Preoperative B-type natriuretic peptide levels are associated with outcome after total cavopulmonary connection (Fontan)

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Objective: The study objective was to determine the association between preoperative B-type natriuretic peptide levels and outcome after total cavopulmonary connection. Surgical palliation of univentricular cardiac defects requires a series of staged operations, ending in a total cavopulmonary connection. Although outcomes have improved, there remains an unpredictable risk of early total cavopulmonary connection takedown. The prediction of adverse postoperative outcomes is imprecise, despite an extensive preoperative evaluation.

Methods: We prospectively enrolled 50 patients undergoing total cavopulmonary connection. We collected preoperative clinical data, preoperative plasma B-type natriuretic peptide levels, and postoperative outcomes, including the incidence of an adverse outcome within 1 year of surgery (defined as death, total cavopulmonary connection takedown, or the need for cardiac transplantation).

Results: The mean age of patients was 4.7 years (standard deviation, 2.1 years). The median (interquartile range) preoperative B-type natriuretic peptide levels were higher in patients who required total cavopulmonary connection takedown and early postoperative mechanical cardiac support (n = 3; median, 55; interquartile range, 42-121) compared with those with a good outcome (n = 47; median, 11; interquartile range, 5-17) ($P < .05$). A preoperative B-type natriuretic peptide level of 40 pg/mL or greater was highly associated with the need for total cavopulmonary connection takedown (sensitivity, 100%; specificity, 93%; $P < .05$), yielding a positive predictive value of 50% and a negative predictive value of 100%. Higher preoperative B-type natriuretic peptide levels also were associated with longer intensive care unit length of stay, longer hospital length of stay, and increased incidence of low cardiac output syndrome ($P < .05$).

Conclusions: Preoperative B-type natriuretic peptide blood levels are uniquely associated with the need for mechanical support early after total cavopulmonary connection and total cavopulmonary connection takedown, and thus may provide important information in addition to the standard preoperative assessment. (J Thorac Cardiovasc Surg 2014;148:212-9)

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The total cavopulmonary connection (TCPC) is the surgical procedure of choice for suitable patients with a variety of univentricular or nonseptable hearts. After the TCPC, there is no subpulmonary ventricle between the systemic venous return and the pulmonary circulation. The disadvantages of this circulation include ventricular contractility-afterload mismatch, absence of right ventricular to pulmonary artery coupling, and systemic venous return, which is dependent on gravity and respiratory-driven forces. This circulation lacks adaptability and often fails in the setting of increased pulmonary vascular resistance (PVR), valvular dysfunction, or decreased ventricular performance.[1-5] Although mortality after TCPC is low with careful patient selection, the accurate prediction of adverse postoperative outcomes is difficult, and there remains an unpredictable risk of early and late TCPC takedown.

B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide hormone secreted by the myocardium in response to various stimuli that has natriuretic, diuretic, and vasoactive properties.[6,7] Recent studies demonstrated that perioperative changes in BNP levels may predict postoperative morbidity and mortality after surgery for the repair or palliation of congenital cardiac defects.[8-12] However, the potential utility of preoperative BNP levels as predictors of postoperative outcomes in patients undergoing a TCPC has not been investigated.

We hypothesized that preoperative BNP levels would be associated with unexpected outcomes after TCPC in

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Abbreviations and Acronyms

AV	= atrioventricular
BNP	= B-type natriuretic peptide
CPB	= cardiopulmonary bypass
ECLS	= extracorporeal life support
ICU	= intensive care unit
LCOS	= low cardiac output syndrome
LOS	= length of stay
PCICU	= pediatric cardiac intensive care unit
PVR	= pulmonary vascular resistance
TCPC	= total cavopulmonary connection

patients otherwise deemed to be suitable operative candidates on the basis of standard preoperative clinical, echocardiographic, and hemodynamic assessments. Therefore, the objectives of this study were (1) to determine preoperative BNP levels in children undergoing TCPC and (2) investigate the association between preoperative BNP levels and postoperative outcomes.

MATERIALS AND METHODS

Design and Subjects

We conducted a prospective cohort study in the pediatric cardiac intensive care unit (PCICU) at the University of California, San Francisco Children's Hospital from July 2005 to July 2006, April 2008 to July 2010, and June 2011 to July 2012 (n = 45) and the PCICU at Lucille Packard Children's Hospital from January 2012 to June 2012 (n = 6). During these time periods, parents of all eligible patients were approached for informed consent and study enrollment. Eligible subjects included all children aged less than 18 years undergoing TCPC. The preoperative anesthesia management, intraoperative surgical strategy, and subsequent PCICU management followed standard institutional practices. In general, a preoperative decision to use a fenestration was based on the following criteria that would characterize the patient as "higher risk": depressed ventricular function, modestly increased PVR, pulmonary parenchymal disease or lung hypoplasia, and the need to perform additional procedures that would require a prolonged cardiopulmonary bypass (CPB) time. A perioperative decision to perform a fenestration was made for an elevated Fontan pressure or poor hemodynamics on emergence from CPB. The surgical and medical teams involved in the management of the patients were blinded to the BNP values.

Informed consent from the patients' parents or guardians was obtained before enrollment in the study. The University of California, San Francisco and the Lucille Packard Children's Hospital review boards approved the study.

Predictor Variables

We collected all available preoperative clinical data, including patient demographics and preoperative hemodynamic data obtained at the time of cardiac catheterization, including the ratio of pulmonary blood to systemic blood flow, PVR, mean pulmonary artery pressure, cardiac index, presence or absence of atrioventricular (AV) valvular regurgitation, and systemic ventricular end-diastolic pressure, and echocardiographic reports of ventricular function and AV valve regurgitation.

Blood samples were obtained from a venous or arterial catheter less than 24 hours preoperatively. The samples were placed immediately on ice in chilled ethylenediamine tetraacetic acid–treated tubes. Whole blood was used immediately to measure BNP levels 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%.

Outcome Variables

The primary end point was TCPC failure within 1 year of surgery. TCPC failure was defined as death or the need for TCPC takedown or cardiac transplantation. Secondary end points were the (1) duration of mechanical ventilation, (2) intensive care unit (ICU) length of stay (LOS), (3) hospital LOS, and (4) development of low cardiac output syndrome (LCOS) within 48 hours after surgery. The definition of LCOS was derived from criteria published by Hoffman,[13] which included a combination of changes in clinical signs and biochemical indicators. Specifically, LCOS criteria includes 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 cardiac pacing.

Postoperative clinical and hemodynamic data were collected daily by an observer blinded to the BNP results, including the following: mean systemic arterial pressure, common atrial pressure, and heart rate on admission to the ICU, postoperative ICU and hospital LOS, time to chest tube removal and chest tube output, pleural effusions on chest x-ray, biochemical evidence of chylothorax, occurrence of LCOS, and duration of mechanical ventilation. Postoperative biochemical data collected included hematocrit, arterial and venous blood gases, serum lactate, blood urea nitrogen, and creatinine on admission to the ICU.

Data Collection and Management

Study data were collected prospectively and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at University of California at San Francisco.[14] REDCap is a secure web-based application designed to support data capture for research studies, providing (1) an interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for data downloads to common statistical packages; and (4) procedures for importing data from external sources.

Statistical Analysis

We analyzed group differences using the *t* test for parametric data and the Wilcoxon rank-sum test for nonparametric data. We used simple and multivariate logistic regression to explore correlations between the continuous predictor variable (BNP) and the binary outcome variables (good/adverse outcome and incidence of LCOS). Next, we fit linear regression models to study correlations between the continuous predictor variable (BNP) and the continuous clinical outcome variables (ICU LOS, hospital LOS, and duration of mechanical ventilation). However, considering the general rule of thumb in formal regression methods is to use only 1 covariate per every 10 outcomes, the rarity of the outcome being studied (n = 3) made meaningful interpretation of our exploratory models unreasonable.[15] Statistical analyses were performed using Stata 12 (StataCorp LP, College Station, Tex).

RESULTS

Subjects

We enrolled 51 patients undergoing TCPC. One patient did not undergo TCPC at the time of surgery and was excluding from the analysis. All remaining patients had an extracardiac conduit placed between the inferior vena cava and the pulmonary artery, 26 of which were fenestrated. All patients had a cardiac catheterization performed within 3 months before surgery. The patients'

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TABLE 1. Preoperative characteristics

Age (y)	4.7 ± 2.1
Weight (kg)	16.1 ± 6.0
Male, n (%)	30 (60)
Type of cardiac lesion, n (%)	
HLHS	23 (46)
Tricuspid atresia	7 (14)
DORV	7 (14)
Unbalanced AVSD	6 (12)
PA-IVS	4 (8)
DILV	1 (2)
TGA-VSD-PS	1 (2)
Ebstein's anomaly-HRV	1 (2)
Preoperative hemodynamic data	
Heart rate (beats/min)	103 ± 15
Mean arterial pressure (mm Hg)	77 ± 12
Arterial oxygen saturation (%)	83 ± 6
Qp:Qs	0.73 ± 0.26
PVR (Wood's units)	2.0 ± 0.9
mPAP (mm Hg)	11 ± 3
CI (L/min/m^2)	3.5 ± 1.2
SVEDP (mm Hg)	8 ± 4

Data are presented as mean ± standard deviation. *AVSD,* Atrioventricular septal defect; *CI,* cardiac index; *DILV,* double inlet left ventricle; *DORV,* double outlet right ventricle; *HLHS,* hypoplastic left heart syndrome; *HRV,* hypoplastic right ventricle; *mPAP,* mean pulmonary artery pressure; *PA-IVS,* pulmonary atresia-intact ventricular septum; *PS,* pulmonary stenosis; *PVR,* pulmonary vascular resistance; *Qp/Qs,* ratio of pulmonary blood flow over systemic blood flow; *SVEDP,* systemic ventricular end-diastolic pressure; *TGA,* transposition of great arteries; *VSD,* ventricular septal defect.

demographics, cardiac lesions, and preoperative hemodynamic data are shown in Table 1.

Outcomes

Primary end points. Three patients (6%) had an adverse outcome. The preoperative diagnoses, surgical details, and specific postoperative events classifying the adverse outcomes are shown in Table 2. All 3 patients with adverse outcome underwent additional procedures at the time of the Fontan (Table 2). Seven patients (15%) with good outcome underwent additional procedures at the time of the Fontan. These procedures included pulmonary artery reconstruction (n = 4), repair of right ventricular outflow tract aneurysm (n = 1), repair of AV valve (n = 1), and coronary artery bypass graft with left internal thoracic artery to left anterior descending coronary artery (n = 1).

No enrolled patients died or required cardiac transplantation during the study period. Patients with an adverse postoperative outcome were older and weighed more (Table 3). The presence or absence of AV valve regurgitation and preoperative hemodynamic indices did not differ between patients undergoing TCPC with and without an adverse outcome (Table 3). Use of aortic crossclamping was not significantly associated with preoperative BNP levels. On return to the PCICU after surgery, first recorded heart rate, common atrial pressure, serum creatinine, and serum lactate were higher in patients receiving TCPC with adverse outcomes, whereas arterial oxygen saturations were lower (Table 3).

Secondary end points. The median (interquartile range) duration of mechanical ventilation was 8 (7-12) hours in patients who underwent TCPC. LCOS developed in 8 patients (16%) within the first 48 hours after surgery. The median (interquartile range) ICU LOS and hospital LOS were 5 (4-9) days and 14 (10-22) days, respectively. Age, gender, and preoperative hemodynamic data obtained from cardiac catheterizations were not associated with any secondary outcomes. Patients with adverse outcomes had a higher incidence of LCOS and longer ICU LOS (Table 3).

Preoperative B-Type Natriuretic Peptide Levels and Outcomes

Preoperative BNP levels were greater in patients who required TCPC takedown than in patients with a good

TABLE 2. Diagnoses and specific postoperative events of patients with adverse outcome

Patient	Surgery	Diagnosis	Outcome
1	TCPC extracardiac and fenestrated, and L pulmonary artery plasty	HLHS	Fontan circulation taken down after return to the OR on POD 1 because of failed Fontan circulation. Unable to separate from CPB; placed on ECLS.
2	TCPC extracardiac and fenestrated, and R atrial maze, R atrial reduction, and oversew of pulmonary valve	Ebstein's anomaly-HRV	Fontan circulation taken down in the OR because of failed Fontan circulation, unable to separate from CPB; another MBTS was added in the same operation.
3	TCPC extracardiac and fenestrated, and focalization of hepatic veins	Unbalanced AVSD	Fontan circulation taken down 11 mo after operation because of poor hemodynamics requiring prolonged and frequent PCICU hospitalizations and the ultimate development of PLE; also had ECLS during the postoperative course of TCPC because of profound LCOS at PODs 2-5.

AVSD, Atrioventricular septal defect; *CPB,* cardiopulmonary bypass; *ECLS,* extracorporeal life support; *HLHS,* hypoplastic left heart syndrome; *HRV,* hypoplastic right ventricle; *LCOS,* low cardiac output syndrome; *LOS,* length of stay; *MBTS,* modified Blalock–Taussig shunt; *OR,* operating room; *PCICU,* pediatric cardiac intensive care unit; *PLE,* protein-losing enteropathy; *POD,* postoperative day; *TCPC,* total cavopulmonary connection.

TABLE 3. Characteristics of patients undergoing total cavopulmonary anastomosis with good postoperative outcome or adverse outcome

Patient characteristics	Good outcome	Adverse outcome	*P*
N (%)	47 (94)	3 (6)	
Age (y)	4.5 ± 1.9	7.2 ± 4.1	**.028**
Weight (kg)	15.7 ± 5.3	23.0 ± 12.2	**.039**
Male, n (%)	27 (57)	3 (100)	.151
Preoperative BNP level (pg/mL)	11 (5-17)	55 (42, 55, 121)	**.007**
Use of CPB, n (%)	34 (72)	3 (100)	.299
Duration of CPB (min)	54 (42-86)	80 (63, 80, 96)	.260
Use of aortic crossclamp, n (%)	6 (13)	2 (67)	**.013**
Duration of aortic crossclamp (min)	31 (19-42)	44 (44-44)	.480
Fenestration, n (%)	23 (49)	3 (100)	.096
Extracardiac conduit, n (%)	47 (100)	3 (100)	
Glenn before Fontan, n (%)	43 (91)	3 (100)	.797
Preoperative hemodynamic and laboratory data			
Mean arterial pressure (mm Hg)	77 ± 12	78 ± 5	.809
Arterial oxygen saturation (%)	83 ± 6	83 ± 4	.839
AV valve regurgitation , n (%)	19 (40)	2 (67)	.382
Qp:Qs	0.72 ± 0.26	0.80 ± 0.30	.623
PVR (Wood's units)	2.0 ± 1.0	2.1 ± 0.6	.779
mPAP (mm Hg)	11 ± 3	10 ± 3	.607
CI (L/min/m^2)	3.5 ± 1.2	2.8 ± 0.3	.322
SVEDP (mm Hg)	8 ± 4	9 ± 2	.848
Serum creatinine (mg/dL)	0.42 ± 0.08	0.55 ± 0.21	**.048**
Creatinine clearance	99 ± 24	114 ± 45	.336
Initial postoperative data on return to PCICU			
Heart rate (beats/min)	119 ± 18	152 ± 11	**.002**
Arterial oxygen saturation (%)	92 ± 8	81 ± 13	**.023**
Mean arterial pressure (mm Hg)	75 ± 11	70 ± 15	.446
Common atrial pressure (mm Hg)	7 ± 4	15 ± 5	**.005**
Serum creatinine (mg/dL)	0.52 ± 0.24	1.1 ± 0.32	**.001**
Creatinine clearance	83 ± 23	51 ± 23	**.022**
Serum lactate (mmol/L)	2.8 ± 1.8	5.6 ± 2.5	**.016**
Outcomes			
LCOS, n (%)	5 (11)	3 (100)	**.000**
ICU LOS (d)	5 (4-8)	11 (8, 11, 56)	**.037**
Hospital LOS (d)	14 (10-21)	36 (14, 36, 64)	.079
Duration of mechanical ventilation (h)	9 (7-12)	7 (7, 7, 24)	.850
Duration of chest tubes (d)	8 (5-14)	9 (8, 9, 19)	.414

Bold indicates statistically significant *P* values ($P < .05$). For the good outcome group (n = 47), data are presented as mean ± standard deviation and median (interquartile range). For the adverse outcome group (n = 3), data are presented as mean ± standard deviation and median (individual values). Creatinine clearance was estimated using the Shull formula. *AV,* Atrioventricular; *BNP,* B-type natriuretic peptide; *CI,* cardiac index; *CPB,* cardiopulmonary bypass; *ICU,* intensive care unit; *LCOS,* low cardiac output syndrome; *LOS,* length of stay; *mPAP,* mean pulmonary artery pressure; *PCICU,* pediatric cardiac intensive care unit; *PVR,* pulmonary vascular resistance; *Qp/Qs,* ratio of pulmonary blood flow over systemic blood flow; *SVEDP,* systemic ventricular end-diastolic pressure.

outcome (Figure 1, Table 3). Preoperative BNP levels were not associated with duration of mechanical ventilation. Preoperative BNP levels correlated with incidence of LCOS and ICU LOS. There was a trend toward longer hospital LOS with higher preoperative BNP levels ($P = .079$). There was no association between preoperative BNP levels and age or gender. Preoperative BNP levels did not correlate with preoperative ratio of pulmonary blood to systemic blood flow, PVR, mean pulmonary artery pressure, cardiac index, systemic ventricular end-diastolic pressure, mean arterial pressure, heart rate, arterial oxygen saturation, presence or absence of AV valve regurgitation, or postoperative serum lactate.

We used receiver operating characteristic curves to evaluate the association between various cutoff values of preoperative BNP and adverse outcome and incidence of LCOS. A preoperative BNP cutoff value of 40 pg/mL was highly associated with adverse outcome, giving a sensitivity of 100% and a specificity of 93% (area under the curve, 0.96, 95% confidence interval, 0.91-1.0) (Figure 2). These results yield a positive predictive value of 50% and a negative predictive value of 100%. Because a preoperative BNP level of 40 pg/mL or greater was strongly associated with

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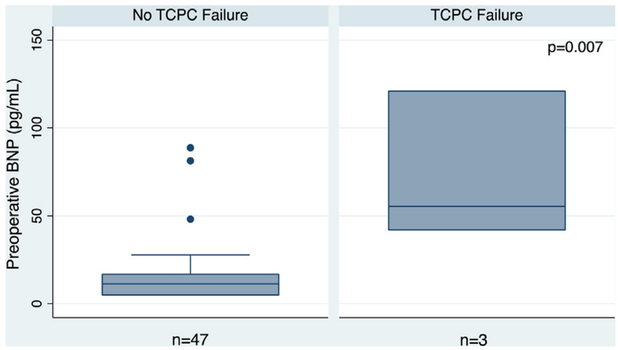

FIGURE 1. Preoperative BNP levels are higher in patients with adverse outcome in the early postoperative period after TCPC. Comparisons of preoperative BNP levels between patients with a good outcome (n = 47) and an adverse outcome (n = 3) after TCPC. *Horizontal lines* represent median values, and interquartile ranges are represented with *shaded boxes*. An adverse outcome is defined as a failed TCPC requiring an intervention within 12 months of the original procedure. *BNP*, B-type natriuretic peptide; *TCPC*, total cavopulmonary connection.

adverse outcome, we dichotomized patients by BNP levels of less than 40 pg/mL or 40 pg/mL or greater. The characteristics of patients with a preoperative BNP level less than 40 pg/mL and 40 pg/mL or greater are shown in Table 4. Patients with a preoperative BNP level 40 pg/mL or greater had a greater incidence of LCOS and a longer ICU and hospital LOS than patients with a preoperative BNP level less than 40 pg/mL (Table 4). Among the 47 patients with good outcomes, no differences were identified between the 3 patients with a preoperative BNP 40 pg/mL or greater and the 44 patients with a preoperative BNP less than 40 pg/mL (data not shown).

One patient enrolled was excluded from the analysis after an intraoperative decision was made to not proceed with the TCPC because of the concern for severe A-V valve regurgitation that was underestimated during the preoperative

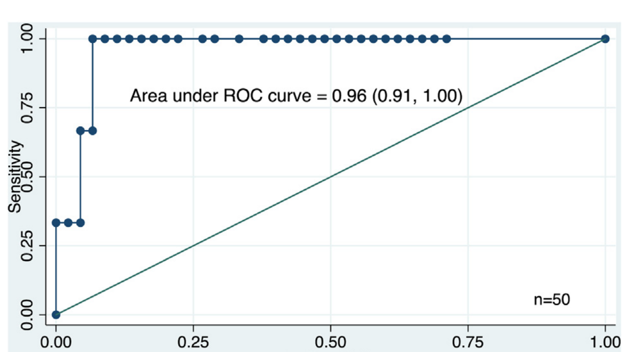

FIGURE 2. Preoperative BNP levels 40 pg/mL or greater are highly associated with adverse outcome after TCPC (sensitivity, 100%; specificity, 93%; area under the curve, 0.96; 95% CI, 0.91-1.0). *ROC*, Receiver operating curve.

evaluation. Of note, this patient had a preoperative BNP level of 120 pg/mL.

DISCUSSION

Outcomes after TCPC have improved markedly since 1971, when the Fontan procedure was first described.[16] However, the incidence of early mortality after TCPC remains between 3% and 8%. Likewise, long-term mortality is estimated to be as high as 10%, 14%, and 18% at 5, 10, and 15 years, respectively.[2,3,17-19] Contemporary risk factors for early and late adverse outcomes after Fontan-type operations include impaired preoperative ventricular function, increased pulmonary artery pressures, and a common AV valve.[3,18,19] In a pilot study, we found that preoperative BNP levels were higher in patients with adverse outcome after TCPC than in patients with good outcomes and that standard preoperative data were not significantly different between these 2 groups.[9] Therefore, in the current study we expanded our initial study to test the hypothesis that preoperative BNP blood levels are associated with early adverse outcome after TCPC. We found that a BNP level greater than 40 pg/mL was highly associated with the need for early postoperative extracorporeal life support (ECLS) or TCPC takedown. Of note, we have shown that in low-risk patients selected to undergo TCPC on the basis of favorable preoperative hemodynamic assessments, BNP levels better discriminate outcome after TCPC than preoperative cardiac catheterization measurements. This is a meaningful finding because the exact preoperative hemodynamics that predict TCPC takedown remain elusive and suggest that measurement of BNP blood levels may be important in the preoperative evaluation.[20]

BNP is a hormone released by the myocardium that has natriuretic, diuretic, and vasoactive properties.[6,7] Produced predominantly in ventricular tissue, BNP has emerged as a powerful biomarker of impaired myocardial performance and has become an established aid in the diagnosis, prognosis, and treatment of a variety of cardiovascular disease states.[8,10-12] Its use in congenital heart disease is emerging, and recent studies demonstrate that perioperative BNP changes may predict outcomes in an age- and lesion-specific fashion, including partial cavopulmonary connections for single ventricular heart disease.[9] However, previous studies in congenital heart disease did not demonstrate associations between outcomes and preoperative levels, only perioperative changes.[8-12,21] In our previous study examining perioperative BNP levels in patients undergoing partial cavopulmonary connections and TCPC, we found that preoperative BNP levels were higher in 2 patients with poor outcome after TCPC compared with 9 patients with good outcome after TCPC. With a 5-fold higher sample size, the present study confirms this preliminary finding and to our knowledge is the first to robustly demonstrate the association between a single

TABLE 4. Characteristics of patients undergoing total cavopulmonary anastomosis with preoperative B-type natriuretic peptide level <40 pg/mL or ≥40 pg/mL

Patient characteristics	Preoperative BNP level <40 pg/mL	Preoperative BNP level ≥40 pg/mL	*P*
N (%)	44 (88)	6 (12)	
Age (y)	4.6 ± 2.0	5.0 ± 2.9	.618
Weight (kg)	15.8 ± 5.6	18.0 ± 7.9	.333
Male, n (%)	25 (57)	5 (83)	.086
Use of CPB, n (%)	31 (70)	6 (100)	.118
Duration of CPB (min)	55 (42-90)	63 (52-96)	.423
Use of aortic crossclamp, n (%)	6 (14)	2 (33)	.225
Duration of aortic crossclamp (min)	31 (19-42)	44 (44-44)	.480
Fenestration, n (%)	22 (50)	4 (67)	.486
Extracardiac conduit, n (%)	44 (100)	6 (100)	
Glenn before Fontan, n (%)	40 (91)	6 (100)	.707
Preoperative hemodynamic and laboratory data			
Mean arterial pressure (mm Hg)	77 ± 13	76 ± 8	.854
AV valve regurgitation, n (%)	16 (36)	5 (83)	.982
Arterial oxygen saturation (%)*	84 ± 6	82 ± 6	.502
Qp:Qs	0.71 ± 0.26	0.84 ± 0.27	.191
PVR (Wood's units)	2.0 ± 0.9	2.1 ± 1.4	.618
mPAP (mm Hg)	11 ± 3	11 ± 2	.812
CI (L/min/m^2)	3.5 ± 1.2	3.0 ± 0.4	.281
SVEDP (mm Hg)	8 ± 4	9 ± 1	.556
Serum creatinine (mg/dL)	0.42 ± 0.08	0.47 ± 0.15	.278
Creatinine clearance	98 ± 24	112 ± 31	.231
Initial postoperative data on return to PCICU			
Heart rate (beats/min)	119 ± 18	134 ± 21	**.041**
Arterial oxygen saturation (%)	92 ± 8	87 ± 11	.133
Mean arterial pressure (mm Hg)	75 ± 10	73 ± 17	.708
Common atrial pressure (mm Hg)	7 ± 4	12 ± 5	**.019**
Serum creatinine (mg/dL)	0.50 ± 0.16	0.83 ± 0.50	**.001**
Creatinine clearance	83 ± 23	69 ± 27	.202
Serum lactate (mmol/L)	2.8 ± 1.9	3.9 ± 2.0	.126
Outcomes			
Adverse outcome, n (%)	0	3 (50)	**.000**
LCOS, n (%)	2 (5)	6 (100)	**.000**
ICU LOS (d)	5 (4-8)	8 (6-18)	**.020**
Hospital LOS (d)	12 (10-19)	22 (15-34)	**.020**
Duration of mechanical ventilation (h)	9 (7-12)	7 (7-17)	.286
Duration of chest tubes (d)	8 (5-13)	10 (7-17)	.392

Bold indicates statistically significant *P* values ($P < .05$). Data are presented as mean ±standard deviation and median (interquartile range). Creatinine clearance was estimated using the Shull formula. *AV,* Atrioventricular; *BNP,* B-type natriuretic peptide; *CI,* cardiac index; *CPB,* cardiopulmonary bypass; *ICU,* intensive care unit; *LCOS,* low cardiac output syndrome; *LOS,* length of stay; *mPAP,* mean pulmonary artery pressure; *PCICU,* pediatric cardiac intensive care unit; *PVR,* pulmonary vascular resistance; *Qp/Qs,* ratio of pulmonary blood flow over systemic blood flow; *SVEDP,* systemic ventricular end-diastolic pressure. *Postoperative arterial saturations were significantly higher among the nonfenestrated Fontans compared with those with fenestrations: 94 ± 8 versus 88 ± 8, $P = .016$.

preoperative BNP value and postoperative outcome in patients undergoing surgery for congenital heart disease.

Although our findings demonstrate the association between an increased preoperative BNP level and poor postoperative outcome in patients undergoing TCPC, the potential mechanisms, particularly at a relatively low cutoff value (40 mg/dL), are unclear. The regulation of the production and release of BNP is not entirely understood, because it depends on multiple, often opposing, factors.[10,11,22,23] Factors known to increase BNP expression and release include increased ventricular wall stress (pressure and volume), hypoxia, increased central blood volume, and neuroendocrine mechanisms.[7] Of note, in patients with single ventricular physiology, Law and colleagues[24] demonstrated an elevation in BNP levels in patients with ventricular failure, independently of cavopulmonary failure. We speculate that in the preoperative TCPC setting, BNP values may reflect important clinical parameters in ventricular performance not captured by our current routine evaluations. This requires further investigation.

Potential alterations in BNP expression, release, and clearance in the setting of abnormal cardiac development

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are unknown. Our results demonstrate that a relatively low preoperative BNP cutoff level (>40 pg/mL) is associated with adverse outcome after TCPC. This is significantly lower than the cutoff levels first established for the diagnosis of congestive heart failure in adults[25,26] but is concordant with 2 previously published studies that showed that a threshold value of greater than 30 to 45 pg/mL showed both sensitivity and specificity for predicting heart failure in children with a single cardiac ventricle. This cutoff level is also greater than published values in similarly aged normal children (5.1-12.1 pg/mL).[27,28] Further, our relatively low BNP cutoff level fits with the results of the Pediatric Heart Network Fontan cross-sectional study that demonstrated normal BNP levels in the majority of ambulatory patients undergoing the Fontan (median time from Fontan, 8.2 years), but higher BNP levels in patients with pre-Fontan systolic dysfunction and in patients with late post-Fontan complications.[21]

Study Limitations

There are several limitations to this investigation that warrant discussion. Most notable is the relatively small sample size, which was associated with a heterogeneous group of anatomic lesions and the use of both fenestrated and nonfenestrated surgical techniques. The small sample size makes it difficult to conclude that BNP is a true predictor of adverse outcome after TCPC. However, there is a clear association between increased preoperative BNP levels and adverse postoperative outcome in this unique population. Further, this precludes our ability to demonstrate potential interactions between preoperative BNP levels and outcomes in subjects with specific cardiac lesions after the TCPC. In addition, all 3 patients experiencing adverse outcome underwent additional procedures at the time of the Fontan compared with 15% of the group with good outcome. Although there were no significant differences in the duration of CPB time or aortic crossclamp time as a result, it is challenging to determine whether these additional procedures played a role in the observed outcomes. Last, our study was undertaken only in children considered eligible for a TCPC. Because we have no data on higher-risk patients (ie, those excluded from TCPC after standard assessment), the associations demonstrated between preoperative BNP and outcomes are applicable only to patients undergoing the Fontan with favorable preoperative hemodynamics.

Because of the robust nature of the data, we are confident that the results are not due to type I error. However, a small possibility of this always exists in pilot studies with small sample sizes such as this. In addition, the enrolled patients were from 2 high-volume pediatric cardiothoracic surgery centers, with the obligate subtle differences in surgical approach/technique and postoperative management. Of note, the strength of the association between postoperative outcome and a BNP cutoff level greater than 40 pg/mL was sustained despite a small sample size from 2 centers, suggesting it is a robust measurement.

CONCLUSIONS

We found that preoperative BNP levels are strongly associated with the need for ECLS and TCPC takedown in the early postoperative period after TCPC. Specifically, we found that a value greater than 40 pg/mL was highly sensitive and specific in its association with TCPC takedown within 12 months of surgery, the need for ECLS, and prolonged ICU and hospital LOS. Large multicentered studies are needed to definitively establish the predictive value of BNP blood levels in the management of patients after TCPC and to overcome the limitations of the present study. However, our current results suggest that preoperative BNP levels have the potential to uniquely predict early outcome after TCPC and thus, after validation in a larger TCPC cohort, should be considered for inclusion in the standard assessment of candidates for a Fontan-type operation.

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