

Postoperative kinetics of common inflammatory biomarkers after congenital heart defect procedures with extracorporeal circulation in children

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Abstract

Background: Extracorporeal circulation is associated with systemic inflammatory response syndrome. Therefore, the diagnosis of infection should be differentiated from a typical postoperative course.

Aim: The aim of the study was to evaluate the kinetics of inflammatory biomarkers in children in the first days after cardiac surgery with extracorporeal circulation.

Methods: Prospective data were collected from 51 consecutive children referred for surgical treatment in Department of Paediatric Cardiac Surgery, St. Adalbertus Hospital in Gdańsk, between February and August 2015. Blood samples were collected on the first, second, and third postoperative days and sent to the institutional laboratory for routine investigations: white blood cell count, serum C-reactive protein (CRP) and procalcitonin concentrations.

Results: The highest levels of procalcitonin were on the first postoperative day (median 3.53 ng/mL), although the peak values of CRP concentration and white blood cell count were on the second postoperative day (96 mg/L and 17.3 G/L). In the group of patients with foreign material implantation (Contegra® or Gore-Tex®), the higher values of procalcitonin concentration and white blood cell count were measured in the subsequent postoperative days.

Conclusions: The kinetics of analysed inflammatory biomarkers on the first days after cardiac surgery for congenital heart disease in children have different characteristics. The knowledge about the kinetics of inflammatory biomarkers could be useful in determining the possibility of evolving infections in the early postoperative period.

Key words: procalcitonin, congenital heart defects, paediatric cardiac surgery, postoperative care, infections, diagnostics

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INTRODUCTION

Infections are a core problem in paediatrics, and are twice as serious in paediatric cardiac surgery. Rapid and reliable diagnosis of infection, whether viral or bacterial, is essential for appropriate treatment also in cardiac surgery. It is critical because uncontrolled infections may lead to sepsis with a high mortality

rate in patients who are in unstable circulatory condition or postoperative shock [1]. However, systemic inflammatory response syndrome (SIRS) is a nonspecific general inflammatory reaction of the organism to both infectious and non-infectious insults. The differentiation between non-inflammatory SIRS and infections caused by microbes is crucial in daily clinical practice.

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Currently used clinical markers of inflammation are white blood cell count (WBC) and leukocyte differentiation, C-reactive protein (CRP), procalcitonin (PCT), and interleukins (IL)-6 and IL-8 [2, 3]. Procalcitonin has gained the position of an early, most specific, and reliable marker of bacterial infection. The advantages of PCT over “traditional” markers are its specificities for bacterial infection vs. general inflammatory reaction of other origin, the rapidity of response after an insult (up to 6 h), and rapid decline with immune control of infection (half-life of 24 h). It is supposed also that PCT correlates with the severity of illness and that anti-inflammatory and immunosuppressive states do not impact its production [2–4].

Current antimicrobial politics needs very precise diagnostics with regard to an important clinical decision to expand or limit the use of antibiotics. The spread of multidrug-resistant pathogens is undoubtedly related to uncontrolled, and sometimes misused, antimicrobial chemotherapeutics worldwide. Therefore, there is a strong need to support the decision of empirical antibiotic therapies with biochemical inflammatory markers. The strategy of daily assessment of patients who are at potential risk of uncontrolled infections needs to be practically supported with new available parameters, which would provide more precise signals of septicemia, to support or exchange the analysis of PCT, CRP, and WBC [5, 6].

On the basis of institutional experience, we decided to perform a prospective single-centre study to evaluate the kinetics of common inflammatory biomarkers in the early postoperative course after extracorporeal circulation (ECC) in children who underwent cardiac surgical procedures for congenital heart defects in our department.

METHODS

Clinical data were collected prospectively from 51 consecutive paediatric patients referred for surgery to the Department of Paediatric Cardiac Surgery, St. Adalbertus Hospital in Gdańsk, Poland, between February and August 2015. All children who were referred for cardiac surgery with the use of ECC were carefully examined preoperatively. The patients referred for surgical procedures did not show any clinical or laboratory signs of infection. Routine preoperative chest X-ray examination, electrocardiogram, echocardiography, complete blood count, and biochemistry were performed in all children. All patients were routinely screened microbiologically at admission due to our individually-designed institutional practice [5]. The children who did not present laboratory features of organ dysfunction were consecutively enrolled in the study.

The main inclusion criteria comprised congenital heart defect; body weight over 3 kg, normalised clinical and laboratory parameters, and negative preoperative microbiological screening. The exclusion criteria were as follows: body weight under 3 kg, uncompensated hypothyroidism, clinically manifested acute infection, preoperative serum PCT value over 0.5 ng/mL and/or CRP value over 5 mg/L, leukocytosis,

perioperative steroid treatment, preoperative haemoglobin concentration under 10 g/dL, and early postoperative death due to reasons other than infection (< 3 postoperative days).

The surgery with ECC was performed under standard general anaesthesia. All patients enrolled in the study received a standard perioperative antibiotic prophylaxis (cefazolin) following the institutional scheme. Surgery was performed through median sternotomy with standard aortic and direct bicaval venous or single right atrial cannulations. A standard left atrial venting line was used. After heparin administration and when the activated clotting time was longer than 400 s the ECC was initiated. A nonpulsatile roller pump (Sorin S5™, Sorin Group Deutschland GmbH, Munich, Germany) equipped with a custom-made oxygenation and veno-arterial drain set was used. Systemic-to-pulmonary shunts were closed just after the initiation of the ECC, and previously implanted pulmonary artery bands were removed, if present. Deep or mild-to-moderate hypothermia (18°C vs. 28°C–32°C) during ECC, and cardiac arrest with standard single-dose antegrade cold crystalloid cardioplegia (Custodiol) were used. For deep hypothermia we adopted deep hypothermic circulatory arrest strategy, as routinely used. Haematocrit values were kept above 30% during the ECC in the rewarming period with continuous haemofiltration commenced in the circuit. For extensive repairs such as reconstruction of the right ventricular outflow tract obstruction we mainly used Contegra® xenograft (Medtronic, Minneapolis, MN, USA), and for ventricular septal defect (VSD) closure and extracardiac Fontan completion we used Gore-Tex® material (LM Gore and Assoc. Inc., Flagstaff, AZ, USA). No steroids were given routinely. The protocol of postoperative biochemical analysis was followed in every consecutive child referred for cardiac surgery in the presented timeframe, and the tests were performed in the institutional laboratory.

Blood samples were collected on the first, second, and third postoperative days (POD1, POD2, and POD3, respectively) as part of our routine investigations during the perioperative period, and were sent to the hospital laboratory. The samples were collected at the same time (6 a.m.) every day, as a part of the morning examination panel, without the need of any additional blood uptake. Classic blood count tests were performed for WBC. Serum CRP concentration was measured using turbidimetric immunoassay (Modular Roche A PB 06-76, Rotkreuz, Switzerland), whereas serum PCT concentration was measured by the immunoluminometric assay with the LUMI-test PCT (B.R.A.H.M.S Diagnostica GmbH, Hennigsdorf, Germany). Normal range of CRP and PCT serum concentrations were below 5 mg/L and 0.5 ng/mL, respectively. The data were simultaneously collected, while the analysis was performed after complete data collection.

For the purpose of further analysis the patients were divided into four groups and then matched as follows: patients who received foreign materials implanted for cardiac

Table 1. The measurements of inflammatory biomarkers in the early postoperative period in patients operated on without the need of foreign materials (classic surgery) versus patients with artificial (Gore-Tex®) and biological (Contegra®) materials

	Classic surgery/no foreign material used	Gore-Tex®/Contegra® implantation	p
Postoperative day 1			
PCT [ng/mL]	1.62 (3; 0.1–9.3)	4.68 (42.7; 0.12–198.7)	0.052
CRP [mg/L]	35 (20; 11–76)	44 (29.6; 2–113)	0.225
WBC [G/L]	11.1 (5.3; 8.9–29.5)	15.8 (5.3; 5.2–28.9)	0.017
Postoperative day 2			
PCT [ng/mL]	1.42 (2.3; 0.2–6.8)	4.5 (45.2; 0.1–198.8)	0.031
CRP [mg/L]	93.5 (56.4; 20–202)	104 (62.8; 7–267)	0.612
WBC [G/L]	14.3 (8.2; 10.7–36.7)	18.6 (7.7; 8.7–41.8)	0.037
Postoperative day 3			
PCT [ng/mL]	0.8 (1.1; 0.15–3.4)	3.26 (55; 0.3–271)	0.002
CRP [mg/L]	52 (38.4; 7–129)	62 (47.5; 3–235)	0.229
WBC [G/L]	11.9 (7.8; 6.8–36.9)	17.4 (7; 6.6–37.7)	0.01

Data are shown as median (standard deviation; range). CRP — C-reactive protein; PCT — procalcitonin; WBC — white blood cells

Table 2. The measurements of inflammatory biomarkers in the early postoperative period in patients operated on in the setting of deep hypothermia (18°C) versus patients who underwent congenital cardiothoracic procedures in mild/moderate hypothermia (28°C–32°C)

	Deep hypothermia (18°C)	Mild and moderate hypothermia (28°C–32°C)	p
Postoperative day 1			
PCT [ng/mL]	5.3 (4; 0.5–11.5)	3.3 (40; 0.1–198.7)	0.538
CRP [mg/L]	17 (20.4; 3–51)	43.5 (27.6; 12–113)	0.037
WBC [G/L]	12.4 (3.1; 10.1–18)	14.2 (5.7; 5.2–29.5)	0.511
Postoperative day 2			
PCT [ng/mL]	3.1 (12.3; 0.75–29.7)	2.9 (42.1; 0.1–198.8)	0.324
CRP [mg/L]	63 (69.3; 7–202)	108 (58; 50–267)	0.059
WBC [G/L]	16.7 (7.9; 13.4–36.7)	17.4 (8; 8.7–41.8)	0.883
Postoperative day 3			
PCT [ng/mL]	1.8 (9.7; 0.4–24.9)	2 (51; 0.2–271)	0.52
CRP [mg/L]	56 (41.7; 3–129)	68.5 (45.4; 18–235)	0.208
WBC [G/L]	14 (9.1; 10.3–36.9)	15.5 (7.2; 6.6–37.7)	0.862

Data are shown as median (standard deviation; range). Abbreviations — see Table 1

reconstructions vs. children operated on without the need of any foreign materials (data presented in Table 1), and children operated on by means of deep hypothermia vs. patients who underwent mild-to-moderate hypothermic ECC (data presented in Table 2).

Statistical analysis

Only the patients with complete data were enrolled in the study, and their data underwent further statistical analysis. For continuous variables the median with standard deviation (\pm SD)

and range was provided. Quantitative data were reported in terms of absolute frequencies and percentages. The data that did not follow normal distribution were analysed using the nonparametric Mann-Whitney U test. A significance level was set at $p < 0.05$. Statistical analysis was performed using SPSS v. 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In the group of 51 consecutive patients who were operated on in the described period and met the inclusion criteria, there

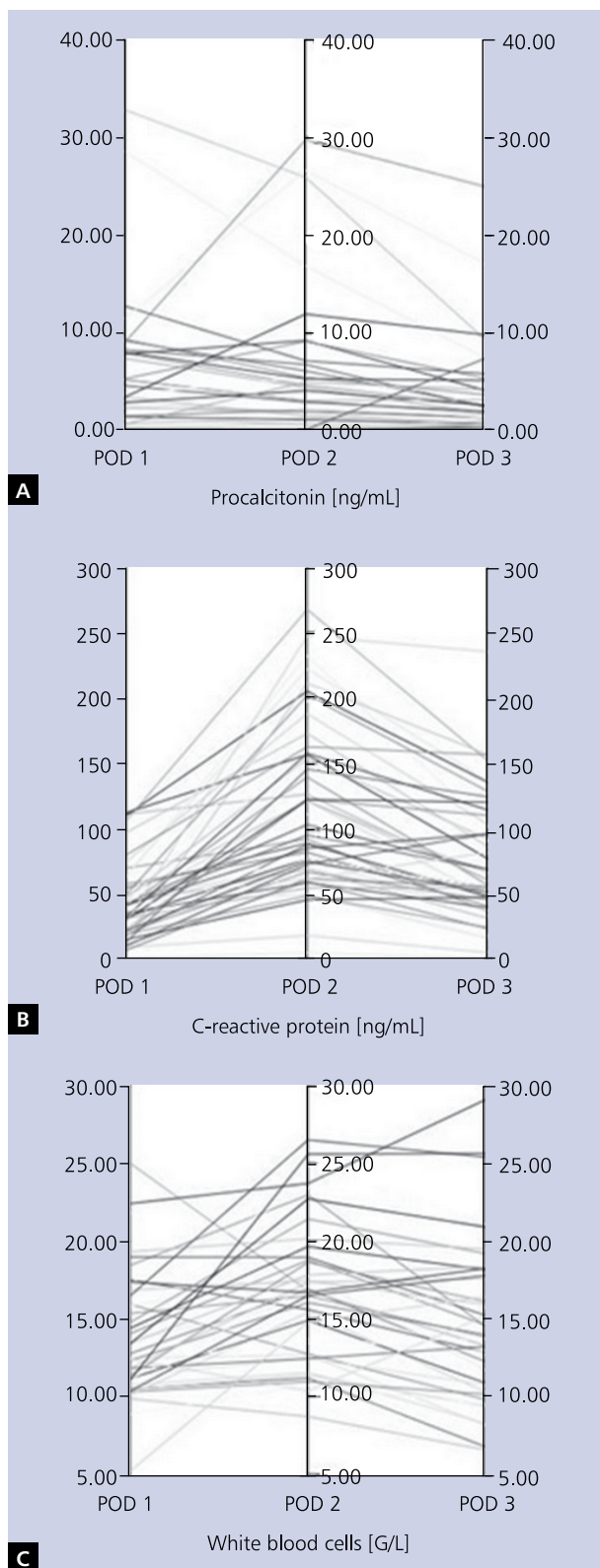


Figure 1. Kinetics of procalcitonin (A), C-reactive protein (B), and white blood cell count (C) in the early postoperative period after paediatric cardiac surgery with extracorporeal circulation (procalcitonin values of three patients are missing in this figure because the values were too high); POD — postoperative days

were 17 (33.3%) boys and 34 (66.7%) girls, with median age of 8.4 ± 22.1 months (min. 4 days; max. 9 years) and median weight of 6.3 ± 7.6 kg (min. 3 kg; max. 44 kg). The spectrum of surgery was as follows: 21 children had VSD closure, 12 had atrial septal defect (ASD) closure, five had total correction of tetralogy of Fallot (ToF), five had Fontan completion (extracardiac Fontan), three had correction of common atrioventricular septal defect (CAVSD), three had anatomical correction of transposition of the great arteries (TGA), and three had other surgery with ECC. There were 14 (27.5%) patients who had CRP and PCT monitoring after classic correction of congenital heart defect without implantation of foreign material and 37 (72.5%) patients with GoreTex® or Contegra® graft implantation, whereas seven (13.7%) patients were operated on in deep hypothermia and circulatory arrest. Elevated CRP and PCT values were observed almost in all children on the early postoperative days after the operation with ECC.

In all analysed patients after the operation with ECC the median PCT values (SD; min.; max.) were: 3.53 ng/mL (37.3; 0.12; 198.7), 2.99 ng/mL (39.3; 0.08; 198.8), and 1.85 ng/mL (47.5; 0.15; 271) on POD1, POD2, and POD3, respectively. The median CRP values (SD; min.; max.) were: 43 mg/L (27.7; 3; 113), 96 mg/L (60.8; 7; 267), and 62 mg/L (45.6; 3; 235) on POD1, POD2, and POD3, respectively. The median WBC values (SD; min.; max.) were: 14.05 G/L (5.4; 5.2; 29.5), 17.3 G/L (7.9; 8.7; 41.8), and 15.2 G/L (7.4; 6.6; 37.7) on POD1, POD2, and POD3, respectively. Kinetics of PCT, CRP, and WBC on POD1, POD2, and POD3 are presented in Figure 1.

In the majority of patients PCT values on POD2 were lower than on POD1 in 31 (62%) patients, while CRP values on POD2 were higher than on POD1 in 46 (8%) patients. In the majority of patients (68%) WBC reached maximal serum concentration on POD2. Median values for PCT, CRP, and WBC (with regard to the type of congenital heart defect correction and severity of hypothermia during ECC) on the first postoperative days are presented in Tables 1 and 2. There were no surgical site infections observed in any of the children during the entire hospital stay (Fig. 1).

DISCUSSION

There are no definitive guidelines to provide proper antibiotic prophylaxis in children undergoing cardiac surgery, especially with relation to ECC [7, 8]. There are many reasons why discussions about limiting antibiotic use and the duration of prophylaxis in paediatric cardiac surgery still have not led to precise guidelines, even though several publications encourage cardiothoracic centres to consider a change [9].

Systemic inflammatory response syndrome, a typical reaction to ECC, is traditionally observed as the potential starting point of sepsis. There are many other conditions that result in severe activation of SIRS; stress-related deep hypothermic circulatory arrest is one of them. Intraoperative

factors promoting SIRS are mainly related to the interaction of blood components with the artificial surfaces of the heart-lung machine, as well as with surgical trauma and reperfusion injury. With regard to the high mortality in sepsis, the early diagnosis and treatment of SIRS can significantly improve the prognosis [10].

On the other hand, the overuse of antibiotics may lead to development of multidrug-resistant microorganisms, and unnecessary increases in the cost of treatment and treatment toxicity. The accurate differentiation of clinically relevant infection after cardiac surgery with use of ECC remains crucial; however, diagnostic cut-off values for PCT, CRP, and PCT for patients in the early postoperative period after surgery with the use of ECC are not established [11]. Our results suggest that clinicians should not concentrate so strongly on single values of inflammatory markers, but follow value changes and their trends in the early postoperative hours. Dissimilarity from typical kinetics of PCT, CRP, and WBC, together with the patient's clinical status, should be an alarm for extended diagnosis to define the onset of infection.

Our daily practice in children referred for surgery with ECC is based on a very strict antibiotic policy with a short period of perioperative routine antibiotic prophylaxis. Intravenous antibiotic prophylaxis administration lasts up to 48 h after every cardiac surgical procedure. Therefore, we sought to find the utility of various biomarkers that could be helpful in differentiation between patients at high risk of postoperative infections, and those in whom classically analysed inflammatory parameters indicate a process (SIRS) secondary to non-infectious reasons.

It is well known that PCT is useful in guiding antibiotic treatment and may help to avoid delayed or unnecessary antimicrobial therapy [12]. In adults after cardiovascular surgery, PCT-guided antibiotic treatment may be safe and cost-effective in postoperative care [13]. Studies confirm that PCT is a reliable serum marker for determining the presence or absence of invasive bacterial infection, as well as for monitoring the response to empirical antibiotic therapy [14, 15]. Moreover, antibiotic chemotherapy tailored to serial PCT measurements may shorten the antibiotic exposure without increasing the risk of treatment failure [15]. However, poor correlation between elevated PCT level and bacterial infections in adult patients after cardiac surgery with ECC has been described [16, 17]. In the paediatric population elevated PCT levels in the early postoperative period after cardiac surgery with the use of ECC were evaluated previously and were regarded as markers of increased risk for major adverse events and postoperative renal failure more potent than of infection [18, 19]. Nevertheless, there is no doubt that elevated levels of common inflammatory biomarkers increased postoperative morbidity in previous studies [20].

The influence of operative factors on PCT levels in children treated surgically in ECC has not been fully established.

Sponholz et al. [21] reviewed 34 publications and concluded that in children PCT levels were increased in ToF patients compared with patients with VSD or CAVSD, and after surgery in ECC below 22°C vs. above 22°C [21]. Also, Hövels-Gürich et al. [22] concluded that in infants with preoperative hypoxaemia PCT on POD1 was significantly higher than in patients with intracardiac left-to-right shunt (i.e. without hypoxaemia) [22]. We did not find any publication that compares children treated surgically in ECC with and without different materials implanted according to inflammatory reaction. We found that patients with Gore-Tex® or Contegra® implantation had higher inflammatory biomarkers on POD1, POD2, and POD3 than those without such an implantation; however, we did not observe any differences regarding the level of hypothermia during ECC.

There are several limitations to be mentioned regarding this study. The presented report is a prospective, single-centre observational study of a small group of children referred for cardiosurgical operation in ECC without randomisation. Although the antibiotic prophylaxis algorithm was homogenous during the observation period (with regard to institutional politics of perioperative prophylaxis), the range of operative trauma might differ in selected groups of patients. Therefore, the differences in values of PCT, CRP, and WBC in the early postoperative period may exist, although we observed reproductive characteristics of biomarker trends. In addition, particular operative strategies at our institution, as well as postoperative care of paediatric patients after cardiac surgery with ECC, may differ from other centres. Further studies on the matter are needed.

The presented single-centre prospective study was performed according to the guidelines of the Ethic Examining Committee of Human Research at the Medical University of Gdańsk, Poland (Approval: NKBBN 178/2012 dated 14th May 2012).

In conclusion, repeated measurements of the serum levels of PCT, CRP, and WBC in children after cardiac surgery with ECC with careful observations of their kinetics could be useful in determining the possibility of evolving infections in the early postoperative period and may guide empirical antibiotics.

Conflict of interest: none declared

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