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Tissue Injury and the Inflammatory Response to Pediatric Cardiac Surgery with Cardiopulmonary Bypass

A Descriptive Study

Michelle S. Chew, M.B.B.S., Ph.D., Ivan Brandslund, M.D., D.M.Sc.,† Vibeke Brix-Christensen, M.D.,‡ Hanne B. Ravn, M.D., Ph.D.,§ Vibeke E. Hjortdal, M.D., D.M.Sc.,‖ Jens Pedersen, M.D.,# Kirsten Hjortholm, M.D.,# Ole K. Hansen, M.D.,** Else Tønnesen, M.D., D.M.Sc.††*

Background: **There are few detailed descriptions of the inflammatory response to cardiac surgery with cardiopulmonary bypass (CPB) in children beyond 24 h postoperatively. This is especially true for the antiinflammatory cytokines and the extent of tissue injury. The aim of the current study was to describe the inflammatory and injury responses in uncomplicated pediatric cardiac surgery with CPB, where methylprednisolone and modified ultrafiltration (MUF) were used.**

Methods: **Blood samples were collected up to 48 h postoperatively. Cytokines (tumor necrosis factor-α and interleukin-6, -1β, -10, and -1ra), complement (C3d and C4d) and coagulation system (prothrombin activation fragments 1 and 2 and antithrombin III) activation, neutrophil elastase, and the resulting tissue injury (creatine kinase, lactate dehydrogenase, alanine transaminase, amylase, and γ-glutamyl transferase) were measured.**

Results: **The proinflammatory cytokine release varied widely, in contrast to a clear-cut antiinflammatory response. Cytokine concentrations did not decrease immediately after MUF, and no rebound increases later in the postoperative period were observed. The coagulation system, but not complement, was activated. There was a late release of C-reactive protein. Tissue injury could be quantified biochemically without evidence of hepatic or pancreatic dysfunction.**

Conclusion: **In this group of uncomplicated subjects, the antiinflammatory cytokine and tissue injury responses were well defined, in contrast to a variable proinflammatory cytokine release. This was accompanied by activation of the coagulation system but not of complement. Concentrations of inflammatory mediators did not decrease immediately after MUF, and there was no evidence for rebound release later in the postoperative period.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

CARDIAC surgery with cardiopulmonary bypass (CPB) evokes a systemic inflammatory response that, in uncomplicated cases, is a temporary event representing a physiologic reaction to tissue injury. When the systemic inflammatory response is exaggerated, the postoperative course may be complicated by organ dysfunction.

Cytokines are believed to be important mediators in the systemic response to cardiac surgery and CPB. The most important cytokines in this regard are interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, and IL-8, which are detectable in peripheral blood in the immediate postoperative period. The proinflammatory cytokines are balanced by an almost simultaneous antiinflammatory cytokine release consisting of IL-10, interleukin 1 receptor antagonist (IL-1ra), and TNF soluble receptors (TNFsr).[1] In contrast to adults, the cytokine response in infants and children seems to be less clear.[2–4] Increased concentrations of proinflammatory cytokines have been demonstrated preoperatively,[3–6] whereas others demonstrate very low or undetectable concentrations perioperatively.[2,7] In addition, the cytokine response in children beyond 24 h postoperatively has been described in only a few studies.

The balance between the proinflammatory and antiinflammatory response is thought to be critical in determining the extent tissue injury and clinical outcome.[1,6,8,9] Most studies, however, have concentrated on the proinflammatory cytokines and their modulation as a means of affecting tissue injury and clinical outcome. We believe that the antiinflammatory cytokine response is a critical part of the inflammatory network; therefore, documentation of its release in the pediatric population could be important for our understanding of clinical outcome. Furthermore, although increased concentrations of inflammatory mediators are often taken to be surrogate markers of tissue injury, few studies actually address the measurement of tissue injury on a biochemical level or the connection between the two.

Modified ultrafiltration (MUF) is capable of removing excess extracellular fluid as well as some inflammatory mediators[3,7] and is thought to be responsible for improved clinical outcome after pediatric cardiac surgery,[10–12] although the evidence for this is not clear.[2–5,7,13–16] It remains to be clarified if cytokines can

* Research Fellow and Resident-in-Training, ‡ Research Fellow, § Senior Registrar, # Consultant in Pediatric Cardiothoracic Anesthesia, †† Professor, Department of Anesthesia & Intensive Care, ‖ Senior Registrar, ** Consultant in Pediatric Cardiothoracic Surgery, Department of Cardiothoracic Surgery, Aarhus University Hospital. † Consultant and Administrative Head, Department of Clinical Biochemistry Vejle County Central Hospital, Vejle, Denmark.

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Address reprint requests to Dr. Chew: Institute of Experimental Clinical Research, Aarhus University Hospital (Skejby), 8200 Aarhus N, Denmark. Address electronic mail to: mchew@iekf.au.dk. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

be removed using MUF and whether it entails a rebound release later in the postoperative period.

The effects of steroids on the inflammatory response after CPB is controversial. Some studies suggest that the administration of systemic steroids decreases cytokine concentrations with beneficial effects on postoperative outcome,[6,17] whereas others demonstrate high cytokine concentrations despite their use.[13] Therefore, whether addition of systemic steroids is actually associated with a modulation of cytokine concentrations, with concurrent use of MUF, remains to be documented.

The aim of the current study, therefore, was to describe the proinflammatory and antiinflammatory cytokine responses, neutrophil degranulation, and complement and coagulation system activation in infants undergoing cardiac surgery and CPB with MUF where methylprednisolone was added to the prime solution. The cytokine response was measured as plasma concentrations of IL-6, IL-1β, IL-10, IL-1ra, and TNF-α; neutrophil degranulation as plasma concentrations of elastase; complement activation as plasma concentrations of the split products C3d and C4d; and coagulation system activation as plasma concentrations of prothrombin activation fragments 1 and 2 (F1+2) and antithrombin III (ATIII) activity. C-reactive protein (CRP) was also measured as a general indicator of inflammatory activity. Furthermore, we aimed to characterize the tissue injury that occurs during and after CPB using the traditional biochemical markers alanine transaminase (ALT), amylase, creatine kinase (CK), lactate dehydrogenase (LDH), and γ-glutamyl transferase (γ-GT). The concentrations of these markers of inflammation and injury were measured preoperatively, perioperatively, and up to 48 h postoperatively.

Materials and Methods

Patient Population

The study was approved by the Regional Scientific Ethical Committee (Den Videnskabsetiske Komite for Arhus Amt, Aarhus, Denmark), and written informed consent was obtained from the parents of all patients. Thirteen consecutive children aged less than 12 months who were undergoing uncomplicated surgical repairs of congenital cardiac defects were enrolled in the study (table 1).

Table 1. Demographic Data of the Study Population

Age (months)	Weight (kg)	Clamp Time (min)	CPB Time (min)	Diagnosis
9	7.8	43	80	VSD
10	10	25	52	VSD
1	3.6	53	130	ASDsec, VSD, coarc
3	3.9	67	104	AVSD
5	5.3	90	137	ASDsec, VSD
7	6.7	57	99	ASD, VSD
6	4.6	39	86	TOF
0	3.0	88	160	TGA, ASD
10	7.2	24	49	VSD
8	5.7	13	40	ASD
6	7.9	57	112	TOF
7	8.4	0	79	VSD, pulm atresia
8	8.9	58	91	TOF

CPB = cardiopulmonary bypass; VSD = ventricular septal defect; ASD_{sec} = artrial septal defect; AVSD = atrioventricular septal defect; TOF = tetralogy of Fallot; TGA = transposition of the great arteries; pulm = pulmonary.

Anesthesia

Anesthesia was induced by inhaled halothane or ketamine (5 mg/kg intramuscularly or 2 mg/kg intravenously). Anesthesia and analgesia were maintained with an infusion of fentanyl (100 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and pancuronium was given for muscular paralysis. All children received 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine from the beginning of rewarming. In addition, 6–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine was administered in arterial-switch operations.

Cardiopulmonary Bypass Technique

A roller pump (Polystan, Vaerlose, Denmark) and Membrane Oxygenator (Masterflo Lilliput 901 or 902; Dideco, Mirandola Modena, Italy) were used in all cases. The circuit was primed with Ringer's lactate, fresh whole blood, and 20% human albumin. At the beginning of CPB, 1 mg/kg furosemide and 30 mg/kg methylprednisolone were added to the prime, and 0.5 g/kg mannitol was added during rewarming. Temperature during cooling was decreased to 18–32°C depending on the surgical procedure. Full flow was defined as $2.4 \cdot m^{-2} \cdot min^{-1}$.

Modified ultrafiltration was performed after cessation of CPB according to the method described by Naik and Elliott[10] using a filter (Diafilter 20; Amicon Ireland Ltd., Limerick, Ireland). The roller pump was used to accelerate blood flow through the filter (rate, 100–200 ml/min) with suction (−25 mmHg) applied to maximize the transmembrane pressure gradient. The end point for MUF was defined as a hematocrit of 38% or no more blood in the bypass circuit.

Sampling

Blood was drawn into vacutainers containing EDTA for the measurement of cytokines (IL-6, IL-1β, IL-1ra, TNF-α), neutrophil elastase, complement split products (C3d, C4d), and CRP. For measurement of coagulation system activation (F1+2 and ATIII), vacutainers containing sodium citrate were used, and heparin vacutainers were used for the measurement of tissue injury markers (ALT, γ-GT, amylase, CK, and LDH). Sampling times for elastase, complement split products, coagulation system markers, and tissue injury markers were at baseline (immediately after induction of anesthesia), before CPB,

before rewarming, after CPB, after MUF, and 3, 6, 12, 24, and 48 h postoperatively. For the cytokines, samples were obtained at baseline, after CPB, after MUF, and 6, 12, 24, and 48 h postoperatively.

Assay Techniques

All samples were immediately spun at 3,000 rpm for 10 min and their supernatants stored at −70°C until analysis. Results of the post-CPB samples were corrected for hemodilution.

Interleukin-6, IL-1β, and IL-10 were analyzed by a double sandwich enzyme-linked immunoassay (ELISA) technique using commercially available kits according to the manufacturer's instructions. The limits of detection for these cytokines were 15, 10, and 30 pg/ml, respectively. TNF-α and IL-1ra were measured by a double sandwich ELISA using monospecific polyclonal rabbit antibodies to purified recombinant cytokines. The assays were calibrated with international standards of the respective cytokines (National Institute for Biological Standards and Controls, Potters Bar, Hertfordshire, United Kingdom). The sensitivity limits of these ELISAs were 8–30 pg/ml.

Complement split products (C3d and C4d) were analyzed using rocket immunoelectrophoresis with commercially available antibodies (DAKO, Glostrup, Denmark), as previously described.[18,19] Plasma elastase was determined using a commercially available kit using a homogeneous immunoassay (Ecoline, Diagnostica Merck, Darmstadt, Germany), as previously described by Antonsen *et al.*[19]

Analysis of prothrombin fragments F1+2 was performed using a commercially available enzyme immunoassay (Enzygnost, Behringwerke AG, Marburg, Germany) according to the manufacturer's instructions. This is an ELISA-based method with a polyclonal antibody.

C-reactive protein was quantified using immunoturbimetry with a Hitachi 717 analyzer with antibodies (cat. no. 67128; Orion Diagnostica, Trosa, Sweden). The accuracy of the measurements were checked with the international reference preparation for immunochemical measurements, BCR/CAP/AFCC CRM 470 (Commission of the European Communities, Bruxelles, Belgium).

Alanine transaminase, amylase and γ-GT were analyzed using commercially available enzymatic reagent kits from Boehringer Mannheim/Roche (Basel, Switzerland). CK and LDH were analyzed using enzymatic reagent kits (Merck, Damstadt, Germany, and Rolf Greiner BioChemica, Flacht, Germany, respectively). All tests were conducted in accordance to the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

Clinical End Points

Calculation of arterial oxygen partial pressure (Pa_{O_2})/fraction of inspired oxygen (F_{IO_2}) was based on the results of arterial blood gas analysis (Radiometer, Copenhagen, Denmark). Blood pressure was measured invasively in the radial or femoral artery.

Table 2. Clinical Data of the Study Population Showing Postoperative Oxygenation (Pa_{O_2}/F_{IO_2}) and Mean Blood Pressure 3, 12, and 24 h Postoperatively, and the Total Transfusion Requirement at 24 h

	3 h	12 h	24 h
Pa_{O_2}/F_{IO_2}	310 ± 139	356 ± 115	360 ± 117
Mean BP (mmHg)	64 ± 12	70 ± 13	69 ± 8
Transfusion requirement (ml/kg)			8.3 ± 7.3

Pa_{O_2} = arterial oxygen partial pressure; F_{IO_2} = fraction of inspired oxygen; BP = blood pressure.

Statistical Analysis

All results are expressed as mean ± SD for normally distributed data, or median (interquartile range) for nonparametric data. Normality was tested for using the Kolmogorov-Smirnoff test. Concentrations of the measured proteins at different time points were compared using one-way repeated-measures analysis of variance (on ranks for nonparametric data). If the analysis of variance was significant, a multiple comparison procedure was used to isolate the group or groups that differed from others. For this we used the Dunn method (for nonparametric data) or the Tukey test (for parametric data). The association between two variables was tested by calculating the product moment correlation coefficient (r) for parametric data and the Spearman rank correlation coefficient (ρ) for nonparametric data. $P < 0.05$ was considered significant. Multiple regression analysis was used to test for the relation between one outcome and several predictor variables.

Results

Demographic data of the study group are shown in table 1. The average clamp and CPB times were 47.2 ± 26.9 and 93.8 ± 35.5 minutes, respectively. The blood transfusion requirement at 24 h postoperatively, Pa_{O_2}/F_{IO_2}, and mean blood pressure at 3, 12, and 24 h postoperatively are shown in table 2.

Cytokines (n = 13)

Interleukin-1β and TNF-α concentrations were high preoperatively and remained so throughout the study period, with no differences with respect to sampling time. IL-6 concentrations increased significantly compared with baseline concentrations ($P < 0.001$), peaking at 48 h postoperatively at 12.5 (4–30) pg/ml (fig. 1).

Interleukin-10 was also detectable preoperatively and increased markedly after CPB to peak after MUF (211 [93–424] pg/ml; $P = 0.003$). After the sixth postopera-

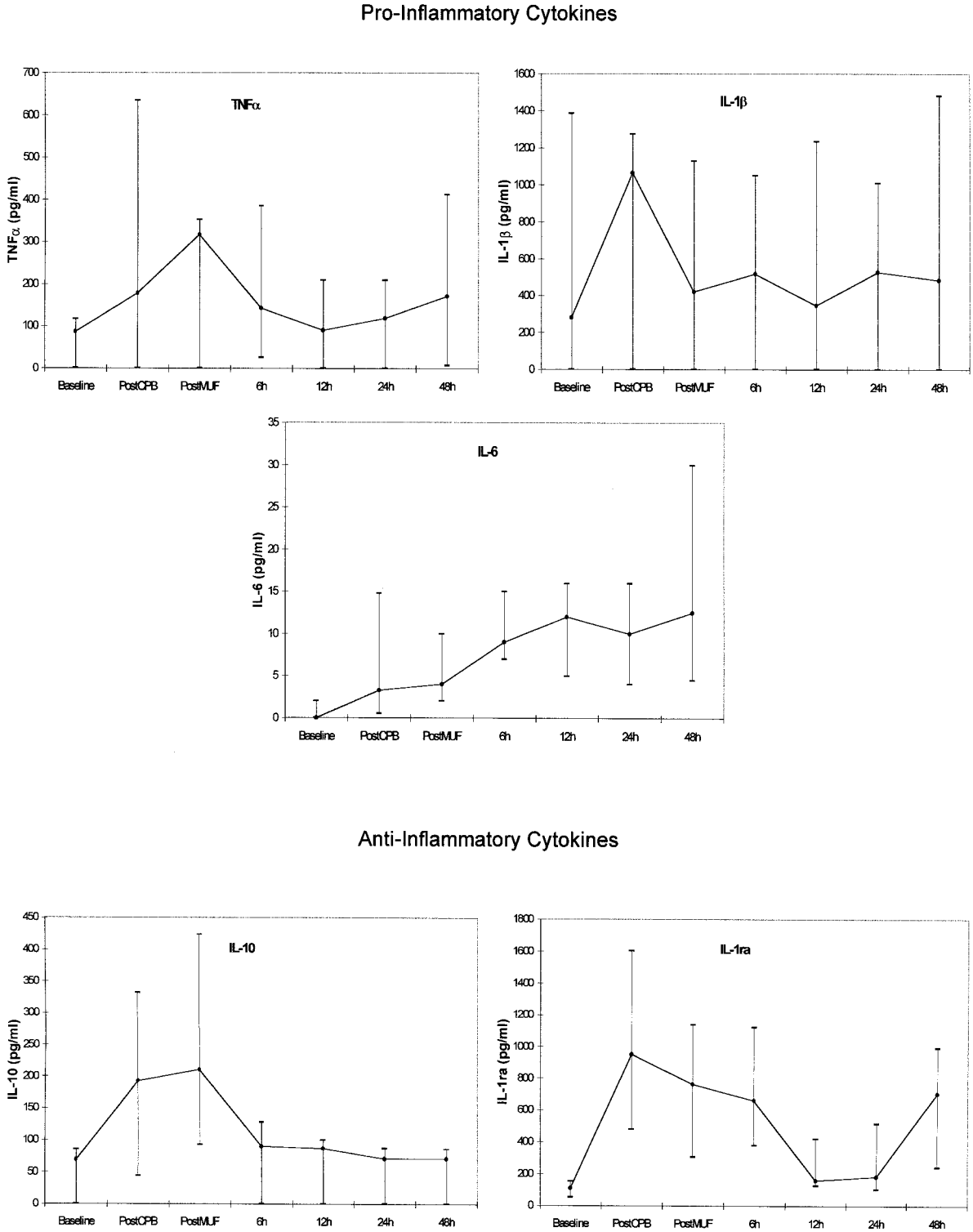

Fig. 1. Proinflammatory and antiinflammatory cytokine responses. TNF = tumor necrosis factor; IL = interleukin; CPB = cardiopulmonary bypass; MUF = modified ultrafiltration.

tive hour, plasma concentrations of IL-10 were not significantly different to baseline values. Similarly IL-1ra was detectable preoperatively and increased sharply after CPB (950 [479–1603] pg/ml). Thereafter they returned to baseline concentrations then increased again after 48 h ($P < 0.001$; fig. 1).

C-reactive Protein (n = 8)

C-reactive protein concentrations increased postoperatively with significant differences from baseline detected from the 12th postoperative hour onward ($P < 0.001$). CRP concentrations were still increased at 48 h (41 [22.5–56.0] pg/ml; fig. 2).

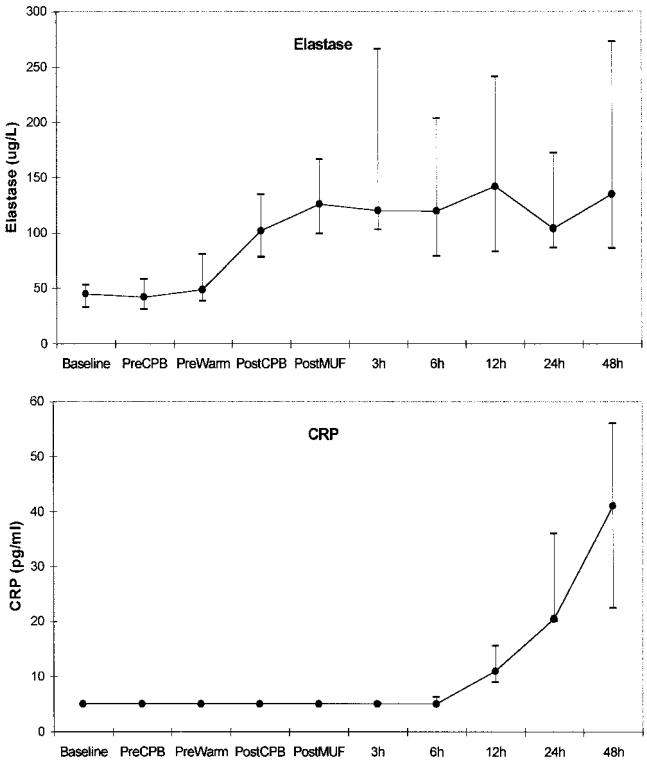

Fig. 2. Other markers of inflammation. CPB = cardiopulmonary bypass; MUF = modified ultrafiltration; CRP = C-reactive protein.

Elastase (n = 13)

Elastase increased after CPB and remained increased ($P < 0.001$) throughout the investigational period, with a maximal concentration at 12 h postoperatively (142 [83–241] μg/l; fig. 2).

Coagulation System Activation (n = 13)

Prothrombin activation fragments 1 and 2 increased markedly and already after CPB reaching its peak here (7.09 [4.16–8.619] nmol/l) and remaining elevated up to 6 h postoperatively ($P < 0.001$). There were no significant differences compared with baseline after this sampling point.

Antithrombin III concentrations decreased significantly perioperatively ($P < 0.001$) but recovered to baseline values 3 h postoperatively and thereafter (fig. 3).

Complement Activation

C3d and C4d concentrations did not differ significantly compared with baseline (fig. 3).

Tissue Injury (n = 8)

Creatine kinase was significantly increased compared with baseline from after CPB and up to 24 h postoperatively ($P < 0.001$). Peak concentrations occurred at 6 h postoperatively (1,672 [1,230–2,391] U/l) then decreased back toward baseline values (normal range, 40–240 U/l[20]). Similarly, LDH concentrations also increased early ($P < 0.001$), with significant differences at 6 h and thereafter compared with baseline. Peak concentrations occurred at 6 h (1,162 [841–1,416] U/l) and did not return to baseline values even at 48 h postoperatively (normal range, 210–420 U/l[20]). Mean concentrations of ALT were all within normal range (0–35 U/l[20]), although there were significant differences ($P < 0.001$) between the samples. Concentrations increased steadily postoperatively to reach a peak at 48 h (34.0 ± 13.5 U/l). There were no differences between the samples of γ-GT. Serum amylase concentrations (normal range, 8–85 U/l[20]) also increased steadily postoperatively ($P < 0.001$), reaching peak concentrations at 24 h (42.5 ± 16.9 U/l; fig. 4).

Discussion

Cytokine Response

This study supports earlier findings that infants do show a cytokine response to CPB and cardiac surgery.[2–4,21] However, the profile of inflammatory cytokines (IL-1β, IL-6, TNF-α) varied widely, in contrast to the adult case. The proinflammatory cytokines in this study, with the exception of IL-6, do not demonstrate significant increases caused by CPB. This may be because of large interindividual variations, in keeping with previous studies.[2,21] IL-6 increased significantly after surgery and remained elevated even 48 h postoperatively, but was detected in considerably lower concentrations than those described previously.[2,4,21] It is interesting to note that IL-1β was detected at high concentrations preoperatively and, to a lesser extent, so was TNF-α. We note that this has also been a finding in other studies[3,6] and have no plausible explanation for this phenomenon, except that abnormal circulating concentrations of cytokines may be a reflection of the preexisting hemodynamic dysregulation. The very high concentrations of IL-1β measured in our study are in contrast to previous findings, where this cytokine is normally not detectable or only found in small amounts.[2,7] One may further speculate whether the lack of a clear increase in IL-1β and TNF-α concentrations were caused by a "preactivated state" in which a definitive response was prevented.

In contrast, the antiinflammatory cytokine profile was characterized by a clear pattern of release into peripheral blood, with IL-1ra and IL-10 increasing markedly after CPB and MUF. This well-defined antiinflammatory cytokine response is similar to that found by McBride *et al.*[8] and Gilliland *et al.*,[14] and presumably counterbalances the proinflammatory cytokines. The fact that both IL-10 and IL-1ra were detectable in low concentrations preoperatively may be a reflection of ongoing proinflam-

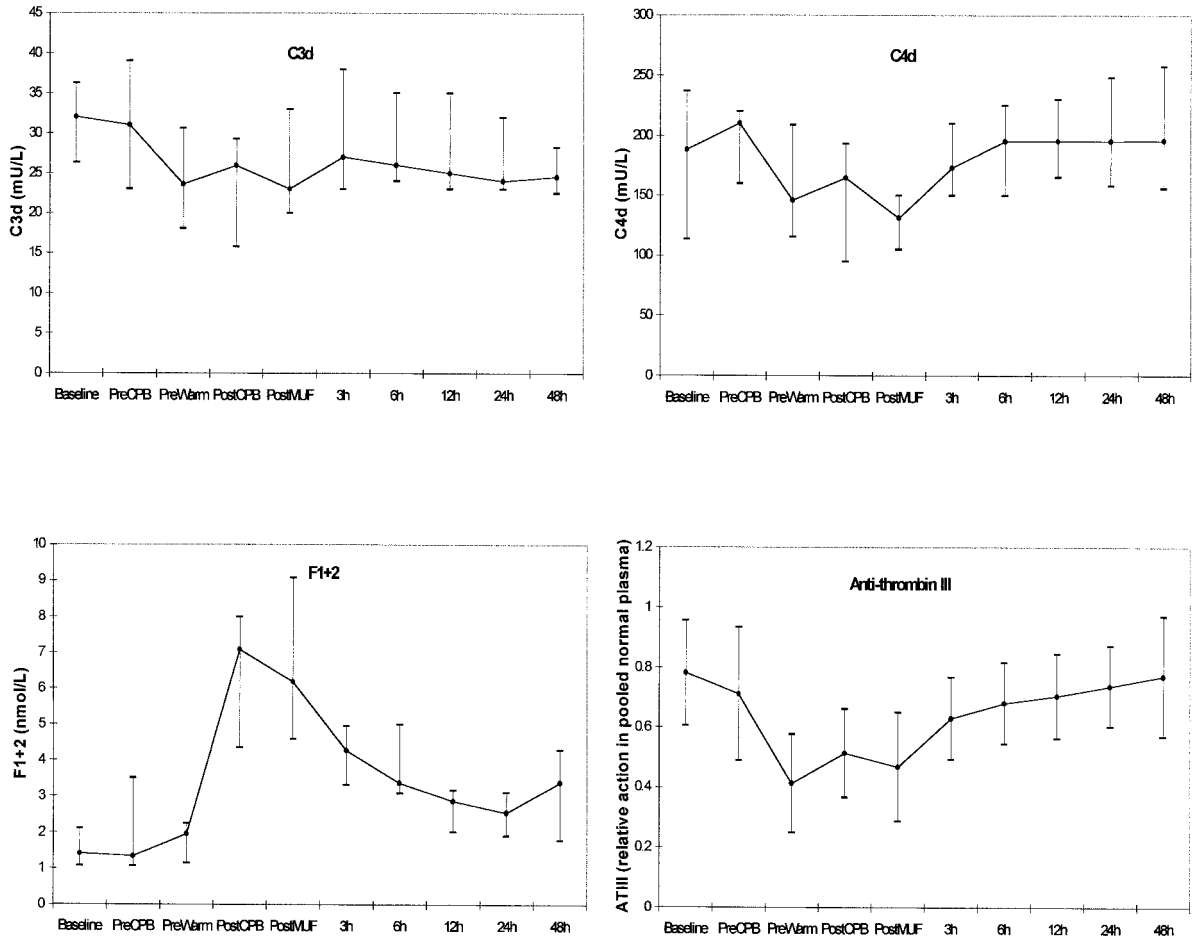

Fig. 3. Complement and coagulation. CPB = cardiopulmonary bypass; MUF = modified ultrafiltration; F1+2 = prothrombin fragments 1 and 2.

matory stimuli. However, because their concentrations are reasonably low at this sampling point, one may speculate that the elevated concentrations of IL-1β preoperatively is of fairly recent origin, in so far as the antiinflammatory response would not have had enough time to develop.

Although MUF is thought to be capable of filtering out cytokines, we found that both the proinflammatory and antiinflammatory cytokines in this study either increased or remained at the same concentration after MUF. This raises the question of whether MUF actually filters out cytokines or in itself induces cytokine release. However, there was no evidence of a rebound response later in the postoperative period.

C-reactive Protein

This study demonstrated a late but very significant increase of CRP with increased concentrations even 48 h postoperatively. This is in keeping with previous studies,[22,23] in which late peaks in CRP were demonstrated. This occurred despite uneventful surgery and recovery and may be important to bear in mind when considering antibiotic therapy because of presumed infection on the basis of increasing CRP.

Elastase

Plasma elastase increased significantly compared with baseline at the post-CPB sample and remained so for the rest of the sampling period, with a peak at 12 h postoperatively. Because the first significant increase was detected at the post-CPB sample (*i.e.*, after rewarming), and assuming no lag time between neutrophil degranulation and the appearance of elastase in peripheral blood, this may be taken to indicate that the rewarming phase itself was responsible for neutrophil degranulation. Alternatively, reperfusion of elastase-containing tissue may be an explanation. High concentrations of the enzyme persisted even after 2 days postoperatively. Although plasma elastase concentrations in our study were somewhat lower than those of previous studies, the results are generally in agreement.[4,21,24] Since neutrophil degranulation is thought to contribute to lung injury, we tested the relation between peak elastase and oxygenation index (data not shown), but no correlation was found

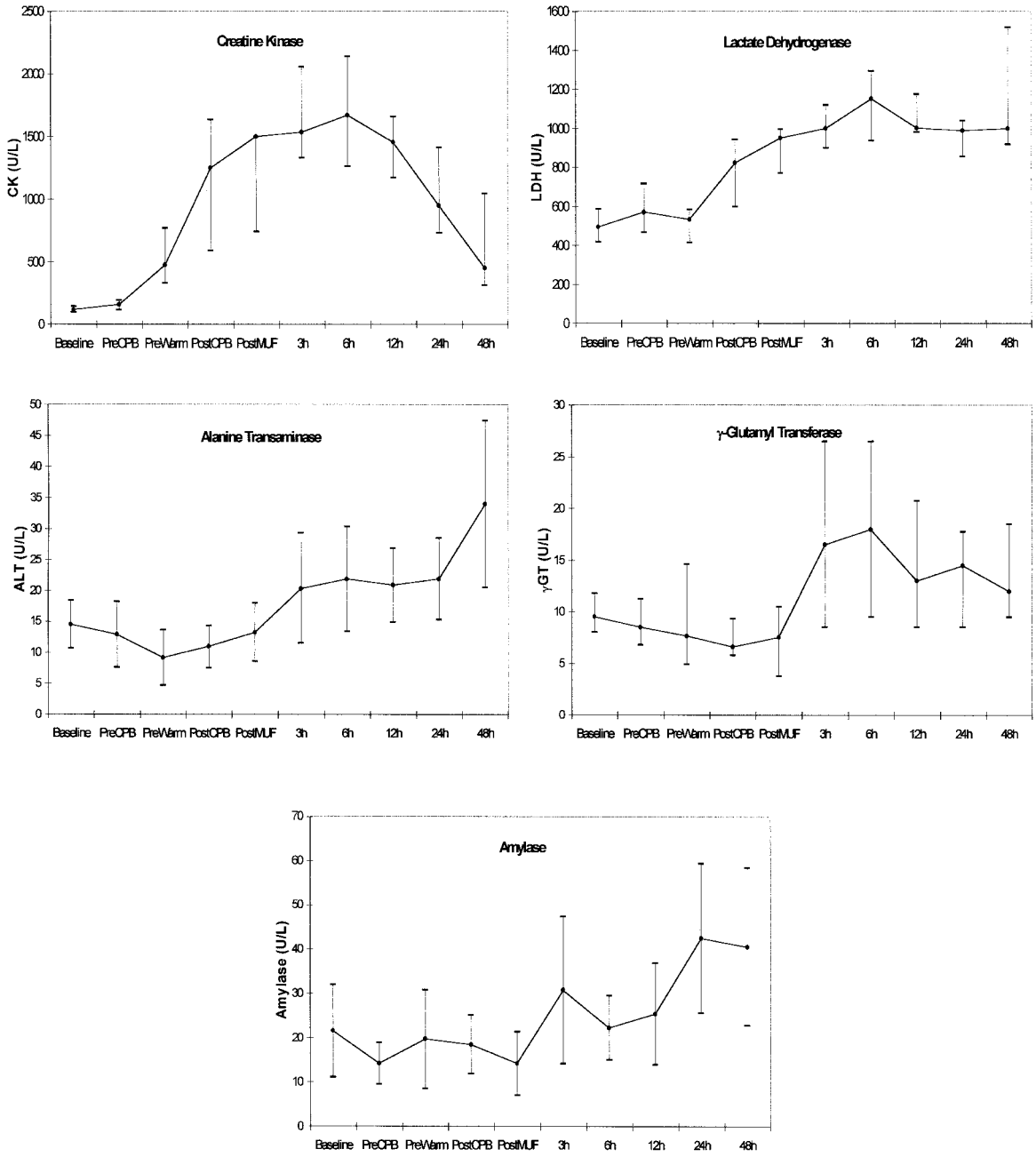

Fig. 4. Tissue injury. CK = creatine kinase; LDH = lactate dehydrogenase; ALT = alanine transaminase; γ-GT = γ-glutamyl transferase; CPB = cardiopulmonary bypass; MUF = modified ultrafiltration.

between the two variables, a finding also reported by Butler *et al.*[23]

Complement Activation

We could not demonstrate complement activation in this study with C3d and C4d concentrations within the normal range, in contrast to previous findings.[5,21,24] This may be because of difficulties in assessing complement activation, which is often complicated by the production of split products that share the same antigenic determinants as the native component (C3d and C3).[18] Increased concentrations of complement split products may be increased because of insufficient precipitation by polyethylene glycol separation methods before measurement of C3d epitopes. Although it is uncommonly used, we chose to measure C3d because it is a more specific assay, is ideally located at the junction of the classical and alternative pathways, and has a reasonably long half-life (4 h). In addition, the quantification of C4d can then elucidate if complement activation has proceeded by the classical or alternative pathway. Another possible explanation for the lack of complement activation in our

study could be that all patients underwent relatively uncomplicated surgery and did not suffer postoperative multiorgan failure.

Activation of the Coagulation System

Activation of the coagulation system is thought to increase the risk of postoperative bleeding and the need for transfusion after CPB.[16] We reaffirm previous findings[15,16] of an intense activation of the coagulation cascade, seen by an increase in the concentrations of prothrombin fragments F1+2. The increase from baseline was significant after CPB and up to 6 h postoperatively, thereafter returning toward baseline. There was a simultaneous decrease in antithrombin III (ATIII) concentrations. This was a transient effect with recovery to baseline concentrations after 3 h postoperatively. In addition, *post hoc* analyses show that samples taken before MUF (after CPB) did not differ significantly from those taken after MUF, in line with previous findings.[15]

Tissue Injury

Tissue injury can be quantified biochemically, using indices such as plasma CK, LDH, ALT, γ-GT, and amylase. Of these enzymes, only CK and LDH increased to concentrations much higher than the normal range. CK and LDH may originate from the myocardium, skeletal muscle, and the gastrointestinal tract. In the present setting, enzyme release from the myocardium may be a consequence of surgery or CPB itself; however, it is not possible to estimate the contribution from the two procedures individually. The pattern of LDH production mirrors that of CK, although it is not as marked and does not return to baseline concentrations even 48 h postoperatively. This may reflect the longer circulating half-life of the latter enzyme. The persistence of increased concentrations of these two markers indicate ongoing tissue injury and are in keeping with increasing CRP concentrations, even in the absence of a well-defined proinflammatory cytokine response.

There were significant increases in concentrations of ALT and amylase. We note, however, that the concentrations of ALT, γ-GT, and amylase were within the normal range for all sampling points, suggesting the preservation of pancreatic and hepatic function.

Cytokine concentrations are thought to be directly related to tissue injury and clinical outcome. This is most likely to be a complex relation and is supported by the lack of correlation between the peak cytokine concentrations and clinical outcome–tissue injury (data not shown). In contrast, clamp and perfusion times were consistently correlated with peak concentrations of CK and LDH as well as postoperative oxygenation (Pao_2/Fio_2; data not shown), indicating the relevance of exposure in this setting.

Limitations of the Study

This study was largely designed to be descriptive and therefore cannot clarify the mechanisms of postoperative organ dysfunction. Because the study was nonrandomized, no conclusions can be made regarding the effect of MUF or systemic steroids on the post-CPB inflammatory response. Not all cytokines were measured, notably IL-8, a major inducer of neutrophil chemotaxis. Although the measurement of plasma concentrations of cytokines in peripheral blood is relatively uncomplicated, it may not be truly indicative of the inflammatory response, being instead the "tip of the iceberg," with spillover to the circulation only after a critical concentration within each organ is exceeded. Furthermore, there may be a lag time between actual inflammation and the appearance of its markers in peripheral blood. The same is true for the markers of tissue injury; therefore, a detailed look at these processes at organ level would provide further insights into the mechanism of injury. We were also unable to quantify injury to other key organs, such as the lungs, kidneys, and brain.

When comparing our data with earlier studies in which MUF was not used, we generally found lower IL-6 concentrations,[13,21,25] higher TNF-α and IL-β concentrations,[2,4,5] and similar IL-1ra and IL-10 concentrations.[6,8] No definitive conclusions can be drawn from the few randomized studies of MUF during pediatric cardiac surgery. Journois *et al.*[2] showed that zero-balanced ultrafiltration significantly reduced plasma concentrations of TNF-α, IL-10, IL-6, IL-8, C3a, and myeloperoxidase in pediatric patients undergoing cardiac surgery with CPB. This occurred in parallel with significant reductions in postoperative blood loss and time to extubation, implying that the removal of inflammatory mediators was responsible for the improvement in clinical outcome. Interestingly, there was a concurrent suppression of the production of the antiinflammatory cytokine IL-10 in the zero-balanced ultrafiltration group. In another pediatric study, removal of IL-8 and endothelin using MUF was associated with a decreased need for transfusion; however, time to extubation and the length of stay in the intensive care unit were not significantly different from a control group.[3] Although MUF is thought to improve clinical outcome, its mechanism of action remains unclear; therefore, a randomized study of MUF is a relevant future investigation.

The addition of steroids in the prime solution is not common practice but is part of the standard protocol at our hospital for children weighing 10 kg or less. The effect of steroids on the inflammatory response after CPB is controversial. It has been shown that the administration of 1 mg/kg dexamethasone during induction delays the appearance of increased cytokine concentrations and decreases the peak in pediatric patients.[6] Furthermore, Bronicki *et al.*[17] demonstrated that 1 mg/kg intravenous dexamethasone given before CPB decreases con-

centrations of TNF-α and complement with an associated improvement in oxygenation postoperatively. In a study by Hauser *et al.*,[13] in which methylprednisolone was added to the CPB circuit, peak IL-6 concentrations occurred earlier and at higher concentrations than in our study. The concentration of IL-6 in the study by Hauser *et al.*[13] is also much higher than that demonstrated in other studies in which no steroids were given.[6,21] The fact that IL-6 concentrations were detected only in low concentrations in our study, compared with other studies in which systemic steroids were not given,[2,4] may be interpreted as a suppressive effect; however, this is not supported by our findings of higher TNF-α, IL-1β, and IL-10 concentrations. Therefore, whether addition of systemic steroids is actually associated with a modulation of cytokine concentrations and whether it is associated with improved clinical outcome cannot be deduced from our study and remains to be investigated.

In conclusion, this study demonstrates that neonates and infants were capable of mounting a cytokine response to CPB and cardiac surgery. However, this response was far from clear cut. Proinflammatory cytokines were found already at baseline and did not increase significantly in response to surgery or CPB, with large variations in plasma concentrations throughout the sampling period. In contrast, the antiinflammatory cytokine profile was much more defined, with peak concentrations occurring immediately after CPB and then decreasing toward baseline values early in the postoperative course. There was no rebound cytokine production later in the postoperative course. Neutrophil degranulation, reflected by plasma elastase, also occurred early and persisted even 3 days after surgery. CRP concentrations increased later postoperatively, reaching peak concentrations 48 h postoperatively. We could not demonstrate complement activation in this study, although there was an intense activation of the coagulation cascade, begetting the question of whether the latter, in combination with cytokine release and neutrophil activation, may be the more important mechanisms of injury. Tissue injury could be quantified biochemically and was accompanied by increases in CK and LDH concentrations. The liver and pancreas did not appear to be injured in this group of patients with uncomplicated surgical and postoperative courses. These results underscore the complexity of the inflammatory process associated with cardiac surgery and CPB in a pediatric setting.

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