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Effects of Modified Ultrafiltration on Coagulation as Measured by the Thromboelastograph

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Abstract: Hemodilution during cardiopulmonary bypass (CPB) continues to be a cause of morbidity associated with coagulation dysfunction, bleeding, and allogeneic blood transfusion. Clot formation and strength have been shown to impact bleeding and transfusions. Strategies to reduce hemodilution may be negated based on the course of the cardiac procedure itself. Modified ultrafiltration (MUF) is commonly used in pediatric cardiac surgery; however, it is not well accepted in adult surgery. This study aimed to evaluate clot formation and strength, bleeding, and transfusions in adult subjects undergoing MUF. Nineteen subjects having primary coronary artery bypass, aortic, or mitral valve surgeries were recruited and randomized to having MUF ($n = 10$) or no-MUF ($n = 9$) performed after the termination of CPB. Five time points for data collection were designated: T1, baseline/induction; T2, termination CPB; T3, post-MUF; T4, post-protamine; T5, 24 hours postoperative. Subjects randomized to MUF had 1505 ± 15.8 mL of effluent removed, and no-MUF subjects had the CPB remnants processed with a cell salvage device. There was no statistical difference seen in 24-hour chest tube output, thromboelastograph values, or allogeneic transfusions at any time point between MUF and no-MUF subjects. There was a significant difference between MUF and no-MUF in the number of autologous cell salvage units processed (1.3 ± .48 vs. 2.9 ± .78, $p = .0013$) and end of procedure net fluid balance (+2003 ± 1211 vs. +4194 ± 1276 mL, $p = .001$), respectively. Estimated plasma loss from the cell salvage device was 477.6 mL greater in the no-MUF group. In primary adult cardiac procedures, MUF did not change coagulation values as measured by thromboelastography, number of allogeneic unit transfusions, or chest tube output at 24 hours postoperatively. There was a significant difference in autologous cell salvage units processed and end of procedure net fluid balance that benefited MUF subjects. **Keywords:** cardiopulmonary bypass, modified ultrafiltration, thromboelastograph. *JECT. 2008;40:229–233*

Bleeding during cardiac surgery continues to be a significant source of patient morbidity. Blood transfusion requirements and hemodynamic instability are a cause for intraoperative and postoperative interventions. Hemodilution of the patient's blood, secondary to the crystalloid prime in the cardiopulmonary bypass (CPB) circuit, may result in the transfusions of packed red blood cells, platelets, and fresh frozen plasma. The ratio of patient blood volume to circuit volume in an adult cardiac procedure reduces the concentrations of several coagulation and fibrinolytic proteins. A recent evidence-based review of CPB in adults (1) recommended that efforts be made to reduce hemodilution to avoid allogeneic blood transfusions. Other authors have reported that hemodilution induced by CPB can reduce factor concentrations, is associated with increased postoperative bleeding, and affects the dynamics of clot formation (2,3).

The hemodilutional effects of CPB have caused some to develop alternative strategies to reduce blood loss and transfusions. Methods (4–9) that suggest transfusion reduction and patient benefit include the use of off-pump procedures, CPB surface modifications, incorporation of mini-circuit technologies, use of augmented venous drainage, antegrade and retrograde autologous priming of the CPB circuit, and pharmacologic strategies. Although each of these strategies may be applicable to a select group of patients, their intended effect in reducing transfusions and hemodilution during a procedure may be negated based on the course of the procedure itself. Volume added during the CPB run also contributes to the degree of hemodilution seen by the end of CPB. Strategies used to address this issue are the use of conventional (CUF) and modified ultrafiltration (MUF). Although CUF is frequently used in adult cardiac surgery, the use of MUF is minimal.

First described in 1991 (10), the use of MUF has shown to concentrate both patient hemoglobin and contents of the CPB circuit. MUF is initiated after the termination of

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CPB and is similar to CUF in that blood is passed through a hollow fiber hemofilter and free water is removed. In many institutions, after the termination of CPB, the remaining fluid within the CPB circuit is transferred to an infusion bag, concentrated with a one-pass hemofilter technique, or centrifuged with the use of a red-cell salvaging device. Each of these three methods provides for return of remnant CPB circuit volume but may not provide an optimal product for the patient. The infusion bag and one-pass hemofilter methods save clotting factors but do not concentrate the hemodiluted patient, whereas the cell salvage technique concentrates the red blood cells but removes vital coagulation factors. By incorporating MUF, both issues can be addressed by concentrating the remaining CPB circuit volume and preserving the coagulation factors, while at the same time concentrating the patient's blood. Multiple studies in adults (11–14) examined the effect of MUF on the coagulation factors of the blood, postoperative bleeding, and transfusions. They showed the use of MUF increased the concentrations of hemoglobin, platelets, albumin, and coagulation factors VII and X. Other studies (12–16) showed reduced postoperative bleeding and decreased transfusion requirements in MUF patients. These studies concluded that the concentration of these factors resulted in reduced bleeding and transfusion requirements. Incorporating MUF not only increased coagulation factor concentration but may also have increased the strength of the clot formed. However, none of these studies examined the coagulation effects by thromboelastography (TEG).

By concentrating patient and circuit volume through MUF, this study sought to examine its effect on clot strength and formation as measured by the TEG. We also examined autologous and allogeneic transfusions and chest tube drainage in the immediate postoperative time period.

MATERIALS AND METHODS

This was a single-center, prospective, randomized trial with planned enrollment of 30 subjects: 15 to receive MUF and 15 having no-MUF. The study protocol was reviewed and approved in January 2007 by the University of Wisconsin Health Science Institutional Review Board, with potential subjects being evaluated and informed at their preoperative visit. Consent was obtained within 24 hours of the procedure. Subject entry criteria are listed in Table 1.

Table 1. Subject entry criteria.

18–75 years of age, male or female
First time cardiac procedures
Elective (scheduled >24 hours in advance)
Coronary artery bypass grafting (CABG), aortic (AVR) or mitral valve repair or replacement (MVR), or combination of these procedures
The ability to give consent
Subjects were not included in the study for any of the following reasons
Planned use of acute normovolemic hemodilution
History of coagulation disorder
Preoperative hematocrit (HCT) <30%, and/or platelet count <150,000/μL
Ejection fraction <35%
Renal insufficiency (creatinine >2.0 mg/dL)
Recent (<7 days) use of anticoagulant or antiplatelet medications
Recent myocardial infarction (<7 days)
Current use of intra-aortic balloon counter-pulsation
Surgical procedure requiring deep hypothermia circulatory arrest
Ventricular assist device implantation
Heart or lung transplantation
Refusal to receive blood product transfusions
Concurrent enrollment in another study
Pregnancy

Operating Room and Postoperative Procedures

Subjects entered the operating room and received general cardiac anesthesia induced and maintained by a standardized technique, with placement of a pulmonary arterial catheter; this was designated as data point T1. A loading dose of 10 mg aminocaproic acid (Xanodine; Newport, KY) was administered over 30 minutes intravenously, followed by a constant infusion of 1 mg/h with a maximum 20 mg administered. Sternotomy incision was made, and in preparation for CPB, a loading dose of heparin (300 units/kg) was administered intravenously. A kaolin activated clotting time (ACT; Hemochron; ITC Medical, Edison, NJ) >400 seconds was required to initiate CPB. The CPB circuit consisted of an open reservoir and a Medtronic (Minneapolis, MN) Affinity membrane oxygenator with Trillium coating throughout, with the exception of the cannulas. CPB flows were maintained between 2.0 and 2.4 L/min/m^2 using a Medtronic BP80 + centrifugal arterial pump while maintaining an ACT >480 seconds and mean arterial blood pressures between 50 and 80 mmHg. Conventional ultrafiltration was set up and primed for all subjects and undertaken at the discretion of the perfusionist using the Hemocor HPH 700 (Minntech, Minneapolis, MN) hemofilter. A 4:1 blood cardioplegia (CPG) system, modified for MUF use, was used to induce and maintain cardioplegic arrest. After release of the aortic cross-clamp and before termination of CPB, the hemofilter was connected to the modified CPG system in preparation for MUF. CPB was terminated at the discretion of the surgeon and designated data point T2. At this time, unblinding of the randomization (MUF vs. no-MUF) occurred.

Saline displacement of the venous line was undertaken with the cannula left in place if MUF was to be performed. If MUF was conducted, it was performed in an arteriovenous mode with a MUF blood flow rate of 250 mL/min and run continuously with an effluent vacuum of –200 mmHg until either 1500 mL of effluent was removed or 20 minutes had elapsed. The end of MUF was designated as data point T3. For subjects randomized to no-MUF, no T3

Table 2. Data time point descriptions.

T1: Baseline/post-anesthesia induction
T2: Termination of CPB
T3: Termination of MUF (no T3 value for subjects randomized to no-MUF)
T4: Post-protamine administration and ACT within 10% baseline
T5: 24 hours postoperative

CPB, cardiopulmonary bypass; MUF, modified ultrafiltration; ACT, activated clotting time.

Table 3. Laboratory measurements for each time point.

TEG: T1–T4
Hemoglobin: T1, T2, and T4
Platelet count: T1 and T4
Fibrinogen: T4
End of procedure net fluid balance: T4
Cumulative blood transfusions, including Cell Saver: T1–T5
Total chest tube output: T5

TEG, thromboelastograph.

Table 4. Baseline demographics.

	Age (yr)	Weight (kg)	Gender (M/F)	CPB Time (min)
No-MUF	57.6 (16.8)	80.4 (14.6)	6/3	138.6 (51.0)
MUF	58.4 (11.4)	87.7 (16.5)	9/1	121.2 (26.7)
p value	.898	.324	.303	.358

Values are mean (SD).
M, male; F, female; CPB, cardiopulmonary bypass.

data were obtained. The contents of the CPB circuit was processed for both groups using the Haemonetics Cell Saver 5 device (Haemonetics, Braintree, MA) at the end of CPB by flushing the circuit with crystalloid solution. Heparin was reversed with protamine sulfate (.7–1.3 mL protamine times total heparin given in milliliters) and an ACT measured 5 minutes later to assess reversal. Additional protamine was administered until the ACT was within 10% of baseline value. Once all blood products, including Cell Saver processed units, were administered, data point T4 occurred. All laboratory and TEG samples were drawn from a radial arterial line. Thromboelastograph samples were analyzed using a TEG 5000 Thrombelastograph Hemostasis Analyzer (Haemoscope, Niles, IL) with kaolin activator and heparinase cups. Subjects were transported to the cardiac intensive care unit (ICU), and data point T5 occurred 24 hours thereafter. Subjects were followed throughout their inpatient course, with complications noted before discharge. Data time point descriptions and laboratory measurements at each data time point are shown in Tables 2 and 3, respectively.

Statistical Analysis

Descriptive statistics were reported using means and SDs for categorical data. Continuous data were compared between groups using a two-tailed *t* test. Categorical data were compared between groups using a χ^2 test. A Fisher exact test was performed on gender and T5 transfusion data. A p value of $\leq .05$ was considered statistically significant.

RESULTS

A total of 19 subjects were entered into the trial. Ten subjects were randomized to MUF and nine to no-MUF. Surgical procedures for the MUF group included six coronary artery bypass graft (CABG), two aortic valve replacement (AVR), and two mitral valve repair/replacement (MVR). Procedures performed for the no-MUF included five CABG, three AVR, and one AVR/CABG. There was no significant difference seen between the procedure groups. Results were examined at each of the five time points described. There were no study participant complications as determined by the Society of Thoracic Surgeon Database criteria.

There were no statistical differences in age, weight, gender, or CPB time between the subjects in the MUF and no-MUF groups (Table 4). Likewise, there were no statistically significant differences in hemoglobin (Hb), platelet count, or TEG results between the two groups at baseline (T1; Table 5). Moreover, there were no statistically significant differences in TEG and Hb values between the MUF and no-MUF subjects at time point T2 (termination of CPB; Table 6). There was no direct effect on TEG values in subjects having MUF performed at the T3 time point (Table 7). Thromboelastograph parameters, Hb, platelet count, and fibrinogen after protamine administration with an ACT within 10% of the baseline value are shown in Table 8 and showed no statistical difference between the two groups.

Conventional ultrafiltration effluent was removed in 7 of 10 (840.0 ± 801.3 mL) and 7 of 9 [605.6 ± 478.6 mL, p = not significant (NS)] subjects for the MUF and no-MUF groups, respectively. Table 9 shows the end of procedure net fluid balance and autotransfusion units processed at

Table 5. TEG, Hb, and platelet count at T1 (baseline).

	R	α	MA	G	LY30	Hb	Plt
No-MUF	7.43 (.95)	61.12 (6.42)	66.56 (8.00)	10.77 (3.92)	2.89 (4.03)	12.73 (.96)	201.78 (39.7)
MUF	8.19 (2.63)	60.43 (8.07)	67.21 (7.51)	11.05 (3.96)	3.86 (4.06)	12.33 (1.07)	211.80 (74.0)
p value	.412	.839	.856	.877	.607	.402	.722

Values are mean (SD).
R, time to initial clot formation in seconds; α, rate of fibrin build-up in angle degrees; MA, maximum amplitude of clot formation in millimeters; G, clot strength in dynes per square centimeter; LY30, percent lysis 30 minutes after MA; Hb, hemoglobin (g/dL); Plt, platelet count (×1000/μL).

Table 6. TEG and Hb at T2 (termination of CPB)

	R	α	MA	G	LY30	Hb
No-MUF	7.21 (1.98)	58.71 (7.59)	57.61 (8.99)	7.31 (2.73)	1.18 (1.88)	9.03 (1.25)
MUF	8.36 (3.28)	57.58 (13.80)	57.74 (10.02)	7.33 (2.38)	1.98 (3.04)	9.21 (.98)
p value	.375	.830	.976	.987	.504	.734

Values are mean (SD).
R, time to initial clot formation in seconds; α, rate of fibrin build-up in angle degrees; MA, maximum amplitude of clot formation in millimeters; G, clot strength in dynes per square centimeter; LY30, percent lysis 30 minutes after MA; Hb, hemoglobin (g/dL).

Table 7. MUF subjects only: TEG difference before/after MUF (T2–T3).

	R	α	MA	G	LY30
T2	8.36 (3.28)	57.58 (13.80)	57.74 (10.02)	7.33 (2.38)	1.98 (3.04)
T3	10.60 (3.77)	47.83 (14.36)	56.05 (10.69)	6.93 (2.67)	0.64 (1.57)
p value	.059	.126	.813	.966	.099

Values are mean (SD).
R, time to initial clot formation in seconds; α, rate of fibrin build-up in angle degrees; MA, maximum amplitude of clot formation in millimeters; G, clot strength in dynes per square centimeter; LY30, percent lysis 30 minutes after MA.

T4. There was significantly lower net end of procedure fluid balance seen in the MUF vs. no-MUF groups (+2003 ± 1211 vs. +4194 ± 1276 mL, $p = .0013$) and autotransfusion units processed (1.3 ± .48 vs. 2.9 ± .78 units, $p = .001$) at T4, respectively. Because of the difference seen in the number of units processed with the autotransfusion device, plasma volume loss from the device was estimated for each subject using the following equations:

Red blood cell mass (RBCM) = (# Cell Saver units) (bowl volume) (bowl HCT*/100)
(*bowl HCT value based on UW Perfusion Quality Assurance data)
Total blood volume processed (TBVP) = (RBCM)/(T2 HCT/100)
Plasma volume lost to autotransfusion device (PVL) = TBVP – RBCM

These calculations produced an estimated plasma volume loss of 384.6 ± 143.2 and 862.2 ± 143.1 mL ($p < .0001$) for the MUF and no-MUF groups, respectively.

There were no significant differences seen in the number of red blood cell (RBC) units, number of subjects transfused, or chest tube output at T5 (Table 9). One subject in the MUF group and two subjects in the no-MUF group received RBCs at T2. There was no significant difference seen in the number of platelets, fresh frozen plasma, or cryoprecipitate units or number of subjects transfused between groups. One subject in the no-MUF group received 7 units of platelets at T4. No subjects in either group received fresh frozen plasma or cryoprecipitate at any data time point.

DISCUSSION

Hemodilution induced by CPB can impact coagulation function, bleeding, and allogeneic blood transfusion. This study sought to examine how these parameters were impacted by comparing the technique of MUF to cell washing at the termination of CPB.

Early termination (October 2007) of the study occurred because of a practice change and the use of acute normovolemic hemodilution. With the publication of the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists clinical practice guideline for transfusion (17), participating investigators felt the use of acute normovolemic hemodilution should be considered a standard of care. In examining the currently enrolled subjects and potential future subjects, it was determined that the 11 remaining subjects yet to be enrolled might have had lower baseline values (Hb and platelet count) than the currently recruited 19 subjects, thus creating the possibility for an imbalance in the baseline characteristics of enrolled vs. yet to be enrolled subjects. Therefore, the decision was made to terminate the study at 19 subjects and perform the analysis based on the collected data.

There was no significant difference seen in the TEG values, number of units of allogeneic blood transfusions, or 24-hour chest tube output between MUF and no-MUF subjects. This could be secondary to the subject popula-

Table 8. TEG, Hb, platelet count, and fibrinogen at T4 (post-protamine).

	R	α	MA	G	LY30	Hb	Plt	Fib
No-MUF	7.42 (1.95)	59.28 (6.57)	57.14 (9.56)	7.23 (2.99)	2.73 (4.70)	11.03 (1.65)	103.33 (33.43)	202.88 (65.90)
MUF	6.45 (1.48)	62.11 (7.15)	60.19 (7.20)	7.88 (2.02)	4.33 (4.94)	10.46 (1.10)	126.10 (37.73)	237.50 (62.63)
p value	.234	.382	.440	.584	.481	.380	.183	.272

Values are mean (SD).
R, time to initial clot formation in seconds; α, rate of fibrin build-up in angle degrees; MA, maximum amplitude of clot formation in millimeters; G, clot strength in dynes per square centimeter; LY30, percent lysis 30 minutes after MA; Hb, hemoglobin (g/dL); Plt, platelet count (×1000/μL); Fib, fibrinogen (mg/dL).

Table 9. End of procedure net fluid balance and Cell Saver at T4 (cumulative transfusions) and chest tube output at T5.

	T4		T5	
Time Point	Net FB (mL)	CS (units)	RBCs (units)	CTO (mL)
No-MUF	4194 (1276.0)	2.9 (.78)	.67 (1.41)	647.2 (203.3)
MUF	2003 (1211.0)	1.3 (.48)	.10 (.32)	730.2 (236.8)
p value	.0013	.001	.582	.426

Values are mean (SD).
Net FB, end of procedure net fluid balance; CS, Cell Saver units processed; RBCs, red blood cells units transfused; CTO, chest tube output.

tion being of relatively low risk for transfusion and bleeding and the small sample size of the study. There was near significance seen in the T2–T3 R-time value of the TEG before and after MUF was performed. This may be because of an increased concentration of antithrombin III as reported by Fujita et al. (11). In addition, there was a decrease seen in the LY30 value at T3, possibly because of the increased concentration of aminocaproic acid and its anti-fibrinolytic properties after MUF as noted by Petterson et al. (18). These value differences did not carry through to time point T4.

There was a significant decrease in autologous units processed in the MUF group compared with the no-MUF group (1.3 ± .48 vs. 2.9 ± .78 units, $p = .001$), primarily because of the no-MUF group having the entire CPB ruminants processed by the autotransfusion device.

Study Observations

End of procedure net fluid balance was significantly decreased in the MUF vs. no-MUF group (+2003 ± 1211 vs. +4194 ± 1276 mL, $p = .0013$; calculated as anesthesia in + CPB in – CUF out – MUF out – total urine output). Estimated plasma loss was greater by 477.6 mL (range, 862.2–384.6 mL) in the no-MUF group because of the 1.6 average unit increase processed by the Cell Saver. Although the total plasma, and thus coagulation factors loss, did not affect TEG values, patients subject to greater autotransfusion processing may have a considerable coagulation deficiency by the end of a procedure. By performing MUF at the end of CPB, additional plasma loss may be averted.

Study Limitations

Because of the change in practice regarding the use of acute normovolemic hemodilution, the early termination of the study produced a smaller sample size than was originally intended. Entry criteria was also limited to a low-risk population for bleeding or transfusion. Further study could include subjects of higher risk of transfusion and bleeding or use of multi-modal strategies used to reduce transfusions summarized in the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists clinical practice guideline publication.

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