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Hemofiltration during Cardiopulmonary Bypass in Pediatric Cardiac Surgery

Effects on Hemostasis, Cytokines, and Complement Components

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Background: **This prospective study was intended to determine in a homogeneous population of children whether hemofiltration, performed during cardiopulmonary bypass rewarming, is able to improve hemodynamics and biologic hemostasis variables, to reduce postoperative blood loss, time to extubation, and plasma cytokines, and complement fragments.**

Methods: **Thirty-two children undergoing surgical correction of tetralogy of Fallot were randomly assigned to a hemofiltration or control group. Hemofiltration was performed with a polysulphone hemofilter during rewarming of cardiopulmonary bypass. Plasma clotting factors, D-dimers, antithrombin-III, complement fragments C3a and C5a, interleukin-1β, interleukin-6, interleukin-8, and tumor necrosis factor-α were measured before and after hemofiltration. Systemic mean arterial pressure, left atrial pressure, time to extubation, and postoperative blood loss were monitored.**

Results: **In the hemofiltration group, significant reductions in 24-h blood loss (250 (176–356) *vs.* 319 (182–500) ml/m^2, median (minimum-maximum)), time to extubation (15 (9–22) *vs.* 19 (11–24) h), plasma concentrations of C3a, C5a, interleukin-6, and tumor necrosis factor-α were observed compared to control. Arterial oxygen tension on admission to the intensive care unit was significantly greater in the hemofiltration group (136 ± 20 *vs.* 103 ± 25 mmHg, mean ± SD). Significant increases in mean arterial pressure, clotting factors, and antithrombin-III were noted for the hemofiltration group. No intergroup difference was observed in left atrial pressure, platelets count, D-dimers, interleukin-8, and duration of stay in the intensive care unit.**

Conclusions: **Hemofiltration during cardiopulmonary bypass in children improves hemodynamics and early postoperative oxygenation and reduces postoperative blood loss and duration of mechanical ventilation. Hemofiltration is able to remove some major mediators of the inflammatory response. (Key words: Anesthesia: pediatric cardiac. Cardiopulmonary bypass. Cytokines: interleukin-1β; interleukin-6; interleukin-8. Hemofiltration. Leukocytes: macrophages; monocytes. Surgery: pediatric cardiac. Tumor necrosis factor-α: complement 3a; complement 5a. Ultrafiltration.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 26A.

THE systemic inflammatory response that occurs in infants and children after cardiopulmonary bypass (CPB) results in a capillary leak syndrome that remains a major cause of morbidity and mortality.[1] This process can lead to fluid overload, impede pulmonary gas exchange, and delay separation from mechanical ventilation. In addition, the CPB-associated hemodilution of platelets and coagulation factors promotes the hemostatic impairment that is generally observed in these children.[2]

The hemofiltration technique uses the convection process to remove water and some low molecular weight substances from plasma under an hydrostatic pressure gradient. Because the hemodilutional effects of CPB are especially pronounced in children because of a disproportionally large priming volume of the CPB circuit, the potential benefit of hemofiltration could be very significant in these small patients. This technique has been used effectively after CPB termination in children and appeared to be an effective therapy to reduce the amount of accumulated tissue water.[3,4]

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This prospective randomized study was designed to determine in a homogeneous population of children whether hemofiltration, performed during CPB rewarming, is able to improve hemodynamics and biologic hemostasis variables and to reduce postoperative blood loss, time to extubation, plasma complement fragments, and cytokines induced by CPB.[5]

Methods

After Institutional Review Committee approval, 32 children undergoing surgical correction of tetralogy of Fallot were studied. None of these children had previous cardiothoracic surgery.

Anesthetic Techniques

All patients were premedicated with atropine and oral flunitrazepam (30 μg/kg). Anesthesia was induced with a continuous infusion of midazolam (2 $\mu g \cdot min^{-1} \cdot kg^{-1}$), alfentanil (2 $\mu g \cdot min^{-1} \cdot kg^{-1}$), and vecuronium (120 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Patients' lungs were ventilated with an inspired oxygen fraction of 1.0, maintaining a mixed expired carbon dioxide fraction of 35 mmHg. Rectal and nasopharyngeal temperatures were monitored continuously using 9F Mon-a-therm temperature probes (Mallinckrodt Medical, St. Louis, MO).

Cardiopulmonary Bypass Techniques

Cardiopulmonary bypass was performed with a stretching roller pump (Rhone-Poulenc-RP06, Lyon, France) and an appropriately sized Dideco hollow fiber oxygenator was used (Dideco, Mirandola, Italy). The tubing of the extracorporeal circuit was constructed of polyvinylchloride or silicone (Dideco). The extracorporeal circuit was primed with 35% volume of 40 g/l albumin solution (CNTS, Paris, France), 8% volume of molar sodium bicarbonate, 40% volume of hydroxyethylstarch (Elohes, Biosedra Lab., Louviers, France) 5% aprotinin (10,000 UI/ml, Trasylol, Bayer Lab., Puteaux, France), 12% of Hartmann's solution, and fresh frozen plasma or erythrocytes according to the patient's needs, to reach a total prime volume of 1,250 ml/m^2 with a minimum of 520 ml. Heparin was added to the priming solution (2 IU/ml).

The pump flow rate was linearly adjusted to provide a blood flow depending on body temperature between 2.4 $l \cdot min^{-1} \cdot m^{-2}$ at 37°C and 1.7 $l \cdot min^{-1} \cdot m^{-2}$ at 24°C. Moderate hypothermia was induced in all patients (26.1°C, range 23.0–30.0°C). Alpha-stat blood gas management was used, and sodium bicarbonate was administered when the base excess was less than −2.5 mM/l during CPB.

Anticoagulation was achieved with an initial bolus of heparin (beef lung sodium heparin, Léo Lab., Paris, France) of 250 IU/kg injected in the right atria before cannulation and followed by a continuous infusion of 62.5 $IU \cdot kg^{-1} \cdot h^{-1}$ until the end of CPB. Aprotinin was administered in all children at a dose of 30,000 UI/kg after the induction of anesthesia and then continuously infused at a rate of 1.35 $KIU \cdot kg^{-1} \cdot min^{-1}$. After CPB, protamine (Choay Lab., Paris, France) was administered at a rate of 10 mg/min up to a total dose of 3.5 mg/kg. A cell separator system (Cell-Saver system IV, Haemonetics, Paris, France) was used in the two groups to wash and centrifuge blood aspirated in the surgical field before the administration of heparin and as the sole aspiration method after the administration of protamine.

Myocardial preservation was achieved using cold blood cardioplegia with an initial dose of 30 ml/kg repeated every 20 min. Fifteen milliliters per kilogram of warm blood cardioplegia was administered before aortic declamping. Cardioplegia solution was aspirated from the right atrium to the cell separator system during administration to avoid any blood dilution.

Rewarming was achieved by an oxygenator heat-exchange with a warming blanket and heated humidified gases to reach a rectal temperature of 36.5°C before terminating CPB.

All patients were separated from CPB during infusion of dopamine at a rate of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. No vasodilator was used throughout the operation.

Hemofiltration Techniques

Patients were randomly assigned to a hemofiltration or control group just before rewarming. Randomization was performed at this time to avoid potential perfusionist bias during CPB by knowing whether hemofiltration was to be used. A Spiraflo polysulphone ultrafilter (HFT02, Sorin Lab., Antony, France) was rinsed with 1,000 ml of saline and inserted between the arterial tubing and the cardiotomy reservoir. Hemofiltration was carried out with a rate adjusted to reach a cardiotomy reservoir level of 0 at the completion of rewarming. Administration of red separator concentrate cells, albumin, or fluids during rewarming was allowed, excepting any solution containing procoagulant factors. The CPB flow was not changed until the completion

of rewarming. After termination of CPB, the blood remaining in the CPB circuit was washed and centrifuged using the cell-separator system and then retransfused in the operating room or in the intensive care unit (ICU).

Variables Recorded

Arterial blood sampling was obtained during the aortic cannulation (T_1), before rewarming (and hemofiltration) (T_2), and at rewarming (and hemofiltration) completion (T_3), and 24 h later in the ICU, the following were measured: plasma protein concentration and hemostatic variables, including platelet count, coagulation factors II, V, VII+X, fibrinogen, celite-activated clotting time, prothrombin time, antithrombin-III, and D-dimers. Blood samples for hemostasis tests were collected in tubes containing 0.109 M sodium citrate. Plasma supernatant was removed after a 15-min centrifugation at 3,000 g and assayed in real-time except for D-dimers aliquots that were immediately frozen, stored at −70°C, and assayed within 2 months by enzyme-linked assay.[6] All the hemostatic assays were provided by Diagnostica Stago Labs. (Asnières, France).

Blood samples for complement fragments, tumor necrosis factor-α (TNFα), and interleukins were withdrawn at T_2 and T_3 only. Sample supernatants were removed and placed into polypropylene tubes of 300 μl after centrifugation (6 min, 3,000 g, 4°C), stored at −70°C, and assayed within 3 months. Enzyme-linked immunoassays for interleukin-6 (IL-6), interleukin-8 (IL-8), and TNFα were performed using Quantikine kits (Research and Diagnostics Systems, Minneapolis, MN). Their sensitivities were less than 5 pg/ml, 5 pg/ml, and 10 pg/ml, respectively. Interleukin-1β was assayed by enzyme-linked immunosorbent assay (Cistron Biotechnology, PineBrook, NJ; sensitivity <5 pg/ml). The complement fractions C3a and C5a were assayed by radioimmunoassay (Amersham, France).

Blood gas analysis was performed after induction of anesthesia, after separation from CPB, and during ICU admission. Systemic arterial pressure, right atrial pressure, colloid or administered donor blood volumes, postoperative blood loss, duration of mechanical ventilation, and ICU stay duration also were recorded. The ICU physicians managing the patients were blinded to group assignment.

Three different-sized CPB circuits were used depending on the patient's body surface area. The priming volume of the extracorporeal circuit, therefore, was not strictly correlated with the patient circulating blood volume. The ratio of ultrafiltrate volume to the estimated total blood volume (UF/TBV) was calculated to compare the relative amount of ultrafiltrate withdrawn in each patient. Total blood volume was defined as prime volume plus patient blood volume.[3] This ratio allowed us to study the correlation between ultrafiltrate volume and any variation in the measured variables.

Statistical Methods

All continuous data were tested for conforming to a normal distribution using the Kolmogorov-Smirnov test (SPSS software, Chicago, IL). All normally distributed data are expressed as mean ± SD. The remaining variables are expressed as median ± (minimum − maximum) and are graphically presented as percentile boxplots.[7] The data were analyzed using the Mann-Whitney nonparametric method for unpaired data. Comparisons of variables between T_2 and T_3 were made using Wilcoxon's test for paired data. All tests were two-sided. Correlations were studied with the nonparametric Spearman's rank correlation test. For all statistical analyses, statistical significance was chosen at $P < 0.05$.

Results

The CPB priming volume was 685 (520–1,180) ml and did not differ between groups. Two patients had polyvinylchloride tubing in the hemofiltration group and three in the control group. There were no significant differences between the hemofiltration (n = 16) and the control (n = 16) groups with respect to duration of bypass, aortic cross-clamping duration (51.5 ± 15 min *vs.* 56.4 ± 23 min), age (2.3 ± (0.49–8.45) yr *vs.* 3.5 ± (0.02–12.1) yr, $P = 0.38$), body surface area (0.55 ± 0.16 m^2 *vs.* 0.62 ± 0.21 m^2), rewarming duration (54 ± 19 min *vs.* 64 ± 24 min), and hemostatic parameters at T_1. The volume of ultrafiltrate was 293 ± 91 ml (569 ± 223). The median UF/TBV ratio was 18.4% (8.4–31.4%).

The hematocrit increased from 22 ± 5% to 30 ± 5% during rewarming without statistical difference between the two groups (table 1). The amount of administered fluid loading during the warming phase of CPB was 554 ± 372 ml/m^2 in the hemofiltration group *versus* 500 ± 307 ml/m^2 in the control group, respectively composed of 70% *versus* 61% of red separator concentrate cells ($P = 0.62$), 20% *versus* 24% of exogenous blood cells ($P = 0.55$), and 10% *versus* 14% of 4% albumin ($P = 0.12$). No difference was ob-

served in left atrial pressure between T_2 and T_3 or between groups (table 1). Mean arterial pressure increased in both groups from T_2 (52 ± 7 mmHg) to T_3 (62 ± 8 mmHg) with a significant difference between groups (table 1). There were no deaths or reoperations for bleeding.

Time to extubation after operation was 15 (9–22) h in the hemofiltration group *versus* 19 (11–24) h in the control group ($P = 0.04$). The postoperative arterial oxygen tension ($Pa_{O_2}2$) at ICU admission differed between groups (136 ± 20 mmHg *versus* 103 ± 25 mmHg, $P = 0.0016$). There was no difference between groups in duration of ICU stay, inotropic requirements, postoperative urinary output. The maximum body temperature in the 1st postoperative day did not differ between groups (36.6 ± 0.49°C in the hemofiltration group *vs.* 36.7 ± 0.48°C in the control group, $P = 0.76$).

Hemostasis

Cumulative blood loss was significantly less in the hemofiltration group comparatively to the control group at the 24th hour (respectively, 250 (176–356) ml/m^2 *versus* 319 (182–500) ml/m^2; fig. 1). No difference was observed between the two groups with respect to postoperative fluid requirements (7.2 ± (0–14) ml·kg^{-1}·d^{-1} *vs.* 9.5 (0–16) ml·kg^{-1}·d^{-1}, $P = 0.32$). No donor blood was transfused postoperatively in either group.

The hemofiltration group demonstrated a significant increase in clotting factor concentrations (fig. 2). Except for platelet count, significant differences were observed in most of the coagulation parameters between groups (table 1). No difference was observed between groups at the 24th hour in the ICU regarding hemostasis parameters. A correlation between UF/TBV ratio and clotting factor changes was observed (table 1).

Complement

The plasma concentrations of C3a and C5a complement fragments before rewarming were 605 ± 98 ng/ml and 30 ± 4.5 ng/ml, respectively, for both groups. For both C3a and C5a, a significant increase occurred between T_2 and T_3 in the control group, whereas a decrease was observed in the hemofiltration group: respectively, 596 ± 102 ng/ml *versus* 506 ± 87 ng/ml ($P < 0.0002$) and 198 ± 34 ng/ml *versus* 182 ± 31 ng/ml ($P < 0.0002$) in the hemofiltration group, and 614 ± 95 ng/ml *versus* 645 ± 100 ng/ml ($P < 0.0005$) and 205 ± 31 ng/ml *versus* 215 ± 33 ng/ml ($P <$

Table 1. Absolute Differences in Measured Parameters between T2 and T3 (Rewarming + Hemofiltration Period)

Difference between T2 and T3	Ultrafiltration	Control	Difference between the Two Groups*(*P*)	Correlation with the UF/TBV Ratio† (*P*)
Hematocrit (%)	10.5 ± 18	5.5 ± 5	NS (0.079)	0.0036
Protein (g/l)	10.5 ± 18	5.5 ± 5	NS (0.079)	0.0036
Left atrial pressure (mmHg)	−1.6 ± 2.2	−1.0 ± 1.9	NS (0.17)	NS (0.20)
Mean arterial pressure (mmHg)	13 ± 9	6 ± 5	0.02	0.0088
Fibrinogen (g/l)	0.23 ± 0.4	−0.13 ± 0.1	0.012	0.044
Factor II (%)	7.46 ± 7.4	−3 ± 3.1	0.0002	0.0002
Factor V (%)	5.2 ± 7.5	0.25 ± 2.2	0.04	0.0355
Factors VII + X (%)	5.3 ± 8.4	−0.17 ± 1.5	0.035	0.0051
Prothrombin time (%)	3.5 ± 4.8	−1.2 ± 2.4	0.006	0.0036
Antithrombin III (%)	6.9 ± 6.3	−1.2 ± 4.4	0.003	0.0038
D-Dimers (ng/ml)	17.3 ± 93	−27.5 ± 122	NS (0.337)	NS (0.81)
Platelets (10^9/mm^3)	20.2 ± 19.9	15.8 ± 19.7	NS (0.59)	NS (0.59)
C3a (ng/ml)	−89.6 ± 15.5	30.6 ± 4.9	<0.0001	0.0005
C5a (ng/ml)	−15.9 ± 2.8	10.2 ± 1.8	<0.0001	0.0006
Tumor necrosis factor-α (ng/ml)	−0.34 ± 0.37	0.52 ± 0.62	0.003	NS (0.34)
Interleukin-6 (ng/ml)	−0.68 ± 0.1	0.003 ± 0.11	0.001	NS (0.16)
Interleukin-8 (ng/ml)	0.005 ± 0.3	0.002 ± 0.04	NS (0.83)	NS (0.76)

Values appeared normally distributed (Kolmogorov-Smirnov test) and are expressed as mean ± SD.

UF/TBV = ratio of ultrafiltrate volume by the estimated total blood volume of circuit + patient.

* Mann-Whitney test for unpaired data.

† Spearman rank correlation test.

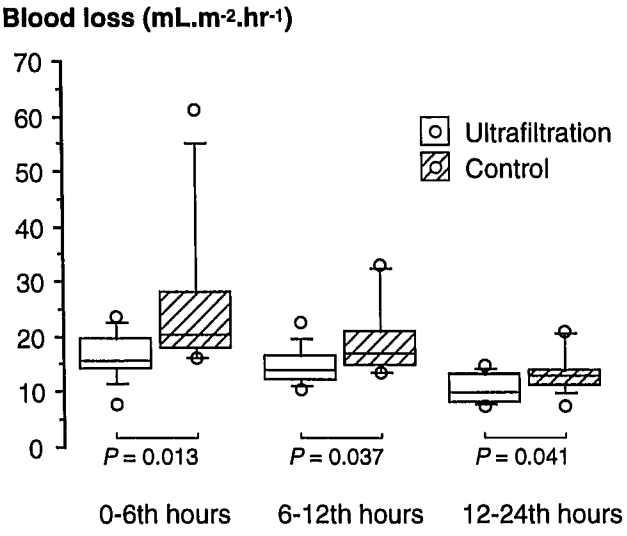

Fig. 1. Differences in postoperative blood loss between hemofiltration and control groups. Mann-Whitney nonparametric test for unpaired data. Data are expressed with box-plots. The lower boundary of the box is the 25th percentile, and the upper is the 75th percentile. The median value is in the box. Outliers are defined as cases with values between 1.5- and 3-box length. Lines are drawn from the end of the box to the largest and smallest observed values that are not outliers.

0.0005) in the control group. Plasma levels of these fractions were significantly different between groups at T_3 ($P < 0.0001$). The complement fragments C3a and C5a variations correlated with the UF/TBV ratio (table 1). Their plasma levels at rewarming completion correlated with the postoperative $Pa_{O_2}2$ (respectively, $P = 0.03$ and $P = 0.02$).

Cytokines

Tumor necrosis factor-α, IL-6, and IL-8 were detected in all patients from both groups. The plasma concentrations of IL-6, IL-8, and TNFα were 1.5 ± 0.5 ng/ml, 1.1 ± 0.6 ng/ml, and 2.9 ± 0.7 ng/ml before rewarming, respectively (fig. 3). A significant difference was noticed between groups with respect to TNFα and IL-6 levels during rewarming, whereas no difference was observed in IL-8 levels. The levels of TNFα, IL-6, and IL-8 did not correlate with the UF/TBV ratio (table 1) but were correlated with the hemofiltration duration ($P = 0.01$). Interleukin-1β (IL-1β) activity was detected in only three patients undergoing hemofiltration and in two who did not undergo hemofiltration. These patients were hypoxemic before the procedure (oxygen saturation 68% (54–73%)); and were among those presenting the higher levels of C5a at T_2 (241 (227–278) ng/ml *versus* 189 ± 28 ng/ml in the rest of the group). Interleukin-1β levels could decrease in the hemofiltration group, but the small number in this data set did not permit statistical testing (fig. 4). The cytokines and complement fragments at T_2 and T_3 of patients having polyvinylchloride tubing were included in the 90% confidence interval of the mean of their group.

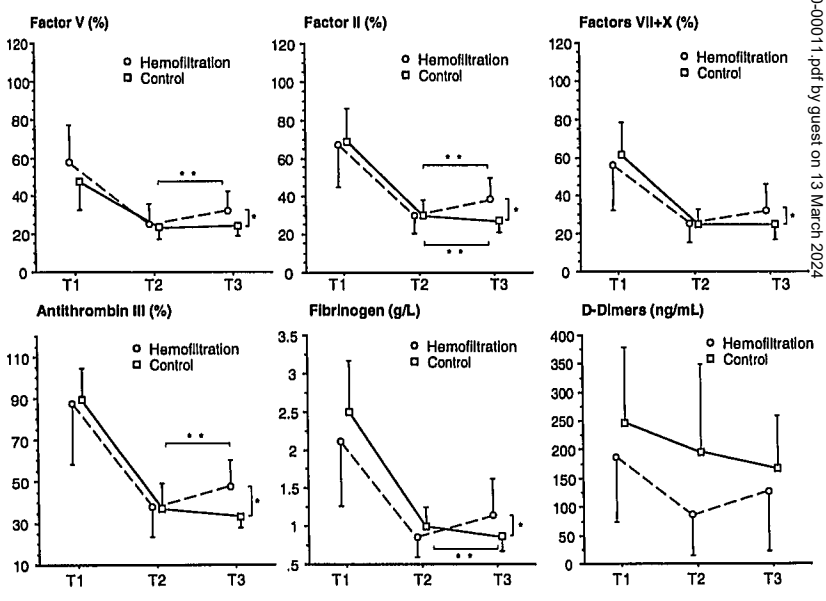

Fig. 2. Coagulation variable trends during the study. T_1 = aortic cannulation; T_2 = beginning of rewarming ± hemofiltration; T_3 = end of rewarming ± hemofiltration. Values are expressed as mean ± SD. *$P < 0.05$, Mann-Whitney test for unpaired data. **$P < 0.05$, Wilcoxon's test for paired data.

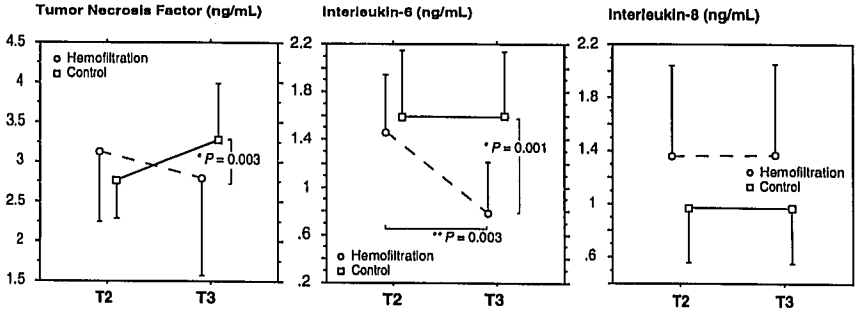

Fig. 3. Evolution of tumor necrosis factor-α, interleukin-6, and interleukin-8 plasma concentrations during rewarming. T_2 = beginning of rewarming ± hemofiltration; T_3 = end of rewarming ± hemofiltration. *$P < 0.05$, Mann-Whitney test for unpaired data. **$P < 0.05$, Wilcoxon's test for paired data.

Discussion

Numerous postoperative strategies, such as peritoneal dialysis, extensive use of diuretics, administration of colloids, or postoperative hemofiltration[8] have been used to reduce the consequences of capillary leak after congenital heart surgery. Naik *et al.* performed the hemofiltration technique after CPB termination to reduce the amount of accumulated tissue water.[3,4] These authors observed significant improvements in hemodynamics that were unlikely to be explained solely by the control of water balance.[4] Therefore, they postulated that hemofiltration might remove some toxic substances that promoted capillary leak.[3] Moreover, some studies have demonstrated the existence of a clearance of the inflammatory reaction mediators by hemofiltration during CPB.[9-11]

Because cytokine release was reported to be maximal during rewarming,[5] our study examined hemofiltration performed throughout the whole period of rewarming. Also, because the results of previous studies in children were confounded by a heterogeneous surgical population with respect to diagnosis, CPB duration, and operation, we examined the effects of hemofiltration in patients with the same diagnosis and the same surgical procedure.[9,11] Only patients with tetralogy of Fallot were studied to avoid any variability due to hemodynamics or water distribution that might have been associated with different congenital heart lesions. Furthermore, the limitation of arterial pulmonary flow, which is a preoperative characteristic of this disease, allowed us to randomize patients without risk of pulmonary water overload in the control, untreated group.

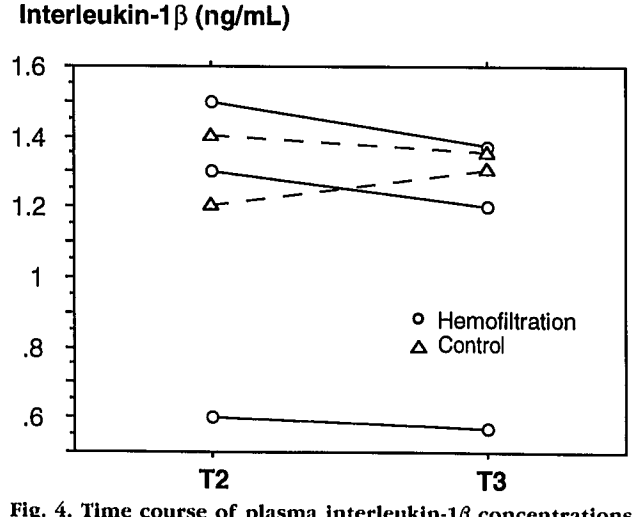

Fig. 4. Time course of plasma interleukin-1β concentrations during rewarming in the five patients in whom this cytokine was detected. T_2 = beginning of rewarming ± hemofiltration; T_3 = end of rewarming ± hemofiltration.

Effects of Hemofiltration on Ventilation

The reduction in duration of mechanical ventilation and the increase in early postoperative $Pa_{O_2}2$ do not, by themselves, justify the use of hemofiltration during correction of Tetralogy of Fallot. Nevertheless, these findings may have important implications for the CPB management of other children operated on for congenital heart defects associated with impaired pulmonary function, especially in those patients with pulmonary artery hypertension. This improvement in oxygenation is likely to be mediated by water removal.[3] Nevertheless, net fluid balance seems to be a poor predictor of postoperative chest radiograph changes,[12] and the beneficial effects on pulmonary function of toxin removal by hemofiltration have been demonstrated.[13] The correlation that we have observed between C3a and C5a levels at the end of rewarming and the postoperative $Pa_{O_2}2$ demonstrates the importance of the inflammatory reaction in the determinism of the postoperative pulmonary function. Nevertheless, no difference between groups was observed regarding the duration of stay in ICU. This finding might be explained by the modest although significant difference between the two groups in duration of mechanical ventilation

and by the short duration of stay in ICU after this procedure.

Hemoconcentration Effects of Hemofiltration

Our results of protein hemoconcentration were reported previously in children when hemofiltration is performed either after CPB or during the postoperative period.[3,4,8,14] In our current "intent-to-treat" study, protein or red cell administration was allowed during rewarming with or without hemofiltration. The absolute effect of hemofiltration on these variables, therefore, is difficult to assess. Nevertheless, the administration of coagulation factors was avoided during rewarming, and our data show a 5–10% hemoconcentration effect of coagulation factors. For the strict purpose of hemoconcentration, the technique described by Naik *et al.*, which exclusively ultrafilters the patient's blood volume and not the volume of the CPB circuit, is likely to be more efficient than the one we used in this study.[3] These authors named their technique "modified hemofiltration." Modified hemofiltration is performed using the arterial and venous tubing that are kept *in situ* after the patient is separated from CPB.[3,4] This technique avoids the relatively ineffective filtration of the CPB circuit.[4] Therefore, the benefit of modified hemofiltration is maximal when a large difference exists between patient blood volume and CPB circuit priming volume (*i.e.*, in younger children). Our observed correlations between UF/TBV and the hemoconcentration effects support this hypothesis because, to increase ultrafiltrate volume while restricting TBV to the patient blood volume, increases the UF/TBV ratio. However, the small circuit prime volume that we used could explain the relative efficiency of blood hemoconcentration using the hemofiltration method applied during CPB. This use of the hemofilter during the rewarming period has the potential advantage of adjusting hematocrit or protein level throughout the operation.

Hemodynamic Improvement by Hemofiltration

The significant increase in mean arterial pressure observed in the hemofiltration group in our study was reported by Naik *et al.*[3] Our finding of a correlation between mean arterial pressure increase and UF/TBV ratio supports the notion that withdrawal of ultrafiltrate is correlated with blood pressure improvement (fig. 5). The mechanism by which blood pressure improves remains uncertain. We speculate that hemofiltration may improve the elimination of some toxic substances[10] or reduce myocardial water content, thereby improving

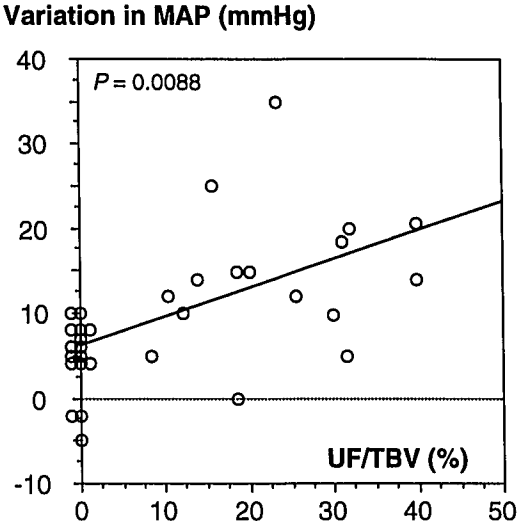

Fig. 5. Correlation between UF/TBV (ratio of ultrafiltrate volume by the estimated total blood volume of circuit + patient) and the variation of the mean arterial pressure (MAP) between the beginning and the end of the rewarming period. Spearman's rank correlation test.

cardiac output. This later hypothesis is supported by some recent findings demonstrating a reduction in myocardial wall volume associated with an improvement of the left ventricle diastolic function produced by hemofiltration.[4] The benefit of this blood pressure improvement is questionable, because hemoconcentration increases hematocrit and should increase blood viscosity leading to increase systemic vascular resistance. Naik *et al.* demonstrated that the overall effect of hemofiltration is an increase in cardiac index, blood pressure, and systemic vascular resistance associated with a decrease in heart rate and pulmonary vascular resistance.[15]

Hemostatic Effects of Hemofiltration

The postoperative bleeding reduction produced by hemofiltration also was observed by Naik *et al.*[3] They speculated that clotting factors and platelets are concentrated by hemofiltration leading to improved clotting conditions.[3] Despite a significant blood loss reduction, our study shows that hemofiltration provides only a limited increase in coagulation factor concentration and no change in platelet count. These results suggest that, when hemofiltration is performed during rewarming, its effects on postoperative bleeding are unlikely to be explained solely by hemoconcentration.

Effects of Hemofiltration on Complement Fragments

The observed levels of C3a and C5a in our study were higher than in adult patients in a previous report.[16] This could be due to a heightened inflammatory response to CPB known to occur in children.[1] The administration of aprotinin might have influenced the inflammatory response of the patients but should not affect comparisons made between the two groups. The small number of patients receiving a polyvinylchloride tubing in this study prevents a direct comparison of the influence of polyvinylchloride and silicone on complement activation. Andreasson *et al.* recently confirmed the activation of the complement cascade by CPB during pediatric cardiac surgery.[9] Moreover, these authors performed hemofiltration after CPB and noticed high concentrations of C3a and C5a in the ultrafiltrate. The lack of a control group in their study limits the interpretation of their data. Our study shows that hemofiltration reduces the plasma concentrations of these complement components. Additional complement activation produced by the hemofiltration circuit may occur during the use of hemofiltration membranes.[17] The use of polyacrilonitrile hemofilters, which are known to induce a lesser complement activation than the polysulphone hemofilters used in this study, may be preferred.[17] In this study, cytokines were not assayed in the postoperative period, avoiding a comparison between the two groups concerning the effects that C3a and C5a removal could have on the delayed cytokines release induced by these fragments that was described by Haeffner-Cavaillon *et al.*[18]

Effects of Hemofiltration on Cytokines

The numerous similarities between post-CPB morbidity and sepsis syndrome have led several groups to investigate cytokine release during and after CPB.[19,20] The elimination of TNFα and IL-1β by continuous hemofiltration[21] and the beneficial effects of continuous hemofiltration on cardiac and pulmonary functions during sepsis states have been reported.[10,13,22] The volume of daily ultrafiltrate appears to influence organ function improvement during sepsis.[23,24] Several reports have demonstrated that TNFα, IL-6, and IL-8 release are stimulated by CPB in adults[18] and even more frequently in children.[5,11] Our study confirms the results of Millar *et al.*, showing that hemofiltration, performed during the late phase of rewarming, can reduce the concentrations of IL-6 and TNFα.[11]

These substances removed from plasma by hemofiltration are not necessarily only removed by convection. Barrera *et al.* showed that incubation of polyacrilonitrile membrane fragments with radiolabeled IL-1β or TNFα yielded a significant binding of both cytokines to the membrane. Removal was most marked in the first minutes, suggesting saturation of the membrane.[25] Therefore, cytokine binding on the hemofilter membrane may be a mechanism to explain the paradoxical lack of correlation between cytokine reduction and UF/TBV that we observed and a correlation between cytokine level reduction and ultrafiltrate duration.

The IL-1β release is well documented in patients undergoing sequential hemodialysis[26,27] and follows exposure to CPB in adult cardiac surgery patients by 20 h.[18] This delay could be explained by the fact that IL-1β release is triggered by complement activation.[28] This could explain the small number of children with a detectable level of IL-1β in this study.

Interleukin-8 is suspected to be a trigger of neutrophil-induced endothelial injury and, therefore, responsible for some of the postoperative CPB adverse effects.[5] The correlation between IL-8 release and the length of CPB has been demonstrated.[5] Our results confirm that IL-8 release is present during rewarming and that IL-8 is poorly eliminated by hemofiltration with the membrane used in this study.

Characteristics of the Different Techniques of Hemofiltration

Although hemofiltration is able to eliminate several cytokines from blood, it would be more meaningful to perform this technique to eliminate the early precursors of the inflammatory response, such as TNFα and complement fractions. There is some evidence that maximal complement and cytokines release coincides with the period of rewarming.[5,9] This preferential timing in cytokine release and hemofiltration use may justify the use of hemofiltration throughout the rewarming period rather than only after CPB weaning. This technique might be a superior method regarding cytokine and complement removal compared to hemofiltration performed after CPB weaning, which seems to be more efficient with respect to water removal.

In conclusion, this study demonstrates that hemofiltration may help to control water balance and concentration of clotting factors during rewarming of CPB. Hemofiltration improves systemic arterial pressure before separation from CPB, improves early postoperative Pa_{O_2}, and reduces postoperative blood loss and time

to extubation. The ability of hemofiltration to remove some major mediators of the inflammatory response that are released during exposure to CPB also may be useful. Future investigations of hemofiltration should address the effects of water and inflammatory mediator removal on major clinical endpoints such as reduced length of hospital stay and improved outcome.

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