Outcomes and Biochemical Parameters Following Cardiac Surgery: Effects of Transfusion of Residual Blood Using Centrifugation and Multiple-Pass Hemoconcentration

Erick McNair, PhD, MSc, CCP, FICA,*† William McKay, MD, FRCPC,‡ Abdul Mohamed Qureshi, MSc, FICA,† Mark Rosin, MSc(s), CCP, CSCP,* Jon Gamble, MD, FRCPC,‡ Greg Dalshaug, MD, FRCSC,* Taras Mycyk, MD, FRCSC,* and Kailash Prasad, PhD, MD, FRCPC§

Objectives: **To determine whether or not there was a significant difference between the methods of centrifugation (CF) and multiple-pass hemoconcentration (MPH) of the residual cardiopulmonary-bypass volume in relation to biochemical measurements and patient outcomes.**

Design: **Prospective, randomized, and controlled.**

Setting: **Conducted at a western Canadian tertiary care hospital.**

Participants: **Consisted of 61 consecutive male and female patients from ages 40 to 80 who were scheduled for cardiac surgery with cardiopulmonary bypass.**

Interventions: **Either the centrifugation or multiple-pass hemoconcentration method was used to process the residual blood from the cardiopulmonary bypass circuit.**

Results: **The 12-hour postoperative levels of serum hemoglobin were not significantly different in the centrifugation group as compared to the multiple-pass hemoconcentration group. However, the serum levels of total protein and albumin were significantly higher in the multiple-pass hemoconcentration group as compared to the centrifugation group. Additionally, after 12-hours postoperatively, the serum fibrinogen and platelet counts were significantly higher in the multiple-pass hemoconcentration group as compared to those of the centrifugation group.**

The allogeneic product transfusion index and the chest-tube blood drainage indices were lower in the multiple-pass hemoconcentration group as compared to the centrifugation group.

Conclusion: **Although the CF method provided a product in a shorter turnaround time, with consistent clearance of heparin, the MPH method trended towards enhanced biochemical and clinical patient outcomes over the 12-hour postoperative period.**

KEY WORDS: centrifugation, multiple-pass hemoconcentration, allogeneic transfusion, chest tube drainage

MORE THAN 500,000 CARDIAC PROCEDURES are performed in North America every year,[1] with approximately 40-90% receiving allogeneic product transfusions. The transfusion rates related to cardiac surgery range from about 40-90% for red blood cells (RBCs) and up to 90% for fresh frozen plasma (FFP) and platelets,[2] with 20% of recipients consuming 80% of the transfused products.[2] The probability of critically ill patients experiencing a major adverse event from a blood transfusion ranges from 2.5%-40%.[3,4] Complications arising from a blood transfusion include but are not limited to acute transfusion reactions, transfusion-related lung injury, incorrect component transfusion, hemolysis, infections, storage errors, and anti-D administration errors.[4] The implication is that the higher the transfusion rate, the higher the complication rate and, thus, the more benefit is derived from reducing/eliminating transfusion requirements in cardiac surgical patients. Differing methods of the salvage of the residual cardiopulmonary bypass (CPB) circuit volume may influence patient blood product transfusion requirements over the 12-hour postoperative period.[5,6] Consequently, changes in transfusion requirements may impact patient outcomes during the 12-hour postoperative recovery period.

Current practice in cardiac surgery requiring CPB dictates the salvage of the residual circuit volume at the end of the procedure into an autologous recovery system. This system uses the centrifugation method (CF) to separate whole blood into red blood cells (RBCs) and plasma components.[7] The RBCs are washed with normal saline and re-infused into the patient while the plasma portion is discarded. Possible disadvantages of this technique include up-regulation of the systemic inflammatory response,[8,9] increased risk of fat emboli,[10] and the loss of plasma proteins including albumin, coagulation factors, and hormones.[7,10]

Ultrafiltration (hemoconcentration) of the residual volume from the CPB circuit utilizing a device called an "ultrafiltrator" (hemofilter) represents an alternative technique of autologous recovery.[11,12] Similar to the filter used during dialysis, a hemofilter removes excess plasma water while preserving plasma protein and coagulation factors thereby minimizing allogeneic blood product use.[12,13] As it concentrates plasma protein, it increases colloid osmotic pressure (COP), reducing the risk of edema.[14,15] Multiple-pass hemoconcentration (MPH) differs from conventional hemoconcentration by passing blood through the hemofilter several times, thereby enhancing the effect of blood concentration.[11,12]

The preservation of the serum protein concentration, specifically serum albumin, may have advantages, including reduced interstitial fluid accumulation and decreased fluid administration during the postoperative period.[15-18] Several clinical conditions often present in cardiac surgical patients increase the transvascular escape rate of albumin. These include the use of CPB,

*From the *Departments of Surgery, †Pathology and Laboratory Medicine, and ‡Anesthesiology and Pain Management, and §Physiology, College of Medicine, University of Saskatchewan and Royal University Hospital, Saskatoon, SK, Canada.*

Address reprint requests to Erick McNair, PhD, MSc, CCP, FICA, College of Medicine of Saskatchewan and Royal University Hospital, Department of Surgery and Department of Pathology and Laboratory Medicine, 103 Hospital Drive, Room 2646, Saskatoon, SK, Canada S7N OW8. E-mail: erick.mcnair@usask.ca

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hypertension, fluid overloading, inflammation, ischemia/reperfusion, congestive heart failure, and diabetes.[15] The use of MPH also enhances preservation of clotting factors, the loss of which could negatively impact patient recovery during the 12-hour postoperative recovery period.[19-21]

The main objective of this study was to determine which of the two methods for the recovery of the residual CPB volume was better at enhancing overall patient outcomes during the 12-hour postoperative period. The means used to carry out this objective were the comparative determination of biochemical/hematologic parameters such as serum hemoglobin (Hb), albumin (ALB), total protein (TP), clotting factors, and markers of inflammation and the secondary outcome parameters previously described.

MATERIALS AND METHODS

The sample population consisted of 61 consecutive male and female patients from 40 to 80 years old scheduled for elective or urgent cardiac surgery with CPB. All of the subjects signed a written informed consent to participate in this study.

Exclusion criteria included (1) emergent cardiac surgery, (2) history of severe liver or kidney dysfunction, (3) anemia, (4) cardiogenic shock, (5) cardiomyopathy, (6) redo-cardiac procedures, (7) history of stroke (8) history of transient ischemic attacks, and (9) preoperatively documented coagulopathies.

With the University Research Ethics Committee approval, patients scheduled for elective or urgent cardiac surgery with CPB were recruited. Patients were assigned to a CF or MPH group according to a computer-generated random number table. Opaque envelopes containing this information were opened when the CPB circuit was set up, and the randomly selected CF or MPH circuit then was incorporated into the CPB circuit.

This study was a prospective, randomized, controlled trial that comprised two groups. It was blinded to the surgeons, operating room staff, ICU staff, and lab personnel. The perfusionist was not blinded for clinical necessity. Due to the inability of the hemofilter to remove all circulating heparin and for the sake of patient safety, the anesthesiologist was not blinded because of the potential need for additional protamine to be administered.

The two groups were as follows: Group I ($n = 31$), the control group, the residual volume underwent centrifugation (CF); and Group II ($n = 30$), the test group, the residual volume underwent multiple-pass hemoconcentration (MPH). Standard procedures were followed during cardiac surgery, and only the salvage of the residual volume of blood in the CPB circuit was affected.

The conduct of anesthesia was left to the discretion of the attending anesthesiologist and generally was based on a standard protocol for cardiac surgery patients. Target mean arterial pressure and heart rate were within 20% of the mean baseline values. Hemodynamic control was provided by modification of the concentration of the inhalation anesthetic or intravenous vasoactive drugs and/or volume repletion. A dose of unfractionated heparin was determined by the Medtronic heparin management system's (HMS) heparin dose-response test (Medtronic, Minneapolis, MN) and administered at the direction of the attending surgeon. Activated coagulation time (ACT) was measured and ensured to be greater than 480 seconds prior to the initiation of CPB. All patients also received 2 grams of intravenous tranexamic acid after heparinization. In coordination with the surgeon, the anesthesiologist administered FFP, platelets and cryoprecipitate based upon the presence of a coagulopathy or nonsurgical bleeding as determined by thromboelastography (TEG), HMS, and complete blood count (CBC).

A Sorin heart-lung machine (Sorin, Munich, Germany) roller pump was used with flows of 2.4 to 2.6 L/min/m^2 in the non-pulsatile setting. The oxygenator used was an Affinity with Trillium (polymer with heparin) coating with a Trillium-coated affinity twenty-micron arterial line filter (Medtronic, Minneapolis, MN). The extracorporeal circuit tubing was made by Sorin S5 with Physio (phosphorylcholine) (Sorin, Mirandola, Italy) coating. Circuits were flushed with carbon dioxide prior to priming. The prime consisted of Plasma-Lyte A (Baxter, Mississauga, ON, Canada), Voluven (Fresenius Kabi, Bad Homburg, Germany), sodium bicarbonate, mannitol, and heparin.

Heparin dosing was determined as described in the previous section. ACT during CPB were kept above 480 seconds while the heparin concentration was maintained at or above 300 u/kg through blood analysis with the HMS.

Cardiac activity was arrested with an induction dose of warm blood cardioplegia followed by intermittent cold doses for the duration of the aortic cross-clamp time. Blood gases, electrolytes, metabolites, and oximetry were monitored every 30 minutes via an 815 Flex ABL analyzer (Radiometer America Inc, Westlake, OH). During the CPB period all patients regardless of age/sex with a hemoglobin less than 70 g/L were transfused with RBCs.

Before separation from CPB, preload was optimized, and an infusion of epinephrine, dopamine, norepinephrine or phenylephrine alone or in combination was used to maintain a systolic blood pressure of greater than 110 mmHg after CPB. Intravenous nitroglycerin was administered as needed.

All patients had chest tubes placed in the anterior mediastinum (9 mm Mediastinum Drain, Axiom Medical Inc, Torrance, CA.), and the posterior pericardial (32 Fr Thoracic Drain, Axiom Medical Inc, Torrance, CA) cavity. These chest tubes were connected to a sterile system (Oasis Dry Suction, Atrium Inc, Hudson, NH) that drained shed blood over the 12-hour postoperative period.

Circulating heparin was reversed by an HMS-determined protamine dose after disconnection from CPB. All patients were transported to the intensive care unit, intubated, and sedated at the completion of the procedure.

Recovery of the residual CPB volume with the CF method used a Medtronic Autolog™ Autotransfusion system (ATS) (Medtronic Inc, Minneapolis, MN). After aortic cannula removal, the sterile end of the vent line was connected to the luer port of the arterial cannula, and the opposite end was connected to the cardiotomy reservoir of the ATS. The residual CPB circuit then was flushed antegrade with Plasma-Lyte® solution to the ATS reservoir. The bidirectional automated fluid pump of the ATS has a maximum flow of up to 600 mL/min and a centrifugation rate of up to 10,000 RPM (± 5%). The packed RBC's are washed with 0.9% NaCl and recovered into a transfusion bag, which was connected to an intravenous anesthesia catheter for infusion as needed. The CF method processed the residual CPB volume in approximately 5-7 minutes, with a mean volume and standard error of the mean (SEM) of 648.36 ± 25.6 mL.

Recovery of the residual CPB volume with the MPH method used a Sorin hemofilter (Milan, Italy) and Medtronic 20-micron cardiotomy reservoir (Milan, Italy). Following aortic decannulation, the vent line was connected to the luer on the arterial cannula while the other end was connected to the cardiotomy reservoir of the hemoconcentration system. The CPB circuit was flushed antegrade with Plasma-Lyte® solution into the reservoir of the hemoconcentration system. MPH via a roller head pump at 250-300 mL/min facilitated the removal of crystalloid under low continuous negative pressure. As determined by the perfusionist following standard protocol, MPH was discontinued when the desired pressure and hemoglobin were achieved. The MPH method processed the residual CPB volume in approximately 10-15 minutes, with a mean volume of 731 ± 54.72 mL. The volumes of processed blood from the two methods were not clinically or statistically different.

Fifteen milliliters of blood for the measurement of biochemical parameters were drawn at the following time intervals: (1) Baseline (after radial arterial catheter insertion) drawn from patient, (2) Hemodilution, drawn from manifold of the circuit of the heart-lung machine after 10 minutes on CPB, (3) Post-Method (after method was complete) drawn directly from the salvaged bag of blood), and (4) 12-Hours postoperatively in the ICU (drawn from patient).

The hourly doses of the following inotropic and vasoactive medications were recorded for the first 12 hours after postoperative admission to the ICU: dopamine, dobutamine, epinephrine, norepinephrine, milrinone, vasopressin, and phenylephrine. The vasoactive-inotrope score (VIS) was calculated as follows: dopamine dose (ug/kg/min) + dobutamine dose (ug/kg/min) + 100 × epinephrine dose (ug/kg/min) + 10 × milrinone dose (ug/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (ug/kg/min) + 10 × phenylephrine dose (ug/kg/min).

The biochemical parameters measured from the serum were as follows: hemoglobin and hematocrit (Radiometer ABL Flex 815), total protein and fibrinogen (Roche Cobas 6000), albumin (Roche Cobas 6000), white blood cells and platelet count (Celldyne 4000), clotting function (Haemonetics Thromboelastograph, TEG®), creatinine, and hs-C-reactive protein (Beckman-Coulter DXE 800). The estimated creatinine clearance (eC_{Cr}) was calculated based upon the Cockcroft-Gault formula.[22] Tumor necrosis factor-alpha (TNF-α) and soluble receptors for advanced glycation end-product (sRAGE) were measured via enzyme–linked immunosorbent assay (ELISA) using commercially available kits (Quantikine, Human sRAGE Immunoassay, R&D Systems, Minneapolis, MN).

The primary outcome variables measured were the levels of serum hemoglobin and total protein (TP) in patients after 12 hours postoperatively in the ICU following transfusion of blood processed with either the CF or MPH method. The secondary outcome variables were the effects of transfusion of blood processed by either method on patients' chest tube drainage, markets of inflammation, volume of allogeneic transfusion, ventilation time, length of stay in the ICU, indicators of kidney function, and vasoactive inotrope score.

Statistical analyses were performed utilizing the Statistical Program for the Social Sciences (SPSS) version 13.0 (SPSS Inc, Chicago, IL) and SAS (v 9.3; SAS Cary, NC). Sample size was calculated to ensure 80% power of a 2-sided Satterthwaite t-test at an alpha level of 5% for the detection of a minimum 11-g/L difference between treatment groups in the average subject's change in hemoglobin value from dilution to the postoperative period. Calculated from previously published raw data, mean changes of 23 g/L and 34 g/L were expected for the CF and MPH groups, respectively, with larger standard deviation of the two groups at 10.4 g/L being employed.[23]

The authors performed Student's t-test for comparisons made at a single time point and repeated measure regression analysis to account for correlation between repeated measurements. Any characteristics found to be statistically significantly different between the groups post-randomization were included in the model to account for their potential confounding. The level of significance was set at 0.05 (two-tailed). The results were expressed as mean ± standard error of the mean (SEM).

RESULTS

Although the design of the study was prospective and randomized, there were significant imbalances in the baseline weight of the two groups due to chance alone (Table 1). The baseline weight (76 ± 2.3 *v* 88.1 ± 3.7 kg) of the CF group was significantly less than that of the MPH group ($p = 0.001$). Upon considering this difference in the sizes of the patients, the authors introduced the chest tube drainage index (volume of chest tube drainage divided by the body surface area) and the allogeneic transfusion index (volume of allogeneic transfusion divided by the body surface area). These calculations allowed a comparable way to evaluate patients of differing sizes. Moreover, patients with a lower body weight may be at an increased risk for transfusion. Given that the CF group had a lower mean weight and were sicker than those of the MPH group, as determined by the EuroSCORE II, they may have had an inherently increased risk of transfusion.

The patients in the CF group had significantly ($p = 0.024$) higher EuroSCORE II values as compared to those of the MPH group (6.2 ± 1.01 *v* 3.5 ± 0.37). There were no significant differences between the two groups in terms of age, gender, smoking status, CPB time, cross-clamp time, body mass index (BMI), or type of procedure.

Estimated starting/baseline hemoglobin values for CF and MPH were 120.83 g/L and 120.76 g/L, respectively (no significant difference between them, $p = 0.97$). HB increased significantly by 0.83 g/L/hour on average for the CF group ($p < 0.0001$) and 0.66 g/L/hour on average for the MPH group ($p = 0.0005$). However, the slope difference was not significantly different between them ($p = 0.50$). Weight and EuroSCORE II were not significant in predicting a hemoglobin value (Table 2).

Estimated starting/baseline albumin values for CF and MPH were 24.73 g/L and 25.88 g/L, respectively (no significant difference between them, $p = 0.27$). ALB decreased significantly by 0.26 g/L/hour on average for the CF group ($p = 0.0002$) and increased significantly 0.31 g/L/hour on average for the MPH group ($p < 0.0001$). Slope difference was significantly different between them ($p < 0.0001$). Weight and EuroSCORE II were not significant.

Estimated starting/baseline total protein values for CF and MPH were 48.75 g/L and 53.56 g/L, respectively (significant difference between them, $p = 0.001$). TP decreased significantly by 0.50 g/L/hour on average for the CF group ($p < 0.0001$). TP did not change significantly for the MPH group ($p = 0.27$). Slope difference was significantly different between them ($p = 0.0004$). EuroSCORE II was significant ($p = 0.01$). An incremental increase of one EuroScore II resulted in an average increase of TP by 0.60 g/L. Weight was not significant (Table 2).

The parameters measured to determine kidney function after 12 hours in the ICU are summarized in Table 3. There were no significant differences between the 2 groups for creatinine and estimated creatinine clearance. The values for urine outputs were significantly ($p = 0.013$) lower in the CF group as compared to the MPH group (1882.2 ± 108.6 *v* 2386.9 ± 110 mL/12 h) although the CF group had a higher fluid intake (4165 ± 134 *v* 3780 ± 240 mL/12 h; ($p = 0.084$). The cumulative balance was also significantly higher ($p = 0.001$) in the CF group as compared to the MPH group (929 ± 65.9 *v* 554 ± 46.3 mL/12h) (Table 4).

The parameters measured that were involved in clotting function after 12 hours in ICU are summarized in Table 3. There was no significant difference between the 2 groups in the parameters of the TEG®. However, at 12 hours, the serum levels of fibrinogen (3.5 ± 0.13 *v* 2.6 ± 0.12 g/L; $p < 0.001$) and platelets (163.2 ± 8.04 *v* 142.7 ± 7.23 × 10^9/L; $p = 0.042$) were significantly higher in the MPH group as compared to the CF group, respectively. However, there was no significant difference between the two groups at baseline.

The measured markers of inflammation after 12 hours in the ICU are summarized in Table 4. There was no significant

Table 1. Demographic Characteristics

Characteristics	CF Group (n = 31)	MPH Group (n = 30)	p Value
Age (years)	65 ± 2.2	67 ± 1.7	NS
Weight (kg)	76 ± 2.3 (Baseline)	88 ± 3.7 (Baseline)	0.001
	81.1 ± 3.4 (12-h)	89 ± 2.7 (Baseline)	NS
	Baseline *v* 12-h	—	0.009
	—	Baseline *v* 12-h	NS
Gender (M/F)	24M/7F	23M/7F	NS
Smoking Status	Ex-smokers	Ex-smokers	—
CPB Time (min)	128 ± 8.8	116 ± 5.7	NS
X Clamp (min)	94 ± 4.7	92.7 ± 5.3	NS
EuroSCORE II	6.2 ±1.01	3.5 ± 0.37	0.024
BMI (kg/m^2)	28 ± 0.8	30 ± 0.93	NS
Type of Procedure	CABG = 22	CABG = 20	NS
	Valve/CABG = 5	Valve/CABG = 5	
	Valve = 4	Valve = 5	

NOTE: Results are expressed ± standard error of the mean (SEM).

difference between the 2 groups in any of the measured variables associated with inflammation.

The outcome parameters measured after 12 hours in ICU are also summarized in Table 4. At 12 hours, there were no significant differences between the 2 groups for chest tube drainage, chest tube drainage index, ventilation time, length of stay in the ICU, volume of allogeneic transfusion, and allogeneic transfusion index. However, the vasoactive-inotrope scores from the patients in the CF group were significantly higher (14.13 ± 3.6 *v* 3.42 ± 0.59; p = 0.006) in comparison to those of the MPH group, respectively.

DISCUSSION

Using repeated measures analysis, it was demonstrated that there was a significantly increasing slope in both groups, suggesting a significant increase in their Hb over the 12-hour period. However, there was no significant difference in the amount of rise experienced between the 2 methods (p = 0.50). Although there was a significant difference between the two groups in terms of EuroSCORE II and weight, they were not significant predictors of hemoglobin in the model. The similarity in the rise of Hb of the CF group to that of the MPH group may be related to the CF group extravasation of fluid into the interstitium, thereby concentrating the plasma. This study demonstrated the CF group's higher fluid intake, cumulative balance, and lower urine output as compared to the MPH group.

Although plasma proteins represent only 7% of the total plasma volume, serum albumin constitutes 50-60% of the total protein concentration and maintains 80% of the colloid osmotic pressure.[15] A low serum albumin concentration during critical illness is correlated with poor outcomes.[24-26] The normal transcapillary extravasation rate for albumin increases by 100% following cardiac surgery[22] due to increased surgical stress,[27,28] resulting in increased capillary leakage into the extravascular space/compartment.[29] The present study has shown that at 12 hours postoperatively, the patients from the MPH group had a significantly (p = 0.001) higher serum albumin 30.2 ± 1.5 *v* 24.1 ± 0.54 g/L) and total protein (p = 0.03) concentration (52 ± 1.3 *v* 45.8 ± 1.5 g/L) as compared to those patients who received blood salvaged through the CF method. Cardiac surgical patients may benefit from having higher albumin levels during the postoperative period to offset surgical stress and capillary leakage of proteins, inflammatory cells, and large volumes of fluid into the interstitial compartment.[30]

The serum levels of fibrinogen (3.5 ± 0.13 *v* 2.6 ± 0.12 g/L; p < 0.001) and platelets (163.2 ± 8.04 *v* 142.7 ± 7.23 x 10^9/L; p = 0.042) were significantly higher in the MPH group as compared to the CF group, respectively. The reference range of serum fibrinogen is 1.5-4.0 g/L.[31] The MPH method produced serum fibrinogen levels at the high end of the normal range. Higher levels of fibrinogen within the MPH group may have contributed to less bleeding and lower chest-tube drainage as compared to those of the CF group. After 12 hours postoperatively in the ICU, the values for chest tube drainage were lower in the MPH group (733.8 ± 44.8) as compared to the CF group (892 ± 101.7) but not significantly (p = 0.31) different. The chest-tube drainage index showed a trend

Table 2. Repeated Measures model for Hemoglobin, Albumin and Total Protein

Covariates	Estimate (S.E.[a])	p Value
Repeated Measure Model for Hemoglobin		
Intercept (CF)	120.83 (6.46)	<0.0001
Intercept (MPH)	120.76 (6.74)	<0.0001
Time*CF	0.83 (0.18)	<0.0001
Time*MPH	0.66 (0.18)	0.0005
Weight	−0.08 (0.07)	0.28
EuroScore	−0.34 (0.45)	0.45
Repeated Measure Model for Albumin		
Intercept (CF)	24.73 (2.69)	<0.0001
Intercept (MPH)	25.88 (2.81)	<0.0001
Time*CF	−0.26 (0.06)	0.0002
Time*MPH	0.31 (0.06)	<0.0001
Weight	−0.03 (0.02)	0.24
EuroScore	0.17 (0.18)	0.38
Repeated Measure Model for Total Protein		
Intercept (CF)	48.75 (3.59)	<0.0001
Intercept (MPH)	53.56 (3.74)	<0.0001
Time*CF	−0.50 (0.11)	<0.0001
Time*MPH	0.13 (0.12)	0.27
Weight	−0.06 (0.03)	0.09
Euro Score	0.60 (0.25)	0.01

[a]Standard Error.

Table 3. Kidney Function and Clotting Factors

	CF Group (n = 30)	MPH Group (n = 31)	p Value
Renal Function			
Estimated Creatinine Clearance (mL/min/1.73m^2)	96.86 ± 6.3	98.11 ± 5.5	0.330
IV Fluid Intake (mL)	4165 ± 134	3780 ± 240	0.084
Urine Output (mL)	1882.2 ± 108.6	2386.9 ±110	0.013
Culmulative Balance (mL 12-h)	929 ± 65.9	554 ± 46.3	0.001
Clotting Factors			
Fibrinogen (g/L)	2.6 ± 0.12	3.5 ± 0.13	0.001
Platelets (× 109/L)	142.7 ± 7.23	163.2 ± 8.04	0.042

NOTE: Results are expressed ± standard error of the mean (SEM).

(361.44 ± 23.1 *v* 483.59 ± 56.4; p = 0.053) towards lower chest tube drainage in the MPH group as compared to the CF group, respectively (Table 4).

Patients in the CF group had higher volumes (1110 ± 204.6 *v* 630 ± 96.1 mL/12 h; p = 0.061) of allogeneic transfusions as compared to those of the MPH group, respectively. The products transfused were primarily platelets and FFP. The allogeneic product transfusion index showed a trend (626.5 ± 98 *v* 307.5 ± 94.9; p = 0.050) towards larger volumes of allogeneic transfusion in the CF group as compared to the MPH group, respectively. Overall, at 12 hours postoperatively, the MPH group demonstrated the following numerical differences: (a) a higher concentration of serum albumin and clotting factors (still within normal range), (b) a lower volume of chest tube drainage, (c) a lower chest tube drainage index, (d) a lower volume of allogeneic transfusion, and (e) a lower allogeneic transfusion index as compared to the CF group. However, only albumin and clotting factors reached statistical significance.

The data from the TEG showed no significant difference in the parameters measured at 12 hours postoperatively. Three patients (10%) from the MPH group experienced excessive postoperative bleeding within an hour of arriving in the ICU, requiring RBC transfusion. These 3 patients had a TEG® and Hepcon immediately upon bleeding. The TEG® demonstrated a prolonged R-time when analyzed with kaolin alone as compared to analysis with kaolin and heparinase, suggesting that bleeding was due to an inadequate clearance of heparin in the residual circuit volume by the hemofilter. The Hepcon also verified the existence of circulating heparin. Subsequently, these three patients received 50 mg of protamine to reverse any residual heparin. Inadequate and/or inconsistent clearance of heparin by the hemofilter may be a disadvantage of this system. The authors recommend performance of a TEG® and HMS within a half hour of patients' arrival in the ICU for institutions considering the MPH system.

Intravenous fluid intake and cumulative balance was higher in the CF group as compared to the MPH group after 12 hours. However, the plasma albumin and total protein levels were lower in the CF group as compared to the MPH group, which may have contributed to a lower COP and, thus, the need for infusion of more fluid to maintain pressure parameters (systolic >110 mmHg and filling pressures at or above 8 mmHg). This data is consistent with the findings of Verheij et al in 2005[31] who reported that the plasma COP increase in colloid-treated patients was effective in keeping fluid within the vascular compartment and prevention of fluid extravasation into the interstitial space. The values for urine outputs after 12 hours in the ICU were significantly (p = 0.013) lower in the CF group as compared to the MPH group although the CF group had a higher fluid intake. Estimated creatinine clearance was not significantly different at 12 hours postoperatively, suggesting no difference in kidney function at that time interval. These data suggest that the higher fluid intake, reduced urine output, and lower serum protein concentration may have resulted in fluid extravasation into the interstitial compartment of patients in the CF group.

It is of interest that at the 12-hour interval in the ICU, there was a significant 7% increase in the weight (76 ± 2.3 *v* 81.1 ± 3.4 kg) of the patients in the CF group from their baseline values (p = 0.009). Taken altogether, these data show a greater fluid intake and a rise in weight, which may be due to the higher fluid intake requirements in the patients in the CF group as compared to those in the MPH group, implying loss of some fluid into the interstitial space, leading to tissue edema.[29]

Vasoactive medications typically are started in the operating room at the discretion of the cardiac surgeon and anesthesiologist based on individual patient characteristics, including age, surgical procedure, transesophageal echocardiographic findings, and physiologic status. These medications are adjusted further after arrival in the ICU under the direction of the ICU medical team. In order to compare the effects of the study interventions on use of postoperative vasoactive medications, the authors used a modified vasoactive inotrope score. The original inotrope score was developed by Wernovsky et al[32] to compare the inotropic requirements of pediatric patients after surgical treatment of congenital heart disease. Subsequently, the inotrope score and several modifications have been used by numerous investigators; however, to date, it only has been applied to pediatric patients.[31-36] To the authors' knowledge, this is the first use of a prospective vasoactive inotrope score in adult cardiac patients to assess the likelihood of a poor postoperative outcome. The vasoactive inotrope scores from the patients in the CF group were significantly higher (14.13 ± 3.6 *v* 3.42 ± 0.59; p = 0.006) in comparison to

Table 4. Biochemical & Clinical Outcome Parameters

PARAMETER (12-H ICU)	CF Group (n = 31)	MPH Group (n = 31)	p Value
Inflammatory Mediators			
TNF-α (pg/mL)	6.38 ± 0.38	6.50 ± 0.47	0.831
hs-CRP (mg/L)	78.5 ± 6.5	77.4 ± 7.0	0.905
sRAGE (pg/mL	726.3 ± 26.7	773.3 ± 40.3	0.326
Other Outcome Parameters			
Ventilation Time (hours)	14.9 ± 0.72	14.3 ± 0.76	0.530
Length of Stay (hours)	20.14 ± 0.77	19.84 ± 1.5	0.850
Chest Tube Drainage (mL)	898.5 ± 102.3	746.6 ± 49.68	0.188
Chest Tube Drainage Index (ml/m2)	483.5 ± 56.73	366.6 ± 25.87	0.070
Vasoactive Inotrope Score	13.72 ± 3.49	3.48 ± 0.65	0.007
Allogeneic Transfusion (mL)	1110 ± 204.6	630 ± 96.1	0.061
Allogeneic Transfusion Index (ml/m2)	626.5 ± 98	307.5 ± 55	0.050

NOTE: Results are expressed ± standard error of the mean (SEM).

those of the MPH group, respectively, possibly indicating an increased risk for adverse outcomes.[37] Higher levels of vasoactive inotrope use and lower plasma protein levels, along with greater fluid administration in the CF group to maintain blood pressure parameters, suggest a poorer physiologic status during the immediate postoperative period for the patients in the CF group as compared to those in the MPH group. However, there are no other studies to which this data can be compared.

The patients in the CF group had significantly ($p = 0.024$) higher EuroSCORE II values as compared to those of the MPH group (6.2 ± 1.01 *v* 3.5 ± 0.37), suggesting an increased risk in surgical cardiac mortality.[38,39] It is likely that because the CF group was at a greater risk for serious complications, the increased use of inotropes[40] and IV fluids to maintain hemodynamic stability could be related to the higher vasoactive inotrope score. Although the CF group had a higher vasoactive inotrope and EuroSCORE II, there was no significant difference in mortality rate between the two groups at thirty days. At 30 days' follow-up, the mortality rate for all patients in the study was 0%.

At 12 hours, there was no significant difference in the levels of measured inflammatory markers, time to extubation, or length of stay in the ICU between the CF group and the MPH group. However, the CF group had significantly poorer outcome variables of urine output, cumulative balance, and increase in weight after 12 hours in the ICU as compared to the MPH group.

There are some limitations in this study: (1) The sample size was calculated for the primary endpoint of Hb. It is possible that the remaining endpoints for the study were not adequately powered, and statistically significant differences may not have been recognized;[2] (2) Data from the viscous hemostasis assay most likely did not show any significant difference between the two methods because of the time interval drawn (12 hours postoperatively). In retrospect, a TEG® and HMS assay performed within a ½ hour of patient arrival in ICU or at the time of any chest tube loss greater than 150 mL/hour may have revealed clotting abnormalities earlier and reduced the transfusion risk;[3] (3) To date, the authors are unaware of any other research group having applied the inotrope score/vasoactive inotrope score to adult patients following cardiac surgery with CPB. This novel data may be controversial, and further validation is needed;[4] and (4) Inconsistent clearance of heparin cleared by the hemofilter.

CONCLUSION

The measured clotting parameters (serum fibrinogen and platelets) were significantly higher in the MPH group as compared to the CF group. These finding are consistent with the MPH group outcome parameters, illustrating a lower-trend allogeneic transfusion index and chest tube drainage index after 12 hours postoperatively in the ICU. Moreover, the MPH method provides significant preservation of serum albumin and total serum protein concentrations that may have contributed to the reduced fluid weight gain, decreased tissue edema, lower cumulative balance, and a lower vasoactive inotrope score as compared to the CF group. Although the CF method may provide a product within a shorter turnaround time, with consistent clearance of heparin, the MPH method suggests enhanced biochemical and clinical patient outcomes over the 12-hour postoperative period. Future studies could investigate whether there is a difference in outcomes between MPH of the residual pump volume and modified ultrafiltration of patients of similar weight undergoing cardiothoracic surgery.

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