Effect of Modified Ultrafiltration on Postoperative Course in Neonates With Complete Transposition of the Great Arteries Undergoing Arterial Switch Operation

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Background The purpose of the present study was to evaluate the effect of modified ultrafiltration (MUF) on neonates with transposition of the great arteries (TGA) undergoing arterial switch operation.

Methods and Results The current study included 36 neonates who underwent an arterial switch operation between 1998 and 2006. Arterio-venous MUF was done in 15 patients (MUF-treated group) and the other 21 patients were controls. Parameters included hematocrit, hemodynamics, pulmonary function, drain loss, leak of peritoneal fluid, length of intubation, and intensive care unit (ICU) stay. The hematocrit increased from 34±2% to 47±4% in the MUF-treated group. Blood pressure in the MUF-treated group was significantly increased without any change of central venous or left atrial pressure. Post-operative oxygenation in the MUF-treated group was greater than that of the control group (P/F ratio: 258±92 vs 170±100 mmHg, p<0.05), which did not contribute to decrease in intubation time (54±33 vs 52±29 h, p=NS). Post-operative chest drain loss and peritoneal fluid leak were comparable. The ICU stay in the MUF-treated group was significantly shorter than that in the controls (101±34 vs 139±42 h, p<0.05).

Conclusions MUF brought improvement in blood pressure and gas exchange capacity and subsequent shorter ICU stay. MUF did not have significant impact on intubation time and capillary leak. (Circ J 2008; 72: 1476–1480)

Key Words: Modified ultrafiltration; Neonates; Transposition of the great arteries

Overall outcomes of neonatal open-heart surgery have been dramatically improved over the past 2 decades owing to refinements of preoperative, intraoperative and postoperative management. The current early mortality rate of patients with transposition of the great arteries (TGA) with intact atrial septum (TGA-IAS) and TGA with ventricular septal defect (TGA-VSD) undergoing arterial switch operation (ASO) is approximately 2–7%, a considerable improvement from the mortality rate of about 15% in earlier eras. Interest has therefore been shifted from reducing operative mortality to facilitating quicker recovery and reducing intensive care unit (ICU) stay and hospital stay by applying an early extubation policy and/or fast-track cardiac surgery pathways. However, stress response to cardiopulmonary bypass (CPB) is much greater in neonates than in older children, and postoperative recovery in neonates can therefore often be compromised by CPB-induced organ dysfunction.

Modified ultrafiltration (MUF), which was introduced by Naik et al in 1991, has become an essential perfusion strategy to minimize CPB-induced adverse effects in pediatric patients undergoing open-heart surgery. A substantial body of evidence showed that MUF improves cardiac, pulmonary and cerebral functions and decreases postoperative bleeding and blood transfusion requirement by reduction of body water accumulation, reversal of hemodilution, and modulation of systemic inflammatory mediators. The beneficial effects of MUF are thought to be greatest in neonates who have the largest body weight/CPB circuit volume mismatch and are therefore most vulnerable to exposure to hypothermia and crystalloid hemodilution; however, the effect of MUF on clinical outcomes in neonates undergoing open-heart surgery has not been clarified in previous studies. We hypothesized that MUF accelerates the recovery in neonates undergoing open-heart surgery by early recovery of hemodynamics and pulmonary function and by attenuation of capillary leakage, thereby contributing to our ‘fast-track’ strategy. To test our hypothesis, we analyzed patients with TGA-IAS and TGA-VSD who underwent ASO with or without MUF because of relative homogeneity of the patients’ characteristics, standardized surgical procedure, low operative mortality, and favorable early and long-term hemodynamic results providing a better picture of impacts of MUF on early clinical outcomes in neonatal patients.

Methods We conducted a retrospective study of neonates who underwent ASO from April 1998 to September 2006 at Okayama University Hospital. The Institutional Review Board approved the study, and informed consent was obtained from the parents of all patients.

We conducted a retrospective study of neonates who underwent ASO from April 1998 to September 2006 at Okayama University Hospital. The Institutional Review Board approved the study, and informed consent was obtained from all patients. The study population included 36 neonates with complete transposition of the great arteries (TGA) undergoing arterial switch operation (ASO) between 1998 and 2006. Arterio-venous MUF was performed in 15 patients (MUF-treated group) and the other 21 patients were controls. Parameters included hematocrit, hemodynamics, pulmonary function, drain loss, leak of peritoneal fluid, length of intubation, and intensive care unit (ICU) stay. The hematocrit increased from 34±2% to 47±4% in the MUF-treated group. Blood pressure in the MUF-treated group was significantly increased without any change of central venous or left atrial pressure. Post-operative oxygenation in the MUF-treated group was greater than that of the control group (P/F ratio: 258±92 vs 170±100 mmHg, p<0.05), which did not contribute to decrease in intubation time (54±33 vs 52±29 h, p=NS). Post-operative chest drain loss and peritoneal fluid leak were comparable. The ICU stay in the MUF-treated group was significantly shorter than that in the controls (101±34 vs 139±42 h, p<0.05).

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Board approved this retrospective study and patient’s consent was waived. Thirty-six consecutive neonates enrolled in the present study included 21 patients who underwent ASO from April 1998 to July 2001 without MUF (control group) and 15 patients who underwent ASO from August 2001 to September 2006 with MUF (MUF-treated group). The patients who underwent concomitant aortic arch reconstruction were excluded from the study. Mean age and weight at surgery were 14±10 days and 3.2±0.6 kg, respectively.

Surgical Procedure
ASO was performed using the standard technique established and described by Mee. CPB was established by ascending aortic and right atrial cannulation for TGA with patient’s body weight of less than 2.5 kg and by ascending aortic and bicaval cannulation for TGA-IAS or TGA-VSD with patient’s body weight of more than 2.5 kg. When cardioplegic arrest had been achieved, the aorta was opened approximately 3–5 mm superior to the upper edge of the coronary ostial bulge and the coronary ostia were excised with a D-shaped cuff. The branch pulmonary arteries were fully mobilized and the main pulmonary artery (PA) was transected. The coronary cuffs were anastomosed to the neo-aortic sinuses by the trap-door technique using either 8-0 or 7-0 polypropylene sutures (Ethicon, Somerville, NJ, USA). The Lecompte maneuver was carried out, and the proximal main PA was anastomosed to the ascending aorta with either 8-0 or 7-0 polypropylene sutures. When VSD coexisted, the defect was closed before completion of coronary transfer and reconstruction of the neo-aorta with a Dacron patch using pledgetted horizontal 6-0 polypropylene mattress sutures. The atrial septal defect (ASD) was directly sutured before the aorta was declamped. In patients with right atrial cannulation, the ASD was closed under suction drainage with or without a short period of low-flow CPB. Defects of the aortic sinuses were repaired under beating heart using a fresh autologous pericardial patch. After completion of neo-PA reconstruction, CPB was terminated with dopamine (5 mg·kg⁻¹·min⁻¹) and nitroglycerin (5 mg·kg⁻¹·min⁻¹) support. A left atrial pressure (LAP)-monitoring catheter and a peritoneal dialysis (PD) catheter were routinely inserted. The chest was primarily closed unless the chest closure resulted in considerable hemodynamic compromise.

CPB and MUF
Priming solution was routinely prepared with blood, which was rinsed and filtrated with 500 ml of acetate Ringer’s solution before starting CPB, and hematocrit in the pump circuit was maintained at 30%. A membrane oxygenator (D901 Lilliput 1, Dideco, Mirandola, Italy) and a roller pump (HAS, MERA, Tokyo, Japan) were used, and the flow rate was maintained at 150–180 ml·kg⁻¹·min⁻¹. Chlorpromazine (0.6 mg/kg), a potent α-blocker, was routinely administered to the pump circuit at initiation of CPB. Moderate hypothermia at 28 degrees was used in all cases. Myocardial protection was obtained by infusion of antegrade crystalloid cardioplegic solution (Modified St. Thomas’ solution, 20 ml/kg at initial injection).

A polysulfon hemoconcentrator (Aquastream 04, JMS, Tokyo, Japan) was used throughout the study period. The hemoconcentrator was placed with the inlet connected to the venous reservoir and the outlet connected to the venous reservoir during CPB and was used for conventional ultrafiltration during CPB. In the MUF-treated group, an arteriovenous MUF was performed immediately after cessation of CPB as previously described. The MUF circuit was established by connection of an accessory arterial line (TERUMO Medical Corporation, Tokyo, Japan) attached to an aortic cannula as an inflow to the ultrafilter and a venous line attached to a venous cannula as an outflow from the ultrafilter. No suction was applied to the filter port. The flow rate was kept at 100 ml/min by the roller pump. The endpoint of MUF was when the hematocrit had reached 45% or when 10 min had passed. The total amount of ultrafiltrate volume in the MUF-treated group was 314±89 ml. The dose of catecholamine and vasodilator remained unchanged during MUF.

Measurements
Systolic blood pressure (SBP), diastolic blood pressure (DBP), central venous pressure (CVP), LAP and hematocrit were recorded at the termination of CPB and at 15 min after termination of CPB (at the termination of MUF in the MUF-treated group). Gas exchange capacity was evaluated by means of the ratio of arterial oxygen tension to fraction inspired oxygen (PaO₂/FiO₂), which was obtained immediately after termination of CPB and at 15 min after termination of CPB. The amount of chest drain loss and the amount of peritoneal fluid drained through a PD catheter in the first 24 h after the operation was measured. The PD catheter was removed when the amount of peritoneal fluid from the catheter was less than 10 ml/kg. The criteria for extubation included acceptable oxygenation (PaO₂/FiO₂>200), adequate tidal volume of more than 8 ml/kg, and respiratory rate of less than 50/min. Operative mortality, duration of intubation, inotropic drug use and length of stay in the ICU were also assessed.

Statistical Analysis
Medical records and operative reports for all patients were reviewed. Results are expressed as mean±standard deviation of the mean. Comparisons between groups were made by using the Mann–Whitney U-test. Comparisons within groups were made by using the paired t-test. A p-value of less than 0.05 was considered statistically significant.

Results
There were no significant differences in age, body weight,

### Table 1 Patients’ Characteristics

<table>
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<th>Control</th>
<th>Modified ultrafiltration-treated group</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (days)</td>
<td>13±4</td>
<td>11±8</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>3.1±0.5</td>
<td>3.4±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>144±41</td>
<td>141±23</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>74±20</td>
<td>71±13</td>
<td>NS</td>
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CPB time, and aortic cross-clamp time between the 2 groups (Table 1). There was no MUF-related complication during the study period. There was no hospital mortality in either group. The hematocrit at the termination of CPB was significantly higher in the control group than in the MUF-treated group (41±3% in the control group vs 34±3% in the MUF-treated group, p<0.05). MUF raised the hematocrit from 34±3% to 47±4% (p<0.05), whereas the hematocrit remained unchanged in the control group, and the hematocrit at 15 min after termination of CPB was therefore significantly (p<0.05) higher in the MUF-treated group (47±4%) than in the control group (41±3%). SBP and DBP in the MUF group were significantly increased without any changes in CVP or LAP (Table 2). There was no difference in PaO2/FiO2 at termination of CPB in either group, whereas PaO2/FiO2 at 15 min after CPB was significantly (p<0.05) higher in the MUF-treated group (258±92 mmHg) than in the control group (170±100 mmHg). There were trends toward decreased post-operative chest drain loss (44±30 ml·kg−1·24 h−1 in the control group vs 28±13 ml·kg−1·24 h−1 in the MUF-treated group, p=NS) and reduced peritoneal fluid loss (30±25 ml·kg−1·24 h−1 in the control group vs 24±10 ml·kg−1·24 h−1 in the MUF-treated group, p=NS) immediately after operation, which were not statistically significant. The amount of peritoneal fluid loss was highest in the day of surgery and was tapered off in 5 days in both the groups (Fig 1). There was a trend toward reduced peritoneal fluid loss in MUF-treated group in the first 48 h without statistical significance. The duration of PD catheter placement was comparable (2.7±1.2 days in the control group vs 2.8±1.2 days in the MUF-treated group, p=NS). PD catheter was removed within 5 days after surgery in all patients. Duration of inotropic drug use in the MUF-treated group was shorter, but the difference was not statistically significant (95±31 h in the control group vs 80±28 h in the MUF-treated group, p=NS). There was no patient who developed prominent capillary leak syndrome in either group. There was no difference in duration of intubation (54±33 h in the control group vs 52±29 h in the MUF-treated group, p=NS). The length of ICU stay in the MUF-treated group was significantly shorter than that in controls (101±34 vs 139±42 h, p<0.05).

Discussion

Using a relatively homogenous cohort, ie, patients undergoing ASO, the present study aimed to elucidate the actual impacts of MUF, as a part of a ‘fast-track’ strategy, on early outcomes of neonatal open-heart surgery. As previously and consistently reported,9,10,12,13 MUF resulted in immediate improvement in hemodynamics and gas exchange capacity. More importantly, the MUF-treated group had a significantly shorter ICU stay than that of the control group. Because there was no difference in duration of ventilation between the groups, the shorter ICU stay might be a result of accumulation of relatively minor improvements in various post-operative parameters, including trends toward decreased chest and peritoneal drain losses and reduced total inotrope support time. Consistent with results of previous studies,9,12 MUF failed to contribute to early extubation, indicating that MUF might facilitate early recovery of patients and shorten the ICU stay by removing excessive water accumulation, which potentially has an impact on attenuation of capillary leak, and by normalizing hemodynamics, rather than by directly shortening the duration of ventilation.

The impact of MUF on neonatal open-heart surgery has not been fully elucidated. In 2 previous studies, the effects of MUF on neonatal patients were analyzed;13,15 however, the population of patients was heterogeneous and small because the neonatal patients were the part of the entire cohort in both studies. The present study, which is the first study focusing exclusively on the effects of MUF on early outcomes in neonates undergoing open-heart surgery, essentially holds the same messages as the previous 2 studies did.13,15

Table 2 Changes in Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
<th>Central venous pressure (mmHg)</th>
<th>Left atrial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-MUF</td>
<td>Post-MUF</td>
<td>Pre-MUF</td>
<td>Post-MUF</td>
</tr>
<tr>
<td>Control group</td>
<td>63±8</td>
<td>64±7</td>
<td>41±7</td>
<td>41±7</td>
</tr>
<tr>
<td>MUF-treated group</td>
<td>52±7*</td>
<td>66±5***</td>
<td>35±5*</td>
<td>46±4***</td>
</tr>
</tbody>
</table>

*p<0.05 vs control, **p<0.05 vs pre-MUF.

MUF, modified ultrafiltration.
A prospective randomized study of 100 children undergoing open-heart surgery, including 21 neonates, showed that MUF reduced the amount of blood loss, requirement of blood transfusion, duration of ventilatory support and length of ICU stay.15 Naik et al also showed that MUF shortened the duration of ventilatory support, ICU stay and hospital stay in 26 children who underwent open-heart surgery under deep hypothermia and/or low-flow perfusion, with only 4 patients having undergone surgery in the neonatal period.13 Compared to the groups of patients in those 2 studies, the cohort in the present study had less magnitude of surgery, ie, moderate hypothermia and reasonable CPB time. In addition, optimal surgical and postoperative management for this entity has already been established to some extent, as confirmed by no mortality and reasonable mechanical ventilation time in the control group; therefore, it is not surprising that the impact of MUF in this study seems to be less than that in the previous studies. Despite less impressive than other studies, MUF clearly minimized some of the burdens in neonates undergoing ASO, thereby assisting quick recovery of this entity.

When this novel perfusion technique emerged in the early 1990s, it was hypothesized that MUF attenuates capillary leak, especially in small infants, by removing excessive fluid as well as some proinflammatory cytokines.14,20 However, this hypothesis has never been tested in any previous studies. In the present study, we compared the changes of the amount of peritoneal fluid between the groups as a parameter of capillary leakage because neonates and infants have a particular propensity for capillary leakage into the peritoneal cavity.21 Although insignificant, there was a trend toward reduced peritoneal fluid discharge in the first 24h in the MUF-treated group. Given the fact that the major factors causing capillary leakage are hemodilution, fluid overload and inflammatory response,14,20 it can be hypothesized that MUF could, not perfectly but partly, address these major factors, thereby potentially attenuating capillary leak after neonatal open-heart surgery. Obviously, this speculation is based on insignificant findings seen in the present study, which is not valid enough to draw a strong conclusion, but further study on the effects of MUF on capillary leak syndrome following CPB is warranted. In the current study, MUF-induced reduction in peritoneal fluid definitely contributed to reduction in ICU stay.

Consistent with results of most previous studies,6,12 MUF immediately improved gas exchange capacity, but this improvement did not contribute to the shortening of the duration of ventilatory support in most cases in the present study. We hypothesized that immediate improvement in gas exchange capacity mainly results from removal of excess fluid from the lung and possibly from mild hemococoncentration. However, ongoing systemic inflammatory response and capillary leakage, as well as ischemia-reperfusion injury, did not allow improved pulmonary function to be sustained, except in particular subgroups such as neonates undergoing open-heart surgery under hypothermia with low-flow CPB or with circulatory arrest.15 We conclude that MUF is not robust enough to shorten the duration of ventilatory support but might, at least, enable avoidance of maximal ventilatory support and prevention of subsequent possible ventilator-induced lung injury in the acute postoperative period.

**Study Limitations**

There are some limitations in this study. The study design was neither prospective nor randomized, and the histological control was used in comparison, raising the possibility that the differences found between the groups might reflect a learning curve, even though surgical, anesthetic and postoperative management was consistent throughout the study period. Furthermore, the levels of inflammatory mediators or other cytokines and ventricular function were not measured; therefore, impacts of removal of inflammatory mediators and/or improvement in cardiac function by MUF on clinical outcomes of this particular patient group are uncertain.

**Conclusions**

The present study showed that MUF shortened the ICU stay but did not change the duration of ventilatory support for patients with TGA-IAS and TGA-VSD undergoing ASO. Immediate improvement in hemodynamics and potential attenuation of capillary leakage might be the mechanism underlying the clinical benefits of MUF in this patient population. Although MUF indeed contributed to facilitate patients’ recovery and therefore should be an essential modality in the ‘fast-track’ strategy, this sole perfusion strategy is not robust enough to shorten the overall postoperative course of neonatal open-heart surgery, and further refinements of surgical, anesthetic and postoperative management are therefore essential to achieve real ‘fast-track’ neonatal open-heart surgery.

**References**


14. Elliott MJ. Ultrafiltration and modified ultrafiltration in pediatric open


