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Clinical Efficacy of Heparin-Bonded Bypass Circuits Related to Cytokine Responses in Children

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Background. **Cardiopulmonary bypass (CPB) induces numerous systemic reactions. This study examined the efficacy of heparin-bonded CPB circuits on inflammatory responses and postoperative status in children.**

Methods. **Thirty-four infants undergoing elective cardiac surgery were randomly divided into two groups: a heparin-bonded CPB group (n = 17) and a non-heparin-bonded group (n = 17). Plasma levels of the inflammatory cytokines were measured before, during, and after CPB, and postoperative status was determined by examining the respiratory index, blood loss, and the post- and preoperative body weight percent ratio.**

Results. **Significant differences in tumor necrosis factor-α, interleukin-6, and interleukin-8 patterns were observed during and after CPB between the two groups ($p < 0.01$, $p < 0.01$, $p < 0.05$, respectively). All cytokines measured were significantly lower in the heparin-bonded group just after CPB ($p < 0.05$). There were no differences in duration of intubation, intensive care unit or hospital stay, or postoperative blood loss, but the respiratory index 3 hours after CPB and body weight percent ratio 24 and 48 hours after CPB were significantly reduced in the bonded group ($p < 0.05$, $p < 0.01$, $p < 0.05$, respectively).**

Conclusions. **Our findings suggest that heparin bonding of the bypass circuits affects early postoperative status and reduces cytokine responses in pediatric cardiac surgery.**

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Cardiopulmonary bypass (CPB) causes systemic inflammatory response syndrome (SIRS) by inducing numerous reactions, including the production of inflammatory cytokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α (TNF-α) [1, 2]. SIRS resulting from CPB is manifested by the development of respiratory distress [3]. The extensive cytokine production in SIRS often leads to multiple organ dysfunction syndrome (MODS) after CPB [4]. These unfavorable responses due to CPB are thought to be more serious in pediatric cardiac surgery, because it involves a greater proportion of blood drawn through cardiotomy suction and a larger bypass circuit surface area in contact with blood components. The use of heparin-treated surfaces in CPB circuits in adult cardiac surgery has decreased activation of leukocytes and the complement cascade [5]. Several reports on pediatric cardiac surgery have also discussed decreased inflammatory responses with heparin-bonded or -coated CPB circuits [6]. However, it remains to be determined whether the use of heparin-immobilized CPB circuits can improve postoperative clinical manifestations in children. The purpose of this study is to assess the effects of heparin-bonded circuits on inflammatory cytokine responses and on early postoperative clinical status, and to determine the interrelationship among cytokine responses and intraoperative and postoperative clinical data in 34 pediatric patients undergoing cardiac surgery.

Patients and Methods

After obtaining the ethics committee approval and the informed consent of the parents, 34 children undergoing elective intracardiac repair with hypothermic CPB for congenital heart diseases were included in this study as subjects and were randomly assigned to undergo cardiac repair using either a heparin-bonded circuit (CAPIOX-SX (HP), Terumo Corporation, Tokyo, Japan) (group H, n = 17) or a matched non-heparin-bonded control circuit (group C, n = 17). In group H, the entire CPB circuit, including the membrane oxygenator, the venous and cardiotomy reservoir, and all tubing, was fully coated with covalently bonded heparin. Basic preoperative data for the patient groups are summarized in Table 1. Between both groups, the diagnoses were similar. There were no statistically significant differences in age, body weight, or hematocrit score before surgery.

Anesthesia and CPB

All patients received modified neurolepto-anesthesia and analgesia, including fentanyl, midazolam, and pancuronium bromide or vecuronium bromide as neuromuscular agent. CPB was provided with central perfusion and bicaval venous drainage. Heparin (300 IU/kg body weight) was given to maintain an activated clotting

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Table 1. Preoperative Patient Data

Variable	Conventional Control Circuit Group (n = 17)	Heparin-Bonded Circuit Group (n = 17)
Diagnosis		
ASD	2	2
VSD	5	5
CAVC	2	2
TOF	4	3
TGA	1	0
VSD and PS	1	2
VSD and ASD and PDA	2	2
DORV and PAPVC and PS	0	1
Age (years)[a]	2.0 ± 0.5	2.5 ± 0.3
Body weight (kg)[a]	9.7 ± 1.3	11.8 ± 0.9
Hematocrit (%)[a]	32.0 ± 1.3	33.4 ± 0.8

[a] Data are expressed as mean plus or minus standard error of the mean. There are no significant differences between the two groups.

ASD = atrial septal defect; CAVC = complete atrioventricular canal; DORV = double-outlet right ventricle; PAPVC = partial anomalous pulmonary venous connection; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TGA = transposition of great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

time of more than 400 seconds during bypass in both groups. Extracorporeal circulation was accomplished using a Stockert-Shiley roller pump (Shiley Inc, Irvine, CA) with pulsatile flow control. The total prime volume (450 mL) of the extracorporeal circuit was primed with 20% mannitol, a 25% volume of albumin solution, Ringer's lactate solution, and a 7% volume sodium bicarbonate. Heparin was added to the priming solution (5 IU/mL). In all patients, the extracorporeal circuit was clearly primed without homologous blood transfusion at the start of CPB. However, when the hematocrit decreased to less than 20%, homologous erythrocytes were transfused. The surgery proceeded under systemic hypothermia at a minimum temperature of 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 rate of 2.5 L/m^2/min was maintained. At the end of CPB, a bolus of protamine sulfate was given to neutralize the heparin effect in a concentration of 1.3 mg/100 IU of heparin.

Blood Sampling and Assay

Blood samples were taken from the indwelling radial arterial catheter after the induction of anesthesia and before CPB (before systemic administration of heparin), at 5 and 60 minutes after the start of CPB, immediately after CPB (before protamine neutralization), and 24 hours after CPB.

From a portion of the samples, leukocytes and platelets were counted using a MAXM-A/L-Retic (Beckman Coulter, Miami, FL). The remainder of the samples were collected in vacuum tubes with ethylenediaminetetraacetic acid (EDTA) and immediately centrifuged at 3,000 *g* for 10 minutes at 4°C. Plasma specimens were frozen and stored at −70°C until the cytokines were assayed. TNF-α, IL-6, and IL-8 were determined using enzyme-linked immunosorbent assay kits (TNF-α, IL-6: R&D Systems, Minneapolis, MN, IL-8: TFB, Inc, Tokyo, Japan). These assays employ the quantitative sandwich enzyme immunoassay technique. A mono- or polyclonal antibody specific for each human cytokine was precoated onto the microplate provided in the kit. Standards and samples were pipetted into the wells, and any cytokine present was bound by the immobilized antibody. After any unbound sample proteins were washed away, a specific enzyme-linked poly- or monoclonal antibody was added to the wells to "sandwich" any cytokine immobilized. After a wash to remove any unbound antibody-enzyme reagent, an enhanced luminol or tetramethylbenzidine/peroxide substrate solution was added to the wells, and light developed in proportion to the amount of cytokine bound in the initial step. A microplate luminometer was used to measure the intensity of the light emitted. Alterations in leukocytes, platelets, and the plasma level of the cytokines at five time points were compared between and among the two groups.

Respiratory Index

Respiratory Index (RI) is an indicator of oxygenation and reflects the presence of pulmonary shunting in a variety of circumstances including atelectasis, pulmonary contusion, and pulmonary emboli. To standardize alveolar-arterial oxygen gradients to the inspired fraction of oxygen during ventilation, the RI was calculated as follows: RI = alveolar-arterial oxygen tension gradient/arterial oxygen tension. The index was calculated immediately after, and 3 and 6 hours after, the end of CPB.

Postoperative Blood Loss

To clarify the difference in postoperative clinical status between the groups, blood loss through chest drainage tubes was measured for 48 hours after surgery and compared between both groups. Postoperative blood loss was expressed in milliliters per 1 kg of body weight.

Postoperative and Preoperative Body Weight Percent Ratio (%R-BW)

The body weight percent ratio (%R-BW) 24 and 48 hours after CPB was determined as an indicator of postoperative body weight gain. In addition, differences in cytokine levels, leukocyte and platelet counts, and postoperative clinical variables between the groups were examined. Furthermore, we investigated both groups as a whole to identify the relationship between the parameters measured over time and the postoperative variables.

Statistical Analysis

All values were expressed as a mean plus or minus the standard error of the mean. Two-way analysis of variance with repeated measures was employed for comparisons of variables measured over time between the groups. Data were further compared by unpaired *t* test or Bonferroni's test. Correlation of independent parameters was determined using Spearman's rank correlation coeffi-

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Table 2. Intraoperative Patient Data

Variable	Conventional Control Circuit Group (n = 17)	Heparin-Bonded Circuit Group (n = 17)
CPB time (min)	148.4 ± 15.3	165.6 ± 22.8
AXC time (min)	89.4 ± 9.9	102.8 ± 18.9
Heparin (U)	2,771 ± 386	3,547 ± 348
Protamine (mg)	32.4 ± 4.7	38.6 ± 3.6
Blood transfusion (U)	1.49 ± 0.29	1.55 ± 0.35
Hemodilution (%)	36.3 ± 2.7	36.3 ± 2.3

There are no significant differences between the two groups.

AXC = aortic cross-clamp; CPB = cardiopulmonary bypass.

cient. The results were considered significant if the *p* value was less than 0.05.

Results

Patients and Postoperative Clinical Variables

Intraoperative clinical data of both groups are summarized in Table 2. There were no significant differences in the CPB or aortic cross-clamp time, the administered heparin or protamine dosages, the amount of transfused blood, or in the hemodilution rate between the groups.

The postoperative clinical data are summarized in Table 3. There were no operative deaths or early reexplorations for bleeding in either group. There were also no significant differences in postoperative blood loss over the first 48 hours, in intubation time, or in duration of intensive care unit (ICU) or hospital stays between the groups. However, 1 patient in group C who had prolonged pulmonary hypertension after a ventricular septal defect (VSD) closure, and 1 in group H who developed low cardiac output after corrective repair of a double-outlet right ventricle (DORV) with partial anomalous pulmonary venous connection (PAPVC) and pulmonary stenosis (PS), were ventilated for more than 24 hours. Two patients in group C and 1 in group H developed pneumonia, and 1 patient in group H developed a sternal wound infection, which required late reexploration. These 4 patients remained in our hospital for over 30 days.

Table 3. Postoperative Patient Data

Variable	Conventional Control Circuit Group (n = 17)	Heparin-Bonded Circuit Group (n = 17)	*p* Value
Blood loss (mL/kg) (from ICU admission to 48 hours PO)	21.1 ± 1.3	17.3 ± 2.7	NS
Respiratory Index			
Just after CPB	0.96 ± 0.27	0.75 ± 0.19	NS
3 hours after CPB	1.16 ± 0.16	0.71 ± 0.13	< 0.05
6 hours after CPB	1.05 ± 0.20	0.82 ± 0.14	NS
%R-BW			
24 hours after CPB (%)	103.5 ± 1.0	99.3 ± 0.8	< 0.01
48 hours after CPB (%)	100.7 ± 1.0	97.6 ± 0.9	< 0.05
Intubation time (hours)	13.9 ± 5.3	10.9 ± 3.2	NS
ICU stay (days)	2.9 ± 0.4	2.7 ± 0.4	NS
Hospital stay (days)	24.5 ± 3.7	21.7 ± 3.2	NS

CPB = cardiopulmonary bypass; ICU = intensive care unit; NS = not significant; PO = postoperatively; %R-BW = post/preoperative body weight percent ratio.

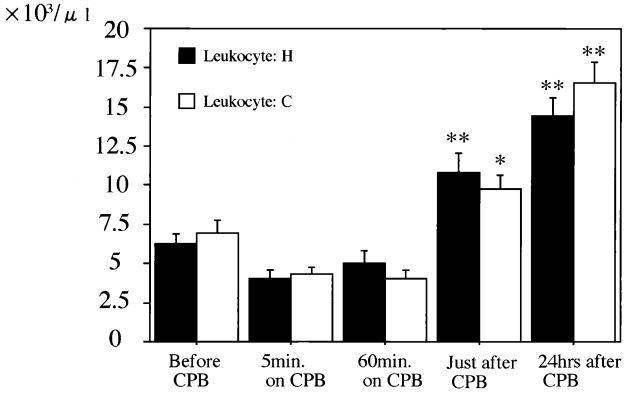

*Fig 1. Changes in leukocyte counts before, during, and after CPB in the heparin-bonded (H) and control (C) groups. There were significant changes within both groups, but no significant difference between the groups. Values are means ± standard error. (*p < 0.05 vs before CPB; **p < 0.01 vs before CPB.)*

Group H had a significantly lower RI than group C only 3 hours after CPB, but no significant differences were noted just after or 6 hours after CPB. Renal function (serum creatinine and urea levels), inotropic agent requirements, and total infusion volume up to 24 hours after CPB (57.7 ± 3.9 mL/kg in group H vs 56.7 ± 3.8 mL/kg in group C), and up to 48 hours after CPB (92.6 ± 12.2 mL/kg in group H vs 87.4 ± 10.9 mL/kg in group C) did not significantly differ between the groups. However, the post- and preoperative %R-BW at 24 and 48 hours after CPB was lower in group H.

Leukocytes

Although leukocyte counts did not significantly increase during CPB in either group, the levels were significantly higher than prebypass levels immediately after and 24 hours after CPB in both groups. However, the leukocyte count pattern was similar over time, and there was no significant difference between the groups at any point (Fig 1).

Platelets

In both groups, platelet counts significantly decreased after beginning CPB, and remained lower than prebypass values for 24 hours after CPB. No significant differences were found between the groups (Fig 2).

Cytokines

TNF-α. Plasma levels of tumor necrosis factor-alpha (TNF-α) did not change significantly during CPB in either

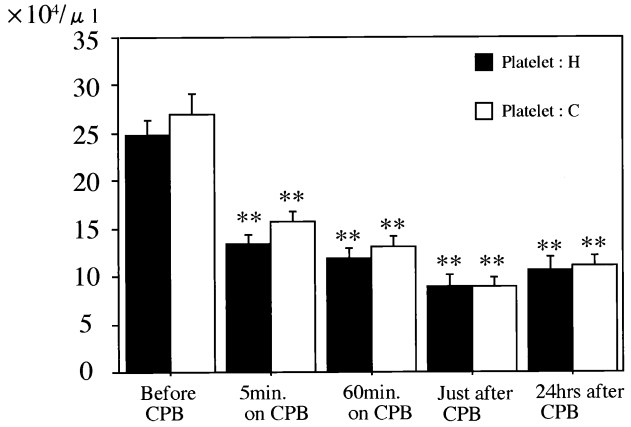

*Fig 2. Changes in platelet counts before, during, and after CPB in the heparin-bonded (H) and control (C) groups. There was a significant decrease in each group, but no significant difference between both groups. Values are means ± standard error. (**p < 0.01 vs before CPB.)*

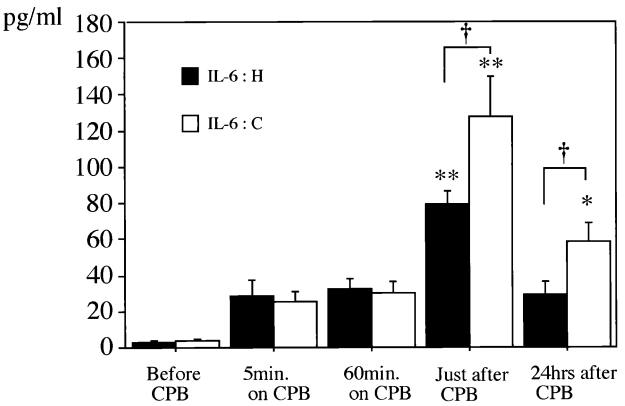

*Fig 4. Change in the plasma levels of IL-6 before, during, and after CPB in the heparin-bonded (H) and control (C) groups. The increase in IL-6 levels just after CPB was significantly lower in group H, and IL-6 levels 24 hours after CPB remained lower in group H. Values are means ± standard error. (*p < 0.05 vs before CPB; **p < 0.01 vs before CPB; †p < 0.05, group H vs group C.)*

group (Fig 3). However, in group C, the TNF-α level just after CPB was significantly higher than before CPB, while in group H, the TNF-α level 24 hours after CPB was significantly lower than the prebypass values. The TNF-α level patterns between the groups differed significantly ($p = 0.0002$). Furthermore, group H showed a significantly lower level than group C just after CPB (3.17 ± 0.40 vs 5.72 ± 0.98 pg/mL; $p = 0.0217$).

IL-6. In both groups, interleukin-6 (IL-6) levels significantly increased just after CPB, compared with prebypass levels (Fig 4). In group C, the level at 24 hours after bypass remained higher than prebypass. Moreover, the IL-6 level patterns differed significantly between the groups ($p = 0.0066$); immediately after CPB, group H showed significantly lower levels than group C (79.03 ± 7.4 vs 127.3 ± 22.2 pg/mL; $p = 0.0477$).

IL-8. Both groups had significant increases in plasma IL-8 levels just after CPB, which then decreased toward preoperative levels 24 hours after CPB in both groups (Fig 5). The IL-8 level patterns of the groups differed significantly ($p = 0.0163$); just after CPB, IL-8 levels in group H were significantly lower than those in group C (27.0 ± 3.7 vs 47.1 ± 8.4 pg/mL; $p = 0.0368$).

Correlations

Significant relationships among cytokine levels and the intra- and postoperative clinical variables examined in this study are summarized for all subjects in Table 4. In particular, TNF-α levels just after bypass correlated with %R-BW 24 hours after CPB (Fig 6), and IL-8 just after CPB correlated with RI 3 hours after CPB (Fig 7). Furthermore, there was a significant correlation between IL-6 24 hours after CPB and both %R-BW and duration of hospital stay ($p < 0.01$, respectively).

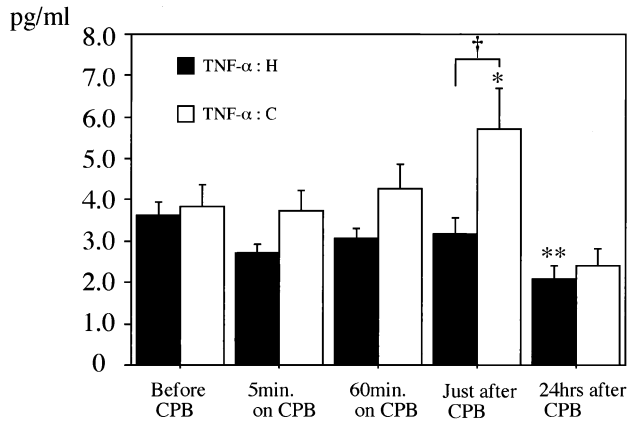

*Fig 3. Changes in the plasma levels of TNF-α before, during, and after CPB in the heparin-bonded (H) and control (C) groups. TNF-α levels just after CPB were significantly lower in group H. Values are means ± standard error. (*p < 0.05 vs before CPB; **p < 0.01 vs before CPB; †p < 0.05, group H vs group C.)*

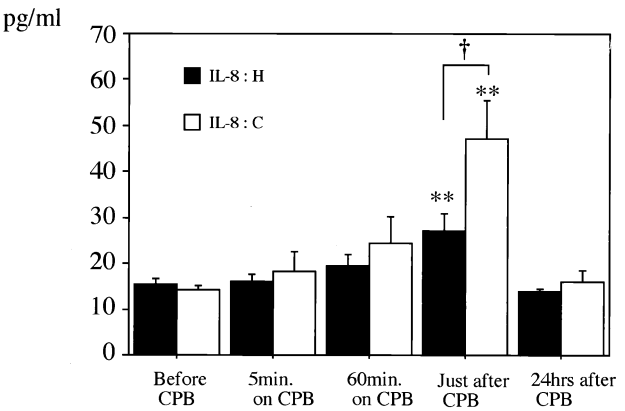

*Fig 5. Change in the plasma levels of IL-8 before, during, and after CPB in the heparin-bonded (H) and control (C) groups. The increase in IL-8 levels just after CPB was significantly lower in group H. Values are means ± standard error. (**p < 0.01 vs before CPB; †p < 0.05, group H vs group C.)*

Table 4. Correlation Coefficients[a] for Cytokine Levels and Intraoperative and Postoperative Clinical Variables

Cytokine	Duration		RI 3 Hours After CPB	%R-BW		Hospital Stay
	AXC	CPB		24 Hours After CPB	48 Hours After CPB	
TNF-α						
Just after CPB	0.40[b]	0.39[b]	0.42[b]	0.56[c]	0.39[b]	NS
24 hours after CPB	NS	NS	NS	0.44[b]	0.36[b]	0.35[b]
IL-6						
Just after CPB	0.48[c]	0.56[c]	NS	NS	NS	NS
24 hours after CPB	0.42[b]	0.35[b]	NS	0.49[c]	0.56[c]	0.48[c]
IL-8						
Just after CPB	0.46[c]	0.40[b]	0.52[c]	NS	NS	NS

[a] Each correlation coefficient was determined using Spearman's correlation method (n = 34). [b] $p < 0.05$. [c] $p < 0.01$.

AXC = aortic cross-clamp; CPB = cardiopulmonary bypass; IL-6 = interleukin-6; IL-8 = interleukin-8; NS = not significant; RI = respiratory index; TNF-α = tumor necrosis factor-α; %R-BW = post/preoperative body weight percent ratio.

Comment

Our findings confirmed the existence of proinflammatory cytokine responses to pediatric CPB and clearly demonstrated that the use of heparin-bonded CPB circuits with an otherwise nonbonded conventional circuit results in reduced inflammatory cytokine responses, as determined by levels of TNF-α, IL-6, and IL-8. It should be noted that changes in leukocyte and platelet counts did not differ between groups, and that heparin bonding did not improve postoperative blood loss, intubation time, or length of ICU or hospital stays. However, the reduction in cytokine response due to heparin bonding positively affected postoperative status by decreasing body weight gain and transiently improving postbypass respiratory index.

Over the past 10 years, a number of unfavorable reactions related to CPB have been reported [2, 7]. The so-called postpump inflammatory response is believed to be caused by blood contact with foreign materials and exposure to abnormal shear forces [8]. CPB initiates a generalized systemic inflammatory response characterized by activation of complement [7], neutrophils [9], and proinflammatory cytokines [1, 10, 11]. This study also noted a significant increase in proinflammatory cytokines after conventional CPB. Moreover, all postbypass cytokine levels significantly correlated with the duration of CPB and aortic cross-clamp in all patients. The dependence of cytokine levels on CPB or cross-clamp time may explain the variation in cytokine levels reported by various investigators [2]. Though variations are commonly introduced by sampling differences and methods of assay, in general, proinflammatory cytokines are induced by CPB, and their levels are associated with the duration of CPB [10, 12].

TNF-α is a powerful inflammatory mediator released by activated monocytes and macrophages [13]. However, recent research on plasma TNF levels associated with CPB has disagreed on detectable levels [1, 2, 10, 14]. These disagreements are probably due to variations in

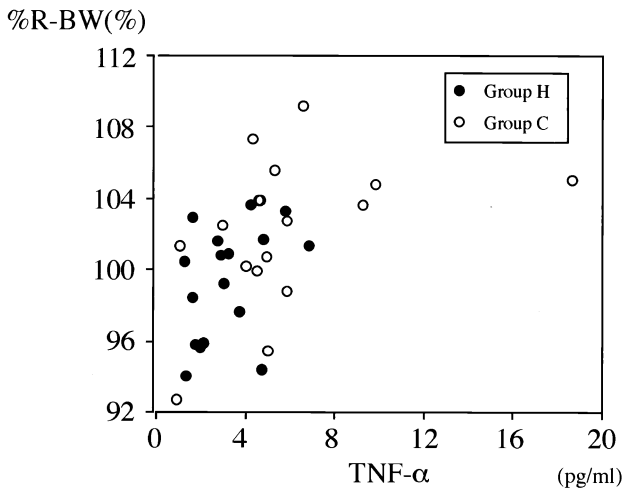

Fig 6. Relationship between TNF-α levels, just after CPB, and the post- and preoperative %R-BW, 24 hours after CPB. Spearman's correlation coefficient = 0.56 (p < 0.005). (Group H = *heparin-bonded group;* Group C = *control group.)*

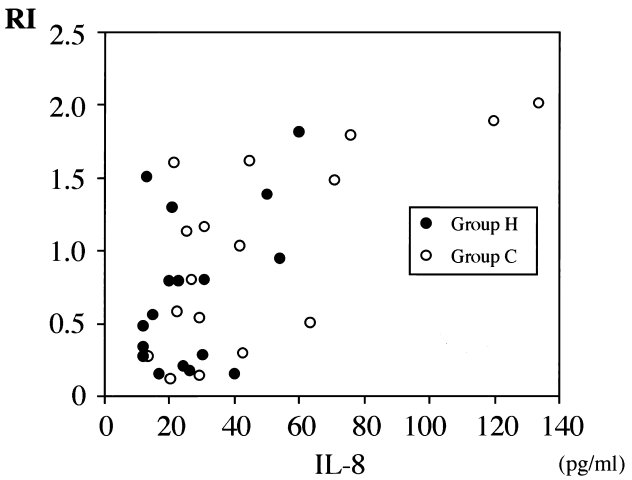

Fig 7. Relationship between the level of IL-8, just after CPB, and RI, 3 hours after CPB. Spearman's correlation coefficient = 0.52 (p < 0.005). (Group H = *heparin-bonded group;* Group C = *control group.)*

the type and detection sensitivity of the assays [15], and to the increases in plasma concentrations in the early stage of the inflammatory response and the rapid decreases through degradation [16]. TNF-α is responsible for fever and postoperative morbidity after CPB [14]. Moreover, inflammatory mediators have the capability to increase microvascular permeability. Among these mediators, TNF-α plays a major role in increased microvascular permeability [17]. In our series, post-CPB TNF-α levels were significantly associated with postoperative body weight gain, respiratory index, and duration of hospital stay. Most importantly, a relatively strong relationship between TNF-α levels and both body weight gain and respiratory deterioration in this study may suggest that TNF-α causes increased microvascular permeability and tissue damage [17], as well as protein leakage due to pulmonary vascular injury [18]. In experimental and human studies, TNF-α can directly cause hypotension, coagulopathy, and renal dysfunction [4]. A study of 20 pediatric patients undergoing corrective cardiac surgery found that TNF-α levels 1 day after CPB were strongly associated with SIRS/MODS, and that TNF-α was most highly correlated with clinical complications due to SIRS/MODS [4]. These results suggest significant interrelationship between every postoperative clinical element and TNF-α.

IL-6 is involved in the modulation of the acute phase response and is synthesized by a variety of activated cell types including monocytes, macrophages, endothelial cells, and fibroblasts after stimulation by TNF-α and IL-1 [2, 19]. IL-6 also appears to be a sensitive early marker of tissue damage, and its level is thought to be of prognostic value for septic shock. Hauser and colleagues [20] demonstrated that serum and alveolar IL-6 levels after infant CPB correlated with postoperative morbidity, and that serum IL-6 levels correlated with mortality. Similarly, our study confirmed that IL-6 levels measured 24 hours after CPB positively correlated with both the post- and preoperative body weight ratio and the duration of hospital stay. Therefore, the plasma level of IL-6 24 hours after CPB may be a meaningful predictor of morbidity and mortality in the early postoperative period.

IL-8 is originally isolated from peripheral blood mononuclear cells and is produced by endothelial cells, alveolar macrophages, and leukocytes, including neutrophils, after stimulation by TNF-α and IL-1β [21, 22]. Finn and colleagues noted a relationship between total CPB time and IL-8 levels [10], which is consistent with our results. This relationship may explain postoperative organ damage, including pulmonary dysfunction, generally associated with longer CPB duration. Administration of IL-8 to animals can cause plasma leakage and lung injury due to accumulation of neutrophils [23]. Furthermore, high levels of this cytokine have been detected in the bronchoalveolar lavage fluid of patients after CPB [24]. Ito and colleagues noted that patients with a lower oxygenation index ($<$ 250) on postoperative day 1 had significantly higher plasma levels of IL-8 just after CPB, compared with a group with a higher oxygenation index ($>$ 250) [12]. Hence, these investigations suggest that peak IL-8 levels are positively associated with respiratory indices after bypass.

Recent clinical studies in adult cardiac surgery [5, 25] have attributed a reduction in systemic inflammatory responses to the superior biocompatibility of heparin-immobilized circuits. In pediatric cardiac surgery, there are additional factors to consider. In comparison with adult surgery, blood components are exposed to a larger foreign surface area in the 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 expected in pediatric CPB. Currently, the effect of heparin-bonded or heparin-coated devices on cytokine production has been documented in children [6] as well as adults [11, 25]. In this study, IL-6 levels in the conventional group remained significantly higher than in the bonded group, not only immediately after, but also 24 hours after CPB. Ashraf and associates [6] observed a significant difference in IL-6 levels, 24 hours after operation, between pediatric groups treated with either heparin-bonded oxygenators or nonbonded oxygenators, and our findings correspond with theirs. The potential of heparin-bonded CPB circuits to decrease TNF-α release remains controversial [6, 25]. However, the fact that we utilized fully heparin-bonded circuits rather than those with only a heparin-bonded oxygenator might have contributed to the significantly lower TNF-α levels in our study [11].

Numerous studies have been undertaken to ascertain postoperative clinical benefits due to heparin-treated CPB. In the present study, we found no significant differences in postoperative blood loss or platelet counts between the groups. Wagner and colleagues [26] also reported that the use of a heparin-coated CPB circuit did not provide significant benefits in postoperative blood loss or hemostatic alterations. Our results are similar, indicating that unless the total amount of heparin administered or activated clotting time are decreased, it may be impossible for heparin-treated CPB circuit to reduce postoperative blood loss. However, another study [6] reported that in young children exposed to heparin-bonded oxygenators, postoperative ventilation time was significantly reduced. Moreover, less pulmonary injury after CPB with heparin-coated circuits has been noted in several studies [27, 28]. We found that there was a transient, but significant, improvement in respiratory function after bypass using a heparin-bonded CPB circuit, probably resulting from significantly lower peak plasma levels of IL-8, which correlated with respiratory indices after bypass. This study, however, failed to demonstrate definite postoperative clinical benefits with respect to intubation time and the length of ICU and hospital stays. Perhaps, the potential of heparin-bonded CPB circuits to ameliorate postoperative clinical outcome is not dramatic, or statistical significance could not be achieved because of considerable variations in clinical data within the groups due to varying patient characteristics, including differences in surgical treatment. Recently, several antiinflammatory strategies, such as leu-

kocyte depletion [29], have been utilized in cardiac surgery with CPB. If heparin bonding of CPB circuits is combined with these strategies, inflammatory responses to CPB may be further reduced.

In conclusion, this study demonstrated that the use of heparin-bonded CPB circuits resulted in reduced proinflammatory cytokine responses, and that this cytokine reduction had a positive impact on body weight gain and respiratory function in children.

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