B-type natriuretic peptide levels predict outcome after neonatal cardiac surgery

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Objectives: Neonates undergoing cardiac surgery are at high risk for adverse outcomes. B-type natriuretic peptide is used as a biomarker in patients with cardiac disease, but the predictive value of B-type natriuretic peptide after cardiac surgery in neonates has not been evaluated. Therefore, the objective of this study was to determine the predictive value of perioperative B-type natriuretic peptide levels for postoperative outcomes in neonates undergoing cardiac surgery.

Methods: Plasma B-type natriuretic peptide determinations were made before and 2, 12, and 24 hours after surgery in 36 consecutive neonates. B-type natriuretic peptide levels and changes in perioperative B-type natriuretic peptide were evaluated as predictors of postoperative outcome.

Results: B-type natriuretic peptide levels at 24 hours were lower than preoperative levels (24-h/pre B-type natriuretic peptide ratio < 1) in 29 patients (81%) and higher (24-h/pre B-type natriuretic peptide ratio $\geq$ 1) in 7 patients (19%). A 24-hour/pre B-type natriuretic peptide level of 1 or greater was associated with an increased incidence of low cardiac output syndrome (100% vs 34%, $P = .002$) and fewer ventilator-free days (17 ± 13 days vs 26 ± 3 days, $P = .002$), and predicted the 6-month composite end point of death, an unplanned cardiac operation, or cardiac transplant (57% vs 3%, $P = .003$). A 24-hour/pre B-type natriuretic peptide level of 1 or greater had a sensitivity of 80% and a specificity of 90% for predicting a poor postoperative outcome ($P = .003$).

Conclusion: In neonates undergoing cardiac surgery, an increase in B-type natriuretic peptide 24 hours after surgery predicts poor postoperative outcome.

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This research was supported in part by grants K08 HL086513 (P.O.), K23 HL079922 (R.L.K.), and HL61284 and MO1RR01271 (J.R.F.) from the National Institutes of Health, and a grant from Biosite Diagnostic. Jeffrey Fineman reports grant support from Biosite, Inc and Fondation Leducq.

Received for publication March 1, 2007; revisions received April 10, 2007; accepted for publication April 16, 2007.

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J Thorac Cardiovasc Surg 2007;134:939-45
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2007.04.017

Surgical repair or palliation of congenital cardiac defects is performed routinely in the neonatal period. Neonates, in comparison with infants and children, have adverse events more often and have greater perioperative mortality. Although risk-adjustment scoring systems and various biomarkers have been investigated, it remains difficult to identify individual neonates with an increased risk for poor postoperative outcome.^{1,2}

B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide hormone, with diuretic, natriuretic, and vasoactive properties, that is used as a biomarker for the management of cardiac disease in both adult and pediatric patients.³⁻⁷ We reported recently that BNP levels predict the development of both low cardiac output

Abbreviations and Acronyms

AVdO ₂	= arteriovenous oxygen saturation difference
BNP	= B-type natriuretic peptide
CPB	= cardiopulmonary bypass
LCOS	= low cardiac output syndrome
SvO ₂	= venous oxyhemoglobin saturation

syndrome (LCOS) and prolonged mechanical ventilation in children with congenital heart defects amenable to biventricular repair.⁸ However, the clinical predictive value of perioperative BNP levels in neonates, who are most at risk for unpredictable adverse outcomes, especially neonates undergoing a palliative modified Norwood stage I procedure, is unknown.

Therefore, the objectives of our study were (1) to determine and compare perioperative BNP levels in neonates undergoing surgical repair or palliation of their cardiac defects and (2) to investigate the potential predictive value of BNP levels and postoperative changes in BNP levels for postoperative outcome.

Materials and Methods

We conducted a prospective cohort study in the Pediatric Cardiac Intensive Care Unit at the University of California, San Francisco Children's Hospital, between June 2005 and June 2006. Eligible patients were neonates with congenital cardiac defects undergoing surgical repair or palliation using cardiopulmonary bypass (CPB). Patients were excluded from the study if their weight was less than 2 kg or if they were less than 36 weeks postconceptual age at surgery.

The preoperative anesthesia management, intraoperative bypass strategy, and subsequent Pediatric Cardiac Intensive Care Unit management followed standard institutional practices. All patients underwent modified ultrafiltration before separating from CPB. An on-service team, blinded to the BNP values, made all patient management decisions.

We obtained written informed consent from the patients' parents or guardians before enrollment in the study. The University of California, San Francisco review board approved the study.

Patient Classification

We divided the patients into 2 groups. Group I consisted of neonates who underwent palliation with a modified stage I Norwood procedure, and group II consisted of neonates who underwent biventricular repair.

Data Collection

Blood samples were obtained from an arterial catheter preoperatively and at 2, 12, and 24 hours after CPB. In patients unable to separate from CPB postoperatively, preoperative but not postoperative samples were obtained because of the potential confounding effects of extracorporeal life support. The samples were placed immediately on ice in chilled ethylenediamine tetraacetic acid tubes and centrifuged at 3000 rpm for 15 minutes at 4°C.

Separated plasma was stored at -20°C. Within 4 days of obtaining the sample, the plasma was thawed to room temperature and BNP levels were measured using a commercially available fluorescence immunoassay (Triage Meter Plus, Biosite Diagnostic, San Diego, Calif). The measurable range of BNP on this device is between 5 and 5000 pg/mL. The estimated coefficient of variation for the assay is 9.2% to 11.4%.

Clinical and biochemical data were collected prospectively at each sampling point and daily thereafter by an observer blinded to the BNP data. The clinical data collected included the patient demographics, CPB duration, aortic crossclamp duration, inotrope dose, mean systemic arterial pressure, central venous pressure, heart rate, intensive care unit days, hospital days, and use of mechanical ventilation. Biochemical data collected included hematocrit, arterial and venous blood gases, serum lactate, blood urea nitrogen, and creatinine. The occurrence of cardiac transplant was monitored for 6 months after surgery.

Outcome Measures

The primary end point was the occurrence of a poor postoperative outcome, within 6 months of surgery, defined as (1) death, (2) the need for an unplanned cardiac operation before discharge, or (3) the need for a cardiac transplant during the 6-month follow-up period.

Secondary end points were the duration of mechanical ventilation and the development of LCOS within 48 hours after surgery. The duration of mechanical ventilation was quantified as the number of ventilator-free days within the first 30 days after surgery. The definition of LCOS was derived from criteria published by Hoffman and colleagues,⁹ which included a combination of changes in clinical signs and laboratory indicators. Criteria included tachycardia, oliguria, poor perfusion, cardiac arrest, or metabolic acidosis, and the need for interventions aimed at augmenting cardiac output, such as increased pharmacologic support relative to the baseline and mechanical pacing.

Calculations

Inotrope use was quantified by a score adapted from Wernovsky and colleagues.¹⁰ The score was calculated from the level of inotropic support the patients were receiving (in micrograms/kilogram/minute) at each sampling point according to the following equation: dopamine + dobutamine + [(epinephrine + norepinephrine) × 100] + (milrinone × 20). The arteriovenous oxygen saturation difference (AVdO₂) was calculated as the co-oximetric arterial oxyhemoglobin saturation minus the central venous oxyhemoglobin saturation (SvO₂).

Data Analysis

Differences in the continuous variables between groups were tested with the Student *t* test or Mann-Whitney *U* test. Differences in the categorical variables between groups were tested with the Fisher exact test. Contingency tables were formulated to determine the sensitivity and specificity of BNP measurements. Correlations between variables were performed by Spearman rank correlation method. Changes in BNP over time were compared by repeated-measures analysis of variance. Statistical analyses were performed with the use of Prism 4.0 (GraphPad Software, Inc, San Diego, Calif) and Stata 9.0 (Stata Corp, College Station, Tex).

TABLE 1. Preoperative demographics of all patients

	Group I	Group II	P
Patients	16	23	
Age, d	7 ± 4	12 ± 10	.03
Weight, kg	3.3 ± 0.5	3.2 ± 0.7	.82
Male, n (%)	6 (38%)	16 (69%)	.06
Type of surgery	Norwood operation*	Two-ventricle corrective repair	
Type of cardiac lesion	11 HLHS 1 DORV, HRV, HAA 1 Tricuspid atresia, TGA, HRV, HAA 1 IAA, HAA 1 AVSD, hypoplastic left ventricle, HAA 1 TGA, HAA	6 TGA, IVS 4 HAA, VSD 3 DORV 2 IAA 2 TAPVR 2 TGA, VSD 1 HAA 1 TA 1 TOF, PA 1 Cor triatriatum	
Heart rate, min ⁻¹	150 ± 15	151 ± 14	.93
Mean arterial pressure, mm Hg	48 ± 6	49 ± 9	.59
Arterial oxygen saturation, %	92 ± 6	91 ± 6	.84
Mechanical ventilation use, n (%)	13 (81%)	14 (61%)	.29
Prostaglandin E1 use, n (%)	16 (100%)	19 (83%)	.13
Serum lactate, mmol/L	1.4 ± 0.4	1.9 ± 0.7†	.02
Hematocrit, %	40 ± 5	37 ± 6	.18
Blood urea nitrogen, mg/dL	15.7 ± 9.1	11.6 ± 7.5	.13
Blood creatinine, mg/dL	0.7 ± 0.3	0.6 ± 0.2	.26

HLHS, Hypoplastic left heart syndrome; DORV, double outlet right ventricle; HRV, hypoplastic right ventricle; HAA, hypoplastic aortic arch; AVSD, atrioventricular septal defect; TGA, transposition of great arteries; IAA, interruption of aorta; IVS, intact ventricular septum; VSD, ventricular septal defect; TAPVR, total anomalous pulmonary venous return; TA, truncus arteriosus; TOF, tetralogy of Fallot; PA, pulmonary atresia. Data are presented as mean ± standard deviation or number (percentage). *Fourteen with right ventricle-pulmonary artery conduits and 2 with modified Blalock-Taussig shunts. †n = 14.

Results

Subjects

Thirty-nine consecutive neonates were enrolled in the study (group I: 16, group II: 23). Three patients in group II could not be separated from CPB after surgery. Therefore, 36 patients (group I: 16, group II: 20) had complete BNP measurements. The patients' preoperative characteristics are shown in Table 1. The patients' ages ranged from 3 to 30 days (mean 10 ± 8 days). Group I was younger than group II at the time of surgery (7 ± 4 days vs 12 ± 10 days, $P = .03$). The mean preoperative serum lactate was lower in group I than that in group II (1.4 ± 0.4 mmol/L vs 1.9 ± 0.7 mmol/L, $P = .02$, Table 1).

The patients' intraoperative and postoperative characteristics are shown in Table 2. The inotrope score 24 hours after surgery tended to be higher in group I than in group II ($P = .05$).

Outcomes

There were 6 patients (15%) who had a poor postoperative outcome. Of the 36 patients who had complete postoperative BNP data available, 5 (14%) had a poor postoperative outcome. Between groups, 3 of 16 patients (19%) in group I, and 3 of 23 patients (13%) in group II had a poor

postoperative outcome (Table 2). The characteristics of patients with a poor postoperative outcome are shown in Table 3.

The number of ventilator-free days was similar between groups (23 ± 5 days vs 24 ± 8 days, Table 2). LCOS

TABLE 2. Intraoperative and postoperative characteristics of all patients

	Group I (n = 16)	Group II (n = 23)	P
CPB time, min	139 ± 32	130 ± 47	.50
Crossclamp time, min	50 ± 14	58 ± 27	.27
24-h inotrope score	13.4 ± 5.1	9.0 ± 7.6*	.05
24-h serum lactate, mmol/L	2.3 ± 1.1	2.0 ± 1.3†	.41
ICU length of stay, d	14 ± 9	10 ± 8	.10
Hospital length of stay, d	25 ± 9	21 ± 12	.32
Ventilator-free days, d	23 ± 5	24 ± 8	.75
LCOS, n (%)	10 (63%)	7 (35%)*	.18
Requirement of ECLS	1 (6%)	3 (13%)	.63
Poor outcomes, n (%)	3 (19%)	3 (13%)	.67

CPB, Cardiopulmonary bypass; ICU, intensive care unit; LCOS, low cardiac output syndrome; ECLS, extracorporeal life support. Data are presented as mean ± standard deviation or number (percentage). *n = 20, excluding 3 patients with ECLS initiated in the operating room. †n = 19.

TABLE 3. Characteristics of patients with poor outcomes

Patient	Group	Diagnosis	Surgery	Major poor outcome
1	I	HLHS	Modified Norwood	Death at POD 13, with ECLS initiated 42 h postoperatively
2	I	HLHS	Modified Norwood	Requiring transplant because of persistent RV dysfunction 4 months after operation
3	I	AVSD, HAA, LV hypoplasia	Modified Norwood	Reoperation at POD 3 for residual aortic arch obstruction
4	II	TAPVR	Repair of TAPVR	Reoperation at POD 10 for residual pulmonary venous obstruction
5	II	DORV	VSD closure, RVOT reconstruction	Death at POD 35
6	II	HAA, VSD	VSD closure, aortic arch repair	Death at POD 14, with ECLS initiated in the OR because of inability to separate from CPB*

HLHS, Hypoplastic left heart syndrome; AVSD, atrioventricular septal defect; HAA, hypoplastic aortic arch; TAPVR, total anomalous pulmonary venous return; DORV, double outlet right ventricle; VSD, ventricular septal defect; ECLS, extracorporeal life support; POD, postoperative day; LV, left ventricle; RVOT, right ventricular outflow tract; OR, operating room; RV, right ventricle; CPB, cardiopulmonary bypass. *This patient did not have postoperative measurements of BNP because ECLS was initiated in the operating room.

developed in 17 patients (44%) within the first 48 hours after surgery (Table 2). Of the 36 patients who had complete postoperative BNP data available, 17 (47%) had postoperative LCOS. The occurrence of LCOS was not different between groups; postoperative LCOS developed in 10 of 16 patients (63%) in group I and in 7 of 20 patients (35%) in group II (Table 2).

Perioperative B-type Natriuretic Peptide Levels

BNP levels preoperatively and at 2, 12, and 24 hours postoperatively for all patients are shown in Figure 1. BNP levels decreased after surgery; BNP levels at 12 hours were significantly lower than preoperative levels ($P < .01$), and BNP levels at 24 hours were significantly lower than levels at all other sample times ($P < .001$). BNP levels for groups I and II are shown in Table 4.

Figure 1. Column bar plots showing the change in BNP before and after CPB. The mean (columns) and the standard error (vertical lines). Twenty-four-hour postoperative BNP levels are significantly lower than preoperative, 2-hour, and 12-hour BNP levels. * $P < .01$. ** $P < .001$. BNP, B-type natriuretic peptide.

Preoperative B-type Natriuretic Peptide Levels and Outcomes

Preoperative BNP levels correlated with postoperative BNP levels at 2 hours ($\rho = 0.64$, $P < .0001$) but not at 12 and 24 hours. There was no association between preoperative BNP levels and age, sex, weight, preoperative mean arterial pressure, heart rate, and arterial oxygen saturation, or preoperative hematocrit, serum lactate, blood urea nitrogen, and creatinine. In addition, preoperative BNP levels were not correlated with the number of ventilator-free days, intensive care unit stay, or days of hospitalization.

Preoperative BNP levels were not different between patients with or without postoperative LCOS or between patients with or without poor postoperative outcome.

Postoperative B-type Natriuretic Peptide Levels and Outcomes

In the 36 patients with postoperative BNP measurements, 24-hour BNP levels correlated with heart rate ($\rho = 0.47$, $P = .004$) and inotrope score ($\rho = 0.46$, $P = .005$). There was no correlation between postoperative BNP levels and mean arterial pressure, central venous pressure, arterial oxygen saturation, or hematocrit, serum lactate, AVdO₂, blood urea nitrogen, creatinine, or duration of CPB. In addition, postoperative BNP levels did not correlate with intensive care unit or hospital length of stay.

Postoperative BNP levels did not correlate with the number of ventilator-free days and were not different between patients with or without postoperative LCOS. In addition, postoperative BNP levels were not different between patients with or without poor postoperative outcome.

Perioperative B-type Natriuretic Peptide Change and Outcomes

Because absolute BNP levels are age and lesion-specific, we examined the relationship between the change in BNP over the first 24 hours after surgery and outcomes. Of the 36 patients with postoperative BNP levels, the 24-hour BNP

TABLE 4. B-type natriuretic peptide levels at different time points

	Pre BNP (pg/mL)	2-h BNP (pg/mL)	12-h BNP (pg/mL)	24-h BNP (pg/mL)	P*
Group I (n = 16)	1866 ± 1019 (698-3450)	1550 ± 916 (321-3720)	1362 ± 832 (543-3060)	638 ± 353 (38-1340)	<.0001
Group II (n = 23)†	1617 ± 1414 (8-5000)	1350 ± 881 (58-2850)	1043 ± 667 (152-2388)	463 ± 239 (91-988)	<.0001

BNP, B-type natriuretic peptide. Data are presented as mean ± standard deviation and range. *Analysis of variance within groups. †n = 20 in 2, 12, and 24 hours, excluding 3 patients with ECLS initiated in the operating room.

level was lower than the preoperative BNP level (24-h/pre BNP ratio < 1) in 29 patients (81%) (group I: 14 of 16, 88%; group II: 15 of 20, 75%, $P = .43$). However, in 7 patients (19%), BNP levels at 24 hours were increased above preoperative levels (24-h/pre BNP ratio ≥ 1). The characteristics of patients with a 24-hour/pre BNP level less than 1 and patients with a 24-hour/pre BNP level of 1 or more are shown in Table 5. LCOS developed within the first 48 hours after surgery in all 7 patients (100%) with a 24-hour/pre BNP level of 1 or more compared with only 10 of 29 patients (34%) with a 24-hour/pre BNP level less than 1 ($P = .002$, Table 5).

In addition, compared with patients with a 24-hour/pre BNP level less than 1, patients with a 24-hour/pre BNP level of 1 or more had significantly fewer ventilator-free days (17 days ± 13 vs 26 days ± 3, $P = .002$, Table 5).

Finally, only 1 of 29 patients (3%) with a 24-hour/pre BNP level less than 1 experienced a poor postoperative

outcome, compared with 4 of 7 patients (57%) with a 24-hour/pre BNP level of 1 or more ($P = .003$, Table 5). The postoperative changes in BNP over time (expressed as the postoperative to preoperative BNP ratio) are shown for patients with and without poor postoperative outcomes in Figure 2. There was a significant interaction between outcome and sample time ($P < .0001$). The postoperative to preoperative BNP ratio was greater in patients with poor postoperative outcome than in patients without poor postoperative outcome at 2, 12, and 24 hours after surgery (Figure 2). A 12-hour/pre BNP level of 1 or more had a sensitivity of 80% and a specificity of 77% for predicting poor postoperative outcome ($P = .02$), and a 24-hour/pre BNP level of 1 or more had a sensitivity of 80% and a specificity of 90% for predicting a poor postoperative outcome ($P = .003$).

AVdO₂ and Lactate

We examined the relationship between AVdO₂ and serum lactate at each sampling point and outcome. There was no association between either the AVdO₂ or serum lactate levels with the number of ventilator-free days or the occurrence of poor postoperative outcome. In addition, postoperative changes in serum lactate were not associated with outcome.

TABLE 5. Characteristics of patients with a 24-hour/pre B-type natriuretic peptide ratio of 1 or greater and patients with a 24-hour/pre B-type natriuretic peptide ratio less than 1

	Decreased (24-h/pre BNP ratio < 1)	Increased (24-h/pre BNP ratio ≥ 1)	P
Patient number	29	7	
Age, d	9 ± 6	12 ± 12	.40
Weight, kg	3.3 ± 0.5	3.5 ± 0.7	.36
Male, n (%)	16 (55%)	4 (57%)	1.0
Group I, n (%)	14 (48%)	2 (29%)	.43
CPB time, min	136 ± 36	121 ± 59	.39
Crossclamp time, min	54 ± 25	46 ± 19	.41
24-h inotrope score	9.9 ± 6.5	14.8 ± 7.1	.07
24-h serum lactate, mmol/L	2.1 ± 1.0*	3.1 ± 1.9†	.20
ICU length of stay, d	10 ± 8	16 ± 14	.69
Hospital length of stay, d	23 ± 11	25 ± 13	.58
Ventilator-free day, d	26 ± 3	17 ± 13	.002
LCOS, n (%)	10 (34%)	7 (100%)	.002
Poor outcome, n (%)	1 (3%)	4 (57%)	.003
	1 reoperation	2 deaths 1 transplant 1 reoperation	

BNP, B-type natriuretic peptide; CPB, cardiopulmonary bypass; ICU, intensive care unit; LCOS, low cardiac output syndrome. Data are presented as mean ± standard deviation. *n = 28. †n = 5.

Figure 2. Comparisons of postoperative changes of BNP ratio over time between patients with good outcomes (n = 31) and patients with poor outcomes (n = 5). The BNP ratios are greater at all sample times in the poor outcome group. The scale of y-axis is log transformed. Data are presented as mean ± standard error. * $P < .05$ versus good outcome. BNP, B-type natriuretic peptide.

Discussion

These data suggest that BNP may be a valuable biomarker for prognostication and risk stratification in neonates undergoing cardiac surgery. We found that an increase in BNP levels above the preoperative baseline over the first 24 hours after surgery was associated with LCOS and an increased duration of mechanical ventilation, and predicted the composite end point of death, an unplanned cardiac operation before discharge, or a cardiac transplant within the 6-month follow-up period.

In a study of infants and children with biventricular cardiac defects, we previously reported⁸ that BNP levels increased after surgery and that the 12-hour level was associated with the need for mechanical ventilation beyond 48 hours and the development of LCOS. In contrast, the current study did not find an association between absolute BNP levels and the primary or secondary outcomes. This may relate to the wide variability in BNP levels found in neonates (Table 4). Several studies suggest that this variability is influenced in part by the age, type of cardiac defect, and exposure to CPB.^{6,11-13} Because we anticipated that potential associations between absolute BNP levels and outcomes would be difficult to demonstrate given this variability, we also studied the predictive value of the postoperative change in BNP. Moreover, because BNP levels likely are altered by mechanisms intrinsic to the myocardium, we hypothesized that perioperative alterations in BNP would capture cardiopulmonary derangements, particularly those resulting in long-term sequelae, in a unique manner. We found that mean BNP levels decreased in the majority of neonates after surgery, in contrast with other studies.^{8,12,14,15} In the present study, only 1 patient with a postoperative decrease in BNP from preoperative baseline had a poor postoperative outcome, whereas an increase in BNP above baseline after surgery was associated with LCOS, an increased duration of mechanical ventilation, and a poor postoperative outcome.

The mechanisms regulating BNP in neonates with congenital cardiac defects undergoing surgery remain to be clarified. Developmental studies in healthy subjects indicate that BNP levels are highest at birth but decrease by the first week of life, and by 2 weeks of age are generally lower than adult levels.^{11,16} Preoperative BNP levels in the present study were more than 10-fold greater than the normal reported values for neonates and were also much greater than levels reported in infants and children with congenital cardiac defects.^{8,11,14,16-18} One potential mechanism for the decrease in BNP after surgery is a reduction in the Qp:Qs ratio. A linear relationship between BNP levels and the Qp:Qs ratio in patients with ventricular septal defects has been reported.¹⁹ In addition, in cardiac defects associated with an obstruction to outflow from the heart, surgical correction or palliation may have reduced the pressure load placed on the ventricle, thus decreasing BNP release. In

fact, a recent study found that BNP levels correlated with the degree of left ventricular outflow tract obstruction in children and that they decreased 24 hours after successful balloon valvotomy in newborns with aortic stenosis.²⁰ Given that numerous studies have demonstrated an increase in BNP after CPB, it is unclear whether surgical palliation or repair of the cardiac defects allowed BNP levels to decrease despite the effect of CPB, or whether the response to CPB differs in neonates in a manner that mitigates against an increase in BNP.^{8,12,14,15}

We found similar changes in BNP levels between neonates undergoing a modified Norwood Stage I operation and a biventricular repair, in contrast with studies of levels in older children.¹⁷ Although BNP levels in group I tended to be higher than group II in our study, we found a similar postoperative decrease in BNP in both groups. We did not find significant outcome differences between groups, despite the increased risks traditionally associated with the modified Norwood stage I procedure.

To date, the 2 most commonly used biomarkers in the management of patients after congenital cardiac surgery are the SvO₂ (or AVdO₂) and serum lactate.^{1,21-24} Determinations of SvO₂ and the AVdO₂ are relatively reliable indicators of the cardiac output at any given time and thus have been used successfully to guide postoperative therapies.²¹ Several studies on serum lactate have found that lactate, especially its rate of change in the postoperative period, predicted outcome, including mortality.^{1,22} Unfortunately, these findings have not been reproduced by other larger studies, and the precise lactate levels that were predictive in the positive studies varied considerably, which has obviated a standardized use of lactate as a prognostic biomarker.^{1,22-24} However, because acute management decisions are aimed at normalizing the SvO₂ and lactate levels, it is likely that only persistently abnormal values refractory to treatment will be predictive of an adverse event in the short term. Therefore, it is not surprising that SvO₂, AVdO₂, and both absolute serum lactate levels and postoperative changes in serum lactate failed to predict postoperative outcome in the current study. The relationship of these factors to LCOS could not be evaluated, because they contributed to its clinical definition.

We used the duration of mechanical ventilation as a secondary outcome measure because it is often used as a surrogate marker of disease severity in various clinical studies. We chose to analyze the duration of mechanical ventilation as ventilator-free days over the first 30 postoperative days to avoid confounding the analysis with patients who died or were transferred to a transplant center while receiving mechanical ventilation. Because validated criteria for weaning from mechanical ventilation are not available for neonates after repair of congenital cardiac defects, the attending physicians made these decisions on an individual

basis. It is important to note that these physicians were blinded to the BNP values.

We also used the development of LCOS as a secondary outcome, because it has been used as an end point in therapeutic trials in pediatric patients after cardiac surgery.⁹ Although postoperative LCOS developed in all patients with a 24-hour/pre BNP ratio of greater than 1, the majority of LCOS cases developed early in the postoperative course before the 24-hour time point. Thus, the perioperative change in BNP did not predict LCOS but rather was associated with it. Whether goal-directed therapies for LCOS that target postoperative changes in BNP could be used in neonates after cardiac surgery was not evaluated but warrants further study. For instance, our study suggests that neonates with an increase in BNP levels at 24 hours compared with baseline should undergo intense scrutiny to detect and treat any residual hemodynamic lesions, including occult or overt heart failure with close follow-up for 6 months.

The primary limitation of the present study relates to sample size. Larger studies will be needed to precisely define the role of BNP in the management of neonates with cardiac disease. Moreover, given the considerable variation between patients, larger longitudinal studies are needed to evaluate BNP in each cardiac defect and at exact developmental time points.

Conclusions

We found that mean BNP levels decreased over the first 24 hours in the majority of neonates after cardiac surgery. However, an increase in BNP levels above preoperative baseline at 24 hours was associated with LCOS and prolonged mechanical ventilation, and predicted death, an unplanned operation, or cardiac transplant with a sensitivity of 80% and specificity of 90%.

The authors thank Megan Tracey, PNP, Julie Bushnell, PNP, Laura Presnell, ACNP, the Pediatric Critical Care Fellows, the Cardiac Intensive Care Nurses, the Pediatric Clinical Research Center, Adam Gorham, and Leslie Kurkjian for their invaluable assistance with the study.

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