

# Bicarbonate-buffered ultrafiltration during pediatric cardiac surgery prevents electrolyte and acid-base balance disturbances

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Pediatric cardiopulmonary bypass is still a challenge because of electrolyte disturbances and inflammation. Many investigations deal with different types of hemofiltration to reduce these potentially harmful side effects. We tested the hypothesis of whether bicarbonate-buffered hemofiltration of the priming solution minimizes electrolyte and acid-base disturbances during the initiation of cardiopulmonary bypass and whether bicarbonate-buffered hemofiltration performed during cardiopulmonary bypass could reduce cytokine levels. Twenty children younger than 2 years of age (mean age  $166 \pm 191$  days; mean weight  $6.42 \pm 3.22$  kg) scheduled for pediatric cardiac surgery with cardiopulmonary bypass were enrolled in this prospective clinical study. Cardiopulmonary bypass circuits were primed with a bicarbonate-buffered hemofiltration solution, gelatin and 1 unit of packed red blood cells. The priming was hemofiltered using an ultrafilter until approximately 1000 mL of ultrafiltrate was restored with the buffered solution. Further hemofiltration was performed throughout the whole bypass time, especially during rewarming. Blood gas analyses and inflammatory mediators were monitored during the operation. Blood gas analysis results after

initiation of cardiopulmonary bypass and throughout the entire study remained within the physiologic ranges. Even potassium decreased from  $4.0 \pm 0.3$  to  $3.4 \pm 0.4$  mmol.l<sup>-1</sup> after initiation of cardiopulmonary bypass. Plasma levels of tumor necrosis factor alpha decreased significantly ( $47 \pm 44$  vs.  $24 \pm 21$  pg.mL<sup>-1</sup>) whereas complement factor C3a ( $5.0 \pm 2.9$  vs.  $16.8 \pm 6.6$  ng.mL<sup>-1</sup>) and interleukin-6 ( $7.3 \pm 15.2$  vs.  $110 \pm 173$  pg.mL<sup>-1</sup>) increased despite hemofiltration. In conclusion, this study shows that bicarbonate-buffered ultrafiltration is an efficient, simple and safe method for performing hemofiltration, both of the priming solution and during the entire bypass time. The use of a physiological restitution solution prevents electrolyte and acid-base balance disturbances. The elimination of inflammatory mediators seems to be as effective as other ultrafiltration methods. *Perfusion* (2009) 24, 19–25.

**Key words:** cardiopulmonary bypass; congenital heart disease; inflammation; metabolic load; priming solution; ultrafiltration

## Introduction

Pediatric cardiopulmonary bypass (CPB) involves a high ratio of prime volume to patient blood volume. The need to add packed red blood cells (RBCs) to the CPB circuit prime implicates unphysiological acid-base, electrolyte and metabolite values far outside the normal range.<sup>1</sup> Preservation of RBCs in citrate-phosphate-dextrose(CPD)-buffered and saline-adenine-glucose-mannitol (SAG-M) solutions leads to high glucose levels and acidosis. The increase in potassium and the decrease in sodium are due to a breakdown of the membrane sodium-potassium

pumps at the cold storage temperature of 4°C, with resultant leakage of potassium from the cells.<sup>2</sup>

During CPB, a number of conditions, such as the exposure of blood to the foreign surface of the pump circuit, tissue trauma, hypothermia, ischemia-reperfusion injury, and anticoagulation, may initiate systemic inflammation which may potentially lead to a systemic inflammatory response syndrome. This is still a focus of interest because of its major contribution to increased morbidity and mortality.<sup>3</sup>

Many investigations deal with different types of hemofiltration, e.g. to normalize the priming solution due to electrolyte imbalances or substrates, to reduce some inflammatory mediators before, during or after CPB, and to provide hemoconcentration at the end of CPB. All these strategies have been found clinically beneficial when used alone or in combination in the

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same patient to provide potentially additive effects.<sup>4</sup> Controversy still remains regarding the optimal ultrafiltration strategy. In a preliminary investigation, we demonstrated that bicarbonate-buffered ultrafiltration (BBUF) of the priming solution is an effective method of reducing the metabolic load and of normalizing the electrolyte and acid-base balance.<sup>5</sup>

In the present study, we tested the hypotheses whether (1) BBUF of the priming solution minimizes electrolyte and acid-base disturbances during the initiation of CPB, and whether (2) BBUF performed during CPB might reduce cytokine levels, stabilize the electrolyte and acid-base-balance and might be used for hemoconcentration at the end of CPB.

## Methods

After approval by the Hanover Medical School Ethics Committee and obtaining parents' written informed consent, 20 children younger than 2 years of age scheduled for pediatric cardiac surgery with CPB were enrolled in this prospective clinical study. Patients with an expected short CPB time, e.g. patients with atrial septal defect, were excluded from this investigation.

Anesthesia was induced intravenously with etomidate (0.5 mg/kg), fentanyl (2–5 µg/kg), and pancuronium (0.1 mg/kg), and maintained with fentanyl (10 µg/kg/h), pancuronium, and sevoflurane. After induction, all patients received dexamethasone 1 mg/kg i.v. and cephazoline 50 mg/kg i.v.

Anticoagulation was achieved with an initial dose of 300 U/kg heparin (Liquemin, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) followed by additional heparin administration to maintain an activated clotting time of greater than 400 seconds.

The same heart-lung machine (SIII, Stoeckert, Munich, Germany) and CPB circuit setup (Figure 1) were used for all patients. Every single CPB circuit consisted of a heparin-coated open system with a hard-shell reservoir and an oxygenator (Hilite 1000 or 2800, Medos AG, Langenselbold, Germany), which is used for flow rates of up to 1 or 2.8 L/min, respectively.

The CPB for pediatric open heart surgery is prepared in a standardized fashion. The circuit was primed with a bicarbonate-buffered hemofiltration solution (BB-HS) (Duosol®, B.Braun, Melsungen, Germany), followed by ten minutes' circulation. After replacing the pre-bypass filter, gelatin 4% (GelaFundin® 4%, B.Braun) and one unit (about 250 mL) of CPD-buffered RBCs in SAG-M solution (stored at 4°C) were added. The fluid was hemofiltered using a

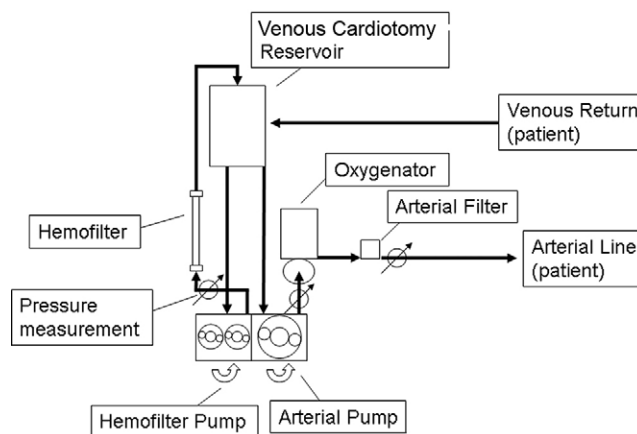


Figure 1 CPB circuit setup.

polysulfone hemofilter with hollow-fiber technology (ME HF0S 0070, Medos AG, Stolberg, Germany) at 300 mL·min<sup>-1</sup> with 150–180 mmHg of positive pressure. When approximately 1000 mL of ultrafiltrate was restored with BB-HS, 1000–2000 I.U. of heparin (Liquemin, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) and 3 mL/kg of mannitol (Mannitol-Infusionslösung 20, Serumwerk Bernburg, Bernburg, Germany) were added. Hypothermia was induced in all patients. BBUF was performed throughout the entire CPB time, especially during rewarming. To achieve a filtrate volume of at least 4000 mL, BB-HS was added to provide sufficient volume in the CPB circuit in order to allow ultrafiltration. Throughout rewarming, all patients received 1 unit of fresh frozen plasma. Towards the end of CPB, replacement with BB-HS was stopped to attain hemoconcentration.

BB-HS is developed for continuous hemofiltration in intensive care patients with acute renal failure. It consists of two chambers, a large one with a volume of 4,445 mL and a small one with a volume of 555 mL, which have to be conflated and mixed to receive the final solution. The composition of the final hemofiltration solution is close to the physiological values of extracellular fluid (Table 1).

Blood samples for blood gas analyses and cytokine measurements were obtained from the arterial

Table 1 Hemofiltration solution

pH	7.0–8.0	
Potassium	2.0	[mmol.L <sup>-1</sup> ]
Sodium	140	[mmol.L <sup>-1</sup> ]
Calcium	1.5	[mmol.L <sup>-1</sup> ]
Magnesium	0.5	[mmol.L <sup>-1</sup> ]
Chloride	111	[mmol.L <sup>-1</sup> ]
Bicarbonate	35	[mmol.L <sup>-1</sup> ]
Glucose	5.5	[mmol.L <sup>-1</sup> ]

catheter after induction of anesthesia (T0), from the arterial line within the circuit 5–10 min after CPB initiation (T1), before rewarming (T2) and at the end of CPB before starting protamine (T3). The last sample (T4) was again obtained from the patient's arterial catheter at the end of the operation. Blood samples were taken for immediate blood gas analysis using a standard blood gas oximetry system (Rapiddlab 860, Siemens Healthcare Diagnostics, Bad Nauheim, Germany).

For the measurement of the three different proinflammatory mediators - tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin 6 (IL-6), and complement factor C3a - aliquots of plasma were stored at  $-80^{\circ}\text{C}$  until assayed. IL-6 and TNF- $\alpha$  were determined in plasma by using specific monoclonal antibody enzyme-labeled, chemiluminiscent immunometric assays. IL-6 was determined on an automatic analyzer (Immulite 2000, Siemens Healthcare Diagnostics) as was TNF- $\alpha$  (Immulite, Siemens Healthcare Diagnostics). C3a was determined in plasma by using a specific competitive binding polyclonal antibody enzyme-linked immunosorbent assay according to the manufacturer's directions (Assay Designs, Ann Arbor, MI, USA). The sensitivity of the assays was  $1.7 \text{ pg.mL}^{-1}$  for TNF- $\alpha$ ,  $2 \text{ pg.mL}^{-1}$  for IL-6, and  $0.12 \text{ ng.mL}^{-1}$  for C3a.

For statistical analysis, the basic assumption of a possible effect was that of a monotonous time-dependent relationship until the end of the study. Therefore, the principle of 'closed test procedures' could be applied in connection with hierarchically ordered hypotheses: the sequence of hypotheses was ordered by time of measurement.<sup>6</sup> Beginning with the last value, each comparison versus baseline (T0) was performed by using a two-sided paired t-test and a significance level of  $\alpha = 0.05$ . The procedure stopped when the first non-significant result occurred. Therefore, *P*-values  $<0.05$  for any comparison done after the procedure was stopped may not be interpreted as significant. The assumption of normal distribution was checked for all parameters by applying the Kolmogorov–Smirnov test. To detect a potential removing effect of BBUF on inflammatory mediators throughout rewarming, we performed a two-sided paired t-test on T2 and T3. Data were analyzed using SPSS 12.0 and presented as mean (SD).

## Results

Twenty infants were enrolled in the study and received BBUF throughout the entire CPB time. Demographic characteristics and operations performed are presented in Table 2. Duration of CPB,

**Table 2** Clinical and operative data

	Mean (SD)	range
No.	20	
Age (days)	166 (191)	2–692
Weight (kg)	6.42 (3.22)	3.0–14.0
Gender (No., males/females)	13/7	
No.		
Ventricular septal defect repair	4	
Tetralogy of Fallot repair	3	
Arterial Switch Operation	3	
Complete atrioventricular canal repair	2	
Pulmonary valve replacement	2	
Mustard	1	
Rastelli	1	
Norwood	1	
Other	3	

aortic cross-clamp time, and the amount of hemofiltered fluid are shown in Table 3. Total volumes of ultrafiltrate divided by body weight were  $600 \pm 381 \text{ mL/kg}$  (range, 127 to 1567 mL/kg). The blood gas analysis results are presented in Table 4.

### Acid-base balance

The acid-base values after induction of anesthesia (T0) showed slight acidosis (pH  $7.33 \pm 0.08$ , actual bicarbonate ( $\text{HCO}_3$ )  $23.0 \pm 2.6 \text{ mmol.L}^{-1}$ , and base excess (BE)  $-2.6 \pm 2.6 \text{ mmol.L}^{-1}$ ). After initiation of CPB, acid-base balance remained unchanged. After BBUF, *i.e.* at the end of bypass (T3), pH increased significantly to normal values and the acid-base balance was balanced overall (pH  $7.43 \pm 0.10$ ;  $\text{HCO}_3$   $23.1 \pm 2.5 \text{ mmol.L}^{-1}$ ; BE  $-0.9 \pm 2.4 \text{ mmol.L}^{-1}$ ). This even applied to T4 (skin closure) (pH  $7.40 \pm 0.08$ ;  $\text{HCO}_3$   $22.6 \pm 3.6 \text{ mmol.L}^{-1}$ ; BE  $-1.6 \pm 2.7 \text{ mmol.L}^{-1}$ ). None of the patients required additional bicarbonate replacement throughout the operation.

### Electrolytes

Two electrolytes changed significantly after bypass started. Potassium decreased from  $4.0 \pm 0.3$  to  $3.4 \pm 0.4 \text{ mmol.L}^{-1}$ , and calcium increased from  $1.2 \pm 0.1$  to  $1.3 \pm 0.1 \text{ mmol.L}^{-1}$ . At the end of bypass, the electrolyte concentrations, except for sodium, compared to T0, changed significantly (sodium from  $137 \pm 2.5$  to  $137 \pm 2.3 \text{ mmol.L}^{-1}$ ; potassium from  $4.0 \pm 0.3$  to  $5.4 \pm 0.7 \text{ mmol.L}^{-1}$ ; calcium from  $1.2 \pm 0.1$  to  $1.5 \pm 0.2 \text{ mmol.L}^{-1}$ ; chloride from  $106 \pm 3.5$  to  $100 \pm$

**Table 3** CPB data

	No. of patients	Mean (SD)	range
Bypass time (min)	20	140 (59)	77–300
Cross-clamp time (min)	17	57 (27)	15–120
Amount of hemofiltered fluid (mL)	20	3076 (953)	1430–5045

**Table 4** Blood gas analysis results

	After induction T0	Start of bypass T1	End of bypass T3	Skin closure T4
pH	7.33 (0.08)	7.38 (0.07)	7.43 (0.10)*	7.40 (0.08)*
Actual bicarbonate [mmol.L <sup>-1</sup> ]	23.0 (2.6)	25.5 (2.4)	23.1 (2.5)	22.6 (3.6)
Base excess [mmol.L <sup>-1</sup> ]	-2.6 (2.6)	-2.2 (2.2)	-0.9 (2.4)	-1.6 (2.7)
Sodium [mmol.L <sup>-1</sup> ]	137 (2.5)	135 (5.4)	137 (2.3)	139 (3.0)*
Potassium [mmol.L <sup>-1</sup> ]	4.0 (0.3)	3.4 (0.4)*	5.4 (0.7)*	4.9 (0.7)*
Calcium [mmol.L <sup>-1</sup> ]	1.2 (0.1)	1.3 (0.1)*	1.5 (0.2)*	1.5 (0.3)*
Chloride [mmol.L <sup>-1</sup> ]	106 (3.5)	105 (4.3)	100 (3.3)*	102 (2.7)*
Glucose [mmol.L <sup>-1</sup> ]	5.2 (1.3)	6.2 (1.1)*	8.0 (1.6)*	8.3 (1.6)*
Lactate [mmol.L <sup>-1</sup> ]	1.1 (0.4)	1.2 (0.7)	2.8 (1.7)*	3.8 (2.6)*
Anion gap [mmol.L <sup>-1</sup> ]	11.6 (3.3)	7.1 (5.5)*	20.3 (6.0)*	19.2 (3.9)*
Hemoglobin [g dl <sup>-1</sup> ]	11.9 (2.1)	9.4 (1.5)	12.7 (1.9)	13.6 (1.8)*
Hematocrit [%]	35.2 (6.2)	27.6	37.6 (5.6)	40.3 (5.2)*

Values are expressed as mean (SD); \* =  $P < 0.05$  compared to T0.

3.3 mmol.L<sup>-1</sup>). All patients received potassium towards the end of bypass to reach high normal serum levels.

### Substrates

Onset of bypass did not produce any changes in lactate levels, but glucose increased significantly from  $5.2 \pm 1.3$  to  $6.2 \pm 1.1$  mmol.L<sup>-1</sup>. From T0 to T3, both measured substrates, *i.e.* glucose and lactate, increased significantly (glucose from  $5.2 \pm 1.3$  to  $8.0 \pm 1.6$  mmol.L<sup>-1</sup>; lactate from  $1.1 \pm 0.4$  to  $2.8 \pm 1.7$  mmol.L<sup>-1</sup>). The increase continued until T4 (glucose  $8.3 \pm 1.6$  mmol.L<sup>-1</sup>; lactate  $3.8 \pm 2.6$  mmol.L<sup>-1</sup>).

### Hemoconcentration

Hemoglobin and hematocrit both increased from the start of bypass to the end of bypass (hemoglobin from  $9.4 \pm 1.5$  to  $12.7 \pm 1.9$  g.dL<sup>-1</sup> and hematocrit from  $27.6 \pm 4.5$  to  $37.6 \pm 5.6\%$ ). Significant changes were also found between T0 and T4 (hemoglobin  $11.9 \pm 2.1$  vs.  $13.6 \pm 1.8$  g.dL<sup>-1</sup> and hematocrit  $35.2 \pm 6.2$  vs.  $40.3 \pm 5.2\%$ ).

### Proinflammatory mediators

Both IL-6 and C3a increased significantly at T3 when compared to T0 and to T2 (IL-6 T0:  $7.3 \pm 15.2$ ; T2:  $12.2 \pm 13.0$  and T3:  $110 \pm 173$  pg.mL<sup>-1</sup>; C3a T0:  $5.0 \pm 2.9$ ; T2:  $7.0 \pm 5.2$  and T3:  $16.8 \pm 6.6$  ng.mL<sup>-1</sup>) (Figure 2). The only inflammatory mediator to have decreased significantly after BBUF (T3) when compared to T0 was TNF- $\alpha$  (T0:  $47 \pm 44$ ; T2:  $32 \pm 64$  and T3:  $24 \pm 21$  pg.mL<sup>-1</sup>). During the entire bypass, TNF- $\alpha$  remained stable within low levels (Figure 2).

### Discussion

In the present study, we were able to show that hemofiltration of the priming solution and replacement with a physiological bicarbonate-buffered solu-

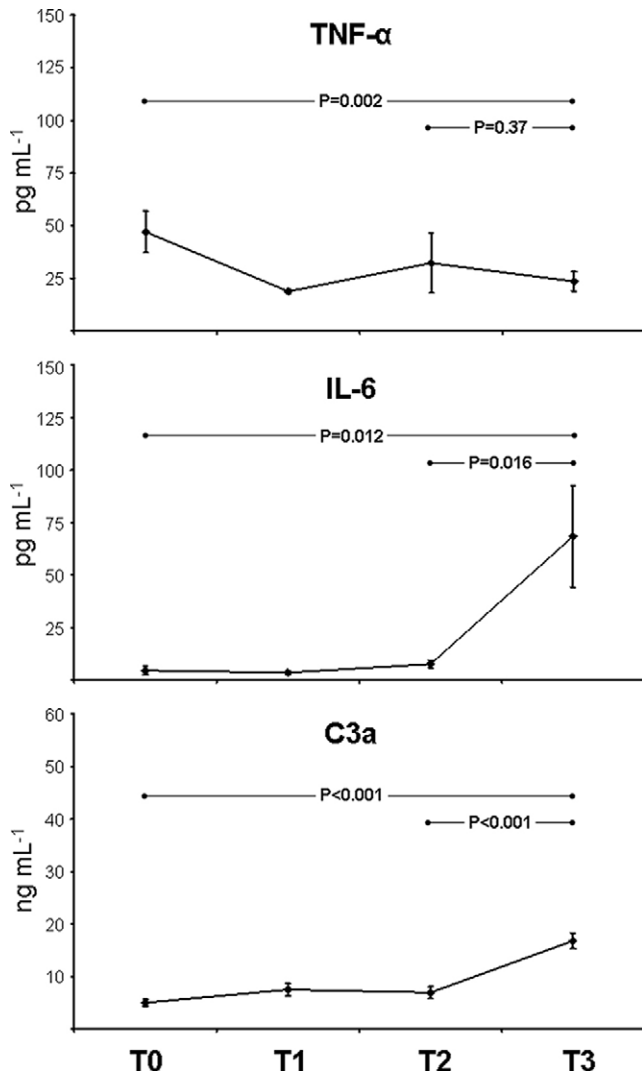
tion leaves electrolytes levels, acid-base balance, and the substrates within the physiological range during the initiation of CPB. BBUF performed during CPB stabilized the electrolyte and acid-base-balance further and might be used for hemoconcentration towards the end of CPB. Furthermore, compared to baseline, BBUF significantly reduced TNF- $\alpha$ , but not C3a and IL-6 levels.

The major limitation of this single-site, prospective study is the lack of a control group. However, because the best hemofiltration solution is a physiological solution, all heart-lung machines have been primed with BB-HS during the last 5 years, and BBUF has been performed during CPB in all of our patients. Due to ethical problems, it was not possible to use a control group and, therefore, we have to compare our data with the results of other investigators. The lack of a control group does limit the claims the study can state and only a controlled trial with a proper control group could fully prove any advantage of BBUF.

There are two main reasons why filtering techniques are used prior to, during or at the end of pediatric cardiac bypass: (1) to prepare a nearly physiological priming solution and, therefore, to avoid potentially harmful acid-base and electrolyte disturbances during the initiation of CPB; (2) to impact favorably on the unwanted inflammatory response by eliminating proinflammatory mediators, which has been correlated with improved outcome.<sup>7,8</sup> The technique presented here is able to fulfil both objectives with only minimal effort because the same ultrafilter could be left in the CPB circuit during the entire bypass procedure.

### Priming

Establishment of CPB may produce similar effects to rapid blood transfusion. Massive and rapid transfusion of RBCs may lead to a substantial load of hydrogen ions, carbon dioxide, and potassium, associated



**Figure 2** Plasma concentrations of inflammatory mediators; (T0) after induction of anesthesia, (T1) 5–10 min after CPB initiation, (T2) before rewarming, (T3) at the end of CPB.

with hemodynamic instability caused by acid-base and electrolyte disorders.<sup>9,10</sup> These problems are mainly caused by the preservative solution and worsen during storage.<sup>1</sup> Many different methods have been developed, such as cell saver washing of the RBCs or ultrafiltration of the priming fluid,<sup>11,12</sup> in order to reduce these disturbances. We found that hemofiltration of the prime and replacement with BB-HS substantially reduced the substrate load.<sup>5</sup> The established priming solution contains low lactate ( $2.3 \pm 1.0$  mmol.L<sup>-1</sup>) and nearly normal glucose ( $6.3 \pm 1.0$  mmol.L<sup>-1</sup>) levels. In contrast, sodium, pH, actual bicarbonate, and base excess increased significantly and also reached levels within the normal physiological range.<sup>5</sup> Consequently, alterations of blood gas analysis results after initiation of CPB were harmless. Potassium, a focus of interest because of its partly excessive amounts in RBCs, decreased

from  $4.0 \pm 0.3$  to  $3.4 \pm 0.4$  mmol.L<sup>-1</sup> after initiation of CPB. Another advantage resulting from a physiological restitution solution is the safety during the entire bypass time. Electrolyte or acid-base balance disturbances do not occur. The only electrolyte that needs to be replaced towards the end of bypass is potassium. The concentration in BB-HS is about 2 mmol.L<sup>-1</sup> so, to reach high normal values of potassium, approximately 0.5–2.0 mmol.kg<sup>-1</sup> has to be administered during rewarming.

### **Inflammatory mediators**

The most important cytokines in relation to cardiac surgery are the pro-inflammatory cytokines, including TNF- $\alpha$ , IL-1, IL-6 and IL-8. Because previous studies have shown comparable filtering properties of IL-1, IL-6, and IL-8, we only determined IL-6. The complement system is also involved early on in the complex process of inflammation. Activation leads to an increase in C3a, a potent anaphylatoxin, via C3-convertase and C3. The C3a fragment indirectly triggers the formation of the terminal complement attack complex, which stimulates neutrophil degranulation and neutrophil pulmonary sequestration. Therefore, C3a is involved in inflammation and capillary leak and it is correlated with several clinical adverse effects.<sup>13–15</sup>

Modified ultrafiltration (MUF) has been an accepted clinical practice for many years. The major advantage of MUF is that it removes fluid from patients, which leads to hemoconcentration, increasing the hematocrit and coagulation factors in the postoperative period. Controversy still remains regarding the beneficial effects of MUF on decreasing the levels of inflammatory mediators. Some results have shown that ZBUF is more effective in removing inflammatory mediators than MUF.<sup>16</sup> Furthermore, MUF has some additional risks, as described by Williams and colleagues.<sup>4</sup> The aortic cannula may entrain air. Removal of blood from the systemic circulation may result in hemodynamic instability or impair aortopulmonary shunt flow. High flow rates through the ultrafilter decrease cerebral blood flow velocities and cerebral mixed venous oxygen saturation.<sup>17</sup> In small infants, the aortic cannula may be obstructive, and its early removal may limit or prevent use of arteriovenous MUF. MUF extends the period of patient exposure to nonendothelialized surfaces. Cooling of the patient will occur if the ultrafiltered blood is inadequately warmed. Whether this investigated smooth continuous technique is safer than previous techniques has to be examined in further comparative studies. We, at least, did not observe any undesirable situation during the last 5 years of performing BBUF.

There seems to be evidence to suggest that the benefits of ultrafiltration correlate with the volume of filtrate removed.<sup>18</sup> Our technique, with replacement of the ultrafiltrate with BB-HS solution, allows us to filter the patient's blood several times. Usually, reported ultrafiltrate volumes reach amounts of up to 186 mL.kg<sup>-1</sup>.<sup>19–22</sup> Depending on CPB time and a patient's body weight, we performed high volume hemofiltration with a mean filtrate volume of 600 mL.kg<sup>-1</sup> (range, 127 to 1567 mL.kg<sup>-1</sup>). So the amount of eliminated inflammatory mediators might be greater than with other methods. Even though the impact of BBUF on inflammatory mediator plasma levels is consistent with the results of previous investigations performing continuous ultrafiltration,<sup>23–25</sup> TNF- $\alpha$  could be removed to a significant extent, whereas C3a and IL-6 increased despite BBUF. Further studies need to be designed to determine whether BBUF has any impact on the short-term or long-term outcome of paediatric cardiac surgery.

In conclusion, BBUF is an efficient, simple and safe method for performing hemofiltration of the

priming solution and throughout the entire bypass time. The use of a physiological restitution solution prevents electrolyte and acid-base balance disturbances, and the level of elimination of inflammatory mediators may be comparable to that achieved with other ultrafiltration methods.

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## Conflict of interest policy

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