

Effects of Conventional Ultrafiltration on Renal Performance During Adult Cardiopulmonary Bypass Procedures

Rick A. Kuntz, MPS, CCT;* David W. Holt, MA, CCT, NRABT;† Scott Turner, BS, CCP;* Lee Stichka, BS, CCP;* Bryan Thacker, BS, CCP*

*Coastal Extracorporeal Technology, Department of Circulation Technology, Bay Medical Center, Panama City, Florida; and
†University of Nebraska Medical Center Clinical Perfusion Education, Graduate Degree Completion Program, University of Nebraska, Nebraska

Abstract: Ultrafiltration has been used successfully in a variety of applications in the perioperative setting to assist in hemoconcentration and volume reduction. This study was designed to investigate the effects of aggressive conventional hemofiltration on bypass urine production, fluid balance, and renal performance in the 24 hours after bypass procedures in the adult population. A prospective, randomized study was designed to determine the effects of conventional ultrafiltration (CUF) during bypass while monitoring urine dynamics intraoperatively and in the 24-hour post-bypass period. Study group 1 (CUF, $n = 49$) was compared to control group 2 (non-CUF, $n = 47$) by monitoring urine values, volume additions, and packed red cell (PRC) use throughout the procedure. The mean total CUF volume removed from group 1 was 5781 ± 2612 . There were no differences in pre-bypass, total bypass, or total operating room (OR) urine be-

tween the two groups. The 24-hour urine totals were significantly higher in group 2 (2389 ± 895) than in group 1 (2035 ± 895). The ending bypass hematocrit was also lower in group 2 (26 ± 2.0) than in group 1 (30 ± 6.0). OR PRC additions were higher in group 2 (395 ± 699) than group 1 (204 ± 300). The non-CUF control group 2 experienced significantly greater ending fluid balance (3006 ± 868) compared with group 1 (744 ± 1271). No significant differences in pre- or postoperative creatinine values were observed. Aggressive CUF can be safely used during cardiopulmonary bypass in the adult population to reduce fluid accumulation and elevate bypass hematocrit without effecting bypass or intraoperative urine production. **Keywords:** conventional ultrafiltration, hemodilution, renal failure, urine output, bypass urine, fluid balance, hematocrit, extracorporeal. JECT. 2006;38:144-153

Extracorporeal circulation contributes to morbidity after cardiac surgery by adversely affecting various physiologic mechanisms. These include, but are not limited to, systemic inflammatory response syndrome (SIRS), hematological alterations, neurological sequelae, and the adverse effects of hemodilution. Various strategies have been used to minimize and reverse the degree of hemodilution in an effort to control the consequences of fluid accumulation, capillary leak syndrome (1-5), postoperative weight gain, and homologous blood use.

Controlling the adverse effects and limiting the extent of hemodilution continue to present challenges to circuit mechanics and operative technique for the clinical perfusionist. Many mechanisms have been used to avoid excessive hemodilution during cardiopulmonary bypass (CPBP) procedures. These range from minimally invasive procedures (MIDCAB) (6-9) to mini-extracorporeal cir-

culation systems (MECC) (10,11). Additionally, various techniques have been used to reduce the crystalloid load before initiating bypass retrograde autologous prime (RAP) (12,13) and vacuum-assisted venous return (VAVR) (14-16) or during the period surrounding bypass zero-balance ultrafiltration (ZBUF) (17,18), modified ultrafiltration (MUF) (19-22), and conventional ultrafiltration (CUF) (23-26).

Conventional ultrafiltration (CUF) is a technique capable of removing large amounts of fluid (isotonic plasma water) while reducing inflammatory mediators complicating CPBP procedures (27-32). Although ultrafiltration can be an effective tool to ameliorate the extent of hemodilution, its effects on diuresis during bypass have not been thoroughly studied. Concern arises whether CUF may influence intraoperative urine production or possibly contribute to renal dysfunction. Acute renal failure (ARF) may occur in 7-30% of cardiac patients, with 1-4% requiring dialysis, thereby increasing postoperative morbidity (33-35). Postoperative renal dysfunction remains a frequent and serious complication after cardiac surgery (36,37). Because the effects of CUF on urine production, fluid balance, and possibly renal function remain largely

Address correspondence to: Rick A. Kuntz, MPS, CCT, CETECH, INC., 612 E. Baldwin Road, Panama City, FL 32405. E-mail: cardiofuse@mac.com

The senior author has stated that authors have reported no material, financial or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

unknown, this study was designed to prospectively investigate a large series of consecutive, randomized patients to 1) determine if aggressive CUF during CPBP effects urine production, 2) examine the comparative effects of CUF on overall fluid balance, and 3) investigate if the performance of CUF throughout CPBP adversely effects renal function.

MATERIALS AND METHODS

Patient Selection

This prospective, randomized study was conducted over a 4-month period and included 100 consecutive adult patients undergoing routine coronary artery bypass grafting or valve replacement surgery by the same surgical and perfusion team. Exclusion criteria for this study are listed in Table 1. The protocol was approved by the local Institutional Review Board, and written consent was waived. The patients were separated into two groups: a treated group 1 (CUF) group and a control group 2 (non-CUF). All patients were assigned to their respective groups in advance by a random number table (0 for control, 1 for CUF).

Data Collection

The primary outcome measurement parameters were urine production and CUF volume during CPBP. For this purpose, a data sheet was designed to collect all continuous and discrete variables. Urine was measured by ultrasonic volumetric analysis at the end of each 15-minute period from the start of CPBP. In the CUF group, the filtrate volume was collected and measured in a graduated cylinder and recorded with the coincident urine volume at the end of each 15-minute bypass period.

Additional data collected included preoperative hematocrit (baseline), pre-bypass hematocrit, last bypass hematocrit (HematoSTAT II; Separation Technology, Altamonte Springs, FL), blood and clear additions by anesthesia, and the perfusionist. Pre-bypass (Foley insertion to CPBP) and total operating room (OR) urine was recorded

for later comparative analysis. At 24 hours after terminating bypass, the following data were collected: 24-hour hematocrit, 24-hour urine (the urine collection is emptied before leaving the OR), red blood cell additions, and 24-hour creatinine. Pre- and postoperative creatinine data were collected for comparative analysis.

Perfusion Technique

A centrifugal arterial pump (Delphin; Terumo, Ann Arbor, MI) was used with a modular heart lung machine (Sarns 8000; Terumo) equipped with a custom closed system tubing pack and membrane oxygenator (Capiiox 1.8; Terumo). The prime consisted of Normosol (1500 mL), 25 g mannitol (50 mL 25%), 12.5 g albumin (25%), 5 ku sodium heparin, 35 mEq sodium bicarbonate, and either Trasylol (2×10^6 KIU) or amicar (10 mg) for a total prime volume of 1800 mL before cannulation. Anticoagulation management was achieved with the HMS system (Hemotec; Medtronic, Minneapolis, MN). Heparin was administered to maintain an activated clotting time (ACT) $\geq$ 480 seconds. Packed red cells (PRCs) were added to the prime whenever necessary to maintain a minimum calculated hematocrit of 25%. Bypass flow ranged from 1.8 to 2.4 L/min/m² to achieve a venous saturation of 0.65–0.75%. Normal systemic vascular resistance was maintained by the addition of phenylephrine or Forane as required. Mild hypothermia was used to a target bladder temperature of 34°C. Intermittent cold blood cardioplegia was administered with a standard 4:1 integrated delivery set (CP-50; Terumo) using Plegisol as the carrier solution per manufacturer guidelines. A warm reperfusion dose followed by warm blood was delivered before cross-clamp removal. pH stat blood gas management was used during the initial cooling phase followed by alpha stat management during baseline hypothermia and throughout the rewarm period. Arterial line temperatures were kept below 37.5°C during rewarm. The patient was separated from CPBP when the bladder temperature reached 36°C.

Anesthesia Technique

All patients were premedicated with 5–10 mg oral Diazepam or 1–2 mg Lorazepam and transferred to preoperative holding, where Fentanyl (50 µg increments) or Diazepam (2.5–5 mg) was administered as needed for sedation. After transfer to the operating room, induction was achieved with 0.3 mg etomidate, 8 mg Pancuronium, and 10 mg fentanyl. After tracheal intubation, patients were mechanically ventilated to give a tidal volume of 10–12 mL/kg body weight, with an inspiratory mixture of N₂O/O₂ 50% and a respiratory rate of 10–14 cycles/min to achieve an end tidal CO₂ between 35 and 45 mmHg. General anesthesia was maintained with Fentanyl (50–100 µg) and Pavulon (2–4 mg) and Diazepam (5–10 mg), with additional doses for maintenance as needed.

Table 1. Patient exclusion criteria.

Patient Exclusion Criteria
1. Renal insufficiency
2. Furosimide administration
3. Chronic dialysis
4. Chronic hypotension
5. Creatinine $\leq$ 1.3 mg/dL
6. OR diuretic use
7. Preoperative IABP insertion
8. Creatine supplements
9. Oliguria (24 urine <400 mL)
10. Catheter insertion problems
11. Diabetes mellitus
12. Liver dysfunction
13. ACE inhibitors
14. Urgent CPBP

Statistical Analysis

A descriptive data sheet was designed in Excel format to collect and perform the relevant calculations. The resulting information was imported into the statistical software package (JMP version 11.0; SAS Institute, Cary, NC) for final analysis.

The null hypothesis tested was that there was no difference between the urine produced on bypass with and without the use of conventional ultrafiltration. To further assess urine function, postoperative creatinine was compared to pre-bypass levels in addition to a 24-hour measurement. Also, 24-hour postoperative urine production was compared between the two study groups. Fluid additions and fluid balance were analyzed in the context of the study groups as well as the maintenance of target hematocrit levels.

Categorical distributions (how a categorical response is distributed) were expressed as percentages and analyzed by a categorical model testing marginal homogeneity. This was accomplished by creating a contingency table looking at the distributions through χ^2 analysis to test for independence (and determine probability). Fisher exact test or Pearson χ^2 test was used to confirm the probable alternative hypothesis, with $p < .05$ being the threshold for statistical significance.

Continuous variables (i.e., age) were expressed as mean $\pm$ SD and compared by a two-tailed Student t test or Wilcoxon rank sum test in nonparametric responses. Comparison of multiple mean values was carried out by ANOVA.

Continuous Ultrafiltration Technique

This study precludes a double-blinded design because the perfusion team must set up the CUF circuit (HPH400; Minntech, Minneapolis, MN) in advance. Despite the single blinded format, researcher bias on part of the perfusionist was considered. To minimize this effect, the technique of CUF was standardized on all patients to eliminate perfusion technique that might otherwise be a factor. Accordingly, CUF will be initiated and controlled through a standardized protocol. CUF was begun on the initiation of CPBP and continued throughout the pump run until bypass was terminated. The ultrafiltrate volume was collected and measured in 15-minute intervals. The CUF circuit is placed between the oxygenator outlet and arterial line filter. Adequate transmembrane pressure (TMP) for brisk filtrate removal (>400 mL/interval) was achieved by maintaining consistent flows and perfusion pressures, which were recorded for analysis. With adequate arterial line pressures, vacuum to the filtrate path was not required to increase TMP to achieve the desired ultrafiltrate flow rates (58 ± 18 mL/min).

If additional volume was required to maintain a safe level in the reservoir, zero-balance ultrafiltration (ZBUF) was used by adding clear volume (plasmalyte or albumin).

A record of additions and fluid balance by the perfusion and anesthesia team was part of the data sheet. Blood was administered as per our normal protocol of minimum bypass hematocrit of 25%. The only difference in the treated group (volume and hct) was the presence of CUF fluid removal. The interim data and results of renal dynamics were not revealed to the perfusionist operating the CUF/design protocol until after the study was complete.

RESULTS

Patient demographic data are summarized in Table 2. Group 2 (non-CUF) contained 47 patients and group 1 (CUF) contained 49 patients. There were no statistically significant differences in age, body size, weight, blood volume, bypass time, or cross-clamp time between the two groups. The average bypass time in group 2 was 103 minutes and was 96 minutes in group 1. The average cross-clamp time was 64 minutes in group 2 and was 68 minutes in group 1. There were 35 (74%) men in group 2 and 39 (79%) in group 1.

Table 3 shows the volume of ultrafiltrate removed during bypass in the study group with a mean of 5781 ± 2612 mL. The values ranged from 1900 to 13,320 mL, with a median of 5560 mL. This resulted in a removal volume of 68 ± 29 mL/kg during bypass at a rate of 41 ± 13 mL/kg/hr or 58 ± 17 mL/min. The average CUF volume removed in any 15-minute period was 871 mL. For relative comparison, Table 2 shows the mean blood volume in the CUF group to be 5.8 ± 1.26 or 67.3 ± 7.5 mL/kg.

Table 4 compares the hematocrit and PRC administration data between the two groups. Both groups had similar initial hematocrits, with group 2 having 37 ± 4.1 and group 1 having 38 ± 4.1 . The pre-bypass hematocrits were also similar between groups, with group 2 having 34 ± 4.5 and group 1 having 34 ± 4.7 . The last bypass hematocrit in group 2 was 26 ± 1.9 , which was significantly lower than in the CUF group 1, which was 30 ± 6.6 . Operating room PRC administration was 395 ± 699 in group 2 and 204 ± 300 in group 1, showing a lot of variability and achieving

Table 2. Patient characteristics.

Continuous Variable	CUF (Group 1) <i>N</i> = 49, Mean $\pm$ SD	No CUF (Group 2) <i>N</i> = 47, Mean $\pm$ SD	<i>p</i> Value (Student's <i>t</i> -test)
Age (years)	63 $\pm$ 12	64 $\pm$ 10	.62
Body surface area (m ²)	2.01 $\pm$.24	2.05 $\pm$.27	.41
Weight (kg)	87 $\pm$ 18	93 $\pm$ 21	.12
Blood volume (mL)	5.8 $\pm$ 1.26	5.9 $\pm$ 1.57	.59
Blood volume (mL/kg)	67 $\pm$ 7.5	64 $\pm$ 9.2	.07
Bypass time (min)	103 $\pm$ 51	96 $\pm$ 36	.44
Cross clamp time (min)	69 $\pm$ 32	65 $\pm$ 23	.44
Males (categorical)	39 (79%)	35 (74%)	.80*

*Fisher exact test (right-sided).

Table 3. CUF study volume distributions.

	Mean	Median	SD	Maximum	Minimum
CUF total removed (mL)	5871	5560	2612	13220	1900
CUF indexed to weight (mL/kg)	68	62	29	145	18
CUF flow rate (mL/min)	58	55	17	97	27

Table 4. Hematocrit and PRC administration.

Variable	CUF (Group 1)	No CUF (Group 2)	<i>p</i> Value (Student's <i>t</i> -test)
First OR hematocrit (%)	37 ± 7.1	38 ± 4.1	.35
Pre-bypass hematocrit (%)	34 ± 4.5	33 ± 4.7	.76
Last bypass hematocrit (%)	30 ± 6.5	26 ± 1.9	.0001*
24-hour hematocrit (%)	34 ± 3.8	34 ± 3.8	.63
OR PRC administration	204 ± 300	395 ± 699	.0443*
OR PRC (mL/kg)	2.8 ± 4.9	5.3 ± 11	.0719*
OR PRC probability	<i>n</i> = 20 (41%)	<i>n</i> = 25 (53%)	.1562†
24-hour PRC administration	219 ± 342	223 ± 337	.95
24-hour PRC (mL/kg)	2.85 ± 4.7	2.65 ± 4.2	.83
24 PRC probability	<i>n</i> = 19 (38%)	<i>n</i> = 18 (38%)	.6015†

**p* < *t*.

†Fisher exact test (right-sided).

significance (0.0449). As a result, the 24-hour hematocrit value was similar in both groups: 34 ± 3.8 in group 2 and 34 ± 3.8 in group 1. A contingency analysis of OR PRCs given by study group revealed that PRCs were administered 53% of the time in group 2 and 41% of the time in group 1, but this did not reach significance (0.1562). Twenty-four-hour PRC administration was similar in both groups; PRC was given 38.8% of the time in group 2 and 38.3% of the time in group 1. (PRC were given inside the OR with less variability between groups than in the 24-hour period.)

Table 5 reviews the creatinine clearance values between the two groups in the pre-, post-, and 24-hour periods. Preoperative creatinine in group 2 (1.03 ± 0.20) was similar to group 1 (1.01 ± 0.17). Similarly, the postoperative and 24-hour creatinine values were comparable in both groups (0.87 ± 0.22 vs. 0.82 ± 0.17) and (1.02 ± 0.19 vs. 1.03 ± 0.28). To show if the effects of hemodilution between groups could alter these results, an attempt was made to adjust for fluid balance and normalize to an average blood volume. After these adjustments were made to the creatinine concentrations, the postoperative and 24-hour values became significantly different. The adjusted postoperative creatinine was 0.98 ± 0.37 in group 1 and 1.4 ± 0.55 in group 2, and the adjusted 24-hour values were 0.83 ± 0.42 in group 1 and 1.2 ± 0.49 in group 2, both interims reaching statistical differences.

Table 5. Creatinine clearance values.

Variable	CUF (Group 1)	No CUF (Group 2)	<i>p</i> Value (Student's <i>t</i> -test)
Preoperative creatinine (mg/dL)	1.01 ± .17	1.03 ± .2	.61
Postoperative creatinine (mg/dL)	.82 ± .17	.87 ± .22	.29
Adjusted postoperative Cr (mg/dL)	.98 ± .37	1.4 ± .55	.0001
24-hour creatinine (mg/dL)	1.03 ± .28	1.02 ± .19	.84
Adjusted 24-hour Cr (mg/dL)	.83 ± .42	1.2 ± .49	.0001
Preoperative clearance (mL/min)	94 ± 32	95 ± 28	.79
Postoperative clearance (mL/min)	114 ± 38	114 ± 33	.97
24-hour clearance (mL/min)	95 ± 35	95 ± 28	.91
Adjusted 24-hour clearance (mL/min)	121 ± 91	86 ± 36	.0149
Postoperative percent change*	25 ± 23	27 ± 39	.78
24-hour percent change	2.2 ± 22	1.4218	.85

*% change = [post - pre]/[pre].

Table 6 reviews the anesthesia and perfusion volume additions as well as the overall fluid balance for the study groups. Anesthesia additions were slightly higher in the study group, with group 2 receiving 2697 ± 687 mL and group 1 receiving 3147 ± 947 mL, giving a mean difference of 450 mL of additional volume in the non-CUF group. The pump additions were significantly higher in the CUF group at 3742 ± 2689 mL compared with the non-CUF group at 745 ± 445 mL. When normalized to body size (mL/kg) to reveal potential (±) hydration errors, these values translated into 8 ± 4 mL/kg for group 2 and 43 ± 29 mL/kg for group 1. Overall fluid balance was significantly higher in the non-CUF group (3006 ± 868 mL) vs. the CUF group (744 ± 1271 mL), with a mean difference of 2261 mL. The CUF patients produced a negative fluid balance on 15 occasions vs. 0 for the non-CUF group.

Figure 1 graphically shows the total pump crystalloid additions and CUF removal volumes in the study group. Only one CUF patient received more pump clear additions than ultrafiltrate removal. Although the CUF patients consistently received more pump additions the overall fluid balance was significantly lower.

Table 7 shows the blood flow patterns during the first 90 minutes of bypass between the two groups. Group 2 (non-CUF) required 7–10% more flow during each interval, which reached statistical significance during most of the

Table 6. Fluid balance/additions.

Variable	CUF (Group 1)	No CUF (Group 2)	<i>p</i> Value (Student's <i>t</i> -test)*
Anesthesia clear additions (mL)	3147 ± 947	2697 ± 687	.009
Pump clear additions (mL)	3742 ± 2689	745 ± 445	.001
Pump additions (mL/kg)	43 ± 29	8 ± 4	.001
OR total fluid balance (mL)	744 ± 1271	3006 ± 868	.001
Fluid balance (mL/kg)	9.2 ± 16	34.5 ± 16	.001
Negative fluid balance	<i>n</i> = 14	<i>n</i> = 0	—

**p* > |*t*|.

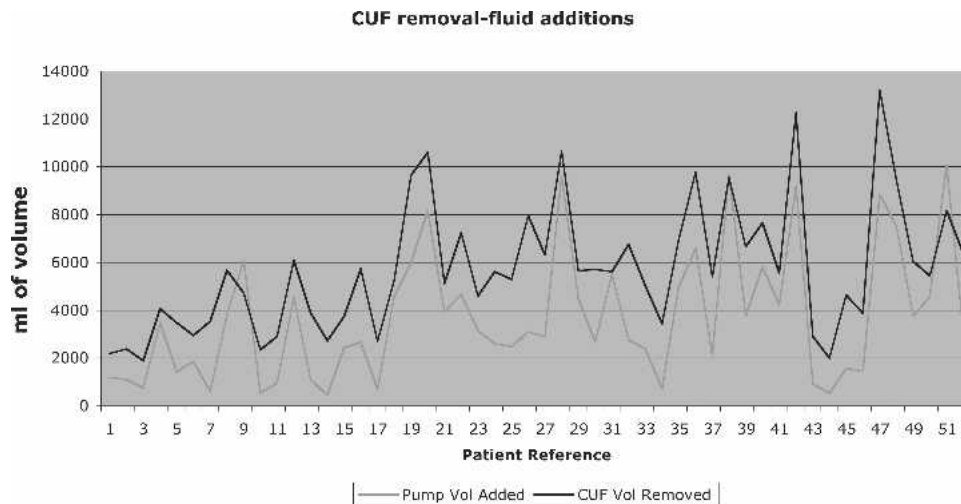


Figure 1. CUF analysis showing volume removed vs. volume additions.

bypass duration. Table 8 reviews the pressure patterns during each interval for each study group. Both groups maintained a consistent and similar blood pressure, with no statistical difference between group 1 and group 2.

Table 9 records the various urine statistics for review. The results of this experiment indicate that there were no differences in pre-bypass, total bypass, or total operating room urine outputs (mL) or flow rates (mL/kg/hr) that reached a level of significance. The 24-hour urine totals were significantly higher in group 2 (2390 ± 896 vs. 2036 ± 663) but the indexed flow per body weight (mL/kg/h) revealed no significant differences. Figure 2 compares the urine, fluids, and ultrafiltrate volume (mL/kg) during the bypass period to show the relative effects of each. Finally, Figure 3 provides the ANOVA analysis comparing the bypass urine rate (mL/kg/h) between study groups. The difference between means in each group was -0.4399 (CUF – non-CUF) with an SE difference of 0.2920 and a p value of $.1355$, showing no significant difference. The final CUF vs. non-CUF bypass urine rates were 1.28 ± 0.18 and 1.56 ± 0.23 , respectively.

DISCUSSION

Principle Findings

Aggressive CUF can remove large amounts of isotonic

solution originating from the priming volume, pre-existing CHF accumulation, and intraoperative anesthesia additions. When applied continuously, during the early phases of bypass, CUF has the ability to remove excessive prime volume, elevate the hematocrit, and concentrate the plasma proteins without compromising hemodynamic stability (38). This process reduces total body water and minimizes interstitial fluid shifts. Recent reports have shown the potential advantage of ultrafiltration in attenuating pulmonary injury by the constant removal of inflammatory mediators produced during CPBP (39,40).

The goal of this study was to determine not only if aggressive ultrafiltration could result in a favorable fluid balance but also whether or not urine production, while on bypass, would be negatively effected. During bypass, fluid leaves the vascular compartment at a steady rate in accordance with the “Starling forces” of colloid osmotic pressure, vascular pressure, interstitial fluid pressure, temperature, degree of inflammatory response, and presence of diabetes mellitus or other conditions altering the vascular endothelium. This study showed that a rapid reversal of hemodilution early in the bypass period, by aggressive fluid removal, can reduce the impact of fluid accumulation while improving bypass hematocrit without excessive transfusion. The inward, positive effects of plasma colloid osmotic pressure (COP) are immediately reduced by the

Table 7. Blood flow comparative group statistics.

Variable	CUF (Group 1)	No CUF (Group 2)	p Value (Student's t -test)*
Blood flow at 00–15 minutes	$4.1 \pm .5$	$4.3 \pm .5$	.05
Blood flow at 15–30 minutes	$4.0 \pm .7$	$4.3 \pm .6$	.03
Blood flow at 30–45 minutes	$4.1 \pm .7$	$4.3 \pm .6$	.06
Blood flow at 45–60 minutes	$4.1 \pm .7$	$4.4 \pm .7$	.06
Blood flow at 60–75 minutes	$4.2 \pm .7$	$4.5 \pm .7$	.07
Blood flow at 75–90 minutes	$4.3 \pm .6$	$4.6 \pm .8$	.21

*Significant at $p < .05$.

Table 8. Perfusion pressure analysis.

Variable	CUF (Group 1)	No CUF (Group 2)	p Value (Student's t -test)*
Blood pressure at 00–15 minutes	70 ± 9.0	68 ± 7.6	.39
Blood pressure at 15–30 minutes	71 ± 9.0	70 ± 7.9	.85
Blood pressure at 30–45 minutes	68 ± 9.2	69 ± 9.4	.45
Blood pressure at 45–60 minutes	67 ± 9.4	68 ± 7.0	.34
Blood pressure at 60–75 minutes	68 ± 10.2	66 ± 8.0	.20
Blood pressure at 75–90 minutes	68 ± 9.98	65 ± 8.5	.69

*Significant at $p < .05$.

Table 9. Urine volume and flow values.

Variable	CUF (Group 1)	No CUF (Group 2)	<i>p</i> Value (Student's <i>t</i> -test)*
Pre-bypass urine (mL)	382 ± 255	321 ± 192	.19
Pre-bypass urine rate (mL/kg/hr)	2.3 ± 1.7	1.8 ± 1.1	.24
Total bypass urine (mL)	347 ± 256	394 ± 238	.35
Bypass urine rate (mL/kg/hr)	2.43 ± 1.28	2.87 ± 1.56	.18
Total OR urine (mL)	876 ± 396	883 ± 353	.92
OR urine rate (mL/kg/hr)	2.29 ± 1.1	2.25 ± 1.03	.99
24-hour urine (mL)	2036 ± 663	2390 ± 896	.03*
24-hour urine rate (mL/kg/hr)	1.07 ± .39	1.21 ± .55	.35

**p* < .05.

effects of acute hemodilution as CPBP begins. Continuous ultrafiltration throughout the bypass period serves to reduce the interstitial accumulation of fluid.

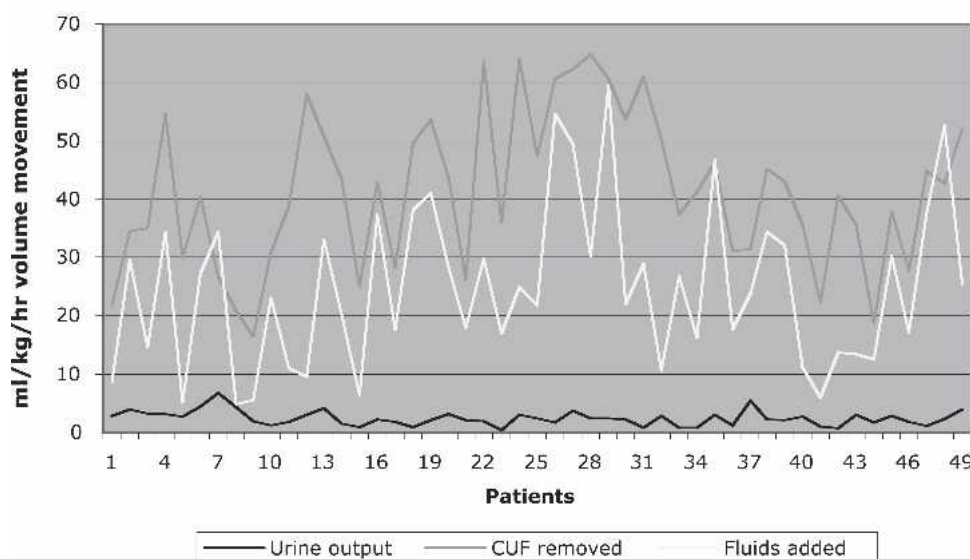
The technique of conventional ultrafiltration during bypass has proven to be a useful modality to treat acute hemodilution by removing excess volume from prime and fluid additions (41–43). Combined techniques of CUF and MUF have been developed in an effort to remove harmful cytokines and inflammatory mediators from the circulation (44–46). Patients undergoing CPB exhibit the adverse effects of increased capillary permeability and decreased colloid oncotic pressure resulting in tissue edema, poor pulmonary compliance, and increase in length of stay (47). The two factors associated with an increased length of stay (multivariate analysis) were age > 70 years and fluid balance > 500 mL. The average interstitial fluid leakage rate is reported to be 34.1 ± 11.1 mL/min (2.04 L/hr) under normothermic conditions (48). The CUF removal rate in this study averaged 58 ± 18 mL/min (3.40 L/hr), which

exceeds the average leakage rate reported. This aggressive fluid removal resulted in an average of 5781 ± 2612 mL of volume removed or 68 ± 29 mL/kg. With an average calculated blood volume (CBV) in our CUF group of 66 ± 8.4 mL/kg, nearly one CBV was removed in each patient.

Although a greater amount of perfusion fluid additions was required to maintain a safe operating level in the venous reservoir, the overall effect on fluid balance in the CUF group was a significant finding in this study. An average (difference in means) of 2261 mL of additional fluid was accumulated in the non-CUF group despite the additional reservoir volume added during bypass (Table 8). This effect was also apparent in the last bypass hematocrit between the two groups (30 ± 6.5 vs. 26 ± 1.9) and the amount of PRC administered in the operating room. The ability to achieve a negative fluid balance occurred 12 times in the CUF group and never in the non-CUF group. Anesthesia additions were not effected by the presence or absence of ultrafiltration.

The maintenance of consistent blood pressures on bypass was similar in both groups, averaging between 63 and 71 mmHg at all times, with no difference reported between groups. The blood flow in the non-CUF group was found to be slightly higher (10%) to achieve the same desired venous saturations of 65–75%. This can be explained by the 10% lower hematocrit on bypass in the non-CUF group requiring the additional flow to provide a consistent oxygen delivery and extraction ratio.

A key element in our null hypothesis was the comparison of urine values while on bypass between our study groups. As shown in Table 7, the difference in bypass urine rates (mL/kg/min) could not achieve statistical significance. Pre-bypass, total bypass, and total OR urine

Major Bypass fluid shifts**Figure 2.** Major bypass fluid shifts in the study group.

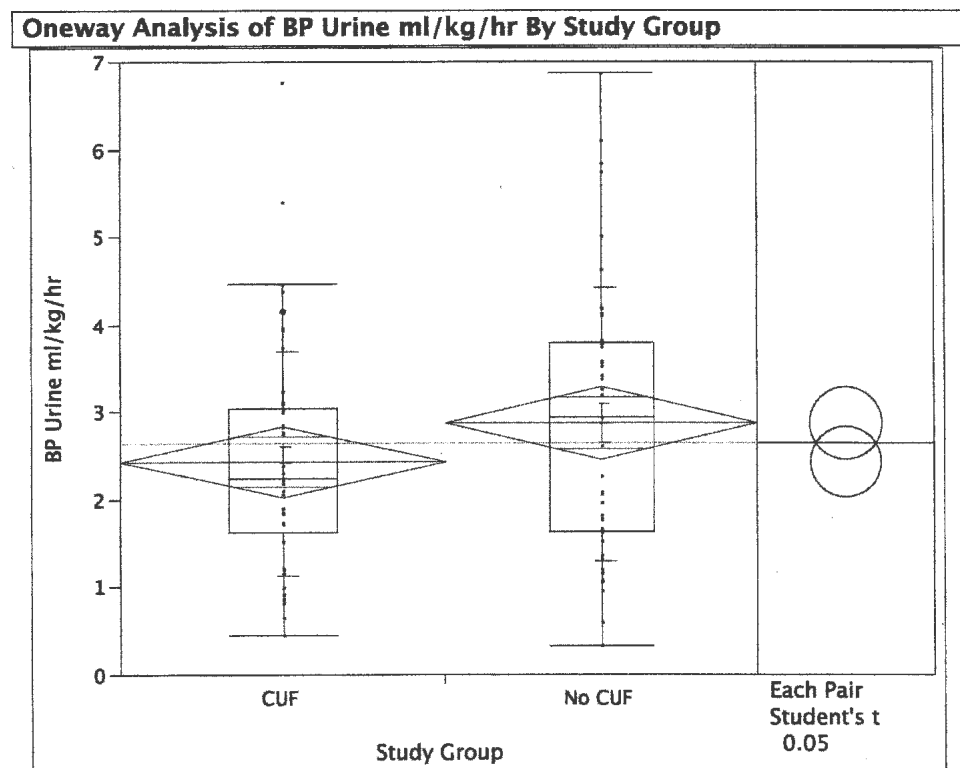


Figure 3. Final group analysis of urine flow during bypass.

Excluded Rows 4

Means and Std Deviations

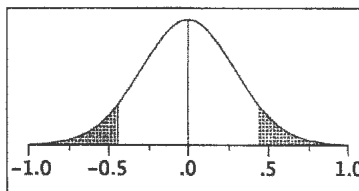
Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
CUF	49	2.42857	1.27981	0.18283	2.0610	2.7962
No CUF	47	2.86851	1.56099	0.22769	2.4102	3.3268

t Test

CUF-No CUF

Assuming unequal variances

Difference	-0.4399	t Ratio	-1.50658
Std Err Dif	0.2920	DF	88.98807
Upper CL Dif	0.1403	Prob > t	0.1355
Lower CL Dif	-1.0202	Prob > t	0.9323
Confidence	0.95	Prob < t	0.0677



volumes and indexed rates were similar in both groups. When looking at total bypass urine, the non-CUF group could only produce an average of 47 mL of additional urine despite having a mean additional fluid balance of 2261 mL. Despite a higher 24-hour urine total (an average difference of 354 mL), the non-CUF group was still 1907 mL behind during this time frame, providing a continued discrepancy in overall fluid balance in the 24-hour time frame.

Pre- and immediate postoperative creatinine and clearance values were very similar in both groups, indicating no change in renal function as a result of the use of ultrafiltration. All patients exhibited a drop in blood creatinine values after bypass, most likely because of the effects of

hemodilution in both groups. The 24-hour creatinine values were statistically higher in the CUF group. To determine if hemodilution could account for this difference alone, creatinine blood concentrations were adjusted for hemodilution and normalized to a standard blood volume. When these calculations were applied, no difference in the 24-hour values was noted. Because creatinine clearance was estimated by using the Cockcroft-Gault (C-G) equation (49,50), it has been reported to be less accurate in extreme obesity or edematous states (51). Although urine was collected in a 24-hour period, the concentration of urine creatinine was not measured, therefore precluding the use of the conventional formula. In addition, the C-G formula may underestimate glomerular filtration rate

(GFR) and conversely overestimate risk in obese patients and in patients with very low plasma creatinine levels (52). Further studies are required to more closely examine renal function in the 24- to 48-hour period with additional discrete tests on renal function. The results of this study could not reveal any significant alterations in creatinine values attributed to the use of conventional ultrafiltration.

The overall effects of cardiopulmonary bypass on renal function have been well-documented (53–55). Reduced creatinine clearance is seen in up to 11% of CPB patients, with overt renal failure requiring dialysis in 3.7% of patients (56). Although acute renal failure (ARF) requiring dialysis is associated with a mortality rate of 45%, studies examining the effects of bypass on renal function have produced conflicting results (57,58). Current evidence suggests that on-pump procedures are associated with an increased risk of developing ARF after bypass surgery (59).

A review of the literature revealed that there is no consensus regarding the complete etiology and risk factors for ARF after CPBP. It has been recently shown that the degree of hemodilution during CPB is an independent risk factor for ARF requiring dialysis, although further research is required to examine the cause-effect relationship (60). Earlier research indicated the most common etiologies for ARF after CPB were found to be acute tubular necrosis caused by inadequate oxygen delivery and renal infarction by microemboli (61,62), both consequences of hemodilution. Mild hemodilution (21–25%) may have some protective effect early in the bypass period by reducing red blood cell injury (63) and RBC trapping (64), but severe (<21%) hemodilution may increase the risk of ARF by adversely affecting renal oxygen delivery and regional blood flow.

There is a well-documented association of hemodilution with adverse outcomes after cardiac surgery (65,66) and an independent association of postoperative creatinine rise (and all creatinine markers of renal injury), with lowest hematocrit during bypass (67). Habib et al. (68) reported that all types of complications, including renal failure, were more frequent as hemodilution severity increased, particularly for hematocrit < 22%. Ranucci et al. (69) reviewed risk factors for renal dysfunction after coronary surgery and found the only determinant for both moderate and severe renal dysfunction was a low hematocrit value during CPBP. In an effort to minimize the potential adverse effects of CPBP procedures, it is apparent that we must control the extent and duration of hemodilution.

The clinician should be acutely aware of fluid flux and volume translocation throughout the bypass procedure. Close monitoring of volume additions, urine flow, and ultrafiltration rates, if applicable, should be made at frequent intervals to best assess the limits of hemodilution in

every patient. Ultrafiltration provides a safe method of aggressive fluid removal without effecting urine production during cardiac surgical procedures.

CONCLUSIONS

The adverse effects of severe hemodilution (<21%) with crystalloid volume reduction can be safely avoided through the use of continuous ultrafiltration during CPBP. Conventional ultrafiltration (CUF), early and throughout the bypass period, provides an effective means to eliminate excess volume, reduce fluid accumulation, and elevate bypass hematocrit without affecting urine production in the operative arena. This study has revealed that native bypass urine production and total operating room urine volume are not adversely affected by the use of aggressive ultrafiltration.

REFERENCES

1. Tassani P, Schad H, Winkler C, et al. Capillary leak syndrome after cardiopulmonary bypass in elective, uncomplicated coronary artery bypass grafting operations: Does it exist? *J Thorac Cardiovasc Surg.* 2002;123:735–41.
2. Sever K, Tansel SK, Basaran M, et al. The benefits of continuous ultrafiltration in pediatric cardiac surgery. *Scan Cardiovasc J.* 2004; 38:307–11.
3. Hamada Y, Kawachi K, Tsunooka N, et al. Capillary leakage in cardiac surgery with cardiopulmonary bypass. *Asian Cardiovasc Thorac Ann.* 2004;12:193–7.
4. Zhang S, Wang S, Yao S. Evidence for development of capillary leak syndrome associated with cardiopulmonary bypass in pediatric patients with homozygous C4A null phenotype. *Anesthesiology.* 2004; 100:1387–93.
5. Mojcić CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *Ann Thorac Surg.* 2001;71: 745–54.
6. Gray DT, Veenstra DL. Comparative economic analyses of minimally invasive direct coronary artery bypass surgery. *J Thorac Cardiovasc Surg.* 2003;125:618–24.
7. Stauder NI, Fenchel M, Stauder H, et al. Assessment of minimally invasive direct coronary artery bypass grafting of the left internal thoracic artery by means of magnetic resonance imaging. *J Thorac Cardiovasc Surg.* 2005;129:607–14.
8. Izutani H, Gill IS. Acute graft failure caused by an intracoronary shunt in minimally invasive direct coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2003;125:723–4.
9. Zimarino M, Gallina S, Di Fulvio M, et al. Intraoperative ischemia and long-term events after minimally invasive coronary surgery. *Ann Thorac Surg.* 2004;78:135–41.
10. Remadi JP, Marticho P, Butoi I, et al. Clinical experience with mini-extracorporeal circulation system: an evolution or a revolution? *Ann Thorac Surg.* 2004;77:2172–5.
11. Remadi JP, Rakotoarivello P, Marticho P, et al. Aortic valve replacement with the minimal extracorporeal circulation (Jostra MECC System) versus standard cardiopulmonary bypass: A randomized prospective trial. *J Thorac Cardiovasc Surg.* 2004;128:436–41.
12. Eising GP, Pfauder M, Niemeyer M, et al. Retrograde autologous priming: is it useful in elective on-pump coronary artery bypass surgery? *Ann Thorac Surg.* 2003;75:23–7.
13. Baufreton C, Brux J, Binuani P, et al. A combined approach for improving cardiopulmonary bypass in coronary artery surgery: A pilot study. *Perfusion.* 2002;17:407–13.

14. Banbury MK, White JA, Blackstone EH, et al. Vacuum-assisted venous return reduces blood usage. *J Thorac Cardiovasc Surg.* 2003;126:680–87.
15. Munster K, Andersen U, Mikkelsen J, Pettersson G. Vacuum assisted venous drainage (VAVD). *Perfusion.* 1999;14:419–23.
16. Kurusz M, Butler B. Bubbles and bypass: an update. *Perfusion.* 2004;19:S49–55.
17. Tallman RD, Dumond M, Brown D. Inflammatory mediator removal by zero balance ultrafiltration during cardiopulmonary bypass. *Perfusion.* 2002;17:111–5.
18. de Baar M, Diephuis JC, Moons KG, et al. The effect of zero-balanced ultrafiltration during cardiopulmonary bypass on S100b release and cognitive function. *Perfusion.* 2003;18:9–14.
19. Wang W, Huang HM, Zhu DM, et al. Modified ultrafiltration in paediatric cardiopulmonary bypass. *Perfusion.* 1998;13:304–10.
20. Bando K, Turrentine W, Vijay P, et al. Effect of modified ultrafiltration in high-risk patients undergoing operations for congenital heart disease. *Ann Thorac Surg.* 1998;66:821–7.
21. Friesen RH, Campbell DN, Clarke DR, Tornabene MA. Modified ultrafiltration attenuates dilutional coagulopathy in pediatric open heart operations. *Ann Thorac Surg.* 1997;64:1787–9.
22. Ungerleider RM. Effects of cardiopulmonary bypass and use of modified ultrafiltration. *Ann Thorac Surg.* 1998;65:S35–9.
23. Kiziltepe U, Uysalel A, Corapcioglu T, et al. Effects of combined conventional and modified ultrafiltration in adult patients. *Ann Thorac Surg.* 2001;71:684–93.
24. Babka R, Petress J, Briggs R, et al. Conventional haemofiltration during routine coronary bypass surgery. *Perfusion.* 1997;12:187–92.
25. Thompson LD, McElhinney DB, Findlay P, et al. A prospective randomized study comparing volume-standardized modified and conventional ultrafiltration in pediatric cardiac surgery. *J Thorac Cardiovasc Surg.* 2001;122:220–8.
26. Daggett CW, Lodge AJ, Scarborough JE, et al. Modified Ultrafiltration versus conventional ultrafiltration: a randomized prospective study. *J Thorac Cardiovasc Surg.* 1998;115:341–2.
27. Chew M. Does modified ultrafiltration reduce the systemic inflammatory response to cardiac surgery with cardiopulmonary bypass? *Perfusion.* 2004;19:S57–60.
28. Chew R, Brix-Christensen V. Effect of modified ultrafiltration on the inflammatory response in paediatric open-heart surgery: A prospective, randomized study. *Perfusion.* 2002;17:327–33.
29. Wand M, Chiu I. Efficacy of ultrafiltration in removing inflammatory mediators during pediatric cardiac operations. *Soc Thorac Surg.* 1996;61:651–6.
30. Shimp H, Shimamoto A, Sawamura Y, et al. Ultrafiltration of the priming blood before cardiopulmonary bypass attenuated inflammatory response and improves postoperative clinical course in pediatric patients. *Shock.* 2001;1(suppl 16):51–4.
31. Journois D, Pouard P, Greeley WJ, et al. Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery. Effects on hemostasis, cytokines, and complement components. *Anesthesiology.* 1994;81:1181–9.
32. Hoffmann JN, Hartl WH, Deppisch R, et al. Effect of hemofiltration on hemodynamics and systemic concentrations of anaphylatoxin and cytokines in human sepsis. *Intensive Med.* 1996;22:1360–7.
33. Chertow GM, Levy EM, Hammermeister KE, et al. Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med.* 1998;104:343–8.
34. Zanardo G, Michielon P, Paccagnella A, et al. Acute renal failure in the patient undergoing cardiac operation: prevalence, mortality rate, and main risk factors. *J Thorac Cardiovasc Surg.* 1994;107:1489–95.
35. Provenchere S, Plantefevre G, Hufnagel G, et al. Renal dysfunction after cardiac surgery with normothermic cardiopulmonary bypass: Incidence, risk factor, and effect on clinical outcome. *Anesth Analg.* 2003;96:1258–64.
36. Ostermann ME, Taube D, Morgan CJ, Evans TW. Acute renal failure following cardiopulmonary bypass: a changing picture. *Intensive Care Med.* 2000;26:565–71.
37. Corwin HL, Sprague SM, DeLaria GA, Norusis MJ. Acute renal failure associated with cardiac operations. A case-control study. *J Thorac Cardiovasc Surg.* 1989;98:1107–12.
38. Waloth BH, Albetini B. Ultrafiltration in cardiac surgery. *J Extra Corpor Technol.* 1984;16:68–72.
39. Huang H, Yao T, Wang W, et al. Continuous ultrafiltration attenuates the pulmonary injury that follows open heart surgery with cardiopulmonary bypass. *Ann Thorac Surg.* 2003;76:136–40.
40. Nagashima M, Shin'oka T, Nollert G, et al. High-volume continuous hemofiltration during cardiopulmonary bypass attenuates pulmonary dysfunction in neonatal lambs after deep hypothermic circulatory arrest. *Circulation.* 1998;98:378–84.
41. Kiziltepe U. Effects of combined conventional and modified ultrafiltration in adult patients. *Ann Thorac Surg.* 2001;71:684–93.
42. Portela F, Pensado A, Sanchez A, et al. A simple technique to perform combined ultrafiltration. *Ann Thorac Surg.* 1999;67:859–61.
43. Klineberg PL, Kam CA, Johnson DC, et al. Hematocrit and blood volume control during cardiopulmonary bypass with the use of hemofiltration. *Anesthesiology.* 1984;60:478–80.
44. Journois D, Israel-Biet D, Pouard P, et al. High-volume, zero-balanced hemofiltration to reduce delayed inflammatory response to cardiopulmonary bypass in children. *Anesthesiology.* 1996;85:965–76.
45. Wang MJ, Chiu IS, Hsu CM, et al. Efficacy of ultrafiltration in removing inflammatory mediators during pediatric cardiac operations. *Ann Thorac Surg.* 1996;61:651–6.
46. Onoe M, Magara T, Yamamoto Y, Nojima T. Modified ultrafiltration removes serum interleukin-8 in adult cardiac surgery. *Perfusion.* 2001;16:37–42.
47. Toraman F, Evrenkaya S, Yuce M, et al. Highly positive intraoperative fluid balance during cardiac surgery is associated with adverse outcome. *Perfusion.* 2004;19:85–91.
48. Koller ME, Bert J, Segadal L, Reed RK. Estimation of total body fluid shifts between plasma and interstitium in man during extracorporeal circulation. *Acta Anaesthesiol Scand.* 1992;36:255–59.
49. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31–41.
50. Vervoort G, Willems HL, Wetzels JF. Assessment of glomerular filtration rate in health subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. *Nephrol Dial Transplant.* 2002;17:1909–13.
51. Fournier A, Achard JM. Mnemotechnical note on the use of Cockcroft creatinine clearance formula for the validation of a 24-h urine collection. *Nephrol Dial Transplant.* 2000;15:1677–78.
52. Spinler SA, Nawarskas JJ, Boyce EG, et al. Predictive performance of ten equations for estimating creatinine clearance in cardiac patients. *Ann Pharmacother.* 1998;32:1275–83.
53. Weerasinghe A, Athanasiou T, Al-Ruzzeh S, et al. Functional renal outcome in on-pump and off-pump coronary revascularization: A propensity-based analysis. *Ann Thorac Surg.* 2005;79:1577–83.
54. Mangano CM, Diamondstone LS, Ramsay JG, et al. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resources utilization. *Ann Intern Med.* 1998;128:194–203.
55. Pathi VL, Morrison J, MacPhaden A, et al. Alterations in renal microcirculation during cardiopulmonary bypass. *Ann Thorac Surg.* 1998;65:993–8.
56. Zanardo G, Michielon P, Paccagnella A, et al. Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. *J Thorac Cardiovasc Surg.* 1994;107:1489–95.
57. Ascione R, Lloyd CT, Underwood MJ, et al. On-pump versus off-pump coronary revascularization: evaluation of renal function. *Ann Thorac Surg.* 1999;68:493–8.
58. Gamoso MG, Phillips-Bute B, Landolfo KP, et al. Off-pump versus on-pump coronary artery bypass surgery and post-operative renal dysfunction. *Anaesth Analg.* 2000;91:1080–4.
59. Stallwood MI, Grayson AD, Mills K, Scawn ND. Acute Renal Failure in Coronary Artery Bypass Surgery: Independent Effect of Cardiopulmonary Bypass. *Ann Thorac Surg.* 2004;77:968–72.

60. Karkouti K, Beattie WS, Wijeyesundera DN, et al. Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J Thorac Cardiovasc Surg.* 2005;129:391–400.
61. Yeboah ED, Petrie A, Pead JL. Acute renal failure and open heart surgery. *BMJ.* 1972;1:415–8.
62. Krian A. Incidence, prevention, and treatment of acute renal failure following cardiopulmonary bypass. *Int Anesthesiol Clin.* 1976;14:87–101.
63. Chen Y, Berglin E, Belboul A, Roberts D. A mathematical analysis of hemorheological changes during heart valve replacement. *J Cardiovasc Surg (Torino).* 2000;41:37–43.
64. Hellberg PO, Bayati A, Kallskog O, Wolgast M. Red cell trapping after ischemia and long-term kidney damage. Influence of hematocrit. *Kidney Int.* 1990;37:1240–7.
65. Defoe G, Ross C, Olmstead EM, et al. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. *Ann Thorac Surg.* 2001;71:769–76.
66. Fang WC, Helm RE, Krieger KH, et al. Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. *Circulation.* 1997;96(Suppl 2):194–9.
67. Swaminathan M, Phillips-Bute BG, Conlon PJ, et al. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. *Ann Thorac Surg.* 2003;76:784–92.
68. Habib RH, Zacharias A, Schwann TA, et al. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: Should current practice be changed? *J Thorac Cardiovasc Surg.* 2003;125:1438–50.
69. Ranucci M, Pavesi M, Mazza E, et al. Risk factors for renal dysfunction after coronary surgery: The role of cardiopulmonary bypass technique. *Perfusion.* 1994;9:319–26.