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Hemofiltration but Not Steroids Results in Earlier Tracheal Extubation following Cardiopulmonary Bypass

A Prospective, Randomized Double-blind Trial

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Background: **Activation of the inflammatory cascade is thought to account for some of the respiratory dysfunction and prolonged mechanical ventilation associated with cardiopulmonary bypass. The objective of this investigation was to identify whether perioperative steroids or hemofiltration during cardiopulmonary bypass, by their attenuation of inflammation, would reduce duration of mechanical ventilation after cardiac surgery.**

Methods: **After Institutional Review Board approval and informed consent, 192 patients scheduled to undergo elective primary coronary artery bypass grafting or valvular replacement or repair were randomized in a double-blind prospective study into three groups. One group (Control) received saline at induction and at 6-h intervals for four doses. Another group (Hemofil) received saline and hemofiltration to obtain 27 ml/kg of hemofiltrate. The final group (Steroid) received 1 g methylprednisolone before anesthesia induction and then 4 mg of dexamethasone at 6-h intervals for four doses. All patients underwent normothermic cardiopulmonary bypass and received propofol for postoperative sedation. Separate two-sample comparisons were performed to compare each experimental group *versus* the control group using the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. In all cases, two-tailed *P* values ≤ 0.05 were considered statistically significant.**

Results: **The median time until the patient reached an intermittent mandatory ventilation of 4/min (258.5 *versus* 385.0 min, respectively; *P* = 0.02) and tracheal extubation (352.0 *versus* 518.0 min; *P* = 0.03) was significantly reduced for group Hemofil but no different for Steroid compared to Control.**

Conclusions: **Hemofiltration and steroids are both previously reported to attenuate the inflammatory response but only hemofiltration reduced time to tracheal extubation for adults after cardiopulmonary bypass in this study.**

CARDIOPULMONARY bypass is responsible for inducing a generalized, whole body inflammatory response comprised of complement activation, proinflammatory mediator release, and neutrophil activation that may result in "postpump syndrome"[1] characterized by increased alveolar-arterial oxygen partial pressure gradients ($A\text{-}aDo_2$), decreased lung compliance, and increased extravascular lung water.[2] The numerous arms of the inflammatory response has contributed to the inability to demonstrate a direct cause and effect relationship between the many effector components of the inflammatory response and adverse outcomes after cardiac surgery.[3] The incidence of significant morbidity associated with the inflammatory response after cardiopulmonary bypass is relatively low, 1 to 2 percent.[1] However, pulmonary dysfunction is common after cardiac surgery and greatly influences hospital length of stay and health care costs.[4,5] Strategies to reduce the inflammatory response have generally focused on pharmacologic means as a result of ready availability and ease of administration compared with mechanical approaches such as the use of biocompatible extracorporeal circuits and filtration techniques.[6]

Complement activation, a primary effector of the inflammatory response, has been associated with clinical pulmonary dysfunction[4] but its significance in the setting of cardiopulmonary bypass is indeterminate.[6] Steroids lessen complement activation based on established *in vitro* inhibition of C3 and C5 convertase[7] but have produced only inconsistent *in vivo* reductions of complement activation during cardiopulmonary bypass.[6] Furthermore, the clinical response to steroids with cardiopulmonary bypass has also been equivocal.[1] Jansen *et al.*[8] reported improved hemodynamic stability, temperature maintenance, and circulation in patients undergoing cardiopulmonary bypass in association with prophylactic dexamethasone, but complement activation was not affected. Frequently, recommendations for steroid use have been based on studies lacking adequate statistical power with small cohorts.[8–10]

Mechanical techniques have also been applied to modify the inflammatory response generated by cardiopulmonary bypass. These techniques have focused largely on two approaches to reducing complement concentrations in the blood: first, by modifying the extracorporeal surface to become more biocompatible so as to reduce the accompanying complement activation or second, by adding filtration devices to remove complement and other proinflammatory proteins. Hemofiltration, also referred to as ultrafiltration, uses a combination of convec-

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tion and osmosis under a pressure gradient to remove fluid and low molecular weight molecules from plasma that include proinflammatory mediators.[3] Yet, the clinical benefit of filtration procedures on the inflammatory response associated with cardiopulmonary bypass in adults has been disappointing in the few studies performed to date.[3] The aim of this study was to evaluate the clinical impact (duration of postoperative mechanical ventilation) of reducing the inflammatory response in patients undergoing primary cardiac surgery by comparing a pharmacologic approach (steroid administration) with a mechanical approach (hemofiltration).

Materials and Methods

After institutional review board approval and written informed consent, 192 adult men and nonpregnant women scheduled to undergo elective primary coronary artery bypass grafting or valvular replacement or repair requiring cardiopulmonary bypass were enrolled. Patients were excluded for presence of congenital heart disease, left ventricular ejection fraction ≤ 0.35, end stage pulmonary disease, previous difficult intubation, pulmonary hypertension, neurologic deficits or disease, serum creatinine ≥ 2.0 mg/dl, recent or long-term steroid usage, insulin dependent diabetics mellitus, and age ≥ 85 years.

Patients were randomized in a double-blinded manner to one of three groups. Group Control received placebo (saline). Group Hemofil underwent hemofiltration during cardiopulmonary bypass with a Pro-Tec™ ultrafiltration device (Pall Biomedical Products Corp., New York, NY) until 27 ml/kg[11] of ultrafiltrate was attained. Group Steroid received 1 g of methylprednisolone intravenously immediately before induction of anesthesia followed by 4 mg of dexamethasone intravenously every 6 h during the next 24 h as described by Engelman *et al.*[9,12] Perfusionists were aware of subjects assigned to Hemofil but no other study assignment. All remaining operating room and intensive care unit personnel were blinded to group identity.

All subjects received an anesthetic consisting of 25 μg/kg of fentanyl, 0.1 mg/kg of midazolam, isoflurane, and muscle relaxant. Standard monitoring for cardiac anesthesia and surgery was utilized including femoral or radial arterial catheterization to measure blood pressure continuously and obtain samples for arterial blood gases. Central venous catheterization was obtained for central venous pressure or pulmonary artery pressure monitoring. Lactated Ringer's and colloid solutions were administered to maintain adequate circulating blood volume and hemodynamic stability.

Cardiopulmonary bypass was conducted with a Univox membrane oxygenator (Bentley Inc., Irvine, CA) and a Sarns 9000 cardiopulmonary bypass machine using a roller head (Sarns Inc., Ann Arbor, MI) The circuit was primed with 2 l of Plasmalyte® solution (Baxter Inc., Deerfield, IL), 25 g mannitol 12.5%, and 50 meq sodium bicarbonate. All patients were expected to undergo normothermic cardiopulmonary bypass (>35°C) monitored by nasopharyngeal temperature. If hypothermic cardiopulmonary bypass was instituted, the patient's participation in the study was terminated and the data were not included in the analysis. Perfusion flow rates were maintained at $2.0-2.4\ l \cdot min^{-1} \cdot m^{-2}$. Mean arterial pressure was maintained at 50–80 mmHg during cardiopulmonary bypass with infusions of phenylephrine or sodium nitroprusside. Hyperkalemic cold blood cardioplegia was given every 20–30 min for myocardial protection. Anticoagulation was initiated with 300 u/kg of heparin (intestine porcine mucosal) (Elkins-Sinn Inc., Cherry Hill, NJ) and maintained according to an activated clotting time (Hemochron 801; International Technidyne, Edison, NJ) of more than 480 s. After separation from cardiopulmonary bypass, the initial protamine dose to neutralize heparin was 0.013 mg per unit of heparin administered. If the postprotamine activated clotting time was greater than 20 percent of the preheparin activated clotting time, 20–50 mg of protamine was given. Blood left in the venous reservoir of the cardiopulmonary bypass circuit was infused to the patient directly or converted to intraoperative autologous blood with a Medtronic AT-1000 (Medtronic Inc., Parker, CO). Cell salvage techniques were used in all three groups. Allogeneic packed erythrocytes were administered if the hemoglobin was ≤ 7.0 g/dl in patients ≤ 70 yr of age and ≤ 8.0 g/dl in patients ≥ 70 yr of age. Transfusion of platelets or fresh frozen plasma were based on clinical evidence of bleeding and the following supporting laboratory studies: for platelets, evidence of platelet dysfunction or platelet count $<50 \times 10^9$/L; and for fresh frozen plasma, an activated partial thromboplastin time or prothrombin time ≥ 1.5 times the upper limit of normal. Cryoprecipitate was generally given if transfusion of fresh frozen plasma and platelets was ineffective and sometimes supported by a fibrinogen concentration less than 100 mg/dl.

Blood glucose concentrations were monitored throughout the study duration because of the propensity for glucocorticoids to increase blood glucose concentrations. Samples for plasma glucose concentration were obtained from the arterial catheter immediately after induction of anesthesia, at onset of cardiopulmonary bypass, and on final separation from cardiopulmonary bypass. Additional samples were obtained as clinically indicated to maintain the plasma glucose between 100 and 200 mg/dl. If the plasma glucose concentration became ≥ 250 mg/dl, 5 units of regular insulin was given intravenously and repeated in 5-unit increments until the plasma glucose was ≤ 200 mg/dl. Assays for complement activation, C3a and C5b-9 concentrations, were obtained

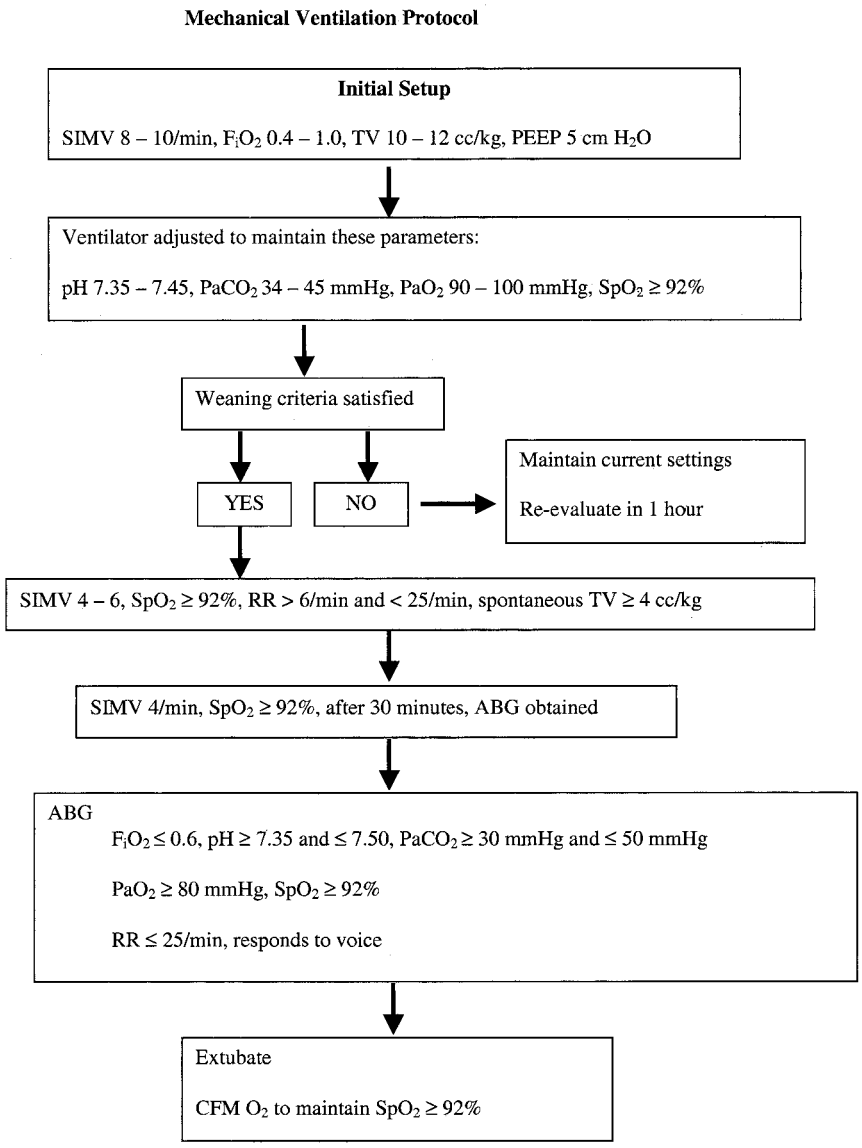

Fig. 1. Mechanical ventilation protocol. ABG = arterial blood gas; CFM = closed fitting mask; F_{IO_2} = inspired oxygen concentration; Pa_{CO_2} = arterial carbon dioxide partial pressure; Pa_{O_2} = arterial oxygen partial pressure; PEEP = positive end-expiratory pressure; RR = respiratory rate; SIMV = synchronized intermittent mandatory ventilation; Sp_{O_2} = pulse oximeter derived oxygen saturation; TV = tidal volume.

from samples drawn from the arterial catheter after induction of anesthesia, 10 min after initiation of cardiopulmonary bypass, immediately after removal of aortic cross-clamp, 20 min after protamine administration, and 3 h after permanent separation from cardiopulmonary bypass. The C3a and C5b-9 concentrations were determined by radioimmunoassay (Quidel, San Diego, CA). The kit measures the concentration of C3a and C5b-9 by using a monoclonal antibody to capture C3a or C5b-9. The trapped complex is subsequently detected with horseradish peroxidase labeled antibodies that bind to the complement antigens.

After permanent separation from cardiopulmonary bypass, heparin neutralization, and stable hemodynamics, a propofol infusion (25–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was begun and continued in the intensive care unit for sedation and until tracheal extubation. On arrival in the intensive care unit, patients were assessed for evidence of neuromuscular blockade by determination of the train-of-four utilizing a neuromuscular blockade monitor. Residual neuromuscular blockade was treated with 0.05 mg/kg of neostigmine and 0.01 mg/kg of glycopyrrolate simultaneously. Morphine sulfate was given for pain in response to clinical assessment of intensive care unit nurses that were blinded to the subject's group assignment. A standardized, ventilation-weaning protocol was instituted for all patients (fig. 1). All patients remained intubated for at least 2 h after arrival in the intensive care unit as per protocol (table 1). Subsequently, the propofol infusion was reduced and eventually discontinued in conjunction with weaning of mechanical ventilation. The critical care physician assigned to the intensive care unit who was blinded to the subject's group designation was responsible for making the final decision regarding tracheal extubation. During the initial 24 h in the intensive care unit, core (blood) temperature was monitored by temperature thermistor of the pulmonary artery catheter, bladder temperature (Critcore, Bard Urologic, Coving-

Table 1. Criteria for Weaning and Early Extubation

Criteria for early weaning of mechanical ventilation
Cardiac Index $> 2.2\ L \cdot min^{-1} \cdot m^{-2}$
No significant dysrhythmias
Epinephrine $\leq 0.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$
Core temperature $\geq 36°C$
Hemoglobin ≥ 8.0 g/dl
Mediastinal chest tube drainage ≤ 100 ml/h
Criteria for extubation
Patient responsive to voice
$F_{IO_2} \leq 0.6$
$Spo_2 \geq 92\%$
$Paco_2 \leq 50$ mmHg
$Pao_2 \geq 80$ mmHg
pH ≥ 7.35
Respiratory rate ≤ 25/min

$Paco_2$ = arterial carbon dioxide partial pressure; Pao_2 = arterial oxygen partial pressure; Spo_2 = pulse oximeter derived arterial oxygenation.

ton, GA), and peripheral (skin) temperature was monitored with an infrared monitoring device, Diateck 900 Instatemp (Diatek Instruments Inc., San Diego, CA). Temperature was recorded every 2 h up to a maximum of 24 h after admission to the intensive care unit.

Variables recorded include age, gender, weight, height, operative procedure, duration of cardiopulmonary bypass, aortic cross-clamp, anesthesia and operative time, time to tracheal extubation, intensive care unit duration, volume of hemofiltrate, perioperative crystalloid and colloid requirements, vasoactive medications, perioperative arterial blood gases (fractional inspired oxygen tension, F_{IO_2}), arterial oxygen partial pressure (Pao_2) and arterial carbon dioxide partial pressure ($Paco_2$), daily weights, and urine output, mediastinal chest tube drainage in the intensive care unit to a maximum of 24 h, perioperative transfusion requirements, sedation and analgesia requirements in the intensive care unit, plasma glucose concentrations, blood and skin temperatures during the first 24 h. The following complications were noted: pneumothorax, pulmonary infiltrates, severe pulmonary congestion, lobar lung collapse, respiratory infection; reintubation, delayed wound healing or infection, cerebrovascular accident (verified clinically and by imaging), myocardial infarction, cardiac arrest, complete heart block, hemodynamically unstable arrhythmias or death. The $A\text{-}aDo_2$ was calculated as $((760(F_{IO_2}) - Paco_2/0.8) - Pao_2)$ for the following times: baseline (before surgical incision), final arterial blood gases before exit from operating room, on arrival in the intensive care unit, before tracheal extubation, and after tracheal extubation.

Statistical Analysis

Previously collected (unpublished) data for patients at our institution who underwent cardiac surgery with cardiopulmonary bypass using early tracheal extubation criteria were analyzed to establish the sample size for this study. From this analysis, it was estimated that 64 subjects per study arm would provide statistical power of >80 percent to detect a 2 h difference in time to tracheal extubation between an experimental group and control using an appropriate parametric technique. Because of skewness in the observed times to tracheal extubation for study patients, we performed a *post hoc* power analysis using the Wilcoxon rank sum test with repeated bootstrap samples of the observed times to tracheal extubation for the control group. From this *post hoc* power analysis, it was determined that a sample-size of 64 subjects per arm would provide statistical power of 82 percent to detect a difference of 2.5 h in the duration of mechanical ventilation between an experimental group and control. For all end points of interest, separate two-sample comparisons were performed to compare each experimental group *versus* the control group using the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. A supplemental comparison of the two experimental groups (Hemofil *versus* Steroid) was performed only if at least one of the two experimental groups was found to differ significantly from Control. In all cases, two-tailed P values ≤ 0.05 were considered statistically significant.

A clinical performance score, similar to that proposed by Jansen *et al.*[13] was calculated; however, due to differences in study design we were not able to exactly replicate their score. Our clinical performance score was calculated using 24 h fluid balance, the time until tracheal extubation, and the average bladder to skin temperature gradient during the first 15 h in the intensive care unit. To have a 15-h mean temperature difference calculated, patients needed to have complete temperature information through 5 h and could not be missing more than two of the 11 measurements during the first 15 h. In addition, patients also needed complete 24 h fluid balance and time until tracheal extubation to be considered for the clinical performance score analysis. To ensure that each component contributed an equal weight, the clinical performance score was calculated as the sum of three standardized component scores. A standardized score was calculated for each component by subtracting the mean and dividing by the SD. The clinical performance score was then calculated as the sum of the three standardized component scores. Using this approach to calculate the clinical performance score, a value less than zero represents an overall inflammatory response that is below average (improved) and a clinical performance score above zero represent an overall inflammatory response that is above average (worsened).

Results

A total of 192 patients were enrolled, but three patients did not complete the study because of protocol

Table 2. Demographic and Surgical Characteristics

Characteristic (Units)	Control (N = 63)	Hemofil (N = 64)	Steroid (N = 62)
Demographics			
Age (years)			
Mean ± SD	62.1 ± 11.8	62.4 ± 10.9	63.7 ± 10.7
Median	65.0	65.0	67.5
IQR (25^{th}, 75^{th}) percentile	52, 71	55, 70.5	57, 71
Gender (%)			
Female	17.5	15.6	12.9
Male	82.5	84.4	87.1
Height (cm)			
Mean ± SD	174.0 ± 9.6	174.8 ± 9.4	176.0 ± 7.9
Median	175	175	176.7
IQR (25^{th}, 75^{th}) percentile	167, 180	169, 182.5	172, 180
Weight (kg)			
Mean ± SD	83.8 ± 14.7	85.5 ± 15.2	86.4 ± 16.2
Median	84.0	84.5	85.6
IQR (25^{th}, 75^{th}) percentile	75, 92	74.4, 96.1	77, 96
COPD (%)			
None	98.4	93.7	92.0
Mild/Moderate	1.6	6.3	8.0
Smoking Status (%)			
Never	46.0	42.9	41.9
Former	50.8	52.4	54.8
Current	3.2	4.7	3.2
Surgical Characteristics			
Duration of Anesthesia (min)			
Mean ± SD	286.8 ± 58.1	273.5 ± 53.3	278.8 ± 53.8
Median	290	275	275
IQR (25^{th}, 75^{th}) percentile	233, 335	232, 300	237, 315
Duration of Aortic cross-clamp (min)			
Mean ± SD	42.8 ± 16.0	43.8 ± 19.5	44.0 ± 17.0
Median	39	44	43.5
IQR (25^{th}, 75^{th}) percentile	31, 55	27.5, 54.5	32, 53
Duration of CPB (min)			
Mean ± SD	66.4 ± 27.2	67.3 ± 29.9	69.9 ± 28.8
Median	65	68.5	61
IQR (25^{th}, 75^{th}) percentile	42, 89	40.5, 86.5	47, 89
Duration of Surgery (min)			
Mean ± SD	211.4 ± 55.8	199.7 ± 51.4	203.8 ± 50.2
Median	210	192.5	202
IQR (25^{th}, 75^{th}) percentile	160, 260	171, 228.5	160, 240
Procedure (%)			
CABG only	57.1	43.8	48.4
Valve (Repair/Replace) only	39.7	53.1	43.5
Both	3.2	3.1	6.5
Neither	0.0	0.0	1.6*

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; Duration of anesthesia = time from entry into the operating room until arrival in the intensive care unit; Duration of surgery = time from incision to closure; IQR = interquartile range.

* One patient underwent Maze procedure only.

violations. In one case, the decision was made to excise an anterior mediastinal mass after sternotomy; another unexpectedly underwent thoracotomy instead of median sternotomy for surgical exposure. The third patient was canceled after administration of intrathecal morphine. Of the remaining 189 patients, 49.7 percent underwent coronary artery bypass grafting alone, 45.5 percent underwent valve repair/replacement alone, 4.2 percent underwent coronary artery bypass grafting and valve repair/replacement, and 0.5 percent underwent a Maze procedure without either coronary artery bypass grafting or valve repair/replacement. There were no differences among the groups concerning demographics or surgical characteristics (table 2). Fourteen patients (six Control, five Steroid, and three Hemofil) had noninsulin dependent diabetes mellitus controlled with either oral hypoglycemic agents or diet.

Group Hemofil, but not Steroid, attained a ventilator setting of intermittent mandatory ventilation of 4 as well as tracheal extubation significantly sooner than Control (table 3). There was no difference in the time to achieve intermittent mandatory ventilation of 4 ($P = 0.54$) or duration of mechanical ventilation ($P = 0.33$) between the Hemofil and Steroid groups. The number of Hemofil and Steroid patients tracheally extubated within 4 to 8 h after arrival in the intensive care unit was 53 percent and

Table 3. Outcomes and Complications

Characteristic (Units)	Control (N = 63)	Hemofil (N = 64)	P*	Steroid (N = 62)	P†
Outcomes					
Time to IMV4 (min)			0.023		0.102
Mean ± SD	512.2 ± 397.2	385.3 ± 300.1		393.0 ± 254.5	
Median	385	258.5		289	
IQR (25^{th},75^{th}) percentile	228, 699	210, 405		200.5, 612.5	
Time to Extubation (min)			0.031		0.210
Mean ± SD	618.0 ± 404.9	481.0 ± 308.5		519.3 ± 292.8	
Median	518	352		390	
IQR (25^{th},75^{th}) percentile	311, 816	272.5, 585.5		300, 730	
Categorized time to Extubation, N (%)			0.055		0.367
0–8 hours	30 (47.6)	44 (68.7)		36 (58.1)	
8–16 hours	21 (33.3)	12 (18.7)		19 (30.6)	
16–24+ hours	12 (19.0)	8 (12.5)		7 (11.3)	
Time to ICU Discharge (hr)			0.479		0.377
Mean ± SD	23.9 ± 8.7	24.8 ± 9.4		25.2 ± 14.0	
Median	22	22.5		23	
IQR (25^{th},75^{th}) percentile	19, 24	19.5, 25		19, 24	
Complications					
Cardiac Compromise (%)	1.6	4.7	0.619	8.1	0.115
Cerebrovascular Accident (%)	0.0	0.0	–	1.6	0.496
Pulmonary Complication (%)	6.4	3.1	0.440	11.3	0.363
Re-intubation (%)	0.0	1.6	1.00	1.6	0.496
Re-operation for Bleeding (%)	6.4	1.6	0.208	0.0	0.119

* Wilcoxon rank sum test/Fisher exact test for categorical variables (Hemofil vs. Control); † Wilcoxon rank sum test/Fisher exact test for categorical variables (Steroid vs. Control).

Cardiac compromise = cardiac arrest, complete heart block, hemodynamically unstable arrhythmias; ICU = intensive care unit; IMV = intermittent mandatory ventilation; IQR = interquartile ranges; Pulmonary complications = pneumothorax, pulmonary infiltrates, severe pulmonary congestion, lobar lung collapse.

45 percent, respectively, compared to 35 percent for Control, but this was not statistically significant (fig. 2). In all three groups approximately 10 to 15 percent of patients remained intubated for 16 to 24 h. Time to tracheal extubation did not influence the time to discharge from the intensive care unit for any group.

Alveolar-arterial oxygen partial pressure gradients were determined at five time points (table 4). The mean A-aDo_2 for Hemofil at all five periods was not different compared to Control. In contrast, the mean A-aDo_2 for Steroid was significantly higher than Control before tracheal extubation (179.2 ± 69.9 *versus* 150.1 ± 65.3 mmHg, respectively, $P = 0.019$). The mean A-aDo_2 for the other four time periods in the Steroid compared to Control was not different. The A-aDo_2 for Steroid was significantly higher than Hemofil before tracheal extubation (179.2 ± 69.9 *versus* 150.2 ± 64.6 mmHg, respectively, $P < 0.02$).

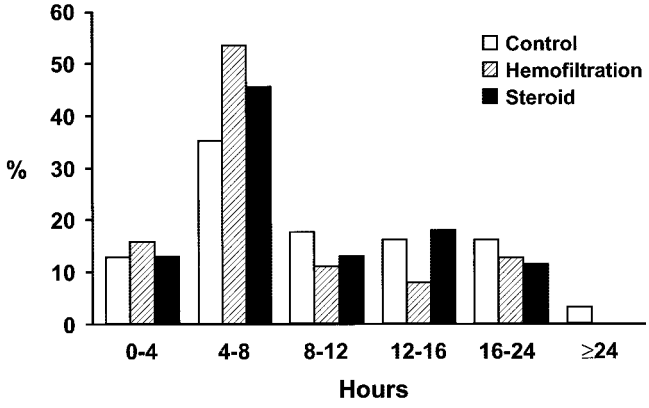

Fig. 2. Categorized time to extubation. Patients are grouped according to time to extubation. *Fisher exact test (Hemofil *versus* Control) and Fisher exact test (Hemofil *versus* Control). There was no difference in the percent of patients tracheally extubated in the defined ranges among the groups.

The cardiopulmonary bypass fluid requirement (table 5) was significantly greater in Hemofil compared with Control (4306 ± 1564 *versus* 2389 ± 830 ml, respectively, $P < 0.01$) and compared with Steroid (4306 ± 1564 *versus* 2258 ± 715 ml, respectively, $P < 0.01$), whereas Steroid had similar fluid requirements to Control (2258 ± 715 *versus* 2389 ± 830 ml, respectively $P = 0.67$). However, fluid balance was significantly better for Hemofil compared with Control (1.18 ± 1.99 l *versus* 1.97 ± 1.69 l, respectively, $P = 0.04$), whereas there was no difference between Steroid and Control. Significantly fewer patients in Steroid required fresh frozen plasma ($P = 0.029$) and platelets ($P < 0.01$) during the first 24 h in the intensive care unit compared with Control. There was no difference between the Hemofil and Steroid groups regarding the incidence of exposure during the first 24 h in the intensive care unit ($P = 0.1$), yet the Steroid group had significantly fewer subjects

Table 4. Alveolar-arterial Oxygen Partial Pressure Gradient

Time	Control (N = 63)	Hemofil (N = 64)	P*	Steroid (N = 62)	P†
First OR (baseline)	229.0 ± 100.6	224.0 ± 115.1	0.524	238.2 ± 110.4	0.915
Last OR	325.2 ± 150.6	300.8 ± 133.6	0.512	374.8 ± 151.9	0.075
First ICU	245.9 ± 84.4	237.5 ± 71.1	0.597	269.1 ± 110.3	0.537
Before Extubation	150.1 ± 65.3	150.2 ± 64.6	0.919	179.2 ± 69.9	0.019
After Extubation	201.0 ± 104.0	198.8 ± 102.9	0.890	218.4 ± 93.0	0.127

Data presented as mean ± SD.

* Wilcoxon rank sum test (Hemofil vs. Control); † Wilcoxon rank sum test (Steroid vs. Control).

Alveolar-arterial oxygen partial pressure gradient = [(760)(F_{IO_2}) − (P_{ACO_2}/0.8)] − P_{AO_2}. The inspired oxygenation was measured, recorded and incorporated in the formula to calculate the A − a gradient. Formula derived from West JB: Respiratory physiology—the essentials, 4th ed. Baltimore: Williams & Wilkins, 1990, pp 51–68.

F_{IO_2} = fractional inspired oxygen tension; First ICU = 30 minutes after arrival in ICU; ICU = intensive care unit; Last OR = at surgical closure; OR = operating room; P_{ACO_2} = arterial carbon dioxide partial pressure; P_{AO_2} = arterial oxygen partial pressure.

given platelet concentrates during this time than Hemofil ($P = 0.01$). There was no difference in the allogeneic packed erythrocyte transfusion exposure between the groups during this time period. Mediastinal chest tube drainage was significantly less for Steroid compared with Control at 4, 12, and 24 h in the intensive care unit (table 6). Hemofil had significantly less mediastinal chest tube drainage compared to Control at 24 h in the intensive care unit. There was no difference between the Steroid and Hemofil groups regarding mediastinal chest tube drainage at 4, 12, and 24 h in the intensive care unit. No patient received aprotinin, but a standardized dose of tranexamic acid was administered solely at the discretion of the physicians caring for the patient. The percentage of patients in Control, Steroid, and Hemofil groups to receive tranexamic acid is 53.9 percent (34 of 63), 53.2 percent (33 of 62), and 57.8 percent (37 of 64), respectively. There was no difference in the intraoperative or 24-h urine output between the groups, although Steroid intraoperative urine output approached significance as compared with Control (920 ± 511 *versus* 1080 ± 601 ml, respectively, $P = 0.056$).

Of the original 189 patients, 159 (51 Control, 53 Hemofil, and 55 Steroid) were considered for the temperature portion of the analysis. Temperature was measured at the core (pulmonary artery catheter blood temperature), bladder, and skin of the peripheral lower extremities hourly to a maximum of 24 h during the initial

Table 5. CPB Fluids, Transfusion Requirements, and Fluid Balance

Characteristic (Units)	Control (N = 63)	Hemofil (N = 64)	P*	Steroid (N = 62)	P†
CPB Fluids (ml)			<0.001		0.667
Mean ± SD	2389 ± 829.9	4306 ± 1564.2		2258 ± 715.0	
Median	2000	4625		2000	
IQR (25^{th}, 75^{th})	1700, 3000	3100, 5000		1750, 2500	
Erythrocytes (%)					
Intraoperative	15.9	17.5	0.844	11.3	0.423
Postop day 1	25.4	19.1	0.482	16.2	0.190
Fresh frozen plasma (%)					
Intraoperative	4.8	3.2	0.652	1.7	0.323
Postop day 1	11.2	7.9	0.496	1.7	0.029
Platelet Concentrates (%)					
Intraoperative	4.8	6.3	0.737	4.9	1.00
Postop day 1	14.3	14.1	0.851	1.7	0.008
Cryoprecipitate (%)					
Intraoperative	0.0	0.0	1.00	0.0	1.00
Postop day 1	4.8	1.6	0.303	0.0	0.084
Fluid Balance (L)	1.97 ± 1.69	1.18 ± 1.99	0.040	1.66 ± 1.72	0.504
Urine output (mL)					
Intraoperative	1079.7 ± 600.9	988.2 ± 536.0	0.357	919.7 ± 511.4	0.056
Postop day 1	2963.1 ± 760.3	3051.6 ± 865.1	0.548	3046.0 ± 891.6	0.399

* Wilcoxon rank sum test (Hemofil vs. Control); † Wilcoxon rank sum test (Steroid vs. Control).

Fluid balance (ml) = (intraoperative and 24 hour crystalloid, intraoperative and 24 hour intensive care unit albumin + intraoperative and 24 hour hetastarch 6% + intraoperative and 24 hour packed red blood cells + intraoperative and 24 hour fresh frozen plasma + intraoperative and 24 hour platelet concentrates + intraoperative and 24 hour cryoprecipitate + total fluids given during CPB) − (ultrafiltrate + intraoperative and 24 hour urine output + 24 hour MCTD).

CPB = cardiopulmonary bypass; IQR = interquartile range; MCTD = mediastinal chest tube drainage; Postop = postoperative.

Table 6. Mediastinal Chest Tube Drainage

Characteristic (Units)	Control (N = 63)	Hemofil (N = 64)	*P**	Steroid (N = 62)	*P*†
4 hours					
Mean ± SD	264.2 ± 208.6	222.3 ± 162.6	0.178	179.2 ± 93.1	0.023
Median	200.0	180.0		157.5	
IQR (25^{th}, 75^{th}) percentile	(130, 300)	(110, 270)		(110, 250)	
12 hours					
Mean ± SD	621.9 ± 467.2	485.3 ± 321.0	0.065	409.6 ± 219.9	0.004
Median	490.0	390.0		335.0	
IQR (25^{th}, 75^{th}) percentile	(300, 750)	(275, 545)		(260, 550)	
24 hours‡					
Mean ± SD	867.8 ± 579.1	677.8 ± 446.6	0.022	589.4 ± 303.3	0.002
Median	740.0	530.0		480.0	
IQR (25^{th},75^{th}) percentile	(480, 1035)	(390, 785)		(350, 773)	

* Wilcoxon rank sum test (Hemofil vs. Control); † Wilcoxon rank sum test (Steroid vs. Control).

‡ Steroid group missing data on 1 patient.

IQR = interquartile range.

duration of the intensive care unit stay. The "Core − Skin" temperature difference is demonstrated in figure 3. The gradient between the core temperature and peripheral temperature (skin) was no different over the initial 24 h in the intensive care unit for the groups.

Of the original 189 patients, seven subjects per treatment group were included in a determination of complement activation. Concentrations of C3a and C5b-9 for Hemofil and Steroid were no different at baseline, 10 min after initiation of cardiopulmonary bypass, after aortic cross-clamp removal, 20 min after protamine administration, and 3 h after separation from cardiopulmonary bypass compared to Control (fig. 4). Blood glucose concentrations obtained before steroid or placebo administration, during cardiopulmonary bypass, and after permanent separation from cardiopulmonary bypass demonstrated a significantly higher value in Steroid compared with Control during cardiopulmonary bypass (127.5 ± 23.5 *versus* 117.1 ± 21.2 mg/dl respectively, $P = 0.008$) and after cardiopulmonary bypass (161.0 ± 32.2 *versus* 135.7 ± 28.8 mg/dl, respectively, $P < 0.001$) whereas blood glucose concentrations were not different for Steroid compared to Hemofil at any of the corresponding time periods.

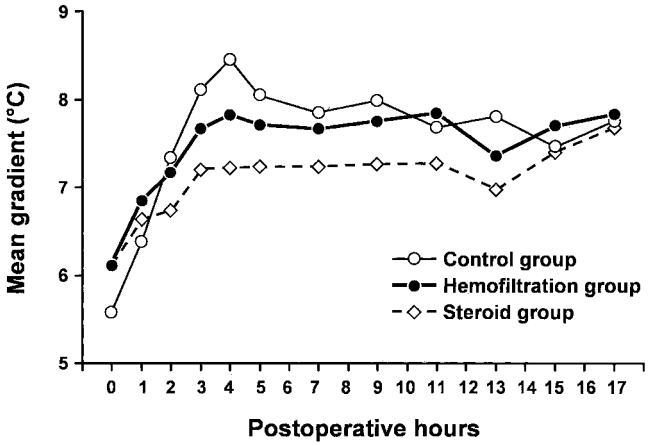

Fig. 3. The mean difference between pulmonary artery catheter temperature (core) and the peripheral temperature (skin) (°C) during the first day in the intensive care unit are displayed. The gradient between the core temperature and skin temperature was no different over the initial 24 h in the intensive care unit for the groups. Data are represented as means ± SD.

Of the original 189 patients, 106 (31 Control, 36 Hemofil, and 39 Steroid) were included in a *post hoc* analysis using a clinical performance score as an overall measure of inflammatory response attributed to exposure to cardiopulmonary bypass. The approach used for calculating the clinical performance score was similar to that proposed by Jansen *et al.*[13] However, because of differences in study design we were not able to replicate exactly their score. To have a 15-h mean temperature difference calculated, patients needed to have complete temperature information through 5 h and could not be missing more than two of 11 measurements during the first 15 h. Patients would also require 24 h fluid balance and time until tracheal extubation to be considered for the clinical performance score analysis. Steroid demonstrated a difference in the clinical performance score compared to Control (−0.46 ± 1.56 *versus* 0.59 ± 2.15 respectively, $P = 0.03$), but Hemofil did not differ from Control (0.00 ± 1.9 *versus* 0.59 ± 2.15 respectively, $P = 0.15$). There was no difference between Steroid and Hemofil regarding the clinical performance score.

There was no difference between the groups concerning the occurrence of stroke, reintubation, or exploration for bleeding. Four patients (three Control, one Hemofil) returned to the operating room for mediastinal exploration secondary to excessive mediastinal chest tube drainage. The incidence of pulmonary complications was similar between the groups, with 11.3 percent in Steroid, 6.4 percent in Control, and 3.1 percent in Hemofil group. One patient was reintubated in the intensive care unit to return to the operating room as a

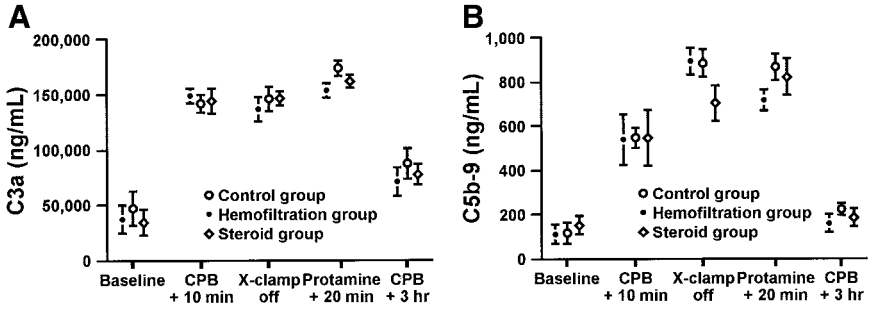

Fig. 4. (*A*) Concentrations of C3a (ng/ml) at the specified time periods. Concentrations of C3a for Hemofil and Steroid were no different at baseline, 10 min after initiation of cardiopulmonary bypass, after aortic cross-clamp removal, 20 min after protamine administration and 3 h after separation from cardiopulmonary bypass compared to Control. Data are presented as mean ± SD. (*B*) Concentration of C5b-9 (ng/ml) at the specified time periods. Concentrations of C5b-9 for Hemofil and Steroid were no different at baseline, 10 min after initiation of cardiopulmonary bypass, after aortic cross-clamp removal, 20 min after protamine administration and 3 h after separation from cardiopulmonary bypass compared to Control. Data are presented as mean ± SD. CPB = cardiopulmonary bypass

result of hemodynamic instability secondary to excessive bleeding. One patient (Steroid) developed a cerebral vascular accident in the left parietal area. There were no deaths perioperatively.

Discussion

Early tracheal extubation after cardiac surgery requiring cardiopulmonary bypass has been associated with improved cardiac function, reduced pulmonary complications and reduced medical costs.[14,15] In this prospective, randomized, double-blind study, hemofiltration, but not steroid administration, resulted in a significantly reduced duration of postoperative ventilation in patients undergoing cardiac surgery with cardiopulmonary bypass. Pulmonary dysfunction associated with the inflammatory response generated by exposure to cardiopulmonary bypass[4] may delay tracheal extubation and lead to morbidity and mortality.[1] Steroids[9,12] and hemofiltration,[16] two currently applied techniques to attenuate the inflammatory response, reduce complement activation and proinflammatory cytokines, but clinical benefit has not always been evident.[6] Some consider steroid administration a fundamental component of a "fast-track" strategy that enhances the likelihood of rapid tracheal extubation after cardiopulmonary bypass.[6,12,15] This partly derives from the capability of steroids to inhibit neutrophils, considered to play a major role in pulmonary dysfunction after cardiopulmonary bypass.[9] However, early tracheal extubation has been achieved without the administration of steroids, mostly in patients undergoing coronary revascularization with a median time to tracheal extubation of 4 h[17,18] but extending to 10 h in patients also undergoing valvular procedures.[19] Measures to successfully tracheal extubate more patients sooner after cardiopulmonary bypass continue to be sought.

Steroid administration in the context of early tracheal extubation for cardiac surgery is reliant on dosing, formulation, and timing of administration to derive any benefit.[3] Engelman *et al.*[12] recommended a specific dosing regimen of steroids for patients undergoing cardiac surgery with cardiopulmonary bypass based on a retrospective comparison of patients that underwent coronary artery bypass grafting with a fast-track regimen including steroids or conventional management. Time to tracheal extubation in the fast-track regimen was significantly decreased as well as intensive care unit duration compared with conventional management. Subsequently, Engelman *et al.*[9] again emphasized the importance of steroids as part of a fast-track regimen. Our study attempted to affirm or reject a role for the aforementioned steroid regimen in the attainment of early tracheal extubation.

Currently, the benefits of hemofiltration to attenuate the inflammatory response and reduce duration of mechanical ventilation have been realized only in pediatric patients undergoing cardiopulmonary bypass.[6,16] Our study found that hemofiltrating to a volume of 27 ml/kg significantly reduced the time to intermittent mandatory ventilation of 4 for Hemofil compared with Control (385.3 ± 300.1 *versus* 512.2 ± 397.2 min, respectively, $P = 0.02$) and the time to tracheal extubation for Hemofil compared with Control (481.0 ± 308.5 *versus* 618.0 ± 404.9 min, respectively $P = 0.03$). Reduced duration of mechanical ventilation occurred although control patients received less fluid than did participants that underwent hemofiltration. This shortened time of mechanical ventilation and earlier tracheal extubation was not accompanied by a detectable improvement in the patient's pulmonary function in terms of A-aDo_2 nor in terms of reduced time of intensive care unit discharge. Measurement of complement concentrations (C3a and C5b-9) was chosen for this study because of the increased pulmonary vascular resistance, appearance of neutrophils in the pulmonary vascular bed, and endothelial injury resulting in increased pulmonary vascular permeability and interstitial edema identified under experi-

mental conditions following activated complement infusions.[7,20] Hemofiltration has been shown to reduce C3a concentrations,[16] which indicates the amount of C3b present that triggers the generation of C5b-9. Accordingly, one might expect reduced concentrations of C3a or C5b-9 associated with the current findings of reduced mechanical ventilation duration in Hemofil patients, but this was not identified. Other inflammatory mediators, such as tumor necrosis factor and interleukin-10, have been observed to decrease with hemofiltration[16] but were not measured in our study. This might account for the observed clinical benefit in Hemofil despite a lack of difference in complement activation compared to Control patients. In addition, Engelman *et al.*[9] have demonstrated that reductions in complement activation with cardiopulmonary bypass may lag other mediators of inflammation like interleukin-8 by 24 h. This could account for the lack of difference in complement activation among the three groups in our study. In fact, Jansen *et al.*[8] has already used other inflammatory markers to successfully demonstrate reductions in tumor necrosis factor and leukotrienes in the absence of reduced complement activation with steroid administration (dexamethasone 1 mg/kg) before cardiopulmonary bypass.

Steroid therapy did not reduce time to intermittent mandatory ventilation of 4 compared to control (393.0 ± 254.5 *versus* 512.2 ± 397.2 min, respectively) or time to tracheal extubation compared to control (519.3 ± 292.8 *versus* 618.0 ± 404.9 min, respectively). Surprisingly, the accompanying A-aDo_2 at the end of surgery, on intensive care unit admission, and before tracheal extubation was worse for those that received steroids in comparison with control patients. Chaney *et al.*[21] reported similar findings regarding A-aDo_2 in cardiac surgical patients requiring cardiopulmonary bypass that were administered steroids prophylactically. They speculated that the worsened A-aDo_2 and delayed tracheal extubation associated with steroid administration was attributable to steroid-induced sodium retention and vasodilation leading to increased shunt and increased lung water resulting in pulmonary edema. Chaney *et al.*[21] also noted a decrease in lung compliance and other indices of pulmonary mechanics coupled with the increased A-aDo_2 subsequent to steroid administration. The worsening laboratory indices of pulmonary function without a demonstrable clinical impact are difficult to gauge. For example, neither our study nor Chaney *et al.*[21] could demonstrate a difference in the percentage of patients tracheally extubated within 4–8 h of cardiopulmonary bypass with steroids as compared to control (fig. 2).

The ability of steroids to affect respiratory status, as reflected in duration of mechanical ventilation after cardiac surgery, is further complicated by the variety of dosing schedules utilized. The larger dose of steroids as administered by Chaney *et al.*[21] as compared with either our group or Engelman *et al.*[9] could have conceivably accounted for the increased interstitial fluid and incipient pulmonary edema described in some of their patients. Using the same steroid dose as Engelman *et al.*[9] we found duration of mechanical ventilation in those receiving steroids compared with control (8.6 ± 4.9 *versus* 10.3 ± 6.7 h, respectively) was less than Engelman *et al.*[9] (13.1 ± 2.3 *versus* 10.5 ± 1.0 h, respectively) and compared favorably with Chaney *et al.*[21] (12.8 ± 4.9 *versus* 10.1 ± 5.3 h, respectively). The dose of steroids for patients that required cardiopulmonary bypass and cardiac surgery has been empirically derived from other studies that administered steroids in situations of sepsis.[22] These steroids are rapidly acting compared to others. Methylprednisolone has a half-life of 3 h and dexamethasone has a slightly shorter half-life of 1.8 h. The optimal dose of steroids associated with a desirable reduction in complement activation, thereby reducing complications, has not been identified.

In this study, we also attempted to determine a mechanism responsible for any clinical improvement that might have occurred with hemofiltration or steroids by analyzing their effect on the inflammatory response. However, the inflammatory response to cardiopulmonary bypass is complex and multifaceted without a predictable or defined magnitude. Actions attributed to the inflammatory response in reaction to initiation of cardiopulmonary bypass include complement activation, release of proinflammatory cytokines, activation of platelets and neutrophils, and endothelial cell-neutrophil interactions, among others. The inflammatory response, triggered by contact activation of the blood with the foreign surface of the extracorporeal circuit, is provoked by other factors such as transfusion, hypothermia, and tissue injury. Unchecked, this response may add to profound organ dysfunction and even mortality. The lungs appear to be particularly affected, giving rise to greater chances of renal, neurologic, infectious involvement and complications.[23] However, the precise role of any element of the stress response remains uncertain, further complicating efforts to limit it. The combination of mediators is also of importance in determining the pathologic nature of the response.[3] Unfortunately, it remains unclear which inflammatory mediators and actions determine the likelihood of an adverse outcome, as evidenced by the many studies showing associations with aspects of the inflammatory response but an inability to convincingly establish cause and effect with outcome.

Steroids have been associated with reductions of cytokines, neutrophil activity, and a host of other immunologic activities. Inhibition of complement activation in association with cardiopulmonary bypass by steroid therapy has been demonstrated by some studies[6] and not demonstrated by others.[8] A lack of evidence regarding complement inhibition with steroids for cardiopulmonary bypass does not necessarily exclude an inflamma-

tory mediated response as a part of the mechanism explaining improved clinical results.[6] Hemofiltration has been shown to reduce the concentrations of C3a.[16] We were not able to detect any significant reduction in complement activation (C3a or C5b-9) with either hemofiltration or steroid administration compared with control. The most plausible explanation for this may be in the choice of complement as a marker of the inflammatory response. Engelman *et al.*[9] have demonstrated that reductions in complement activation with cardiopulmonary bypass may lag other mediators of inflammation like interleukin-8 by 24 h. This could account for the lack of difference in complement activation among the three groups in our study. It has been suggested that interleukins may play a greater role in the occurrence of "pump lung" or postbypass syndrome than complement activation[24] by modulation of endothelial injury through interleukin-mediated neutrophil activation.[9] Jansen *et al.*[8] administered dexamethasone (1 mg/kg) before cardiopulmonary bypass and demonstrated reductions in tumor necrosis factor and leukotrienes in the absence of reduced complement activation. This could have accounted for improved hemodynamic stability and temperature maintenance without evidence of complement inhibition.[6] In our investigation, hemofiltration was not associated with a reduction in complement concentrations yet selected clinical respiratory indices were improved. The effect of hemofiltration on plasma narcotic concentrations may partially explain this outcome. The ultrashort-acting narcotic, alfentanil, is reduced during ultrafiltration.[16] Reduced narcotic blood concentrations, not measured in this study, could account for shorter durations of mechanical ventilation in Hemofil without a corresponding reduction in inflammatory mediators. However, anesthetic agents, such as fentanyl, that bind to large protein compounds are not removed by hemofiltration as effectively and are less likely to be responsible for any improved durations of mechanical ventilation associated with hemofiltration.[25]

Jansen *et al.*[13] developed a clinical performance score to aid in the recognition of an attenuated inflammatory response expressed with subtle clinical findings. The clinical performance score incorporates fluid balance, tracheal extubation time, and temperature gradient as measures that would reflect changes in the inflammatory response. Temperature gradients between the skin and core temperature are in part reflective of the status of the peripheral circulation. Fluid balance in part reflects the degree of capillary leak and edema. Despite the lack of any significant difference between any individual parameters in either of the treated groups, the composite clinical performance score suggests a significant antiinflammatory response with steroids. Jansen *et al.*[13] similarly found no difference in the individual scores for fluid balance, temperature gradient, or tracheal extubation time, but the composite score was significantly different with one of the antiinflammatory regimens in their study compared with control. The results of our clinical performance score would suggest a minor effect of steroids on the inflammatory response that is consistent with the previous work of Jansen *et al.*[8] in which significant gradients between core and skin temperature were noted in patients who did not receive any antiinflammatory interventions.

The significant reduction in both perioperative blood loss (table 6) and transfusion requirements (table 5) in patients that received steroids was an unexpected finding in this study. Blood loss, reflected by mediastinal chest tube drainage, was significantly reduced at 4, 12, and 24 h after admission to the intensive care unit compared with control patients. Reductions in platelet and fresh frozen plasma transfusions, but not packed erythrocytes, formed the basis for the improved transfusion requirements in patients that received steroids. Because transfusion requirements and mediastinal chest tube drainage were both reduced and transfusions were administered in a blinded manner, this surprising finding merits further investigation. Tassani *et al.*[26] demonstrated a significant reduction in 6-h mediastinal chest tube drainage for patients undergoing coronary artery bypass grafting treated with steroids but no corresponding improvement in transfusion requirements. These findings of reduced bleeding with or without concomitant transfusion requirements in the steroid-treated group may be a function of the interconnecting relationship between the coagulation-fibrinolytic cascade and the inflammatory response[3] linked to steroid attenuation of fibrinolysis.[27] Proinflammatory mediators initiate the coagulation process leading to thrombosis and subsequent excessive fibrinolysis that contributes to the coagulopathy noted in patients following cardiopulmonary bypass.[3] Steroid attenuation of fibrinolysis may be partially responsible for the significantly reduced bleeding and transfusion requirements identified in this study.

In contrast to the reduced postoperative transfusion requirements and bleeding for patients that received steroids, reduced transfusion requirements were not observed with Hemofil, although 24 h mediastinal chest tube drainage was significantly reduced compared with Control (677.8 ± 446.6 *versus* 867.8 ± 579.1 ml, respectively, $P = 0.02$). Recently, hemofiltration has been associated with reduced blood loss and transfusion requirements in pediatric patients undergoing cardiopulmonary bypass[16] and more rapid return of platelet function postoperatively in adults undergoing cardiopulmonary bypass.[28] The improvements in mediastinal chest tube drainage observed with hemofiltration in adults undergoing cardiopulmonary bypass were similar to reductions obtained with aprotinin in cardiac surgical patients.[28] An argument can be made for substitution of antifibrinolytic agents with steroids in view of the increased morbidity and mortality associated with bleed-

ing and mediastinal exploration[29] and risks of antifibrinolytic agents.[30–32] However, our study did not show a significant reduction in the incidence of reexploration for bleeding in either Hemofil (1.6 percent *versus* 6.4 percent, respectively) or Steroid (0.0 percent *versus* 6.4 percent respectively) compared to Control.

Complications were minimal with the two antiinflammatory techniques employed. There was no evidence of electrolyte imbalance in patients receiving steroids. Steroid administration may cause glucose intolerance, impaired wound healing, and a higher risk of infection in part as the result of suppression of T cell function.[33] Glucose concentrations were significantly higher in patients receiving steroids, but the elevations were clinically lower than the glucose concentrations recently shown to be associated with worse morbidity and mortality.[34] Based on our work and others,[9] steroids given in the manner described in this study appear to be associated with few measurable complications.

There are several limitations with this study. Sampling for complement activation was completed 3 h after permanent separation from cardiopulmonary bypass, but the inflammatory response is still evident for hours after arrival in the intensive care unit. Consequently, biochemical evidence to support the clinical findings may have been present but missed because of the study design. Clinical findings may have been more likely to correlate with interleukin-8 rather than the complement measurements performed in our investigation. Complement concentrations were measured based on evidence of increased pulmonary vascular resistance, neutrophil infiltration in the pulmonary vascular bed, and endothelial injury resulting in increased pulmonary vascular permeability and interstitial edema following infusions of activated complement in an experimental model and the likelihood that clinically recognizable signs would follow in patients after cardiopulmonary bypass in the presence of complement activation.[7,20] The strong relationship of proinflammatory cytokines and adverse outcomes associated with cardiac surgery as well as the timing of their elevations may have rendered these inflammatory mediators better makers of the inflammatory response than complement for our investigation. Another limitation of the study concerns the simplicity of the pulmonary indices used to assess therapeutic efficacy in relationship to the inflammatory response. Additional indices beyond $A\text{-}aDo_2$ such as lung compliance and total lung water would have provided a more complete assessment of these antiinflammatory therapies.

In conclusion, although the administration of steroids is considered by some to be a basic component of strategy to tracheally extubate patients early postoperatively, time to tracheal extubation was not reduced with this steroid treatment regimen. In contrast, hemofiltration significantly reduced the time to tracheal extubation, but no mechanism was elucidated to account for these results. Steroid administration was associated with significant reductions in bleeding and transfusion. Hemofiltration should be considered to achieve earlier tracheal extubation whereas the benefits of steroids on hemostasis require further study in patients undergoing cardiac surgery and cardiopulmonary bypass.

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