Modified ultrafiltration removes serum interleukin-8 in adult cardiac surgery

Masahiko Onoe, Tatsuo Magara, Yoshio Yamamoto and Takehisa Nojima Department of Cardiovascular Surgery, Kinki University School of Medicine, Osaka-sayama, Osaka and Shiga Seijinbyo Medical Center, Moriyama, Shiga

Cardiopulmonary bypass (CPB) causes an increase in serum cytokine levels and systemic inflammatory responses, which may trigger the onset of various types of postoperative organ failure. In the present study, modified ultrafiltration (MUF) was applied in cases of adult cardiac surgery and an attempt was made to determine whether MUF reduces serum interleukin-8 (IL-8) levels.

Nine patients who underwent cardiovascular surgery with CPB and MUF between June 1996 and June 1997 were compared with nine control patients who underwent cardiovascular surgery without MUF in the same period. Modified ultrafiltration was performed, based on a method proposed elsewhere. Serum IL-8 was measured by enzyme immunoassay at the start of CPB, immediately after CPB, immediately after MUF and 3 h after MUF.

The mean filtrated volume was 1550.0 ± 173.2 ml. In the MUF group, haematocrit increased significantly from 21.2 ± 2.0 to 24.9 ± 3.3% (p = 0.0008), while systolic blood pressure increased from 97.5 ± 16.7 to 116.5 ± 23.9 mmHg (p = 0.0024) after MUF. In contrast, there were no changes in either haematocrit or blood pressure in the control group. In the MUF group, serum IL-8 was reduced from 69.5 ± 33.5 to 58.9 ± 32.4 pg/ml after MUF (p = 0.0029), whereas it was not reduced in the control group.

The results of the present study suggest that MUF has beneficial effects on postoperative haemodynamics, and can reduce serum IL-8 levels in adult cardiac surgery.

Address for correspondence: M Onoe, Department of Cardiovascular Surgery, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osaka-sayama, Osaka 589-8511, Japan.

© Arnold 2000
Introduction

Cardiopulmonary bypass (CPB) during cardiac surgery reportedly causes an increase in serum cytokine levels and systemic inflammatory responses,1–3 which may trigger the onset of various types of postoperative organ failure.4

Interleukin-8 (IL-8), a neutrophil chemotactic factor with a molecular weight of 8 kDa, is known to cause infiltration and degranulation of neutrophils in tissue. Its participation has also been suggested in acute respiratory distress syndrome.5,6 Furthermore, a reduction in IL-8 is believed to suppress these serious conditions after CPB.7

Modified ultrafiltration (MUF) was developed by Elliott and co-workers to rapidly increase hematocrit levels just after (CPB) and to reduce postoperative oedema in paediatric open heart surgery.8–10 This procedure is reported to have a beneficial effect on respiration and haemodynamics after surgery,9–12 to decrease postoperative bleeding9,13 and to reduce the amount of blood transfused.9,12,13 In addition, MUF has been shown to effectively improve cerebral blood flow and metabolism in piglets.14 It has been suggested recently that not only the rapid concentration of blood but also the removal of humoral mediators, such as cytokines, from blood may account for the effects of MUF.15

In the present study, MUF was performed in adult cardiac surgery to clarify its effectiveness, especially in decreasing blood IL-8 levels.

Materials and methods

The present study was a prospective randomized study. According to our institutional ethical rules, informed consent was obtained prior to inclusion in the study. Modified ultrafiltration was performed in nine adults who underwent cardiovascular surgery with CPB at Shiga Seijinbyo Medical Centre between June 1996 and June 1997. The control group consisted of nine adult patients who underwent cardiovascular surgery without MUF during the same period (Table 1). As shown in Table 1, the surgery in the two groups was not the same. Emergency cases and cases treated with left ventricular assist devices were excluded from the present study. Thus, a total of 33.3% of all CPB cases during this period were included in the study.

For patients in both groups, autologous blood donation (400 ml) was carried out after induction of anaesthesia.

Modified ultrafiltration was performed according to the method proposed by Elliott and co-workers.8–10 As shown in Figure 1, the inlet of the HPH-1000 ultrafilter (Minntec Co., Minneapolis, MN, USA) was connected to the arterial line, while the outlet was connected to the venous line. CPB, a conventional ultrafiltration system was used. Immediately after cessation of CPB, the inlet of the cardiotomy reservoir was clamped and MUF was started. Blood flowed from the aorta through the arterial line to the ultrafilter and then through the venous line into the right atrium. The MUF flow rate, 220 ml/min, was controlled by an additional roller pump which was placed at the inlet of the ultrafilter. Negative pressure of about −100 mmHg was applied to the filtrate port of the ultrafilter. To maintain a constant central venous pressure, an appropriate volume of blood was redirected from the venous reservoir back through the arterial line. The resultant loss of volume in the venous reservoir was compensated for by the addition of a crystalloid solution.

All doses of drugs known to have a haemodynamic effect, such as inotropic agents and vasodilators, were not altered during MUF; and other anaesthesiologists refrained from fluid infusion.

Arterial blood samples were taken at the start of CPB (point I), immediately after CPB (before MUF; point II), immediately after MUF (point III)
and 3 h after the end of MUF (point IV) to measure serum IL-8 levels, and to perform blood gas analysis. Blood samples were centrifuged immediately after collection and the serum was cryopreserved at $-70^\circ$C. An enzyme-linked immunosorbent assay (Human Interleukin-8 ELISA Kit, Toray-Fuji Bionics Inc., Tokyo, Japan) was used to measure serum IL-8 levels.

In the control group, the observation period was 15 min, which corresponded to the duration of MUF immediately after CPB. This observation period was referred to as the MUF time in the present study.

Statistical analysis was performed using Statview 4.01 (Abacus Concepts Inc., Berkeley, CA, USA). Data were compared using the Mann–Whitney U-test between groups and the paired t-test within groups. Data were expressed as mean ± standard deviation. A $p$ value of less than 0.05 was considered significant.

Results

There were no hospital deaths and no major complications in either group. The mean filtrate volume during MUF was $1550 \pm 173.2$ ml and the mean MUF time $18.9 \pm 3.2$ min. In the MUF group, haematocrit increased significantly from $21.2 \pm 2.0$ (point II) to $24.9 \pm 3.3\%$ (point III) after MUF.
In the control group, however, no significant changes were noted in haematocrit between point II and point III after MUF time (Figure 2). In the MUF group, systolic blood pressure increased significantly from 97.5 ± 16.7 to 116.5 ± 23.9 mmHg immediately after MUF, while no significant changes in systolic blood pressure were observed in the control group (Figure 3). The serum IL-8 level was less than the cut-off value (10 pg/ml) at point I in both groups (Figure 4). At the end of CPB (point II), serum IL-8 levels increased to 69.5 ± 33.5 pg/ml in the MUF group and 36.5 ± 28.3 pg/ml in the control group. In the MUF group, the serum IL-8 level decreased significantly to 58.9 ± 32.4 pg/ml immediately after MUF (point III) \( (p=0.0029) \). In the control group, however, the IL-8 level did not significantly change after MUF (39.1 ± 30.9 pg/ml at point III, \( p = 0.3289 \)). A significant but weak positive correlation was noted between IL-8 at point III and alveolar–arterial oxygen gradient (AaDO₂) at the time of postoperative ICU admittance (Figure 5). There were no significant differences in PaO₂ (343.8 ± 149.3 vs 381.5 ± 102.9 mmHg) or AaDO₂ (326.5 ± 146.5 vs 292.5 ± 104.1 mmHg) between the two groups at the time of postoperative ICU admittance.

Furthermore, there were no significant differences in time to extubation or in doses of inotropes administered postoperatively.

\( (p=0.0008) \).
Comment

Modified ultrafiltration was developed by Elliott and co-workers to rapidly increase haematocrit levels just after CPB and to reduce postoperative oedema in paediatric cardiac surgery. Several advantages of MUF have since been reported: MUF improved respiratory function and haemodynamics after surgery,9–12 effectively improved cerebral blood flow and metabolism in an experimental study,13 and improved contraction of the left ventricle.14 Postoperative bleeding decreased9,13 and, thus, the amount of blood transfused was reduced.9,12,13

MUF has been used in cases of adult cardiac surgery,16 not only to return the residual blood effectively in a short period of time but also to purify the blood. Haematocrit increased from 21.2 ± 2.0 to 24.9 ± 3.3% immediately after MUF. The increase in haematocrit was smaller in adult cases than in paediatric cases because the amount of residual blood in the CPB circuit was comparatively small in adult cases. However, MUF increased haematocrit rapidly and effectively and, therefore, gave the anaesthesiologists ample time to prepare for post-CPB management. When combined with an autologous blood recovery system or preoperative autologous blood donation, MUF is useful in cardiac surgery without homologous blood transfusion.

The present study found a decrease in serum IL-8 levels after MUF in adult cardiac surgery. However, Staatvedt et al. reported that MUF did not decrease serum cytokine levels (TNF and IL-6) in paediatric cases of cardiac surgery.17 Compared with the amount of residual blood at the end of CPB, the volume filtered by MUF is small in paediatric cases. Therefore, almost the entire decrease in circulating blood volume is replaced by the residual blood in the CPB circuit. Modified ultrafiltration exclusively concentrates the circulating blood, which is why haematocrit shows an almost two-fold increase in a short period in paediatric cases. After MUF, substances with a large molecular mass (such as albumin, globulin and cytokines, including TNF and IL-6) may be concentrated. Thus, serum levels of these substances would be expected to increase after MUF. This may explain why Staatvedt et al. observed that serum cytokine levels did not decrease after MUF in paediatric cases. However, compared with other cytokines, IL-8 has a small molecular mass (8 kDa), which possibly allows for greater filtration. Wang et al. recently took the effect of blood concentration into account and corrected serum IL-8 levels for serum albumin levels.18 They reported that corrected serum IL-8 levels decrease after MUF in paediatric cardiac surgery.

On the other hand, the volume of residual blood in the CPB circuit decreases to zero 4–5 min after MUF is initiated in adults. Blood apheresis is carried out thereafter by the addition of a crystalloid solution. Therefore, MUF is used in adults more for blood purification than for concentrating blood. This may be the reason why serum IL-8 levels decreased in the present study. Similarly, it was reported previously that haemofiltration (HF) and haemodialysis (HD) effectively remove various cytokines from the blood in critically ill patients.19,20 However, blood apheresis in the above studies was performed over the course of many hours, or even days. On the other hand, the entire MUF procedure was performed within approximately 19 min and yet decreased serum IL-8 levels.

Some researchers have reported that serum IL-8 increases after CPB17 and participates in acute respiratory distress syndrome after CPB.5 Moreover, it has been suggested that a decrease in IL-8 suppresses organ dysfunction after CPB.2 MUF may be an effective technique for decreasing serum IL-8 levels and suppressing organ dysfunction, especially pulmonary damage after surgery.

Unfortunately, we were unable to evaluate the clinical effects of IL-8 removal after MUF. In particular, the relationship between serum IL-8 removal and pulmonary function was not clearly identified in this study. Because of the nature of our institution, it was not possible to include a large number of patients in this study. Moreover, the type of surgery performed was not the same in the two groups, and this resulted in differences in serum IL-8 levels immediately after CPB. These factors may account for the failure to find a difference in postoperative pulmonary function between the two groups. Further studies are needed to clarify these points. However, the most important finding of the present study was the removal of serum IL-8 after MUF in adult patients.
References


