

Original article

Cardiac Biomarkers of Low Cardiac Output Syndrome in the Postoperative Period After Congenital Heart Disease Surgery in Children



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ABSTRACT

Introduction and objectives: To assess the predictive value of atrial natriuretic peptide, β -type natriuretic peptide, copeptin, mid-regional pro-adrenomedullin (MR-proADM) and cardiac troponin I (cTn-I) as indicators of low cardiac output syndrome in children with congenital heart disease undergoing cardiopulmonary bypass (CPB).

Methods: After corrective surgery for congenital heart disease under CPB, 117 children (aged 10 days to 180 months) were enrolled in a prospective observational pilot study during a 2-year period. The patients were classified according to whether they developed low cardiac output syndrome. Biomarker levels were measured at 2, 12, 24, and 48 hours post-CPB. The clinical data and outcome variables were analyzed by a multiple logistic regression model.

Results: Thirty-three (29%) patients developed low cardiac output syndrome (group 1) and the remaining 84 (71%) patients were included in group 2. cTn-I levels > 14 ng/mL at 2 hours after CPB (OR, 4.05; 95%CI, 1.29-12.64; $P = .016$) and MR-proADM levels > 1.5 nmol/L at 24 hours following CPB (OR, 15.54; 95%CI, 4.41-54.71; $P < .001$) were independent predictors of low cardiac output syndrome.

Conclusions: Our results suggest that cTn-I at 2 hours post-CPB is, by itself, an evident independent early predictor of low cardiac output syndrome. This predictive capacity is, moreover, reinforced when cTn-I is combined with MR-proADM levels at 24 hours following CPB. These 2 cardiac biomarkers would aid in therapeutic decision-making in clinical practice and would also enable clinicians to modify the type of support to be used in the pediatric intensive care unit.

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Biomarcadores cardiacos en el síndrome de bajo gasto cardiaco en el posoperatorio de cirugía de cardiopatías congénitas en niños

RESUMEN

Introducción y objetivos: Determinar el valor del péptido natriurético auricular, el propéptido natriurético cerebral, la copeptina, la región medial de la proadrenomedulina (MR-proADM) y la troponina I cardiaca (cTn-I) como indicadores de síndrome de bajo gasto cardiaco posoperatorio en niños con cardiopatía congénita intervenidos en circulación extracorpórea (CEC).

Métodos: Estudio piloto prospectivo observacional, realizado durante 2 años, que incluyó a 117 niños (edad, 10 días-180 meses) intervenidos de cardiopatías congénitas en CEC, clasificados según presentaran o no síndrome de bajo gasto cardiaco. Los biomarcadores se determinaron a las 2, 12, 24 y 48 h del posoperatorio. Se utilizó un modelo de regresión logística multivariable para evaluar los factores asociados al bajo gasto cardiaco.

Resultados: Tenían síndrome de bajo gasto cardiaco 33 pacientes (29%). Tras el ajuste por las demás variables, los valores plasmáticos de cTn-I > 14 ng/ml a las 2 h de CEC (*odds ratio* = 4,05; intervalo de confianza del 95%, 1,29-12,64; $p = 0,016$) y de MR-proADM $> 1,5$ nmol/l a las 24 h (*odds ratio* = 15,54; intervalo de confianza del 95%, 4,41-54,71; $p < 0,001$) fueron los únicos predictores independientes de bajo gasto cardiaco.

Palabras clave:

Biomarcadores cardiacos

Niños

Cardiopatía congénita

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Conclusiones: Nuestros resultados indican que las concentraciones de cTn-I elevadas 2 h después de la CEC son, por sí solas, un predictor independiente de síndrome de bajo gasto cardiaco. Este valor predictivo se incrementa cuando se asocia con cifras de MR-proADM elevadas 24 h tras CEC. Estos 2 biomarcadores cardiacos podrían ayudar en la toma de decisiones terapéuticas en cuidados intensivos pediátricos, incluidas modificaciones en el tipo de soporte circulatorio.

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Abbreviations

ADM: adrenomedullin
 BNP: β -type natriuretic peptide
 CPB: cardiopulmonary bypass
 cTn-I: cardiac troponin I
 LCOS: low cardiac output syndrome
 MR-proADM: mid-regional-regional pro-adrenomedullin

INTRODUCTION

Low cardiac output syndrome (LCOS) is a well-recognized entity occurring in 25% to 60% of pediatric patients undergoing open heart surgery with an accepted collection of hemodynamic and physiologic disturbances.¹ The onset of LCOS follows a predictable course in the hours following cardiopulmonary bypass (CPB), as myocardial performance declines in the face of an elevated demand for cardiac output. When demand outstrips supply, shock ensues and early recognition and intervention can decrease morbidity and mortality.²

A wide variety of cardiac biomarkers have been reported in adults with heart failure. However, the behavior of cardiac biomarkers—mid-regional-regional pro-atrial natriuretic peptide, β -type natriuretic peptide (BNP), copeptin, mid-regional-regional pro-adrenomedullin (MR-proADM) and cardiac troponin I (cTn-I)—in the postoperative period following cardiac surgery under CPB in children with congenital heart disease has seldom been studied. There have been studies involving children with acute heart failure,³ although most have focused on children with chronic heart failure.⁴ These reports have noted positive correlations between plasma ANP and BNP levels and the degree of heart failure.⁵ Currently, BNP and N-terminal-pro-brain natriuretic peptide appear to be prognostic markers of heart failure.

Copeptin, which is more stable than arginine vasopressin peptide, is a prognostic marker of acute myocardial infarction and of acute and chronic cardiac failure in adult patients.^{6,7} cTn-I and troponin T are highly sensitive and specific biochemical markers of myocardial injury and their levels are associated with hemodynamic status after cardiac surgery in neonates and children.⁸ Some authors have reported correlations between cTn-I levels and LCOS. They may also predict early in-hospital outcomes and can be useful for identifying young children at increased risk for LCOS and death after heart surgery under CPB.⁹

Adrenomedullin (ADM) is reportedly associated with the pathophysiology of LCOS. ADM is a prognostic indicator of chronic heart failure in adults, as well as of acute destabilized and ischaemic left ventricular dysfunction.^{10,11} In addition, high levels of ADM predict long-term adverse clinical events after myocardial injury. However, ADM has barely been studied in the pediatric population.

The objective of this study was to determine whether any of the above-mentioned cardiac biomarkers correlate with the hemodynamic status of children after corrective surgery for congenital heart disease under CPB. If such a relationship were established,

the cardiac biomarkers in question could be used as a prognostic maker of LCOS. These cardiac biomarkers would assist in therapeutic decision-making in clinical practice in the pediatric intensive care unit immediately after cardiac surgery under CPB.

METHODS

Study Design: Population

This prospective observational pilot study was conducted at a single referral hospital during a 2-year period. The study enrolled 117 consecutive patients (aged 10 days to 180 months) admitted to the pediatric intensive care unit after corrective surgery for congenital heart disease under CPB. The exclusion criteria included: *a*) infection, *b*) renal failure, *c*) polymalformative syndromes, *d*) congenital metabolic defects, and *e*) chronic diseases. Patients who died during surgery or within the first 6 hours after surgery were also excluded from the study.

Following pediatric intensive care unit admission, the management and monitoring of the patients were performed in accordance with a specific protocol for each type of congenital heart disease. Postoperative hemodynamic monitoring included: *a*) insertion of an arterial line: a PiCCO catheter was placed into 1 femoral artery. For patients weighing 5 to 15 kg, a 3-F catheter (PV 2013 L07 Pulsioath) was used and a 4-F catheter (PV 2014 L08 Pulsioath, Pulsion Medical Systems AG, Munich, Germany) was inserted in patients who weighed more than this body-weight threshold. Because of the problems that catheterization may cause, we dispensed with the placement of a PiCCO catheter in the patients weighing < 5 kg; *b*) insertion of a central venous catheter (tip either in or close to the right atrium), which was checked by a chest radiograph, and *c*) occasionally, another catheter was placed into the left atrium of the patients at risk of postoperative left ventricular dysfunction. All patients received mechanical ventilation and were sedated with midazolam and fentanyl.

After corrective surgery, the patients were divided into 2 groups according to the presence (group 1) or absence (group 2) of LCOS. LCOS was diagnosed when the following 2 major criteria were met: *a*) left ventricular ejection fraction < 40% (Teichholz) via echocardiography, and *b*) cardiac index < 2.5 L/min/m² via an arterial thermodilution catheter (PiCCO) in all the children weighing \geq 5 kg. LCOS was considered in children weighing < 5 kg when they exhibited ventricular ejection fraction < 40% (left ventricle, with the exception of hypoplastic left heart syndrome, in which the right ventricle functions as the systemic ventricle), and they met at least 3 of the following minor criteria: *a*) systolic blood pressure < p5 for age and sex, *b*) urine output < 1 mL/kg/h without diuretics, *c*) lactate \geq 3.5 mmol/L or HCO₃ < 18 mEq/L, *d*) inotropic score \geq 20,¹² and *e*) oxygen extraction ratio > 35%.

Blood Sampling

Baseline blood samples were collected from a central venous catheter prior to corrective surgery and at 2, 12, 24, and 48 hours post-CPB. Assessment of the patient's general biochemical

parameters and quantification of BNP and cTn-I levels were carried out in our department of clinical analysis. Blood samples were collected and centrifuged at 3500 g for 10 minutes. Serum was separated into aliquots and frozen at -82°C until the day of analysis.

BNP and cTn-I were measured using an automated electrochemiluminescence immunoassay (Architect system, Abbott Diagnostics Division, Illinois, United States). The Architect BNP assay was designed with a ≤ 10 pg/mL detection limit. The detection limit of the ARCHITECT STAT troponin I assay was ≤ 0.01 ng/mL. N-terminal pro-atrial natriuretic peptide, MR-proADM, and copeptin were measured using a simultaneous multianalyte detection immunoassay BRAHMS KRYPTOR compact (Hennigsdorf, Germany), as well as assay kits and a Multiplex system using Luminex xMAP technology. The analytical detection limits were 0.05 nmol/L for MR-proADM, 4.8 pmol/L for copeptin, and 2.1 pmol/L for N-terminal pro-atrial natriuretic peptide.

Statistical Analysis

Data are expressed either as mean \pm standard deviation or as median (interquartile ranges). Comparisons between group 1 and group 2 were undertaken using the Student *t* test for continuous variables when the distribution was normal (Kolmogorov-Smirnov test) and the Mann-Whitney U test when the distribution was not normal. The relationships between the categorical variables were assessed using either the chi-square test or the Fisher exact test. Comparisons among the monitored time points were tested via a Mixed-designs ANOVA test and a Sidak correction as a post-hoc test. The data were adjusted for the age and body weight of the patients, using age and body weight as covariates. The cTn-I analysis was adjusted for aortic cross clamping and CPB time.

The correlations between the peak postoperative values of each of the biomarkers listed above were assessed via the Spearman correlation test. Univariate logistic regression was undertaken at 48 hours following surgery to identify the independent predictors of LCOS. The relationships between the variables were assessed via an odds ratio with 95% confidence interval. In the multivariate analysis, the independent predictors of LCOS were considered risk factors ($P < .05$), based on the results of the univariate analysis. The Hosmer-Lemeshow test and the receiver operating characteristic curves were applied to assess the goodness-of-fit of the model. The analysis of the receiver operating characteristic curves and the area under the curve was generated with 95% confidence intervals to determine the cutoff points for cTn-I and MR-proADM, which might have provided a more accurate identification of the LCOS patients. Sensitivity, specificity, positive and negative predictive values for MR-proADM, cTn-I, and the combination of both biomarkers were also calculated using the marker-specific cutoffs. All the tests were 2-tailed and the results were considered statistically significant when $P < .05$. The data were analyzed using SPSS 18.0.0 2010 (SPSS Inc., Chicago, Illinois, United States).

Patient Medical Reports

Data were obtained from the case history of each child. Informed written consent was obtained from the patients' parents or legal guardians. Our study was approved by the Hospital Biomedical Ethics Committee and conformed to the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS

One hundred seventeen congenital heart disease patients aged 10 days to 180 months (mean 39.3 ± 52.4 months) were

Table 1

Patient Description by Type of Congenital Heart Disease

	No. patients (%)
Tetralogy of Fallot	18 (15.4)
Atrioventricular canal defect	15 (12.8)
CoA/interrupted arch	13 (11.1)
Pulmonary atresia	12 (10.3)
TGA	14 (12)
Type of CHD	
VSD/ASD	22 (18.8)
CAT	8 (6.8)
HLHS	6 (5.1)
Mitral/aortic regurgitation	3 (2.6)
TAPVC	3 (2.6)
Others	3 (2.6)

ASD, atrial septal defect; CAT, common arterial trunk; CHD, congenital heart disease; CoA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; VSD, ventricular septal defect.

enrolled in the present study: 19 infants (16%) were younger than 30 days.

The patient's type of congenital heart disease is described in Table 1. Thirty-three (29%) patients developed LCOS (group 1) after corrective surgery and the remaining 84 (71%) patients were included in Group 2. Six patients (2 neonates) developed cardiogenic shock and required extracorporeal membrane oxygenation within the first 48 hours following CPB. One patient received extracorporeal membrane oxygenation in the operating theatre, 2 within the first 12 hours and 3 patients 24 to 48 hours postoperatively.

The characteristics of all the patients and the neonates < 30 days, as well as the surgery data and the classification of the patients into groups according to the presence or absence of LCOS after CPB are shown in Table 2. The children in group 1 were younger and weighed less than the children in group 2. The duration of aortic cross-clamping and CPB was prolonged in group 1 ($P < .001$). The sex distribution of the 2 groups was homogeneous.

In all patients, comparisons of baseline levels of the cardiac biomarkers (median and interquartile range) with their levels at 2 hours post-CPB showed statistically significant increases in cTn-I levels: 12.3 (4.6–36.1) vs 0.02 (0–0.04) ng/mL; $P < .001$; MR-proADM, 2.24 (1.34–3.26) vs 0.51 (0.35–0.99) nmol/L; $P < .001$; and copeptin levels, 132.8 (46.64–309.5) vs 6.9 (4.7–28.5) pmol/L; $P < .001$. BNP peaked at 12 hours of CPB (441.4 [241.9–1023.5] pg/mL vs 50.5 [25.7–186.15] pg/mL, $P = .020$). N-terminal pro-atrial natriuretic peptide concentrations remained unchanged compared with their baseline values.

cTn-I was the earliest biomarker of LCOS that showed significant differences between group 1 and group 2 at 2 hours after heart corrective surgery. Copeptin and BNP values had a similar course in the 2 groups. However, after attaining a peak value at 2 hours postoperatively, cTn-I and MR-proADM levels decreased in group 2 but increased in group 1 (Figure 1). Postoperative biomarkers in neonates showed a similar profile to those in the rest of the patients (Figure 2)

BNP, N-terminal pro-atrial natriuretic peptide, MR-proADM, and copeptin remained unchanged at the different monitoring time points compared with their baseline levels in the 6 patients requiring extracorporeal membrane oxygenation. However, cTn-I levels peaked at 2 hours after surgery: 19.33 (3.7–32.5) vs 0.02 (0.01–0.03) ng/mL; $P < .001$, but remained without significant changes in the next postoperative time points.

Table 2
Patient Characteristics in the Study Groups

	All patients			Patients < 30 d		
	Group 1 n=33	Group 2 n=84	P	Group 1 n=8	Group 2 n=11	P
Sex, male	36 (60%)	27 (47.4%)	.171	4 (50%)	9 (81.8%)	.319
Genetic Abnormalities ACC, min ^a	10 (16.7%)	8 (14%)	.693	1 (12.5%)	0	.421
Age ^a	8.5 (1.25-9.7) ^b	38 (10.5-92.5)	< .001	8.5 ± 4 ^c	9.5 ± 4	.609
Weight, kg ^a	6.5 (3.7-10)	12.7 (6.7-21.6)	< .001	3.37 ± 0.45	3.36 ± 0.52	.951
ACC, min ^a	82 (35-105)	35 (15-65)	< .001	81 ± 30	89 ± 38	.637
CPB time, min ^a	130 (105-170)	90 (62-120)	< .001	172 (111-180)	175 (130-190)	.442
Aristotle score ^a	9 (8-10)	6 (6-8)	< .001	10 (7-11)	10 (10-11)	.598
Duration of MV, h ^a	109 (24-240)	10 (5.5-24)	< .001	156 (109-774)	96 (48-120)	.012
Stay at PICU, d ^a	15 (9-23)	6 (5-8.5)	< .001	22.5 (12-39)	11 (9-16)	.062
Mortality	4 (12.1%)	2 (2.4%)	.05	2 (25%)	1 (9.1)	.546

ACC, aortic cross-clamping; CPB, cardiopulmonary bypass; MV, mechanical ventilation; PICU, pediatric intensive care unit. Group 1: Patients with low cardiac output syndrome; group 2: Patients without low cardiac output syndrome.

P values in bold are statistically significant.

^a Values are given as medians (interquartile ranges).

^b Age in months.

^c Age in days.

Correlations

The peak cTn-I values at 2 hours correlated with CPB time ($r = 0.408$; $P < .001$). However, the peak MR-proADM values inversely correlated with patient age ($r = -0.560$; $P < .001$) and directly correlated with CPB time ($r = 0.408$; $P < .001$) and the pediatric intensive care unit discharge ($r = 0.490$; $P < .001$).

There was a positive association between MR-proADM plasma levels (48 hours after surgery) with lactate levels in group 1 ($r = 0.572$, $P < .001$) but not in group 2 ($r = 0.247$, $P < .12$). We found no correlation between the oxygen extraction ratio and MR-proADM levels in the 2 groups. Likewise, no correlation was found between cTn-I and lactate levels or the oxygen extraction ratio.

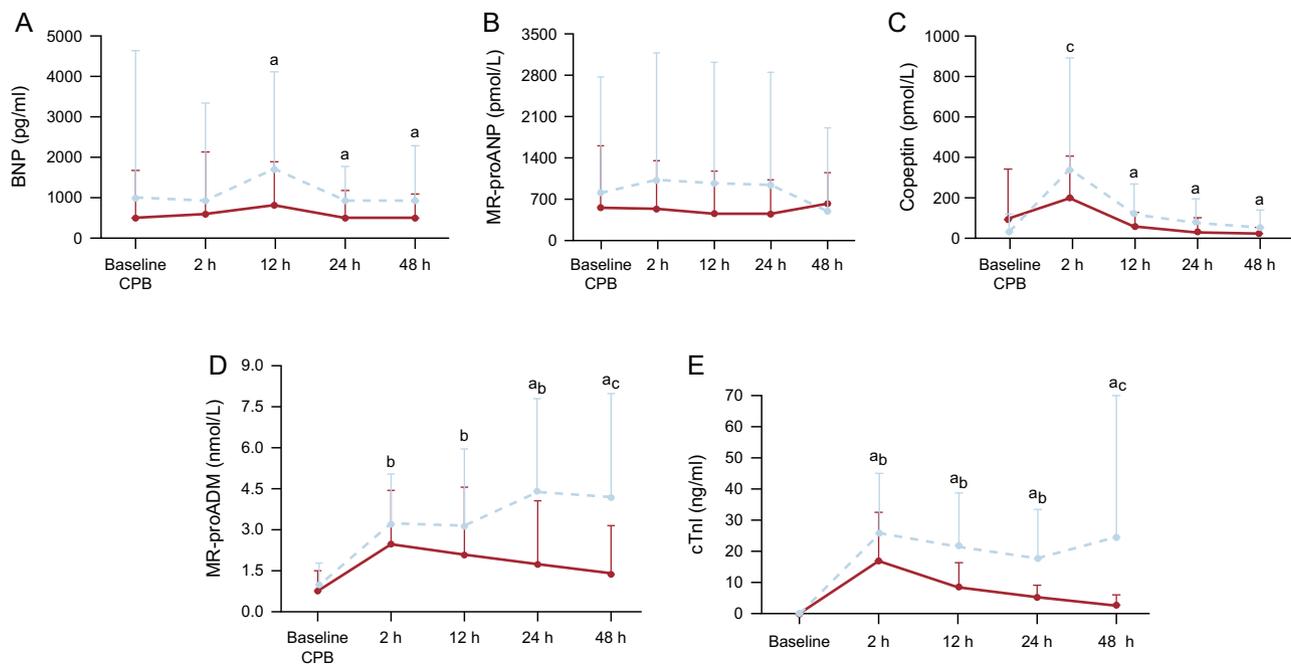


Figure 1. Changes in biomarker levels over time for all the study patients stratified according to the presence or absence of postoperative heart failure. A: BNP. B: MR-proANP. C: copeptin. D: MR-proADM. E: cTn-I levels. BNP, β -type natriuretic peptide; CPB, cardiopulmonary bypass; cTn-I, cardiac troponin-I; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide.

--- Group 1

— Group 2

• Represents the mean, and error bars indicate the standard deviation.

^a Significant differences between group 1 and group 2.

^b Significant differences vs baseline in both groups ($P < .05$).

^c Significant differences vs baseline in group 1 ($P < .05$).

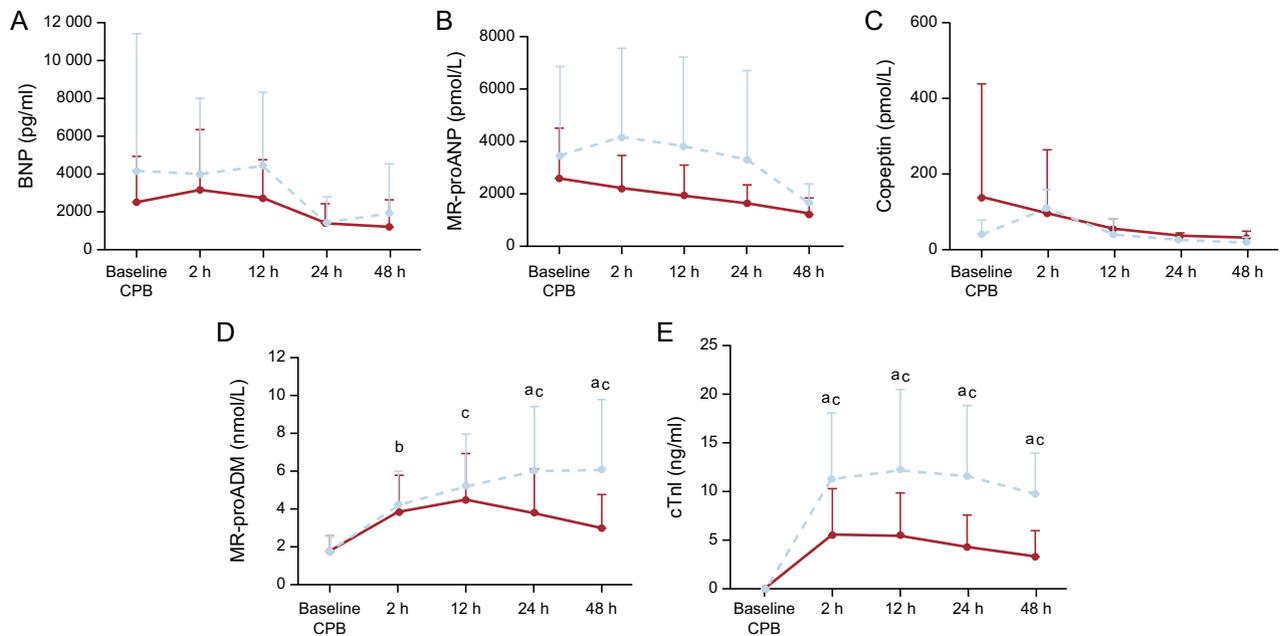


Figure 2. Changes in biomarker levels over time for patients younger than 30 days stratified according to the presence or absence of postoperative heart failure. A: BNP. B: MR-proANP. C: copeptin. D: MR-proADM. E: cTn-I levels. BNP, β -type natriuretic peptide; CPB, cardiopulmonary bypass; cTn-I, cardiac troponin-I; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide.

--- Group 1
 — Group 2

• Represents the mean, and error bars indicate the standard deviation.

^aSignificant differences between group 1 and group 2.

^bSignificant differences vs baseline in both groups ($P < .05$).

^cSignificant differences vs baseline in group 1 ($P < .05$).

Logistic Regression Analysis

Table 3 describes the most significant parameters obtained via the univariate and multivariate logistic regression analyses in relation to the prediction of LCOS after CPB. cTn-I levels (> 14 ng/mL) at 2 hours following heart corrective surgery under CPB and MR-proADM levels (> 1.5 nmol/L) at 24 hours postoperatively were independent predictors of LCOS. The logistic regression results and the areas under the curve of cTn-I and MR-proADM are depicted in Figure 3. Comparisons among the areas under the curve of these biomarkers showed no statistically significant differences. Sensitivity, specificity, and positive and negative predictive values were calculated at cutoff values of 14 ng/mL for cTn-I and 1.5 nmol/L for MR-proADM (Table 4). The combination of MR-proADM and cTn-I had high specificity and provided more accurate detection of LCOS than the use of MR-proADM alone.

DISCUSSION

Monitoring cardiac biochemical markers after corrective surgery is highly effective in adults with heart failure.⁴ However, there are few studies involving children after corrective surgery under CPB to establish their effectiveness.^{1,3} The present prospective observational pilot study was conducted with a large sample size and with minimal variability for patient management. We observed that the prediction of LCOS was strengthened by a cutoff point of > 14 ng/mL for cTn-I at 2 hours post-CPB, regardless of the age of the patients, the physiological heart defect, and the duration of CPB. cTn-I is a specific and sensitive marker of myocardial injury after cardiac surgery and it may predict early in-hospital outcomes. The prediction of LCOS is, by itself, evident but it was reinforced when cTn-I values at 2 hours following CPB were combined with a cutoff point of > 1.5 nmol/L for MR-proADM at 24 hours after CPB.

Table 3

Univariate and Multivariate Logistic Regression for the Prediction of Low Cardiac Output Syndrome After Cardiac Surgery Under Cardiopulmonary Bypass

Prognostic factor of LCOS after CPB	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
Age, months	0.978	0.963–0.994	.006			
CPB time, min	1.019	1.009–1.029	$< .001$			
cTn-I 2 h PO > 14 ng/mL	7.2	2.87–18.03	$< .001$	4.045	1.29–12.64	.016
BNP 12 h PO, pg/mL	1	1–1.001	.023			
Copeptin 12 h PO, pmol/L	1.007	1.002–1.011	.004			
MR-proADM 24 h PO > 1.5 nmol/L	13.75	4.4–42.99	$< .001$	15.54	4.41–54.71	$< .001$

95%CI, 95% confidence interval; BNP, β -type brain natriuretic peptide; CPB, cardiopulmonary bypass; cTn-I, cardiac troponin I; LCOS, low cardiac output syndrome; MR-proADM, mid-regional pro-adrenomedullin; OR, odds ratio; PO, postoperative. Hosmer-Lemeshow test = 2.93; $P = .711$.

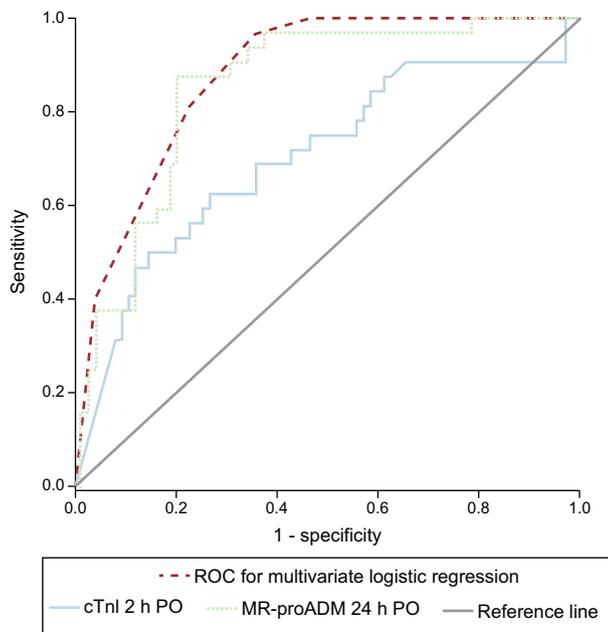


Figure 3. Receiver operating characteristic curves for the diagnosis of low cardiac output syndrome at 48 hours PO. The area under the curve of MR-proADM at 24 hours PO was 0.848 (95%CI, 0.771-0.924); area under the curve of cTn-I at 2 hours PO was 0.702 (95%CI, 0.581-0.812); area under the curve of cTn-I > 14 ng/mL at 2 hours PO + MR-proADM > 1.5 nmol/L at 24 hours PO was 0.885 (95%CI, 0.823-0.947). cTn-I, cardiac troponin I; MR-proADM, mid-regional pro-adrenomedullin; PO, postoperative; ROC, receiver operating characteristic.

Levels of BNP, N-terminal pro-atrial natriuretic peptide and copeptin were not found to be early predictors of LCOS in the early hemodynamic monitoring of the patients.

LCOS is defined as the inability of the heart to maintain adequate minute volume to provide oxygen and nutrients to the tissue. This concept involves the influence of cardiac output and peripheral vessels on resistance to blood flow and tissue perfusion. Usually, decreased ventricular function reaches a peak between 8 and 12 hours and recovers gradually at 24 to 48 hours following CPB.¹ In addition to routine monitoring methods, ventricular function may also be assessed by analyzing cardiac biomarkers.

There are few studies of the reference intervals for biomarker assays in the pediatric population. Moreover, there are no data on the reference levels of copeptin and MR-proADM in children. In our study, all the data were adjusted for the patients' age and bodyweight to prevent these variables from influencing our results. Although no studies have reported sex-related alterations in cardiac biomarkers, the sex distribution in our study was homogenous.

Elevation of plasma levels of the studied biomarkers, regardless of whether the patients had LCOS, suggested that important alterations occur in children exposed to CPB during surgical repair.

Some studies have observed an increase in N-terminal pro-BNP levels and few changes in N-terminal pro-atrial natriuretic peptide.^{9,13} The plasma levels of these 2 cardiac biomarkers appear to vary depending on the patient's hemodynamic status and on the characteristics of congenital heart disease.¹⁴

BNP is eliminated through the hemofiltration process, akin to ultrafiltration mechanisms, in the last stage of CPB.¹⁵ Consequently, the biological activity of the natriuretic hormone system may decrease and the infusion of natriuretic hormones might be clinically beneficial.^{16,17} Several studies have noted an association between an increase in N-terminal pro-BNP and a higher incidence of complications in the postoperative period.¹⁶ Carmona et al.⁹ have reported a correlation between LCOS and N-terminal pro-BNP levels preoperatively. In contrast, in our study, no useful tool was provided for identifying children at increased risk of LCOS following corrective surgery. There are no studies on postoperative levels of copeptin in children undergoing cardiac surgery. In the present study, serial measurement of copeptin proved to be ineffective.

cTn-I and troponin T indicate the presence of injury-associated necrosis of myocardial cells. The levels of cTnI increase rapidly after cardiac injury and could serve as a predictive cardiac biomarker during the postoperative course of patients with congenital heart disease undergoing cardiac surgery.^{9,18} Previous studies have indicated that cTn-I levels at 4 hours post-CPB enable clinicians to predict the postoperative course of pediatric patients after cardiac surgery.¹⁹ Bojan et al.²⁰ have determined that an early increase in cTn-I levels can be useful in predicting the postoperative course of neonates and infants undergoing cardiac surgery. Moreover, the duration of aortic clamping may stimulate cTn-I levels to increase.²¹ Using a cutoff point of 13 ng/mL at 4 hours post-CPB, Froese et al.²² have demonstrated that the early measurement of cTn-I can enable clinicians to recognise the development of LCOS after cardiac surgery in children. In contrast, a cutoff point of > 14 ng/mL for cTn-I at 2 hours post-CPB in the present study showed high sensitivity and specificity. cTn-I is a specific and sensitive marker of myocardial injury after cardiac surgery and is, by itself, an evident independent early predictor of LCOS, regardless of patient age, the physiological heart defect, and the duration of CPB.

Little research has been conducted on the effects of CPB on plasma MR-proADM levels. ADM is difficult to measure in plasma; however, MR-proADM is more stable than the active molecule, being secreted in equimolar amounts to ADM. Circulating ADM levels are increased in heart failure and are related to low left ventricular ejection fraction. Hence, ADM secretion appears to be a compensatory mechanism in LCOS, which also plays an important role in fluid homeostasis.

Our findings differ from those reported by Abella et al.,²³ who have described an initial decrease in ADM levels during and after CPB in LCOS children. Takeuchi et al.²⁴ have also noted a decrease in ADM plasma levels at 24 hours following CPB. Both studies were conducted with a limited number of patients; therefore, these results should be interpreted with caution.

Table 4

Diagnostic Information for the Prediction of Low Cardiac Output Syndrome Via Cardiac Troponin I and Mid-regional Pro-adrenomedullin Levels

Cutoff concentration	Sensitivity (95%CI)	Specificity (95%CI)	PPV, %	NPV, %	Accuracy, %
cTnI > 142 h PO, ng/mL	55 (36-73)	86 (78-94)	60 (41-73)	83 (74-91)	76 (69-85)
MR-proADM > 1.5 24 h PO, nmol/L	88 (75-100)	66 (55-76)	50 (36-64)	93 (86-100)	72 (63-80)
MR-proADM 24 h PO > 1.5 + cTnI 2 h PO > 14, nmol/L	45 (27-64)	91 (84-97)	65 (44-87)	81 (72-89)	78 (70-86)

95%CI, 95% confidence interval; cTn-I, cardiac troponin I; MR-proADM, mid-regional pro-adrenomedullin; NPV, negative predictive value; PO, postoperative; PPV, positive predictive value.

Accordingly, it seems plausible that in most critical patients ADM levels could be increased. The increase in ADM in LCOS could be a compensatory mechanism which increases cyclic adenosine monophosphate levels, activates protein kinase A, and stimulates myocardial contractility, coronary flow, and cardiac output.²³ Given the small number of patients requiring extracorporeal membrane oxygenation in our study, we deemed it inappropriate to conduct a statistical analysis of the studied cardiac biomarkers. The transit of blood through the extracorporeal circuit may result in the degradation and/or sequestration of these biomarkers. As reported by Luyt et al.,²⁵ monitoring these cardiac biomarkers in extracorporeal membrane oxygenation patients would not aid therapeutic decision-making.

Postoperative measurement of cTn-I and MR-proADM, besides the use of hemodynamic monitoring and markers of tissue perfusion, could be used in congenital heart disease patients to determine the risk of LCOS after corrective surgery under CPB. Aside from the monitoring of hemodynamic and respiratory parameters, serum lactate monitoring and continuous near-infrared spectroscopy measurement of tissue oxygen saturation are essential to detect LCOS. Research into the levels of these biomarkers may also help in the evaluation of cardiac output and tissue oxygenation. This would facilitate therapeutic decision-making in clinical practice and would enable clinicians to modify the type of support. The analysis of the studied cardiac biomarkers at 2 and 24 hours after surgery cannot be considered separately but should be complemented with data further monitoring, which is usually obtained postoperatively.

Limitations

The limitations of the current study mainly involve the genomic aspects of the cardiac biomarkers, the interactions among these biomarkers, which can be complex, and the fact that individual variations in these biomarkers can be large. However, these aspects have not yet been sufficiently studied. In the multivariate analysis, there was a wide range of confidence intervals for odds ratios. This factor is outside our influence and it mainly depends on variability in the measurements. Some relevant variables that may influence LCOS were not included in the multivariate analysis. The variability in the clinical postoperative complexity of patients undergoing CPB, as well as the surgical procedures, make it difficult to perform an exhaustive monitoring of all the possible variables predictive of LCOS. However, we previously conducted a descriptive and a univariate analysis to prevent such variability. The validity of our results is also supported by the high values obtained for odds ratios.

The major strengths of this study are its large sample size and the minimal variability in patient management. LCOS was considered based upon restrictive and objective inclusion criteria.

CONCLUSIONS

Our study demonstrated that LCOS prediction at 48 hours was strengthened by a cutoff point of > 14 ng/mL for cTn-I at 2 hours post-CPB. cTn-I is a specific and sensitive marker of myocardial injury after cardiac surgery. The early prediction of LCOS is, by itself, evident, regardless of the physiological heart defect and the duration of CPB. This result was reinforced when cTn-I values at 2 hours following CPB were combined with a cutoff point of > 1.5 nmol/L for MR-proADM at 24 hours after CPB. Levels of these cardiac biomarkers, combined with monitoring of hemodynamic and respiratory parameters, could provide complementary information to aid in therapeutic decision-making and prevent

hemodynamic deterioration in the immediate postoperative period in congenital heart disease.

WHAT IS KNOWN ABOUT THE TOPIC?

- A wide variety of cardiac biomarkers has been reported in adults with heart failure. The behavior of cardiac biomarkers in the postoperative period following cardiac surgery under CPB in children with congenital heart disease has seldom been studied.
- If any of the studied cardiac biomarkers correlated with the hemodynamic status of the children after corrective surgery for congenital heart disease, the cardiac biomarker in question could be used in therapeutic decision-making in clinical practice after surgery.

WHAT DOES THIS STUDY ADD?

- The prediction of LCOS was strengthened by a cutoff point of > 14 ng/mL for cTn-I at 2 hours post-CPB. The early prediction of LCOS is, by itself, evident, regardless of the physiological heart defect and the duration of CPB. This result was reinforced when cTn-I values were combined with a cutoff point of > 1.5 nmol/L for MR-proADM at 24 hours post-CPB.
- Levels of these cardiac biomarkers could provide complementary information to aid in therapeutic decision-making and to prevent hemodynamic deterioration in the immediate period post-CPB.

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CONFLICTS OF INTEREST

None declared.

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