



## Nt-proBNP in Pediatric Cardiac Surgery: A Correlation Study with the Postoperative Course and Morbidity

### ABSTRACT

**Objectives:** B-type natriuretic peptides, synthesized by cardiac myocytes in response to increased ventricular wall stress, are secreted as prohormones and cleaved into biologically active hormone (BNP) and the inactive N-terminal fragment, known as Nt-proBNP. They possess diuretic, natriuretic, and vasodilatory effects. Recently, B-type natriuretic peptides have been identified as valuable parameters in detecting acute and chronic left ventricular dysfunction. This study aims to investigate the relationship between preoperative and postoperative Nt-proBNP levels, the postoperative course, and morbidity in congenital cardiac surgery patients.

**Methods:** Thirty-one patients, aged between 3 months and 16 years, undergoing open-heart surgery with cardiopulmonary bypass due to congenital heart disease, were examined. The patients had left-to-right shunt lesions or stenosis in the ventricular outflow tract. Patients were divided into two groups based on the need for high-dose (>5mcg/kg/min) inotropic therapy during the postoperative period: those requiring high-dose inotropic support and those requiring low-dose or no inotropic support. Nt-proBNP levels were measured preoperatively (T0), at 2 hours postoperatively (T1), and 24 hours postoperatively (T2). Additionally, postoperative inotropic support, cardiopulmonary bypass, cross-clamp, and mechanical ventilation durations were recorded.

**Results:** There was a statistically significant difference in cross-clamp durations between the groups. Statistically significant differences were also observed in the duration of inotropic therapy, mechanical ventilation, and length of stay in the intensive care unit. Our study revealed a correlation between the dose and duration of inotropic therapy administered during the postoperative period and Nt-proBNP levels, with patients requiring high-dose inotropic support showing a mean serum level of  $1009.10 \pm 1345.43$  pg/ml. This finding suggests an association between elevated Nt-proBNP levels and increased postoperative inotropic requirements.

**Conclusion:** In the context of adult heart illnesses and cardiac surgery, serum Nt-proBNP levels are a biochemical marker that can effectively assess low functional capability and prognosis. Elevated levels of preoperative serum Nt-proBNP in individuals having cardiac surgery for congenital heart abnormalities offer crucial insights into myocardial function and the efficacy of medicinal interventions.

**Keywords:** Congenital cardiac surgery, inotrope, natriuretic peptide

Congenital heart diseases (CHDs) are conditions resulting from defects in the development of the heart and major blood vessels during fetal development. They are observed in approximately 0.8–1% of live births, with 1,035,795 live births recorded in Turkey in 2022 (1). In light of these data, it is estimated that approximately 10,000 babies are born with CHDs each year, and about one-fourth of them require surgical intervention within the first year of life (2). Moreover, the postoperative mortality rate in these patients exceeds 10% (2). Changes in cardiac output can rapidly occur in patients with CHDs, either in the preoperative period or, more commonly, in the postoperative period. Low cardiac output syndrome (LCOS) is a clinical syndrome characterized by a cardiac index below  $2L/min/m^2$ , resulting in inadequate oxygen delivery to tissues and terminal organs and failure to meet metabolic demands. LCOS significantly increases the risk of multiorgan dysfunction and is highly associated with mortality. The incidence of LCOS after surgery in children with CHDs ranges from 25% to 60%, typically manifesting 6 to 18 hours postoperatively, with a mortality rate exceeding 20% (3).

A variety of cardiac biomarkers have been reported in adults with heart failure. Since the measurability of natriuretic peptides in 2002, they have become essential for diagnos-

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**Received:** April 01, 2024

**Accepted:** April 16, 2024

**Cite this article as:** Koç M, Tak S, Baş T, Kaya K, Bolat A, Kutsal A. Nt-proBNP in pediatric cardiac surgery: A correlation study with the postoperative course and morbidity. Acad J Health 2023;1(4):114-117.

DOI: 10.14744/ajh.2023.92400



**Table 1. Diagnostic distribution of patients included in the study**

Diagnosis	Number	Rate (%)
Atrial Septal Defect	4	12.9
Atrioventricular septal defect, Infundibular Pulmonary Stenosis	1	3.2
Tetralogy of Fallot	12	38.7
Partial Pulmonary Venous Return Anomaly	2	6.5
Transposition of the Great Artery Pulmonary Stenosis	1	3.2
Ventricular Septal Defect	11	35.5

tic and prognostic monitoring in patients with cardiac problems. The early elevation of BNP levels before the onset of heart failure symptoms enhances this peptide's diagnostic sensitivity and importance (4). Elevated BNP levels are observed not only in patients with heart failure due to systolic dysfunction but also in those with heart failure due to diastolic dysfunction (5). However, studies on biomarkers predicting preoperative and postoperative mortality and morbidity in children with CHDs are limited.

The aim of this study is to investigate the utility of serially measured Nt-proBNP levels in serum as a significant biomarker that predicts the early development of low cardiac output syndrome in congenital heart disease, thus contributing to the prevention of mortality and morbidity.

## METHODS

After obtaining the approval of the hospital's education and planning committee and ethics committee, a prospective, randomized study was conducted at Dr. Sami Ulus Maternity and Child Health Research and Training Hospital in accordance with the Universal Code of Ethics contained in the Declaration of Helsinki. A total of 31 patients aged between 3 months and 16 years who underwent open-heart surgery with cardiopulmonary bypass due to congenital heart disease were included in the study. Patients with left-to-right shunt lesions and stenosis in the ventricular outflow tract were included in the study group. Patients who underwent single ventricle repair, had previously undergone palliative surgery, had residual defects, or received mechanical support therapy were excluded from the study.

Patients were categorized into two groups based on their postoperative need for inotropic medication: Patients in Group 1 needed high-dose inotropic support, which meant they needed at least 10 mcg/kg/min of dopamine or dobutamine, 0.1 mcg/kg/min of epinephrine or norepinephrine, or 0.5 mcg/kg/min of milrinone. In contrast, Group 2 consisted of patients not requiring inotropic therapy or receiving low-dose inotropic medication (<5 mcg/kg/min).

All patients discontinued oral intake 8 hours before surgery, and premedication was administered using 0.1 mg/kg midazolam 15 minutes before anesthesia induction. Patients were routinely monitored with two-lead ECG (DII-V5), pulse oximetry, and non-invasive blood pressure. Anesthesia induction was achieved with 15 mcg/kg fentanyl, 0.2–0.3 mg/kg midazolam, and 0.1mg/kg vecuronium. All patients were ventilated with  $FiO_2 = 1.0$ , tidal volume (TV) set at 15–20 ml/kg, respiratory rate adjusted according to age to maintain  $PaCO_2$  at 35 mmHg, and an inspiration/expiration ratio of 1:2. Radial artery cannulation and right atrium catheterization

were performed using the Seldinger technique. Anesthesia maintenance included additional doses of 2 µcg/kg fentanyl, 0.1 mg/kg midazolam, and 0.05 mg/kg vecuronium as needed. Sevoflurane, at approximately 1 MAC, was added if necessary. Patients were cooled to 28–32°C according to their cardiac pathologies. Cardiac arrest was induced with antegrade hypothermic crystalloid cardioplegia, and corrective surgical procedures were performed under cardiopulmonary bypass.

All patients underwent preoperative transthoracic echocardiography to record their pathologies, and Nt-proBNP blood levels were measured one day before surgery (T0). Central venous pressure (CVP), heart rate (HR), systolic arterial blood pressure (SAB), diastolic arterial blood pressure (DAB), mean arterial blood pressure (MAB), postoperative inotropic support therapy durations and doses, and arterial blood gas samples were recorded after anesthesia induction.

For Nt-proBNP measurements, 3ml of venous blood was collected into EDTA-containing Lavender Vacutainer tubes 24 hours before surgery. The plasma was separated by centrifugation at 1600rpm for 15 minutes at +4°C and stored at -70°C in polypropylene tubes. Hemodynamic data, blood gas samples, and Nt-proBNP values were sampled again at 2 hours (T1) and 24 hours (T2) postoperatively. Postoperative inotropic therapy requirements and durations, cardiopulmonary bypass times (CPBT), cross-clamp (CC) times, mechanical ventilation times (MVT), and intensive care unit (ICU) stay durations were recorded. Plasma Nt-proBNP measurements were performed using the chemiluminescence method with Roche Diagnostic's Nt-proBNP kit on Elecsys 2010. The manufacturer's reference ranges for Nt-proBNP were accepted as 0–100 pg/mL for males and 0–150 pg/mL for females.

## Statistical Analysis

Data were analyzed using the SPSS for Windows 22 statistical package. Comparisons were made using Student's t-test and Mann-Whitney U test. Pearson's correlation analysis was applied for correlation analysis, and  $p < 0.05$  was considered statistically significant.

## RESULTS

The mean age of the 31 patients included in the study was  $5.87 \pm 4.02$  years (65% male, 35% female). The diagnostic distribution of patients is shown in Table 1.

Statistically significant differences were found in right ventricular pressure when examining preoperative hemodynamic data and Nt-proBNP levels between the two groups ( $p < 0.05$ ). There were no statistically significant differences in left ventricular pressure,

**Table 2. Preoperative hemodynamic data and Nt-proBNP level**

	Shunt Lesion	Stenosis Lesion	Sensitivity
Right Ventricular Pressure	46.59±21.05	98.57±14.92	p<0.01
Left Ventricular Pressure	103.76±15.35	97.79±14.76	NS
Mean Pulmonary Artery Pressure	29.76±9.80		NS
Systemic/Pulmonary Flow Ratio	2.52±1.18		NS
Preoperative Nt-ProBNP Level	39.29±30.42	37.92±62.25	NS

NS: No significant difference

**Table 3. Operative and postoperative data of the groups**

	Group I	Group II	p
Cardiopulmonary bypass duration	51.62±26.72	81.40±48.00	NS
Cross-clamp duration	33.12±22.12	54.00±32.01	p<0.05
Duration of inotropic treatment	22.82±21.10	52.43±36.67	p<0.01
Duration of mechanical ventilation	6.25±6.52	14.93±11.55	p<0.01
Duration of Intensive Care	37.06±26.46	104.87±67.30	p<0.01

NS: No significant difference

**Table 4. Postoperative 1<sup>st</sup> hour and 24<sup>th</sup>-hour NtproBNP levels of the groups**

	Group I	Group II	p
Nt-ProBNP (1 <sup>st</sup> hour)	99.66±89.09	353.45±251.40	p<0.05
Nt-ProBNP (24 <sup>th</sup> hour)	144.41±128.94	1009.10±945.43	p<0.01

mean pulmonary artery pressure, systemic-pulmonary artery flow ratio, or preoperative Nt-proBNP levels (Table 2).

Statistically significant differences between the groups were found in cross-clamp times (p<0.05). There were statistically highly significant differences in the durations of inotropic therapy, mechanical ventilation, and ICU stay durations (p<0.01) (Table 3).

There was a statistically significant difference in postoperative 1-hour Nt-proBNP levels between the two groups (p<0.05), and a highly significant difference was observed in 24-hour Nt-proBNP levels (p<0.01) (Table 4).

There was a weakly significant positive correlation between the duration of inotropic therapy and serum Nt-proBNP levels at 1 hour postoperatively (r= 0.430, p<0.05). A moderately significant positive correlation was observed between the duration of inotropic therapy and serum Nt-proBNP levels at 24 hours postoperatively (r= 0.718, p<0.01).

There was a moderately significant positive correlation between serum Nt-proBNP levels at 24 hours postoperatively and mechanical ventilation duration (r= 0.619, p<0.01) and ICU stay duration (r= 0.484, p<0.01).

## DISCUSSION

Type B natriuretic peptide (BNP) was first isolated from the porcine brain in 1988 by Sudoh and initially named brain natriuretic peptide (6). However, it was later shown that most circulating BNP originates from the ventricular myocardium. The brain natri-

uretic peptide exerts diuretic, natriuretic, and vasodilatory effects. It induces arterial and venous dilation by relaxing the vascular smooth muscle. It lowers peripheral vascular resistance, making the heart pump more blood and lowering filling and capillary wedge pressure (7). Unlike atrial natriuretic peptide, primarily produced in the atria and ventricles, BNP's main source is the ventricles. This renders BNP more sensitive and specific as a determinant of ventricular dysfunction compared to other natriuretic peptides (8).

After recognizing the heart's endocrine function, extensive studies have been conducted on the effects of natriuretic peptides, particularly in adult cardiac patients. Many studies have demonstrated that Nt-proBNP can be used in the diagnosis of symptomatic heart failure and correlates with the NYHA classification (9,10). In a study by Richards et al. (11), Nt-proBNP was shown to be an independent predictor of symptomatic heart failure and poor prognosis in patients with left ventricular systolic dysfunction following myocardial infarction. Lemos et al. (12) reported that detecting BNP serum levels in the early days following the onset of ischemic symptoms provides crucial information for risk stratification in acute coronary syndromes. Several studies have reported preoperative BNP plasma levels as determinants of postoperative left ventricular systolic function in patients undergoing coronary artery bypass surgery (13,14).

In a study conducted by Suda et al. (15) involving 59 patients with ventricular septal defects, a correlation was found between serum BNP levels and the left-to-right shunt, and a significant positive correlation was observed between the size of the shunt and serum

BNP levels ( $r=0.45$ ,  $p<0.01$ ). Kunii et al. (16) also demonstrated a positive correlation between serum BNP levels and the magnitude of left-to-right shunts ( $r=0.45$ ,  $p<0.01$ ), suggesting that plasma BNP levels could serve as a non-invasive method for determining the need for surgical treatment in left-to-right shunt lesions. However, in our study, although patients with left-to-right shunts had elevated serum Nt-proBNP levels in the preoperative period, no statistically significant correlation was found between the shunt magnitude and serum Nt-proBNP levels. This result was attributed to the preoperative cardiac evaluation of patients and the implementation of medical treatment to preserve myocardial function.

Our study observed a correlation between the dose and duration of inotropic therapy administered during the postoperative period and Nt-proBNP levels, with patients requiring high-dose inotropic support exhibiting an average serum level of  $1009.10 \pm 1345.43$  pg/ml. This indicates that neurohumoral mechanisms increase endogenous compensatory activity to resolve myocardial dysfunction. Finding Nt-proBNP levels above 1000 pg/ml after surgery suggests a risk for low cardiac output syndrome, which means that the right treatment should be started right away.

## CONCLUSION

In conclusion, serum Nt-proBNP levels, as a readily measurable biochemical parameter, can determine low functional capacity and prognosis, particularly in adult heart diseases and cardiac surgery. Preoperative serum Nt-proBNP levels in patients undergoing cardiac surgery due to congenital heart anomalies provide essential information about myocardial function and the effectiveness of medical treatment. Additionally, serum Nt-proBNP levels persistently elevated above 1000 pg/ml in the postoperative period serve as a warning sign for postoperative heart failure, low cardiac output, and residual defects, providing valuable insights into the effectiveness of cardiac support therapies.

**Ethics Committee Approval:** This study was conducted with the permission of the Ankara University, Faculty of Medicine Local Ethics Committee (decision no: 38-812, date: 24.01.2008).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – M.K., A.K., A.B.; Design – M.K., K.K., T.B.; Supervision – M.K., S.T., A.K., K.K.; Resource: M.K., S.T.; Materials: M.K., A.B., S.T.; Data Collection and/or Processing – M.K., A.B., S.T., A.K.; Analysis and/or Interpretation – M.K., K.K.; Literature Search – M.K., S.T., T.B., K.K., A.B., A.K.; Writing – M.K., S.T., T.B., K.K., A.B., A.K.; Critical Review – M.K., S.T., T.B., K.K., A.B., A.K.

**Declaration of Interests:** The authors have no conflict of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

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