Perioperative NT-proBNP level: Potential prognostic markers in children undergoing congenital heart disease surgery

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ABSTRACT

Objectives: To assess the relationship between N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at different time points and early outcome, and to evaluate the reliability of NT-proBNP level as a predictor of early outcome after surgery in a large series of children with congenital heart disease (CHD).

Methods: A retrospective observational study involving 363 consecutive children with CHD was used. Plasma NT-proBNP records were obtained for each patient before and 1, 12, and 36 hours after surgery. The specificity, sensitivity, and prediction value of NT-proBNP in predicting early postoperative outcomes were determined.

Results: Analyses confirmed that time-varying NT-proBNP level, particularly 1-hour postoperative levels, had prognostic value on the prediction of prolonged duration of mechanical ventilation, intensive care unit (ICU) stay, and inotropic therapy. Joint modeling analyses of a linear mixed effects model for NT-proBNP from before to 36 hours after surgery and generalized linear models for the duration of the mechanical ventilation, ICU stay, and inotropic therapy showed that a 1% increase in NT-proBNP was associated with 5.5%, 3.9%, and 3.5% relative increases in expected duration of mechanical ventilation, ICU stay, and inotropic therapy, respectively; related *P* values were .001, .001, and .01, respectively.

Conclusions: After CHD surgery, the perioperative NT-proBNP levels might be powerful markers to identify subjects at higher risk for worse outcome. (J Thorac Cardiovasc Surg 2017;154:631-40)

ROC curve for 1-hour NT-proBNP predicting ventilation >48 hours, ICU stay, and inotropic therapy >3 days.

Central Message

For children after CHD surgery, perioperative NT-proBNP levels might be early, accurate, and sensitive predictors of prolonged ventilation, ICU stay, and inotropic support duration.

Perspective

We found that perioperative NT-proBNP levels, particularly 1-hour postoperative levels, were correlated with duration of mechanical ventilation, ICU stay, and inotropic therapy. We used joint models to quantify the degree of the correlation between perioperative NT-proBNP level and the length of mechanical ventilation, ICU stay, and inotropic therapy. It will help clinicians to predict early outcome and plan their therapeutic protocols more quickly after surgery.

See Editorial Commentary page 641.

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Received for publication April 6, 2016; revisions received Dec 16, 2016; accepted for publication Dec 29, 2016; available ahead of print March 7, 2017.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2016.12.056>

Although great progress has been made, surgical intervention for the treatment of children with congenital heart disease (CHD) is still carrying significant early and late

Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms

ACC	= aorta crossclamp
AKI	= acute kidney injury
AUC	= area under the curve
CHD	= congenital heart disease
CICU	= cardiac intensive care unit
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
ICU	= intensive care unit
LCOS	= low cardiac output syndrome
LME	= linear mixed effects
LRS	= left to right shunt
MCMC	= Markov chain Monte Carlo
NT-proBNP	= N-terminal pro-brain natriuretic peptide
PAH	= pulmonary artery hypertension
RACHS-1	= the Risk Adjustment in Congenital Heart Surgery, version 1
ROC	= receiver operating characteristic
STAT	= Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery
TGA	= d-transposition of the great arteries
TOF	= tetralogy of Fallot
UVH	= univentricular heart
VSD	= ventricular septal defect

morbidity and mortality. Making the continued search for improved prognostic biomarkers besides commonly measured clinical and physiologic parameters is of increasing importance of children admitted to intensive care units (ICUs) after surgery for CHD. Accumulating evidence suggests that both active B-type natriuretic peptide (BNP) and inactive N-terminal pro-BNP (NT-proBNP) have been shown to have prognostic value in adults with cardiac diseases (eg, chronic congestive heart failure and acute myocardial infarction), and to predict morbidity and major adverse cardiac events after adult heart surgery.

Recently, more concerted efforts for the prognostic value of BNP/NT-proBNP after surgical intervention for CHD in pediatrics have also occurred.¹ For example, Hsu and coauthors² found that BNP level of 1 or greater at 24 hours after cardiac surgery in neonates was correlated with poor postoperative outcome, including low cardiac output syndrome, fewer ventilator-free days, and 6-month major adverse cardiac events. Niedner et al³ reported that higher levels of early postoperative BNP were associated with longer inotropic requirement and hospitalization in children after surgery for single-ventricle CHD. Nahum and colleagues⁴ reported similar results in a prospective comparative study on 19 infants aged 1 to 12 months with CHD undergoing complete repair. In a prospective study on 587 children undergoing

cardiac surgery, Cantinotti et al⁵ showed independent and incremental prognostic value of BNP in pediatric cardiac surgery, supporting its routine use in this setting.

However, current evidence is limited to BNP.⁶ Despite the equivalence in clinical efficacy of BNP and NT-proBNP supported by many studies, significant differences between circulatory levels has been reported for any given disease state.^{7,8} To our knowledge, besides a few studies focusing on the role of NT-proBNP in pediatric patients with cardiac disease,⁹ there are much fewer data on the prognostic value of perioperative NT-proBNP levels in children after surgical repair of structural congenital heart defects, particularly large-scale studies with high statistical power.

Therefore, the primary objectives of this article were to determine and (1) to investigate potential patterns of association between perioperative circulating NT-proBNP levels and early outcomes after repair of congenital heart defects and (2) to evaluate the reliability of NT-proBNP level as a predictor for postoperative outcomes in a large series of children undergoing cardiac surgery for CHD.

PATIENTS AND METHODS**Subjects**

The clinical information system databases of the Guangzhou Women and Children's Medical Center were scanned for pediatric patients enrolled for cardiac surgery having CHD. Patients younger than 18 years with CHD who underwent cardiac surgery were eligible for the study. Children who had preoperative arrhythmia (potentially malignant ventricular arrhythmias and high-degree atrioventricular block), rheumatic heart disease, infective endocarditis, myocarditis, pericardial disease, renal dysfunction, or neoplasms,¹⁰⁻¹² or who could not be separated from cardiopulmonary bypass (CPB) were excluded.

Between June and December 2014, 415 eligible consecutive patients undergoing corrective or palliative CHD surgery at the Department of Pediatric Cardiac Surgery and admitted to the Cardiac Intensive Care Unit (CICU) at the Guangzhou Women and Children's Medical Center, Guangzhou, were identified. However, to display the results in a more homogeneous population, we excluded 38 cases without CPB and 14 single-ventricular cases from the final analysis according to the reviewers. Thus, results from 363 cases were presented in the current study. The institutional review board at the Guangzhou Women and Children's Medical Center reviewed and approved this study.

Clinical Procedure

The preoperative anesthesia management, surgical procedure (including sternotomy, establishing CPB, correction of cardiac defects, closure of thoracic cavity, and suturing the skin; [Video 1](#)), and subsequent CICU management followed standard institutional practices. All patients were admitted to the CICU intubated and mechanically ventilated after operation. If postoperative urine output was less than 0.5 mL/kg per hour lasting for more than 2 to approximately 4 hours under the premise of the application of diuretics, peritoneal dialysis was adopted until the urine output was more than 2 mL/kg per hour, blood urea nitrogen, creatinine, and electrolytes were maintained in the normal range. Termination of the surgical procedure means ending with suturing the skin.

Sample and Data Collection

Blood samples were obtained from an arterial catheter preoperatively and at 1, 12, and 36 hours after the surgical procedure at CICU according

VIDEO 1. The whole procedure of the artery switch operation (ASO) for transposition of great artery (TGA) treatment. This kind of surgical procedure is one of the typical surgeries for congenital heart disease undergoing cardiopulmonary bypass. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30188-5/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30188-5/addons).

to our routine clinical protocol. The NT-proBNP levels were measured with a commercially available fluorescence immunoassay (competitive Enzyme Immuno Assay; ReLIA II, Shenzhen, China) and Multi-Detection Microplate Reader (VICTOR X5; PerkinElmer, Waltham, Mass). The measurable range of NT-proBNP on this device is between 5 and approximately 35,000 pg/mL (range of normality according to age and gender).

Clinical and biochemical data were collected retrospectively from the medical records. The clinical data collected included patient demographics (age, weight, gender, main diagnosis), the Risk Adjustment in Congenital Heart Surgery, version 1 (RACHS-1) score, CPB duration, aorta cross clamp (ACC) time, and follow-up measurements after surgical procedure, including duration of mechanical ventilation, intensive care duration, inotropic drug duration, mean systemic arterial pressure, central venous pressure, serum creatinine, and urine output. The patients were divided into 3 subgroups of age according to clinically relevant data (neonates <30 days, infants up to 1 year, and 1 to 12 years).

Data Analysis

Categorical data were expressed as percentages and compared by using the Fisher exact test or the χ^2 test. Continuous variables were expressed as mean and standard deviation. They were assessed for normality by the Kolmogorov-Smirnov test and compared by using the Student *t* test or by the 1-way analysis of variance for 2- or multiple-group comparisons. Because of their abnormal distribution, NT-proBNP levels and the primary predictors (including the duration of mechanical ventilation, the length of ICU stay, and the duration of inotropic therapy) were all log-transformed for analytical purposes. Given repeated measures of NT-proBNP at fixed time points before and after surgery, we fit linear mixed effects model, combining fixed and random subject effects, for log(NT-proBNP) levels over time.

Moreover, we were also interested in the association between peri-operation NT-proBNP changes over time and the duration of mechanical ventilation, ICU stay, and inotropic therapy. To analyze these data, we propose a Bayesian joint model with (1) a linear mixed effects (LME) model for the longitudinal analysis of repeated NT-proBNP measurements, and (2) a generalized linear model for the continuous primary outcomes. We used the Markov chain Monte Carlo (MCMC) technique via Gibbs sampler to estimate the unknown

TABLE 1. Clinical characteristics of cases undergoing congenital heart disease surgery

Characteristics	No.
Type of congenital heart disease	
Ventricular septal defect	180
Atrial septal defect	38
Total anomalous pulmonary venous connection	13
Tetralogy of Fallot	27
Transposition of the great arteries	25
Pulmonary atresia	20
Complete atrioventricular septal defect	15
Coarctation	17
Double outlet right ventricle	6
Interrupted aortic arch	2
Pulmonary stenosis	5
Other types of CHD	15
RACHS-1 score	
I/II	271 (74.7)
III/IV	92 (25.3)
V/VI	0 (0)
Demographics	
Age, mo	15.8 ± 27.4
Female/male	128/235
Body weight, kg	7.4 ± 5.7
NT-proBNP level, pg/mL	
Preoperative level	808.6 (267.0-2535.0)
1-h postoperative level	916.9 (295.9-2561.7)
12-h postoperative level	4561.3 (2760.3-8684.2)
36-h postoperative level	3465.1 (2065.6-5991.1)
CPB time, min	68 (54-97)
Aortic crossclamp time, min	36 (27-53)
Mechanical ventilation, h	23 (9-46)
Intensive care unit stay, d	3 (2-5)
Inotropic duration, d	2 (1-4)

Data are expressed as n (%) or median with range. CHD, Children with congenital heart disease; RACHS-1, risk Adjustment for Congenital Heart Surgery-1.

parameters simultaneously using publically available WinBUGS software. See Chen et al¹³ and Lunn et al¹⁴ for detailed discussions of the Bayesian modeling approach and the implementation of the MCMC procedures.

Receiver operating characteristic (ROC) curves were used to assess the various cutoff values of NT-proBNP to predict the need for mechanical ventilation beyond 48 hours, ICU stay beyond 3 days, and duration of inotropic therapy more than 72 hours. The areas under the curve (AUCs) for the NT-proBNP measured at different time points were compared by using De Long's method. Next, NT-proBNP levels were dichotomized to being equal to or less than the cutoff values. All tests were performed 2-tailed, with *P* < .05 considered statistically significant. Statistical analysis was performed using SPSS version 19.0 (IBM SPSS Statistics for Windows; IBM Corporation, Somers, NY) and R software (version 3.2.2).

RESULTS

The patients' clinical characteristics are listed in Table 1. There was no mortality among the enrolled patients during the study period. A total of 363 patients experienced CPB,

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excluding those diagnosed of patent ductus arteriosus, coarctation, and the single-ventricular group that accepted palliative operations. Ninety patients (24.79%) had cyanotic CHD.

The level of postoperative NT-proBNP showed a rising trend regardless of preoperative condition. Mean levels of NT-proBNP increased significantly to the peak at 12 hours to 36 hours after CPB or surgical procedure.

The fixed effects estimates from the longitudinal LME model for change in log(NT-proBNP) are presented in Table 2. NT-proBNP levels were found to have significantly relative decreases of 76.8% and 74.1% at preoperative and 1-hour postoperative time points, but an increase of 47.7% at 12 hours after surgery, compared with that measured at 36 hours after surgery. Neonates and infants were found to have 124.8% and 76.8% higher expected NT-proBNP than the group of older children. Children who had RACHS-1 score ≤ 2 or with deep hypothermic circulatory arrest (DHCA) were found to have 31.6% and 56.0% lower expected NT-proBNP than the score ≥ 3 or patients without DHCA, respectively. Postoperative creatinine level and weight were also significant predictors of NT-proBNP levels. However, no differences in expected NT-proBNP

were found between male and female patients, or with the change of the length of ACC and CPB time; respective *P* values were .16, .10, and .36.

As shown in Table 3, the results for the longitudinal submodel were consistent with the results from the separate LME analysis. The differences in magnitudes of the parameter estimates were negligible and there was no material difference in terms of statistical significance (Tables 2 and 3). Hence, in what follows, we discuss only the results for the second submodels. Most importantly, we found that a 1% increase in NT-proBNP level was associated with a relative increase of 5.5% in expected duration of the mechanical ventilation. Compared with 36-hour postoperative NT-proBNP level, 1-hour (*P* = .03) and 12-hour postoperative NT-proBNP (*P* = .01) were also significantly associated with the duration of mechanical ventilation.

All patients were discharged between 1 and 41 days. Time-varying NT-proBNP was associated with the prolonged ICU stay. A 1% increase in NT-proBNP was associated with a 3.9% prolonged duration of ICU stay. Patients whose RACHS-1 score was ≤ 2 were found to have 8.6% lower expected ICU stay than patients with a

TABLE 2. Estimates for linear mixed model of repeated NT-proBNP

Variables	Estimate	SE	95% CI	<i>P</i>	RE%
Intercept	8.79	0.30	8.20 to 9.38	<.0001*	NA
Time points					
Before surgery	−1.46	0.08	−1.62 to −1.30	<.0001*	−76.78
1 h after surgery	−1.35	0.07	−1.49 to −1.21	<.0001*	−74.08
12 h after surgery	0.39	0.06	0.27 to 0.51	<.0001*	47.70
36 h after surgery	Reference				
Gender					
Female	−0.13	0.09	−0.31 to 0.05	.16	−12.19
Male	Reference				
Age					
Neonates (<30 d)	0.81	0.25	0.32 to 1.30	.002*	124.79
Infants (<1 y)	0.57	0.13	0.32 to 0.82	<.0001*	76.83
1–12 y	Reference				
RACHS-1					
≤ 2	−0.38	0.13	−0.63 to −0.13	.004*	−31.61
≥ 3	Reference				
DHCA					
No	−0.82	0.19	−1.19 to −0.45	<.0001*	−55.96
Yes	Reference				
Serum creatinine, $\mu\text{mol/L}$					
Preoperative	−0.004	0.008	−0.02 to 0.01	.63	−0.40
Postoperative	0.03	0.006	0.02 to 0.04	<.0001*	3.05
CPB time, min	0.003	0.002	−0.001 to 0.01	.10	0.30
ACC time, min	0.003	0.003	−0.003 to 0.01	.36	0.30
Weight, kg	−0.08	0.01	−0.10 to −0.06	<.0001*	−7.69

The response variable is log-transformed NT-proBNP, RE% corresponding to an estimate β , expressed as expected percentage change in NT-proBNP, calculated as $(\exp[\beta] - 1) \times 100$. NT-proBNP, N-terminal pro-brain natriuretic peptide; SE, standard error; CI, confidence interval; RE%, percentage relative effects; NA, not available; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1; DHCA, deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; ACC, aorta cross clamp. **P* < .05.

TABLE 3. Results for the joint modeling analysis of a linear mixed effects model for NT-proBNP from before to 36 hours after surgery and a generalized linear model for the duration of the mechanical ventilation

Variables	Estimate (95% CI)	SE	P	RE%
The first submodel				
Intercept	8.85 (8.44-9.26)	0.21	<.0001*	NA
Time points				
Before surgery	−1.41 (−1.59 to −1.23)	0.09	<.0001*	−75.59
1 h after surgery	−1.3 (−1.48 to −1.12)	0.09	<.0001*	−72.75
12 h after surgery	0.37 (0.21 to 0.53)	0.08	<.0001*	44.77
36 h after surgery	Reference			
Gender				
Female	−0.12 (−0.24 to −0.002)	0.06	.06	−11.31
Male	Reference			
Age				
Neonates (<30 d)	0.81 (0.46 to 1.16)	0.18	<.0001*	124.79
Infants (<1 y)	0.6 (0.42 to 0.78)	0.09	<.0001*	82.21
1-12 y	Reference			
RACHS-1				
≤2	−0.38 (−0.56 to −0.20)	0.09	<.0001*	−31.61
≥3	Reference			
DHCA				
No	−0.75 (−1.00 to −0.50)	0.13	<.0001*	−52.76
Yes	Reference			
Serum creatinine, μmol/L				
Preoperative	−0.004 (−0.02 to 0.02)	0.01	.69	−0.40
Postoperative	0.03 (0.02 to 0.04)	0.01	<.0001*	3.05
CPB time, min	0.004 (0.002 to 0.01)	0.001	.002*	0.40
ACC time, min	0.0003 (−0.004 to 0.004)	0.002	.87	0.03
Weight, kg	−0.07 (−0.08 to −0.06)	0.007	<.0001*	−6.76
The second submodel				
Log(NT-proBNP)	0.05 (0.02 to 0.09)	0.02	.001*	5.51
Time points				
Before surgery	0.0004 (−0.06 to 0.06)	0.03	.99	0.04
1 h after surgery	0.08 (0.01 to 0.16)	0.04	.03*	8.64
12 h after surgery	−0.25 (−0.43 to −0.07)	0.09	.01*	−22.06
36 h after surgery	Reference			
Gender				
Male	−0.03 (−0.08 to 0.03)	0.03	.37	−2.51
Female	Reference			
Age				
Neonates (<30 d)	0.66 (−0.71 to 2.03)	0.70	.34	93.65
Infants (<1 y)	−0.31 (−1.16 to 0.54)	0.43	.47	−26.80
1-12 y	Reference			
RACHS-1				
≤2	−0.04 (−0.15 to 0.06)	0.05	.41	−4.28
≥3	Reference			
DHCA				
No	0.12 (−0.02 to 0.26)	0.07	.08	12.75
Yes	Reference			
Serum creatinine, μmol/L				
Preoperative	−8.14 (−22.96 to 6.68)	7.41	.28	−99.97
Postoperative	−0.09 (−11.42 to 11.24)	5.66	.99	−8.61
CPB time, min	0.06 (−22.11 to 22.23)	11.27	1.00	5.97
ACC time, min	−4.13 (−18.70 to 10.44)	7.40	.58	−98.39
Weight, kg	−0.34 (−1.07 to 0.38)	0.37	.35	−29.08

RE% corresponding to an estimate β , expressed as expected percentage change in NT-proBNP, calculated as $(\exp[\beta] - 1) \times 100$. NT-proBNP, N-terminal pro-brain natriuretic peptide; SE, standard error; CI, confidence interval; RE%, percentage relative effects; NA, not available; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1; DHCA, deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; ACC, aorta cross clamp. * $P < .05$.

TABLE 4. Results for the joint modeling analysis of a linear mixed effects model for NT-proBNP from before to 36 hours after surgery and a generalized linear model for the duration of intensive care unit stay

Variables	Estimate (95% CI)	SE	P	RE%
The second submodel				
Log(NT-proBNP)	0.04 (0.02 to 0.06)	0.01	.001*	3.87
Time points				
Before surgery	0.004 (−0.04 to 0.04)	0.02	.85	0.37
1 h after surgery	0.03 (−0.02 to 0.08)	0.03	.30	2.83
12 h after surgery	−0.15 (−0.28 to −0.02)	0.06	.02*	−13.70
36 h after surgery	Reference			
Gender				
Male	0.02 (−0.02 to 0.06)	0.02	.32	1.99
Female	Reference			
Age				
Neonates (<30 d)	0.29 (−0.67 to 1.25)	0.49	.55	33.77
Infants (<1 y)	−0.11 (−0.70 to 0.49)	0.30	.72	−10.11
1–12 y	Reference			
RACHS-1				
≤2	−0.09 (−0.16 to −0.02)	0.04	.02*	−8.63
≥3	Reference			
DHCA				
No	0.10 (0.003 to 0.19)	0.05	.04*	10.33
Yes	Reference			
Serum creatinine, $\mu\text{mol/L}$				
Preoperative	−1.28 (−11.97 to 9.41)	5.34	.81	−72.20
Postoperative	1.30 (−6.87 to 9.48)	4.09	.75	266.93
CPB time, min	−7.91 (−23.45 to 7.62)	7.89	.32	−99.96
ACC time, min	1.44 (−8.76 to 11.65)	5.19	.78	323.64
Weight, kg	0.25 (−0.26 to 0.76)	0.26	.33	28.92

RE% corresponding to an estimate β , expressed as expected percentage change in NT-proBNP, calculated as $(\exp[\beta] - 1) \times 100$. NT-proBNP, N-terminal pro-brain natriuretic peptide; CI, confidence interval; SE, standard error; RE%, percentage relative effects; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1; DHCA, deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; ACC, aorta cross clamp. * $P < .05$.

score ≥ 3 . Patients who experienced DHCA were estimated to have a 10.3% higher expected ICU stay than patients who did not experience DHCA (Table 4).

On joint model analysis, NT-proBNP and RACHS-1 score were found to be independent predictors of prolonged duration of inotropic therapy (Table 5). Having adjusted for confounding variables, there was still a 3.5% (multivariate $P = .01$) increase in the likelihood of prolonged duration of inotropic therapy for each 1% increase in NT-proBNP.

On ROC curve analyses, NT-proBNP measured at 1 hour after surgery had better performance as compared with the 36-hour postoperative level in predicting longer duration of mechanical ventilation (>48 hours) (AUC, 0.84 vs 0.76; $z = 2.08$; $P = .04$), as shown in Figures 1–4. However, no significant differences in discrimination between the perioperative NT-proBNP levels at different time points for both prolonged ICU stay (>3 days) and duration of inotropic therapy (>3 days) were found. The optimal cut points for preoperative and 1-hour, 12-hour, and 36-hour postoperative NT-proBNP and the corresponding sensitivity and specificity in detecting longer duration of mechanical

ventilation, ICU stay, and inotropic therapy are shown in Figure 1.

DISCUSSION

The current study suggests and expands some already present views that perioperative NT-proBNP levels in the children undergoing CHD constructive surgery are predictive of postoperative affairs (eg, the prolonged mechanical ventilation time, ICU stay, and inotropic support duration after surgery).

The prognostic values of perioperative NT-proBNP levels in the setting of cardiac surgery have been mainly determined in the adult population and to a lesser extent in pediatrics. As far as we know, this is the largest study to assess the prognostic value of NT-proBNP in unselected heterogeneously aged children undergoing cardiac surgery for CHD. Furthermore, this is also the first study reporting the prognostic utility of NT-proBNP level at as early as 1 hour after surgery in this population, suggesting an important role for its use in postoperative management.

This study also characterized the alternations of NT-proBNP levels during the perioperative period of children

TABLE 5. Results for the joint modeling analysis of a linear mixed effects model for NT-proBNP from before to 36 hours after surgery and a generalized linear model for the duration of inotropic therapy

Variables	Estimate (95% CI)	SE	P	RE%
The second submodel				
Log(NT-proBNP)	0.03 (0.01 to 0.06)	0.01	.01*	3.46
Time points				
Before surgery	0.001 (−0.04 to 0.05)	0.02	.98	0.07
1 h after surgery	0.05 (−0.01 to 0.11)	0.03	.10	5.21
12 h after surgery	−0.17 (−0.31 to −0.02)	0.07	.03*	−15.40
36 h after surgery	Reference			
Gender				
Male	Reference			
Female	0.002 (−0.04 to 0.05)	0.02	.92	0.22
Age				
Neonates (<30 d)	0.11 (−0.99 to 1.22)	0.56	.84	12.07
Infants (<1 y)	0.01 (−0.67 to 0.69)	0.35	.97	1.22
1-12 y	Reference			
RACHS-1				
≤2	−0.09 (−0.17 to −0.01)	0.04	.03*	−8.60
≥3	Reference			
DHCA				
No	0.10 (−0.01 to 0.21)	0.06	.07	10.74
Yes	Reference			
Serum creatinine, μmol/L				
Preoperative	−3.52 (−14.98 to 7.94)	5.73	.54	−97.04
Postoperative	1.06 (−7.71 to 9.82)	4.38	.81	188.64
CPB time, min	−1.63 (−19.42 to 16.16)	9.04	.86	−80.43
ACC time, min	−0.64 (−12.34 to 11.05)	5.94	.91	−47.48
Weight, kg	−0.03 (−0.62 to 0.55)	0.30	.91	−3.37

RE% corresponding to an estimate β , expressed as expected percentage change in NT-proBNP, calculated as $(\exp[\beta] - 1) \times 100$. NT-proBNP, N-terminal pro-brain natriuretic peptide; CI, confidence interval; SE, standard error; RE%, percentage relative effects; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1; DHCA, deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; ACC, aorta cross clamp. * $P < .05$.

undergoing surgical repair for CHD. Postoperative NT-proBNP values begin to increase 1 hour after surgery, reaching a maximum level at 12 hours after surgery. However, Pérez-Piaya et al¹⁵ observed the NT-proBNP values start to rise 6 hours after surgery, peaking at 24 hours after the operation in a prospective study of 68 children (0-15 years) submitted to open-heart surgery. The inconsistencies among studies may result from a variety of reasons; for example, different sampling time, different bypass or myocardial protecting techniques, or different postoperative medical management.

Given the difference of BNP/NT-proBNP levels in children according to age,^{9,16} we also evaluated the alterations in NT-proBNP levels of children and neonates over time in separate analyses. Neonates (n = 30), however, on average show relatively lower levels at 1 hour after surgery (before surgery: 12,131 ± 10,123 pg/mL → 1 hour after surgery: 9610 ± 5592 pg/mL → 12 hours after surgery: 13,438 ± 9711 pg/mL → 36 hours after surgery: 12,037 ± 6298 pg/mL). Similar results were reported by Cannesson et al¹⁷ in neonates (n = 30) undergoing transposition of the great arteries, of which BNP level progressively declined after surgery compared with the baseline and then

increased gradually over the next 24 hours. This different postsurgery pattern of BNP/NT-proBNP kinetics compared with older children may in part be contributed to the generally higher disease severity and greater operation complexity.

Among perioperative NT-proBNP values at 4 different time points (from before to 1, 12, and 36 hours after surgery), all were found to be positively correlated with duration of mechanical ventilation, ICU stay, and inotropic drug therapy. Value at 1 hour after operation had the highest prediction value (Figure 1). Thus, why are 1-hour postoperative NT-proBNP levels more strongly correlated with subsequent prognoses compared with the preoperative value? It may be that BNP/NT-proBNP values after cardiac surgery reflect the comprehensive cardio-renal function and the extension of surgical response.¹⁸ The significant prognostic value of BNP level occurring as early as 8 to 12 hours after operation has been reported,^{4,19,20} but it is noteworthy that many adverse events occurred within the first 12 hours.²¹ Thus, BNP/NT-proBNP levels measured either before or at 12 hours after surgery will prevent prognostic utility among these patients. To our delight, the 1-hour NT-proBNP level after surgery (Figure 1) was also predictive

FIGURE 1. Receiver operating characteristic curve for N-terminal pro-brain natriuretic peptide level before surgery predicting the need for mechanical ventilation beyond 48 hours, intensive care unit (ICU) stay and duration of inotropic therapy beyond 3 days. AUC, Area under the curve; CI, confidence interval.

of prolonged mechanical ventilation, ICU stay, and inotropic support treatment; that is, this earlier time point might also have clinical utility within the first 12 to 48 hours postoperatively.²⁰

Furthermore, it is well known that circulating levels of BNP/NT-proBNP in patients can be affected by various extracardiac conditions. Thus, it needs to be highlighted that postoperative NT-proBNP levels and their subsequent prognostic value may be affected by several factors. First, given different NT-proBNP response at 1-hour after surgery between neonates and older children, the predictive values of this index have been evaluated in separate analysis. In neonates, results showed that with the exception of the relationship between preoperative levels and ICU stay, no significant association between perioperative NT-proBNP levels and mechanical ventilation, ICU stay, or inotropic support treatment duration were found. Similarly, a study about BNP by Hsu et al² showed that both preoperative and postoperative (2, 12, and 24 hours after cardiac surgery) levels in 36 neonates had no significant prognostic value.

In addition, changing BNP/NT-proBNP levels were proportionally influenced by the CPB.^{22,23} Besides the current study, we also evaluated it in a homogeneous cohort without CPB ($n = 38$). It is confirmed that results of patients without CPB were consistent and in line with the results of cases with CPB.

Another major factor is with regard to the assessment of renal function, which could confound the blood NT-proBNP levels.^{24,25} In our study, children were excluded

FIGURE 2. Receiver operating characteristic curve for N-terminal pro-brain natriuretic peptide level at 1 hour after congenital heart disease surgery predicting the need for mechanical ventilation beyond 48 hours, intensive care unit (ICU) stay and duration of inotropic therapy beyond 3 days. AUC, Area under the curve; CI, confidence interval.

from the analysis if they had evidence of impaired renal function before surgery. Moreover, acute kidney injury (AKI) (defined mainly based on the urine output for early identification) was recorded in 15 cases. Subgroup

FIGURE 3. Receiver operating characteristic curve for N-terminal pro-brain natriuretic peptide level at 12 hours after congenital heart disease surgery predicting the need for mechanical ventilation beyond 48 hours, intensive care unit (ICU) stay and duration of inotropic therapy beyond 3 days. AUC, Area under the curve; CI, confidence interval.

FIGURE 4. Receiver operating characteristic curve for N-terminal pro-brain natriuretic peptide level at 36 hours after congenital heart disease surgery predicting the need for mechanical ventilation beyond 48 hours, intensive care unit (ICU) stay and duration of inotropic therapy beyond 3 days. AUC, Area under the curve; CI, confidence interval.

analysis showed no significant difference of NT-proBNP levels before and after surgery in patients with and without AKI. This may be related to our timely intervention to the potential AKI patients using peritoneal dialysis.

Limitations

There are several limitations of the present study that may provide further extension of the research. First, we did not use Doppler imaging for the assessment of ventricular systolic and diastolic function, which may add further prognostic information. Compared with the RACHS-1 scoring system, the Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery (STAT) for surgical complexity is a more widely accepted risk score in the current era. STAT was not routinely used in pediatric cardiac surgery in our center until now. We cannot adjust STAT as a confounder in the multivariable regression models. However, one recent study²⁶ comparing stratification of complexity models (RACHS-1, Aristotle basic score, and STAT) in patients younger than 18 years with CHD, showed that 3 models are with similar discriminatory capacity for hospital mortality. Compared with comprehensive use of both RACHS-1 model and STAT model, the RACHS-1 single model used in our center has some limitations. Obviously, there was also certain rationality based on the results of the comparison of the 2 models. Obviously, we will try to introduce the STAT system in our clinical setting to keep with modern clinical practices. Second, prognostic cutoff points from the ROC analyses are specific for the

mentioned population of children without impaired renal function before surgery. The results are specific and can be recommended for use in homogeneous populations. Finally, our study was also limited by the sample size and was not powered to perform subgroup analyses to evaluate the effect of age (eg, neonates), type of CHD, and kinds of reconstruction performed. There is insufficient power to draw definitive conclusions in these subgroups.

CONCLUSIONS

In conclusion, perioperative NT-proBNP levels in the children undergoing CHD surgery, particularly levels measured 1 hour after surgery, provide stronger prognostic information and might be a more early, accurate, and sensitive predictor of prolonged ventilation, ICU stay, and inotropic support duration. Further studies are warranted to confirm if the routine NT-proBNP monitoring should be performed during postoperative management to identify individuals at high risk of adverse events who might benefit from alternative treatment strategies.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

The authors thank the doctors and nurses at the Department of Heart Center, Guangzhou Women and Children's Medical Center, in particular Xinxin Chen, MD, and his team of surgeons. We thank Ramit Kumar Gupta, MD, for assisting with the English language and preparing the manuscript, and Dr Taishan Zeng from the School of Mathematical Sciences, South China Normal University, for his statistical support, particularly for the joint model using.

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Key Words: N-terminal pro-brain natriuretic peptide, congenital heart disease, surgery, predictor, children

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