

Does Modified Ultra Filtration Affect Clinical Outcome Following Pediatric Cardiac Surgery

Akram Allam¹, Wael Hassanein¹, Walid Abu Arab^{1,2}, Ahmed Othman³, Mohsen AbdelAzeem³

¹Department of Cardiothoracic Surgery, University of Alexandria, Alexandria, Egypt

²Service of Thoracic Surgery, University of Sherbrooke, Quebec, Canada

³Department of Critical Care Medicine; Cairo University, Cairo, Egypt

Email address:

akram13@hotmail.com (A. Allam), waelhassanien@yahoo.com (W. Hassanien), walidabuarab@yahoo.com (W. Abu Arab), aar_zaher@yahoo.com (A. Othman), Mohsensalah70@hotmail.com (M. AbdelAzeem)

To cite this article:

Akram Allam, Wael Hassanein, Walid Abu Arab, Ahmed Othman, Mohsen AbdelAzeem. Does Modified Ultra Filtration Affect Clinical Outcome Following Pediatric Cardiac Surgery. *International Journal of Cardiovascular and Thoracic Surgery*. Vol. 1, No. 1, 2015, pp. 13-19. doi: 10.11648/j.ijcts.20150101.14

Abstract: Background: Modified ultra filtration (MUF) has become widely used in pediatric cardiac surgery. MUF is capable to remove large amounts of fluid with significant improvement in the post-cardiopulmonary bypass status and laboratory parameters of the patients. There is; however; contradicting reports in the overall clinical outcome benefit following MUF. Methods: Thirty patients weighing less than 15 kg and their median age was 10 months. Undergoing open-heart surgery over a one year period was randomized to either MUF group or conventional ultrafiltration group (CUF). Parameters of investigations included perioperative laboratory findings, hemodynamic status, and duration of hospitalization, and morbidity and mortality rates. The volume of fluid removed with each method was standardized as a percentage of effective fluid balance. Results: There was no significant difference between both groups in age, weight, or duration of cardiopulmonary bypass. MUF patients group received less volume than the CUF group (175 + 72 vs. 196 + 111 ml/kg; $p=0.05$). There was no difference in the percentage of effective fluid balance that was removed in both groups. The MUF group showed significant higher post-cardiopulmonary bypass hematocrit levels and higher mean arterial blood pressure. Moreover, a significant reduction in chest tube drainage (27 + 16 vs 36 + 11 ml/kg $p<0.001$) was noted in this group. However, no difference was detected between both groups as regard duration on ventilator, number of days at ICU or at hospital. Conclusion: MUF seems to produce temporary improvement in the immediate post cardiopulmonary bypass period. However; its long term effects is similar CUF.

Keywords: Cardiopulmonary Bypass, CUF, MUF

1. Introduction

A number of adverse effects are associated with the use of cardiopulmonary bypass (CPB) in infants and children (1,2,3). There is an increased capillary permeability, which results in an increase in tissue water content and manifested as an increase in total body water (TBW) after cardiac surgery. The increase in TBW content is more severe in low weight infants underwent long periods of CPB requiring hemo-dilution. In addition, myocardial and pulmonary edema following cardiac surgery has been reported. They can lead to myocardial diastolic dysfunction and decreased pulmonary compliance as well as gas transfer (4, 5). Several mechanisms; that contribute to the increase in capillary permeability; include direct physical consequences of hemo-dilution, fluid overload and activation of the systemic inflammatory mediators including

tumor necrosis factor (TNF), interleukins and leukocyte elastase (2,3). These substances were suggested to be responsible for postoperative organ dysfunction and morbidity (6, 7).

CPB has been associated with an increased pulmonary vascular resistance and pulmonary hypertension in infants (8,9). Endothelin-1 (ET-1); a polypeptide produced by vascular endothelium; has potent vasoactive properties that have been implicated in the patho-physiology of pulmonary hypertension (10). In patients with pulmonary hypertension and congenital heart disease; plasma concentration of ET-1 increased immediately after CPB and showed significant correlation to the ratio of pulmonary to systemic arterial pressure (11, 12).

Several methods have been suggested to decrease tissue edema including use of small circuits to decrease prime

volume, the use of steroids, increasing hematocrit in the pump prime and the use of post-operative peritoneal dialysis. Since the 1980s; a number of teams begin to use ultrafiltration during pediatric CPB. The value of this technique is the ability to remove large volumes of water and the inflammatory response mediators (13).

There are two basic approaches to ultrafiltration. The first technique is termed conventional ultrafiltration (CUF). In this technique; the inlet of the ultra-filter is placed distal to the oxygenator of the CPB circuit. Ultrafiltration is carried out during the rewarming phase before discontinuation of CPB. The volume present in the CPB circuit limits the total amount of fluid that can be removed.

The second technique was described by Naik *et al.* in 1991 at great Ormond Street hospital. It is referred as Modified Ultra-filtration (MUF) (14). This is carried out after the cessation of CPB. The criteria for the duration of MUF include target hemoglobin, complete salvage of the circuit content and cutoff time of 15-20 minutes. At the completion of the procedure; 600 to 800 c.c. of fluid is usually removed. This amount is more than the fluid removed during CUF. This difference has been claimed to result in greater attenuation of deleterious effect of hemo-dilution and inflammatory response syndrome by MUF. These studies have nonetheless compared MUF to no filtration (13, 15).

More recent reports suggest that there is no difference between these two techniques. Keenan *et al.* stated that the pulmonary compliance in the group that received MUF improved after the procedure, although the compliance at the end of the operation and at 24 hours following surgery was similar to those who received CUF only (16). In addition, there was no difference in intubation period or length of stay at the ICU. Some studies included small groups of patients reported no difference in the level of inflammatory response mediators between patients who had CUF only and those who had both MUF and CUF (17, 18). Thompson *et al.* have shown that MUF and CUF have similar clinical effects when a standardized volume of fluid was removed (19).

2. Objectives

The aim of this study was to compare CUF in one group with MUF in a second one. The following parameters were recorded: operative mortality, hemodynamic parameters (heart rate, blood pressure, pulmonary artery pressure, and myocardial contractility), fluid balance, blood transfusion / haemoglobin loss, length of intubation length of stay at ICU, and need for inotropic support.

The primary objective of the study was to determine the clinical outcome following MUF. The primary end points were operative mortality, duration of mechanical ventilation, length of ICU stay and total hospital stay. The second objective was to determine the changes in patients' variables that may help to explain any observed differences. The secondary end points were; therefore; the volume of blood and transfused blood products, the absolute change in total body hemoglobin, the incidence of renal and cerebral dysfunction

and the total amount of inotropic agents infused.

3. Patients and Methods

Thirty patients below 15 kgm of body weight undergoing cardiac surgery and requiring cardiopulmonary bypass were randomized to either of the two arms of the study. One group (15 patients) is subjected to MUF. The other 15 patients were subjected to CUF only. Inclusion criteria included any child below 15 kg of weight and less than 18 years if he requires correction of congenital heart disease/s under CPB, irrespective of his pre-operative status, mode of ventilation or medical therapy (including steroid therapy). Children who required repeat runs of CPB during the same operating session where only one instance of modified ultrafiltration was implemented were included. All anatomical lesions and all forms of congenital cardiac surgical procedures were not criteria for exclusion.

Exclusion criteria included patients, who required the institution of a second cardiopulmonary bypass for the correction of residual, recurrent or omitted lesions during the same admission, but not the same operative session. Patients who required two or more runs of cardiopulmonary bypass during the same operative session, and are subjected to more than one instance of modified ultrafiltration were excluded. Patients and parents who would not give consent for the randomization were not included.

A standard pediatric perfusion protocol was used in all patients with aortic, right atrial or bicaval cannulation. Flow rate was 2.4 – 3.5 L/min/m². Blood prime was used whenever necessary to get perfusion hematocrit of 25% and the priming volumes determined by the cannula and tubing sizes. Cold blood cardioplegia was used during the aortic cross-clamping with repeated doses every 20 minutes. The first dose ran for 4 minutes while the repeat doses for 2 minutes at the delivery rate of BSA (body surface area) X 110 ml/min. A dose of warm blood cardioplegia administered for 2 minutes at BSA X 110 ml/min prior to the release of the aortic cross-clamp. The total amount of cardioplegia solution was accurately recorded. The patient was cooled to 32 °C for moderate hypothermia, 24 °C whenever low flow perfusion was required and 16 °C if deep hypothermic circulatory arrest was needed.

Conventional Ultra-filtration (CUF)

All patients were subjected to conventional ultrafiltration. This was carried out as soon as the patient was on full CPB, during both the cooling and the re-warming phase of bypass, until the patient was successfully separated from CPB. The hemo-filter (Hemcor HPH 400, Minntech Corporation, Minneapolis, Minn, USA or its equivalent) was primed with lactated Ringer's solution and connected with ¼ inch tubing to the venous reservoir, proximal to the roller pump head. Blood from the reservoir was pumped at 15-30 ml/kg/min through the hemo-filter (with a maximum of 300 mL/min) and the filtered blood returned to the reservoir. A negative suction pressure of -180 mmHg was applied to the filtration post and the filtrate collected separately in a container in which the volume of the effluent would be accurately recorded. A

maximum volume was filtered so as to leave enough perfusate in the venous reservoir for adequate arterial inflow.

In MUF group, only arteriovenous modified ultrafiltration was utilized. Following the end of formal CPB, one of the venous cannulae, usually that of IVC was removed and the other one was left in the right atrium or inside the superior vena cava. The venous line was connected via the Luer lock of the Y-connector for the venous cannulae. MUF was carried out by allowing blood to be drained from the aortic cannula through the cardioplegia circuit via a connecting circuit prepared before cardiopulmonary bypass. A roller pump was used to direct the blood into the hemo-filter to reach a maximum ultrafiltration rate of 75 ml/min. Following filtration the blood would be returned by a pump via the cardioplegia tubing connected to the indwelling venous cannula. A suction pressure of -180 mmHg was applied to the hemo-filter port to achieve an ultrafiltration rate of 3-5 ml/kg/min. The filtrate was collected and its volume was accurately measured and recorded. The MUF would continue for 20 minutes and the filtered blood was subjected to heat exchange to maintain the patient's core temperature above 36 °C.

The target used to accomplish optimal ultrafiltration is the desired final hematocrit (Hct) and the formula to calculate the volume of fluid to be filtered was as follows:

$$\text{Volume to be filtered} = \frac{PBV (Final\ Hct - Hct\ at\ end\ of\ bypass)}{Hct\ at\ end\ of\ bypass}$$

PBV is the patient's calculated blood volume (100 X body weight in kg for neonates and 90 X body weight in Kg for infants and older children)

Randomization of patients was performed as follows: Thirty sealed envelopes containing labeled cards were prepared, 15 with yes and the others with no, the perfusionist selected randomly, if a (yes) envelope was selected then MUF would be performed proceed as described above. If a (no) was selected, the patient would not receive MUF.

The post-operative care proceeded as usual and the intensivists had freedom in the choices of volume replacement, inotropic support, blood and blood products transfusion, timing of extubation, diuretics, vasodilator and renal replacement therapy, and transfer from the ICU.

Continuous data are presented as a median and range, nominal data are presented as percentage. Chi-square test for nominal data and t test for continuous data were used to compare the two operative groups (surgical closure or non-closure of PDA). A *p*-value less than 0.05 was considered significant.

4. Results

The two groups were well matched for age, weight and sex distribution (Table 1). Both groups underwent similar operations. The most frequent surgery was repair of ventricular septal defect (43%) (Table 2).

Table 1. Patient data.

Parameter	MUF (n=15)	CUF (n=15)	p-value
Age (months)	10 + 11.6	12 + 14.1	0.15
Weight (kg)	7 + 4.3	8.2 + 3.3	0.07
Height (cm)	67 + 13	69 + 18	0.97
CPB time (min.)	124 + 61	121 + 57	0.8
Clamp time (min.)	68 + 23	58 + 26	0.74
Total Surgery time (min.)	245 + 51	239 + 62	0.85
Total fluid Received (ml/kg)	185 + 72	225 + 111	0.05
Urine output (ml/kg)	13 + 21	12 + 17	0.87
Effective fluid balance (ml/kg)	172 + 51	213 + 94	0.09
Ultra-filtrate volume (ml/kg)	94 + 75	115 + 62	0.03
48 hrs tube drainage (ml/kg)	27 + 16	36 + 11	< 0.001
Baseline Hct%	36.2 + 7.1	37.4 + 6.9	0.4
Hct % at end of bypass	27.7 + 6.4	33.2 + 2.8	-
Hct % at end of MUF	38.3 + 4.3	33.32 + 2.8	0.09

Kg = Kilogram, CPB = Cardio-Pulmonary Bypass, cm = centimeter, min. = minute,
hrs = hours, Hct. = Hematocrite

Table 2. Type of surgery.

Type of surgery	MUF	CUF
VSD	6	7
TOF	3	1
Bi-directional Glenn shunt	2	3
Atrioventricular septal defect (ASD)	2	1
Fontan	1	2
RVOTO relief	1	1

VSD = Ventricular Septal Defect, TOF = Tetralogy of Fallot, RVOTO = Right Ventricle Outlet Obstruction

The duration of CPB was similar in both groups (124 + 61 in the MUF group and 121 + 57 minutes in the CUF group; *p* = 0.8). There was no differences in the aortic cross-clamping (62 + 23 vs. 58 + 26 minutes; *p* = 0.74).

The total volume of fluid received was significantly larger in patients undergoing CUF than those with MUF. Urine output during CPB did not differ between both groups. The effective fluid balance; defined as total fluid received in the prime and during CPB minus urine output; was greater in patients undergoing CUF, *p* = 0.06. In both groups, an average of approximately 50 % of effective fluid balance was removed in the ultrafiltration effluent. There was no morbidity related to the technique used. The time used for MUF did not increase the total operative time *p* = 0.85.

In the MUF group, the heart rate increased during CPB from 132 + 15 beats /min before CPB to 152 + 18 at the end of CPB (*p* = 0.0002) (Fig. 1). No significant differences were observed after finishing modified ultrafiltration (147 + 13 beats /min). The central venous pressure showed no significant changes during the procedure (6.9 + 3.1 mmHg before CPB, 8.3 + 2.4 mmHg at end CPB, 10.3 + 3.5 at the end of MUF and 11 + 2.7 mmHg postoperatively). The systolic BP decreased during CPB from 85 + 18 mm Hg before CPB to 68 + 11 mmHg at the end of CPB. During MUF, the systolic BP increased significantly to 84.3 + 12.6 mmHg at the end of MUF (*p* = 0.00001) (Fig. 2). Following that, no significant difference was observed between the end of MUF and the postoperative values. There was no statistical difference in the

inotropic support before and after MUF.

In the CUF group, the heart rate increased during CPB from 127 ± 16 beats / min before CPB to 154 ± 14 at end of CPB ($p = 0.0002$). The systolic BP decreased during CPB from 87 ± 19 mmHg before CPB to 74 ± 13 mmHg at the end of CPB which is less than the MUF group but did not differ significantly. Patients in MUF group received less inotropic drug support during the first 24 hours after the operation

(252.6 ± 87.4 ug/kg in 24 hours) than patients of CUF group (457.6 ± 189.2 ug/kg in 24 hours, $p = 0.03$). All patients in MUF group received dopamine. In CUF group, all patients received dopamine except 3 patients, two received epinephrine, and one received milrinone. The doses of inotropic agents received in the first 24 hours after the operation were fairly standard in the MUF group, but showed a large variation in the CUF group.

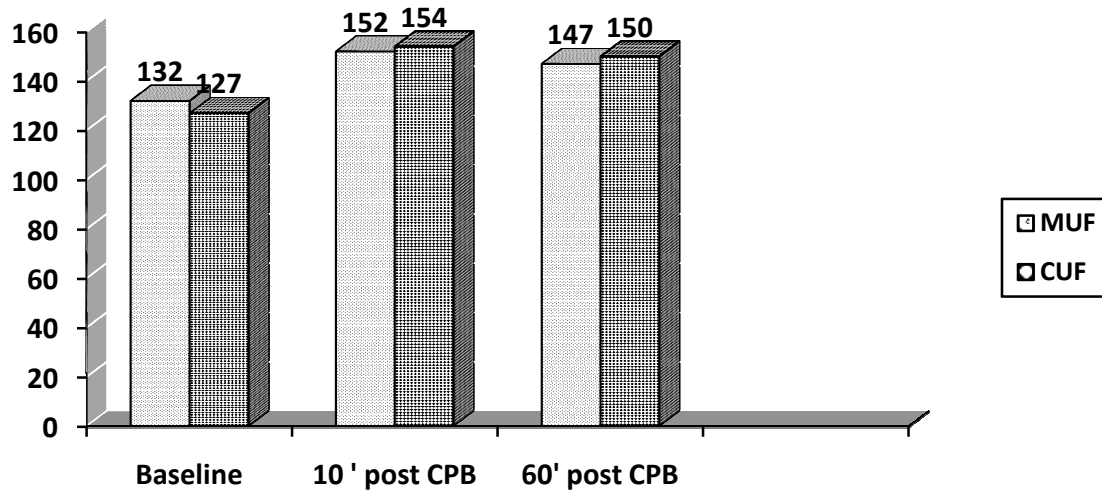


Fig. 1. Heart rate before CPB (baseline), 10 minutes and 60 minutes after CPB or MUF.

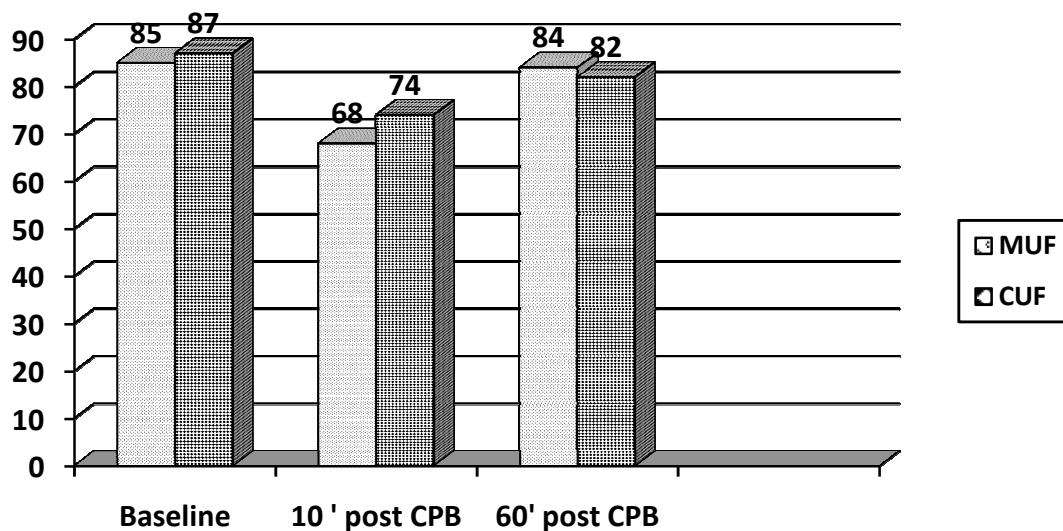


Fig. 2. Systolic blood pressure before, 10 minutes and 60 minutes after CPB or MUF.

There was no significant difference in both groups in baseline hematocrit ($p = 0.4$), and there was a trend toward a higher hematocrit in the MUF group ($p = 0.09$). In MUF group, the hematocrit value immediately before ultra-filtration (after CPB) was significantly lower than that at baseline ($36.2 \pm 7.1\%$ vs. $27.7 \pm 6.4\%$ $p < 0.001$) and there was a significant increase

in hematocrit from the initiation to the completion of MUF ($27.7 \pm 6.4\%$ vs. $38.3 \pm 4.3\%$; $p < 0.001$). The hematocrit after MUF was higher than that at baseline. In the CUF, the hematocrit value after discontinuation of CPB did not differ significantly from baseline (Fig. 3).

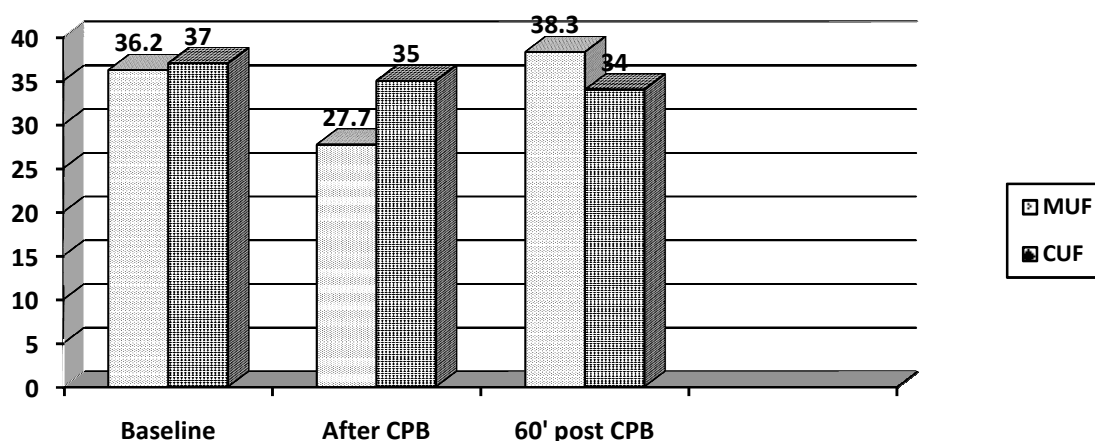


Fig. 3. Hematocrit changes.

As regard blood transfusion, the amount of blood transfused was less in the MUF group but did not reach statistical difference ($p = 0.62$). No differences were found between both groups in the proportion of patients who received platelet transfusions (MUF 32% vs 27% CUF $P=0.68$) or fresh frozen plasma (MUF 75% vs. CUF 84% $p = 0.2$).

Chest tube drainage during the first 48 hours following surgery was less in patients randomized to MUF than those who received CUF $p < 0.0001$. As regards mechanical Ventilation, ICU (Intensive Care Unit) and Hospital stay; there was no significant difference between both groups (Table 3).

Table 3. Postoperative comparative parameters between MUF and CUF groups.

Parameter	MUF	CUF	p-value
Duration of mechanical ventilation (d)	2 + 0.4	2.2 + 1.4	0.82
ICU stay (d)	4.8 + 1.5	5 + 1.2	0.21
Hospital stay (d)	6.8 + 1.4	7 + 1.6	0.09
Mortality	0	0	-

d = days, ICU = Intensive Care Unit

5. Discussion

Many of perioperative morbidity that occurs following cardiac surgery in the pediatric population can be attributed; in large sector; to pathophysiologic process caused by extracorporeal circulation.(19) Ultrafiltration is a strategy that has been used for many years in an effort to attenuate the effects of hemo-dilution that occurs when young children undergo surgery with CPB. Over the past few years, a modified technique of ultra-filtration commonly known as MUF has been used with increasing enthusiasm. MUF was first described by Naik, Knight, and Elliott (14) in 1991 and was shown to be more effective than conventional ultrafiltration in reducing the rise in TBW and in elevating hematocrit value after CPB. It was also shown to reduce the donor blood requirement associated with CPB in children (18, 19). In addition it reduces the incidence of pleural or pericardial effusion and shortens the hospital stay (20). It was

suggested that removal of some factors in the blood like interleukin 6 or 8 and tumor necrosis factor may be the reason. In another study; removal of PGE2 was found to be correlated with the improvement in blood pressure (21). However, most of these studies compared MUF to no filtration and the volume removed was not mentioned.

In this study, we tested the hypothesis that CUF and MUF will not differ in their clinical effects when a standardized volume of fluid is removed on the basis of patient weight and the volume added in the prime and during CPB. Hematocrit levels after the termination of CPB were significantly higher in MUF patients than in CUF patients. The higher hematocrit in MUF patients reflects the higher efficiency of hemo-concentration in MUF compared with CUF. High hematocrit levels after bypass can help to reduce the need for transfused blood. This agrees with other studies that showed a reduction in blood transfusion in MUF patients (22, 23, 24), while other studies showed no difference (25).

Our study showed that MUF patients had higher blood pressure after CPB, which reflects the recovery of the circulatory system in MUF patients. Myocardial edema resulting from hemo-dilution and increased vascular permeability contributes to myocardial dysfunction after CPB. In the dysfunctional heart, myocardial thickness and decreased systolic function are often observed by ultrasound examination in the post-bypass period (26). Previous studies have illustrated that MUF reduces the edema of the myocardium and facilitated the restoration of normal myocardium function.(26,27) Another possible cause of higher blood pressure after MUF could be decreased concentrations of anesthetics owing to filtration process. Hodges and colleagues, (28) measured plasma anesthetic concentration after MUF. They concluded that the higher blood pressure in the MUF group was not likely a result of the decreased plasma anesthetic level (28).

In this study, chest tube drainage was significantly less in the MUF group. Coagulopathy and hemostatic difficulty are common after CPB in pediatric patients. The coagulation system of a neonate who is undergoing CPB is known to be profoundly affected by hemo-dilution (29). MUF is expected

to reverse the adverse effects of hemo-dilution on the coagulation system. Indeed, previous reports have suggested that MUF increased the concentration of coagulation factors and that it attenuated the coagulopathy associated with CPB (29). Hemostatic abnormality after CPB does not have a simple pathologic cause, however, multiple factors are involved (30). Increased inflammatory responses, platelet dysfunction, and increased fibrinolysis are other major factors that should be considered as reasons for abnormal hemostasis. The effects of MUF on preserving platelet function and fibrinolysis have not yet been fully clarified.

Pulmonary dysfunction after CPB is common and may result in significant morbidity and mortality. The reasons for CPB induced lung injury include interstitial lung water owing to hemo-dilution, lung ischemia during aortic cross-clamping, and inflammatory reaction elicited by CPB. Because MUF can eliminate excess water and can ameliorate inflammatory reactions, the advantages of MUF are widely accepted. In this study there was no difference in the postoperative ventilatory data or ICU stay. This agrees with Mahmoud and associated (31) who pointed out, that the advantages of MUF on lung function might be of limited duration only rather than sustained for long postoperative periods.

To counteract pathologic fluid accumulation during CPB, ultra-filtration to remove excess water is now widely accepted practice in pediatric cardiac surgery. Theoretically, MUF has a much higher efficiency in terms of fluid removal than does CUF; because it is carried out after the termination of CPB. Indeed previous reports (31) have indicated that the ultra-filtered fluid volume was larger in MUF. Meanwhile, Thompson and associates, (19) conducted a prospective randomized study to assess the hypothesis that MUF and CUF have similar clinical effects when a standardized volume of fluid is removed. They concluded that hematocrit, hemodynamics, ventricular function, blood product requirements, and postoperative resources used do not differ between pediatric patients receiving CUF and those receiving MUF (19). It remains unknown whether the benefits of MUF depends solely on its greater efficiency at fluid removal.

Another potential advantage of ultrafiltration is cytokine removal and inflammatory response attenuation. Surgical trauma and CPB are associated with the production of various kinds of cytokines and inflammatory responses. Indeed, Allan *et al.* (32) have demonstrated that postoperative interleukin 6 and 8 are correlated with the length of the ICU stay. Since MUF has higher efficiency in terms of fluid removal, it may be capable of filtering out inflammatory mediators more efficiently as well.

6. Conclusion

In conclusion, our study indicates that MUF resulted in significantly higher post-bypass hematocrit levels and higher mean arterial blood pressure. It also showed a significant reduction in chest tube drainage. However, it failed to show any difference in ventilator time, ICU and hospital stay. These findings suggest that MUF compared to CUF, can improve

clinical conditions in the immediate post-bypass period, although the benefit of MUF on patient overall outcome might not be significant.

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