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SCIENTIFIC ARTICLE

The predictive value of plasma B-type natriuretic peptide levels on outcome in children with pulmonary hypertension undergoing congenital heart surgery

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Abstract

Background and objectives: In children undergoing congenital heart surgery, plasma brain natriuretic peptide levels may have a role in development of low cardiac output syndrome that is defined as a combination of clinical findings and interventions to augment cardiac output in children with pulmonary hypertension.

Methods: In a prospective observational study, fifty-one children undergoing congenital heart surgery with preoperative echocardiographic study showing pulmonary hypertension were enrolled. The plasma brain natriuretic peptide levels were collected before operation, 12, 24 and 48 h after operation. The patients enrolled into the study were divided into two groups depending on: (1) Development of LCOS which is defined as a combination of clinical findings or interventions to augment cardiac output postoperatively; (2) Determination of preoperative brain natriuretic peptide cut-off value by receiver operating curve analysis for low cardiac output syndrome. The secondary end points were: (1) duration of mechanical ventilation ≥ 72 h, (2) intensive care unit stay > 7 days, and (3) mortality.

Results: The differences in preoperative and postoperative brain natriuretic peptide levels of patients with or without low cardiac output syndrome ($n = 35$, $n = 16$, respectively) showed significant differences in repeated measurement time points ($p = 0.0001$). The preoperative brain natriuretic peptide cut-off value of 125.5 pg mL^{-1} was found to have the highest sensitivity of 88.9% and specificity of 96.9% in predicting low cardiac output syndrome in patients with pulmonary hypertension. A good correlation was found between preoperative plasma brain natriuretic peptide level and duration of mechanical ventilation ($r = 0.67$, $p = 0.0001$).

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PALAVRAS-CHAVE

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 Pós-operatório

Conclusions: In patients with pulmonary hypertension undergoing congenital heart surgery, 91% of patients with preoperative plasma brain natriuretic peptide levels above 125.5 pg mL^{-1} are at risk of developing low cardiac output syndrome which is an important postoperative outcome. © 2013 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. All rights reserved.

O valor preditivo do peptídeo natriurético tipo-B em resultados de crianças com hipertensão pulmonar submetidas à cirurgia cardíaca congênita

Resumo

Justificativa e objetivo: em crianças submetidas à cirurgia cardíaca congênita, os níveis plasmáticos de peptídeo natriurético cerebral (PNC) podem ter um papel no desenvolvimento da síndrome de baixo débito cardíaco (SBDC), definida como uma combinação de achados clínicos e intervenções para aumentar o débito cardíaco em crianças com hipertensão pulmonar.

Métodos: em um estudo prospectivo observacional, foram inscritas 51 crianças submetidas à cirurgia cardíaca congênita, com avaliação ecocardiográfica pré-operatória que mostrava hipertensão pulmonar. Os níveis plasmáticos de PNC foram avaliados antes e 12, 24 e 48 h após a operação. Os pacientes incluídos no estudo foram divididos em dois grupos em função de: (1) desenvolvimento de SBDC; (2) determinação dos valores de corte de PNC no pré-operatório pela análise da curva de funcionamento do receptor para SBDC. Os desfechos secundários foram: (1) duração da ventilação mecânica ≥ 72 h, (2) permanência em unidade de terapia intensiva > 7 dias e (3) mortalidade.

Resultados: os níveis de PNC nos períodos pré- e pós-operatório dos pacientes com ou sem SBDC ($n = 35$, $n = 16$, respectivamente) apresentaram diferenças significantes nos tempos de mensuração repetidos ($p = 0,0001$). O valor de corte de PNC de $125,5 \text{ pg mL}^{-1}$ no pré-operatório obteve a maior sensibilidade de 88,9% e especificidade de 96,9% para prever a SBDC em pacientes com hipertensão pulmonar. Uma boa correlação foi descoberta entre o nível plasmático de PNC no pré-operatório e duração a ventilação mecânica ($r = 0,67$, $p = 0,0001$).

Conclusões: em pacientes com hipertensão pulmonar submetidos à cirurgia cardíaca congênita, 91% com níveis plasmáticos de PNC acima de $125,5 \text{ pg mL}^{-1}$ no período pré-operatório estão em risco de desenvolver a SBDC, que é um desfecho importante no pós-operatório.

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Introduction

Plasma brain natriuretic peptide (BNP) is a neurohormone that is secreted mainly by the ventricles in response to an increase in right or left ventricular pressures as well as volume overload. This neurohormone has natriuretic, diuretic and vasodilatory properties.^{1,2} Right ventricular (RV) dysfunction refers to abnormalities of filling or contraction without reference to signs or symptoms of heart failure. Pulmonary hypertension (PH) is defined as; an echocardiographic finding of a mean pulmonary artery pressure ≥ 25 mm Hg at rest and heart failure (HF) is defined as; left ventricular pump dysfunction causing dilation, thinned walls, and poor contractility of the heart are important causes of RV dysfunction.^{1,3} The use of brain natriuretic peptide (BNP) as an indicator of RV dysfunction in children with PH undergoing congenital heart surgeries remains largely unknown. Previous studies demonstrated an increase in BNP levels preoperatively and postoperatively in patients with ventricular septal defect or ventricular dysfunction.³⁻⁶ In recent studies, the goal was to investigate whether BNP levels can be used as a tool in determination of diagnosis and prognosis of children.⁶⁻⁹ It was reported that plasma BNP levels increased immediately

after congenital heart surgeries despite hemodynamic unloading and also a correlation between peak BNP level to cardiopulmonary bypass (CPB) time was demonstrated.¹⁰ The development of low cardiac output state (LCOS) has recently been used as a postoperative outcome measure in patients undergoing congenital cardiac surgery.^{11,12} LCOS is defined as: tachycardia, poor peripheral perfusion, oliguria, cardiac arrest, need for a 100% increase in pharmacological support or administration of a new inotropic agent, metabolic acidosis with an increase in base deficit.^{13,14} There are only a few studies providing data that plasma BNP levels may help to identify children with PH causing RV dysfunction.^{6,11,12} Also, it was demonstrated that in children with moderately symptomatic HF, BNP level greater than or equal to 140 pg mL^{-1} and age greater than 2 years are independently associated with poorer outcomes.¹⁵

Our goal was to investigate a relation between plasma BNP levels and postoperative clinical outcomes such as LCOS, duration of mechanical ventilation, intensive care unit stay and mortality in a 30-day postoperative period in patients undergoing congenital heart surgeries with CPB. In addition, we compared plasma BNP levels before and after surgery in patients with or without LCOS.

Methods

Patients

Fifty-one patients with a diagnosis of PH and congenital heart disease were enrolled in a prospective observational study design. This study was conducted after local Ethical Committee approval during the period of July 2008–September 2009. We obtained written informed consent from the patients' parents or guardians before enrollment in the study. In all patients, the presence of PH and RV dysfunction was shown by an echocardiographic study before operation. PH is defined as: systolic systemic arterial pressures of at least 35 mm Hg or exceeding 50% of the systemic mean arterial pressure (MAP).^{12,15,16} The detection of PH is based on the systolic pulmonary artery pressure (P_{ap}) calculated from velocities of the tricuspid or pulmonary valve regurgitations obtained by echocardiographic Doppler studies.^{16,17} During this measurement the following diagnostic criteria were used in this study; (1) estimated ratio of pulmonary to systemic pressure (P_p/P_s) using Doppler echocardiography >0.5, (2) Systolic P_{ap} was measured by Doppler analysis of tricuspid regurgitant velocity Doppler flow and depending on previous studies on children a relationship of systolic P_{ap} to diastolic and mean P_{ap} were made accordingly,¹⁷ (3) significant tricuspid regurgitation, (4) enlarged or hypertrophied RV without evidence of pulmonary stenosis, and (5) intraventricular septal flattening. RV dysfunction is diagnosed based on the echocardiographic data and the most important parameter in the diagnosis include: tricuspid annular plane systolic excursion (TAPSE) value that is based on the age of the patient to assess RV systolic function.^{16,17} The echocardiographic studies were done by the same pediatric cardiologist preoperatively and postoperatively every 12 h and if there are clinical signs of PH crisis.

All patients had one of the congenital heart diseases that have high risk for developing postoperative pulmonary hypertension and these include: (1) isolated VSD, (2) Ventricular septal defect (VSD) and total anomalous pulmonary venous connection (TAPVR), (3) Ventricular septal defect (VSD) and partial anomalous pulmonary venous connection (PAPVR), (4) VSD with or without atrial septal defect (ASD) and/or PAPVR, and (5) atrioventricular canal defect (AVSD).¹⁸ Patients with single ventricle pathologies were included into the study. Patients having cardiomyopathies, transposition of the great arteries, truncus arteriosus and hypoplastic left heart syndrome were not included. In the study group all patients had systolic P_{ap} values between 40 and 70 mm Hg with systemic MAP values between 50 and 60%. Patients with systolic P_{ap} values above 70 mm Hg with a systemic MAP value above 60% were excluded from the study.

All of the patients underwent congenital heart repair surgery with CPB. In our study the same surgical team was involved in all surgical procedures. The patients were divided into two groups depending on: (1) Development of LCOS postoperatively and (2) preoperative BNP cut-off value was determined by receiver operating curve (ROC) analysis for LCOS.^{11,13,14} Oliguria is defined as a urine output that is less than 1 mL kg⁻¹ h⁻¹ in infants, less than 0.5 mL kg⁻¹ h⁻¹ in children.¹⁹ In children, the normal reference values for

heart rate (HR) and systemic mean arterial pressure were provided in previous guidelines.^{20,21}

Primary and secondary end points

The primary end point was the development of LCOS within 30 days of surgery which is an adverse postoperative outcome. The secondary end points include the development of other adverse outcomes within 30 days of surgery and these include: (1) Duration of mechanical ventilation longer than 72 h postoperatively, (2) Duration of intensive care unit stay longer than 7 days, (3) Mortality in the 30-day postoperative period, and (4) Development of other complications such as neurologic deficit, pneumonia, renal failure, ventricular and atrial arrhythmias, complete atrioventricular block.

Intraoperative anesthetic management

The preoperative anesthesia management, intraoperative surgical strategy, and pediatric intensive care unit management protocols are explained in detail previously.²⁰ Standard anesthetic monitoring include: five-lead electrocardiogram, pulse oximeter, rectal temperature probe, end tidal carbon dioxide, arterial catheter and central venous catheter. Intraoperative transesophageal echocardiography was used only occasionally. At the end of CPB, RV systolic and diastolic pressures were measured via an appropriate sized arterial catheter inserted to the right ventricle. The catheter was pulled out during closure of the sternum. RV mean pressure was collected at the end of CPB. Children with hemodynamic instability had transthoracic or transesophageal echocardiographic studies done in the ICU; however, echocardiographic evaluation was not available during operation. During surgery, general anesthesia was induced with the use of midazolam at a dose of 200 µg kg⁻¹, fentanyl sulfate at a dose of 25 µg kg⁻¹, and pancuronium bromide at a dose of 0.1 mg kg⁻¹. Patients received repeated doses of fentanyl at a dose of 5 µg kg⁻¹ and midazolam at a dose of 50 µg kg⁻¹ every half an hour throughout surgery and inhalational anesthetic of sevoflurane at a dose of 1.0–2.0 MAC (minimum alveolar concentration) was also provided depending on systemic MAP. Neonates and infants were intubated with uncuffed endotracheal tubes and intraoperative and postoperative ventilation was maintained with volume- or pressure-controlled ventilation. Perioperative antibiotic prophylaxis included cefazolin. Methylprednisolone was administered to all patients intravenously in two equally divided doses of 10 mg kg⁻¹ each before the start of CPB.

Cardiopulmonary bypass protocol

The CPB circuit included a roller pump, a disposable membrane oxygenator, and an arterial filter. CPB was established using an arterial cannula and bicaval or a single two-stage venous cannulae. Cooling and rewarming were carried out with a heat exchanger. The priming solution consisted of a crystalloid solution of isotonic sodium chloride and mannitol at a dose of 3 mL kg⁻¹. Packed red blood cells were used to obtain a haematocrit value of 25% before start of CPB. Heparinization was achieved with heparin sulfate. During CPB, a perfusion index of 2.4–2.6 L min⁻¹ m⁻¹ was

used. Moderate hypothermia was performed at 28 °C. After cross-clamp placement, blood cardioplegia with addition of potassium chloride, sodium bicarbonate, magnesium sulfate was given at the dose of 30 mL kg⁻¹. Intermittent antegrade cold blood cardioplegia at 4 °C was used for myocardial protection. Heparin was neutralized with protamine sulfate in a 1:1.5 ratio. Intravenous administration of vasodilator and inotropic agents were used if necessary to wean patients from CPB. Volume substitution was carried out with fresh frozen plasma or 5% human albumin.

Perioperative and postoperative care

The parameters that were collected during surgery and in the 24 h postoperative period include: demographic data, CPB, aortic cross-clamp time, HR, systemic MAP, mean RV pressure, central venous pressure (CVP), arterial oxygen saturation, urine output, fluid balance, inotrope agents and doses. Parameters were recorded every 30 min throughout the operative procedure and every 30 min in the intensive care unit after operation. Postoperative adverse outcome related parameters including duration of mechanical ventilation, intensive care unit (ICU) stay, hospital stay and 30-day mortality were collected. Prolonged mechanical ventilation is described as mechanical ventilation (MV) ≥ 72 h following operation.²² Prolonged ICU stay >7 days is considered as an adverse event.²³ The patients were evaluated for postoperative adverse events every 12 h by the research team including a physician and resident.

Postoperative PH crisis was defined as an increase in systolic PAP to the level of systemic MAP or greater and is accompanied by a fall in systemic MAP, a fall in arterial or venous oxygen saturation, or both. The definition is also associated with hypoxemia, development of metabolic acidosis and/or hypovolemia. In all of our children PAPs (systolic and correlated diastolic and mean PAPs)¹⁷ were calculated by echocardiographic Doppler studies in the ICU as described in patients section. The detection of postoperative PH was based on clinical signs and echocardiographic studies in the ICU.^{16,17} The important treatment measures to avoid an increase of PAPs intraoperatively and in the postoperative period in ICU include: (1) To support oxygenation with inspiratory FiO₂ at a level of 0.6–1.0; (2) To provide moderate hyperventilation (to keep PaCO₂ level between 30 and 35 mm Hg); (3) To avoid development of metabolic acidosis (to keep pH above 7.4); (4) To provide a recruitment maneuver to avoid ventilation/perfusion mismatch; (5) To provide a low-tidal-volume ventilation to avoid overinflation of aveoli (to keep tidal volume between 6 and 8 mL kg⁻¹ ideal body weight); (6) To provide a temperature management to maintain body temperature of 36–37 °C at the end of CPB and (7) To provide a “goal-directed” fluid and volume therapy the effectiveness of hemodynamical monitoring was followed by measurements of necessary parameters which include; HR, systemic MAP, mean RV pressure, central venous pressure (CVP), arterial oxygen saturation, urine output and fluid balance.^{24,25}

Children at risk for or with signs of postoperative PH were sedated, received mechanical ventilatory support, and usually received inotropic support (dobutamine and/or dopamine, additional inotropes of adrenaline and/or noradrenaline). Intravenous nitroglycerin at a dose of

0.5–3 $\mu\text{g kg}^{-1} \text{min}^{-1}$ was provided to patients by appropriate follow-up of the hemodynamical parameters. These agents are administered through a right central venous line in an attempt to keep PAPs less than 40% of systemic MAP. The administration of nitroglycerin is recommended for intravenous vasodilation. As the effect of this medication is not limited to the pulmonary circulation and therefore also induces systemic vasodilation, its administration often causes a considerable decrease in systemic MAP and involves the risk of right-ventricular perfusion pressure falling below a critical limit.^{16,24,25} In the acutely decompensated PH, inhaled nitric oxide, intravenous or inhaled epoprostenol, iloprost, and inotropic support are the most useful agents.¹⁸ However, in our study routine use of these agents was not available.

PH related events were treated with manual hyperventilation with 100% oxygen and intravenous use of opiate; fentanyl at a dose of 5–10 $\mu\text{g kg}^{-1}$. For patients with PH, mechanical ventilation was continued until the echocardiographic studies showed well-controlled measurements of PAPs as well as an improvement in clinical status indicating that myocardial function had recovered. After extubation and when there was no longer any need for invasive monitoring or vasoactive drugs, the child was transferred to the ward.^{16,24,25}

Perioperative measurements

Plasma levels of BNP and arterial blood gases were collected preoperatively, 12, 24 and 48 h postoperatively from blood samples of an arterial catheter that was inserted at the beginning of the surgery before induction of anesthesia. The surgical and medical teams that are involved in the management of the study patients were blinded to plasma BNP values. The plasma levels of BNP were measured using a commercially available fluorescence immunoassay (Triage, Beckman Coulter, Inc. San Diego, California, USA). The measurable range of BNP on this device is between 5 and 5000 pg mL⁻¹.

Statistical analysis

Statistical analyses were performed using SPSS 17.0.1 for Windows software (SPSS Software, Chicago, IL, USA). In the study by Hsu et al. a sample size of 32 including 16 patients in each group with or without LCOS is needed to detect a difference of prolonged intensive care unit stay of 1 day (1 standard deviation) using 2-sided significance, a power (1 – β) of 80% and an $\alpha = 0.05$.¹¹ All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Differences of categorical variables were tested with chi square test. Differences of continuous variables that are not normally distributed were tested with Mann–Whitney *U* test. Changes in plasma BNP levels were compared using repeated-measures analyses of variance (ANOVA). The utility of preoperative BNP as a prognostic indicator of postoperative outcome was evaluated using receiver operating characteristic (ROC) curves and the areas under curve (AUC) as well as sensitivity and specificity were calculated. Differences with a *p*-value below 0.05 were considered statistically significant.

Results

Patient data

Fifty-one patients were included into the study group. Age, weight, gender, and the type of cardiac lesions are shown in Table 1. The median age of the study group of 51 patients was 1.10 years (range 0.3–3.0 years). The median weight was 7.00 kg (range 4.00–26.00). In this group, there were 23 (45.1%) male and 28 (54.9%) female patients. In the whole group, there were 5 patients (9.8%) with isolated VSD, 2 (3.9%) patients with VSD with TAPVR, 13 (25.5%) patients with VSD and PAPVR (w/wo ASD), 15 (29.4%) patients had VSD with ASD and 16 (31.4%) patients had AVSD. Six patients had trisomy 21. In the whole group of patients, thirty-seven patients (72.5%) showed one or more of the signs of HF and these include: failure to thrive, respiratory distress, or hepatomegaly and all of them had one or more of the following medications: digitalis, diuretic and angiotensin converting enzyme inhibitor.

The distribution of baseline characteristics of patients after determination of preoperative BNP cut-off value by receiver operating curve (ROC) analysis for LCOS is presented in Table 1. The preoperative BNP cut-off value of 125.5 pg mL⁻¹ was found to have the highest sensitivity of 88.9% and specificity of 96.9% in predicting LCOS in patients with PH and the area under curve (AUC) is 91% (Fig. 1). This finding shows that 91% of patients with a preoperative plasma BNP level above 125.5 pg mL⁻¹ value is at very high risk of developing LCOS. Perioperative BNP levels in both groups are shown in Table 2. There were significant differences in the comparison of plasma BNP levels of patients in repeated measure time points with or without LCOS ($p=0.0001$).

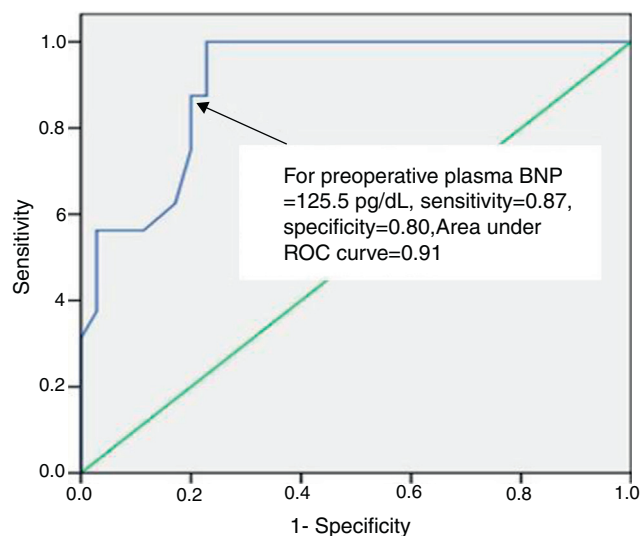


Figure 1 ROC (receiver operating curve) for preoperative plasma BNP values. A cut-off value of 125.5 pg mL⁻¹ has a sensitivity of 88.9%, a specificity of 96.9% and area under curve (AUC) of 91% for predicting low cardiac output state (LCOS).

Five infants with PH died within 30 days after operation ($n=5/51$, 9.8%). Two of the deaths occurred within two days after correction. The two infants, a 30-month-old, 11-kg girl with history of Down syndrome and AVSD and a 14-month-old, 9-kg boy with VSD and TAPVR were detected to show increased mean RV pressure and severe right to left shunting with a transcutaneous oxygen saturation of 45–84% during surgery. At the end of the correction, both infants required inotropic support of dopamine, dobutamine, adrenaline and noradrenaline in addition to vasodilator therapy of iloprost

Table 1 The distribution of baseline characteristics of patients after determination of preoperative BNP cut-off value by receiver operating curve (ROC) analysis for LCOS.

Patients	LCOS (–) <i>n</i> = 35	LCOS (+) <i>n</i> = 16	<i>p</i> ^a	preBNP ≤ 125 <i>n</i> = 30	preBNP > 125 <i>n</i> = 21	<i>p</i> ^a
Age (year) (median, range) ^a	2.00 (0.3–3.0)	0.95 (0.4–3.0)	0.072	2.00 (0.3–3.0)	0.80 (0.4–3.0)	0.009
Weight (kg) (median, range) ^a	10.0 (4.0–26.0)	5.25 (4.0–26.0)	0.017	10.3 (4.0–26.0)	5.5 (4.0–26.0)	0.024
Male/female, <i>n</i> (%) ^a	18 (35.3)/17 (33.3)	5 (9.8)/11 (21.6)	0.179	15 (50)/15 (50)	13 (61.9)/8 (38.1)	0.290

^a $p < 0.05$ statistically significant, median (range; minimum and maximum) values were provided for not normally distributed data. *n* (%), number (percentage); LCOS, low cardiac output syndrome; preBNP, preoperative plasma brain natriuretic peptide (pg mL⁻¹).

Table 2 The comparison of changes in plasma BNP levels over time before and after surgery.

	Preoperative BNP	Postoperative 12-h BNP	Postoperative 24-h BNP	Postoperative 48-h BNP	<i>p</i> ^a
All patients (<i>n</i> = 51)	138.6 ± 109.6	482.9 ± 501.8	850.2 ± 1186.9	914.6 ± 1199.3	0.0001
LCOS (–) (<i>n</i> = 35)	88.9 ± 60.9	264.2 ± 184.5	337.1 ± 232.5	289.3 ± 222.7	0.0001
LCOS (+) (<i>n</i> = 16)	247.1 ± 115.5	961.3 ± 637.8	1972.4 ± 1617.5	1331.9 ± 2222.5	0.0001
<i>p</i> ^a	0.0001	0.0001	0.0001	0.0001	

^a $p < 0.05$ statistically significant; analysis was performed using repeated measures analysis of variance (ANOVA) and Greenhouse–Geisser test; BNP, plasma brain natriuretic peptide (pg mL⁻¹).

Table 3 The parameters significant for outcome in the 30-day early postoperative period.

Patients	LCOS (-) (n=35)	LCOS (+) (n=16)	<i>p</i> ^a	preBNP ≤ 125 (n=30)	preBNP > 125 (n=21)	<i>p</i> ^a
CPB ^a time, (min) ^b	92.0 (30.0–120.0)	102.0 (65.0–217.0)	0.003	41.5 (10.0–93.0)	56.0 (15.0–217.0)	0.128
Aortic cross clamp time, (min) ^b	41.0 (10.0–77.0)	48.0 (20.0–126.0)	0.431	91.0 (40.0–120.0)	97.0 (30.0–126.0)	0.066
Duration of mechanical ventilation, (day) ^b	2.0 (1.0–5.0)	5.0 (2.0–32.0)	0.0001	2.0 (1.0–4.0)	4.0 (1.0–32.0)	0.0001
Intensive care unit stay, (day) ^b	4.0 (2.0–10.0)	9.0 (2.0–32.0)	0.008	4.0 (2.0–15.0)	8.0 (2.0–32.0)	0.026
Development of LCOS, n(%)	0 (0)	16 (100)	0.0001	2(6.7)	14 (66.7)	0.0001
30-day mortality, n(%)	0 (0)	5 (31.3)	0.0001	0(0)	5 (23.8)	0.0001

^a *p* < 0.05 statistically significant; data are presented as mean ± standard deviation or *n*: number, percentage.

^b Median (minimum and maximum) values were provided for not normally distributed data. BNP, plasma brain natriuretic peptide (pg mL⁻¹); CPB, cardiopulmonary bypass; LCOS, low cardiac output state.

and nitroglycerine; however, cardiac arrest was unpreventable within 36–48 h after surgery. In both cases, PH and tricuspid insufficiency were observed by the echocardiographic Doppler studies that were performed within 12 h after surgery. The third patient was a boy at age of 12 months and weight of 8 kg. He had a diagnosis of VSD and PAPVR and this patient survived five days in the ICU before cardiac arrest secondary to a PH crisis which was diagnosed with clinical findings. The two other patients had both ASD and VSD as well as severe PH before surgery. One of them was a 4-month-old, 5-kg boy and the other was a 3-month-old, 4-kg girl with a diagnosis of Down syndrome. The male patient survived for only three days in ICU before cardiac arrest secondary PH crisis whereas the female patient had symptoms of LCOS within 12 h after surgery requiring peritoneal dialysis and inotropic support. Despite adequate therapy, she survived 13 days in the ICU before cardiac arrest secondary to LCOS. Inhalation of nitric oxide was provided to only six patients with signs of severe PH in ICU.

Outcome measures

The LCOS (-) group had no deaths and better outcome in the 30-day postoperative period after surgery whereas in LCOS (+) group 5 of the 16 patients (31.25%) died in the early postoperative period. Four patients died within 7 days period whereas one patient survived for 12 days postoperatively. The data on postoperative outcomes as well as 30-day mortality are provided in Table 3.

The differences between systemic MAPs, mean RV pressures and CVPs during surgery and on postoperative 12 h are shown in Table 4. Systemic MAPs were not significantly different between LCOS (-) and LCOS (+) groups at the end of CPB. However, at this time point, the patients with LCOS showed higher RV pressures of 43.50 ± 5.96 mm Hg in comparison to the other patients showing a value of 38.89 ± 5.03 mm Hg (*p* = 0.005). The comparison of arterial oxygen saturation and CVP showed no significant differences between groups (98.04 ± 2.56% vs. 96.01 ± 9.24%, *p* = 0.191 and 10.26 ± 2.15 mm Hg vs. 10.19 ± 2.29 mm Hg, *p* = 0.385,

Table 4 Division of intraoperative and postoperative characteristics of patients depending on low cardiac output state.

Parameters	Group LCOS (-) (n=35)	Group LCOS (+) (n=16)	<i>p</i> ^a
<i>Intraoperative hemodynamical data (at the end of CPB)</i>			
Heart rate (/min)	159.42 ± 9.25	156.30 ± 8.82	0.213
Mean systemic arterial pressure (mm Hg)	81.91 ± 14.08	77.44 ± 11.44	0.359
Mean right ventricular pressure (mm Hg)	39.89 ± 5.63	43.50 ± 5.96	0.005
Arterial oxygen saturation (%)	98.04 ± 2.56	96.01 ± 9.24	0.191
Central venous pressure (mm Hg)	10.26 ± 2.15	10.19 ± 2.29	0.385
<i>Postoperative 12 h hemodynamic data</i>			
Heart rate (min)	165.42 ± 7.81	166.42 ± 8.43	0.581
Mean systemic arterial pressure (mm Hg)	79.94 ± 13.16	81.44 ± 10.98	0.329
Arterial oxygen saturation (%)	95.75 ± 3.80	86.06 ± 7.57	0.0001
Central venous pressure (mm Hg)	10.14 ± 2.43	16.19 ± 3.26	0.0001

^a *p* < 0.05 statistically significant; data are presented as mean ± standard deviation or *n*: number, percentage; CPB, Cardiopulmonary bypass; LCOS, Low cardiac output state.

respectively). On postoperative 12 h, while there was no difference in comparison of systemic MAPs between LCOS (–) and LCOS (+) groups, patients with LCOS showed higher CVps and lower arterial oxygen saturations in comparison to the patients without LCOS ($95.75 \pm 3.80\%$ vs. $86.06 \pm 7.57\%$, $p=0.0001$ and 10.14 ± 2.43 mm Hg vs. 16.19 ± 3.26 mm Hg $p=0.0001$, respectively) (Table 4).

A good correlation was found between preoperative plasma BNP level and duration of mechanical ventilation ($r=0.67$, $p=0.0001$); however, weak correlations were present between preoperative plasma BNP level and aortic cross clamp time ($\rho=0.431$, $p=0.002$), intensive care unit stay ($r=0.42$, $p=0.002$) and mortality ($r=0.47$, $p=0.001$).

Discussion

The major findings of this study include: (1) In comparison to preoperative plasma BNP levels, postoperative values show significant increase in repeated measurement time points of 12, 24 and 48 h after surgery in patients with or without development of LCOS in the postoperative period. (2) In patients with PH undergoing congenital heart surgery, 91% of patients with preoperative plasma BNP levels above 125.5 pg mL^{-1} are at high risk of developing LCOS which is an important risk factor for determination of early 30-day postoperative outcome. (3) The preoperative plasma BNP level accurately predicts postoperative LCOS in children with PH and these findings have not been reported previously in studies investigating pulmonary hypertension in children.^{16,24–27} (4) Secondary outcome measures in the early postoperative period such as duration of mechanical ventilation and intensive care unit stay were prolonged in patients with LCOS in comparison to patients without LCOS ($p=0.0001$, $p=0.008$, respectively).

In the study by Hoffmann et al., 238 patients were divided into three groups as: placebo, low-dose milrinone, and high-dose milrinone groups and LCOS rates were 25.9%, 17.5%, and 11.7% respectively in the first 36 h after congenital heart surgery. LCOS patients had a significantly longer duration of mechanical ventilation (3.1 vs. 1.4 days, $p=0.001$) and hospital stay (11.3 vs. 8.9 days, $p=0.016$) in comparison to patients without LCOS.¹³

In children with congenital heart disease who present with significant PH and predominant left-to-right shunt, a ratio of pulmonary to systemic resistance $\leq 2/3$ is used as a threshold associated with better surgical outcomes.¹⁸ The causes of signs of development of RV failure at the operation may be related to: (1) different initial volume status, (2) varying baseline end-diastolic volumes, or (3) varying degrees of ischemic burden and injury and for treatment of this pathophysiological finding an initial fluid challenge of normal saline followed by diuresis is required.^{17,24} In the study by Bando et al. children with AV canal, truncus arteriosus, TAPVR, transposition of the great arteries, hypoplastic left heart syndrome, and VSD were determined to be at high risk for the development of postoperative pulmonary hypertensive events.²⁵ In this study 880 patients at high risk of developing postoperative pulmonary events were evaluated and the number of pulmonary hypertensive events were recorded in 138 (16%) of the patients and the mortality in this patient population was 75 (8.5%). The data show

that the mortality rates in children with a diagnosis of PH undergoing congenital heart repair surgery is significantly higher than patients without PH. Furthermore, the number of early deaths associated with PH event was 31 (22.5%) in 138 patients. Regarding patients with severe PH crisis, the study by Bando et al. found a mortality of 35.5% ($n=11/31$) in 1990 through 1994 whereas in recent studies it is also noted that one complication in addition to simple correction of congenital heart disease is associated with a mortality rate up to 9.0%.²⁶ Lindberg et al. reported a mortality rate of 7.4% ($n=2/27$).²⁴ The mortality rate in our study group is 9.8% and this primary outcome result is compatible with previous reports.^{24–27}

Our patients presented later to the clinic at sicker health status in comparison to the reported case series in the literature. In our study group the median age of 12 months was higher than the median age (4.2–8.6 months) of the reported studies showing that early diagnoses and treatment was not always possible in our group of patients.^{24,27} In our study, the patients with LCOS had lower mean body weights and the incidence of preterm birth history in this group was 9 out of 16 patients (56.3%) whereas patients without LCOS had higher mean body weight with an incidence of preterm birth history was 4 out of 35 (11.4%) (Table 2). Our findings support the data provided by the literature that failure to thrive is a significant finding in congenital heart diseases with PH.³ Remarkably, outcome of preterm infants with CHD was significantly worse than that for full-term infants.²⁷

An increased PVR and PAP and RV failure may have played an important role in the cause of deaths of our patients. In prevention of PH crisis in the early postoperative period inhaled nitric oxide, intravenous or inhaled epoprostenol, iloprost, and inotropic support are the most useful agents and newer emerging methods include: extracorporeal membrane oxygenation and continuous monitoring of mixed venous saturation (SvO₂) through pulmonary artery catheter.^{16,18,24} We were not able to perform pulmonary artery catheterization in all of our patients and inclusion of the data of these measurements was not possible in our study although our observations support that pulmonary artery catheterization is beneficial in detecting pulmonary hypertensive events in the early period. It has been reported that PAs and CVPs gradually increase and SvO₂ decreases before severe pulmonary hypertensive crises occur.^{24,25,28} Hypoxemia, hypercapnia, metabolic acidosis, restlessness, and tracheal suctioning may increase pulmonary vasoreactivity and thus trigger postoperative pulmonary hypertensive events. For prevention of these events, moderate hyperventilation with a high inspired oxygen fraction, sedation, and paralysis have been used in our study. Inhaled nitric oxide was available in only six patients who had severe PH crisis in the ICU in our study group.

A decision for a cutoff value for BNP levels was unable to be established even for noncomplex lesions. In a study by Koch and his colleagues, 65 patients were evaluated as a single group of patients undergoing congenital heart surgery and afterwards a division into two groups depending on their complexity of their cardiac lesion was made. The difference between the preoperative BNP and postoperative BNP on the first day was significantly greater in patients with complex heart defects than in patients with more simple defects (median 213 pg mL^{-1} vs. 453 pg mL^{-1} , $p=0.03$). In their

study, postoperative BNP levels were significantly higher in patients with univentricular hearts (median 1300 pg mL⁻¹).¹⁰ Oosterhof and his coworkers showed that in univentricular heart morphologies with systemic right ventricular dysfunctions, preoperative BNP levels greater than 45 pg mL⁻¹ detect right ventricular insufficiencies with a sensitivity of 78% and a specificity of 84%.²⁹ Mainly, these two studies provide data for need of further investigation of preoperative plasma BNP levels in children with pulmonary hypertension undergoing congenital heart surgery and our study provides valuable data that a preoperative plasma BNP level greater than 125.5 pg mL⁻¹ detects LCOS which is an important prognostic risk factor in the early 30-day postoperative period with a sensitivity of 88.9 and a specificity of 96.9%. LCOS has been used as a tool to determine outcome after congenital heart surgeries.^{11,29} An important finding is that the patients with LCOS showed significantly higher preoperative BNP values in patients undergoing congenital heart surgery with CPB. Our observation is similar to a recent study by Hsu and his colleagues that: (1) LCOS is associated with poor postoperative outcome, (2) LCOS actually develops before 48 h after operation, (3) Postoperative BNP levels do not predict LCOS; however, these values are associated with LCOS.¹¹ A preoperative BNP value or postoperative 2, 4, 12 or 24 h BNP values were reported as independent biomarkers of postoperative outcome related risk factors such as ICU stay or prolonged mechanical ventilation.^{24,27-30}

A correlation between plasma BNP levels and duration of mechanical ventilation was shown in previous studies by Hsu and Shih et al.^{12,31} The study by Hsu and his coworkers was mainly on neonates undergoing Norwood or two-ventricle corrective repair and it supports the valuable role of BNP in predicting poor postoperative outcome after congenital surgery with CPB especially in the 24 h period after operation.³¹ In a recent study Shih and his colleagues showed that 12-h B-type natriuretic peptide levels were associated with the duration of mechanical ventilation and the presence of a LCOS after surgical intervention. In their study, the cut-off value of 12 h B-type natriuretic peptide level greater than 540 pg mL⁻¹ predicted mechanical ventilation beyond 48 h with a sensitivity of 88.9% and a specificity of 82.5%.¹² In our patient population, a good correlation was found between preoperative plasma BNP level and duration of mechanical ventilation ($r=0.67$, $p=0.0001$) which is similar to the findings of Shih et al. We think the study needs to be performed on larger group of patients to demonstrate the importance of plasma BNP values in patients with a diagnosis of PH undergoing congenital heart surgeries.

There are several limitations of the present study. One important limitation is the selection of patients into the study group. We used general echocardiographic diagnostic criteria for measurement of PAs instead of cardiac catheterization. However, we think the whole group of patients represents a single group as we evaluated systolic PAs with systemic MAPs. Our patients presented at an older age after a period of inadequate medical treatment causing deterioration of clinical status. In our study group we had eleven patients (11/51, 21.6%) with preterm birth history and it has been reported that preterm babies show poorer postoperative outcomes.^{3,27} We did not have a transthoracic echocardiography in our clinic and pulmonary artery catheterization was not performed in these sicker children.

During completion of this study inhaled nitric oxide was not available to all patients and other newer agents such as intravenous or inhaled epoprostenol, iloprost were not used to prevent PH crisis during or after surgery.

In conclusion, the preoperative plasma BNP level accurately predicts postoperative LCOS which is an important prognostic risk factor for determination of early 30-day postoperative outcome and 91% of patients with preoperative plasma BNP levels above 125.5 pg mL⁻¹ are at high risk of developing LCOS in children undergoing congenital heart surgery with CPB.

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Authorship

Ayşe Baysal contributed toward the collection of data, study design, statistics and preparation of manuscript text. Ahmet Şaşmazel contributed towards the collection of data, study design and statistics. Ayşe Yıldırım contributed towards the collection of echocardiographic data. Buket Ozyaprak contributed towards the collection of data during surgery; Narin Gundogus contributed towards the collection of data in intensive care unit and Tuncer Kocak contributed towards the study design.

Conflicts of interest

The authors declare no conflicts of interest.

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