Original Research

Relationship of preoperative NT-pro-BNP with clinical, perioperative and prognostic markers in cardiac surgery: Preliminary study results

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Abstract

Objective: We aimed to define the relationship of preoperative N-terminal-pro-brain type natriuretic peptide (NT-pro-BNP) testing in routine practice of cardiac surgery with clinical, perioperative variables, surgical outcomes and complications in pediatric and adult cardiac surgery patients. In addition, we assessed relationship of NT-pro-BNP with EuroSCORE II in adult patients undergoing cardiac surgery.

Methods: A total of 48 patients who underwent cardiac surgery in our institution were enrolled into this retrospective observational cohort study. According to age aspects pediatric (PG, n=20) and adult (AG, n=28) group of patients were separately evaluated. Each group further was categorized into two subgroups (group 1 and 2) on the basis of cut-off points of NT-pro-BNP level (430 and 250pg/ml in adults and children, respectively). Preoperative NT-pro- BNP was obtained from patients. Statistical tests were conducted to reveal differences in clinical and perioperative variables among NT-pro-BNP groups and relationship of the assay with baseline clinical and operative parameters, as well as postoperative outcomes.

Results: In adults undergoing cardiac surgery, statistically significant differences were found between groups with low and high levels of NT-pro-BNP by NYHA classes (I to III, p<0.001), body mass index (BMI) values (mean (SD) - 31.7(3.15) vs 25.9 (3.8) kg/cm^2, p=0.017), estimated glomerular filtration rate (eGFR) (111.4 (26.4) vs 77.9 (22.4) ml/min/1.73m^2, p=0.036), moderately impaired renal function (20% vs 72.7%, p=0.049), need for inotropes (28.6% vs 86.7%, p=0.006), and mean EuroSCORE II (0.81 (0.19) vs 1.7 (0.5), p=0.008). There was the positive significant correlation of NT-pro-BNP levels with EuroSCORE II, NYHA class, need for inotropes, renal function and left ventricular (LV) function categories, while its negative correlation was found with BMI, LV ejection fraction and eGFR parameters. In PG – NT-pro-BNP was negatively correlated with age, body surface area, LV end-diastolic and end-systolic dimensions.

Conclusion: In adult patients undergoing cardiac surgery, preoperative NT-pro-BNP level correlated well with several baseline and clinical-operative parameters, including BMI, renal and LV function, NYHA class, need for inotropes support, and EuroSCORE II. Further studies are needed to define its exact diagnostic and prognostic significance in pediatric patients.

Key words: cardiac surgery procedures, congestive heart failure, NT-pro-BNP, correlation, prognosis, surgical risk, surgery outcomes, early postoperative complications, EuroSCORE, renal failure

Introduction

Heart failure may be a result of vast majority of cardiovascular disorders including myocardial damage, valve pathology, conduction and rhythm abnormalities, and pericardial diseases (1, 2). History of most of the patients reveals both cardiac and non-cardiac comorbid conditions as the underlying factors of chronic heart failure (HF) (3). The incidence of HF is steadily increasing and remains the leading cause of hospitalization and in-hospital mortality in elderly population (age≥65 years) (4-6). By the improvement of current management, great successes have been achieved both in pharmacologic and surgical treatment of chronic HF.

Heart surgeries are quite challenging procedures, which require a cardiac-pulmonary bypass (CPB), and other settings. Additionally, high risk of complications are observed in postoperative period. Advanced age of patients and huge number of comorbid issues lead to increase of disease severity requiring more complex operations including simultaneous, hybrid and multistage procedures (7, 8). Furthermore, despite the significant improvement of healthcare, surgical operations performed in children with congenital heart diseases (CHD) are accompanied by high morbidity and mortality both early and late postoperative periods. Implementation of the robust prognostic biomarkers besides the routine ones used in daily clinical practice is crucial in postoperative management of pediatric patients in intensive care unit (ICU).

Several multifactorial scores have been used for preoperative risk stratification and surgery outcomes. But, no single risk assessment tool for cardiac surgery includes preoperative measurement of brain-type natriuretic peptides (BNP) in spite of their accurate correlation with ventricular dysfunction and HF (10). On the other hand, some studies recommend cautious application of risk assessment models in cardiac surgery for different population groups, due to existence of great variety by gender, ethnicity and geographic factors (11).

BNP, a valuable marker of HF is the member of natriuretic peptides family, which is secreted into bloodstream in response to volume overload or conditions causing myocardial stretching of ventricles. Compared to atrial natriuretic peptides (ANP), BNP is synthesized not only by atria, but also by ventricles, particularly in patients with HF (12). Circulating concentrations of several cardiac natriuretic peptides, including ANP, BNP and their N-terminal prohormones (NT-pro-ANP and NT-pro-BNP) are elevated both in patients with HF signs and asymptomatic left ventricular (LV) dysfunction (13-15). In practical sense, BNP and NT-pro-BNP are interchangeable and can be used according to local preference and availability. For diagnostic workup of mild HF and subclinical LV dysfunction NT-pro-BNP is preferred over BNP (15).

Duceppe E et al. proposed the prognostic role of NT-pro-BNP in adverse cardiovascular outcomes and mortality risk assessment of patients undergoing non-cardiac surgery within postoperative thirty days (16). In cardiac surgery, preoperative levels of NT-pro-BNP well correlate with ventilation time, duration of intensive care stays and perioperative pharmacological inotropic support (17). According to Hutfless et al, the level of BNP>385pg/ml may predict postoperative complications and mortality within twelve months after the cardiac surgery (10).

The study of Liu H. et al. revealed the level of NT-pro-BNP at 2773.5 pg/ml as a cut-off value (sensitivity 63.6% and specificity 80.8%) for mortality prognosis within 30 days after surgery (18). However, the evidence of clinical and prognostic utility of NT-pro-BNP in cardiac surgery is still emerging.

In this preliminary study, we objected to define the relationship of preoperative NT-pro-BNP testing in routine practice of cardiac surgery with clinical, perioperative variables (cardiopulmonary bypass time, aortic cross-clamp time, ventilation duration, need for inotropes, duration of intensive care stays), surgical outcomes and complications in pediatric and adult cardiac surgery patients. In addition, we assessed relationship of NT-pro-BNP with EuroSCORE II in adult patients undergoing cardiac surgery.

Methods

Study design
Retrospective, observational cohort study.

Study population
A total of 48 patients enrolled into study underwent elective cardiac surgery in Scientific Research Institute of Heart Surgery and Organ Transplantation (SRIHSOT) within two months of 2019 (September-November). Pediatric patients constituted 42% (n=20) operated due to CHD, adults comprised 58% (n=28) and underwent coronary artery bypass surgery (CABG), aortic (AVR) and mitral valve (MVR) replacement surgeries and myxoma resection surgery.

Study population was categorized into two groups by age aspects: pediatric (PG) and adult (AG) ones. Further each age group was divided into two subgroups, according to NT-pro-BNP levels: 1st subgroup included cases with less than 430pg/ml (AG) (19) and 250pg/ml (PG) (20), 2nd subgroup more than those cut-off points.

The NYHA IV class patients were excluded, though they did not undergo surgery. Patients with altered renal function (chronic kidney disease IIIB-V) were also excluded. Due to absence of NT-pro-BNP data 4 pediatric and 6 adult patients were excluded from the study.

Informed consent for procedures was obtained from all adult patients and from parents (guardians) of children patients.

Data analysis

We collected the following baseline demographic data from patient records: age (expressed in years (AG) and months (PG)), sex (male or female), body mass index (weight/height^2 in AG), body surface area (by Haycock formula in PG), underlying diagnoses, type of surgical operations, presence of risk factors for adverse outcomes of CHF (presence or absence of the dyslipidemia/atherosclerosis, myocardial infarction (MI), arterial hypertension, diabetes mellitus (DM), preoperative cardiac arrhythmia).

For preoperative assessment of CHF in adults, we used New-York Heart Association functional classification (NYHA) proposed in 1964, while for pediatric patients - modified Ross classification for pediatric HF (21, 22).

For baseline clinical data we collected serum creatinine levels, estimated glomerular filtration rate (eGFR) assessed by modified Cockroft-Gault formula (23), renal function categories (normal renal function (≥85 ml/min/1.73m^2), moderately or severely impaired (85-45 ml/min/1,73m^2 and <45 ml/min/1,73m^2), echocardiographic LV indices (LV end-diastolic (LVEDD) and end-systolic (LVESD), dimensions, LV ejection fraction (EF) by Teichholz and Simpson methods) and LV systolic function categories (reduced EF<40%, moderate (EF 40-50%) or preserved (EF≥50%)), Doppler-derived systolic pulmonary artery pressure (SPAP), pulmonary artery hypertension (PAH) categories (normal SPAP (<30mmHg), moderate PAH (31-55 mmHg) and severe PAH (>55 mmHg)).

For perioperative data we collected CPB and aortic cross-clamp (ACCT) times, duration of ICU stay, ventilation time and need for pharmacological inotropes, bleeding event. Surgical risk was calculated according to EuroSCORE II by evaluating following factors: age, gender, eGFR, NYHA functional class, urgency and volume of the cardiac surgery, SPAP, LVEF, Canadian Cardiovascular Society functional class of angina, presence/absence of extracardiac arteriopathy, poor mobility, previous cardiac surgery, chronic obstructive pulmonary disease, active endocarditis, recent MI, DM on insulin treatment, critical state, thoracic aorta surgery (24, 25).

For postoperative analysis surgery outcomes (alive vs died), complications (acute kidney injury (AKI), acute respiratory failure, chronic HF exacerbation) and arrhythmia (presence or absence) were used.

NT-pro-BNP assay

First sample was obtained in operation theatre prior to anesthesia. Second sampling was performed after 24 hours of operation in patients ventilated and intravenously supported by inotropes. Serum investigation was performed immediately after blood sampling in UPT – 3A analyzer, by electrochemiluminescence immunoassay (ECLIA) method, measurement units - pg/ml (Beijing Hotgen Biotech Co.LTD, China).

In adults, a <300pg/ml level of NT-pro-BNP could safely exclude likelihood of HF at any age. According to age aspects, for individuals aged 21-50 years ≥450pg/ml, 50-75 years ≥900pg/ml, and elder 75 years ≥1800pg/ml levels confirm HF. The values between 300pg/ml and aforementioned levels remained as grey zone (26).

In pediatric patients to date, no clear standards and no normal ranges of NT-pro-BNP were established. Based on ROC curve some studies revealed the 598ng/l as a cut-off level for HF diagnosis in children (27).

We used as cut-off values 430 pg/ml for adult cardiac surgery patients, as the higher values were associated with adverse outcomes after cardiac surgery in adults (19) and 250 pg/ml for pediatric cardiac surgery patients (20).

Statistical analysis

Statistical analysis was performed using SPSS for Windows software (IBM, New York, USA).

Continuous variables are depicted in mean (standard deviation, SD), median (min-max range), categorical variables as counts (percentage).

Chi-square test was used to assess differences for categorical variables, and Mann Whitney U test - for continuous variables. Nonparametric Spearman correlation analysis was used to assess correlation of NT-pro-BNP level with baseline and clinical-perioperative variables. P value of less than 0.05 was accepted as significant value determination (p<0.05).

Due to scarcity of data and small sample size we used only descriptive statistics for pediatric groups and Spearman correlation analysis of relationship of NT-pro-BNP with clinical and perioperative variables.

Results

Adult cardiac surgery patients
Baseline population demographics
Patient population was categorized into two groups on the basis of preoperative NT-pro-BNP level. A 430pg/ml was accepted as the cutoff value for grouping in AG. Baseline clinical variables and their statistical results are highlighted in Table 1. Mean age was 60.01 years. Age range: 34 to 72 years. All operations were performed in circumstance of CPB except the stent-graft implantation: CABG, AVR, MVR, AVR and MVR, left atrial (LA) myxoma resection, and stent-graft implantation.

According to age, sex, main diagnosis, surgery type, risk factors of HF and postoperative clinical outcomes no significant differences were found among groups. Significant results were obtained for BMI ranges and categorizations (slim ($<25kg/m^2$) and overweight or obese ($\geq25kg/m^2$)): p-value was 0.03 and 0.017, respectively. More patients that are obese were in group of low NT-pro-BNP level. There were significantly more patients with higher NYHA class in group of patients with high NT-pro-BNP levels (p<0.001), especially more patients with class III (p=0.03).

Clinical and operative variables

All results are depicted in Table 2. Echocardiographic data regarding cardiac chamber values, LV systolic function and estimated SPAP did not show significant differences (p>0.05). Similar calculations were obtained for creatinine level, intraoperative and ICU parameters, namely, ventilation time (VT), CPB, ACCT, and duration of ICU stay. Nevertheless, significant differences were observed among groups by estimated glomerular filtration rate (EGFR, p=0.036), frequency of renal function impairment (moderately impaired, p=0.049), need for inotropes in early postoperative period (p=0.006) and EuroSCORE II scale (p=0.008). Patients with high NT-pro-BNP levels had markedly lower eGFR rate (p=0.036), higher number of patients with renal function impairment (p=0.049), and more patients in this group needed inotropic support (p=0.006). The patients with higher NT-pro-BNP had higher surgical risk values compared to subjects with lower levels of NT-pro-BNP (p=0.008). However, there were no differences in adverse outcomes and complications between groups. We also did not observe any bleeding events.

Correlations of NT-pro-BNP with clinical and perioperative variables (Table 3)
NT-pro-BNP levels positively, strongly and significantly correlated with EuroSCORE II, NYHA classes and eGFR (p=0.001) with rho-values 0.73, 0.87 and -0.73, respectively. Significant results (p<0.05) were also found for the following parameters with corresponding rho-values: need for inotropes (0.62), renal function categories (0.72), EF obtained by Teichholz method (-0.47) and LV function categories (0.52).
NT-pro-BNP was negatively correlated with BMI ranges (-0.73), meaning higher BNP levels in lower BMI values. But higher NT-pro-BNP levels were related to lower values of EF (-0.47), and NT-pro-BNP levels were positively correlated to systolic indices (categories <40% and <50% of EF) (rho 0.52, p=0.01).

Pediatric cardiac surgery patients

Baseline demographic indices
According to cut-off point of NT-pro-BNP level PG was grouped into less or more than 250pg/ml. As can be seen from tables 4 and 5, only descriptive statistics of baseline clinical and operative parameters were highlighted. The mean age was 32.1±30.3months, median: 23 months, age range 14 days (0 months)-96 months (8 years).

Table 1. Baseline clinical characteristics of adult patients

Variable	Group 1 NT-pro-BNP<430, pg/ml	Group 2 NT-pro-BNP>430, pg/ml	p
Age, years Mean (SD) Median (range)	 58.0 (12.17) 60 (34-69)	 61.46 (6.32) 62 (48-72)	0.672
Sex, n (%) Male Female	 5 (71.4) 2 (28.6)	 9 (60.0) 6 (40.0)	0.604
Surgery, n (%) CABG MVR AVR Myxoma resection AVR+MVR	 4 (57.1) 1 (14.3) 1 (14.3) 0 1 (14.3)	 8 (53.3) 1 (6.7) 3 (20) 1 (6.7) 2 (13.3)	0.928
Diagnosis, n (%) CAD RVHD BiAV Myxoma IE	 4 (57.1) 1 (14.3) 1 (14.3) 0 1 (14.3)	 7 (46.7) 6 (40) 1 (6.7) 1 (6.7) 0	0.405
NYHA class, n (%) I II III	 5 (71.4) 2 (28.6) 0	 0 5 (33.3) 10 (66.7)	<0.001
BMI, kg/cm^2 Mean (SD) Median (range)	 31.7 (3.15) 30.7 (28.6-36.5)	 25.9 (3.8) 25.5 (19.5-32.5)	0.017
BMI categories, n (%) <25 25-30 >30	 0 2 (40) 3 (60)	 5 (50) 4 (40) 1 (10)	0.06
Dyslipidemia n (%)	3 (42.9)	9 (64.3)	0.35
Myocardial infarction, n (%)	1 (14.3)	5 (35.7)	0.306
Hypertension, n (%)	4 (57.1)	8 (66.7)	0.678
Diabetes mellitus, n (%)	6 (85.7)	11 (91.7)	0.683
Preoperative Arrhythmia, n (%)	0	3 (23.1)	0.23
Postoperative Arrhythmia, n (%)	0	8 (61.5)	0.03
Outcome, n (%) Alive Died	 6 (85.7) 1 (14.3)	 12 (80) 3 (20)	0.746
Complications, n (%) AKI AKI+CHFe CHFe Resp.F+CHFe none	 0 0 1 (14.3) 0 6 (85.7)	 1 (6.7) 1 (6.7) 0 1 (6.7) 12 (80)	0.469

AKI –acute kidney injury, AVR-aortic valve replacement, BMI-body-mass index, BiAV-bicuspid aortic valve, CABG-coronary artery by-pass grafting, CHFe-chronic heart failure exacerbation, MVR-mitral valve replacement, NT-pro-BNP-N-terminal pro brain type natriuretic peptide, NYHA class-New-York Heart Association class, Resp.F-respiratory failure

Table 2. Clinical and operative variables in an adult cardiac surgery group			
Variable	Group 1 NT-pro-BNP<430 pg/ml	Group 2 NT-pro-BNP>430 pg/ml	p
LVESD, mm			0.501
Mean (SD)	37.2 (10.6)	38.6 (7.6)	
Median (range)	33 (30-60)	39 (29-52)	
LVEDD, mm			0.626
Mean (SD)	54.4 (5.6)	53.9 (5.8)	
Median (range)	55 (43-60)	52 (46-63)	
EF Teichholz, %			0.156
Mean (SD)	63.4 (5.3)	56.6 (10.01)	
Median (range)	63 (57-70)	59 (34-69)	
LV function, n (%)			0.194
reduced EF<40%	0	1 (7.1)	
moderate reduced EF 40-50%	0	4 (28.6)	
preserved EF>50%	7 (100)	9 (64.3)	
EF Simpson, %			0.454
Mean (SD)	54.5 (4.13)	51.8 (6.3)	
Median (range)	54.5 (49-60)	54 (43-59)	
Creatinine, µmol/l			0.794
Mean (SD)	85.3 (19.4)	92.06 (21.9)	
Median (range)	85.3 (56.1-115.4)	86.3 (66.2-149.4)	
EGFR, ml/min/1.73m^2			**0.036**
Mean (SD)	111.4 (26.4)	77.9 (22.4)	
Median (range)	119.7 (78.8-137.7)	75.5 (55.4-132)	
RF, n (%)			**0.049**
Normal (>85 ml/min/1.73m^2)	4 (80)	3 (27.3)	
Moderate impairment (60-45 ml/min/1.73m^2)	1 (20)	8 (72.7)	
SPAP, mm Hg			0.187
Mean (SD)	34.6 (5.5)	39 (5.1)	
Median (range)	35 (28-40)	40 (30-50)	
PAH, n (%)			0.119
No (<30 mmHg)	2 (40)	1 (8.3)	
Moderate PAH (31-55 mmHg)	3 (60)	11 (91.7)	
ICU duration, days			0.817
Mean (SD)	3.8 (4.5)	2.6 (2.9)	
Median (range)	1.0 (1.0-1.13)	1.0 (1.0-1.10)	
CPB time, min			0.938
Mean (SD)	124.0 (93.7)	108.3 (58.6)	
Median (range)	84.5 (64.0-263.0)	103.0 (40.0-219.0)	
ACCT, min			0.643
Mean (SD)	88.2 (66.5)	74.3 (50.3)	
Median (range)	56.5 (52.0-188.0)	65.0 (29.0-180.0)	
Inotropes need, n (%)	2 (28.6)	13 (86.7)	**0.006**
Ventilation time, hours			0.84
Mean (SD)	38.5 (62.3)	9.7 (4.4)	
Median (range)	8.0 (6.0-132.0)	8.0 (4.0-19.0)	
EuroSCORE II			**0.008**
Mean (SD)	0.81 (0.19)	1.7 (0.5)	
Median (range)	0.75 (0.64-1.13)	1.83 (0.67-2.2)	

ACCT-aortic cross-clamp time, CPB-cardiac-pulmonary bypass, EF-left ventricular ejection fraction, EGFR-estimated glomerular filtration rate, ICU-intensive care unit, LV – left ventricle, LVEDD-left ventricular end-diastolic diameter, LVESD-left ventricular end-systolic diameter, NT-pro-BNP-N-terminal pro brain type natriuretic peptide, PAH-pulmonary arterial hypertension, RF-renal function, SPAP-systolic pulmonary artery pressure

Table 3. Correlation of NT-pro-BNP with baseline, clinical and operative variables in adult group		
Variable	**Rho**	**p**
EuroSCORE II	0.73	0.001
NYHA class	0.87	<0.001
Inotropes need	0.62	0.002
BMI	-0.73	0.002
EF Teichholz	-0.47	0.02
LV function	0.52	0.01
EGFR	-0.73	0.001
Renal function	0.72	0.02
BMI − body mass index, EGFR-estimated glomerular filtration rate, EF − ejection fraction, LV − left ventricle, NT-pro-BNP-N-terminal pro brain type natriuretic peptide, NYHA class-New-York Heart Association class		

Of 16 patients 9 are males (45%). The average NT-pro-BNP level was 3602.5 (9094) pg/ml, min 217.9 pg/ml, max 35000pg/ml. Mean body surface area (BSA): 0.48 (0.21m^2), median: 0.45m^2 range: 0,21-0,91m^2. Patients were distributed according to underlying CHD as follows: ventricular septal defect (VSD, n=6), atrial septal defect (ASD, n=2), ASD+VSD (n=1), ASD+partial anomalous pulmonary venous return (PAPVR) (n=1), patent ductus arteriosus (PDA, n=1), Fallot tetralogy (TOF, n=2), complete atrioventricular septal defect (AVSDc, n=1), coarctation of aorta (CoA, n=1), pulmonary stenosis (PS, n=1). Performed surgical interventions with use of CPB were as follows: ASD closure (n=2), VSD correction (n=6), VSD+ASD closure (n=1), ASD closure and PAPVR repair (n=1), complete AVSD correction (n=1), radical correction of TOF (n=1), pulmonary valvulotomy (n=1). Surgical procedures without CPB were systemic-pulmonary shunting in TOF (n=1), PDA ligation (n=1), and CoA correction (n=1). According to NYHA Ross classification children were distributed by: I (n=3), II (n=4) and III (n=9).

Clinical and operative variables (Table 5)

Echocardiographic indices: LVEDD: 29.07 (7.08) mm, LVESD: 17.28 (4.7) mm, LVEF: 72.1 (4.4)%. Systolic pulmonary artery pressure (SPAP): 56.8 (17.1)mmHg. Creatinine level: 38.2 (14.9) µmol/l. CPB time: 50.2 (21.4)min, ACCT: 26.0 (11.5) min, ICU duration: 2.07(1.6) days, ventilation time: 17.7 (34.8) h, need for inotropic support: 12 (75%). Only single lethal case was observed during hospital stay due to exacerbation of CHF (0.62%).

Correlations

A non-parametric correlation represented statistically significant correlation of NT-pro-BNP with following variables: age (p=0.038), BSA (p=0.002), left ventricular diastolic (p=0.024) and systolic diameters (p=0.053) (all are negatively correlated) (Table 6).

Table 4. Baseline clinical characteristics of pediatric patients

Variable	Group 1 NT-pro-BNP<250, pg/ml	Group 2 NT-pro-BNP>250, pg/ml	Number of cases
Age, months			14
Mean (SD)	52.0 (27.7)	26.7 (29.9)	
Median (range)	36 (36-84)	11 (1-96)	
Sex, n (%)			16
Male	1 (33.3)	6 (46.2)	
Female	2 (66.7)	7 (53.8)	
Surgery, n (%)			16
ASD closure		2 (15.3)	
VSD closure	3 (100)	3 (23.07)	
ASD+VSD correction		1 (7.6)	
PDA ligation		1 (7.6)	
AVSDc correction		1 (7.6)	
TOF radical correction		1 (7.6)	
MBTS		1 (7.6)	
CoA correction		1 (7.6)	
PV surgery		1 (7.6)	
Diagnosis, n (%)			16
ASD		2 (15.3)	
VSD	3 (100)	3 (23.07)	
ASD+VSD		1 (7.6)	
PDA		1 (7.6)	
ASD+PAPVR		1 (7.6)	
AVSDc		1 (7.6)	
PS		1 (7.6)	
TOF		2 (15.3)	
CoA		1 (7.6)	
NYHA Ross, n (%)			16
I	1 (33.3)	2 (15.3)	
II	1 (33.3)	3 (23.07)	
III	1 (33.3)	8 (61.5)	
BSA, m2			14
Mean (SD)	0.7 (0.17)	0.42 (0.18)	
Median (range)	0.65 (0.59-0.91)	0.37 (0.21-0.80)	
Outcome, n (%)			16
Alive	3 (100)	12 (92.3)	
Died	0	1 (7.6)	
Complications, n (%)			16
CHFe	0	1 (7.6)	
None	3 (100)	12 (92.3)	

ASD–atrial septal defect, AVSDc-complete atrio-ventricular septal defect, BSA-body surface area, CHFe-exacerbation of chronic heart failure, CoA- coarctation of aorta, MBTS-modified Blalock-Tausig shunt, NT-pro-BNP-N-terminal pro brain type natriuretic peptide, NYHA Ross-Modified Ross New-York Heart Association functional class, PAPVR-partial anomalous pulmonary venous return, PDA-patent ductus arteriosus, PS-pulmonary stenosis, PV – pulmonary valvotomy, TOF-Tetralogy of Fallot, VSD-ventricular septal defect

Table 5. Clinical and operative variables in pediatric patients			
Variable	Group 1 NT-pro-BNP<250 pg/ml	Group 2 NT-pro-BNP>250 pg/ml	Number of cases
LVESD, mm Mean (SD) Median (range)	 20.0 (2.6) 19 (18-23)	 16.5 (4.9) 16 (10-25)	14
LVEDD, mm Mean (SD) Median (range)	 33.6 (5.5) 34 (28-39)	 27.8 (7.1) 28 (16-41)	14
EF Teichholz, % Mean (SD) Median (range)	 71.0 (5.5) 72 (65-76)	 72.4 (4.3) 73 (64-78)	14
Creatinine, µmol/l Mean (SD) Median (range)	 47.5 (14.4) 49.4 (32.2-60.9)	 35.7 (14.7) 37.1 (17.6-58.6)	14
SPAP, mm Hg Mean (SD) Median (range)	 47.5 (3.5) 47.5 (45-50)	 59.1 (18.6) 57.5 (30-85)	10
ICU duration, days Mean (SD) Median (range)	 1.3 (0.57) 1 (1.0-2.0)	 2.2 (1.7) 1.0 (1.0-1.6)	14
CPB time, min Mean (SD) Median (range)	 64.3 (28.5) 75.0 (32.0-86.0)	 45.0 (17.5) 45.0 (19.0-73.0)	11
ACCT, min Mean (SD) Median (range)	 32.6 (18.4) 28.0 (17.0-53.0)	 23.5 (8.1) 24.0 (11.0-34.0)	11
Inotropes need, n (%)	1 (33.3)	11 (84.6)	16
Ventilation time, hours Mean (SD) Median (range)	 7.6 (1.5) 8.0 (6.0-9.0)	 20.5 (39.2) 8.0 (2.0-138.0)	11
ACCT-aortic cross-clamp time, CPB-cardiac-pulmonary bypass, EF-left ventricular ejection fraction, ICU-intensive care unit, LVEDD-left ventricular end-diastolic diameter, LVESD-left ventricular end-systolic diameter, NT-pro-BNP-N-terminal pro brain type natriuretic peptide, SPAP-systolic pulmonary artery pressure			

Table 6. Correlation of NTpro-BNP with clinical and operative variables in pediatric patients		
Variable	rho	p
Age	-0.55	0.038
BSA	-0.75	0.002
LV EDD	-0.59	0.024
LV ESD	-0.52	0.053
BSA-body surface area, LVEDD-left ventricular end-diastolic diameter, LVESD-left ventricular end-systolic diameter, NT-pro-BNP-N-terminal pro brain type natriuretic peptide		

Discussion

Preliminary results of our study in adult patients who underwent cardiac surgery demonstrated that preoperative NT-pro-BNP levels are elevated in patients with advanced NYHA classes, LV dysfunction, higher surgical risk, worsened kidney function and need of inotropic support. In addition, a significant positive correlation was found between NT-pro-BNP level and EuroSCORE II, a prognostic scoring index which defines the complexity of surgery and patients' cardiac surgical risk; renal function categories, whether normal or moderately impaired; CHF NYHA functional class grading, from mild symptoms to limited daily activities; systolic function categories on the basis of LVEF; as well as need for inotropic support in early postoperative period. A negative correlation was observed by BMI, EF and GFR levels. However, we did not observe difference in surgery outcomes due to presumably small sample size.

Previous studies revealed the good correlation of LV global systolic dysfunction and symptom severity with NT-pro-BNP by means of LVEF with cut-off level of 50% (28). Nevertheless, recent findings advocate the relationships of BNP molecules with novel indices of global systolic function.

Several studies including large trials represented negative correlations between natriuretic peptides and BMI. According to these studies low NT-pro-BNP levels were detected both in overweight (BMI=25-30kg/m^2) and obese (BMI≥30kg/m^2) subjects. Furthermore, these investigations defined similar levels of NT-pro-BNP levels as the cutoffs, in PRIDE-study which included 204 subjects it was chosen 900pg/ml, in another trial with 1103 study population it was considered as 986ng/l (29, 30). Recent evidence supports the involvement of posttranslational processing of pro-BNP molecules, specifically the augmented glycosylation of threonine in 71st position of pro-BNP and consequent decreasing in concentration of NT-pro-BNP molecules in overweight and obese patients (31). Despite the small sample size (n=28) our patients also represented negative correlation with statistically significant results (rho=-0.73, p=0.002) as in aforementioned literature reviews.

A univariate analysis showed that renal dysfunction was closely correlated with NT-pro-BNP level in assessment of the 30-day mortality (18). According to Su et al, NT-pro-BNP was found as an independent risk factor for development of acute kidney injury requiring renal replacement therapy in early postoperative period of cardiac surgery patients (32). Both continuous (eGFR) and categorical (renal impairment) variables in our study showed significant results among adult subgroups, as well as significant negative correlation of eGFR and positive correlation with renal impairment severity with NT-pro-BNP level, thus confirming previous studies.

Controversial findings exist in literature regarding to correlation of NT-pro-BNP and inotropic support in early postoperative period. According to Oztekin et al., no relationship was found between NT-pro-BNP level and need for inotropic support in patients who underwent isolated CABG surgery (33). In pediatric cardiac surgery, perioperative NT-pro-BNP accurately determines the prognosis of postoperative outcome including duration of mechanical ventilation, ICU stay and inotropic therapy (34).

Recent findings revealed the reliability and simplicity of preoperative NT-pro-BNP in predicting cardiac surgery risk or assisting the EuroSCORE II grading system (35, 36). Though in another study NT-pro-BNP and Euroscore II had both good predictive value for 3-year mortality, no relation between them was reported (37). Our results extended those studies showing strong positive correlation of NT-pro-BNP with EuroSCORE II (rho 0.73, p=0.001). Further studies are needed to explore the additive predictive value of NT-pro-BNP and EuroSCORE II.

Study limitations

The main limitations of this preliminary study are small sample size and retrospective design. Results will be validated and reported in a further larger sample size study.

Conclusion

Preoperative NT-pro-BNP level in our cohort of adult patients is related to higher NYHA class, LV dysfunction, renal impairment and consequently higher requirement for inotropic support after surgery and is related with prognostic indicator as EuroSCORE II independently of type of surgery. There is a negative relation with BMI. Further study is needed to support our findings in adult and pediatric patients.

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