P value	0.003	0.001	< 0.001

Table 3. nalysis of postoperative course by B-type natriuretic peptide levels

B-type natriuretic peptide cutoff	Days on mechanical ventilation (mean ± SD)	Days in ICU (mean ± SD)	Hospitalization days (mean ± SD)
Preoperative			
≤ 170 pg/ml (n=13)	1.1 ± 0.9	2.1 ± 1.4	7.9 ± 3.6
> 170pg/ml (n=6)	4.5 ± 3.1	6.5 ± 2.9	11.8 ± 6.2
P value	0.118	0.05	0.128
8 hours postoperative			
≤ 1720 pg/ml (n=13)	1.10 ± 0.89	2.0 ± 1.4	7.7 ± 3.5
> 1720 pg/ml (n=6)	4.50 ± 3.11	6.5 ± 2.9	11.8 ± 6.2
P value	0.115	0.048	0.102

BNP LEVELS, INOTROPIC SUPPORT AND FRACTIONAL SHORTENING

A preoperative BNP level of 170 pg/ml was found to be the value with the best prediction for postoperative course and was used as the cutoff point. Table 2 shows the inotropic support values by BNP level. Patients (n=5) with a preoperative BNP > 170 pg/ml required significantly more inotropic support than patients (n=14) with a preoperative BNP ≤ 170 pg/ml at all time points evaluated (8, 24 and 48 hours postoperatively). Parallel findings were noted on analysis of the 8 hour postoperative BNP value, using a cutoff of 1720 pg/ml [Table 2].

A preoperative BNP level > 170 pg/ml had a positive predictive value of 100% for a calculated inotropic support level ≥ 7.5 µg/kg/min at 24 hours (specificity 100%, sensitivity 57%). An 8 hour postoperative BNP level > 1720 pg/ml was found to have a positive predictive value of 100% (specificity 100%, sensitivity 75%) for 24 hour inotropic support ≥ 7.5 µg/kg/min and of 100% (specificity 100%, sensitivity 100%) for 48 hours inotropic support ≥ 7.5 µg/kg/min. Although we could not find a statistically significant correlation between preoperative and 8 hours postoperative BNP levels and total inotropic support 8, 24 and 48 hours post-surgery, a post hoc analysis showed a statistically significant correlation between preoperative BNP levels and 24 hours postoperative adrenaline support ($r = 0.56$, $P < 0.05$) and milrinone support ($r = 0.47$, $P < 0.05$). Similarly, 8 hours postoperative BNP levels showed a statistically significant correlation with 24 hours postoperative dopamine and milrinone support ($r = 0.52$, $P < 0.05$, and $r = 0.48$, $P < 0.05$, respectively). There was no correlation between age and inotropic support.

Mean fractional shortening, 8 hours after surgery in infants with preoperative BNP ≤ 170 pg/ml was 35.9 ± 4.4 compared to 35.2 ± 2.9 for those with preoperative BNP > 170 pg/ml ($P = 0.84$). Similar findings were found measuring fractional shortening 24 hours after surgery (37.6 ± 6.2, 35.2 ± 3.7, $P = 0.56$, respectively).

BNP LEVELS AND LACTATE

Division of patients according to preoperative BNP level revealed that those with BNP > 170 pg/ml had a higher mean level of lactate at 8 hours (39.5 ± 22.8 mg/dl) than patients with BNP ≤ 170 pg/ml (12.5 ± 4.5 mg/dl), but the difference was not statistically significant ($P = 0.1$). At 24 hours post-surgery, lactate level was less than 20 mg/dl in all patients but one. Pearson's correlation revealed a significant correlation between preoperative BNP levels and 8 hours postoperative lactate levels ($r = 0.62$, $P < 0.05$) and between 8 hours postoperative BNP levels and 8 hours lactate levels ($r = 0.54$, $P < 0.05$).

BNP LEVELS AND INTENSIVE CARE COURSE

Table 3 compares the time on mechanical ventilation, duration of ICU and hospital stay in patients with a preoperative BNP ≤ 170 pg/ml (n=13) or > 170 pg/ml (n=6) and 8 hours BNP < 1720 pg/ml or higher. Significant differences were found between the groups for length of ICU stay by both parameters (preoperative BNP, $P = 0.05$; 8 hours BNP, $P = 0.048$). We found a statistically significant correlation between preoperative and 8 hours postoperative and duration of mechanical ventilation ($r = 0.48$, $P < 0.05$ and $r = 0.69$, $P < 0.05$, respectively).

DISCUSSION

The present study suggests that in infants aged 1 month to 1 year with heart disease scheduled for biventricular repair, the preoperative and early postoperative BNP levels are predictive of the need for inotropic support during the first 48 hours post-surgery and of the duration of ICU stay, in accordance with our hypothesis.

The BNP kinetics in the setting of cardiac surgery have been investigated mainly in adults and to a lesser extent in the pediatric population. In a study of 30 neonates with transposition of the great arteries, Cannesson et al. [19] found that serum BNP levels decreased immediately after surgery compared to the preoperative levels and then rose gradually over the next 24 hours. Similar results were reported by Ationu and collaborators [20] in older children (age 2–9 years) undergoing surgery with cardiopulmonary bypass for various types of congenital heart disease. By contrast, Berry et al. [13], in a study of 23 children after surgical palliation of congenital single-ventricle heart disease, reported an increase in BNP levels 6–12 hours

after surgery. These results were supported by Walsh et al. [21] and others [16,22,23]. The discrepancies among the studies may be attributable to differences in the techniques used for bypass or myocardial protection during bypass, the extent and duration of ultrafiltration, or the immediate postoperative medical management and fluid challenge practices. Furthermore, the sampling time was not identical in all studies and "inter-sampling time" may be missed.

Gessler et al. [24], using a different measuring method, investigated preoperative BNP levels in 40 children aged 3 months to 7 years with three types of heart disease (obstructive, left-to-right shunt, cyanotic). They found no significant difference in the preoperative values among the groups. Their analysis, performed on all patients as a single group, showed that preoperative BNP value correlated with the inotropic support. Our study, which was limited to one age group – infants less than one year old – found that preoperative BNP level ≥ 170 pg/ml was predictive of a more complicated postoperative course, manifested by the need for inotropic support over the first 48 hours. Patients with a higher BNP level also showed a clear tendency for longer mechanical ventilation and longer ICU and hospital stays than those with a lower level, although these differences failed to reach statistical significance. Hsu et al. [15] showed that preoperative levels in 36 neonates, 16 after palliative cardiac surgery and 20 after biventricular repair, were not correlated with ventilator-free days, ICU stay or days of hospitalization. They also found that post/preoperative BNP ratio > 1 was associated with an increased incidence of low cardiac output syndrome and fewer ventilator-free days. Shih et al. [23], in a study of infants aged 1 day to children aged 15 years and analyzed as a single group, found that 12 hour BNP level proved to be a significant predictor of duration of mechanical ventilation ($r^2 = 0.32$, $P < 0.0001$). Similarly, a recently published study by Pérez-Piaya et al. [25] showed that peak BNP values correlated with maximal inotropic support, length of mechanical ventilation and ICU stay.

However, It should be emphasized that postoperative BNP levels, and as a consequence, their predictive value for postoperative course, can be affected by several factors such as stress forces on the ventricle wall, which in turn are affected by the fluid loading practices of the specific ICU, the diuretic and inotropic regimens used, and the ventilation strategy.

We suggest that preoperative BNP measurement may assist clinicians in planning the work load in the ICU. We calculated the positive predictive value of specific pre- and postoperative BNP values for a complicated postoperative course. Analysis of the correlations between the two parameters (e.g., BNP level and postoperative course) may equip pediatric intensivists, cardiologists and thoracic surgeons with a practical tool to determine which patients might need a prolonged ICU stay.

In the present study, the preoperative BNP level was not predictive of the postoperative fraction shortening on echocardiography. It can probably be explained by the significant predictive value of the preoperative BNP for inotropic support: that is, the higher degree of inotropic support required by the patients with a higher BNP level improved their fractional shortening and their resultant cardiac output according to body requirements. This assumption is supported by the normalization in lactate levels observed in the first 24 hours after surgery in all patients.

Our study was limited by the small sample size and was not powered to perform multivariate analysis to evaluate the effect of gender and type of congenital heart disease. The small sample size may also explain the discrepancy in the statistical significance between 8 hours BNP levels prediction of ICU stay and 8 hours BNP prediction of hospitalization days.

In summary, in infants under age 1 year with various types of congenital heart disease, a preoperative BNP level > 170 pg/ml suggests the need for more inotropic support during the first 48 hours post-surgery, and for longer mechanical ventilation and longer ICU and hospital stay. These data may have important implications for the clinical identification of patients at risk of a more complicated course after cardiac surgery. Further studies with a larger number of infants aged 1 month to 1 year as well as a single type of congenital heart disease are needed to confirm our findings and broaden BNP values as a marker for postoperative course.

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Capsule

Probing the microbial mix

In the past decade, it has become apparent that we are colonized by microbes that probably shape many of our most important physiological processes. Much of the work has taken a metagenomics approach – characterizing what microbes are there and what genes they express. Maurice et al. now go one step further; they are investigating how our microbial inhabitants respond to pharmacological perturbations. A combination of single-cell analysis by flow cytometry, DNA sequencing, and metatranscriptomics revealed that the bacteria within the human gut vary with respect to membrane integrity, polarization, and metabolic activity. Metabolic activity was enriched in Firmicutes, whereas Bacteroidetes were less metabolically active. Exposure to both antibiotics and host-targeted drugs resulted in alterations in the physiology, structure, and gene expression profile of the bacteria. An increase in genes associated with resistance, stress responses, and metabolism was observed after antibiotic treatment. These results represent an important step toward understanding on a broad scale how specific perturbations affect our microbial communities.

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Eitan Israeli

Capsule

Enhanced survival of lung tissue-resident memory CD8+ T cells during infection with influenza virus due to selective expression of IFITM3

Infection with influenza virus results in the deposition of anti-influenza CD8+ resident memory T cells (TRM cells) in the lung. As a consequence of their location in the lung mucosal tissue, these cells are exposed to cytopathic pathogens over the life of the organism and may themselves be susceptible to infection. Wakim et al. found that lung TRM cells selectively maintained expression of the interferon-induced transmembrane protein IFITM3, a protein that confers broad resistance to viral infection. Lung TRM cells that lacked IFITM3 expression were more susceptible to infection than were their normal counterparts and were selectively lost during a secondary bout of infection. Thus, lung TRM cells were programmed to retain IFITM3 expression, which facilitated their survival and protection from viral infection during subsequent exposures.

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