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PEDIATRIC BRIEF REPORT

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Value of brain natriuretic peptide in the perioperative follow-up of children with valvular disease

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Abstract *Objective:* To characterize N-terminal pro-brain natriuretic peptide (N-proBNP) and troponin I (TnI) profile following mitral and/or aortic valve surgery and to evaluate correlations with echocardiography measures and outcome criteria. *Design and setting:* Prospective cross-controlled study in a university children's hospital. *Patients:* Twenty children with acquired valvular disease requiring valvular surgery. *Interventions:* We prospectively studied clinical, biochemical, and echocardiographic characteristics at baseline and 6, 12, 24 h and 3–4 weeks postoperatively. *Results:* TnI peaked 6 h after surgery and remained elevated during the first 24 h. N-proBNP was significantly lower 3–4 weeks after surgery than during the perioperative period. Overall, N-proBNP was correlated with the Pediatric Heart Failure Index, left ventricle shortening fraction, left atrium to aorta ratio, left ventricle mass index, end-systolic wall stress, and with outcome measures such as inotropic score, duration of inotropic support, and ICU length of stay. Preoperative N-proBNP was significantly more elevated in patients with complicated outcome than in patients with uneventful postoperative course. *Conclusions:* In pediatric valvular patients, perioperative N-proBNP is a promising risk stratification predicting factor. It is correlated with evolutive echocardiographic measures, need for inotropic support, and ICU length of stay.

Keywords Pediatric · Heart failure · N-terminal pro-brain natriuretic peptide · Troponin · Valvular surgery · Nesiritide

Introduction

As the prognosis of children with congenital heart disease improves, managing heart failure both perioperatively and at an outpatient clinic requires sensitive and adapted tools. Recently brain natriuretic peptide (BNP) was shown to reliably identified adults and children with dyspnea of cardiac origin and to be correlated with heart failure severity [1]. Similarly to BNP, cardiac troponin I (TnI) was shown to be correlated with postoperative outcome following cardiac surgery [2–4]. However, no study has compared plasma TnI and BNP values and analyzed the relationship to outcome measures and recovery over a prolonged timed period in a homogeneous pediatric population.

This study compare the accuracy of N-proBNP and that of TnI in characterizing the degree of heart failure severity and analyzed the correlation with standard echocardiographic measurements and recovery following corrective surgery in children with acquired valvular disease.

Patients and methods

Patient population and power analysis

The study was carried out among children referred to the University Children's Hospital of Geneva for corrective surgery of acquired mitral and/or aortic valvular heart disease. Twenty patients, cross-controlled ($\alpha = 0.05$, $\beta = 0.20$) were recruited to identify a 33% decrease (standardized effect size: 1.0) in the perioperative New York University Pediatric Heart Failure Index (PHFI) indicating clinical recovery [5]. Patient's characteristics are presented in the Electronic Supplementary Material (ESM Table 1). Most patients were severely or mildly malnourished and showed significant height and weight retardation. Eighteen patients required mitral surgery (16 valve plasties, 2 mechanical valve replacements) associated in seven with aortic valve surgery (five plasties, one homologous valve replacement, one mechanical valve replacement) and in one with tricuspid valve plasty. Two patients had isolated aortic valve surgery (one homologous valve replacement and one plasty). The study was approved by the internal Institutional Review Board and subjects' representatives gave informed consent. Data were prospectively collected and analyzed by a single observer (P.T.). No deaths occurred intraoperatively, and one patient died 4.5 days after surgery of terminal heart failure.

Outcome measurements

Short-term outcome was evaluated based on duration of inotropic support, inotropic score and length of stay in the pediatric ICU. Mean inotropic score was calculated by adding the mean doses of dopamine and dobutamine in micrograms per kilogram per minute and assigning an arbitrary equivalent value of 10 $\mu g\,kg^{-1}\,min^{-1}$ inotrope for each 0.1 $\mu g\,kg^{-1}\,min^{-1}$ epinephrine and 2 $\mu g\,kg^{-1}\,min^{-1}$ inotrope equivalent value for each 0.1 $\mu g\,kg^{-1}\,min^{-1}$ milrinone [6, 7]. Patients were classified as uneventful postoperative course if they were weaned from inotropic support within the first 24 h and/or discharged from the ICU before 4 days, or else as complicated postoperative course. A 4-days cutoff was chosen as corresponding to the median ICU length of stay.

Echocardiography

All children underwent repeated (before and 24 h and 3–4 weeks after surgery) comprehensive transthoracic two-dimensional segmental and Doppler echocardiographic studies using a Vingmed System Five ultrasound system. Echocardiographic examinations were matched with TnI and BNP measures. Echocardiography left ventricular shortening fraction (LVSF), end-systolic wall stress (ESWS), left atrium to aorta diameter (LA/AO) ratio, and left ventricular mass (LVM) were systematically calculated as described in the ESM.

TnI, N-ProBNP measurements

Whole blood was collected on ice in a 4 ml lithium-heparinized plastic tube (Vacutainer, Becton-Dickinson, Plymouth, U.K.), immediately centrifuged (3000 rpm for 15 minutes) and stored at –70 °C. TnI andN-ProBNP were measured in all patients before and 6, 12, 24 h and 3–4 weeks after surgery. TnI (Access AccuTnI Troponin I Assay, Access DXI 800, Beckman Coulter., Fullerton, CA, USA) and N-proBNP (Elecsys proBNP, Elecsys 2010, Roche Diagnostic, Mannheim, Germany) were analyzed according to manufacturer. TnI and N-proBNP measures were kept blinded until the end of patients' recruitment. Normal ranges were: TnI less than 0.04 μg/l, and N-proBNP less than 299 ng/l (adapted from [8]).

Data analysis

Results are presented as range and median for continuous variables and as proportion of total for categorical variables. The Wilcoxon rank sum test was applied to analyze continuous variables between the two groups. Continuous variables in patients in independent groups (e.g., patients having an uncomplicated or a complicated postoperative course) were compared using the Mann–Whitney *U* test. Correlations were determined by Spearman's rank correlation coefficient. Reciever operating characteristic curves were constructed using the following cutoff values:

Table 1 Correlation and ROC curve area under the zone between TnI, N-proBNP, and echocardiographic workup (*AZ*, area under the zone as obtained from receiver operating characteristic curves; *PHFI*, Pediatric Heart Failure Index; *LVSF*, left ventricle shortening fraction; *LA/Ao*, left atrium to aorta diameter ratio; *LVM*, left ventricle mass index; *ESWS*, end-systolic wall stress)

	TnI			N-proBNP		
	ρ	*p*	Az	ρ	*p*	Az
PHFI	–0.07	n.s.	0.351	0.57	0.0007	0.774
LVSF	–0.52	< 0.0001	0.791	–0.37	0.008	0.679
LA/Ao ratio	–0.09	n.s.	0.533	0.28	0.04	0.618
LVM index	0.03	n.s.	0.498	0.37	0.008	0.651
ESWS	0.03	n.s.	0.461	0.42	0.002	0.552

PHFI 4 (compensated heart failure under angiotensin-converting enzyme inhibitors and diuretics with functional effort limitation), LA/AO ratio 1.2, LVSF 28%, LVM index 184 g, ESWS 40×10^3 dynes/cm^2. Differences with a *p*-value below 0.05 were considered statistically significant. Data were processed using the SPSS version 15.0.1 for Windows software (SPSS, Chicago, IL, USA).

Results

Perioperative profiles

TnI peaked 6 h after surgery and remained elevated for the first 24 h postoperatively (ESM Table 2). TnI was normalized 3–4 weeks after surgery. N-proBNP kinetic failed to show a significant modification in the early postoperative period. However, it was significantly lower 3–4 weeks after surgery, although still remaining abnormally elevated. LVSF, LVM index, and LA/Ao ratio showed an early (24 h) modification from preoperative values. Although LA/Ao ratio and LVM index normalized, LVSF was significantly altered 24 h after surgery. End-systolic wall stress did not change significantly over time.

N-proBNP was correlated with PHFI and echocardiographic measures. TnI was not correlated with any parameter except LVSF. Construction of the receiver operating characteristic curve showed closer correlation of N-proBNP than TnI with PHFI and echocardiographic measures (Table 1). In addition, preoperative N-proBNP values were correlated with all outcome measures, such as need for and duration of inotropic support (respectively, $\rho = 0.50$, $p = 0.031$, and $\rho = 0.55$, $p = 0.019$) and length of stay in ICU ($\rho = 0.45$, $p = 0.045$). Postoperative TnI and N-proBNP levels were not associated with outcome with the exception of 6-h postoperative N-proBNP level which was correlated with inotropic score ($\rho = 0.53$, $p = 0.022$).

Because of the significant difference in N-proBNP level between patients with complicated vs. uncomplicated postoperative course (ESM Table 3), the postoperative course of N-proBNP kinetic was analyzed in the two subgroups (Fig. 1). Patients with uneventful postoperative course showed a statistically significant early postoperative increase in N-proBNP level, whereas patients with complicated outcome displayed unchanged postoperative N-proBNP values, and even a decreased values in one-half of them ($n = 5$). Preoperative N-proBNP (Az = 0.789) was better than TnI (Az = 0.556) in discriminating patients with complicated outcome.

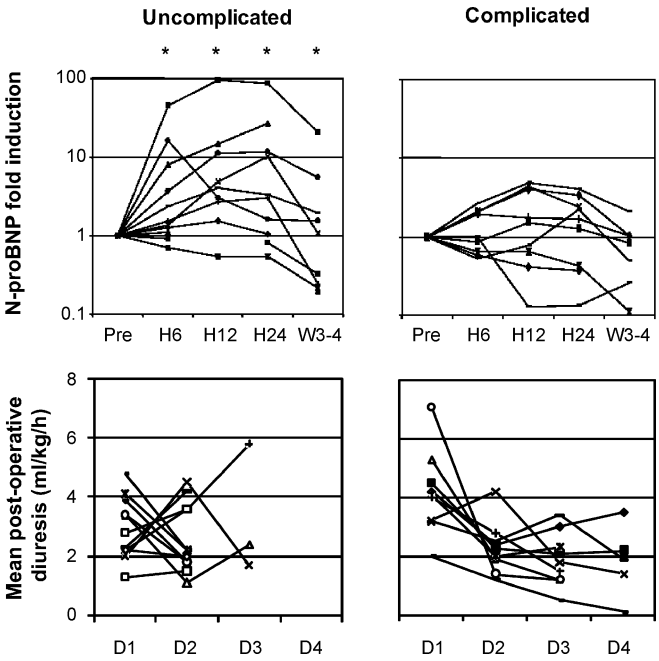

Fig. 1 Postoperative N-proBNP kinetics and diuresis in patients with complicated or uncomplicated outcome. N-proBNP data are expressed as "fold" induction from preoperative value (baseline) 6, 12, 24 h and 3–4 weeks after surgery. * $p < 0.03$ vs. basal (Wilcoxon signed rank test). Mean daily diuresis was measured from day 1 to day 4 following surgery

Discussion

The results of the present study demonstrate the superiority of N-proBNP over TnI in reflecting clinical and echocardiographic postoperative recovery of children undergoing valvular surgery. Furthermore, it suggests that

preoperative N-proBNP reflects postoperative myocardial functional capacity, thus helping in the early identification of patients who will require prolonged resources and/or additional support.

BNP has recently emerged as a useful tool to evaluate myocardial function and functional capacity and to discriminate between cardiac and noncardiac disease [9]. BNP has various physiological effects. It reduces preload by vasodilating the cardiovascular system, increases glomerular filtration and sodium excretion, and suppresses sympathetic activity [10–12]. In young adults and children with congenital heart disease BNP level is associated with the severity of heart failure [13]. In our study N-proBNP was correlated with most echocardiographic measures, confirming previous studies performed in adults with valvular disease and in children with right heart disease. In a recent study Logeart et al. [14] showed that BNP accuracy was greater than that of TnI in identifying right ventricle failure secondary to pulmonary embolism. In adults the preoperative BNP level was shown to be a strong predictor of postoperative complications and 1-year mortality [15, 16]. Our series showed a correlation between baseline N-proBNP and inotropic score, duration of inotropic support, and ICU length of stay, confirming recent data in children with various congenital heart defect [17].

Among pediatric series analyzing perioperative BNP, postoperative BNP increase was not invariably found [18–20]. Although Shih et al. [6] documented a global increase in BNP level, they noted that 38% of the children did not show a BNP peak at 12 h. Interestingly, in our series patients with a less complex postoperative course showed a statistically significant early (6 h) and sustained (up to 24 h) increase in postoperative N-proBNP values which was not found in patients with complicated postoperative course (Fig. 1). Similarly, a number of studies have demonstrated that adults with the most severe chronic heart failure do not have increase in BNP level during exercise [21–23]. Moreover, these show that BNP release is correlated with a better functional capacity, independently of other clinical parameters [23], and a decrease in 2-year mortality [22]. In the present study early postoperative decrease in N-proBNP levels occurred in patients with the higher preoperative PHFI (ESM Table 3) undersigning the most severe heart failure. Reduction in BNP production may occur as a result of overwhelmed myocardial capacity to synthesize BNP in regard to the advanced heart failure, as shown by Redfield et al. [24] in an experimental model of chronic severe heart failure.

The interpretation of our results is limited by the study design as power was calculated to reflect a definite expected postoperative clinical improvement as previously reported [5]. Therefore interpretation of the correlation between TnI and outcome is limited by the study power. However, although correlations are weak, superiority of N-proBNP over TnI is unquestionable.

In conclusion, in pediatric valvular patients, perioperative N-proBNP is a promising risk stratification predicting factor. It is correlated with evolutive echocardiographic measures, need for inotropic support, and ICU length of stay. These findings suggest that N-proBNP kinetics reflect postoperative myocardial functional capacity, thus helping in the early identification of patients who will require prolonged or intensive therapy. In addition, these preliminary results allow the hypothesis that a postoperative "BNP insufficiency" is present in patients with the most severe cardiac condition, helping in determining which patients may benefit of exogenous BNP, nesiritide, therapy. Further clinical and experimental studies are required.

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