Superior Biocompatibility of Heparin-bonded Circuits in Pediatric Cardiopulmonary Bypass

***Background*: Heparin bonding of pediatric cardiopulmonary bypass circuits may decrease activation of blood compartments as inflammatory responses. We studied the biocompatibility of heparin-bonded circuits in infant cardiac surgery. *Methods*: Twenty-four infants undergoing elective cardiac surgery were randomly assigned to either a nonheparin-bonded control circuit ($n = 12$) or a fully heparin-bonded circuit ($n = 12$) including membrane oxygenator, reservoir, and all tubing. Blood samples were used to identify differences in complement activation and cytokine release between groups during and after cardiopulmonary bypass. The postbypass oxygenation index was also compared. *Results*: The C3 activation product in the heparin-bonded group was significantly lower during ($p < 0.01$) and just after ($p < 0.05$) cardiopulmonary bypass. No statistically significant difference in C4 activation products was observed. Lower interleukin-6 and tumor necrosis factor-α were found immediately after cardiopulmonary bypass ($p < 0.05$) and a higher mean postbypass oxygenation index was also seen ($p < 0.05$) in the heparin-bonded group. *Conclusion*: We found that a heparin-bonded cardiopulmonary bypass circuit reduced inflammatory response and improved oxygenation in pediatric cardiac surgery. These results suggest that the superior biocompatibility of the bonded circuit may reduce pulmonary complications. (JJTCVS 1999; 47: 592–599)**

Index words: heparin-bonded cardiopulmonary bypass, pediatric cardiac surgery, complement, cytokine

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Blood component interaction with artificial cardiopulmonary bypass (CPB) circuit surfaces triggers contact reactions including the activation of complements[1,2] and the kallikrein-kinin system.[3] Complement-derived fragments activate the production of cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α).[4–6] These complement and cytokine increases adversely affect inflammatory response during and after CPB. Clinical studies of the heparin-coated or bonded surface of CPB circuits used in adult cardiac surgery showed reduced leukocyte activation,[7] decreased activation of the complement cascade,[8] and decreased pulmonary damage after CPB,[9] all of which suggest improved biocompatibility. In pediatric open-heart surgery, additional factors, including the larger bypass circuit surface in contact with blood components and the greater proportion of blood drawn through cardiotomy suction must be considered. Some reports discussed cytokine release[10,11] and complement activity associated with pediatric CPB; biocompatibility of heparin-bonded[12] or coated[13] pediatric CPB circuits in respiratory function such as postperfused

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Table I. *Preoperative profiles of 24 infants undergoing cardiopulmonary bypass with heparin-bonded or nonbonded bypass circuits*

Variable		*Group*		*p*
		Heparin-bonded (n = 12)	*Nonbonded controls (n = 12)*	
Diagnosis	ASD	1	1	
	VSD	3	4	
	Complete AV canal	2	2	
	ASD & VSD & PDA	2	1	
	TOF	2	3	
	VSD & PS	2	1	
Age (years)		22 ± 0.5	1.8 ± 0.5	0.58
Body weight (kg)		10.4 ± 1.0	9.4 ± 1.3	0.34
Hematocrit (%)		34.0 ± 1.6	34.8 ± 2.5	0.86
Leukocytes (/μl)		6158 ± 695	7142 ± 943	0.40
Platelets (10^4/μl)		23.6 ± 2.8	27.0 ± 2.7	0.55

Data is expressed as mean plus or minus standard error of the mean, or as the number of patients.
ASD, Atrial septal defect; *AV*, atrioventricular; *PDA*, patent ductus arteriosus; *PS*, pulmonary stenosis; *TOF*, tetralogy of Fallot; *VSD*, ventricular septal defect.

oxygenation in infants has not been well-documented. We assessed changes in complements and cytokines during and after infant CPB and evaluated the biocompatibility of heparin-bonded circuits including the clinical variable of postperfused oxygenation in 24 cases of pediatric open-heart surgery.

Subjects and Methods

Following ethical committee approval and informed parental consent, 24 children undergoing elective intracardiac repair with hypothermic CPB for congenital heart disease were included in this study as subjects (sans reoperative cases and neonates) and randomly assigned to undergo cardiac repair using either a heparin-bonded circuit (CAPIOX®-SX (HP), TERUMO® Corporation, Tokyo, Japan; HB, n = 12) or a matched nonheparin-bonded control circuit (NC, n = 12). In HB, the entire CPB circuit including the membrane oxygenator, the venous and cardiotomy reservoir, and all tubing were fully coated with covalently bound heparin. Preoperative profiles are given in Table I. Diagnoses were similar between groups. No statistical difference was seen in presurgical age, body weight, hematocrit, or leukocyte or platelet count.

Cardiopulmonary bypass and surgery. All patients received modified neurolepto-anesthesia and analgesia, including fentanyl and midazolam, and pancuronium as a neuromuscular agent. CPB was done with an arterial cannula in the ascending aorta and venous cannulas through the superior and inferior vena cava. Heparin (300 IU/kg body weight; BW) was given to maintain an activated clotting time exceeding 400 seconds during bypass in both groups. Extracorporeal circulation used a Stöckert-Shiley roller pump (Shiley Inc., Irvine, Calif., USA) with pulsatile flow control. The extracorporeal circuit was primed with 20% mannitol, 25% volume of albumin solution, Ringer's lactate solution, and 7% volume of sodium bicarbonate, to reach a total prime volume of 450 ml. Heparin was added to the priming solution (2250 IU). In all patients, the extracorporeal circuit was clearly primed without homologous blood transfusion at the start of CPB. When the hematocrit decreased less than 20%, however, homologous erythrocytes were transfused as the patient needed. Surgery proceeded under systemic hypothermia at 28°C and with antegrade intermittent cold cardioplegia, which included glucose, insulin, potassium, and topical cooling with ice slush in all patients. A pump flow of 2.5 L/m^2 per minute was

Table II. *Clinical profiles of patient groups in surgery*

Variable	*Group*		*p*
	Heparin-bonded (*n* = 12)	*Nonbonded controls* (*n* = 12)	
CPB time (min)	158.5 ± 24.2	163.5 ± 22.7	0.98
Cross-clamp time (min)	100.3 ± 22.2	95.2 ± 13.7	0.82
Heparin (units)	3109 ± 339	2737 ± 334	0.50
Protamine (mg)	33.1 ± 3.4	32.7 ± 5.6	0.67
Transfused blood (units)	0.85 ± 0.17	0.61 ± 0.21	0.41
Hemodilution rate (%)	37.5 ± 4.5	37.4 ± 2.7	0.97
Postoperative hematocrit (%)	24.8 ± 1.4	26.2 ± 1.2	0.56
Postoperative leukocytes (/μl)	7900 ± 1115	10125 ± 1194	0.08
Postoperative platelets (10^4/μl)	8.5 ± 0.86	8.15 ± 1.2	0.71

Data is expressed as mean plus or minus standard error of the mean. Hemodilution rates were calculated by using hematocrit scores before and after 60 minutes of bypass. Total dosages administered during surgery are presented for both heparin and protamine. *CPB*, cardiopulmonary bypass.

maintained whenever possible. At the end of CPB, the bolus dose of protamine sulfate for neutralization of the heparin effect was 1.3 mg/100 IU of heparin.

Blood sampling and measurement of complement activation products and cytokines. Blood samples were taken from the indwelling radial arterial catheter after the induction of anesthesia and before CPB (before systemic administration of heparin) and at 5 minutes and 60 minutes after the start of CPB, immediately after CPB (before protamine neutralization), and 24 hours after CPB. These samples were collected in vacuum tubes with ethylenediaminetetraacetic acid (EDTA) and immediately centrifuged at 3,000 g for 10 minutes at 4°C. Plasma samples were frozen and stored at −70°C until complement activation products and cytokines were assayed.

Complement activation products (C3a, C4a) were measured in plasma by radioimmunoassay kits (Amersham Corporation, Buckinghamshire, UK). IL-6 and TNF-α were determined by an enzyme-linked immunosorbent assay using Quantikine™ HS kits (catalog Nos. HS 600 and HSTA 0; R & D Systems, Minneapolis, Minnesota). Changes in plasma levels of complement activation products and cytokines at 5 time points were evaluated in both groups and compared.

Oxygenation index. We determined the oxygenation index (OI) by dividing arterial oxygen tension (PaO2) by inspired oxygen fraction (FiO2) (i.e., PaO2/FiO2) before CPB and 3 hours after CPB ended. Indices of both groups were compared to assess differences in clinical response to different CPB circuits. The time point 3 hours after bypass was chosen to exclude any influence due to microatelectasis following CPB.

We studied whether OI correlated with complement activation products or cytokines to identify relationships between postoperative respiratory function and the magnitude of inflammatory response.

Statistical analysis. Not data was corrected for blood dilution and was expressed as mean ± SE. Because of the smallness of groups, the nonparametric Mann-Whitney U test was used to compare groups. For variables measured over time, Friedman's test was used to identify time-dependent changes within groups. Spearman's rank correlation coefficient was assessed for independent parameter correlation. Results are significant at a $p < 0.05$.

Results

1. Subjects

Clinical patient profiles in surgery are summarized in Table II. No significant differences were

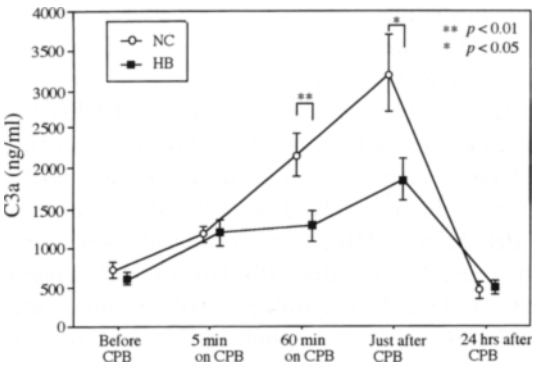

Fig. 1. Plasma levels of C3 activation product (C3a) are shown at 5 time points during and after cardiopulmonary bypass (CPB) with nonbonded control (open circles) and heparin-bonded (closed squares) circuits. C3a levels increased continuously in a similar pattern in both groups during and after CPB. The increase in C3a was significantly lower in the heparin-bonded group than in controls 60 minutes on bypass (**$p < 0.01$) and just after CPB (*$p < 0.05$). Results are expressed as the mean plus or minus standard error of the mean. *Group NC*: non-heparin-bonded control group; *Group HB*: heparin-bonded group.

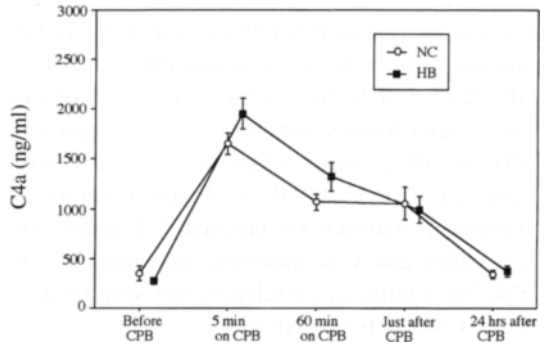

Fig. 2. Plasma levels of C4 activation product (C4a) are shown at 5 time points during and after cardiopulmonary bypass (CPB) with nonbonded control (open circles) and heparin-bonded (closed squares) circuits. C4a levels increased markedly and peaked 5 minutes into bypass, then declined to prebypass levels 24 hours after bypass in both groups. There was no statistical difference between the 2 groups.

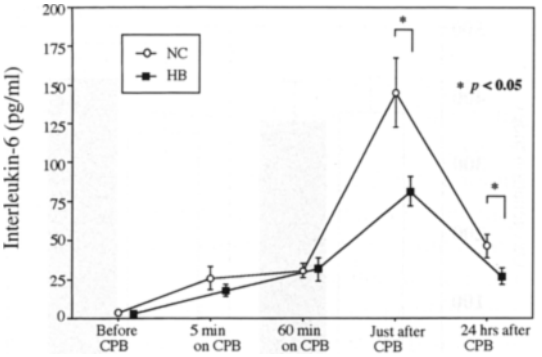

Fig. 3. Changes in the plasma concentration of interleukin-6 (IL-6) over time in patients undergoing cardiopulmonary bypass (CPB) with nonbonded control (open circles) and heparin-bonded (closed squares) circuits. IL-6 levels increased gradually after initiation of CPB, and rose considerably and nearly identically just after CPB in both groups. The heparin-bonded group had significantly lower IL-6 levels immediately and 24 hours after CPB (*$p < 0.05$).

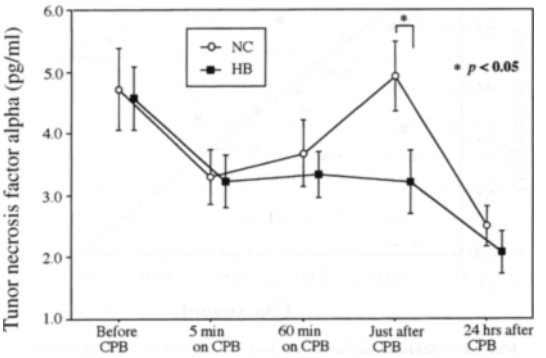

Fig. 4. Changes in the plasma level of tumor necrosis factor-α (TNF-α) over time in patients undergoing cardiopulmonary bypass (CPB) with nonbonded control (open circles) and heparin-bonded (closed squares) circuits. The TNF-α level decreased 5 minutes into CPB in both groups and, in controls gradually increased until the termination of CPB. The heparin-bonded group had a significantly lower TNF-α level just after CPB (*$p < 0.05$).

seen in CPB and aortic crossclamp time, heparin administration, or protamine dosage, transfused blood, hemodilution, postoperative hematcrit score, or leukocyte or platelet counts between groups.

No operative deaths or significant adverse complications occurred. No patients required postoperative reexploration due to hemorrhaging.

2. Complement activation

a. C3 activation product (C3a)

C3a concentration steadily increased after CPB started, rising significantly and continuously until immediately after CPB ended in both groups (Friedman's test: $p < 0.0001$) (Fig. 1); 60 minutes after CPB initiation, and immediately after CPB,

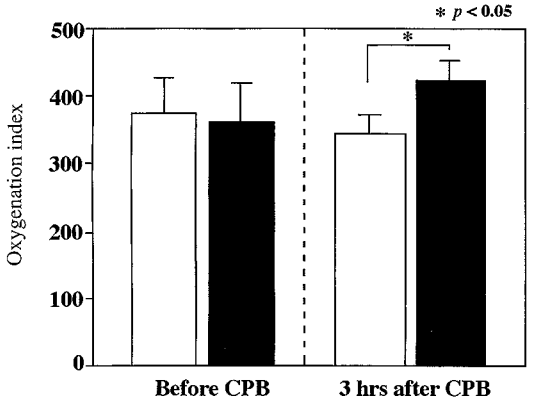

Fig. 5. Oxygenation indices, i.e., PaO2/FiO2, just before and 3 hours after cardiopulmonary bypass (CPB) with nonbonded control (open bars) and heparin-bonded (closed bars) circuits. Although prebypass oxygenation indices did not differ, a significant difference existed after CPB (*p < 0.05).

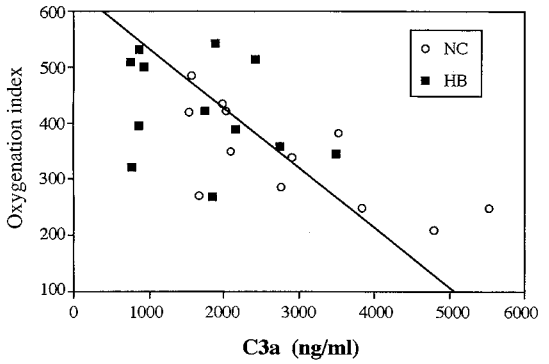

Fig. 6. Relationship between the level of C3 activation product (C3a), immediately after cardiopulmonary bypass (CPB) and the oxygenation index, i.e., PaO2/FiO2, 3 hours after CPB in all 24 patients. Spearman's correlation coefficient = –0.55 ($p < 0.01$).

C3a levels in heparin-bonded (HB) group were significantly lower than those in nonheparin-bonded controls (NC) (60 minutes on CPB, HB: 1290 ± 187 ng/ml; NC: 2158 ± 255 ng/ml, $p < 0.01$; immediately after CPB, HB: 1715 ± 258 ng/ml; NC: 3072 ± 516 ng/ml, $p < 0.05$).

b. C4 activation product (C4a)

In both groups, C4a levels dramatically increased at CPB onset and peaked 5 minutes after CPB started, unlike C3a (Fig. 2). These increases in C4a concentration during CPB were significant in both groups (Friedman's test: $p < 0.0001$). No significant differences were seen between groups.

3. Cytokines

a. Interleukin-6 (IL-6)

IL-6 levels gradually increased during CPB, rose considerably just after CPB, and rapidly decreased 24 hours after CPB in both groups ($p < 0.0001$) (Fig. 3). Immediately after CPB and 24 hours after CPB, IL-6 in HB were significantly lower than those in NC (just after CPB, HB: 81.4 ± 9.5 pg/ml; NC: 144.9 ± 22.3 pg/ml, $p < 0.05$; 24 hours after CPB, HB: 27.2 ± 5.3 pg/ml; NC: 46.4 ± 7.6 pg/ml, $p < 0.05$).

b. Tumor necrosis factor-α (TNF-α)

TNF-α levels dropped 5 minutes on CPB due to dilution in both groups (Fig. 4). In NC, these tended to increase steadily until just after CPB, when they decreased 24 hours after CPB. Only just after CPB was the TNF-α concentration in HB lower than that in NC (HB: 3.21 ± 0.52 pg/ml, NC: 4.92 ± 0.57 pg/ml, $p < 0.05$).

4. Oxygenation index

There was a significant difference between groups in OI 3 hours after CPB ended, although no difference was seen before bypass (Fig. 5). In HB, a significantly higher OI was calculated after CPB (HB: 424.5 ± 26.9, NC: 345.4 ± 23.7, $p < 0.05$). OI 3 hours after bypass correlated with C3a just after CPB in all patients (Spearman's correlation coefficient = –0.55, $p < 0.01$). Figure 6 shows the relationship between OI calculated 3 hours after CPB ended and C3a measured immediately after CPB. No significant correlation was seen between OI and C4a, IL-6, or TNF-α.

Discussion

We found that heparin-bonded cardiopulmonary bypass circuits significantly reduced complement activation and inflammatory cytokine release. Superior respiration was seen simultaneously after CPB in the bonded group. This is, to our knowledge, the first demonstration of changes in plasma complement and cytokine levels and relationships between these levels and postoperative oxygenation capacity in infants undergoing corrective cardiac surgery with heparin-bonded CPB circuits. Unfavorable reactions related to CPB, such as postperfusion syndrome,[1,14,15] have been reported

for nearly 2 decades. Recent clinical studies in adult cardiac surgery[8,16] have attributed the superior biocompatibility of heparin-immobilized circuits to decreased activated blood components and systemic inflammatory response. Infant open-heart surgery presents additional factors for concern. Compared to adult surgery, blood components are exposed to a larger foreign-surface area in CPB circuits, and a greater proportion of the patient's blood is drawn from the operative field. Because even more pronounced inflammatory reactions to CPB may occur in infants, greater biocompatibility is required in pediatric CPB.

The primary inflammatory response is mediated by the activation of complements, such as C3a, that play a part in leukocyte activation.[1,15] A number of investigators[1,8] have found that C3a rises dramatically after CPB initiation and peaks when CPB ends, and that the level increases with lengthening CPB. Our study of heparin-bonded and nonbonded CPB agrees substantially with previous work on changes in C3a concentration. Recent studies showed that heparin-coated surfaces reduce complement activation through 2 recognized pathways of complement cascade.[1,8,17] Earlier, Chenoweth[18] showed that C3a elevation evidences either classical or alternative pathway activation, and that elevated C4a, in contrast to C3a, indicates activation via the classical pathway, whereas normal C4a is associated with activation via the alternative pathway. The blood/oxygen interface[19] and protamine-heparin complex[20] are known to activate complement cascade through the classical pathway. In our study, no differences were seen in heparin or protamine dosage between groups, but our observation of a significant plasma reduction in C3a, but not in C4a, in the heparin-bonded group supports the hypothesis that heparin-bonded circuits mainly suppress alternative pathway activation, triggered by contact reactions between blood and foreign-material surfaces in the complement cascade. Kagisaki et al.[13] also demonstrated significantly lower C3a during and after CPB in a heparin-coated circuit infant group administered almost identical heparin and protamine dosages as a control group, although C4a was not measured. Our conclusions concur with theirs, i.e., that heparin-bonded or coated circuits reduce complement activation via the alternative pathway.

Elevated anaphylatoxin C3a is associated with a greater probability of postoperative death and cardiac, renal, or pulmonary dysfunction.[1] One of the most damaging effects of complement activation may be the effect on granulocytes. Small amounts of C5a induce granulocyte aggregation and margination, and the binding of C5a to specific granulocyte receptors[21] stimulates granulocyte adhesion to vascular endothelium.[22] These sequential reactions may seriously affect lung reperfusion. Indeed, granulocyte aggregation in pulmonary vessels has been observed in differences in left and right atrial leukocyte counts and demonstrated accumulation in pulmonary capillaries and venules in serial lung biopsies before and after CPB.[23] Because we were unable to measure plasma concentrations of C5a or C5b-9 (i.e., terminal complement complex)[4,8] generated through complex amplification, our study is limited in detailing relationships between the activation of the complement system and postperfusion pulmonary injury. The fact that, in this study, oxygenation indices after bypass correlated significantly with plasma C3a gives us good reason to suspect a causal relationship between significantly lower C3a and higher oxygenation indices in the bonded group.

Numerous studies have shown a CPB-related increase in proinflammatory cytokines.[4,10,11,17] IL-6 is a major promotor of acute responses to injury and infection, and is synthesized by monocytes, macrophages, endothelial cells, and fibroblasts after stimulation by TNF-α and IL-1.[2] Steinberg et al. demonstrated that the IL-6 increase during and after CPB is preceded by that of the anaphylatoxins C3a and C5a, and by C5b-9.[4] In our study, increases in IL-6 associated with CPB came after those of C3a. Moreover, the time points of significant intergroup differences in IL-6 also occurred immediately after those for C3a.

TNF-α is a powerful inflammatory mediator released by activated leukocytes,[24] including monocytes and lymphocytes, and is currently considered a factor responsible for fever and postoperative morbidity after CPB.[25] Recent reports on plasma TNF associated with CPB disagree on detectable levels.[2,4,10,25] These discrepancies in TNF-α are, perhaps, attributable to the type of assay[26] or a failure

to specify whether TNF-α figures have been adjusted for hemodilution.

The efficacy of heparin-bonded or coated devices on cytokine production has been documented in adults[16,17] and children.[12,13] In our study, IL-6 in controls remained significantly higher than in the bonded group, both immediately and 24 hours after CPB. Ashraf et al.[12] showed a significant difference in IL-6 24 hours after operation between pediatric groups treated with either heparin-bonded oxygenators or nonbonded oxygenators. These findings are consistent with ours, indicating that IL-6 plays an important role in postoperative inflammatory response. Although the potential of heparin-bonded CPB circuits to decrease TNF-*a* release remains controversial,[12,16] we believe that significantly lower TNF-*a* in the heparin-bonded group results from the fact that fully heparin-bonded circuits are superior to circuits with only a heparin-bonded oxygenator.

Conclusion

The use of fully heparin-bonded bypass circuits reduces inflammatory response, including complement activation and cytokine release, associated with pediatric CPB, and improves postbypass respiration. These results suggest that the superior biocompatibility of heparin-bonded circuits may decrease morbidity after open-heart surgery in infants.

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