Influence of Two Different Perfusion Systems on Inflammatory Response in Pediatric Heart Surgery

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Background. **This study tests the hypothesis that a cardiopulmonary bypass system that combines complete heparin-coating, a centrifugal pump, and a closed circuit in comparison with a conventional system (uncoated system, roller pump, and hard shell venous reservoir) attenuates the inflammatory response in pediatric heart surgery.**

Methods. **In a prospective randomized controlled clinical study 40 consecutive children weighing 10 kg or less were included and divided into two groups. Concentrations of complement proteins (C3a, sC5b-9, C4d, and Bb), granulocyte degranulation products (polymorphonuclear [PMN] elastase), and proinflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-6, and IL-8) were measured.**

Results. **C3a and sC5b-9 concentrations were lower (C3a, $p < 0.001$; sC5b-9, $p = 0.01$) in the combined (heparin-coated/centrifugal pump/closed reservoir) group, the peak values being 58% and 37% of conventional group values. The Bb- and C4d-fragment values indicated activation of the complement system through the alternative pathway in both groups. PMN elastase concentrations were lower ($p = 0.02$) in the combined group, the peak values being 43% of conventional group values. There were no significant intergroup differences regarding TNF-α, IL-6, or IL-8 concentrations.**

Conclusions. **The use of a fully heparin-coated system, a centrifugal pump, and a closed circuit during CPB in children (10 kg or less) leads to a lower degree of complement activation and PMN elastase release compared with a conventional system.**

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Open heart surgery with cardiopulmonary bypass (CPB) induces activation of a systemic inflammatory response [1-3]. The underlying causes are surgical trauma, blood exposure to foreign surfaces, ischemia/reperfusion injury, mechanical shear stress, hemodilution, and hypothermia. The complement and coagulation systems are activated and cytokine production stimulated, which may lead to neutrophil activation with degranulation, platelet activation, endothelial dysfunction and cellular entrapment in organs. Concentrations in blood of complement factors and cytokines reflect the magnitude of the inflammatory response and are related to clinical outcome in pediatric heart surgery [4].

In this paper we address the role of the cardiopulmonary bypass system. Its role may be amplified in pediatric surgery owing to the relatively larger blood-artificial surface interface [3]. Efforts have been made previously to improve various aspects of the CPB system. In this study we have included three components, each of which when tested individually has been shown in previous studies to improve biocompatibility [5–12]. The combination of a fully heparin-coated system, a centrifugal pump, and a closed reservoir may have a potentially additive effect in preventing or attenuating the inflammatory response superior to the individual effect of each component of the CPB circuit involved.

The aims of the present study were to determine the inflammatory response detected as plasma concentrations of complement factors, proinflammatory cytokines, and products of granulocyte degranulation in small children (10 kg or less) using the combination of a fully heparin-coated system, a centrifugal pump, and a closed circuit and to compare it with a conventional CPB system.

Patients and Methods

Patients

Inclusion criteria were congenital heart defects, body weight 10 kg or less, an estimated perfusion time exceeding 60 minutes, and a target cooling temperature of 28°C or less. Patients with Down's syndrome were excluded from the study as they have higher plasma concentrations of interleukin (IL)-6 after CPB than other children with congenital heart disease [4]. Forty consecutive children fulfilling the inclusion criteria were included in this prospective study (Table 1).

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Table 1. Demographic and Surgical Data From the Preoperative and Perioperative Periods

	Group HC (n = 19)		Group C (n = 21)		
	Number or Mean ± SEM	Range	Number or Mean ± SEM	Range	*p* Value
Gender (male/female)	11/8		10/11		0.55
Age (months)	4.9 ± 1.0	0–16	5.5 ± 0.8	0–12	0.62
Weight (kg)	5.8 ± 0.5	3.6–10.0	5.6 ± 0.4	2.6–8.9	0.74
Preop. oxygenation saturation (%)	92 ± 1.2	80–97	92 ± 1.5	68–97	1.0
Anomaly					
VSD	7 (1 redo)		7 (two redos)		
VSD + PS	1		1		
Fallot	6 (1 redo)		4		
TGA	2		1		
Truncus arteriosus	2		1		
CAVSD			1		
MI			1 (redo)		
DILV			1		
DORV			2		
AS			1		
TAPVR			1		
Cor triatriatum, VSD	1				
Cross-clamping time (minutes)	64 ± 6	24–116	62 ± 6	29–127	0.76
CPB time (minutes)	110 ± 8	59–178	109 ± 8	54–176	0.88

Differences in clinical variables between groups were tested with Student's *t* test or Fisher's exact test when appropriate. Two operations in group HC and three in group C were second procedures (redos). Group C, use of conventional noncoated system and roller pump; group HC, use of fully heparin-coated closed system and centrifugal pump.

AS = aortic stenosis; CAVSD = complete artrioventricular septal defect; CPB = cardiopulmonary bypass; DILV = double inlet left ventricle; DORV = double outlet right ventricle; Fallot = tetralogy of Fallot; MI = mitral insufficiency; preop. = preoperatively; PS = pulmonary stenosis; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; VSD = ventricular septal defect.

Anesthetic Management

Anesthesia was induced with intravenous midazolam (0.1 to 0.2 mg/kg) and ketamine (2 mg/kg). Pancuronium (0.1 to 0.2 mg/kg) was used for muscle relaxation. Fentanyl (50 μg/kg) was given before cardiopulmonary bypass to provide analgesia. The patients were ventilated with oxygen or a mixture of oxygen and air. Isoflurane was given if tolerated. Noninvasive monitoring consisting of electrocardiogram, pulse oximetry and measurements of inspiratory and expiratory gas concentrations was used as well as invasive monitoring of arterial and central venous pressure. Albumin was used for volume expansion. Phentolamine or isoflurane was given to reduce peripheral vascular resistance during CPB. Weaning from CPB was managed with bolus injections of calcium gluconate and infusion of dopamine. Postoperative status was evaluated daily by clinical examination, laboratory tests, and cardiac ultrasonography. Patients were weaned from the respirator when having a mean arterial pressure adequate for age, FiO_2 40% or less, stable blood gases, and urine production of at least 2 mL $\cdot$ kg^{-1} $\cdot$ hour^{-1}.

Cardiopulmonary Bypass Technique

Before cannulation all patients were heparinized (activated clotting time >480 seconds). Hepcon HMS (Medtronic, Minneapolis, MN), autodose mode, was used for monitoring of anticoagulation and calculation of heparin and protamine doses during the procedure. CPB was performed with nonpulsatile flow at a minimum rate of 2.8 L $\cdot$ min^{-1} $\cdot$ m^{-2}. A Minimax Plus hollowfiber membrane oxygenator (Medtronic, Anaheim, CA) was used in both groups. The priming solution was composed of 150 mL to 300 mL of buffered electrolyte solution (Ringeracetat, Fresenius-Kabi, Sweden), 100 mL albumin 200 mg/mL, 50 to 100 mmol of a buffer solution (Tribonat, Fresenius-Kabi, Sweden), 2 mL/kg mannitol (150 mg/mL), and heparin 100 U/kg. Erythrocyte concentrate was added in order to achieve a hematocrit between 20% and 25%. Blood gases were continuously monitored in venous and arterial tubing by a blood gas analyzer for invasive monitoring (CD1400; Cardiovascular Device Instruments, Anaheim, CA). PvO_2 was kept above 4.5 kPa and blood gas regimen was performed using α-stat management. Cardioprotection was achieved with intermittent cold (4°C) blood-cardioplegia. The temperature in the nasopharynx and rectum was measured continuously. Surgery was performed with hypothermia (<20°C, 3 patients; 20°C, 3 patients, 25°C, 13 patients; and 28°C, 21 patients). Weaning from CPB was commenced at a rectal temperature of 36°C. All patients but 1 were treated with modified (Great Ormond Street) ultrafiltration (hemofilter FH22; Gambro, Sweden) immediately after CPB (the exception for technical reasons) [13]. The filter used for hemofiltration was not heparinized as according to the manufacturer (Medtronic, Minneapolis, MN) this was not within the range of possibility.

Study Protocol

The patients were randomly allocated to either of two regimens by a computerized program for randomization with sequential allocation depending on weight, age, gender and preoperative oxygen saturation. The study protocol was approved by the Research Ethics Committee of the Medical Faculty, Göteborg University. Informed consent was given by the parents of the children studied.

One regimen (group HC, n = 19) comprised an extracorporeal system with a centrifugal pump (Biomedicus [Medtronic Inc, Minneapolis, MN]) and a closed, fully heparinized circuit (Carmeda Bioactive Surface, CBAS [Medtronic Inc]). The other regimen was a conventional, nonheparinized system with a hard shell venous reservoir (Minimax [Medtronic Inc]) and a roller pump (group C, n = 21).

Blood samples for measuring the concentrations of C3a, sC5b-9, C4d fragment (C4d), Bb fragment (Bb), tumor necrosis factor (TNF)-α, IL-6, IL-8, and polymorphonuclear (PMN) elastase were drawn from the arterial line on four occasions during the procedure: after induction of anesthesia, after rewarming at 35°C,1 hour after CPB, and in the morning of the first postoperative day (POD1). All samples were drawn into tubes with EDTA (ethylene diamine tetra-acetic acid). Immediately after collection the blood samples were centrifuged and plasma was stored in individual tubes at −60°C for later analysis. The assays were performed in duplicate. Samples for measuring hemoglobin, leukocyte count, and platelet count were drawn on the same occasions.

The concentrations of plasma C3a, TNF-α, IL-6, and IL-8 were determined by sandwich enzyme-linked immunosorbent assay (ELISA). The C3a assay is specific for $C3a_{desArg}$, which has a much longer half-life in plasma than C3a. Modified enzyme-immunoassays (EIAs) were used to quantify sC5b-9, C4d, Bb, and PMN elastase concentrations. The assays were performed according to the manufacturer's procedure. The following assays were used: C3a, ELISA (Quidel, CA); sC5b-9, C4d, Bb, EIA (Quidel, CA); TNF-α, IL-6, IL-8, ELISA (R&D Systems, Minneapolis, MN); and PMN elastase, EIA (DPC, CA). The limit of sensitivity of each assay was C3a = 1 ng/mL, sC5b-9 = 0.06 ng/mL, C4d = 0.01 ng/mL, Bb = 0.063 ng/mL, TNF-α = 4.4 pg/mL, IL-6 = 0.7 pg/mL, IL-8 = less than 10 pg/mL, and PMN elastase = 3 ng/mL.

Statistical Analysis

Results are presented as means ± standard error of means (SEM). Differences in clinical variables between groups were tested with Student's *t* test or Fisher's exact test when appropriate. Intergroup differences were analyzed using multiple analysis of variance (MANOVA) for repeated measures followed if significant by Student's *t* test for each sample. Univariate regression analysis was used. A *p* value less than 0.05 was considered statistically significant.

Results

Clinical Course

Clinical and demographic data are presented in Table 1. All patients survived the perioperative and postoperative periods. Dopamine was used in all patients during the early postoperative hours. Nitric oxide therapy was used postoperatively in 3 patients in each group because of pulmonary hypertension. Three patients had late closure of the sternotomy in group HC, compared with five in group C. Two patients underwent reoperation in group C because of excessive bleeding. One of them developed a heart tamponade with circulatory arrest because of the bleeding. This patient had to be reexplored twice during the first 24 hours. One patient in group C underwent reoperation in the evening of postoperative day 1 because of suspicion of an embolus in the right atrium that turned out to be a hematoma. One patient in group C who was operated on because of total anomalous pulmonary venous return had to be reintubated 4 days after the initial extubation. This patient stayed in the intensive care unit for 21 days owing to sepsis and arrhythmia. The other patients all had a postoperative course within the normal range. There were no significant differences in postoperative clinical variables between the groups (Table 2).

Complement

There was a significant intergroup difference in C3a (Fig 1, $p < 0.001$), sC5b-9 (Fig 2, $p = 0.01$), and Bb (Table 3, $p = 0.04$) concentrations, with lower concentrations in group HC. The release pattern concerning the Bb fragment indicated activation of the complement system through the alternative pathway in both groups. There was a significant difference between the groups after rewarming at 35°C ($p = 0.03$). The concentrations of C4d were not elevated and there were no intergroup differences (Table 3). Regression analysis was performed with CPB-time as a predictor of peak C3a and sC5b-9 responses. No significant correlation was observed (Figs 3 and 4).

PMN Elastase and Cytokines

PMN elastase concentrations showed significant intergroup difference, with lower concentrations in group HC (Fig 5, $p = 0.02$). There were no significant intergroup differences regarding TNF-α, IL-6, or IL-8 concentrations (Table 3).

Regression analysis was performed with CPB-time as a predictor of IL-6 response and showed that CPB-time correlated with peak IL-6 response ($r = 0.74$, $p = 0.001$, Fig 6).

Comment

The main finding of this study is that activation of the complement system and the formation of PMN elastase are reduced when using a fully heparin-coated system, centrifugal pump, and a closed circuit in comparison with a conventional system. In contrast, no significant effect on the cytokine response was detected.

Table 2. Clinical Variables From the Postoperative Period

	Group HC (n = 19)		Group C (n = 21)		
	Mean ± SEM	Range	Mean ± SEM	Range	*p* Value
Blood loss first 12 h postoperative ($mL \cdot kg^{-1} \cdot h^{-1}$)	2.6 ± 0.3	1.1–5.3	3.3 ± 0.5	1.0–9.3	0.24
Urine production first 12 h postoperative ($mL \cdot kg^{-1} \cdot h^{-1}$)	3.4 ± 0.3	0.3–5.8	3.4 ± 0.3	1.4–7.0	0.93
Time in ventilator (h)	59.8 ± 8.6	20–145	65.1 ± 12.8	19–220	0.73
Time in ICU (days)	3.4 ± 0.4	1–8	4.1 ± 1.0	1–21	0.53
Time in hospital (days)	10.0 ± 0.6	7–15	12.3 ± 1.3	6–25	0.11
C-reactive protein POD2 (mg/mL)	73 ± 10	10–150	62 ± 7	23–120	0.39
Platelets POD1 (10^9/L)	115.8 ± 8.2	63–193	121.3 ± 10.5	46–216	0.69
White blood cells POD1 (10^9/L)	8.5 ± 0.8	3.6–17.3	9.9 ± 0.8	4.6–18.5	0.21

Differences in clinical variables between groups were tested with Student's *t* test. Group C, use of conventional noncoated system and roller pump; Group HC, use of fully heparin-coated closed system and centrifugal pump.

h = hours; ICU = intensive care unit; POD1 = first postoperative day; POD2 = second postoperative day.

Complement

The complement system, which is important for self/nonself discrimination and is one of the major effector pathways of inflammation, is activated during open heart surgery with CPB in a multifactorial way. Activation takes place predominantly through the alternative pathway (which was confirmed in our study) and results in the generation of the anaphylatoxins C3a and C5a and formation of the membrane attack complex (C5b-9). The half-life of C5a in the circulation is extremely short and instead sC5b-9 is often used as a more reliable but indirect measure of C5a activation. We found that both the C3a and sC5b-9 responses were attenuated in the combined system group in comparison with the conventional system group. In fact there was no detectable sC5b-9 response when the combined system was used. We interpret this as that the CPB system used in group HC is less provocative in the activation of the complement cascade and that the combined system provides significantly higher biocompatibility than the conventional system.

The contribution of the surgical trauma, ischemia/reperfusion, and so forth, cannot be separated from the effect of the CPB system used when evaluating complement response. In a previous study we observed a positive correlation between bypass time and C3a re-

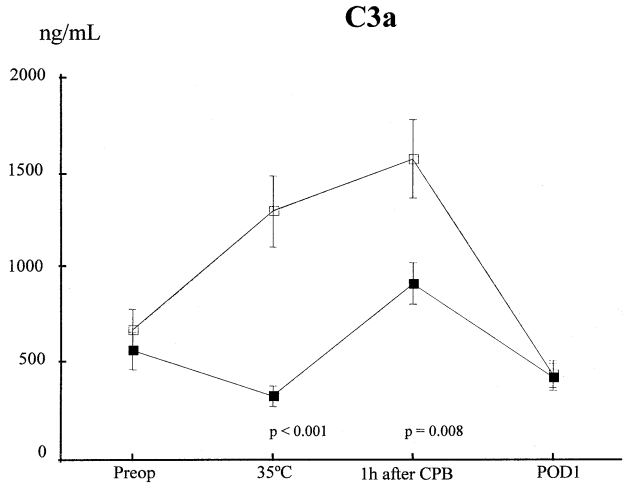

Fig 1. Plasma concentrations of C3a in the two groups at the four different sampling times. Intergroup differences were analyzed using multiple analysis of variance (MANOVA) for repeated measures, followed if significant by Student's t *test for each sample. MANOVA result: group,* $p < 0.001$*; time,* $p < 0.001$*; interaction,* $p < 0.001$*.* Filled squares = *patients treated with a fully heparin-coated closed system and a centrifugal pump;* open squares = *patients treated with a conventional noncoated system and a roller pump;* Preop = *after induction of anesthesia, before surgery;* 35°C = *after rewarming at 35°C;* 1 h after CPB = *1 hour after termination of cardiopulmonary bypass;* POD1 = *in the morning of the first postoperative day.*

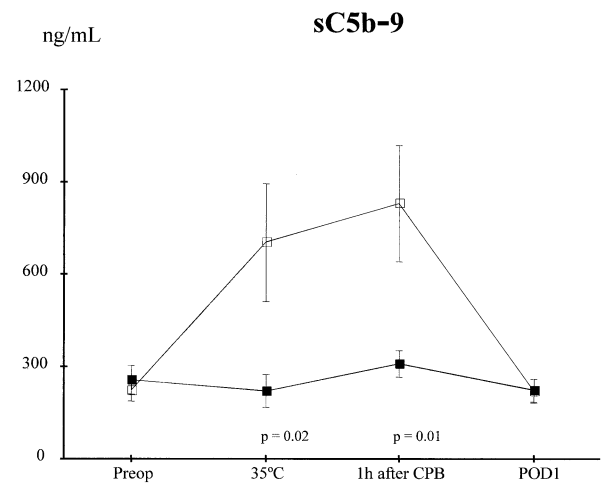

Fig 2. Plasma concentrations of sC5b-9 in the two groups from the four different sampling times. Intergroup differences were analyzed using multiple analysis of variance (MANOVA) for repeated measures, followed if significant by Student's t *test for each sample. MANOVA result: group,* $p = 0.013$*; time,* $p = 0.002$*; interaction,* $p = 0.015$*.* Filled squares = *patients treated with a fully heparin-coated closed system and a centrifugal pump;* open squares = *patients treated with a conventional noncoated system and a roller pump;* Preop = *after induction of anesthesia, before surgery;* 35°C = *after rewarming at 35°C;* 1 h after CPB = *1 hour after termination of cardiopulmonary bypass;* POD1 = *in the morning of the first postoperative day.*

Table 3. Concentrations of Complement Factors and Cytokines From the Four Sampling Times[a]

		Preoperative	35°C	1 h After CPB	PODI	MANOVA Group	MANOVA Time	MANOVA Interaction
Bb (ng/mL)	Gr. HC	297 ± 126	717 ± 161	648 ± 145	236 ± 69	$p = 0.41$	$p = 0.2$	$p = 0.042$
	Gr. C	115 ± 22	1019 ± 212	743 ± 156	313 ± 100			
C4d (ng/mL)	Gr. HC	3.7 ± 0.6	1.2 ± 0.2	1.3 ± 0.2	2.5 ± 0.4	$p = 0.2$	$p < 0.001$	$p = 0.26$
	Gr. C	3.3 ± 0.5	0.6 ± 0.1	1.3 ± 0.4	1.9 ± 0.2			
TNF-α (pg/mL)	Gr. HC	10 ± 1	10 ± 1	24 ± 4	17 ± 6	$p = 0.85$	$p = 0.01$	$p = 0.43$
	Gr. C	12 ± 2	15 ± 4	28 ± 9	11 ± 1			
IL-6 (pg/mL)	Gr. HC	2 ± 0.5	14 ± 3	102 ± 13	146 ± 28	$p = 0.71$	$p < 0.001$	$p = 0.11$
	Gr. C	8 ± 4	33 ± 8	111 ± 20	101 ± 17			
IL-8 (pg/mL)	Gr. HC	11 ± 2	22 ± 4	194 ± 75	48 ± 7	$p = 0.81$	$p < 0.001$	$p = 0.75$
	Gr. C	14 ± 5	61 ± 31	178 ± 54	53 ± 13			

Data are presented as means and standard error of the means. Intergroup differences were analyzed using MANOVA for repeated measures.

C3a, sC5b-9, and PMN elastase are presented in Figs 1–3.

Gr. C = conventional noncoated system and roller pump; Gr. HC = fully heparin-coated closed system and centrifugal pump; 1 h after CPB = 1 hour after termination of cardiopulmonary bypass; POD1 = in the morning of the first postoperative day; Preoperative = after induction of anesthesia, before surgery; 35°C = after rewarming at 35°C; TNF = tumor necrosis factor; IL = interleukin.

sponse [4]. In the present material we found no such relationship, suggesting that this was disrupted by the more biocompatible bypass system.

Neutrophil Activation

Circulating levels of PMN elastase provide a measure of degranulation of neutrophils. Both C5a and IL-8 are important triggering mechanisms for activation of neutrophils in the inflammatory response. Degranulation induces tissue damage during CPB. The observed reduction in PMN elastase production in group HC indicates less neutrophil activation and degranulation. This may be an effect of less complement activation in group HC as there was no difference between the groups regarding IL-8 concentrations. Two other studies in children describing the inflammatory response in connection with heparin-coated systems show the same pattern, with lower levels of complement factors and PMN elastase in the groups using heparin-coated systems and no difference in IL-8 concentrations between groups [14, 15].

Cytokines

A noteworthy observation from our study is that although we had clear signs of less activation of the complement system in group HC, we did not find any significant differences between the two groups concerning cytokine concentrations. C5a is known to induce IL-6 production. Theoretically this would imply that we would

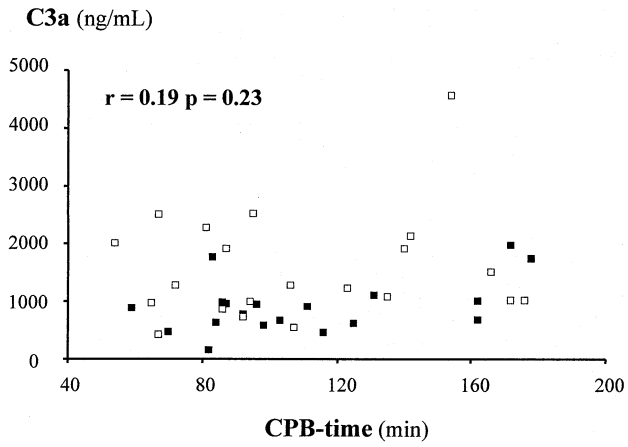

Fig 3. Cardiopulmonary bypass (CPB) *time (minutes) versus C3a levels (ng/mL) 1 hour after CPB in 40 children undergoing open heart surgery.* Filled squares = *patients treated with a fully heparin-coated closed system and a centrifugal pump;* open squares = *patients treated with a conventional noncoated system and a roller pump.*

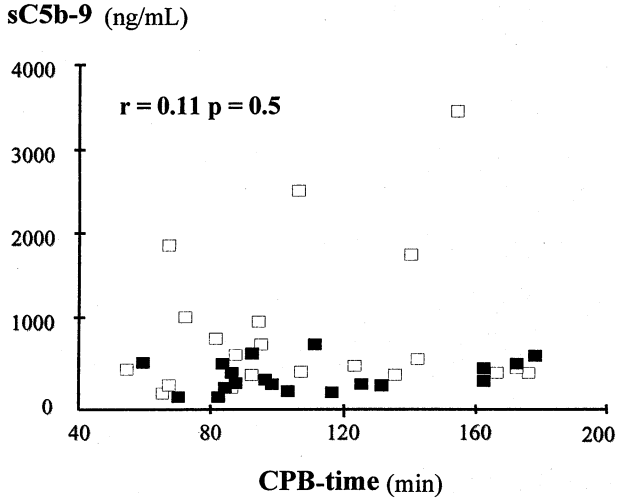

Fig 4. Cardiopulmonary bypass (CPB) *time (minutes) versus sC5b-9 levels (ng/mL) 1 hour after CPB in 40 children undergoing open heart surgery.* Filled squares = *patients treated with a fully heparin-coated closed system and a centrifugal pump;* open squares = *patients treated with a conventional noncoated system and a roller pump.*

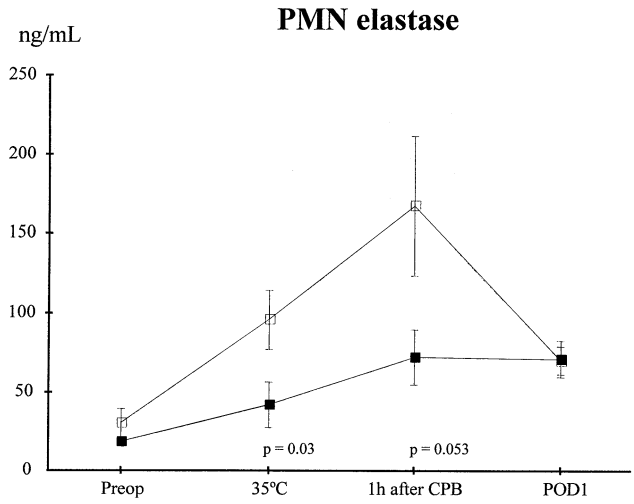

*Fig 5. Plasma concentrations of polymorphonuclear (*PMN*) elastase in the two groups from the four different sampling times. Intergroup differences were analyzed using multiple analysis of variance (MANOVA) for repeated measures, followed if significant by Student's* t *test for each sample. MANOVA result: group,* p = *0.063; time,* p = *0.005; interaction,* p = *0.022.* Filled squares = *patients treated with a fully heparin-coated closed system and a centrifugal pump;* open squares = *patients treated with a conventional noncoated system and a roller pump;* Preop = *after induction of anesthesia, before surgery;* 35°C = *after rewarming at 35°C;* 1 h after CPB = *1 hour after termination of cardiopulmonary bypass;* POD1 = *in the morning of the first postoperative day.*

expect lower IL-6 concentrations in group HC than in group C. Contrary to our expectations there was no difference between groups regarding either IL-6, IL-8, or TNF-α. There are, however, conceivable explanations for this finding. The causes of cytokine release as of complement activation are multifactorial. Other factors than the exposure to artificial surfaces such as surgical trauma and tissue ischemia may possibly be more powerful stimuli. If so, this could conceal improved biocompatibility. Still our data clearly show, in line with previous observations by our group and others, that the exposure to bypass has important effects on cytokine response as a correlation was observed between bypass time and IL-6 levels (Fig 6).

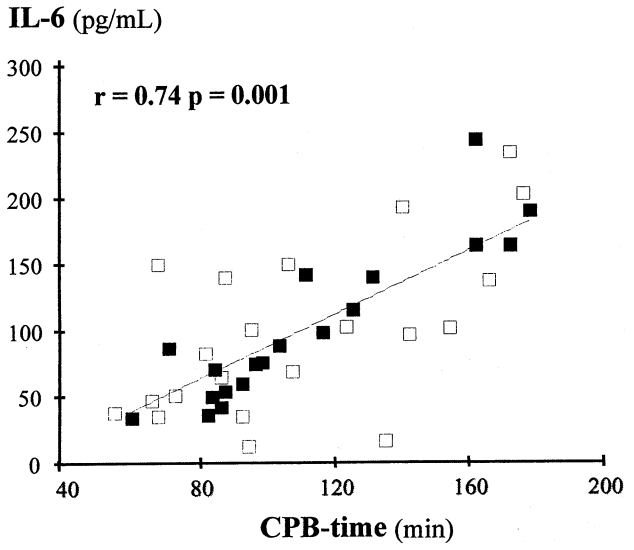

*Fig 6. Cardiopulmonary bypass (*CPB*) time (minutes) versus interleukin (*IL*)-6 levels (pg/mL) 1 hour after CPB in 39 children undergoing open heart surgery.* Filled squares = *patients treated with a fully heparin-coated closed system and a centrifugal pump;* open squares = *patients treated with a conventional noncoated system and a roller pump.*

Studies in children and adults using heparin-coated systems have shown conflicting results regarding cytokine response. Some investigators have found an attenuated cytokine response, while others have not. A review of previously published papers suggests that the papers which report beneficial effects generally have a common denominator: long procedures (CPB-time ≥120 minutes). In the paper by Steinberg and associates [5] the bypass time in the heparin-coated group was on average 279 minutes. The corresponding figure in a study by Kagisaki and colleagues [15] was 150 minutes, and in a paper by Ozawa and colleagues [16] it was 166 minutes. In our study the average bypass time was 110 minutes and in the study by Defraigne and colleagues [17] and the work by Horton and coworkers [18] it was 92 and 105 minutes, respectively (neither detected effects on cytokines).

Reports from in vitro studies and in adults have described the centrifugal pump as being more biocompatible but in a pediatric study Ashraf and associates [19] could not detect any significant difference between roller and centrifugal pumps with respect to IL-6 or IL-8 [9-11]. The lack of effect on cytokines found in our study might be an unexplained deficiency of the three-factors CPB approach.

Study Design and Limitations

The study design could be criticized because it does not allow evaluation of the role of the individual components of the bypass system. Although desirable, an alternative design where this would be possible would have required significantly larger resources. It was reasoned that if the three-component bypass system proved to be superior to the conventional system, the results could be compared with previous data where the three components had been studied separately. If there appeared to be additional effects of the current system, this would motivate a more elaborate and resource-demanding protocol. A comparison between our data and previous reports is difficult to make and has to be done cautiously and with certain reservations. Still, focusing on sC5b-9 (or TCC) could suggest a difference in reports concerning the effect of heparin-coated systems in pediatric heart surgery [8, 14, 20]. None of these studies have shown a reduction in peak sC5b-9 concentration similar to the value observed in our study, the peak value in group HC being 37% of the group C value (corresponding value 77% or more in the other studies).

Conclusions

The study demonstrates that the use of a fully heparin-coated system, a centrifugal pump, and a closed circuit during CPB in children (10 kg or less) leads to a lower degree of complement activation and PMN elastase release than a conventional nonheparinized system.

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