Phosphorylcholine or heparin coating for pediatric extracorporeal circulation causes similar biologic effects in neonates and infants

Andreas Böning, MD^a
 Jens Scheewe, MD^a
 Thomas Ivers, ECCP^a
 Christine Friedrich, PhD^a
 Jürgen Stieh, MD^b
 Sandra Freitag, PhD^c
 Jochen T. Cremer, PhD^a

Objective: Cardiac surgery for complex congenital malformations with use of extracorporeal circulation predisposes to an excessive systemic inflammatory response and a consecutive capillary leak syndrome. In a prospective randomized study the influence of 2 oxygenators especially designed for pediatric use on inflammatory markers and clinical outcome was investigated.

Methods: Forty neonates and infants (body surface area, $<0.36 \text{ m}^2$) undergoing cardiac surgery with extracorporeal circulation were randomized into one of 3 groups: in the first group ($n = 14$) the Medtronic Minimax Oxygenator and in the second group ($n = 12$) the Dideco Lilliput 1 Oxygenator, both with a 750-mL priming volume, were used. In the third group the Dideco Lilliput 1 Oxygenator was filled with a reduced priming volume of 450 mL. Parameters of interest for evaluation of a systemic inflammatory response after extracorporeal circulation were interleukin 6, tumor necrosis factor α , neutrophil elastase, complement C3, and free hemoglobin. In addition, erythrocyte, leukocyte, and thrombocyte counts and hemoglobin and C-reactive protein values were determined at different measurement points before, during, and after the operation.

Results: In all 3 groups peak values for tumor necrosis factor α were observed during the operation, whereas interleukin 6, elastase, and free hemoglobin values peaked in the first 4 hours. The highest values for leukocytes and C-reactive protein were obtained between 24 and 72 hours after the operation. Erythrocyte and thrombocyte counts, as well as hemoglobin values, were lowest at extracorporeal circulation onset, normalizing under substitution in the first 4 hours after the operation. By using the Lilliput/750 oxygenator, higher interleukin 6 values 1 and 4 hours after the operation and higher tumor necrosis factor α values during and 1 hour after the operation could be observed compared with results with the Minimax and Lilliput/450 oxygenators. In spite of our randomization protocol, patients in the Lilliput/750 group were significantly smaller and younger than those in the Minimax group. However, the statistical analysis showed no correlation between age and interleukin 6 or tumor necrosis factor α values, but it did show a correlation between younger age and the occurrence of capillary leak syndrome. Accordingly, the number of children with clinically complicated course (capillary leak, longer duration of catecholamine therapy, and ventilation) was higher in the Lilliput/750 group than in the Minimax group.

Conclusion: By using an adequate priming volume, the systemic inflammatory response is similar after use of the Dideco Lilliput 1 Oxygenator and the Medtronic Minimax Oxygenator. Tip-to-tip surface coating of the extracorporeal circulation with either heparin or phosphorylcholine seems to have similar biologic effects in neonates and infants undergoing cardiac surgery.

From the Department of Cardiovascular Surgery,^a the Department of Pediatric Cardiology,^b and the Institute of Medical Informatics and Statistics,^c University Hospital, Kiel, Germany.

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Address for reprints: Andreas Böning, MD, Department of Cardiovascular Surgery, University Hospital, Arnold-Heller-Str 7, 24105 Kiel, Germany (E-mail: aboening@kielheart.uni-kiel.de).

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Excessive systemic inflammatory response (SIR) and a consecutive capillary leak syndrome are known to be adverse events after complex pediatric cardiac procedures using extracorporeal circulation (ECC). Such deleterious effects have been described in up to 27.5% of neonates.¹ Coating of ECC surfaces either with heparin² or with phosphorylcholine³ has protective effects on the SIR compared with uncoated ECC surfaces. For ECC, aortic clamping, and circulatory arrest times, see Table 1. However, most of the reported studies only show differences in inflammatory mediators without assessing the effect for the clinical course of the young patients. Moreover, the 2 different surface coatings have not been compared yet in pediatric cardiac surgery. Our intention was to compare the 2 pediatric ECC systems and oxygenators used in our institution (Lilliput 1; Dideco, Nürnberg, Germany, and Minimax; Medtronic, Düsseldorf, Germany) in a prospective randomized study. This study in neonates and infants with a body surface area (BSA) of less than 0.36 m² comprises laboratory parameters and clinical data to get a more complete idea of negative ECC effects and to look for the potential for clinical improvement.

Patients and Methods

Patient Inclusion Criteria

Forty consecutive patients with a BSA of less than 0.36 m² undergoing surgical intervention for congenital heart defects were included in the study. The upper limit of flow to be reached with the Dideco Lilliput 1 Oxygenator is 1 L/min. Therefore our policy to allow for a flow of $3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ BSA limits the use of this oxygenator to patients with a BSA of less than 0.36 m². A blocked randomization was carried out by using a randomization table created by Campbell and Machin.⁴ This table contains digits that are assigned to one of the 3 study groups. Starting at the top of the randomization table, each patient receives one digit that assigns him or her to one of the study groups.

Except for one patient, children undergoing the Norwood I procedure were excluded from the study because they took part in another investigation. The need for extracorporeal circulatory assist after the operation was a postoperative exclusion criterion. Demographic data of the children, the kind of procedure, and the percentage of cyanotic malformations are listed in Table 2.

Ethical approval was obtained from the Ethics committee of the University of Kiel. Parents were informed about the study by the surgeons and gave their written informed consent.

ECC Setup

The ECC circuit was an open system and consisted of a heparin-coated system in the first group of patients: a Minimax Plus CB 3381 oxygenator (Medtronic) with an uncoated hardshell reservoir, a coated CB1339 arterial filter (Medtronic, Düsseldorf, Germany), and heparin-coated polyvinylchloride tubing. In the other group of patients, a Lilliput D 902 oxygenator (Dideco-Sorin, Puchheim, Germany) was combined with a coated D 736 arterial filter and

polyvinylchloride tubing, and the whole circuit was coated with phosphorylcholine.

With this setup, the Medtronic Minimax Oxygenator required a 750-mL priming volume, whereas a 450-mL priming volume was sufficient for the Dideco Lilliput 1 Oxygenator (Lilliput/450). To exclude the volume effect, we therefore formed another group of patients treated with the Dideco Lilliput 1 Oxygenator with a 750-mL priming volume (Lilliput/750). The composition of priming volumes is given in Table 3.

The ECC prime was adjusted to a hematocrit level of 20 to 25 g/dL and a pH of more than 7.2, depending on the condition of the children. Cardiopulmonary bypass (CPB) was conducted by using an alpha-stat regimen for patients who were cooled to greater than 30°C or a pH-stat regimen during the cooling period, followed by an alpha-stat regimen during the warming period for patients who were cooled to 18°C for circulatory arrest.

The cardioplegia lines were uncoated. Because crystalloid cardioplegia was given from the anesthesiologist's position, this line did not have contact with blood. Other material and methods that might affect SIR (aprotinin and modified ultrafiltration, as well as homograft material) were not used throughout the study.

Anesthesia and Surgical Procedures

Total intravenous anesthesia was introduced with sufentanil and pancuronium, sometimes aided by the application of isoflurane. Premedication (midazolam) was only given in children older than 6 months. Steroid pretreatment (1.5 mg/kg dexamethasone) was administered the evening before the operation and not during ECC.

After median sternotomy and hemithymectomy, the pericardium was opened, and heparin (300 U/kg body weight) was administered. Cannulation of the main systemic artery and the right atrium or the caval veins was performed, followed by induction of the ECC. Depending on the procedure, the children were either kept in moderate hypothermia or cooled down to deep hypothermia. The surgical procedure was carried out under low-flow perfusion to avoid long uninterrupted periods of total circulatory arrest. In cases with aortic crossclamping, St Thomas II cardioplegia was infused in an antegrade manner with a dose of 10 mL/kg body weight. A cardioplegia dose of 20 mL was repeated every 30 minutes.

None of the patients received aprotinin intraoperatively. Hemofiltration or ultrafiltration was not used routinely but rather in 1 or 2 patients in each group. The heparin effect was monitored throughout the procedure by using the activated clotting time with an ACT II device (Medtronic), maintaining the activated clotting time at greater than 400 seconds. Neutralization of heparin at the end of CPB was achieved with protamine sulfate (1:1 heparin dosage).

Depending on the individual cardiac performance, dopamine, adrenalin, or nitroprusside sodium was infused continuously before weaning from CPB, and phosphodiesterase inhibitors were given as a bolus.

Collection of Blood Samples

Blood samples (interleukin [IL] 6, tumor necrosis factor [TNF] α , elastase, C3, free hemoglobin, hemoglobin, erythrocytes, leukocytes, thrombocytes, and C-reactive protein [CRP]) were taken before skin incision, after ECC induction, after protamine appli-

TABLE 1. Intraoperative times

	Minimax	<i>P</i> value M/L750, <i>t</i> test	Lilliput 750	<i>P</i> value L750/L450, <i>t</i> test	Lilliput 450	<i>P</i> value L450/M, <i>t</i> test
ECC time (min)	123 ± 45	.609	133 ± 51	.722	127 ± 34	.786
Aortic clamping time (min)	46 ± 31	.495	57 ± 46	.219	36 ± 34	.434
Circulatory arrest time (min)	10 ± 17	.149*	19 ± 19	.066*	6 ± 9	.910*
	Median: 10,4 (0/33)		Median: 19,1 (0/38)		Median: 6,2 (0/14)	

M, Minimax Oxygenator; L750, Lilliput 1 Oxygenator with 750-mL priming volume; L450, Lilliput 1 Oxygenator with 450-mL priming volume; ECC, extracorporeal circulation.

*Wilcoxon rank sum tests (all others *t* test).

TABLE 2. Patient demographic data and type of procedure

	Minimax	<i>P</i> value M/L750, <i>t</i> test	Lilliput (750 mL, L750)	<i>P</i> value L750/L450, <i>t</i> test	Lilliput (450 mL, L450)	<i>P</i> value L450/M, <i>t</i> test
No. of patients	14		12		14	
Age (d)	140 ± 54	.012	77 ± 65	.143	121 ± 81	.484
Body weight (kg)	5254 ± 847	.014	4373 ± 839	.327	4757 ± 1073	.185
Body surface area (m ²)	.28 ± 0.04	.015	0.25 ± 0.03	.172	0.27 ± 0.04	.361
Type of procedure (n)						
Norwood I			1			
Hemi-Fontan	4		3		5	
Arterial switch			3		1	
AV canal correction	1		1		2	
VSD closure	8		3		4	
Unifocalization	1					
Aortic arch correction					1	
					1	
RVOT correction			1			
TOF correction						
Cyanotic malformation	n = 5/42.9%		n = 8/75%		n = 7/64.3%	

M, Minimax Oxygenator; L750, Lilliput 1 Oxygenator with 750-mL priming volume; L450, Lilliput Oxygenator 1 with 450-mL priming volume; AV, atrioventricular; VSD, ventricular septal defect; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot.

TABLE 3. Composition of priming for the extracorporeal circulation

	Minimax	Lilliput 750	Lilliput 450
Packed red cells (mL)	300	300	100
Fresh frozen plasma (mL)	200	200	200
Ringer's lactate (mL)	200	200	100
Heparin	1000 IE	1000 IE	1000 IE
NaHCO ₃ (mL)	7	7	5
HES (mL)	50	50	50
Sum (mL)	757	757	455

HES, Hydroxy ethyl starch.

cation, and 1, 4, 8, and 24 hours after skin closure. On the second, third, and fifth day after the operation, only levels of hemoglobin, erythrocytes, leukocytes, thrombocytes, and CRP were determined.

IL-6 was measured as a marker for white cell interaction and complement activation, neutrophil elastase and TNF- α were mea-

sured as markers for activation of leukocytes, and complement C3 was measured as a marker for activation of both complement pathways. All samples were immediately centrifuged and either stored at -80°C or freshly analyzed. CRP and leukocyte counts were registered as markers for systemic inflammation, and free hemoglobin and total hemoglobin values were registered as markers for hemolysis by the ECC. Erythrocyte and thrombocyte counts were obtained to detect differences in blood dilution and cellular coagulation disorders. Samples for these values were directly analyzed in the hospital's laboratory by using routine methods.

Collection of Clinical Data

Seghaye and associates¹ defined multiple system organ failure (MSOF) as the acute simultaneous occurrence in the first postoperative week of the failure of at least 2 vital organs in addition to cardiac insufficiency, thrombocytopenia ($<100,000/\mu\text{L}$), and high fever ($>39^{\circ}\text{C}$). For our study, thrombocyte counts, body temperature, diuresis, creatinine levels, peritoneal dialysis, prothrombin time, coma or seizure, and abdominal bleeding were documented. In addition, the durations of adrenalin support and ventilation were

Figure 1. Peak values for TNF- α during surgical intervention do not differ significantly between groups but are highest in the Lilliput/750 group. *Preop*, Preoperative; *postop*, postoperative.

Figure 2. IL-6 values during surgical intervention were insignificantly higher in the Lilliput/750 group.

recorded. A capillary leak syndrome was defined as clinically detectable local or generalized edema.

Statistical Analyses

Statistical analyses were performed with SPSS computer software. Depending on violations of normal distribution (Kolmogorov-Smirnov test), we described the data either by mean values with SDs or by median values with 25th and 75th percentiles. To detect differences between treatment groups, we performed *t* tests, Wilcoxon rank sum tests, Fisher exact tests, or χ^2 tests adjusted with the Bonferroni correction for multiple testing. The relationship between the possible confounding variables of age and capillary leak, duration of catecholamine therapy, ventilation time, IL-6 value, and TNF- α is expressed by the Spearman correlation coefficient. For all tests, a 2-tailed significance level of 5% was set.

Results

TNF- α

Peak values were reached during the procedure (Lilliput/750, 60 ± 95 pg/mL; Lilliput/450, 20 ± 25 pg/mL; and Minimax, 35 ± 62 pg/mL), with a gentle decrease over the next 24 hours (Figure 1). Within the groups, there were major differences between the lowest and highest value at each measurement point, resulting in high SDs. Thus statistically significant differences could not be detected. However, the mean TNF- α peak value in the Lilliput/750 group was higher than that in the Lilliput/450 group.

IL-6, Elastase, and Free Hemoglobin

IL-6, elastase, and free hemoglobin each resulted in peak values at the end of the procedure and 1 hour after the

Figure 3. Complement C3, hemoglobin, and erythrocyte values showed a similar decrease caused by dilution on ECC and normalized under substitution.

Figure 4. During bypass, a nearly 70% reduction of thrombocyte numbers occurs, which is reversed by transfusion during the first postoperative hours.

operation but decreased during the next 24 hours. IL-6 (Figure 2) peaked at 115.3 ± 106 pg/mL 1 hour postoperatively in the Lilliput/750 group, but this was not significantly different ($P = .067$) than that seen in the Lilliput/450 group (38.3 ± 30.4 pg/mL) and the Minimax group (58.8 ± 36.1 pg/mL, $P = .160$). Interestingly, there was an increase of IL-6 in the Lilliput/450 group at 8 and 24 hours after the operation.

Free hemoglobin values increased symmetrically in each group to a peak at the end of the procedure (Lilliput/750, 86.4 ± 64.5 mg/dL; Lilliput/450, 84.8 ± 41.1 mg/dL; and Minimax, 68.5 ± 22.8 mg/dL) and returned to baseline values after 8 hours.

Neutrophil elastase peaked at the end of the operation in the Lilliput/450 (305 ± 233.7 pg/mL) and Minimax (221.4

± 105.2 pg/mL) groups, whereas its maximum in the Lilliput/750 group (261 ± 348.8 pg/mL) was reached only at 4 hours after the operation. In contrast to TNF- α and IL-6, the highest mean values of elastase were detected in the Lilliput/450 group, which might represent a more intensive activation of neutrophils in the Lilliput/450 group.

Leukocytes and CRP

Leukocytes and CRP reacted with an increase during the first hours after the operation and peaked at 24 hours (Lilliput/750: leukocytes, 16.7 ± 6.5 nL; CRP, 6.4 ± 4.1 mg/dL; Lilliput/450: leukocytes, 14 ± 4.2 nL; CRP, 7.5 ± 5.2 mg/dL; Minimax: leukocytes, 13.8 ± 4.2 nL; CRP, 7.7 ± 3.1 mg/dL), without significant differences between the groups. CRP values decreased rapidly after this peak, and leukocyte values remained at a higher level, as before the operation.

Erythrocytes, Thrombocytes, Complement C3, and Total Hemoglobin

Because of dilution with onset of the ECC (Figure 3), low counts of erythrocytes, thrombocytes, complement C3, and total hemoglobin were seen. The parameters normalized under substitution at the end of the operation and remained stable until the fifth postoperative day. This is also shown in Figure 4, in which a 50% to 70% reduction of thrombocyte numbers during bypass is shown. This is reversed after bypass by thrombocyte transfusions during the first 4 hours.

Clinical Data

According to the definition of Seghaye and colleagues,^{1,2} (5%) of our patients had MSOF. One of these patients died (mortality of the whole group, 2.5%) on day 35 after the operation, and the other patient recovered fully. Eight (20%)

TABLE 4. Patients' postoperative clinical data

		<i>P</i> value M/L750, <i>t</i> test		<i>P</i> value L750/L450, <i>t</i> test		<i>P</i> value L450/M, <i>t</i> test
	Minimax		Lilliput 750		Lilliput 450	
Highest creatinine level (mmol/L)	56.2 ± 10.5	.092	68.4 ± 18.1	.802	65.6 ± 28.6	.342
Diuresis (mL/24 h)	781 ± 248	.122	620 ± 200	.852	604 ± 162	.065
Lowest thrombocyte count (×1000/μL)	119 ± 37	.148	146 ± 46	.583	133 ± 50	.448
Adrenalin support (h)	32 ± 24	.016	64 ± 36	.254	44 ± 38	.276
Ventilation (h)	59 ± 71	.430	84 ± 70	.236	48 ± 58	.684
Capillary leak	n = 2 (14.3%)	.074*	n = 5 (41.7%)	.16*	n = 2 (14.3%)	.59*
Mortality	n = 1		0		0	

M, Minimax Oxygenator; L750, Lilliput 1 Oxygenator with 750-mL priming volume; L450, Lilliput 1 Oxygenator with 450-mL priming volume.

*Results of Fisher exact test.

patients, including the 2 already mentioned with MSOF, had a capillary leak syndrome; 7 of them recovered during their stay. More often, patients in the Lilliput/750 group had capillary leak syndromes, the highest creatinine levels, a longer ventilation time, and a longer time of adrenalin support than patients in the other groups (Table 4). In spite of our randomization protocol, patients in the Lilliput/750 group were significantly smaller ($P = .012$) and younger ($P = .014$) than those in the Minimax group (Table 2). After having obtained a good correlation between age, weight ($r = 0.776$), and BSA ($r = 0.824$) by using a Spearman-Rhodes test for nonparametric data, we could not find correlations between age and intraoperative times, immune response markers, and clinical data (Appendix). There was no significant difference regarding postoperative bleeding among the 3 groups, but there was a tendency toward a lower blood loss in the Lilliput/450 group.

Discussion

This study compares 2 pediatric ECC circuits with different surface coatings of their oxygenators. Our results show no superiority of one coating (heparin, Medtronic Minimax) over the other (phosphorylcholine, Dideco Lilliput 1). The fact that the results showed no significant differences in the Minimax and the Lilliput/450 groups indicates that the 2 different coatings have a biologically similar effect on the onset of an SIR. Unfortunately, in spite of a thorough randomization process,⁴ the patients in the Lilliput/750 group were statistically significantly smaller and younger than those in the Minimax group. However, we could not find a correlation between age, bypass, clamping, and arrest time and IL-6 and TNF- α values. On the other hand, there was a correlation between younger age and the onset of capillary leak syndrome. In a t test we found that patients with capillary leak (mean age, 48 ± 54 days) were significantly ($P = .002$) younger than those without capillary leak (mean age, 142 ± 54 days). This seems to be the reason why we observed an increase of the SIR with the smaller oxygenator (Dideco Lilliput 1) with a priming volume (750

mL) as high as that in the bigger oxygenator (Medtronic Minimax). This increase is proved by a worse clinical outcome (higher number of capillary leaks and longer duration of ventilation and adrenalin support) and not by a difference in immune system mediators.

The clinical results (Table 4) during this trial were satisfying. The mortality was 2.5% (one patient died from multiple organ failure after cavopulmonary anastomosis), and the incidence of clinically apparent MSOF, as defined by Seghaye and colleagues¹ was 5% (one was the patient who died subsequently, and another patient recovered fully). Compared with the high incidence of MSOF, reported by Seghaye and colleagues¹ as being as high as 27.5% with a noncoated CPB circuit, our results seem to be comparably good. The apparently high incidence of capillary leak syndromes is caused by the fact that for this study, every patient with the mention of edema (also only eyelid and face edema) was defined as having a capillary leak syndrome.

In our series of neonates and infants with a BSA of less than 0.36 m^2 , these good results are achieved by means of a management that includes some factors diminishing the probability of SIR formation:

- Surface coating of ECC materials, such as oxygenators, filters, and tubing, reduces the SIR in pediatric patients, which has been proved especially for heparin⁵⁻⁷ but also for phosphorylcholine.³ The reduction in SIR caused by surface coating is not only detectable on the basis of laboratory results like a lower cytokine release but also by clinical results like reduced respiratory index and body weight percent ratio⁶ and improved pulmonary and coagulation function.⁵ Other studies prove exactly the opposite: Horton and coworkers⁸ showed that heparin bonding in pediatric patients does not affect the IL-6 or IL-8 concentrations during and after CPB. In this study, however, heparin bonding was limited to the oxygenator only, which separates their methodology from our tip-to-tip coated systems and therefore might explain differences in the results. De-

fraigne and associates⁹ and Steinberg and coworkers¹⁰ showed in adults that TNF- α , IL-6, IL-8, and elastase levels showed no significant differences irrespective of whether heparin coating was used. The adult patient is far less prone to SIR than the neonate, which makes the author's results difficult to compare with ours.

- Administration of a phosphodiesterase-inhibiting agent (milrinone) suppresses the cytokine production (IL-1 and IL-6) in adult patients by increasing cyclic adenosine monophosphate levels¹¹ while leaving the TNF- α and IL-8 values unchanged. Looking at our patients, we could not find a significant difference in cytokine levels between the patients receiving milrinone and those without.
- Treatment with the nitric oxide donor sodium nitroprusside in adults decreases the cardiac production of TNF- α and IL-6,¹² which could also be a beneficial effect in our pediatric patients.
- Corticosteroids reduce plasma levels of elastase and TNF- α during and after CPB,¹³ the administration of methylprednisolone to the pump prime abrogates the patient's response to CPB,¹⁴ and steroid pretreatment reduces endotoxin release during bypass.¹⁵
- Centrifugal pumps cause greater complement and neutrophil activation during surgical intervention than roller pumps, with this effect ending soon after the procedure.¹⁶ Therefore the use of roller pumps might have contributed to a lower SIR in our patients.

One factor that cannot be avoided increases the probability of SIR formation: the transfusion of packed red cell units intraoperatively contributes to the inflammatory response by increasing the IL-6 levels after the operation.¹⁷ Because every patient in our study was treated with an ECC prime containing packed red cells and every patient received transfusions after the operation, it is likely that this fact contributed to an increase in IL-6 concentrations. Possibly the lower quantity of packed red cells in the Lilliput/450 group is one of the factors leading to improved results with the low-prime compared with the high-prime circuit. Interestingly, in spite of the uneven distribution of packed red cells in the priming (Table 3), in the Minimax group (300 mL of packed red cells) and the Lilliput/450 group (100 mL of packed red cells), the IL-6 course (Figure 2) was nearly identical.

The most severe limitations of this study are the uneven distribution of age and cyanosis in the 3 groups in spite of a prospective randomized design and the relatively small number of patients included in the study. However, post hoc statistical analysis showed no influence of age on the results, except for capillary leak syndrome. The development of a study design excluding cyanotic patients would only reflect half the truth about our clinical reality and lead to a further reduction of the patient numbers in the study.

Because of the young patient's individual variability, it would have been better to include 200 than 40 patients in such a study. Owing to limited financial and personal sources, it is not possible to produce such big numbers not only in our hospital but in most institutions.

We did not add a study arm with uncoated ECC tubing because we have used coated ECC equipment only since 1996 for pediatric and adult patients. Because there is evidence^{3,5,6} that ECC circuits with surface coatings have several advantages over uncoated oxygenators and tubing, we did not find it acceptable to go a step backwards and use uncoated tubing again.

In conclusion, our results show no superiority of one coating (heparin, Medtronic Minimax) over the other (phosphorylcholine, Dideco Lilliput 1). By using the same priming volume, the SIR was more pronounced after use of the Dideco Lilliput 1 Oxygenator than after use of the Medtronic Minimax Oxygenator. Tip-to-tip surface coating of the ECC with either heparin or phosphorylcholine seems to have similar biologic effects in neonates and infants undergoing cardiac surgery.

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APPENDIX 1

Spearman correlation coefficients of age and study results

Correlation with age (d)	r Value	P value
Body weight (kg)	0.776	.000
Body surface area (m²)	0.824	.000
ECC time (min)	−0.066	.700
Aortic clamping time (min)	−0.316	.054
Circulatory arrest time (min)	−0.063	.703
IL-6 during bypass	−0.156	.403
IL-6 1 h after the operation	−0.142	.431
TNF-α during bypass	0.183	.381
Adrenalin support (h)	−0.396	.116
Ventilation (h)	−0.215	.392

ECC, Extracorporeal circulation; IL, interleukin; TNF, tumor necrosis factor.