Original article

Proteolytic and cytokine balance abnormalities in children with congenital heart disease undergoing cardiac surgery with cardiopulmonary bypass

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Abstract

Background: Cardiac surgery with cardiopulmonary bypass (CPB) in children with congenital heart disease induces a systemic inflammatory response. This inflammatory response is thought to be produced by exposing patients to proinflammatory factors.

Aim: To explore the role of cytokines and proteolytic enzymes in inflammatory complications after cardiac surgery in children.

Methods: We investigated the dynamics of concentrations of IL-6, IL-8 and IL-10, and metalloproteinases (MMPs) MMP-2 and MMP-9, and their inhibitors – tissue inhibitors of metalloproteinases (TIMPs) TIMP-1 and TIMP-2. These investigations were carried out in 28 children, aged 4-34 months, who underwent a cardiac operation with CPB. Serum concentrations of proteins were sequentially measured before induction of anaesthesia, at the initiation of CPB, after 30 minutes of CPB, at the end of CPB, and 4 and 48 hours after CPB.

Results: The serum levels of IL-6 increased dramatically 4 hours after CPB compared with the level before anaesthesia (141.83±25.49 vs. 10.68±5.01 ng/ml, p=0.00004) and correlated with duration of CPB (r=0.74, p=0.00028). The serum levels of IL-8 increased 4 hours after CPB compared with the level before anaesthesia (267.1±41.3 vs. 8.5±6.3 ng/ml, p=0.00002). A significant increase of IL-10 concentration at the end of surgery and 4 hours after CPB was detected (95.12±23.57 vs. 10.34±6.45 ng/ml, p=0.000004 and 59.41±21.4 vs. 10.34±6.45 ng/ml, p=0.00004, respectively). The MMP-9 concentration increased at the end of CPB and remained elevated for a period of 48 hours (44.40±13.95 vs. 19.53±7.58, p=0.000004 and 38.97±10.76 vs. 19.53±7.58, p=0.00004, respectively). The concentration of MMP-9 detected at the end of CPB positively correlated with duration of CPB (r=0.68, p=0.0045). The TIMP-1 concentration decreased significantly after 30 minutes of CPB, and remained lowered to the end of CPB (respectively 52.68±17.72 vs. 83.29±17.06 ng/ml, p=0.000006 and 34.94±10.58 vs. 83.29±17.06 ng/ml, p=0.00004,respectively).

Conclusions: Cardiac surgery causes an increase of IL-6 and IL-8 concentrations in peripheral blood 4 hours after CPB termination. The concentration of anti-inflammatory IL-10 cytokine increases immediately after the end of CPB. We showed an increase of the MMP-2 and MMP-9 concentrations during and after CPB and simultaneous decrease of TIMP-1 inhibitor. We demonstrated a link between CPB duration and IL-6 and MMP-9 concentrations.

Key words: cardiopulmonary bypass, cardiac surgery, congenital heart disease, cytokines, metalloproteinases

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Introduction

Inflammatory complications are the most frequent causes of death in patients after cardiac surgery. Their development depends on many factors, such as clinical condition of the patient before surgery, type of procedure and techniques applied during surgery: cardiopulmonary bypass (CPB), hypothermia, aortic cross-clamping, cardioplegic arrest, inotropic agents and oxygenator system priming solutions [1, 2]. Exposure of blood cells to the non-physiological surface of the CPB device as well as of afferent and efferent cannulas, together with

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ischaemia and reperfusion injury, activate the immune system and lead to the development of systemic inflammatory response syndrome (SIRS) [3].

The role of multiple cells and inflammatory mediators secreted by these cells is postulated in the pathogenesis of SIRS. The important role of phagocytes, endothelial cells and oxygen free radicals has been documented. Many reports emphasise that an uncontrolled life-threatening inflammatory response is associated with an imbalance between inflammatory and anti-inflammatory cytokines [2, 3]. An excessive increase of the levels of inflammatory cytokines, such as interleukin-8 (IL-8), IL-6 and tumour necrosis factor α (TNF-α), observed after cardiac surgery, activates phagocyte degranulation and thus the release of large amounts of proteases as well as factors involved in surrounding tissue damage [1, 2].

The immune system immaturity in children means that SIRS symptoms in these patients can be particularly intense. In some reports attention has been paid to additional dysfunction of the immune system related to a congenital heart defect [4]. Compared with healthy children, phagocytes in patients with congenital heart defects present different morphology favouring adhesion to the vascular wall, and endothelial cells are more susceptible to injury caused by proteases [4].

The aim of the study was to assess the balance between inflammatory cytokines IL-6 and IL-8, and anti-inflammatory cytokine IL-10, and also to assess the levels of matrix metalloproteinases (MMP-2, MMP-9) and tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2 in the peripheral blood plasma of children subjected to cardiac surgery with the use of CPB. We also attempted to evaluate the effects of procedures applied during surgery, i.e. CPB, hypothermia, aortic cross-clamping, cardioplegic arrest and inotropic agents use on kinetics of these cytokine and enzyme levels.

Methods

Patients

The study involved 28 children with congenital heart disease, in whom cardiac surgery with CPB was performed. Diagnosis of the heart defect was established based on echocardiographic assessment. Approval for the study protocol was granted by the local Ethics Committee for Scientific Research.

All children received routine premedication (midazolam). General anaesthesia with i.v. sufentanil 1 mg/kg, thiopental 3-5 mg/kg and pavulon 0.1-0.15 mg/kg was used. In some cases, i.e. in children with body weight less than 15 kg, induction with ketamine (in a dose of 7.5-10 mg/kg) was administered. Endotracheal intubation was applied. Extracorporeal circulation used a Jostra HL 20 device (AG, Hirrlingen, Germany) equipped with Safe Micro or Safe Mini oxygenators (Polystan AS, Vaerlose, Denmark) featuring laminar flow. Two central as well as two peripheral veins were cannulated. During CPB, the following parameters were monitored: central venous and arterial blood pressure, ECG, arterial oxygen saturation (SaO_2), body temperature, hourly diuresis, electrolyte balance and haematocrit.

Unfractionated heparin 3 mg/kg body weight was administered intraoperatively to all patients. Anticoagulation was given under control by means of activated partial thromboplastin time (APTT) and the clotting time was maintained above 300 s. Heparin was antagonised with protamine sulphate at a dose of 2 mg for 1 mg of infused heparin.

Exclusion criteria included intraoperative complications such as blood pressure drop, prolonged perfusion or low cardiac output syndrome, genetic syndromes (microdeletion 22q11.2 syndrome), steroid therapy and immunosuppression. Clinical characteristics of the analysed patients are given in Table I.

Blood samples were collected in tubes containing heparin and stored at 4°C. Measurements were performed within four hours after sampling. Peripheral blood samples were taken six times: A – before general anaesthesia, B – at CPB start, C – at 30 minutes of CPB, D – at the end of CPB, E – at 4 hours after weaning from CPB, F – at 48 hours after weaning from CPB.

All patients were clinically evaluated on consecutive days after surgery. The SIRS, defined as recommended by the American College of Chest Physicians Society consensus, was diagnosed in 9 patients. Progression of severity of signs of SIRS was not observed in the early postoperative period. Respiratory tract infection occurred in four patients.

Table I. Clinical characteristics of patients

Parameter	Study patients (n=28)
Age [months]	11.3 (4-34)
Gender (female/male)	15/13
Type of defect	
Tetralogy of Fallot	10
Transposition of the great arteries	6
Aortic stenosis	6
Pulmonary stenosis	4
Left heart hypoplasia	2
Surgery duration [min]	95-220
Cardiopulmonary bypass duration [min]	85-165
Aortic cross-clamping duration [min]	55-80
Body temperature during hypothermia phase [°C]	19-25
Inotropic agents support after surgery (number of patients)	6
Infections after surgery (number of patients)	4

Laboratory investigations

Interleukin IL-6, IL-10 and IL-8 concentrations were measured using a CBA Inflammation kit (BD-Biosciences, Heidelberg, Germany) and cytometric method using a FACScan flow cytometer (BD-Biosciences, Heidelberg, Germany). Levels of metalloproteinases MMP-2 and MMP-9 and their inhibitors TIMP-1 and TIMP-2 were measured using standard tests (R&D Systems, Minneapolis, USA) and ELISA enzyme immunoassay (Diagnostics Pasteur, Paris, France). All samples were analysed twice. Measured values were corrected according to the following formula:

$$C_{corr} = C_{meas} \times Ht_{anesth}/Ht_{CPB} \quad [2]$$

where: C_{corr} – corrected level, C_{meas} – measured level, Ht_{CPB} – haematocrit value during CPB, Ht_{anesth} – haematocrit values before anaesthesia induction. The mean correction factor was 1.47±0.59.

Statistical analysis

Mean value, standard deviation and standard error of the mean (SEM) were calculated for measured parameters. Because analysed variables were not normally distributed (verified by Shapiro-Wilk test), nonparametric tests were used for further analysis. Wilcoxon test was used for the evaluation of dependent variables. Analysis of the relationship between two continuous variables was performed using Spearman rank correlation coefficient (r). A p value <0.05 was considered statistically significant.

Results

The study revealed a significant increase of IL-6 level at 4 hours after surgery in comparison with levels noted before sedation (Table II). A significant relationship between IL-6 level measured at 4 hours after surgery and CPB time (r=0.74, p=0.00028) was found.

There was a significant increase of IL-8 level noted at 4 hours after surgery, in comparison with levels observed before sedation. The IL 8 level remained elevated at 48 hours after CPB, in comparison with levels observed before sedation (Table III).

An increase of the IL-10 level was observed during surgery. The study showed a significant increase of IL-10 at the end and at 4 hours after CPB, in comparison with values observed before sedation.

A slow increase of MMP-2 and MMP-9 levels in successive stages of surgery, as well as in the perioperative period, was observed. A significant increase of peripheral blood MMP-2 level at 4 hours after CPB (Table III) was found. The level of analysed proteases remained elevated at 48 hours after surgery.

The MMP-9 plasma level after CPB was significantly higher in comparison with levels before anaesthesia induction (Figure 1). At 4 and at 48 hours after surgery the MMP-9 level remained elevated in comparison with levels observed before anaesthesia. A significant relationship between MMP-9 level measured after surgery and CPB time (r=0.54, p=0.0018) was found.

Measurements of the peripheral blood levels of MMP inhibitors revealed a decrease of TIMP-1 level during

Table II. Peripheral blood levels of IL-6, IL-10 and TIMP-1

	IL-6 [ng/ml]	IL-10 [ng/ml]	TIMP-1 [ng/ml]
Before anaesthesia induction	10.7±5.1	10.3±6.4	83.3±17.1
Beginning of CPB	13.2±4.7	11.4±5.8	74.9±20.7
30 min of CPB	17.9±7.2	11.8±5.9	52.7±17.7
End of CPB	25.8±10.4	95.1±23.6*	34.9±10.6*
4 h after CPB	141.8±25.5*	59.4±21.4*	44.5±10.9*
48 h after CPB	26.9±10.5	7.5±4.8	50.1±9.6**

** p <0.001, ** p <0.05 – difference between the level before anaesthesia induction and the level at the measurement point*

Table III. Peripheral blood levels of IL-8, MMP-2 and TIMP-2

	IL-8 [ng/ml]	MMP-2 [ng/ml]	TIMP-2 [ng/ml]
Before anaesthesia induction	8.5±6.3	85.5±26.8	69.5±36.8
Beginning of CPB	25.8±7.3	99.6±20.7	89.5±37.9
30 min of CPB	47.5±21.8**	121.5±45.8	46.5±25.1
End of CPB	213.3±34.8*	134.5±30.8**	51.3±20.1
4 h after CPB	267.1±41.3*	245.6±45.3*	78.9±39.9
48 h after CPB	100.6±11.5*	234.6±51.6*	63.6±37.8

** p <0.001, ** p <0.05 – difference between the level before anaesthesia induction and the level at the measurement point*

surgery with CPB and its slow increase after the procedure (Table II). There was a significant decrease of TIMP-1 plasma level at 30 minutes of CPB as compared with levels observed before anaesthesia. The lowest level of this inhibitor was demonstrated after CPB. Measurements of TIMP-2 at successive stages of the surgery and after the procedure revealed no statistically significant differences in comparison with levels observed at baseline (Table III).

Discussion

Results of the present study suggest a significant role of cytokines and MMPs in development of the inflammatory response after cardiac surgery in children. Systemic inflammatory response syndrome, observed in most children subjected to surgery with CPB, disturbs the dynamic balance between inflammatory and anti--inflammatory cytokines [2, 3]. Previous reports have demonstrated a significant increase of plasma levels of both groups of cytokines in patients after cardiac surgery [2, 5]. An increase of cytokine levels is caused by increased expression of genes of these proteins in cardiomyocytes [6]. Most patients present a typical course of inflammatory response, which runs in two phases: inflammatory and anti-inflammatory [2, 5]. An increase of plasma levels of such cytokines as IL-6 and IL-8 in patients after cardiac surgery is a diagnostic indicator of inflammatory phase [2]. Interleukin IL-6 is one of the most important inflammation markers. Its pro-inflammatory activity is associated with stimulation of lymphocytes T and B as well as mesangial cell proliferation [2].

In the present study a significant increase of IL-6 and IL-8 plasma levels was demonstrated in children at 4 hours after surgery. These results are consistent with observations of other authors. As previously reported, the IL-8 mRNA expression was found to be increased in cardiomyocytes and skeletal muscle cells in children subjected to surgery with CPB [7]. Ben-Abraham et al. showed in their study a significant increase of IL-8 plasma level in children at one hour after cardiac surgery [8]. These authors demonstrated an association between IL-8 level and surgical duration, CPB duration and severity of myocardial contractility disorders.

Cardiac surgery in adult patients induces an increase of IL-6 gene expression in monocytes up to six hours after surgery [9]. The analyses performed in children indicate CPB to be an important factor inducing IL-6 production and release to the peripheral blood. Tarnok et al. demonstrated significantly higher IL-6 levels in children after cardiac surgery with CPB, in comparison with children subjected to surgery without CPB [2]. Our study revealed a significant correlation between the level of analysed cytokine measured at 4 hours after the procedure and surgery duration. A similar relationship between these two parameters was presented in the reports of other authors

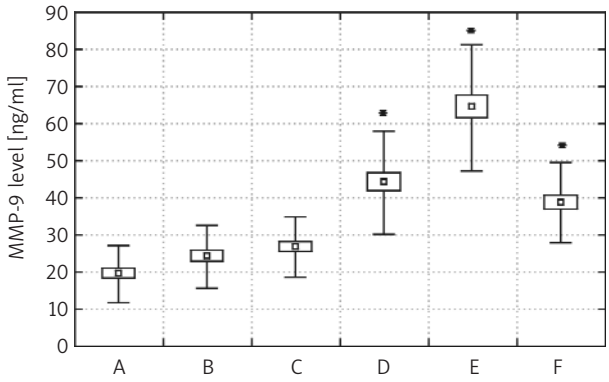

Figure 1. MMP-9 level in peripheral blood: A – before surgery, B – CPB beginning, C – 30 min of CPB, D – CPB end, E – 4 h after CPB, F – 48 h after CPB

**p <0.05 – difference between the level before anaesthesia induction and the level at the measurement point*

[2]. As shown by Hirai et al., plasma levels of IL-6 after the procedure also depend on the aortic cross-clamping time (myocardial ischaemia) and on total surgery time [3]. A relationship between IL-6 synthesis and the depth of hypothermia used during surgery has been proven [10]. Pre-operative IL-6 levels depend on the type of congenital heart disease. In comparison with shunting defects, they are significantly higher in children with severe congenital abnormalities, such as a single ventricle [10]. In the present study, two children with hypoplastic left heart syndrome (HLHS) enrolled in the study group presented elevated preoperative Il-6 and IL-8 levels, and the strongest increase of these cytokine levels at 4 hours after the procedure.

Parallel to the inflammatory reaction, a compensatory anti-inflammatory response develops after cardiac surgery, aimed at reversing the systemic effects of inflammatory cytokines [2, 5]. Elevation of IL-10 serum levels is a diagnostic indicator of anti-inflammatory phase. The anti- inflammatory action of this cytokine consists of inhibition of inflammatory mediators such as IL-10, IL-6 and IL-8 [5]. Furthermore, IL-10 stops the synthesis of TNF-α and reduces effector functions of monocytes and NK cells (natural killers) [2, 5]. In the present study significant elevation of this cytokine level was observed just after the procedure. In the study of Franke et al. a double increase of this anti-inflammatory cytokine level was observed: at 1 and at 4 hours after surgery [5]. The authors conclude that cardiac surgery induces a multiphasic inflammatory response. In the first 24 hours after surgery a non-specific response develops with simultaneous release of both inflammatory and anti--inflammatory cytokines. In the second stage, after a few postoperative days and after activation of specific elements of the immune system, synthesis of anti--inflammatory cytokines such as IL-10 increases again. Intensified anti-inflammatory phase of the inflammatory response after cardiac surgery may be protective against

the development of inflammatory complications. This has been confirmed by the results of Duggan et al., who observed that a decrease of IL-10 mRNA levels after surgery was associated with increased incidence of inflammatory complications in adult patients [11]. However, the observations in children are different. In a group of children with low IL-10 levels observed after CPB, there was a reduced peripheral blood cell response to stimulation with endotoxin and increased incidence of inflammatory complications in the postoperative period [12]. In the present study inflammatory complications occurred in four children. Two of them presented low IL-10 levels after the procedure.

Cytokine imbalance in the peripheral blood of patients after surgery with CPB stimulates the immune cells to release inflammatory mediators, such as MMPs. These are proteases released from phagocytes by degranulation and present unfavourable effects on the surrounding tissues. MMPs activated during cardiac surgery cause, among other things, degradation of connective tissue matrix including collagen type I surrounding cardiomyocytes [13]. Replacement of collagen type I by the less valuable collagen type III, as well as by new particles of collagen type I of qualitatively worse molecular bridges, results in a decrease of left ventricular compliance and dilatation [13, 14]. Inflammatory cytokines, such as TNF-α and IL-1, participate in inflammatory activation of MMPs. An association between elevation of these cytokine levels and expression of MMPs, measured by the levels of mRNA for these proteins, has been shown [15]. In vitro studies revealed a decrease of MMP synthesis and release by phagocytes under the influence of anti-IL-6 and anti-TNF-α antibodies [16]. In the present study a significant increase of MMP-9 serum level was noted in children after cardiac surgery. However, no relation between changes of levels of these enzymes and analysed cytokines was found. This may result from different methods used in the assessment of these two groups of mediators.

The amount of proteases secreted after cardiac surgery may depend on various medical techniques used during the procedure. The present study demonstrated an association between MMP-9 level measured after surgery and CPB duration. The studies performed in adult patients confirmed a role of myocardial ischaemia in the MMPs activation. Total myocardial ischaemia caused by aortic cross-clamping results in increased phagocyte degranulation and proteases release [14]. The elevation of MMP levels in the peripheral blood of patients after cardiac surgery, dependent on the aortic cross-clamping time, was confirmed by Joffs et al. [1].

In physiological conditions MMP level is regulated by natural tissue metalloproteinase inhibitors – TIMPs. They are found in complexes with enzymes and regulate extracellular matrix degradation by formation of covalent bonds with their active and latent forms [17, 18]. In the present study, elevation of MMP-9 level observed after CPB was accompanied by decrease of TIMP-1, a non-specific inhibitor of this enzyme. Similar kinetics of changes in MMP-9 and TIMP-1 levels was described in adult patients by Lin et al. [19]. In their opinion, disturbances in the balance of MMPs and their inhibitors in peripheral blood in patients after cardiac surgery with CPB may have an adverse effect on the development of inflammatory complications as well as organ damage.

The infectious hypothesis is also considered in the pathogenesis of SIRS occurring after cardiac surgery. According to this theory, bacterial endotoxins originating from the GI system enter the peripheral circulation during surgery done with CPB. The presence of gram--negative bacterial cellular wall lipopolysaccharides was confirmed in the serum of adult patients after such surgery [20, 21]. Systemic endotoxin release is associated with compromised visceral blood flow. Perfusion disturbances lead to mesenteric vessels vasospasm [22]. It results in intestinal mucosal injury and translocation of bacteria and their toxins from the intestinal lumen to the circulation [22, 23]. Endotoxin occurring in peripheral blood during surgery with CPB initiates an inflammatory response, which in turn together with additional mediators leads to the development of SIRS [23]. Bacterial endotoxins are capable of stimulating the release of acute-phase factors, such as procalcitonin. We previously demonstrated an increase of procalcitonin level in the peripheral blood of two children in whom infectious complications were observed after surgery with CPB [24].

The results of the present study confirm that cardiac surgery with CPB may significantly disturb the cytokine and proteolytic balance in peripheral blood of children with heart disease. Apart from CPB itself, also other medical procedures used during and after cardiac surgery add to the development of inflammatory complications in these patients. Future studies on pathomechanisms of the inflammatory response after surgery may help to develop new methods of protection that will reduce the risk of such complications.

Conclusions

1. Cardiac surgery is associated with increased levels of inflammatory cytokines IL-6 and IL-8 in peripheral blood at four hours after the procedure. Immediately after surgery the elevation of anti-inflammatory IL-10 cytokine level is observed.
2. An increase of MMP-2 and MMP-9 levels with simultaneous reduction of inhibitor TIMP-1 is observed in children during and after surgery with CPB.
3. Elevation of MMP-9 and IL-6 levels in children after cardiac surgery depends on the CPB time.

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Zaburzenia równowagi proteolitycznej i cytokinowej u dzieci z wrodzoną wadą serca poddanych zabiegowi kardiochirurgicznemu z użyciem krążenia pozaustrojowego

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Streszczenie

Wstęp: Zabieg kardiochirurgiczny z użyciem krążenia pozaustrojowego (CPB) u dzieci z wrodzoną wadą serca wywołuje uogólnioną odpowiedź zapalną ustroju. Czynnikiem sprawczym jest ekspozycja ustroju na działanie silnych bodźców zapalnych. Nadmierna, niekontrolowana reakcja zapalna może niekiedy prowadzić do zaburzeń narządowych. W większości doniesień podkreśla się, że niebezpieczna dla życia reakcja zapalna związana jest z zaburzeniami równowagi cytokin zapalnych i przeciwzapalnych. Nadmierny wzrost stężeń cytokin zapalnych, takich jak: interleukina-8 (IL-8), interleukina-6 (IL-6) i czynnik martwicy nowotworów α (TNF-α), obserwowany po zabiegu kardiochirurgicznym wpływa aktywująco na komórki żerne, które w procesie degranulacji uwalniają duże ilości enzymów proteolitycznych i czynników uszkadzających otaczające tkanki. Istotne znaczenie w rozwoju powikłań zapalnych i uszkodzeń narządowych po zabiegach mają metaloproteinazy (MMPs). Enzymy te, aktywowane w trakcie zabiegu kardiochirugicznego, powodują m.in. rozkład zrębu tkanki łącznej, w tym kolagenu typu I otaczającego kardiomiocyty.

Cel: Wyjaśnienie roli zaburzeń równowagi cytokin zapalnych i przeciwzapalnych i enzymów proteolitycznych w rozwoju powikłań zapalnych u dzieci poddanych zabiegowi kardiochirurgicznemu z wykorzystaniem oceny stężenia tych czynników we krwi obwodowej.

Metodyka: Badano dynamikę zmian stężeń cytokin: IL-6, IL-8, IL-10 oraz MMPs: MMP-2, MMP-9 oraz ich inhibitorów (TIMPs): TIMP-1 i TIMP-2, we krwi obwodowej. Badania prowadzono u 28 dzieci (w wieku 4–34 mies.) poddanych zabiegowi kardiochirurgicznemu z wykorzystaniem CPB. Ocenę stężeń cytokin, MMPs i TIMPs wykonywano: przed sedacją, na początku CPB, po 30 min od rozpoczęcia CPB, po zakończeniu CPB, po 4 i 48 godz. od zakończenia CPB. Badania stężenia cytokin wykonywano metodami cytometrii przepływowej. Pomiar stężeń MMPs i TIMPs wykonywano przy użyciu metody immunoenzymatycznej ELISA.

Wyniki: Cztery godziny po zakończeniu CPB stężenie IL-6 wzrastało w porównaniu z wartościami oznaczanymi przed sedacją (141,83±25,49 ng/ml *vs* 10,68±5,01 ng/ml, p=0,00004) i wykazywało współzależność z czasem trwania CPB (r=0,74, p=0,00028). Stężenie IL-8 wzrastało 4 godz. po zakończeniu CPB w porównaniu z wartościami oznaczanymi przed sedacją (267,1±41,3 ng/ml *vs* 8,5±6,3 ng/ml, p=0,00002). Wykazano istotny statystycznie wzrost stężenia IL-10 w momencie zakończenia zabiegu i 4 godz. po zakończeniu CPB w porównaniu z wartościami przed sedacją (odpowiednio 95,12±23,57 ng/ml *vs* 10,34±6,45 ng/ml, p=0,000004 i 59,41±21,4 ng/ml *vs* 10,34±6,45 ng/ml, p=0,00004). Stężenie MMP-9 wzrastało po zakończeniu zabiegu i pozostawało podwyższone do 48 godz. po CPB (odpowiednio 44,40±13,95 ng/ml *vs* 19,53±7,58 ng/ml, p=0,000004 i 38,97±10,76 ng/ml *vs* 19,53±7,58 ng/ml, p=0,00004). Wykazano dodatnią współzależność stężenia MMP-9 mierzonego po zakończeniu CPB i czasu trwania CPB (r=0,68, p=0,0045). Wykazano istotny statystycznie wzrost stężenia MMP-2 w osoczu krwi obwodowej dzieci 4 godz. po zakończeniu CPB (245,6±45,3 ng/ml *vs* 85,5±26,8 ng/ml, p=0,00032). Stężenie TIMP-1 uległo istotnemu obniżeniu 30 min po rozpoczęciu CPB i pozostawało obniżone po zakończeniu CPB (odpowiednio 52,68±17,72 ng/ml *vs* 83,29±17,06 ng/ml, p=0,000006 i 34,94±10,58 ng/ml *vs* 83,29±17,06 ng/ml, p=0,00004).

Wnioski: Zabieg kardiochirurgiczny powoduje wzrost stężeń cytokin zapalnych IL-6 i IL-8 w krwi obwodowej 4 godz. po jego zakończeniu. Bezpośrednio po zakończeniu zabiegu wzrasta stężenie przeciwzapalnej IL-10. W trakcie i po zabiegu z CPB u dzieci obserwuje się wzrost stężenia MMP-2 i MMP-9, z jednoczesnym spadkiem stężenia inhibitora TIMP-1. Wzrost stężenia MMP-9 i IL-6 u dzieci po zabiegu kardiochirurgicznym zależny jest od czasu trwania CPB.

Słowa kluczowe: krążenie pozaustrojowe, zabieg kardiochirurgiczny, wrodzona wada serca, cytokiny, metaloproteinazy

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