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Review article

The effects of modified ultrafiltration on clinical outcomes of adult and pediatric cardiac surgery

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Background: Cardiopulmonary bypass (CPB) can contribute to the development of an inflammatory response and postsurgical morbidity. Conventional ultrafiltration and modified ultrafiltration (MUF) can mitigate the adverse effects of CPB by removing free water and inflammatory mediators, at least in part.
Objectives: To evaluate evidence for the effects of MUF on clinical outcomes of cardiac surgery in pediatric and adult patients.
Methods: A literature review of MEDLINE-indexed articles published between 1990 and June 2014 was conducted on PubMed. A search on the CTS.net website and the Cochrane Central Register of Controlled Trials was also performed with relevant keywords. The search was limited to English language articles and human studies.
Results: Our primary search identified 84 potential articles, of which 55 articles were relevant to conventional ultrafiltration, modified ultrafiltration, ultrafiltration, cardiopulmonary bypass, extracorporeal circulation, pediatric and adult cardiac surgery. There were 3 meta-analyses, 7 review literatures, 21 randomized controlled trials. The remainder consisted of 18 controlled and 6 observational studies. MUF has been beneficial effects on postoperative bleeding, chest drainage, transfusion requirement, and improvement cardiac function, but effects in adult cardiac surgery inconclusive because data was relatively limited.
Conclusions: MUF may improve post-CPB hemodynamic activity and cardiac function in pediatric cardiac surgery. By contrast, the clinical trials in adults are limited mostly by small sample sizes that preclude an adequately powered assessment of clinically relevant outcomes. The available data are conflicting and several studies show no differential outcomes. Further studies are required to identify patients who will most likely benefit from ultrafiltration and to establish standard protocols.

Keywords: Adult cardiac surgery, cardiopulmonary bypass, conventional ultrafiltration, modified ultrafiltration, pediatric cardiac surgery

Cardiopulmonary bypass (CPB) is used in most cardiac surgery. However, the CPB is a nonphysiological procedure that can induce generalized systemic inflammatory responses and eventually result in “post-pump syndrome” [1, 2]. CPB-associated systemic inflammatory responses are mediated by several factors including the interaction of blood components with synthetic surfaces, fluid overload, change in body temperature, nonpulsatile flow, and ischemic reperfusion injury. A consequence of this inflammatory reaction is increased capillary leakage caused by higher capillary permeability leading to fluid retention in interstitial compartment. Moreover, CPB might be involved in the development of multiple organ dysfunction through inflammatory cytokine activation [3]. All of these consequences could adversely affect postoperative outcomes and lead to clinical sequelae including bleeding diathesis, dysfunction of an organ (e.g. heart, liver, kidney) or organ system (e.g., respiratory system, nervous

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system) or multiple organ system failure [3, 4]. Ultrafiltration can mitigate the adverse effects of CPB by removing free water and inflammatory mediators from patients, at least in part. There are two different methods of ultrafiltration; conventional ultrafiltration (CUF) and modified ultrafiltration (MUF) [5, 6]. CUF is performed during CPB. If fluid is added to the CPB circuit during CUF to increase the volume of ultrafiltrate, sometimes the process is called dilutional ultrafiltration (DUF) [5]. Unfortunately, CUF was not found to limit adequately the postoperative accumulation of total body water in children. Modified ultrafiltration (MUF) was introduced in 1991 by Naik et al. [6] and is performed immediately after the termination of CBP. This method does not depend on the volume contained in the circuit and can decrease volume overload after cardiac surgery **(Figure 1)**.

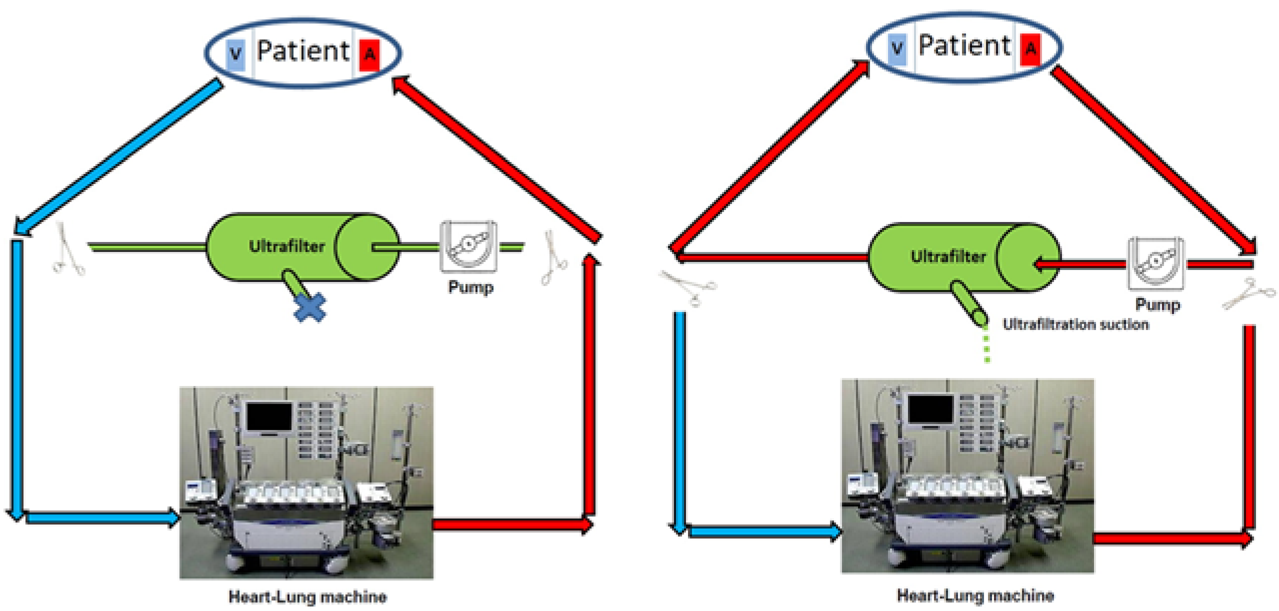
MUF is more effective in removing excess fluid from the patients than CUF, and therefore has several advantages. MUF can reduce systemic inflammatory response syndrome (SIRS) and improve clinical outcomes by removing inflammatory mediators generated during CPB [7, 8]. Despite being used routinely for pediatric patients, ultrafiltration is used less frequently in adults. Small, unblinded clinical trials in pediatric cardiac patients suggest that ultrafiltration can reduce the presence of inflammatory mediators, improve cardiac function, and reduce hemodilution [8]. However, there is currently little evidence to support an improvement in postoperative morbidity by the use of such ultrafiltration techniques in adults [9].

Furthermore, most clinical trials in adult patients are limited by small sample size, which precludes an adequately powered assessment of clinically relevant outcomes [10]. This review attempts to evaluate the currently available scientific evidence for the effects of modified ultrafiltration on clinical outcomes of cardiac surgery in adult and pediatric patients.

Materials and methods

Literature search

A literature review of MEDLINE-indexed articles published in English between 1990 and June 2014 was conducted using PubMed [11]. CTS.net and the Cochrane Central Register of Controlled Trials were also searched with the keywords including conventional ultrafiltration, modified ultrafiltration, ultrafiltration, cardiopulmonary bypass, extracorporeal circulation, pediatric and adult cardiac surgery, complications, and morbidities. The identified articles were subsequently screened for their relevancy. The searches were limited to English language articles and human studies. The relevant studies were further assessed for their level of evidence and quality using several criteria including type of research studies, randomization, blinding, sample size, sample selection, intention to treat analysis, inclusion and exclusion criteria, and methods.



During on cardiopulmonary bypass After separation from CPB

Figure 1. Schematic showing modified ultrafiltration

Results

Our literature search identified 84 potential articles of which 55 articles were found to be relevant to conventional ultrafiltration, modified ultrafiltration, ultrafiltration, cardiopulmonary bypass, extracorporeal circulation, pediatric and adult cardiac surgery. The resulting reference list of relevant articles consistedof 3 meta-analyses, 6 review literatures, 21 randomized, controlled trials (RCT). The remainder consisted of 18 controlled studies (12 prospective, 6 retrospective), and 6 observational studies **(Figure 2)**.

Ultrafiltration techniques and the application of MUF in clinical practice

Although extracorporeal circulation has been used in most cardiac surgery, it can result in SIRS and increased total body water with subsequent postoperative morbidity. Ultrafiltration has been implemented to alleviate these CPB-associated adverse effects. The ultrafiltration procedures involve applying a positive transmembrane hydrostatic pressure gradient across a semipermeable membrane to remove free water and inflammatory cytokines [12].

CUF is relatively easy to perform and does not affect the duration of CPB [5]. However, in some cases, it can only achieve moderate hemoconcentration because the amount of eliminated fluid is limited by the level contained in the venous reservoir. By contrast with CUF, MUF is performed after CPB is finished and is independent of the volume contained in the circuit [6]. Both techniques are considered safe and reliable [4,8]. However, there are differences that warrant consideration. Technically, CUF demands little attention of the surgeon, whereas MUF is demanding immediately after CPB. DUF can enable the removal of inflammatory mediators throughout CPB and does not increase the duration of CPB, but it can only achieve moderate hemoconcentration. MUF can provide more effective hemoconcentration than CUF, removing more free water, and has a greater potential to reduce inflammatory mediators. However, a shortcoming of this method is that it extends the time for which blood is exposed to nonendothelial surfaces (after CPB is complete, 10–15 min are usually needed before removal of cannulae) [13-17]. One meta-analysis showed the advantage of MUF compared with CUF was a significant improvement of clinical status in the immediately after CBP in pediatric patients [18].

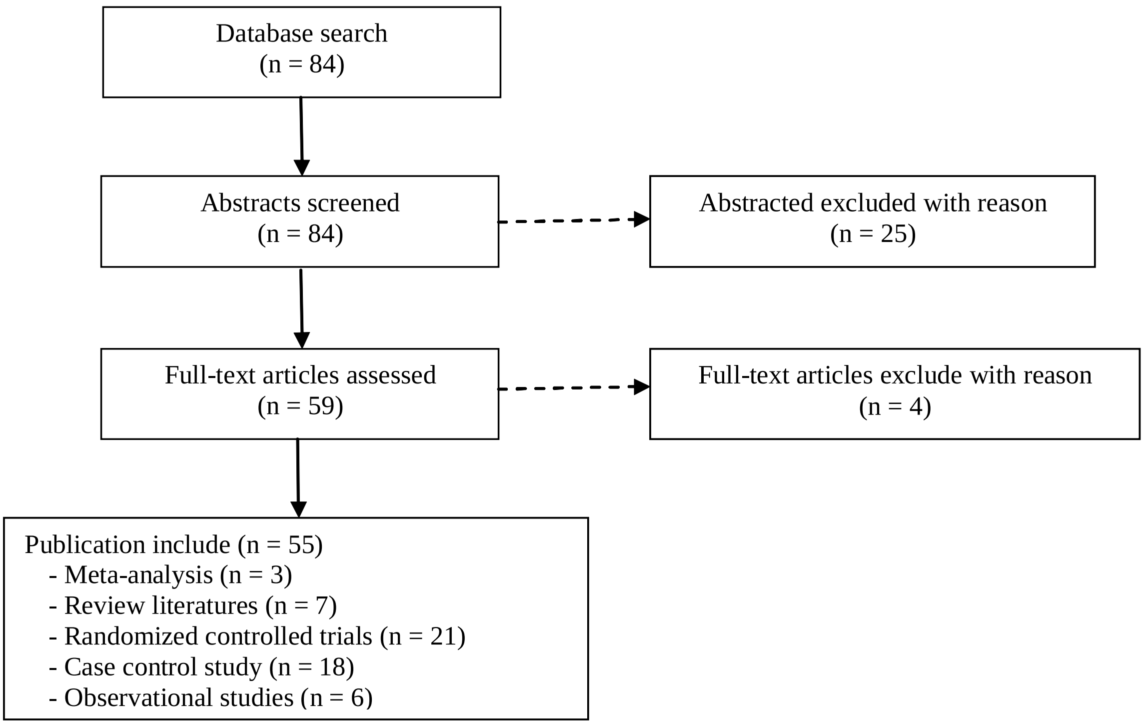


Figure 2. Flow diagram for the literature review

In December 1999, a survey from 145 North American pediatric open-heart institutes indicated that the use of ultrafiltration had risen by over 30% within a decade [19]. In a more recent study conducted in January 2005, questionnaires were sent to 180 North American open-heart centers. The content and format of the questionnaires was nearly identical to the three previous surveys (published in 1989, 1994, and 1999) with an exception that new questions were added to address the emergence of new techniques and devices. Responses were received from 76 (42%) hospitals. Out of the 76 responding centers, 53 (70%) hospitals. Interestingly, MUF was used in 75% of those centers [20]. The routine use of MUF after adult cardiac surgery can potentially be a cost effective and complication-free technique. The overall compliance to the treatment of 98% suggests that ultrafiltration is safe in any adult cardiac patient [17].

Effect of MUF on systemic inflammatory response

The increased capillary permeability and accumulation of excess total-body water resulting from CBP can lead to multiple organ dysfunction. This morbidity mainly results from hemodilution effects of the CPB and a systemic inflammatory response caused by the exposure of blood components to the nonendothelial surfaces of the CPB circuit. The organs most affected in this condition are the heart, lungs, and brain.

CBP is a potent stimulus for the release of proinflammatory cytokines from leukocytes, including tumor necrosis factor-a, interleukin (IL)-1, IL-6, and IL-8. These proinflammatory cytokines play important roles in the pathogenesis of SIRS or post-pump syndrome [21-23]. Several risk factors have implicated in the accumulation of excess water such as children, long CPB duration, hypothermia and hemodilution; however, they have not been thoroughly investigated. Effects of MUF on clinical outcomes in pediatric cardiac surgery have been reported by several randomized, nonrandomized studies and meta-analysis although the results were inconclusive [1, 12, 14, 18, 21-31].

In adults, the available data is contradictory with several studies showing no difference in plasma markers of inflammation and coagulation [32-35]. Whereas 2 studies reported that cytokine concentrations are reduced by MUF. One study found only transient effects of MUF on the level of proinflammatory cytokines (e.g. IL-6 and IL-8) during the immediate post-CPB period, without effect on the levels of anti-inflammatory cytokines levels (e.g. IL-10 and IL-1ra) [36]. Another study found decreased serum levels of adhesion molecules, IL-6 and IL-8, but only after hypothermic CPB; such effects were not detected in normothermic CPB [37]. It is noteworthy that reduced levels of inflammatory mediators were not associated with improvements in clinical outcome. These data suggest that beneficial effects of MUF are achieved by mechanisms further to the removal of inflammatory mediators from the plasma.

Effect of MUF on coagulation and blood transfusion requirement

Cardiac surgery usually requires blood transfusion for several reasons, including perioperative blood losses and CPB-induced hemodilution. The hemodilution is also responsible for increased postoperative blood loss and coagulopathy, which includes decreased levels of coagulation factors, thrombocytopenia and platelet dysfunction as well as coagulation–fibrinolysis imbalance [7, 14]. Several strategies, including ultrafiltration have therefore been applied to minimize the impact of hemodilution. The resulting hemoconcentration may improve coagulation by increasing hematocrit levels and coagulation factor concentrations [33, 38-40].

One meta-analysis involving over 1000 adult patients who underwent cardiac surgery found that ultrafiltration was associated with reductions in postoperative bleeding and blood transfusions. These effects appeared to be greater in patients where MUF was applied than in patients where CUF was applied. MUF was associated with a 0.7 units per patient decrease in blood product use. This decrease was extended by an approximately 70 mL per patient decrease in postoperative bleeding in those treated with ultrafiltration, and these benefits should be considered against with the disadvantages of ultrafiltration [15].

Effect of MUF on cardiovascular function

The exposure of blood from patients to foreign surfaces (such as tubing and pumps) during CBP can lead to leukocyte activation and subsequent release of various cytotoxic products, which can increase vascular permeability. In addition, several predisposing factors including hypothermic CPB are implicated in fluid retention in the body. Hypothermic CPB with cardiac arrest is an extremely nonphysiological condition for the circulatory system [41]. Furthermore, ischemia can predispose the myocardium to pathological fluid accumulation after restoration of coronary flow. Hemodilution together with increased vascular permeability may lead to myocardial edema, which contributes to myocardial dysfunction after CPB. In agreement, increased myocardial thickness and decreased systolic function are observed in dysfunctional hearts by ultrasound examination during the post-CPB period [18, 41]. Gaynor et al. confirmed the reduction in myocardial cross-sectional area after applying MUF [42].

Studies in pediatric patients found that MUF reduced myocardial edema and facilitated restoration of normal myocardial function [7, 30, 42]. Naik et al. measured heart rate, blood pressure, left and right atrial pressure, pulmonary artery pressure, and cardiac output before and after MUF. At a constant left atrial pressure, implementing MUF was associated with decreased heart rate, increased systolic pressure, improved cardiac index, and dramatically reduced pulmonary vascular resistance without a change in systemic vascular resistance [27]. The hemodynamic improvements seen after MUF are associated with an improvement of intrinsic left ventricular systolic function [30]. The improved left ventricular function resulted in decreased inotropic requirements during the first postsurgical day [7, 43]. Another cause of higher blood pressure after MUF may be decreased concentrations of anesthetics used because of the filtration. However, this possibility was questioned by Hodges et al. who measured plasma anesthetic concentration after MUF and showed that plasma concentration of fentanyl remained stable throughout ultrafiltration. The meta-analysis demonstrated that MUF in pediatric patients resulted in higher systemic blood pressure after CPB. This higher systemic blood pressure reflects the augmented recovery of the circulatory system in patients who receive MUF [40, 44].

The data from adult patients is relatively limited compared with that from pediatric patients. A few studies have shown only minimal and transient hemodynamic improvement by MUF [32, 36]. Boodhwani et al. demonstrated that patients underwent MUF were more likely to require vasopressor support after the intervention [45]. Nevertheless, others have demonstrated that the advantages of MUF to improve postoperative hemodynamic status, atrial fibrillation [35, 46] and cardiac function [15, 33, 34, 47] are unclear.

Effects of MUF on pulmonary function

CBP is associated with acute lung injury. CPB-associated pulmonary dysfunction varies from clinically undetectable changes in oxygenation, compliance, and vascular resistance, to respiratory failure. The incidence of adult respiratory distress syndrome is estimated to be between 0.5% and 1.7% [48].

Pulmonary dysfunction after CPB is common in pediatric cardiac surgery and may result in significant morbidity and mortality. The mechanisms for CPB-induced lung injury include increased interstitial water, lung ischemia during aortic cross-clamp, and inflammatory reaction elicited by CPB. Because MUF can eliminate excess water and ameliorate inflammatory reactions, it is unsurprising that the advantages of MUF on pulmonary function have been noted and widely accepted. In children, improvements of pulmonary function indexes including lung compliance, pulmonary vascular resistance, and oxygenation after ultrafiltration have been shown [7, 13, 14, 31, 41, 48, 49]. Nevertheless, a meta-analysis of RCT in pediatric patients failed to demonstrate the benefit of MUF on postoperative ventilation time. However, the findings from this meta-analysis cannot exclude the possibility that MUF facilitates the restoration of lung function in the immediate post bypass period [18].

Likewise, studies in adults have found decreases in postoperative intrapulmonary shunt fraction after ultrafiltration [4]. Nevertheless, the effect of ultrafiltration on the duration of mechanical ventilatory support is not established [4, 17, 19].

Effect of MUF on cerebral function

Effects of MUF on intracranial hemodynamics in children are unknown. During MUF, the blood driven through the ultrafiltration unit is withdrawn from the patient from the aortic cannula and arterial line. High blood flow rates are often applied through the ultrafiltration unit to decrease the time taken for MUF. However, rapid blood withdrawal from the aortic cannula, particularly in small infants (<10 kg), may cause diastolic runoff from the aorta and divert flow from the carotid circulation [50, 51]. Previous studies have indicated that carotid "stealing" may be associated with reduced cerebral perfusion [52]. This carotid "stealing" may be particularly critical in newborn infants who have dysfunctional cerebral autoregulation [53]. Despite the extensive use of MUF in clinical practice and the outcomes discussed above, the detailed effects of high blood flow rates on intracranial cerebral hemodynamics in young children remain unknown.

Rodriguez et al. [54] evaluated effects of various blood flow rates during MUF on cerebral hemodynamics in children who were above and below 10 kg. They concluded that in small infants (<10 kg) the application of high blood flow rates (≥20 mL/kg/min) through the ultrafiltration unit during MUF was associated with decreased cerebral blood flow and transcranial mixed venous oxygen saturation compared with the use of lower blood flow rates in older children. An explanation for these effects is the increased diastolic runoff from the aorta into the MUF circuit, which diverts flow from the cerebral circulation [52]. The changes in the cerebral circulation associated with the use of high MUF flow rates may be important, particularly after deep hypothermic circulatory arrest and in newborn infants with dysfunctional cerebral autoregulation [53]. However, the clinical relevance of these hemodynamic changes to the postoperative neurological outcome in young infants remains to be determined.

In adults, studies have been conducted to evaluate the effects of MUF on cerebral function and complications [13, 17, 24]. Old age, a history of cerebrovascular disease, hypertension, type of surgery, duration of CPB, circulatory arrest, and low-output syndrome are recognized risk factors for perioperative stroke and neurological dysfunction [55]. Interestingly, neurological complications are reported to be less in adult patients receiving MUF. Central nervous system injury may affect as many as 6% of adult patients undergoing open-heart surgery. The lower incidence of cognitive dysfunction (delirium, coma) observed be explained by the ability of MUF to mitigate tissue edema and systemic inflammation. Other reasons may exist, including that the arterial cannula is positioned in the least dependent site of the ascending aorta and that the drainage of blood via the aorta may subsequently promote the clearance of air or fat emboli from the systemic circulation [17]. As a consequence, the MUF could theoretically lower the risk of postoperative cerebral embolism. Eventually, we need further studies or meta-analysis to support this effect.

Effect of MUF on multi-organs function, morbidity, and mortality

The reported incidence of digestive tract morbidity after cardiac surgery is from 0.7% to 1% [34]. The predisposing and contributing factors of CPB-associated gastrointestinal complications include old age, pre-existing digestive pathology, vascular disease, type of surgery, duration of CBP, and low-output syndrome. Moreover, the gut is recognized as both a major source and an important target of inflammatory mediators during CBP [34].

In routine adult cardiac surgery, application of arteriovenous MUF is associated with reduced hospital morbidity because of lower rates of respiratory, neurological, gastrointestinal, and to a lesser extent, renal and hemorrhagic complications [17].

Only one study found technical problems related to morbidity and mortality after MUF [8]. Williams et al. reported 2 cases of early termination of MUF owing to significant hypotension [56]. Bando et al. found no complications related to MUF in their study, but reported one postoperative death in the MUF group of a patient who died of low cardiac output after an arterial switch repair that was followed by 5 days of extracorporeal circulatory support [31]. Wang et al. reported that one patient in the MUF group and one in the CUF group died of cardiac failure and could not be weaned from CPB [1]. Luciani et al. showed that the routine use of MUF in adult cardiac surgery is cost-effective and that no complication was recorded in a series of 289 patients. This represents an overall compliance to the treatment of 98%. The conclusion is that MUF is safe in any adult cardiac patient [17].

Conclusion

Extracorporeal circulation has been used in most cardiac surgery. However, it can be associated with capillary leakage, increased interstitial fluid, and SIRS. The latter can result in multiorgan dysfunction and postoperative morbidity.

MUF has been widely used in pediatric cardiac surgery where MUF apparently improves post-CPB hemodynamic activity with beneficial effects on postoperative bleeding, chest drainage, transfusion requirements, and cardiac function. However, the impact of MUF on the systemic inflammatory response, pulmonary function, and cerebral function in children is controversial [57]. Caution should be applied when using high blood flow rates (≥20 ml/kg/min) during MUF.

The impact of MUF on adult patients remains unclear. Some evidence suggests, it can reduce blood transfusion, but whether this is cost effective is inconclusive. The impact of MUF on the systemic inflammatory response, cardiac function, pulmonary function, and cerebral function in adults is not well known. Because existing clinical trial outcomes in adults are limited by small sample sizes that preclude an adequately powered assessment of clinically relevant outcomes, the findings need to be confirmed in meta-analysis, and larger prospective studies or randomized trials. Further studies are required to identify which patients will most likely benefit from the ultrafiltration and to establish standard protocols.

Conflicts of interest statement

The authors have no conflict of interest to declare.

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