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Cytokine Response in Children Undergoing Surgery for Congenital Heart Disease

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Abstract Pediatric cardiac surgery with cardiopulmonary bypass (CPB) induces a complex inflammatory response that may cause multiorgan dysfunction. The objective of this study was to measure postoperative cytokine production and correlate the magnitude of this response with intraoperative variables and postoperative outcomes. Serum samples from 20 children (median age, 15 months) undergoing cardiac surgery with CPB were obtained preoperatively and on postoperative days (POD) 1–3. Serum levels of interleukin (IL)-6, IL-8, and IL-10 increased significantly on POD 1 ($p < 0.01$) vs pre-op values to 271 ± 68, 44 ± 9, 7.5 ± 0.8 pg/ml, respectively, whereas serum IL-1β, IL-12, and tumor neurosis factor -α were not significantly changed. The serum IL-6 and IL-8 levels correlated positively ($p < 0.01$) with the degree of postoperative medical intervention as measured by the Therapeutic Interventional Scoring System and indicated a greater need for inotropic support ($p = 0.057$). A negative correlation ($p < 0.01$) between IL-6, IL-8, and mixed venous oxygen saturation suggested compromised cardiopulmonary function. Patients with single ventricle anatomy had the highest levels of IL-6 and IL-8 (629 ± 131 and 70 ± 17 pg/ml, respectively), with a mean CPB time of 106 ± 23 minutes. Thus, the proinflammatory response after surgery with CPB was associated with postoperative morbidity with increased need for medical intervention.

Keywords Cytokines · Interleukin · Cardiopulmonary bypass · TISS · Inotropes

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Introduction

Pediatric patients who undergo heart surgery involving cardiopulmonary bypass (CPB) are at risk of developing inflammatory complications that can result in multisystem organ dysfunction [5, 6, 7]. Several factors can trigger the postoperative systemic inflammatory response including surgical trauma, ischemia–reperfusion injury, endotoxemia, and activation of leukocytes by artificial surfaces, [20, 33]. This inflammatory process involves the activation of lymphocytes, monocytes/macrophages, endothelial cells, and cardiac myocytes that can express and secrete many proinflammatory cytokines, including tumor necrosis factor (TNF-α), interleukins (IL-1 , IL-6, and IL-8), as well as antiinflammatory cytokines IL-4, IL-10, and transforming growth factor (TGF-β) [14, 16, 17, 29, 34]. These biologically active factors have been implicated in the complications after cardiac surgery, including pulmonary dysfunction, depressed cardiac contractile activity and impaired hypothalamic–pituitary–thyroid axis [9–11, 13, 26, 31].

Global myocardial ischemia followed by reperfusion injury may result during surgery involving CPB with aortic

cross-clamping. Jansen and colleagues reported that TNF-α could be detected after release of the aortic cross-clamp, and that the duration of aortic cross-lamp was an independent predictor of postoperative serum TNF-α and IL-6 levels [21]. Furthermore, myocardial production and release of biologically active TNF-α and IL-8 may be involved in the postischemic myocardial depression or ''stunning'' after CPB [4, 11, 22, 27, 34). Complement activation and cytokine production have also been reported in cardiac surgery performed without the aid of cardiopulmonary bypass [32].

The antiinflammatory cytokine IL-10 is also released during CPB and has been shown to either directly inhibit the release of proinflammatory cytokines [12, 14] or exert antiinflammatory effects by triggering the release of IL-1 receptor antagonist and TNF soluble receptors 1 and 2 [25].

Several therapeutic strategies have been proposed that aim to modulate the inflammatory response in this clinical setting, including hemofiltration [2, 30], use of steroids and nonsteroidal antiinflammatory agents [3, 15, 24], and complement receptor blocking agents [8]. Ultrafiltration procedures have been widely adopted and shown to be effective in attenuating the inflammatory response, resulting in improved postoperative hemodynamics, decreased duration of mechanical ventilator support, and decreased length of stay in intensive care unit [2, 30]. Treatment of adults undergoing heart surgery with cardiopulmonary bypass with methylprednisolone has yielded promising results showing reduced production of proinflammatory cytokines, TNF-α, IL-6, and IL-8 and increased IL-10 [24, 32]. However, administration of steroids to pediatric patients undergoing CPB has not been shown to suppress the inflammatory reaction, nor has it improved postoperative outcome measures [15]. Thus, novel therapeutic targets and approaches are still necessary to minimize the systemic inflammatory response in children undergoing cardiac surgery.

The objective of this study was to measure the cytokine response in the postoperative period and correlate these results with intraoperative variables and postoperative outcomes.

Materials and Methods

The study protocol was approved by the institute's committee on human rights in research. Informed consent was obtained from either parent(s) or guardian(s) before the operation, and patients older than 7 years of age gave consent. Twenty children of either gender younger than age 18 years who were subject to surgical correction of congenital heart defects with CPB were recruited into the study. The median age, gender, and specific anatomic defects of these patients are listed in Table 1.

Surgery and Anesthesia

Operations were performed by one cardiothoracic surgeon, and conventional general anesthesia was used in all patients. Endotracheal intubation and placement of central venous and arterial catheters were performed after induction of anesthesia. Antibiotic prophylaxis was given at the induction of anesthesia and at the end of the surgical procedure. Heparinization was achieved with heparin sulfate, and its effect was reversed using protamine sulfate. Aprotinin was administered to all patients, performed with aortic and venous cannulation, membrane oxygenation, and nonpulsatile flow. Similar techniques to maintain hematocrit and pH were used in all patients. If necessary at the end of the surgical procedure intracardiac catheters (left and right atria) were placed for postoperative care. Patients received standard care in the postoperative period in the pediatric intensive care unit. Corticosteroids were not administered.

Postoperative Management and Measures of Clinical Outcome

Patients were continuously monitored in the intensive care unit. Data on clinical outcomes, including quantities of vasodilator and inotropic drugs, blood gas and lactate analyses, urine output, blood pressures, cardiac rhythm, and heart rates, were recorded daily. Mixed venous oxygen saturation (MV_{Sat}) (%) of blood samples obtained from the superior vena cava or pulmonary artery (when accessible) was determined by standard blood gas analysis. The degree of inotropic support required was calculated as described by Wernovsky et al. [35]. The overall degree of postoperative care was analyzed by calculating the Therapeutic Interventional Scoring System (TISS). TISS scores were derived daily for 76 different therapeutic and monitoring procedures and reflected the invasiveness, intensity, and complexity of care rendered to the patient.

Cytokine Analysis

Blood samples for cytokine analysis were collected after induction of anesthesia and before institution of CPB, and on postoperative days (POD) 1–3. One milliliter of blood was collected in a heparinized tube and the serum separated by centrifugation (5000*g* for 10 minutes at 4°C) and stored at −20°C until analyzed.

TNF-α and IL-1β, IL-12, IL-6, IL-8, and IL-10 were measured by means of two commercially available kits, the Human Th1/Th2 and Human Inflammatory Cytokine Bead Array (BD Biosciences Pharmingen, San Jose, CA, USA). The Cytokine Bead Array system generates data that are comparable to enzyme-linked immunosorbant assays but in

a ''multiplexed'' or simultaneous fashion employing a series of particles with discrete fluorescence intensities to simultaneously detect multiple soluble analytes. The concentration of unknowns is calculated for the cytometric bead array through the use of known standards and plotting unknowns against a standard curve.

Statistical Analysis

Results are expressed as median (ranges) or mean ± SE. Analysis of the data at different time points was performed using one-way repeated measures analysis of variance (ANOVA) and pairwise multiple comparison procedures by the Holm–Sidak method. Strength of association between cytokines and clinical measures were assessed by Pearson product moment correlation test. A p value < 0.05 was considered significant. Data were analyzed using SigmaStat statistical software, version 3.1 (Systat Software, Richmond, CA, USA).

Results

Table 1 shows the types of congenital heart disease and the number in each category. The median age was 15 months (range 0.1–180), with equal gender distribution. The mean duration of CPB was 106 ± 44 minutes (n = 20 patients), and the mean aortic cross-clamp time was 69 ± 40 minutes (n = 18 patients). Postoperative outcome measures are listed as median values and ranges. The TISS and inotropic score for each patient represent the sum of the scores on POD 1–3. MV_{sat} (%) and blood lactate (mmol/L) levels are those measured on POD 1.

Inflammatory Response to CPB

Figure 1 shows the serum levels of proinflammatory cytokines IL-6 and IL-8 and the inflammatory cytokine IL-10 following corrective heart surgery. Concentrations of all three cytokines were significantly elevated on POD 1 compared to their preoperative values. POD 1 serum IL-6 and IL-8 values were 271 ± 68 and 44 ± 9 pg/ml (mean ± SE), respectively, compared with preoperative values of 46 ± 12 and 16 ± 2 pg/ml, respectively. All three cytokines declined on POD 2 and 3 and were not significantly different from their preoperative values. Serum IL-6 levels correlated positively with IL-8, with a statistically significant ($p < 0.001$) correlation coefficient (r^2) of 0.7742. Intraoperative variables, including cardiopulmonary bypass time and aortic cross-clamp time, did not significantly correlate with the maximum postoperative serum IL-6 and IL-8 response (data not shown).

Table 1 Patient characteristics and intra- and postoperative parameters

Patients (n)	20
Age (months)[a]	15 (0.1–180)
Gender	Female (45%) Male (55%)
Anatomical defect (n)	
Tetralogy of Fallot	5
Singled ventricle	4
Endocardial cushion defect	4
Ventricular septal defect	2
Transposition of the great arteries	2
Others (ASD, RHD, Ebstein's)	3
Intraoperative data[a]	
CPB time (minutes) (n = 20)	91 (42–212)
Cross-clamp time (minutes) (n = 18)	54 (22–156)
Postoperative outcomes[a]	
Intensive care unit stay (days)	5 (2–90)
Mechanical ventilation (days)	2 (0–90)
Hospital stay (days)	8 (3–90)
TISS (cumulative POC 1–3)	125 (48–188)
Inotropic score (cumulative POD 1–3)	10.5 (0–63)
MV_{sat}, % (POD 1)	69 (34–78)
Lactate, mmol/L (POD 1)	2.1 (1.1–8.1)

ASD, atrial septal defect; RHD, rheumatic heart disease; POD, postoperative day; TISS, Therapeutic Interventional Scoring System; MV_{sat}, mixed venous oxygen saturation

[a] Data are median (range)

Patients with single ventricle anatomy had the highest serum IL-6 and IL-8 levels on POD 1, with mean ± SE values of 629 ± 131 and 70 ± 17, respectively, and a mean CPB time of 106 ± 23 minutes. Six of eight cyanotic patients had maximum serum IL-6 values > 100 pg/ml, whereas only 3 of 12 noncyanotic patients had these high values.

Table 2 summarizes the serum concentrations of TNF-α, IL-1β, and IL-12 measured pre- and post-CBP. Although serum TNF-α and IL-12 increased by POD2 these increases did not reach statistical significance.

Correlations of Clinical Outcomes with Cytokine Responses

The postoperative outcomes that were examined are listed in Table 1. No significant correlation was found between the maximum cytokine (IL-6, and IL-8 on POD 1) response and total time in the intensive care unit, length of hospital stay, and days of mechanical ventilation. However, serum IL-8 concentrations on POD 1 correlated negatively with MV_{sat}, an indicator of decreased oxygen delivery to the peripheral tissue, and positively with cumulative TISS scores on POD 1–3. These correlations reached a level of significance of $p = 0.009$, as shown in Fig. 2. Higher IL-8 levels also correlated with higher inotropic scores on POD 1 ($p = 0.057$), whereas no correlation was found with blood lactate values (Table 3). Similar correlations were found between the maximum serum IL-6 response and these clinical outcome measures, as shown in Table 3.

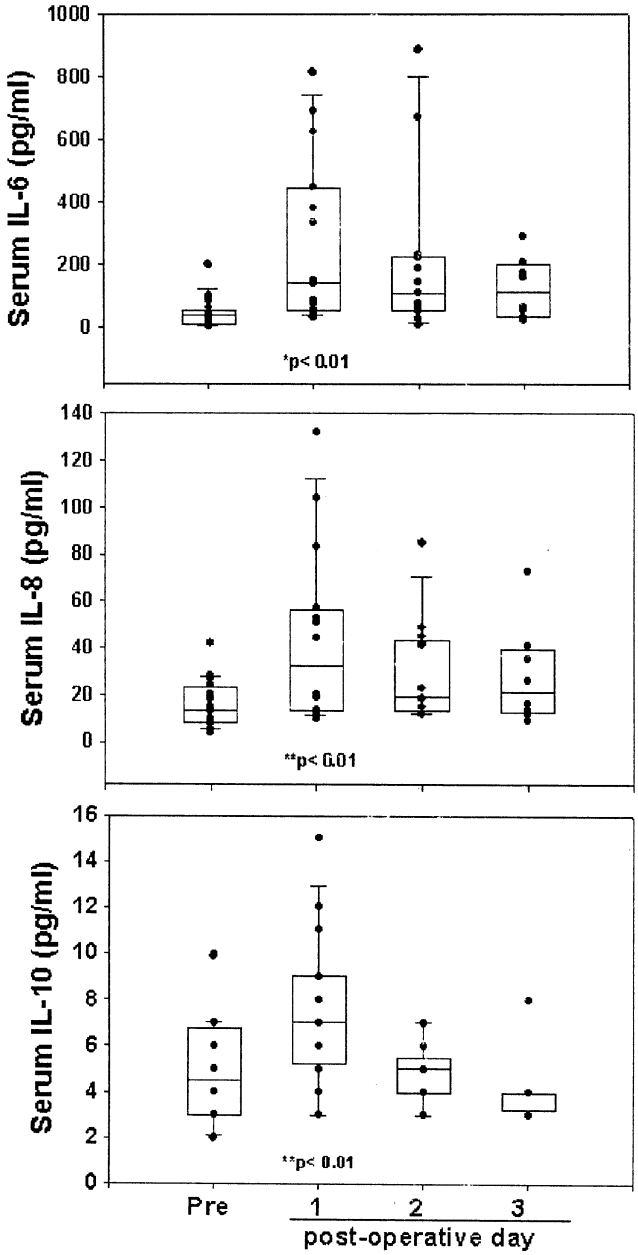

Fig. 1 Systemic inflammatory response after CPB. Serum concentrations of IL-6, IL-8, and IL-10 were measured preoperatively and on postoperative day (POD) 1–3. Twenty patients underwent cardiopulmonary bypass surgery; $n = 20$ on pre- and POD 1, $n = 13$ on POD 2 and $n = 8$ on POD3. The horizontal line is the median value; the box encompasses 25th to 75th percentiles, and caps represent 10 and 90%. *$p < 0.01$ vs preoperative value; **$p < 0.01$ vs mean values at all other time points. Statistical significance was determined by repeated measures ANOVA with pairwise multiple comparison procedure (Holm–Sidak method)

Table 2 Cytokine response in the postoperative period[a]

	TNF-α (pg/ml)	IL-1β (pg/ml)	IL-12 (pg/ml)
Pre-CPB ($n = 20$)	1.9 ± 2.1	189 ± 168	106 ± 142
POD 1 ($n = 18$)	1.6 ± 1.6	121 ± 119	89 ± 124
POD 2 ($n = 13$)	3.4 ± 5.9	191 ± 163	157 ± 189
POD 3 ($n = 8$)	1.1 ± 1.4	130 ± 167	86 ± 160

[a] Serum concentrations of TNF-α, IL-1β, and IL-12 taken pre- and postsurgery (mean ± standard deviation). Values are not significantly different among POD 1–3

POD, postoperative day

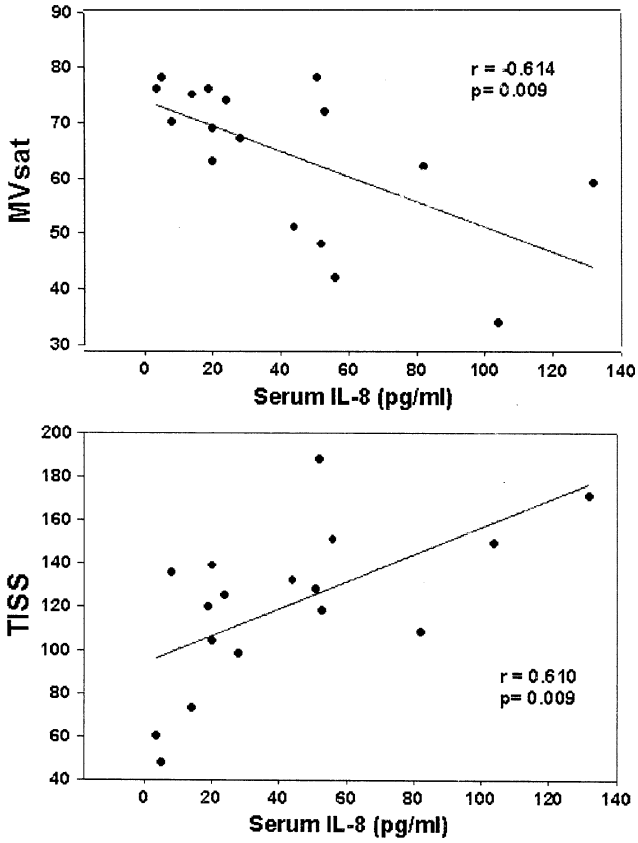

Fig. 2 Cytokine response correlates with postoperative outcomes. On postoperative day (*POD*) 1, patient mixed venous oxygen saturation (MV_{sat}, %) values show significant negative correlation with serum IL-8 levels ($p < 0.009$). Cumulative TISS scores from POD 1–3 correlate significantly with serum IL-8 levels ($p < 0.009$). The line represents the best fit linear regression curve. Significance of the correlation coefficient was determined by ANOVA

Discussion

In this study, we showed a significant positive correlation between the magnitude of the inflammatory response as measured by serum concentrations of IL-6 and IL-8 after CPB surgery and the degree of medical intervention (TISS and inotropic score) of the pediatric patient in the early postoperative period. Higher TISS scores with a greater proinflammatory response reflected an increase in postoperative management requirements. Similarly, the need for inotropic support was greater in patients with higher postoperative serurn IL-8 levels. MV_{sat} was 34–78% on POD 1, and these values correlated negatively

Table 3 Linear regression analysis between cytokine production and postoperative outcomes

	Postoperative outcome measurement			
	TISS[a]	Inotropic scores[a]	MV_{sat}[b]	Blood lactate[b]
IL-8				
r	0.610	0.470	−0.614	0.010
p[c]	0.009	0.057	0.009	0.969
IL-6				
r	0.513	0.291	−0.575	0.084
p[c]	0.035	0.257	0.016	0.748

TISS, Therapeutic Interventional Scoring System; MV_{sat}, mixed venous oxygen saturation

[a] cumulative score for postoperative days 1–3

[b] Value on postoperative day 1

[c] determined by Pearson correlation test

with serum IL-8 concentrations, further supporting the hypothesis that the magnitude of the inflammatory response has a direct effect on oxygen delivery to the peripheral tissues and postoperative morbidity of the pediatric patient. This inflammatory response was observed despite the routine use of modified ultrafiltration procedures and aprotinin in our surgical practice to reduce circulating cytokines and complement factors, and to increase hemoglobin, hematocrit, and platelet levels, as has been reported by others [2, 18, 28, 30]. Our data support a recent study showing significant correlations of postoperative serum IL-6 and IL-8 with increased inotropic requirements and reduced arterial oxygen tension (PaO_2) 2 hours after CPB [16]. In addition, these authors found that the cytokine response correlated positively with length of mechanical ventilation post-surgery which we did not observe. In contrast to other studies [20], we did not find a correlation between postoperative serum cytokines and the duration of CPB or aortic cross-clamp, possibly due to the diverse nature of the surgical procedures. However, we did observe higher serum proinflammatory cytokines postoperatively in six of eight cyanotic patients in whom the duration of CPB was > 90 minutes. Furthermore, all patients with single ventricle anatomy had the highest levels of IL-6 and IL-8 (629 ± 131 and 70 ± 17 pg/ml, respectively), with a mean CPB time of 106 ± 23 minutes. One patient (with double ventricle anatomy) with bronchomalacia had the highest postoperative serum IL-6 and IL-8 concentrations (888 and 132 pg/ml, respectively), with a CPB time of 145 minutes and a complex postoperative course. Taken together, these data support the hypothesis that the duration of CPB, the complexity of anatomical defect and surgical repair, and the presence of cyanosis are contributing factors to the postoperative inflammatory response.

Results from a recent study that tested the efficacy of corticosteroid treatment to reduce the inflammatory response in pediatric cardiac surgery patients were negative, with no effect on postoperative recovery [15]. Steroid pretreatment remains controversial because steroids may inhibit TNF-α, IL-6, and IL-8 production, thus preventing peripheral vasodilatation, but they may also increase the release of endotoxin [1, 3]. Thus, the search for novel therapeutic targets is warranted in this clinical setting. The identification of other mediators of inflammation, including macrophage migration inhibitory factor and HMGB1 (high mobility group box-1 protein), as well as a focus on pulmonary-derived cytokines may provide another strategy in the treatment of postoperative inflammation in the heart surgery patient [10, 23]. Since pulmonary injury and multiorgan dysfunction remain significant complications following cardiac surgery, continued efforts to identify the mediators of these effects are required to potentially reduce postoperative morbidity in the pediatric patient.

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