Int J Clin Exp Med 2016;9(3):5842-5847
www.ijcem.com /ISSN:1940-5901/IJCEM0017318

Original Article

The dynamic change of serum cTnT and NT-ProBNP during the intervention therapy for congenital heart disease and the value for prognosis prediction

Shunyang Fan[1*], Hua Huang[1*], Deyin Zhang[2], Qun Li[1], Hongliang Xu[1], Yunfei Xu[1], Junying Qiao[1]

[1]Department of Heart Center, Third Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China; [2]Department of Internal Medicine, The Third People's Hospital of Henan Province, Zhengzhou 450052, Henan, China. [*]Equal contributors.

Received October 5, 2015; Accepted March 1, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Brain natriuretic peptide (BNP) and its stable form, N-terminal proBNP (NT-proBNP), can work as a clinical index for cardiac function. Cardiac troponin T (cTnT) is another specific indicator for the condition of myocardial injury. This study investigated the level of cTnT and NT-ProBNP in congenital heart disease (CHD) children before and after intervention therapy, in an attempt to discuss their features and potential values in prognosis prediction. A total of 128 CHD patients who received catheter intervention surgery (including 43 cases of secundum atrial septal defect (ASD), 44 cases of membranous ventricular septal defect (VSD) and 41 cases of patent ductus arteriosus (PDA)) were enrolled. Serum cTnT and NT-ProBNP levels were measured by enzyme-linked immunosorbent assay (ELISA). The predictive value in prognosis prediction was analyzed by ROC curve. Echocardiography results showed no significant change of cardiac function in ASD patients 48 hours after surgery, but lowered LVEDD and elevated LVEF levels were observed in VSD and PDA sub-groups ($P<0.05$). Levels of cTnT and NT-ProBNP were elevated immediately after surgery, reaching a peak and then decreased 48 hours later. Levels of cTnT and NT-ProBNP were significantly higher in those with endpoint events ($P<0.05$). ROC analysis revealed the highest evaluative efficacy of those two factors for VSD, followed by PDA and ASD. Serum cTnT and NT-ProBNP levels showed time-dependent pattern in CHD patients and had implications in evaluating the prognosis of CHD patients after intervention surgery.

Keywords: Congenital heart disease, prognostic prediction, cardiac troponin, N-terminal pro-brain natriuretic peptide

Introduction

Congenital heart disease (CHD) is one type of common cardiovascular diseases in children. Among all subtypes of CHD, atrial septal defect (ASD), ventricular septal defect (VSD) and patent ductus arteriosus (PDA) are common types of shunting disorders [1, 2]. Classical treatment plan for CHD is open-chest surgery, which, however, may cause major trauma and various complications. The introduction of intervention therapy had less incidence of trauma and complications, with rapid postoperative recovery. The stretch of catheter, dilation of balloon and blocking materials all can cause injury of myocardial tissues [3, 4]. Even in those with smooth surgery, no significant alternation of echocardiography, clinical symptom and vitals, and stable myocardial enzyme, but examination has shown the existence of minor injury of myocardial tissues [5, 6]. Current study about myocardial injury after intervention therapy for CHD mainly focuses on the short-term effect [7, 8]. Sensitive indexes for myocardial tissue injury include cardiac troponin (cTn, cTnT and cTnI) and creatine kinase isoenzyme (CK-MB), which is an important indicator for myocardial tissue necrosis. As one myocardial tissue-specific antigen, cTn is also a specific indicator for myocardial injury. It is released immediately after even minor injury of myocardial tissue, and can persist for long term, thus benefiting the evaluation of perioperative cardiac injury and postoperative efficacy [9, 10]. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-ProBNP) are both clinical indexes for evaluating cardiac function. BNP is known to be positively correlated with cardiac function

Table 1. General information of CHD patients

Group	ASD	VSD	PDA	t/χ^2 value	*P* value
N	43	44	41	-	-
Sex ratio (M:F)	20:23	19:25	18:23	0.1073	0.948
Average age (years)	5.54±1.42	5.48±1.26	5.61±1.59	0.416	0.678
Average body weight (kg)	20.58±7.21	20.81±6.92	20.71±7.41	0.149	0.882
Diameter of defect or PDA (mm)	6.14±2.14	5.83±0.86	5.74±1.12	1.081	0.284
Cardiac function grade I~II	32	30	32	1.0912	0.579
Cardiac function grade III~IV	11	14	9		

scale. Due to its relatively longer half-life, NT-ProBNP is more stable than BNP. Serum BNP and NT-ProBNP levels thus can effectively predict the prognosis of heart failure patients, and can reflect the pressure load and volume of CHD children, thus working as indexes for assisting CHD diagnosis and evaluating disease condition [11, 12]. This study investigated the serum cTNT and NT-ProBNP levels at different time points before and after intervention therapy of childhood CHD patients, in an attempt to elucidate the changing pattern and the value in prognostic prediction.

Materials and methods

Clinical information

A total of 128 CHD children who successfully received cardiac catheter intervention surgery from March 2012 to April 2015 in Third Affiliated Hospital of Zhengzhou University were recruited in this study. Among all patients, there were 43 cases of secondary atrial septal defect (ASD), 44 cases of membranous ventricular septal defect (VSD), and 41 patients with patent ductus arteriosus (PDA). All patients had no pulmonary hypertension. This study has been pre-approved by the ethical committee of our hospital and has obtained written consents form all participants' families. General clinical information of all patients was listed in **Table 1**.

Inclusive/exclusive criteria

Inclusive criteria: CHD patients with left-to-right shunting disorder fitted guideline for intervention therapy; Aging between 2 and 8 years old; No infection, muscular disease or liver/kidney function before surgery.

Exclusive criteria: With infection or sepsis before or after surgery; Complicated with other cardiac deformation that requires surgery; With moderate to severe pulmonary hypertension.

Observing indexes

Echocardiography examination was performed before the surgery on all patients to measure left ventricle ejection fraction (LVEF) and left ventricle end-diastolic dimeter (LVEDD). Serum cTnT and NT-ProBNP levels were measured using enzyme linked immunosorbent assay (ELISA) using test kits (Roche, Swiss) before surgery, and at 0, 6, 24, 48, 72 hours and 7 days after surgery. The myocardial injury was determined when cTnT >0.1 ng/mL. Cardiac dysfunction was identified when NT-ProBNP >300 pg/mL. Postoperative follow-ups were performed within 6 months after surgery. The endpoint of follow up was identified as cardiac function deterioration for in-patients or death.

Statistical methods

SPSS 19.0 software was used to compare all collected data. The comparison of ratios was performed by chi-square test with correction. Measurement data were firstly tested for normality. Data fitted normal distribution were expressed as mean ± standard deviation (SD). Comparison across multiple groups was performed by one-way analysis of variance (ANOVA), followed by LSD test for paired comparison. Non-parametric data were presented by median and percentiles, and were compared by rank-sum test. ROC analysis was used to predict the value of NT-ProBNP on endpoint events. Youden index J was calculated as sensitivity + specificity-1. Cut off values were determined as the best sensitivity and specificity value. A statistical significance was defined when $P<0.05$.

Results

Clinical observation

All patients had successful intervention therapies. No signs of short breath, fever, heart failure or cyanosis were observed in patients after

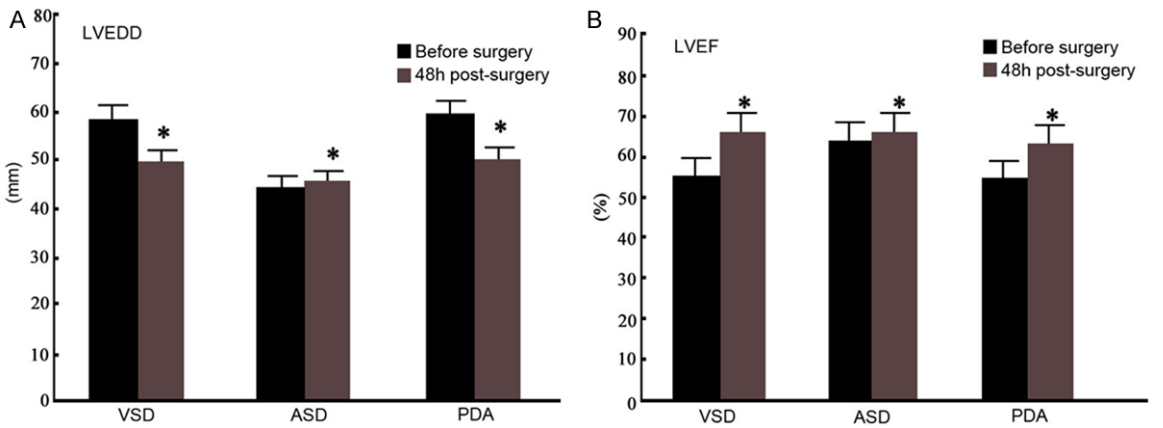

Figure 1. Cardiac function indexes. A: LVEDD; B: LVEF. ASD, secondary atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus. *, P<0.05 compared to those before surgery.

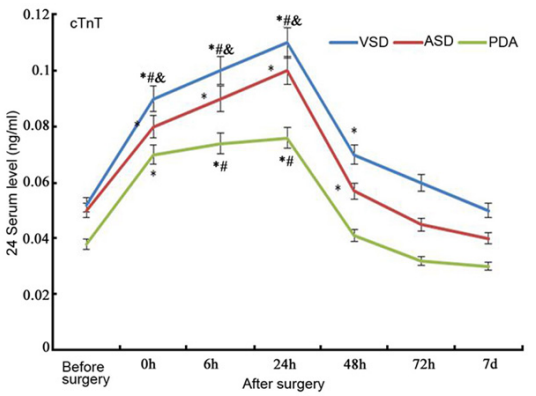

Figure 2. Serum cTnT level. ASD, secondary atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus. *, P<0.05 compared to ASD group; #, P<0.05 compared to ASD group; &, P<0.05 compared to PDA group.

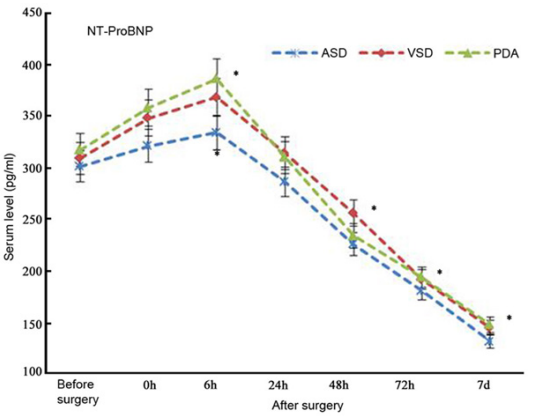

Figure 3. Serum NT-ProBNP level. ASD, secondary atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus. *, P<0.05 compared to those before surgery.

surgery. Leukocyte count was normal 48 hours after surgery. Chest X-ray showed success of repair surgery. Echocardiography showed no significant difference of LVEDD or LVEF in ASD patients after surgery (P>0.05, **Figure 1**). VSD and PDA patients, however, had lowered LVEDD level and elevated LVEF level after surgery (P<0.05). These results suggested restored abnormal blood flow and decreased left heart volume/pressure load in VSD or PDA patients after surgery.

Serum cTnT level

All patients had normal cTnT levels before surgery. After surgery, cTnT level was immediately increased, reaching a peak at 24 hours post-surgery. VSD group had above-normal level of cTnT at 24 hours post-surgery. The elevated cTnT levels were restored to pre-operative level in PDA group after 48 hours of surgery. VSD and ASD individuals had decreased cTnT level but still higher than normal people. All abnormalities were restored to the pre-operative level (**Figure 2**).

Serum level of NT-ProBNP

All patients had normal NT-ProBNP levels before surgery. After surgery, NT-ProBNP levels were elevated and reached a peak at 6 hours (P<0.05, **Figure 3**). Then it was gradually decreased to normal levels until 48 hours.

Predictive value of serum NT-ProBNP on prognosis

During 6-month postoperative follow-up, 34 patients had endpoint events, including 22 ca-

Table 2. Area under the curve

Test statistics	Area	Standard error[a]	Progressive Sig.[b]	95% confidence interval	
				Lower limit	Upper limit
VSD	.955	.033	.000	.891	1.000
PDA	.911	.061	.000	.792	1.000
ASD	.891	.070	.000	.755	1.000

[a]Under non-parametric hypothesis; [b]Null hypothesis: area = 0.5.

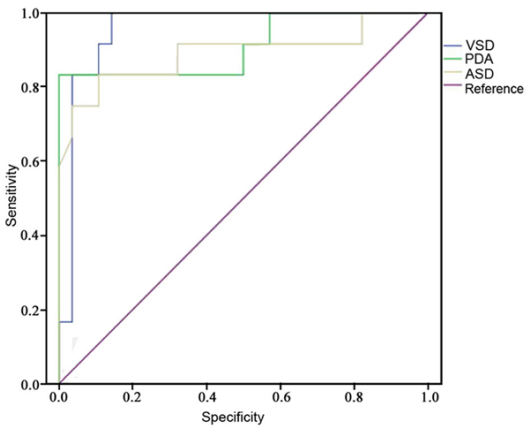

Figure 4. Predictive power of serum NT-ProBNP.

ses of cardiac function deterioration (9 form VSD, 6 cases of ASD, and 7 from PDA subgroup) and 12 death cases (3 VSD, 5 ASD and 4 PDA patients). Using serum NT-ProBNP level at discharge for predicting endpoint events by ROC analysis, cut-off values of VSD, PDA and ASD groups were determined to be 349 pg/mL, 449 pg/mL and 499 pg/mL, respectively. The areas under the curve were 0.955, 0.911 and 0.891 for VSD, PDA and ASD patients, respectively (**Table 2**). The sensitivity and specificity were determined as 90.90% and 84.09%, 87.80% and 85.36%, 83.72% and 88.37% for VSD, ASD and PDA, respectively (**Figure 4**).

Correlation between endpoint events and serum levels of cTnT and NT-ProBNP

As shown in **Figure 5**, those patients with endpoint events had significantly higher serum cTnT and NT-ProBNP level ($P<0.05$).

Discussion

The intervention therapy has inherent advantages over traditional open chest surgery for CHD. Certain complications including detach of implants, hemolysis, thrombosis, obstruction and arrhythmia may also occur during or after intervention therapy [13, 14]. The direct stimulus on myocardial tissues by contrast agent, catheter or guide wire, dilation of balloon against valves, frication or compression on peripheral tissues by implant, and body's immune functions all can affect myocardial tissues [15, 16]. Most CHD patients had elevated serum cTnT levels, which are negatively correlated with body weight or age, after intervention therapy, which also increase serum CK-MB level [17, 18]. This study measured serum cTnT and NT-ProBNP levels at different time points before and after surgery. Results found normal cTnT level before surgery, and immediate surge after surgery, suggesting the effect by mechanical stimuli including guide wire, catheter and sheath. At 6 hours and 24 hours after surgery, VSD patients had elevated cTnT level, which was restored to normal at 48 hours. The significant elevation of cTnT level in VSD patients is highly likely to be related with myocardial tissue injury, probably due to the friction of peripheral tissue by blocking implant, which can cause focal tissue edema. During the manipulation of cardiac catheter, inflammation can be induced as a result of mechanical injury on vascular endothelial cells. The disintegration of myocardial cells may increase the permeability of the membrane, through which small molecule cTnT was released into the blood. Intervention therapy for VSD requires the intra-cavity angiography and implant of blocker at ventricular septum. Similar to VSD, PDA treatment require less intra-cavity manipulation and extra-cavity implant and angiography. The intervention therapy of ASD was performed in atrium and inferior vena cava without contrast agent. Therefore, VSD requires the most complicated surgical procedures, leading to higher probability injury on myocardial tissues and subsequent elevation of cTnT levels. In a word, the amplitude and duration of the increase of myocardial marker is correlated with specific sub-type of CHD.

As one neuropeptide secreted by ventricles, BNP has major functions including vascular dilation, diuresis and inhibiting renin-aldosterone. BNP is abundantly synthesized when cardiac function is compromised, making its level being positively correlated with cardiac function scale. Meanwhile, left ventricular fractional shortening ratio and LVEF are both negatively correlated with serum BNP level [19, 20].

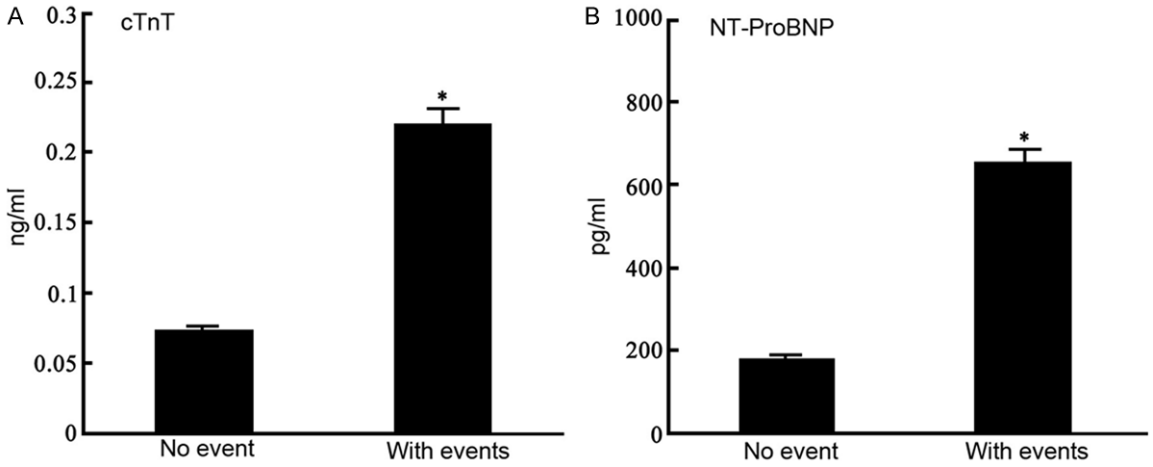

Figure 5. Relationship between endpoint events and serum cTnT (A) or NT-ProBNP (B) levels. *, P<0.05 compared to those without events.

NT-ProBNP is mainly secreted by left ventricle and is more stable than BNP in serum, making it a common index for cardiac function and prognostic evaluation [21, 22]. Results from this study showed elevated serum NT-ProBNP in CHD children before surgery. After intervention surgery, NT-ProBNP levels in all three subgroups increased, reaching a peak at 6 hour, followed by gradual decrease till normal range after 48 hours. In VSD and PDA patients, the heavy burden of left ventricle was relieved by intervention surgery, thus decreasing serum level of NT-ProBNP. In ASD patients, the malformation of left ventricle is caused by dilation of right heart. The surgical repair may cause temporary dysfunction or even failure of left heart, thus causing elevated NT-ProBNP level, which, however, can be restored by the recovery of heart function. During the 6-month postoperative follow-up, cut-off values of VSD, PDA and ASD groups were determined to be 349 pg/mL, 449 pg/mL and 499 pg/mL, respectively. The areas under the curve were 0.955, 0.911 and 0.891 for VSD, PDA and ASD patients, respectively. The sensitivity and specificity were determined as 90.90% and 84.09%, 87.80% and 85.36%, 83.72% and 88.37% for VSD, ASD and PDA, respectively. The overall evaluative efficacy of NT-ProBNP is the highest in VSD patients compared to PDA or ASD ones, suggesting the significance of serum NT-ProBNP in evaluating the prognosis of intervention surgery for VSD children.

In summary, this study revealed the time pattern of serum cTnT and NT-ProBNP levels for evaluating the myocardial injury after intervention surgery for CHD children. Serum level of NT-ProBNP can predict the unfavorable prognosis of intervention surgery to certain extents, while serum cTnT is related with heart injury.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Junying Qiao, Department of Heart Center, Third Affiliated Hospital of Zhengzhou University, No. 7, The Two Seven District Rehabilitation, Zhengzhou 450052, Henan, China. Tel: +86-0371-66903236; Fax: +86-0371-66903064; E-mail: junyingqiao@sina.com

References

[1] Bucholz EM, Whitlock RP, Zappitelli M, Devarajan P, Eikelboom J, Garg AX, Philbrook HT, Devereaux PJ, Krawczeski CD, Kavsak P, Shortt C, Parikh CR; TRIBE-AKI Consortium. Cardiac biomarkers and acute kidney injury after cardiac surgery. Pediatrics 2015; 135: e945-56.

[2] Eliyahu S, Roguin A, Kerner A, Boulos M, Lorber A, Halabi M, Suleiman M, Nikolsky E, Rispler S, Beyar R. Patient safety and outcomes from live case demonstrations of interventional cardiology procedures. JACC Cardiovasc Interv 2012; 5: 215-24.

[3] Gupta-Malhotra M, Kern JH, Flynn PA, Schiller MS, Quaegebeur JM, Friedman DM. Early pleural effusions related to the myocardial injury after open-heart surgery for congenital heart disease. Congenit Heart Dis 2010; 5: 256-61.

[4] Mildh L, Hiippala A, Rautiainen P, Pettilä V, Sairanen H, Happonen JM. Junctional ectopic

tachycardia after surgery for congenital heart disease: incidence, risk factors and outcome. Eur J Cardiothorac Surg 2011; 39: 75-80.
[5] Ricci Z, Garisto C, Morelli S, Di Chiara L, Ronco C, Picardo S. Brain natriuretic peptide is removed by continuous veno-venous hemofiltration in pediatric patients. Interact Cardiovasc Thorac Surg 2009; 9: 33-6.
[6] Mir TS, Haun C, Lilje C, Läer S, Weil J. Utility of N-terminal brain natriuretic peptide plasma concentrations in comparison to lactate and troponin in children with congenital heart disease following open-heart surgery. Pediatr Cardiol 2006; 27: 209-16.
[7] Cantinotti M, Law Y, Vittorini S, Crocetti M, Marco M, Murzi B, Clerico A. The potential and limitations of plasma BNP measurement in the diagnosis, prognosis, and management of children with heart failure due to congenital cardiac disease: an update. Heart Fail Rev 2014; 19: 727-42.
[8] Ploegstra MJ, Roofthooft MT, Douwes JM, Bartelds B, Elzenga NJ, van de Weerd D, Hillege HL, Berger RM. Echocardiography in pediatric pulmonary arterial hypertension: early study on assessing disease severity and predicting outcome. Circ Cardiovasc Imaging 2015; 8.
[9] Elkiran O, Sandikkaya A, Kocak G, Karakurt C, Taskapan C, Yologlu S. Evaluation by N-terminal prohormone of brain natriuretic peptide concentrations and ross scoring of the efficacy of digoxin in the treatment of heart failure secondary to congenital heart disease with left-to-right shunts. Pediatr Cardiol 2013; 34: 1583-9.
[10] Takatsuki S, Wagner BD, Ivy DD. B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide in pediatric patients with pulmonary arterial hypertension. Congenit Heart Dis 2012; 7: 259-67.
[11] Lowenthal A, Camacho BV, Lowenthal S, Natal-Hernandez L, Liszewski W, Hills NK, Fineman JR, Bernstein HS. Usefulness of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide as biomarkers for heart failure in young children with single ventricle congenital heart disease. Am J Cardiol 2012; 109: 866-72.
[12] Pérez-Piaya M, Abarca E, Soler V, Coca A, Cruz M, Villagrá F, Giannivelli S, Asensio A. Levels of N-terminal-pro-brain natriuretic peptide in congenital heart disease surgery and its value as a predictive biomarker. Interact Cardiovasc Thorac Surg 2011; 12: 461-6.
[13] Johns MC, Stephenson C. Stephenson, Amino-terminal pro-B-type natriuretic peptide testing in neonatal and pediatric patients. Am J Cardiol 2008; 101: 76-81.
[14] Lisy M, Babal P. Babal, Brain natriuretic peptide--the biological marker in the diagnosis of overt congestive heart failure and myocardial ischemia. Bratisl Lek Listy 2007; 108: 170-3.
[15] Mir TS, Flato M, Falkenberg J, Haddad M, Budden R, Weil J, Albers S, Laer S. Plasma concentrations of N-terminal brain natriuretic peptide in healthy children, adolescents, and young adults: effect of age and gender. Pediatr Cardiol 2006; 27: 73-7.
[16] Kozar EF, Plyushch MG, Popov AE, Kulaga OI, Movsesyan RR, Samsonova NN, Bokeriya LA. Markers of myocardial damage in children of the first year of life with congenital heart disease in the early period after surgery with cardioplegic anoxia. Bull Exp Biol Med 2015; 158: 421-4.
[17] Caputo M, Mokhtari A, Miceli A, Ghorbel MT, Angelini GD, Parry AJ, Suleiman SM. Controlled reoxygenation during cardiopulmonary bypass decreases markers of organ damage, inflammation, and oxidative stress in single-ventricle patients undergoing pediatric heart surgery. J Thorac Cardiovasc Surg 2014; 148: 792-801, e8; discussion 800-1.
[18] Zhou FJ, Zhou CY, Tian YJ, Xiao AJ, Li PL, Wang YH, Jia JW. Diagnostic value of analysis of H-FABP, NT-proBNP, and cTnI in heart function in children with congenital heart disease and pneumonia. Eur Rev Med Pharmacol Sci 2014; 18: 1513-6.
[19] Nassef YE, Hamed MA, Aly HF. Inflammatory cytokines, apoptotic, tissue injury and remodeling biomarkers in children with congenital heart disease. Indian J Clin Biochem 2014; 29: 145-9.
[20] Rüffer A, Münch F, Potapov S, Purbojo A, Toka O, Dodge-Khatami A, Dittrich S, Cesnjevar RA. Troponin I levels in extracorporeal membrane oxygenation following congenital heart surgery. World J Pediatr Congenit Heart Surg 2014; 5: 229-35.
[21] Uner A, Doğan M, Ay M, Acar C. The evaluation of serum N-terminal prohormone brain-type natriuretic peptide, troponin-I, and high-sensitivity C-reactive protein levels in children with congenital heart disease. Hum Exp Toxicol 2014; 33: 1158-66.
[22] Eerola A, Poutanen T, Savukoski T, Pettersson K, Sairanen H, Jokinen E, Pihkala J. Cardiac troponin I, cardiac troponin-specific autoantibodies and natriuretic peptides in children with hypoplastic left heart syndrome. Interact Cardiovasc Thorac Surg 2014; 18: 80-5.