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The benefits of continuous ultrafiltration in pediatric cardiac surgery

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Background—Systemic inflammatory response and capillary leak syndrome, caused by extracorporeal circulation, have negative effects on the function of vital organs during the postoperative period. Modified ultrafiltration (MUF) has been developed as an alternative method to reduce the detrimental effects of cardiopulmonary bypass. The aim of this prospective, randomized study is to analyze the effects of MUF in a pediatric population undergoing congenital cardiac surgery.

Methods—Twenty-seven patients who underwent open-heart surgery at our institution were included in this prospective study. They were randomized into two groups as follows: Group I ($n = 14$) of conventional ultrafiltration during bypass and Group II ($n = 13$) receiving both conventional and modified ultrafiltration during and after the cessation of the bypass, respectively. The amount of prime volume, postoperative chest drain loss, transfusion requirements, hemodynamical parameters, duration of mechanical ventilatory support, and length of intensive care unit stay were compared between the two groups. During the postoperative period, the concentrations of hematological, biochemical and inflammatory parameters were also compared by analyzing the blood samples obtained at various time points.

Results—MUF resulted in a significant increase in hemoglobin, hematocrit and platelet levels, and significantly reduced the amount of chest tube output and transfused blood and blood products. MUF also shortened the duration of postoperative mechanical ventilatory support, length of the intensive care unit stay and improved postoperative hemodynamical parameters. During the early postoperative hours, IL-8 is significantly reduced in patients undergoing MUF, however, the concentrations of IL-8 were similar in both groups at the end of 24 h.

Conclusions—MUF decreases the duration of mechanical ventilatory support, the length of intensive care unit stay, the need for blood transfusion and improves postoperative hemodynamics. It is associated with increased levels of hemoglobin, hematocrit and platelets. We can conclude that MUF attenuates the inflammatory response by decreasing the levels of inflammatory mediators.

Key Words: cardiopulmonary bypass, continuous ultrafiltration, conventional ultrafiltration, modified ultrafiltration, pediatric cardiac surgery

The use of cardiopulmonary bypass (CPB) is usually associated with a number of adverse effects, especially in children undergoing surgery for congenital cardiac defects (1, 2). CPB itself produces an important "systemic inflammatory response and capillary leak syndrome" that may lead to an overall increase in total body water and results in end-organ dysfunction during the postoperative convalescence period (3). Since the conventional measures used to avoid the detrimental effects of capillary leakage after bypass have limited effectiveness, Naik et al. (1) developed the technique of modified ultrafiltration (MUF) as an alternative method to decrease the total body water content in children undergoing open-heart surgery. They reported that excess body water was effectively removed by using the ultrafiltration method after the cessation of CPB. They also revealed that MUF, which is performed after weaning from CPB, significantly increased the concentrations of many important plasma proteins and decreased postoperative bleeding and transfusion requirements (1). Following studies from the same center have also documented that MUF significantly decreased body water, removed inflammatory mediators, decreased the duration of mechanical ventilatory support and improved postoperative hemodynamics (4).

In this prospective study, we randomized the patients into two groups according to the method used to remove the excess body water. In one group, we used only conventional ultrafiltration (CUF) and in the other, conventional ultrafiltration was followed by modified

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ultrafiltration (CUF + MUF) after the termination of CPB. Both groups were compared in terms of hemodynamical, hematological and biochemical parameters during the early postoperative period.

The study was approved by the Ethical and Scientific Committee (BEKADEB) of Istanbul University. It is the residency thesis of Kenan Sever, MD and was conducted with the financial aid of BEKADEB.

PATIENTS AND METHODS

Twenty-seven consecutive patients operated in Istanbul University, Department of Cardiovascular Surgery were included in this prospective clinical trial. Informed consent was obtained from each family. The study protocol was also approved by the Scientific Committee of Istanbul University (BEKADEB). The patients were divided randomly into two groups as follows: Group I ($n = 14$) undergoing CUF during CPB and Group II ($n = 13$) undergoing CUF + MUF during and after CPB. The diagnosis of patients included in this study were transposition of the great arteries (three patients in Group I and one patient in Group II), complete AV canal defect (two patients in Group I and five patients in Group II), ventricular septal defect (seven patients in Group I and seven patients in Group II), double-outlet right ventricle (one patient in Group I) and total anomalous pulmonary venous return (one patient in Group I).

Anesthesia and surgical management

The anesthetic management did not change during the study period. Anesthesia was started with 2–3 mg/kg intramuscular ketamine. The intravenous anesthesia was done with 1 mg/kg ketamine, 5 μg/kg fentanyl and 0.1 mg/kg vecuronium. The maintenance of general anesthesia was achieved with an infusion of 5 μg/kg/h fentanyl and isoflurane in 0–1% inspiratory concentration.

All operations were conducted under low flow CPB with standard aortic and bicaval cannulations at moderate hypothermia (25°C). The Minimax Plus (Medtronic, Minneapolis, MN, USA) hollow fiber membrane oxygenator and Sarns Inc. (Terumo Cardiovascular System Corporation, 6200 Jackson Road, Ann Arbor, MI 48103, US) roller pump were used in all patients. The left side of the heart was vented through the right superior pulmonary vein. Myocardial protection was achieved with an initial dose of 20 ml/kg cold crystalloid Saint Thomas II solution followed by 10 ml/kg crystalloid cardioplegia given intermittently every 30 min and topical ice saline solution. Hypothermic circulatory arrest was not used in any of the cases. CPB circuits were primed with a balanced Ringer's solution 400–700 ml, sodium bicarbonate 20 mEq, albumin 20% (50–100 ml) and blood volume sufficient to maintain a hematocrit value greater than 20%.

Technique of conventional ultrafiltration

In Group I, the CUF was performed during CPB to remove excess body fluid. In such patients, the inlet and outlet portions of a hemofilter (Baxter PSHF 400, Baxter Healthcare Corporation, One Baxter Parkway, Deerfield, IL 60015-4625, US) were inserted into the arterial line and venous reservoir, respectively. The ultrafiltration process was begun during the rewarming phase and was performed until the end of bypass. Excess volume in the CPB circuit was reduced to the lowest, safe operating level before the termination of CPB.

Technique of conventional + modified ultrafiltrations

An arterio-venous MUF method of 15 min was used on all patients in the MUF group. A Baxter PSHF 400 (Baxter Healthcare Corporation) hemoconcentrator was used in all patients. The inlet of the ultrafilter was connected to the arterial cannule while the outlet portion was connected to the superior vena caval cannule. Following CUF, after the cessation of CPB, the inlet is completely opened and blood flows from the patient through the arterial cannule with the aid of a roller pump through the hemoconcentrator and back to the patient through the venous cannule. The blood flow velocity was set at 100–300 ml/min during the ultrafiltration process. The duration of MUF was approximately 10–15 min. After MUF, protamine was administered and the patients were transfused if required with the residual MUF circuit blood.

The following indices were analyzed: CPB prime volume, transfused blood and blood products volume after the operation, chest tube output, arterial pressure, cardiac rhythm, right atrial pressure, duration of mechanical ventilatory support and the length of intensive care unit stay. Blood samples were obtained from the patients' arterial line pre- and post-bypass, and from the venous line of the bypass circuit while on CPB. Postoperative values were compared and blood samples were obtained pre-bypass (T_1), at the end of CPB (T_2), at 6 h (T_3) and 24 h (T_4) after bypass. The postoperative hematocrit level, leukocyte and platelet counts, BUN (Blood urine nitrogen), creatinine, albumin, SGOT (Serum glutamic oxaloacetic transaminase) and SGPT (Serum glutamic pyruvic transaminase) were compared between the groups. The samples collected from the patients were stored at −20°C and the supernatant was assayed for IL-8 (Diaclone, Besançon, France).

Statistical analysis

All values were expressed as mean ± standard deviation of the mean. The Mann–Whitney U-test was used to compare variables at different time points. The repeated values were compared using the ANOVA test.

RESULTS

In Group II, there were eight male and five female patients. Mean age was 9.38 ± 1.94 months (3–30 months). Mean weight was 7.27 ± 0.73 kg (4.2–14 kg). In the CUF group, there were 10 male and 4 female patients. Mean age was 12.94 ± 12.98 months (0.06–42 months). Mean weight was 7.31 ± 1.00 kg (3.4–15 kg). Both groups were similar in terms of preoperative diagnoses and surgical procedures. No differences were found for the CPB time, cross-clamp time and CPB circuit prime volume between groups (Table I).

Postoperative comparison of the patients

The change of mean systemic arterial pressure with time was compared in each group. In Group II, systemic arterial pressure improved from a mean of 79.07 ± 11.2 mmHg at T_2 to 83.53 ± 9.35 mmHg at T_3 ($p = 0.0073$). Although there was an improvement of mean systemic arterial pressure in the CUF group at the same interval, this difference was not significant (63.53 ± 7.65 mmHg vs 66.46 ± 8.62 mmHg, $p = 0.258$). Postoperative mean systemic arterial pressures at T_2 and T_3 in Group II were significantly higher when compared with those patients receiving CUF ($p = 0.007$ and 0.0001, respectively). Postoperative right atrial pressure

Table I. *Pre-, peri- and postoperative characteristics*

	MUF	CUF	*p*-Value
Mean age (months)	9.38 ± 1.94	12.94 ± 12.98	0.61
Mean weight (kg)	7.27 ± 0.73	7.31 ± 1.00	0.31
CPB time (min)	102.84 ± 19.3	111.8 ± 19.6	0.294
Cross-clamp time (min)	72.76 ± 18.51	78.21 ± 21.40	0.338
Prime volume (ml)	558.75 ± 149.0	524.66 ± 151.0	0.651

Table II. *Postoperative hemodynamics*

	T_1	T_2	T_3	T_4	p-Value
Cardiac rate (n/min)					
MUF	115.84	110.30	109.23	110.61	0.0001
CUF	136.00	157.86	158.40	150.40	0.02
	$p = 0.213$	$p < 0.0001$	$p < 0.00001$	$p < 0.00001$	
Mean arterial pressure (mmHg)					
MUF	71.30	79.07	83.53	76.15	0.0073
CUF	68.26	63.53	66.46	70.33	0.258
	$p = 0.51$	$p = 0.007$	$p = 0.0001$	$p = 0.001$	
Right atrial pressure (mmHg)					
MUF	6.9	7.7	7.3	6.7	0.086
CUF	7.6	8.9	8.5	8.2	0.38
	$p = 0.525$	$p = 0.0012$	$p < 0.0001$	$p < 0.0001$	

and cardiac rate were also significantly lower in patients who underwent MUF (Table II).

The duration of mechanical ventilatory support was significantly shorter in Group II (CUF + MUF: 19.76 ± 19.75 h vs CUF: 50.6 ± 51.99 h, $p = 0.017$). The length of intensive care unit stay was shorter in the CUF + MUF group compared to those of the CUF patients overall (CUF + MUF: 38.76 ± 22.53 h vs CUF: 82.13 ± 61.59 h, $p = 0.014$).

Hematological and biochemical evaluation

Blood loss was determined by the chest tube output during the first 24 h. Mean postoperative chest drain loss was significantly lower in the patients who underwent CUF + MUF: 79.23 ± 24.65 ml/kg vs 154.33 ± 44.59 ml/kg ($p < 0.0001$). Requirements for blood transfusion were significantly lower in Group II patients compared to those of patients who underwent CUF (78.46 ± 29.95 ml vs 142.0 ± 41.09 ml, $p = 0.0004$) (Table IIIA). The change of hematocrit level obtained at various time points in both groups was analyzed. In the MUF group, hematocrit was improved from $29.15 \pm 4.65\%$ at T_1 to $39.07 \pm 2.2\%$ at T_4 ($p < 0.0001$). In the CUF group, the change in hematocrit level was not significant ($32.12 \pm 8.1\%$ at T_1 and $35.3 \pm 2.6\%$ at T_2, $p < 0.057$). The hematocrit levels measured at various time points (T_2, T_3, T_4) were significantly higher in patients who received CUF + MUF (Table IIIB). The analysis of leukocyte counts did not reveal a significant difference between groups (Table IV). The changes of platelet counts in both groups between time periods T_1 and T_4 were significantly different statistically ($p < 0.0001$ in the MUF group and $p = 0.0031$ in the CUF group). In addition, thrombocyte count at T_4 was significantly higher in Group II ($p = 0.0017$). The biochemical comparison did not reveal a significant difference between the groups (Table IV).

Inflammatory mediators

There was a significant difference in the evaluation of the change of IL-8 level with time in both groups. In the CUF + MUF group, IL-8 levels at T_2 and T_3 were significantly lower in patients who received MUF when compared to those patients who underwent CUF ($p = 0.0005$ and 0.038 at T_2 and T_3, respectively). However, at the end of 24 h, the concentrations of IL-8 were similar ($p = 0.512$) (Table V).

DISCUSSION

With the recent refinements in cardiac anesthesia,

Table III. *Postoperative drainage and hematocrit levels*

	MUF	CUF	p-Value
A			
Chest tube output (ml/24 h)	79.23 ± 24.65	154.33 ± 44.59	<0.0001
Blood transfusion (ml)	78.46 ± 29.95	142.0 ± 41.09	0.0004
Blood products transfusion (ml)	86.92 ± 21.75	143.33 ± 46.08	0.001

	T_1	T_2	T_3	T_4	p-Value
B					
Hematocrit (g/dl)					
MUF	29.15 ± 4.6	41.46 ± 4.9	37.3 ± 2.4	39.0 ± 2.2	0.0001
CUF	32.12 ± 8.1	32.66 ± 2.7	35.6 ± 3.3	35.3 ± 2.6	0.057
	$p = 0.454$	$p < 0.0001$	$p = 0.0017$	$p = 0.006$	

Table IV. *Hematological and biochemical analysis*

	T_1	T_4	p-Value
Leukocyte (10^3)			
MUF	9.6 ± 2.5	11.6 ± 2.3	0.467
CUF	9.1 ± 3.2	12.4 ± 5.3	0.1
	$p = 0.525$	$p = 0.617$	
Thrombocyte (10^3)			
MUF	292 ± 73	217 ± 53	0.0081
CUF	247 ± 99	139 ± 50	0.0001
	$p = 0.06$	$p = 0.0017$	
Albumin[a]			
MUF	4.33 ± 0.8	4.15 ± 0.9	0.08
CUF	3.99 ± 0.34	3.47 ± 0.41	0.06
Creatinine[a]			
MUF	0.36 ± 0.1	0.4 ± 0.09	0.322
CUF	0.56 ± 0.17	0.55 ± 0.19	0.625
SGOT[a]			
MUF	46.46 ± 25	205.69 ± 77	<0.001
CUF	44.07 ± 26	151.92 ± 83.7	<0.001
SGPT[a]			
MUF	22.26 ± 12.46	52.84 ± 33.24	<0.001
CUF	25.5 ± 16	36.6 ± 20.5	<0.001

[a] Comparison of values at T_1 and T_4 between the groups did not reveal significant difference.

myocardial protection and postoperative care, many complex congenital cardiac defects may be surgically managed today with acceptable morbidity and mortality rates. However, with increasing knowledge and experience, we learned that the success of a surgical operation also depends on the prevention of the negative effects of CPB and hypothermia. During pediatric cardiac surgery, hypothermia and crystalloid hemodilution influences worsen the capillary permeability that may result in an increase of total body water content. With the "whole body inflammatory response" caused by CPB, all these factors may have negative consequences in the postoperative functions of vital organs, particularly the heart, lungs and brain.

In the classical surgical era, CUF is a widely used method to remove excess body water. However, the need to maintain a minimum level in the venous CPB reservoir has limited its effectiveness, especially in the pediatric population because of their lower prime volumes. In 1991, Naik et al. (1) developed the technique of MUF as an alternative method to reduce the adverse effects of CPB. They reported that the usage of ultrafiltration for 10–15 min immediately after the cessation of CPB diminishes significantly the total body water increase and postoperative blood or blood products transfusion requirements. Previous studies on MUF revealed that it decreased blood usage and decreased chest tube drainage in pediatric cardiac patients (2, 5). A recent publication by Freisen et al. demonstrated that the concentrations of hematocrit, fibrinogen and plasma proteins are significantly increased by MUF in infants undergoing repair of congenital cardiac defects (6).

MUF removes water from the circulation and leads to an increase in hemoglobin and hematocrit levels. It diminishes the need for blood or blood products transfusion and also decreases postoperative chest drain loss. Another contributing factor that reduces the chest tube output postoperatively is probably the increased levels of platelets in patients undergoing MUF. Our study confirmed the results of previous reports and revealed the superiority of MUF over CUF for the maintenance of desired hemoglobin and hematocrit levels during the postoperative period.

A previous study from Great Ormond Street Hospital revealed that MUF does improve both diastolic and systolic functions (7). In the analysis of ventricular function, it was demonstrated that MUF may decrease myocardial cross-sectional area, end-diastolic length and lead to an increase in mean ejection pressure. One of the most important factors improving the myocardial performance postoperatively is probably the decrease of myocardial edema by any ultrafiltration method used. In our study, the patients who received MUF were found to have higher mean systemic arterial pressure. They were also found to have lower cardiac rate and right atrial pressure during the postoperative period. However, we believe that this possible advantage of MUF should be viewed by more sophisticated studies containing large series of patients.

It has also been reported that MUF improves postoperative pulmonary function. Recent publications showed a marked decrease in the duration of mechanical ventilatory support and intensive care unit stay (8, 9). They also concluded that this advantage is most pronounced in patients with preoperative pulmonary hypertension (9). The more effective removal of lung water by MUF improves pulmonary compliance and mechanics in the intensive care unit stay period. This is especially more important in neonates that are usually associated with an increased risk of prolonged ventilation period. The shorter duration of mechanical

Table V. *IL-8 levels of both groups*

	T_1	T_2	T_3	T_4	p-Value
MUF	252.38 ± 63.61	346.46 ± 73.46	286.0 ± 60.95	233.14 ± 35.26	<0.0001
CUF	238.93 ± 85.51	533.0 ± 177.72	382.26 ± 134.33	289.73 ± 142.57	<0.0001
	$p = 0.166$	$p = 0.0005$	$p = 0.038$	$p = 0.512$	

ventilatory support reduces the intensive care unit and hospital stay periods. Therefore, we can speculate that this advantage directly effects positively postoperative morbidity and cost.

Increased levels of inflammatory factors including TxB2, TNF-α, IL-6, IL-8 and ET-1 have been documented in humans undergoing CPB. The inflammatory cytokines released from many tissues and activated cells are the major cause of "whole body inflammatory response". MUF procedures effectively decrease the levels of both pro- and anti-inflammatory mediators (10, 11). Wang et al. reported that ultrafiltration was more efficient at removing TNF-α than the other mediators (12). In many studies, there was no difference between CUF and MUF in terms of removing the inflammatory mediators (13). In addition, some of the studies failed to show the decrease in the plasma concentrations of all these substances by ultrafiltration despite passage of these mediators into the ultrafiltrate. Other studies suggested that the effectiveness of MUF in removing these inflammatory mediators is relatively transient and the levels of these substances at the end of 24 h does not differ between the patients undergoing either CUF or MUF. In our study, despite the lower levels of IL-8 during the early postoperative hours in patients who received MUF, the levels of this cytokine did not differ significantly at the end of 24 h.

In conclusion, we analyzed prospectively two comparable groups of patients undergoing MUF and CUF during cardiac surgery. We conclude that MUF resulted in a significant increase in hemoglobin, hematocrit and platelet levels; significantly lower amount of transfused blood requirement and chest drain loss. MUF also decreases the duration of mechanical ventilatory support, the length of intensive care unit stay and improves postoperative hemodynamics. The lower levels of IL-8 during the early postoperative hours may diminish the inflammatory response; but this aspect requires more sophisticated and extensive controlled studies.

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