Modified Ultrafiltration Reduces Morbidity After Adult Cardiac Operations

A Prospective, Randomized Clinical Trial

Giovanni Battista Luciani, MD; Tiziano Menon, CP; Barbara Vecchi, MD; Stefano Auriemma, MD; Alessandro Mazzucco, MD

Background—Extracorporeal circulation contributes to morbidity after open-heart surgery by causing a systemic inflammatory reaction. Modified ultrafiltration is a technique able to remove the fluid overload and inflammatory mediators associated with use of cardiopulmonary bypass. It has been shown to reduce morbidity after cardiac operations in children, but the impact on adult cardiac procedures is unknown.

Methods and Results—Five hundred seventy-three consecutive adult patients were prospectively randomized to either ultrafiltration after cardiopulmonary bypass (treatment) or to no ultrafiltration (control). Parsonnet score was used to assess the severity of the patients' clinical conditions. Analysis was done with Student's *t* test or Mann-Whitney *U* test for continuous variables and Fisher's exact test or Pearson's χ^2 for discrete variables. Hospital mortality was 2.5% (7 of 284) in the treatment group versus 3.8% (11 of 289) in the control group ($P=0.357$). Hospital morbidity was lower in treated patients (66 of 284 [23.2%] versus 117 of 289 [40.5%], $P=0.0001$). Cardiac morbidity was similar (26 of 284 [9.1%] versus 35 of 289 [12.1%], $P=0.251$), whereas significantly lower rates of respiratory (20 of 284 [7.0%] versus 36 of 289 [12.5%], $P=0.029$), neurological (5 of 284 [1.8%] versus 14 of 289 [4.8%], $P=0.039$), and gastrointestinal (0 of 284 versus 4 of 289 [1.4%], $P=0.044$) complications were found in treated patients. Transfusion requirements were also lower in treated patients (1.66 ± 2.6 versus 2.25 ± 3.8 U/patient, $P=0.039$). Duration of intensive care (39.9 ± 49.2 versus 46.3 ± 72.8 hours, $P=0.218$) and hospital stay (7.6 ± 3.5 versus 7.9 ± 4.4 days, $P=0.372$) were comparable.

Conclusions—Modified ultrafiltration after cardiopulmonary bypass is associated with a lower prevalence of early morbidity and lower blood transfusion requirements. The impact on length of hospital stay needs further analysis. Routine application of modified ultrafiltration after adult cardiac operations is warranted. **(*Circulation*. 2001;104[suppl I]:I-253-I-259.)**

Key Words: cardiopulmonary bypass ■ ultrafiltration ■ surgery ■ morbidity

The use of cardiopulmonary bypass for cardiac surgical procedures may be responsible for postoperative morbidity by causing a systemic inflammatory response syndrome (SIRS).[1,2] Many consequences of extracorporeal circulation have been implicated in the genesis of the systemic inflammatory state, including the exposure of blood components to synthetic surfaces, the fluid overload necessary for priming the circuit, body temperature changes, nonpulsatile flow, ischemia, and reperfusion of end organs.[1,2] It is currently believed that cellular and humoral factors, including cytokines, may be activated during bypass, which will mediate organ damage.[3] The clinical manifestations of the SIRS include cardiac, respiratory, renal, hepatic, and neurological dysfunction, bleeding diathesis, and even multiple-system organ failure.[2,4–6]

Among the therapeutic maneuvers proposed to mitigate the consequences of postperfusion syndrome, modified ultrafiltration has recently increasingly come into favor. The technique entails removal of water and low-molecular-weight substances under a hydrostatic pressure gradient after separation from cardiopulmonary bypass. This method has been demonstrated to induce hemoconcentration and reduce bleeding and total body water accumulation in children.[7] Because of the properties of counteracting tissue edema and eliminating inflammatory mediators, further observations have attributed to modified ultrafiltration the ability to improve postperfusion end-organ function and to attenuate morbidity after pediatric cardiac operations.[8–14] Information on the clinical effects, if any, of modified ultrafiltration after open-heart surgery in the adult population is limited to 2 trials on highly selected patient cohorts undergoing coronary artery bypass graft surgery.[15,16]

The present study was undertaken in an effort to define the impact of modified ultrafiltration on early morbidity after adult cardiac operations.

From the Division of Cardiac Surgery, University of Verona, Verona, Italy.

Correspondence to Giovanni Battista Luciani, MD, Division of Cardiac Surgery, University of Verona, OCM Piazzale Stefani 1, Verona, 37126, Italy. E-mail luciani@netbusiness.it

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Methods

Patient Selection

After approval by the hospital review committee, all consecutive patients ≥16 years old referred to our institution for a cardiac surgical procedure requiring the use of cardiopulmonary bypass between March 1 and July 31, 1999, were asked for informed consent to participate in the clinical trial. The only exclusion criterion was age <16 years. Five hundred seventy-eight patients agreed to the study and were subsequently enrolled. Patients were randomly assigned to receive either modified ultrafiltration at the end of cardiopulmonary bypass (treatment group) or no ultrafiltration (control group).

Perfusion Technique

Cardiopulmonary bypass was performed with a Stöckert roller pump system (Stöckert Instrumente GmbH) and a Sorin-Dideco Masterflow D-703 hollow-fiber oxygenator (Dideco). The circuit was primed with lactated Ringer's solution, mannitol, and packed red blood cells to achieve and maintain a hematocrit value >20%. Anticoagulation was achieved by administration of heparin sulfate (300 IU/kg IV) and then adjusted to maintain an activated coagulation time >480 seconds. Heparin was neutralized with protamine sulfate at the end of cardiopulmonary bypass in control patients and by the modified ultrafiltration procedure in treatment patients. During cardiopulmonary bypass, nonpulsatile flow was maintained at 50 to 70 mL · kg^{-1} · min^{-1}. All patients were cooled with the perfusate to a moderate hypothermic state (28°C rectal temperature) except for patients needing aortic arch procedures, in which deep hypothermic (18°C rectal temperature) circulatory arrest was used instead. Myocardial protection was done with Buckberg blood cardioplegia with an initial dose of 15 mL/kg. Infusions of 300 mL were repeated every 20 minutes, or earlier if electrical activity returned. Before aortic declamping, 500 mL warm blood cardioplegia was administered at 37°C for 2 minutes at a pressure of 50 mm Hg. Aprotinin was never used during the study period. Modified ultrafiltration was performed in heparinized patients between the arterial and the venous tubings of the bypass circuit by use of a polysulfone fiber Minntech Diafilter D30-NR with an effective membrane area of 0.66 m^2 and an internal fiber diameter of 260 μm. The technique adopted was a modification of the method proposed by Groom and coworkers.[17] Briefly, on termination of cardiopulmonary bypass, the venous line was interrupted, and the venous return cannula was left in the right atrium. The latter was connected via a 3-way connector to the blood cardioplegia line. The arterial blood was then allowed to drain via the ascending aortic cannula through the cardioplegia circuit, where the ultrafilter had been interposed preventively. The blood flow through the filter was maintained at a rate of ≈150 mL/min by a roller pump on the inlet part of the filter. Suction was applied to the filtrate port to achieve an ultrafiltration rate of 100 to 120 mL/min. In addition, the heat exchanger and the bubble trap of the cardioplegia line were used to maintain the filtered blood at body temperature and to prevent gas embolism, respectively. The process was carried out for 20 minutes, a time that generally allowed filtration of ≥50% of the net bypass-volume balance. Intraoperative recovery of mediastinal blood shed before and after bypass was performed with a cell separation device (Cell Saver System IV, Hemonetics) in all patients.

During the postoperative period, a hemoglobin concentration <9 g/dL was considered an absolute indication for packed red blood cell transfusion.

Statistical Methods

Continuous variables were expressed as mean±SD and compared by a 2-tailed Student's t test or Mann-Whitney U test as appropriate. Comparison of multiple mean values was carried out by ANOVA. Discrete variables were expressed as percentages and compared by Fisher's exact test or Pearson's χ^2 test as required. Statistical significance was inferred at a value of $P<0.05$. End points of the study were prevalence and cause of hospital mortality, prevalence and cause of hospital morbidity, resource utilization (inotropic drugs, assisted ventilation, intensive care, and blood products), and cost of hospital stay. Definitions of variables are listed in the Appendix.

TABLE 1. Demographic and Operative Data

	MUF	Control	*P*
Patients, n	284	289	
Male, n (%)	187 (66)	209 (74)	0.087
Age, y	63.8±10.6	62.6±13.5	0.207
Weight, kg	72.9±12.1	72.5±12.0	0.714
Diagnosis IHD, n (%)	163 (57)	173 (60)	0.548
Previous cardiac operation, n (%)	14 (5)	16 (6)	0.744
Emergent operation, n (%)	16 (6)	13 (4)	0.539
Procedure, n			
CABG	163	173	0.548
AVR	36	37	0.963
MVR/repair	28	24	0.517
AVR+MVR	8	7	0.767
AVR+CABG	11	8	0.460
MVR+CABG	2	5	0.264
Aortic root replacement	9	8	0.777
Ascending aorta replacement±AVR	8	7	0.767
Heart transplantation	8	3	0.121
Other	9	17	0.118

MUF indicates modified ultrafiltration; IHD, ischemic heart disease; CABG, coronary artery bypass graft surgery; AVR, aortic valve replacement; and MVR, mitral valve replacement. Other procedures include repair of (in MUF group) congenital heart defect, 6 patients; left ventricular aneurysm, 2; and ventricular septal rupture, 1; (in control group) congenital heart defect, 13 patients; left ventricular aneurysm, 3; and ventricular septal rupture, 1. Values are number (%) of patients or mean±SD.

Results

Patient Population

Five patients assigned to undergo modified ultrafiltration were withdrawn from the study for reasons specified below, leaving 573 patients for analysis. Thus, 284 patients received modified ultrafiltration (treatment group) and 289 did not (control group). The patient age ranged from 16 to 86 years (median 66 years in each group), with 192 patients >70 years old (95 [33.4%] in the treatment versus 97 [33.6%] in the control group, $P=0.859$). Demographic and operative variables were comparable in the 2 groups (Table 1).

Classification of operative risk was based on the scoring system proposed by Parsonnet and associates.[18] The patients were further subdivided into those with low risk (operative risk 1%, 5%) and those with high risk (operative risk 9%, 17%, and ≥31%), with a cutoff Parsonnet score of 10, in agreement with previous clinical work.[19] Distribution of patients in the low (125 [44.0%] treatment versus 140 [48.4%] control group, $P=0.287$) and high (159 [56.0%] treatment versus 149 [51.6%] control group, $P=0.287$) risk classes was similar in the 2 groups.

Examination of perfusion variables disclosed comparable mean aortic cross-clamp and cardiopulmonary bypass duration in the 2 groups (Table 2). The proportion of patients with cardiopulmonary bypass time >2 hours was represented

TABLE 2. Perfusion Data

	MUF	Control	*P*
Aortic cross-clamp time, min	67.3±32.5	63.3±30.3	0.192
CPB time, min	111.3±39.2	108.7±40.6	0.305
Circulatory arrest, n (%)	3 (1)	3 (1)	0.983
PRBC in primer, n (%)	76 (27)	95 (33)	0.120
PRBC in primer, U/patient	0.51±1.04	0.54±0.92	0.691
Intraoperative fluid balance, L	1.503±1.2	2.85±1.35	0.001
Cell saver volume, L	0.32±0.23	0.45±0.30	0.001

MUF indicates modified ultrafiltration; CPB, cardiopulmonary bypass; and PRBC, packed red blood cells. Values are number (%) of patients or mean±SD.

identically in the treatment and control groups (94 [33.1%] versus 97 [33.6%], $P=0.859$). The percentage of patients requiring transfusion of packed red blood cells during perfusion and the average amount of blood product transfused were similar in the 2 groups. On the contrary, the mean intraoperative fluid balance was less positive and the mean cell saver volume was smaller in the treatment group because of the design of the study. On average, modified ultrafiltration yielded 18 mL filtrate/kg body wt (absolute volume, 1.3 L/patient).

Mortality

Overall hospital mortality was 3.1% (18 of 573 patients) and was lower, although not significantly so, in the treatment group (7 [2.5%] versus 11 [3.8%], $P=0.333$). Cardiac events, and in particular acute myocardial infarction and low-output syndrome, were the leading cause of death in both groups. No significant difference between groups was encountered with regard to the specific cause of early mortality (Table 3).

Morbidity

The overall incidence of morbid, including lethal, events was 31.9% (183 of 573). The incidence of morbid events in patients having modified ultrafiltration after cardiopulmonary bypass was almost half as low as that observed in control patients (Table 3). The lower morbidity of treated patients proved to be significant both in the lower- and in the higher-operative-risk groups (16 of 125 [12.8%] versus 43 of 140 [30.7%] in low-risk patients, $P=0.0007$; 50 of 159 [31.4%] versus 74 of 149 [49.7%] in high-risk patients, $P=0.001$). The incidence and specific cause of cardiac complications were similar in the 2 groups (Table 4). The lower incidence of respiratory complications in the treatment group was due to lower rate of respiratory insufficiency, including cases of acute respiratory distress syndrome (none in the treatment versus 8 of 289 [2.8%] in the control group, $P=0.002$) (Table 4). Likewise, the difference in neurological events was credited primarily to the lower prevalence of postoperative coma in the treatment group, although cerebrovascular accidents also tended to be less common in these patients (Table 4). Finally, most but not all morbid events listed in the miscellaneous group were less common among patients having modified ultrafiltration, including postoperative hemorrhage requiring surgical reexploration, acute renal failure needing dialysis, and gastrointestinal complications. Only the difference in the latter, however, reached statistical significance (Table 4).

TABLE 3. Overall Hospital Mortality and Morbidity

	MUF	Control	*P*
Mortality	7 (2.5)	11 (3.8)	0.333
Cause			
Myocardial infarction	3	8	0.135
LOS	2	1	0.552
Arrhythmia	...	1	0.321
Tamponade	...	1	0.321
MOF	1	...	0.312
Sepsis	1	...	0.312
Morbidity	66 (23)	117 (40)	0.001
Cause			
Cardiac	26	35	0.251
Respiratory	20	36	0.029
Neurological	5	14	0.039
Other	15	32	0.011

MUF indicates modified ultrafiltration; LOS, low-output syndrome; and MOF, multisystem organ failure. Values are number (%) of patients.

TABLE 4. Morbidity

	MUF	Control	*P*
Myocardial infarction	15	21	0.302
Low-output syndrome	9	13	0.407
Arrhythmia	2	1	0.552
Respiratory failure	11	28	0.005
Pneumonia	4	2	0.399
Pneumothorax	4	3	0.686
Hydrothorax	1	3	0.324
Stroke	2	3	0.667
TIA	1	3	0.324
Coma	1	6	0.056
Delirium	1	2	0.572
Hemorrhage	5	12	0.091
Acute renal failure	5	8	0.418
Sepsis	4	4	0.980
Gastrointestinal	0	4	0.044
Metabolic	0	2	0.165
MOF	1	0	0.312
Wound	0	1	0.321
Tamponade	0	1	0.321

MUF indicates modified ultrafiltration; TIA, transient ischemic attack; and MOF, multisystem organ failure. Values are number of patients.

Resource Utilization

The need for infusion of ≥1 inotropic agent was identical between groups (Table 5). The durations of assisted ventilation, stay in the intensive care, and stay in the regular ward were shorter in the treatment group, but the difference did not attain statistical significance. When overall length of hospitalization was analyzed, including recovery at outside units

TABLE 5. Resource Utilization

	MUF	Control	P
Inotropes, n (%)	114 (40)	125 (43)	0.682
Ventilation, h	22.5±41.3	27.6±64.0	0.260
ICU stay, h	39.9±49.2	46.3±72.8	0.218
Ward stay, d	7.6±3.5	8.0±4.4	0.494
Total hospitalization, d	8.5±15.3	10.1±33.8	0.372
Total bleeding, mL	542.4±300.0	599.5±471.3	0.075
Transfusions, U/patient	1.66±2.6	2.25±3.8	0.039

MUF indicates modified ultrafiltration; ICU, intensive care unit. Values are number (%) of patients or mean±SD.

after transfer from our division, the difference in hospital stay seemed to be greater, yet still was not significant. Average postoperative bleeding volume was lower in patients undergoing modified ultrafiltration, even though the difference failed to reach significance. On the contrary, the mean volume of packed red blood cells transfused for each patient proved to be significantly lower in the treatment group. In addition, the proportion of patients who received no transfusion was significantly higher in the treatment group (147 [51.8%] versus 111 [38.1%], $P=0.001$). Table 6 shows that the average hemoglobin concentration remained constant throughout hospitalization within each group and comparable between the 2 groups.

The additional cost of modified ultrafiltration after cardiopulmonary bypass was represented solely by the ultrafilter ($85), because the method used the same circuit as used for extracorporeal circulation. The additional expense of modified ultrafiltration was largely covered by the difference in estimated average cost of postoperative care ($6378 in treated versus $6994 in control patients). The cost of postoperative care was calculated by adding the cost of average intensive care stay ($1000/d), regular ward stay ($500/d), and packed red blood cell transfusion ($500/unit) in each group.

Complications of Modified Ultrafiltration

No complication specifically related to the practice of modified ultrafiltration, such as pulmonary air embolism, arrhythmia, hypothermia, or sustained systemic hypotension, could be identified. Nevertheless, 5 patients (1.7%) assigned to treatment did not undergo ultrafiltration because of high-volume intraoperative hemorrhage before separation from bypass and were thus withdrawn from the study. In each case, the surgeon arbitrarily decided that the hemostatic conditions of the patient were not stable enough to tolerate ultrafiltration.

Discussion

The SIRS is more common in children than in adults because of the greater extent of hemodilution, the immaturity of major organs, and the often greater complexity of operative procedures, requiring longer periods of extracorporeal circulation.[1] Advanced patient age, comorbid conditions, and complex operations have become routine in adult cardiac surgery, however, increasing the likelihood of postperfusion syndrome in this population.[2] Accordingly, one third of the patients in the present series were >70 years of age, one third underwent procedures requiring cardiopulmonary bypass for >2 hours, and more than half ranked in the high (≥9%) operative risk category. Therefore, interest in the use of modified ultrafiltration as a means to control the SIRS in the adult population has also recently grown.[15–17] Analysis of the impact of this technique on overall postoperative morbidity has thus far not been available. Two controlled studies on the effect of ultrafiltration after cardiopulmonary bypass in patients undergoing elective myocardial revascularization have failed to disclose any influence of modified ultrafiltration on indices of clinical outcome, possibly because of limitations inherent in the sample type and size.[15,16] Larger-scale trials focusing primarily on clinical parameters have been recommended.

TABLE 6. Blood Hemoglobin Concentration During Admission

	MUF	Control	P
Preoperative	11.5±1.6	11.4±1.6	0.221
After cell saver infusion	10.7±1.4	10.4±1.5	0.949
First postoperative day	11.1±1.6	11.2±1.8	0.356
At discharge	10.4±1.1	10.5±1.3	0.563

MUF indicates modified ultrafiltration. Values are g/dL, mean±SD.

The present prospective, randomized trial was designed to establish whether modified ultrafiltration has an effect on morbidity after adult cardiac operations. The distribution of demographic and operative variables and the estimates of overall hospital mortality and morbidity observed agree well with the results reported in the STS National Database and in the EuroSCORE Multinational Database.[20,21] This confirms that the experience described here is adequately representative of current adult cardiac surgical practice worldwide. The present study shows that application of arteriovenous modified ultrafiltration to routine adult cardiac surgery is associated with reduced hospital morbidity as a result of lower rates of respiratory, neurological, gastrointestinal, and to a lesser extent, renal and hemorrhagic complications.

The use of ultrafiltration has no evident effect on hospital mortality after adult cardiac operations. Comparison with existing studies on adult patients is unsound, because these were conducted only on highly selected patients who suffered no early deaths.[15,16] Observations made in the pediatric population, including high-risk patients, have shown that ultrafiltration after cardiopulmonary bypass is associated with a mortality rate similar to the estimate for control patients.[7,9,11,12,14] Apparently, the severity of heart disease and the complexity of the operation have a more direct influence on operative mortality than bypass-related inflammatory reaction. The fact that the majority of early casualties in this study were due to untoward cardiac events would support this hypothesis.

The incidence of early cardiac morbidity was also comparable in treated and control patients. Previous works in infants and children have demonstrated that modified ultrafiltration improves both regional and global systolic left ventricular function.[11,13] Despite improvement in cardiac performance, mortality in the latter series has remained high (10% to 13%) and cardiac morbidity undefined.[11,13] As for cardiac mortality, it is possible that cardiac complications in the present series may be more strictly dependent on the severity of disease and complexity of the operation rather than on inflammatory changes due to cardiopulmonary bypass.

Respiratory complications were less common in patients undergoing modified ultrafiltration. Cardiopulmonary bypass has been associated with acute lung injury and, more rarely, with adult respiratory distress syndrome (ARDS) for quite some time.[4,22] Pulmonary dysfunction varies widely, from clinically undetectable changes in oxygenation, compliance, and vascular resistance to clinically relevant respiratory failure requiring prolonged ventilatory support and, rarely, leading to death. The incidence of the most severe forms of lung injury after cardiopulmonary bypass, such as ARDS, has been estimated at between 0.5% and 1.7%.[22] The present experience reports an incidence of 1.4% (8 of 573), in agreement with the latter figures. Previous studies in children have shown improvement of pulmonary function after ultrafiltration in terms of lung compliance, pulmonary vascular resistance, and oxygenation.[12,14,23] The net clinical effect of these changes, with time to extubation used as an end point, has often been controversial.[12,14,19,23] Likewise, experience in adults has demonstrated decreases in postoperative intrapulmonary shunt fraction after ultrafiltration.[15] Nevertheless, the conclusions regarding duration of mechanical ventilatory support have thus far been conflicting.[15,16] These observations underscore the limitations inherent in the use of time to extubation, an arbitrary end point, as an index of postoperative respiratory performance. Accordingly, the duration of assisted mechanical ventilation in the present series of unselected patients was similar in the treatment and control groups. Yet, the incidence of respiratory insufficiency was almost 3-fold greater in the control group, and all cases of ARDS were clustered among these patients. The incidence of respiratory failure in the 2 existing series of adult patients was not reported, but it was probably negligible, given the strict selection criteria that were applied for entry into the studies.[15,16] Other respiratory complications, including infections, were equally distributed in the 2 groups, in agreement with the work of Grünenfelder and associates.[16] The relevance of this finding is unclear, because the relationship between pneumonia and postperfusion syndrome is not well established.

Neurological complications were less common in adult patients receiving modified ultrafiltration. Central nervous system injury may affect as many as 6% of adult patients undergoing open-heart operations.[24] The overall incidence of 3.3% found in this study is in line with this estimate. Advanced age, history of cerebrovascular disease, presence of hypertension, type of operation, duration of cardiopulmonary bypass, circulatory arrest, and low-output syndrome are recognized risk factors for perioperative stroke and neurological dysfunction.[24] Several variables related to the use of cardiopulmonary bypass, such as nonpulsatile flow, hypothermia, fluid overload, ischemia, and reperfusion of the brain, play a role in postoperative cognitive alterations by causing an inflammatory reaction.[24] On these grounds, the use of modified ultrafiltration appears to be rational to reduce neurological morbidity after adult cardiac operations. In an experimental model of deep hypothermic circulatory arrest, an increase of cerebral metabolism after ultrafiltration has been shown, suggesting a beneficial role in reversing postoperative cerebral injury.[8] Clinical studies analyzing neurological outcome after ultrafiltration are unavailable, making comparison with the present findings impossible. The lower incidence of cognitive dysfunction (delirium, coma) observed in treated patients may be explained by the ability of modified ultrafiltration to control tissue edema and systemic inflammation. Justification for the lower rate of cerebrovascular accidents is less intuitive, because factors unrelated to cardiopulmonary bypass may exert a predominant role. Nevertheless, arteriovenous modified ultrafiltration has one property that could in theory lower the rate of postoperative cerebral embolism. Because the arterial cannula is positioned in the least dependent site of the ascending aorta, drainage of blood via the aorta may promote clearance of air or fat emboli from the systemic circulation.

Gastrointestinal complications, including complicated peptic ulcer and mesenteric ischemia, were found only among control patients. The incidence of digestive tract morbidity after cardiac surgery has been reported to be $\approx$1%,[25] similar to the estimate of 0.7% observed here. A series of conditions predispose to gastrointestinal complications, including advanced age, preexisting digestive pathology, vascular disease, type of operation, duration of cardiopulmonary bypass, and low-output syndrome.[25] Furthermore, it has been recognized that the gut is both a major source and an important target of inflammatory mediators during bypass.[25] Whether the lower incidence of gastrointestinal complications observed in treated patients is in part a result of the practice of modified ultrafiltration remains a matter of speculation.

Bleeding diathesis after open-heart operations is due to a variety of factors, including hemodilution, platelet dysfunction, abnormal fibrinolysis, and hypothermia.[6] The present study demonstrated lower average bleeding and lower incidence of reexploration for postoperative hemorrhage in patients undergoing ultrafiltration, even though the results failed to reach significance. The average volume of packed red blood cells transfused in these patients and the proportion of patients requiring transfusion were significantly lower than in control patients. Although the decision to transfuse is arbitrary, the observation that the homeostasis of hemoglobin concentration was maintained in the 2 groups throughout the study rules out major bias in treatment. Coagulopathy after cardiopulmonary bypass is critically dependent on hemodilution in children. It is therefore intuitive how modified ultrafiltration has repeatedly been shown to reduce postoperative bleeding in the pediatric population.[7,9,12,23] Because of the relatively lower extent of crystalloid fluid overload, dilutional coagulopathy appears to be less of a problem in the adult patient, in whom platelet dysfunction and fibrinolysis play a greater role. Previous experience with modified ultrafiltration after adult cardiac operations has failed to show any beneficial effect on postoperative bleeding.[15,16] The 2 studies available, however, were conducted on low-risk patients undergoing elective and first-time procedures. Furthermore, in 1 of these works, the antifibrinolytic agent aprotinin was routinely administered.[16] Conversely, the results of the present study on a large series of unselected adult patients are highly suggestive of a favorable impact of ultrafiltration in reducing postoperative hemorrhage and in increasing the proportion of completely blood-free cardiac operations.

The lower incidence of acute renal failure requiring postoperative dialysis in patients receiving modified ultrafiltration has several theoretical explanations. The kidneys, in fact, are among the organs most commonly affected by the postperfusion inflammatory syndrome.[1,2,5] On the basis of the present findings, however, the indication of a beneficial role of ultrafiltration in preventing renal failure is still uncertain.

Contrary to the results of Tassani and associates[15] and Grünenfelder and associates,[16] the present study shows that modified ultrafiltration is associated with reduced prevalence of overall postoperative complications not only in patients with higher operative risk but also in those with lower risk. The difference in patient selection may explain this discrepancy. It must be noted that the risk scoring system used here was originally devised for assessment of operative mortality in acquired adult heart disease.[18] More recent evidence has identified the Parsonnet score as being among the best predictive systems not only for hospital mortality[26] but also for hospital morbidity after adult cardiac operations.[19] On the basis of the work of Lawrence and colleagues,[19] who demonstrated a direct correlation between Parsonnet score and prevalence of perioperative complications, a choice was made to condense the risk categories into low (1% to 5%) and high (>9%) risk and to stratify postoperative morbidity accordingly.

Despite a significantly lower incidence of complications among treated patients, this study was unable to show any significant difference in postoperative clinical course between the 2 groups in terms of need for inotropic support, duration of ventilatory and intensive care unit assistance, or length of hospital stay. This observation is common to most clinical series in both the pediatric[14,23] and the adult populations.[15,16] It is conceivable that standardized institutional policies on patient management may attenuate any discrepancy in outcome. In our service, for instance, weaning from the ventilator is started 6 hours after return from the operating room, and the patient is observed in the regular ward for 5 days after discharge from the intensive care unit.

The routine use of modified ultrafiltration after adult cardiac operations has the potential for being cost-effective. In fact, the projected savings from reduced transfusion and hospital stay largely cover the modest additional expense of the ultrafilter. In addition, no complications related to the practice of modified ultrafiltration were recorded in a series of 289 consecutive patients, aside from the surgeon's decision to withdraw the patient from the study in 5 cases. This represents an overall compliance to the treatment of >98% and allows us to conclude that ultrafiltration is safe in any adult cardiac patient.

Limitations

Despite randomization, blinding of all physicians caring for the patients was not possible. This may have introduced bias in favor of treatment. Onset of hospital complications was not specified, although most were identified during the stay in the intensive care unit. Because development of the SIRS extends well after the immediate postbypass period, a decision was made to record all hospital complications. This may in theory have led to overestimation of the negative influence of cardiopulmonary bypass. No measurement of inflammatory mediators was carried out in this study. The exact relationship between the concentration of cytokines in the blood and filtrate and postoperative morbidity, however, remains to be proved. In addition, the large sample of patients under scrutiny did not allow for systematic dosages of cytokines, for both logistic and financial reasons.

In conclusion, the use of modified ultrafiltration after cardiopulmonary bypass is associated with lower hospital morbidity in the largest study to date conducted on a series of unselected consecutive adult patients. The rate of respiratory, neurological, and gastrointestinal complications and blood transfusion requirements are lower after ultrafiltration. The technique is cost-effective and adds no risk to the operation. Routine adoption of modified ultrafiltration in adult cardiac operations seems to be warranted.

Appendix

Definitions

Previous cardiac operation indicates previous cardiac procedure requiring use of cardiopulmonary bypass; emergent operation, procedure performed immediately after diagnosis; hospital mortality, mortality before discharge or within 30 days of operation; hospital morbidity, morbidity before discharge or within 30 days of operation; myocardial infarction, a new Q wave of >0.04 ms or a reduction in R waves >25% in ≥2 leads on 12-lead ECG; low-output syndrome, a state of hypoperfusion characterized by a cardiac index $<2.0\ L \cdot min^{-1} \cdot m^{-2}$ measured by the thermodilution method with right heart catheterization; arrhythmia, ventricular tachycardia or fibrillation on 12-lead ECG and requiring treatment; cardiac tamponade, hemodynamically significant cardiac compression due to accumulating pericardial contents diagnosed by 2D echocardiography and requiring drainage; multiple organ system failure, concomitant failure of ≥3 end organs; sepsis, an inflammatory response to infection with signs of remote organ dysfunction characterized by body temperature >38°C or <36°C and bacteremia diagnosed by blood cultures; respiratory failure, Pa_{O_2}<60 mm Hg or Pa_{CO_2}>50 mm Hg on room air measured by arterial blood gas examination; ARDS, Pa_{O_2}/Fi_{O_2} <200, left atrial or pulmonary artery wedge pressure <4 mm Hg measured directly by left heart catheterization or indirectly by right heart catheterization, and bilateral pulmonary infiltrate at chest roentgenogram; pneumonia, body temperature >38°C or <36°C, positive expectorated or endotracheal aspirate sputum culture, and pulmonary infiltrate at chest roentgenogram; pneumothorax, pleural air collection diagnosed by chest roentgenogram requiring chest tube drainage; hydrothorax, pleural fluid collection diagnosed by chest roentgenogram requiring chest tube drainage; stroke, any new focal central neurological defect lasting >24 hours; transient ischemic attack, any new focal central neurological defect lasting <24 hours; coma, state of unconsciousness lasting >24 hours; delirium, mental disturbance marked by illusions, confusion, and cerebral excitement lasting >24 hours; hemorrhage, postoperative bleeding requiring surgical reexploration; acute renal failure, persistent oliguria (<500 mL of urine/d) or anuria requiring dialysis; gastrointestinal, any ischemic or hemorrhagic bowel complication diagnosed either clinically or by direct visualization at endoscopy or surgery; metabolic, metabolic acidosis or alkalosis diagnosed by arterial blood gas examination in the absence of low cardiac output or sepsis; wound, any deep sternal wound infection or wound dehiscence requiring surgical management; and inotropes, need for infusion of ≥1 inotropic drug. All complications listed are defined as newly presenting events (ie, not present preoperatively).

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