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The predictive value of preoperative B-type natriuretic peptide in children undergoing cardiac surgery

Boulos Ksontini Tatiana

UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Centre Hospitalier Universitaire Vaudois
Département Médico-Chirurgical de Pédiatrie
Unité de Cardiologie Pédiatrique

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Tatiana BOULOS KSONTINI

Médecin diplômé de la Confédération Suisse
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Madame la Professeure Stephanie Clarke
Directrice de l'Ecole doctorale

Abstract (en français)

Introduction: Le peptide natriurétique type B (BNP) est un marqueur reflétant le stress myocardique. Dans la population pédiatrique, la signification des valeurs préopératoire de BNP, en particulier sur l'évolution postopératoire, n'est pas clairement établie. Le but de l'étude est de déterminer la valeur prédictive de la partie NT sérique du BNP (NT-proBNP) sur l'évolution post opératoire d'enfants porteur d'une cardiopathie congénitale et ayant eu une chirurgie cardiaque.

Résultats: Nonante-sept enfants ont été inclus dans l'étude, avec un âge médian de 3.3 ans [0.7-5.2]. La valeur médiane du NT-proBNP préopératoire était de 412 pg/ml [164-1309]. Le NT-proBNP préopératoire était supérieur au P95 des valeurs de référence pour l'âge chez 56 patients (58%). Le NT-proBNP préopératoire était significativement plus élevé chez les patients ayant eu plus de deux jours de ventilation mécanique dans la période postopératoire (1156 pg/ml [281-1951] vs. 267 pg/ml [136-790], *p=0.003*) et ayant été hospitalisés plus de 6 jours dans l'unité de soins intensifs pédiatrique (727 pg/ml [203-1951] vs. 256 pg/ml [136-790], *p=0.007)*. Par contre, le NT-proBNP préopératoire n'était pas significativement plus élevé chez les patients ayant eu un score d'inotrope élevé pendant leur hospitalisation aux soins intensifs, un temps de circulation extracorporelle prolongé ou ayant subi une chirurgie avec un risque chirurgical élevé.

Conclusions: Un NT-proBNP sérique élevé en préopératoire reflète l'importance du stress myocardique induit par l'hémodynamique et la dysfonction myocardique, il est un marqueur qui permet d'améliorer l'identification des patients à risque d'avoir une évolution post opératoire compliquée.

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The predictive value of preoperative B-type natriuretic peptide in children undergoing cardiac surgery

Tatiana Boulos[1†] MD, Marie-Hélène Perez[2†] MD, David Longchamp[2] MD, Vivianne Amiet[2] MD, Julia Natterer[2] MD, Jacques Cotting[2] MD, Stefano Di Bernardo[1] MD

1. Pediatric Cardiology Unit, University Hospital and Medicine and Biology Faculty of Lausanne, Switzerland
2. Pediatric Intensive Care Unit, University Hospital and Medicine and Biology Faculty of Lausanne, Switzerland

† Contributed equally to work

@mails: Tatiana.Boulos@chuv.ch, Marie-Helene.Perez@chuv.ch, David.Longchamp@chuv.ch, Vivianne.Amiet@chuv.ch, Julia.Natterer@chuv.ch, Jacques.Cotting@chuv.ch, Stefano.Di-Bernardo@chuv.ch.

Corresponding author: Di Bernardo Stefano

Pediatric Cardiology Unit

CHUV-BH11-632

Rue du Bugnon 46

CH- 1011 Lausanne

Switzerland

Tel +41 79 556 10 05

Fax +41 21 314 36 65

E-mail: Stefano.Di-Bernardo@chuv.ch

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Abstract

Introduction: B-type natriuretic peptide (BNP) is a biomarker of myocardial stress. In children, the value of preoperative BNP on postoperative outcome is unclear. The aim of this study was to determine the predictive value of preoperative NT-proBNP on postoperative outcome in children after congenital heart surgery.

Results: Ninety-seven patients were included in the study with a median age of 3.3 years [0.7-5.2]. Preoperative median NT-proBNP was 412 pg/ml [164-1309]. NT-proBNP was above the P95 reference value for age in 56 patients (58%). Preoperative NT-proBNP was significantly higher in patients who had mechanical ventilation duration of more than 2 days (1156 pg/ml [281-1951] vs. 267 pg/ml [136-790], *p=0.003*) and who stayed more than 6 days in the pediatric intensive care unit (727 pg/ml [203-1951] vs. 256 pg/ml [136-790], *p=0.007*). However, preoperative NT-proBNP was not significantly higher in patients with an increased inotropic score, a prolonged cardiopulmonary bypass time or an increased surgical risk category.

Conclusions: An elevated preoperative NT-proBNP reflects hemodynamic status and cardiac dysfunction, and, therefore, is a valuable adjunct in predicting a complicated postoperative course.

Introduction

Low cardiac output syndrome (LCOS) is a frequent complication after heart surgery for congenital heart disease in children, and may result in a poor outcome, increased mechanical ventilation duration and use of inotropic support, as well as increased length of stay in the pediatric intensive care unit (PICU). The early detection of LCOS can be challenging. Its prediction and anticipation allow improvement of postoperative management strategies thereby preventing further hemodynamic compromise. Causes of LCOS are multifactorial and include pre and perioperative factors [1].

Means to reliably identify, in the preoperative period, those patients at risk of developing LCOS, is a subject of great interest because of its impact on patient morbidity. The use of a reliable, easy-to-use, cardiac biomarker, predictive of early postoperative complications would be a valuable addition to the patient's evaluation. Preoperative dosage of NT-proBNP has been shown to be a useful prognostic biomarker of death and major cardiovascular complications in adults after heart surgery [2-5]. In the pediatric population, only a few studies suggest the usefulness of this biomarker as a preoperative risk stratification tool for children undergoing heart surgery [6-11].

B-type natriuretic peptide (BNP) is a cardiac hormone, with natriuretic, diuretic and vasodilator properties, secreted by the cardiomyocyte in response to volume or pressure overload [12,13]. It is produced within the cardiac ventricles, as a biologically inactive prohormone, proBNP. It is then cleaved in the bloodstream into BNP, the active hormone, and NT-proBNP, the inactive N-terminal fragment. NT-proBNP is a stable peptide at room temperature with a longer half-life than BNP, which makes it a readily measurable biomarker [14]. Measured NT-proBNP concentrations and reference values are method-dependent and are influenced by age and gender of patients. Nir and colleagues published, in 2009, reference values and upper limits of NT-proBNP in healthy infants and children using the

electrochemiluminescence assay, Elecsys system 1010/2010, Roche Diagnostics [15]. These reference values have been used for our analysis.

The aim of our study was to determine the predictive value of preoperative NT-proBNP on postoperative outcome in children undergoing cardiac surgery for congenital heart disease. Due to the difficulty of assessing LCOS with objective parameters we opted to use mechanical ventilation duration (MVD), inotropic score (IS) and length of stay in PICU (LOS) as endpoint surrogates for LCOS.

Materials and methods

Our institutional research ethics committee approved the study and specifically waived the requirement for informed consent.

Preoperative NT-proBNP was measured in a prospective cohort of successive patients, aged 0-16, undergoing cardiac surgery for congenital heart disease and admitted, after surgery, to the PICU for postoperative management.

Measurements of NT-proBNP were performed with the Elecsys 2010 proBNP kit (Roche Diagnostics), which uses an electrochemiluminescence (ECLIA) immunoassay with an analytical range between 5-35000 pg/ml. Other preoperative data included demographics of patients, diagnosis of congenital heart disease and surgical risk categories. Intraoperative data included cardiopulmonary bypass (CPB) time and aortic cross-clamping time. Postoperative data included mechanical ventilation duration, inotropic score at 24 hours postoperatively and PRISM score. Data were prospectively collected using our point-of-care Clinical Information System (Metavision®, iMDSoft) and retrospectively analyzed. Age-dependent reference values (mean and P95) of NT-proBNP were used [15].

Preoperative NT-proBNP was correlated to postoperative outcome measures used as surrogate endpoints for LCOS: mechanical ventilation duration (MVD), inotropic score (IS) and length of stay (LOS).

The maximal amount of inotropic support needed in the first 24 hours postoperatively was calculated using the modified inotropic score (IS) which is

defined by the following formula: dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + (milrinone dose (mcg/kg/min) x 10) + (adrenaline dose (mcg/kg/min) x 100) + (noradrenaline dose (mcg/kg/min) x 100) [16,17]. According to other publications, we determined an increased inotropic score above 20 [17].

In order to define group categories of prolonged MVD and LOS for the analysis, we decided, according to our experience, that a prolonged MVD was more than 2 days and a prolonged LOS more than 6 days.

The PRISM-II (Paediatric Risk of Mortality) score was developed from the Physiologic Stability Index (PSI) to reduce the number of physiologic variables required for paediatric ICU mortality risk assessment and to obtain an objective weighing of the remaining variables. According to the literature, a score above 10 is predictive of increased mortality in PICU patients [18].

RACHS-1 (Risk Adjusted classification for Congenital Heart Surgery) was created in order to compare in-hospital mortality for groups of children younger than 18 years undergoing surgery for congenital heart disease [19]. RACHS groups surgical procedures for congenital heart disease into six categories of increasing predictive operative risk. We defined categories of surgical risk and CPB time as RACHS ≥ 3. We determined prolonged CPB time as more than100 minutes in order to identify confounding factors for LCOS.

Statistical analysis was done using Stata 13.1 version. Data is presented as median with interquartile range. Chi-square test was used to assess the association between preoperative NT-proBNP and MVD, IS and LOS. Wilcoxon's rank sum test was used to test associations for skewed variables. The significance level was set at 5 percent.

Results

A total of 97 patients, 37 females and 60 males, were included in the study. Age ranged from 1 day to 16 years (median 3.3 years [0.7-5.2]).

RACHS categories and major diagnostic groups are defined in Table 1. Major diagnostic groups included conotruncal anomalies (tetralogy of Fallot, double outlet

right ventricle, and truncus arteriosus), atrial septal defects, ventricular septal defects, atrioventricular septal defects, right and left outflow tract obstructive lesions (subvalvar, valvar and supravalvar aortic and pulmonary stenosis), aortic coarctation, partial and total anomalous pulmonary venous return, coronary anomalies and single ventricle defects.

Insert Table 1

Preoperative NT-proBNP ranged from 12 to > 35000 pg/ml (median 412 pg/ml [164-1309]). Cardiopulmonary bypass time ranged from 25 to 319 minutes (median 95 minutes [70-135]). Aortic cross-clamping time ranged from 0 to 222 minutes (mean 53 minutes [34-72]). PRISM ranged from 0 to 23 (median 4 [2-7]). LOS ranged from 2 to 56 days (median 6 days [4.1-9.9]). MVD ranged from 0.5 to 17.5 days (median 1.8 days [0.9-5.8]). Inotropic score ranged from 0 to 92 (median 14.5 [5-36]). There was no mortality in our study group. The demographic and outcome data are summarized in Table 2.

Insert Table 2

Preoperative NT-proBNP was above the median reference value for age in 91 children (94%) of the population studied, and above the P95 reference value for age in 56 children (58%).

Children with a preoperative NT-proBNP > P95 were significantly younger than those with a preoperative NT-proBNP < P95 (1.7 years [0.5-4.8] vs. 4.3 years [1.9-5.2], *p=0.02*). Children younger than one year were more frequently found to have a preoperative NT-proBNP above P95 compared to the children older than 1 year (24/32 patients (75%) vs. 32/65 patients (49%), *p=0.016*).

Insert Table 3

Table 3 summarizes our outcome results. Preoperative NT-proBNP values were significantly higher in patients ventilated more than 2 days compared to those patients ventilated less than 2 days (1156 pg/ml [281-1951] vs. 267 pg/ml [136-790], *p=0.003*). Preoperative NT-proBNP was also significantly higher in children with a LOS greater than 6 days compared to those with a LOS shorter than 6 days (727

pg/ml [203-1951] vs. 256 pg/ml [136-790], *p=0.007*). Similarly, preoperative NT-proBNP was significantly higher in patients with a PRISM score above 10 compared to patients with a PRISM score under 10 (1856 pg/ml [952-6267] vs. 350 pg/ml [161-1200], p=0.01). Preoperative NT-proBNP values did not statistically differ between RACHS groups (RACHS < 3 and ≥ 3), cardiopulmonary bypass time (CPB ≤ 100 min and CPB > 100 min) and inotropic score (IS ≤ 20 and IS > 20) groups.

Discussion

Our study demonstrates that patients requiring more prolonged mechanical ventilation support and having a longer length of stay had a significantly higher preoperative NT-proBNP than those with shorter MVD and LOS. Furthermore, patients with a high PRISM score upon admission in PICU had a significantly higher preoperative NT-proBNP than those with a low PRISM score. These outcome measures reflect disease severity and a complicated postoperative course, and were used as surrogate endpoints of LCOS. However, our study failed to show any significant correlation between preoperative NT-proBNP and the maximal inotropic score over the first 24 hours in PICU. This suggests the influence of other factors than LCOS alone on the in IS, such as, the duration of CPB, the inflammatory cascade triggered by CPB leading to varying degrees of vasoplegia, the need for sedation, etc... Interestingly, patients with a higher RACHS category, who underwent more complex surgical repairs, as well as patients that had a longer CPB duration, did not show any significant differences in preoperative NT-proBNP values. This suggests that preoperative NT-proBNP is somehow an independent risk factor for a complicated postoperative course and doesn't influence intraoperative factors as the type of surgical repair or CPB duration. Preoperative NT-proBNP reflects the severity of heart failure symptoms and cardiac function impairment and is, therefore, indicative of the preoperative hemodynamic status of the patient, irrespective of the congenital heart defect. This, however, appears to be unrelated to the difficulty of the surgery performed on the patient.

The interpretation of preoperative NT-proBNP measurements must take into account the method of measure, the gender of the patient, but, above all, the age of the patient, in particular infants who show higher reference values than the older child. Interestingly, we found that children younger than one year had higher preoperative NT-proBNP, which not only reflects the usual tendency to have a higher NT-proBNP in that age group, but also suggests that younger children with heart defects may present with more severely impaired cardiac function.

In the pediatric literature, there is conflicting evidence concerning the benefit of preoperative NT-proBNP and its predictive value on postoperative outcome. For example, Gessler and colleagues examined the outcome of 40 patients, aged 3 months to 7 years with various congenital heart defects undergoing cardiac surgery and found that preoperative NT-proBNP correlated significantly with the inotropic score in the first 24 hours, the duration of inotropes as well as the duration of mechanical ventilation. However, no correlation was found between preoperative NT-proBNP and RACHS categories [6]. By looking at results in 38 patients younger than three years with left ventricular volume overload cardiac lesions only, Walsh and colleagues showed, similarly, a significant correlation between preoperative NT-proBNP and duration of mechanical ventilation, LOS in the PICU, CPB duration and the Therapeutic Intervention Scoring System (TISS) score over the first 72 hours [9] Likewise, Nahum and colleagues found a significant correlation between increased preoperative BNP and need for increased postoperative inotropic support, longer MVD and LOS in infants younger than 1 year [11]. In contrast, Hsu and colleagues found no association between preoperative BNP levels and ventilator-free days or length of PICU stay in 36 neonates (<30 days) undergoing cardiac surgery [8]. These different studies demonstrate that the correlation of preoperative BNP with operative and postoperative outcomes can be confusing in the congenital cardiac population. Pediatric congenital heart surgery is particular in that it deals with a great number of heterogeneous heart defects requiring specific surgical repairs, which differ quite significantly depending on the heart defect. The age, hemodynamic and clinical

status at the time of surgery can also be quite variable. These above-mentioned factors inevitably impact on BNP secretion. Due to the relative infrequence of patients with similar heart defects and demographic variables, it is, in that respect, quite a challenge to study homogeneous groups. This fact certainly explains, in part, the conflicting results found in the literature concerning the predictive value of preoperative NT-proBNP. Our cohort of patients, even though heterogeneous in terms of age and congenital heart defect is one of the largest found in the literature on the subject and constitutes thereby one of the strength of this study.

In contrast to what is found in the pediatric literature, numerous studies done with adults undergoing cardiac surgery have clearly shown the prognostic value of pre-operative NT-proBNP as it correlates significantly with in-hospital ventricular dysfunction and need for inotropic or mechanical support, length of stay and 5 year mortality [2-4]. They have clearly demonstrated the benefit of adding preoperative NT-proBNP to the already existing cardiac surgical risk stratification models. Preoperative NT-proBNP may indeed help discriminate the marginal patients, with few clinical symptoms, that can benefit from a better preoperative medical and surgical preparation.

Approximately 25% of children develop LCOS after cardiac surgery for congenital heart disease [1,20]. It occurs typically within the first 12 hours after cardiopulmonary bypass and often has a multifactorial origin; some factors are intraoperative, like CPB duration and aortic cross-clamping duration, some are postoperative, like reperfusion injuries, increase in systemic or pulmonary vascular resistances or a CPB induced inflammatory cascade. LCOS is fundamentally a clinical diagnosis, yet a number of direct methods of assessment, like lactate levels and mixed venous oxygen saturation, are available to aid in the diagnosis. Direct and continuous measurement of cardiac output is rarely performed in pediatric patients due to the invasiveness of these techniques. LCOS is a predictable event and so, anticipation is the cornerstone to diagnosis and management. The development of a predictive LCOS score, including objective variables, like a reliable biomarker such as

NT-proBNP, could certainly assist in identifying those patients at risk of presenting a complicated postoperative course rather than using surrogates of LCOS, like IS, MVD and LOS, which are, when taken individually, partial and incomplete indicators. For these patients management strategies of the perioperative and postoperative period could be improved by adopting more aggressive measures aimed at preventing low cardiac output syndrome.

Certain limitations to this study should be noted, including the heterogeneous nature of the population studied, notably with regards to age of patients and diversity of congenital heart defects, which both independently influence NT-proBNP measurements, complicating the interpretation of results. It would be preferable to study age-specific and lesion-specific subset of patients in order to minimize the biases. The retrospective nature of this group of surgical patients may introduce as well some bias into the analysis of the data. To overcome these limitations, further studies are needed, yet this implies working in a prospective multi-centric fashion in order to increase the number of patients recruited.

Conclusions

Preoperative NT-proBNP appears to be a valuable marker that can help identifying, before surgery, certain patients at risk of developing postoperative complications. A high preoperative NT-proBNP in children with congenital heart defect is indicative, above all, of significant myocardial stress. This population could benefit from more aggressive strategy in the postoperative period, aimed at preventing low cardiac output syndrome. Further studies are needed to confirm our findings and strengthen the value of preoperative NT-proBNP as a reliable and predictive marker of postoperative outcome in children undergoing cardiac surgery.

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Table 1. RACHS-1 categories and major diagnostic groups

RACHS-1	Diagnosis	Number of patients (n=97)
1	ASD	2
	Aortic coarctation (>30 days)	1
2	VSD	23
	Tetralogy of Fallot	21
	Pulmonary stenosis (valvar/supravalvar)	1
	Aortic stenosis (valvar/subvalvar)	3
	Partial AVSD	1
	TAPVR	1
	Common atrium with PAPVR	1
3	Tetralogy of Fallot	10
	DORV	5
	Aortic stenosis/insufficiency (valvar, supravalvar)	7
	Pulmonary stenosis (valvar/supravalvar)	2
	Complete AVSD (balanced and unbalanced)	7
	Cor triatrium	1
	Tricuspid & mitral insufficiency	3
	Coronary anomalies	2
	Tricuspid atresia	3
	PA-IVS and hypoplastic RV	1
4	Truncus arteriosus	1
6	Double-inlet single ventricle	1

ASD, Atrial septal defect ; *AVSD*, Atrioventricular septal defect ; *DORV*, Double outlet right ventricle ; *PA-IVS*, Pulmonary atresia with intact ventricular septum ; *PAPVR*, partial anomalous pulmonary venous return ; *RACHS-1*, Risk adjusted classification for congenital heart surgery; *TAPVR*, total anomalous pulmonary venous return.

Table 2. Demographic and outcome data

N=97	Median [IQR]
Weight (kg)	11.3 [6.5-16.0]
Height (cm)	91 [68–108]
Age (years)	3.3 [0.7–5.2]
NT-proBNP (pg/ml)	412 [164–1309]
CPB time (min)	95 [70–135]
Aortic clamping time (min)	53 [34–72]
MVD (days)	1.8 [0.9–5.8]
LOS PICU (days)	6.0 [4.1–9.9]
Inotropic score at 24 hours	14.5 [5–36]
PRISM score	4 [2–7]

Data are presented as median [IQR]. *CPB*, Cardiopulmonary bypass; *LOS*, Length of stay; *MVD*, Mechanical ventilation duration; *PICU*, Pediatric intensive care unit; *PRISM*, Pediatric risk of mortality score.

Table 3. NTpro-BNP values and outcomes

	NT-proBNP (pg/ml)	*p*
MVD ≤ 2 days vs. > 2 days	267 [136-790] vs. 1156 [281-1951]	***0.003***
LOS PICU ≤ 6 days vs. > 6 days	256 [136-790] vs. 727 [203-1951]	***0.007***
Inotropic score ≤ 20 vs. > 20	350 [161-1171] vs. 555 [198-1908]	*0.27*
PRISM score ≤ 10 vs. > 10	350 [161-1200] vs. 1856 [952-6267]	***0.01***
CPB time ≤ 100 min. vs. > 100 min.	425[164-1229] vs. 368 [147-1848]	*0.85*
RACHS-1 < 3 vs. ≥ 3	364 [144-1171] vs. 467 [199-1951]	*0.22*

Data are presented as median [IQR]. *CPB*, Cardiopulmonary bypass; *LOS*, Length of stay; *MVD*, Mechanical ventilation duration; *PICU*, Pediatric intensive care unit; *PRISM*, Pediatric risk of mortality score; *RACHS-1*, Risk adjusted classification for congenital heart surgery.