

The Effects of Ultrafiltration on e-Aminocaproic Acid: An In Vitro Analysis

Craig M. Petterson, MPS, CCP; Alfred H. Stammers, MSA, CCP; Ryan J. Kohtz, MPS, CCP;
Scott A. Kmiecik, MPS, CCP; Jeffrey D. Nichols, MPS, CCP; Nancy J. Mills, MPS;
Jun-Li Liu, MD, PhD, CCP

Division of Clinical Perfusion Education, School of Allied Health Professions, University of Nebraska Medical Center,
Omaha, Nebraska

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Abstract: Blood conservation strategies have become a standard of practice in cardiac surgery, with the use of antifibrinolytic agents and ultrafiltration two popular techniques. The purpose of this study was to evaluate the effects of continuous ultrafiltration on e-aminocaproic acid (EACA) utilizing functional coagulation analysis. A fibrinolytic assay was developed to detect EACA using the thromboelastograph (TEG) and urokinase ($0.138 \text{ units } 0.360 \text{ mL}^{-1}$). Fresh bovine blood ($23 \pm 1\%$ hematocrit) was pumped (100 mL min^{-1}) through an ultrafiltrator (HPH 400) at 37°C with a transmembrane pressure of 280 mmHg. EACA (0.065 mg mL^{-1}) was circulated for 10 minutes before initiating ultrafiltration. Samples (pre- and postultrafiltrator) were obtained at baseline, 5, and 10 min of ultrafiltration and analyzed via the fibrinolytic assay for EACA determination. TEG profiles significantly decreased from concentrations of

0.065 mg to 0.0325 mg of EACA mL^{-1} blood (maximum amplitude MA, 75.4 ± 4.0 versus 63.3 ± 2.9 , $p < .05$, TEG index 5.4 ± 0.7 versus 4.0 ± 0.3 , $p < .05$). Fibrinolysis at 30 min increased as EACA concentrations declined (0.065 mg , 0% versus 0.032 mg , $16.4 \pm 2.8\%$, $p < .05$). During ultrafiltration the MA increased significantly from baseline to 10 min postultrafiltrator (68.2 ± 3.0 versus 75.8 ± 10.0 , $p < .05$) and from 5 min pre- to 10 min postultrafiltrator (69.7 ± 4.2 versus 75.8 ± 10.0 , $p < .05$). The TEG index showed no significant change, and no fibrinolysis was detected at 30 min from any datapoint during ultrafiltration. In conclusion, this study demonstrates that the antifibrinolytic properties of EACA are maintained during ultrafiltration with a 25% reduction in total circulating volume. **Keywords:** ultrafiltration, e-aminocaproic acid, fibrinolysis, thromboelastograph. JECT. 2002;34:197-202

Coagulation disorders are the number one complication following cardiopulmonary bypass (CPB) (1). CPB activates a number of physiological responses; such associations are immunologic and hemostatic compromises. In addition, hyperfibrinolytic activity is heightened when blood comes in contact with foreign surfaces. There is an increase in kallikrein activity, which directly induces activation of tissue-plasminogen activator and Factor XII. These fibrinolytic factors can impair or prevent the formation of a clot, leading to an increase in postoperative bleeding and the need for transfusions (2). It has been

demonstrated by Arom et al, that by adding e-aminocaproic acid (EACA) to cardiac surgery protocols, the patient may be spared autogenic blood product exposure resulting in savings of \$206.18 (US). The cost is not the greatest concern; the availability of blood products in the United States is (3).

EACA is the most widely used antifibrinolytic agent today because it is readily available and safe. EACA is a 131-dalton synthetic monoaminocarboxylic acid closely related to the lysine structure. Elimination is primarily via the renal system in which 65% of the dose is recovered in the urine unchanged (4). The mechanism of action is related to its ability to saturate the lysine-binding sites of plasminogen activators. This action prevents the dissolution of postoperative clotting by inhibiting plasminogen activators. Dosing regimens vary with the use of EACA;

Address correspondence to: Craig Petterson, MPS, CCP, Operating Room/Perfusion Services, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160, E-mail: cmpett@hotmail.com

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including preoperatively, pump prime, and postoperatively (3). Del Rossi et al, demonstrated significant reductions in blood loss when EACA was used before CPB (5).

Ultrafiltration can be defined as the selective separation of plasma water from the plasma proteins and various other formed elements. The process is a result of a hydrostatic pressure gradient (6). It was first used during cardiac surgery in 1976 to reduce fluid volumes associated with CPB. Today, it has been reported that more than 90% of the pediatric centers in North America have incorporated ultrafiltration into their protocols (7). Holt et al. summarized the effects of ultrafiltration in 1982. These included increased hematocrit, plasma protein concentrations, and circulating clotting factors, and a decrease in such small molecules as heparin (8). However, recent studies by Groom et al. and Kohtz et al. have demonstrated that molecular size is not the only influencing factor during ultrafiltration. Conversely, these two groups demonstrated a concentrating effect of both heparin and low molecular weight heparin while using an ultrafiltrator (7, 9). The effect of ultrafiltration on plasma concentrations of various pharmacological agents has created controversy. Thus, the purpose of this study was to determine the effects of continuous ultrafiltration on EACA using functional coagulation analysis.

MATERIALS AND METHODS

Blood Collection and Preparation

With the written consent and assistance from slaughterhouse management, 2400 mL of whole blood was collected from a single bovine subject in anticoagulant citrate dextrose (Baxter Healthcare Corporation, Glendale, CA) in a ratio of nine parts blood to one part anticoagulant. The blood was brought to the laboratory and transferred into a nonfiltered cardiomy reservoir for preparation. Sodium Bicarbonate (Abbott Laboratories, North Chicago, IL) was added to achieve a pH of 7.40 ± 0.05 and physiologic solution was used initially to dilute the blood to a hematocrit of $23 \pm 1\%$.

Preliminary Assay Development

Ten mL of blood were transferred into a vial. From the vial, blood (1.0 mL) was then pipetted into a prewarmed 1% celite vial, the vial was inverted five times, and 0.335 mL were pipetted into a prepared thromboelastograph® (Haemoscope Corporation, Skokie, IL) (TEG) cup. The prepared TEG cup consisted of 0.020 mL 0.2M CaCl_2 and 0.005 mL urokinase (#U-131, Sigma Chemical, St. Louis, MO) (0.138 units). Fibrinolysis was determined by performing a TEG with acceptance of lysis at 30 min $>80\%$. The fibrinolytic state was confirmed in quadruplicate, and the test was terminated at 30 min. Once a fibrinolytic state was achieved, a standard curve was developed for varying concentrations of EACA.

Ten mL of blood were transferred from the nonfiltered cardiomy into six separate vials. EACA (American Reagent Laboratories, Inc, Shirley, NY) was added to each vial at varying concentrations (0.260 mg, 0.130 mg, 0.065 mg, 0.0325 mg, 0.01625 mg, and 0.008125 mg mL^{-1} blood). All vials were inverted 10 times and placed into a holder. Individual concentrations were then analyzed via the fibrinolytic assay for EACA determination. One mL of blood from each concentration was introduced into a prewarmed 1% celite vial and inverted five times. 0.335 mL of blood were then transferred into the prewarmed, prepared TEG cup. The prepared TEG cup contained 0.020 mL 0.2M CaCl_2 and 0.005 mL of urokinase (0.138 units). All concentrations were performed in quadruplicate and allowed to run for 30 min before termination.

Experimental Model

All components of the circuit were used per manufacturer's instructions. Figure 1 is a detailed illustration. A heparin-coated soft-shell venous reservoir (Edwards Lifesciences, Irvin, CA) acted as the holding and mixing chamber. From the reservoir, blood was propelled through the $\frac{1}{4}$ -inch tubing (COBE Laboratories, Arvada, CO) via twin-roller positive displacement pump (Stockert roller pump, Sorin Biomedical, Irvin, CA) which was calibrated before use. Blood then passed through a heat exchanger (MYOTherm™ XP, Medtronic, Minneapolis, MN) connected to an external heater-cooler (Dual Cooler/Heater, 3M Sarns, Ann Arbor, MI). Pre-ultrafiltration pressure (Medtronic DLP, Grand Rapids, MI) and temperature were monitored from the heat exchanger. The heat exchanger was also utilized for pre-ultrafiltration sampling and recirculation. During ultrafiltration, blood was directed from the heat exchanger to a wye. Three parallel ultrafiltrators (HPH 400, Lifestream International, The Woodlands, TX) were located at this point, each capable of being isolated from the circuit. Post-ultrafiltrator blood passed through another wye with a three-way stopcock attached. Pressure and blood samples were obtained from this point. Blood returned to the soft shell reservoir completing the recirculating system.

The experimental circuit was primed according to the manufacturer's instructions. The circuit was initially primed with 700 mL of physiologic solution. Temperature was maintained at 37°C , and after 15 min of equilibrium, 750 mL bovine blood was introduced. The blood was allowed to circulate through all three ultrafiltrators. An initial hematocrit of $23 \pm 1\%$ was achieved, with an initial circulating volume of 1135 mL. EACA (0.065 mg mL^{-1} blood) was introduced into the circuit and circulated for 10 min before ultrafiltration through the recirculation line and the three parallel ultrafiltrators. After 10 min of equilibrium, the investigated membrane was isolated, and the recirculation line remained open. Three minutes before the initiation of ultrafiltration, the recirculation line was

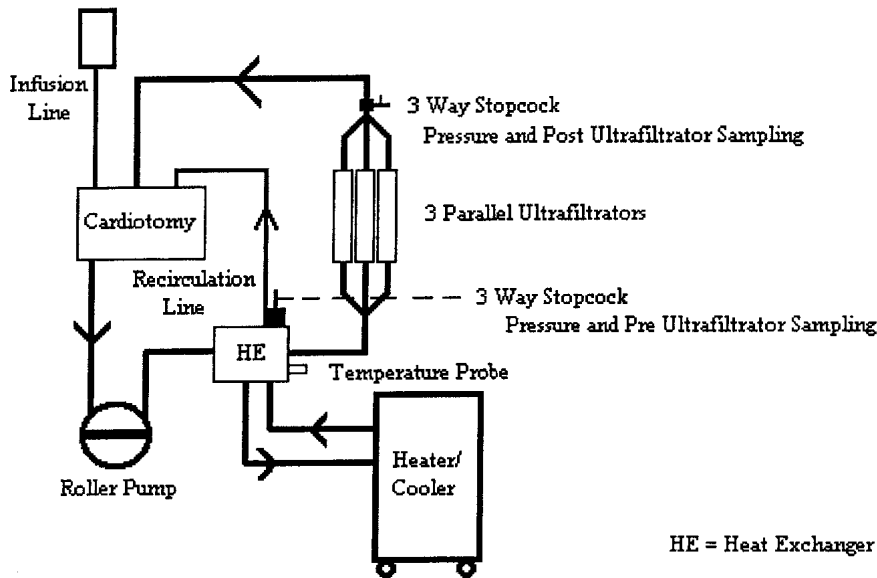


Figure 1. Schematic diagram of the experimental circuit.

HE = Heat Exchanger

clamped, leaving the investigated membrane the only path for blood flow.

Before ultrafiltration, 2.5 mL of blood were aspirated from the pre-ultrafiltration sample port for baseline analysis. Analysis performed included spun hematocrits and TEGs via the fibrinolytic assay for EACA determination. One mL of blood was introduced into a prewarmed 1% celite vial and inverted five times. From the vial, 0.335 mL of blood were transferred into the prepared TEG cup. The prepared TEG cup included 0.020 mL of 0.2M CaCl_2 and 0.005 mL of urokinase (0.138 units). The TEG was terminated at 30 min and performed in triplicate. Hematocrits were performed in quadruplicate.

Ultrafiltration began as baseline analysis was completed. A flow of 100 mL min^{-1} at 37°C with a transmembrane pressure (TMP) of 280 mmHg was maintained. After 5 min of ultrafiltration, samples (2.5 mL) were obtained instantaneously from the pre- and postultrafiltrator sample ports. The ultrafiltrate line was clamped, and blood was directed through the investigated membrane and the recirculation line. Samples for analysis included spun hematocrits as well as TEGs via the fibrinolytic assay for EACA determination, as previously described.

The recirculation line was clamped 3 min before reinstitution of ultrafiltration. Ultrafiltration recommenced for 5 additional min (10 min total). A flow of 100 mL min^{-1} at 37°C with a TMP of 280 mmHg was maintained. Upon the completion of ultrafiltration, a 10-min pre- and postultrafiltrator sample (2.5 mL) was drawn concurrently. Samples were analyzed in the same fashion as stated for baseline and 5 min of ultrafiltration.

The protocol above was repeated with the other membranes. All ultrafiltrators were treated equally in regard to the technique of ultrafiltration, sampling, and analysis. Following 10 min of ultrafiltration, the ultrafiltrate line

was clamped. The ultrafiltrate volume ($280 \pm 20 \text{ mL}$) was measured and added back to circulation. Blood was allowed to flow through the three parallel ultrafiltrators and the recirculation line for 30 min to ensure proper mixing. After 30 min of equilibrium, the investigated membrane was isolated, and the recirculation line remained open. The recirculation line was clamped 3 min before the experimental run. All TEGs were performed using the described fibrinolytic assay for EACA determination and were performed in triplicate.

Thromboelastograph®

A description of the TEG has been previously described (10,11). Measurements obtained via the TEG have been defined and are described below.

Reaction Time (R time): R time represents the whole blood clotting time. The R time correlates with the initiation of coagulation and transpires when the amplitude of the trace is equal to 2 mm.

Clot Growth Kinetics (K time) and Alpha Angle: Clot growth rate can be evaluated as the difference in time between initial clot formation (R time) and a deflection in amplitude of 20 mm. Combined analysis of alpha angle and K time provides the clinician with a mapping of polymerization and the structural elements involved in clotting. This phenomenon is the rate of clot growth and is related to the function of the platelets and plasma components on the surface of the platelets.

Clot Strength Maximum Amplitude (MA): This is the strength of the clot. This measurement is a direct result of the function of platelets and plasma components (fibrinogen) and its combined interaction.

TEG Index: The TEG index is a mathematical equation that combines the R time, K time, MA, and alpha angle. A positive value is indicative of a hypercoagulable

state, and a negative value correlates with a hypocoagulable state.

Lysis at 30 This is the percentage of clot lysis at 30 min following complete clot formation. It is a tool used to identify fibrinolytic states.

Statistics

All data were collected and loaded in spreadsheet format into a personal computer. Data were analyzed with one-way and two-way analysis of variance (ANOVA) with a commercially available statistics program (SuperANOVA, Abacus Concepts, Berkeley, CA). When significant *f* ratios were achieved, the Fisher's protected least significant difference multiple comparison test was performed. Statistical significance was accepted to $p < .05$. All data are presented as mean \pm standard deviation.

RESULTS

Preliminary Assay

Table 1 and Figure 2 represent the findings of the preliminary work. All samples contained 0.005 mL of urokinase (0.138 units), 0.02 mL CaCl_2 , and 0.335 mL of blood. The concentration of EACA is represented as mg mL^{-1} blood. Samples titled urokinase contained no EACA.

The addition of urokinase created a profile reflecting a state of fibrinolysis. The R time was significantly prolonged. MA and TEG index were significantly low, and fibrinolysis at 30 minutes was significantly increased.

After creating a state of fibrinolysis, various concentrations of EACA were alloquated and tested. The trend was a declining coagulation profile as the EACA concentration was reduced. The R time increased as the EACA concentration declined. The K time and alpha angle remained stable throughout the various concentrations. The MA and TEG index decreased as the concentration of EACA diminished. Lysis at 30 min increased as the concentration of EACA declined.

Experimental Model

Ultrafiltration resulted in a significant increase in the hematocrit as blood was concentrated through the membrane, as shown in Figure 3. There was also a significant decrease from 5 min postultrafiltrator to 10 min preultra-

filtrator (34.3 ± 1.9 vs. 31.8 ± 2.6 , $p < .05$) caused by recirculating circuit.

Ultrafiltration affected several variables in regard to the fibrinolytic assay for EACA determination and is shown in Table 2. The R and K time increased as it passed through the ultrafiltrator. The MA also trended upward as it passed through the ultrafiltrator. There was no significant change in the alpha angle or the TEG index at any datapoint during ultrafiltration. No samples produced lysis at 30 min.

DISCUSSION

The ultrafiltrability of drugs has raised questions and concerns among many clinicians. Most manufacturers recommend an increased awareness of anticoagulation status during ultrafiltration. Differences of opinions have led to numerous studies. In 1988, Golpher et al. described a theoretical model that involved a sieving coefficient. This study was thought to determine the fate of various drugs during continuous ultrafiltration (6, 12). In 1995, Clar et al. determined the sieving coefficients for a number of cardiac drugs used during extracorporeal circulation by using Golpher's study (13). Groom et al. proved the mathematical formula to be inaccurate, as they demonstrated a linear increase in heparin as it passed through an ultrafiltrator, while Clar calculated heparin to be removed at a sieving coefficient of 0.20 (7). It seems that drug removal via ultrafiltration is more complicated than mathematical models would suggest. Rather, it is determined by both drug and membrane characteristics. These properties include: protein binding, molecular weight, molecular charge, porosity, and membrane charge (14).

EACA has a molecular size of 131 daltons, and the ultrafiltrators used were a glycerin-free polysulfone membrane capable of removing a 65,000-dalton molecule. The results of our in vitro study do not suggest appreciable elimination following a 25% reduction in total circulating volume. Two factors play a key role in our findings. EACA is thought to bind to plasminogen (15). Plasminogen has a molecular mass of 92,000 daltons (16). EACA that is bound to plasminogen may not be removed via ultrafiltration. EACA has also been reported to distribute

Table 1. Fibrinolytic assay for EACA determination.

	0.260 mg	0.130 mg	0.065 mg	0.0325 mg	0.01625 mg	0.008125 mg	Urokinase
R time	$2.1 \pm 0.3^{c,f}$	2.5 ± 0.6^c	2.4 ± 0.3^c	2.5 ± 0.0^c	2.5 ± 0.0^c	3.0 ± 0.4	2.8 ± 0.3
K time	1.0 ± 0.0	1.1 ± 0.3^f	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	0.9 ± 0.1
α	76.9 ± 0.7	75.6 ± 1.9	79.1 ± 2.5^d	80.4 ± 0.3	81.6 ± 1.1	78.6 ± 4.0	77.1 ± 7.4
MA	$72.9 \pm 3.0^{a,c,d,e,f}$	$66.7 \pm 1.5^{b,e,f}$	$75.4 \pm 4.0^{c,d,e,f}$	$63.3 \pm 2.9^{e,f}$	$63.8 \pm 2.5^{e,f}$	53.8 ± 7.7^f	38.8 ± 2.5
TI	$5.3 \pm 0.3^{a,c,e,f}$	$4.1 \pm 0.5^{b,e,f}$	$5.4 \pm 0.7^{c,d,e,f}$	$4.0 \pm 0.3^{e,f}$	$4.3 \pm 0.3^{e,f}$	2.5 ± 1.5^f	0.8 ± 0.9
Lys 30	$0.0 \pm 0.0^{c,d,e,f}$	$0.1 \pm 2.5^{c,d,e,f}$	$0.0 \pm 0.0^{c,d,e,f}$	$16.4 \pm 2.8^{d,e,f}$	$41.0 \pm 12.6^{e,f}$	64.4 ± 21.6^f	90.3 ± 4.0

α = alpha angle; Lys 30 = percentage lysis at 30 min; MA = maximum amplitude; TI = TEG index; a = $p < .05$ vs. 0.130 mg; b = $p < .05$ vs. 0.065 mg; c = $p < .05$ vs. 0.0325 mg; d = $p < .05$ vs. 0.01625 mg; e = $p < .05$ vs. 0.008125 mg; f = $p < .05$ vs. urokinase.

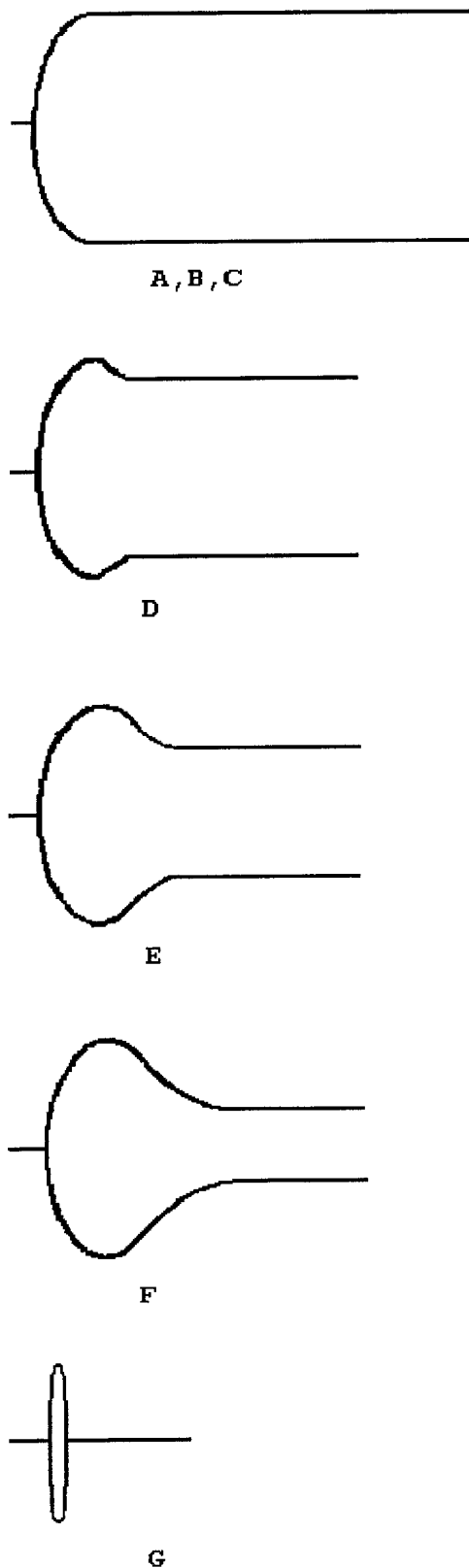


Figure 2. TEG tracings of the fibrinolytic assay for EACA determination; A = 0.260 mg; B = 0.130 mg; C = 0.065 mg; D = 0.0325 mg; E = 0.01625 mg; F = 0.008125 mg; G = urokinase.

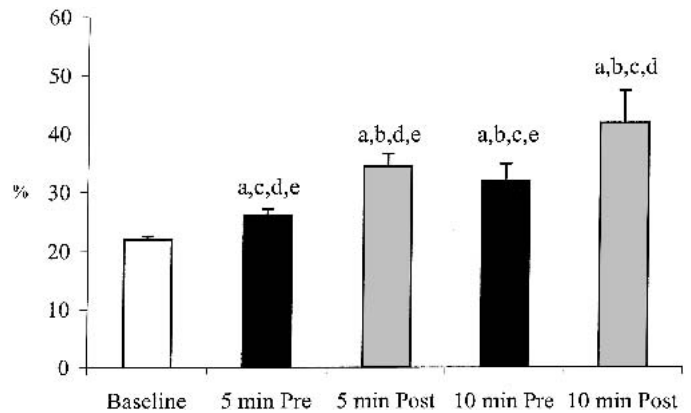


Figure 3. Change in hematocrit over time; % = percentage hematocrit; a = $p < .05$ vs. baseline; b = $p < .05$ vs. 5 min preultrafiltrator; c = $p < .05$ vs. 5 min postultrafiltrator; d = $p < .05$ vs. 10 min preultrafiltrator; e = $p < .05$ vs. 10 min postultrafiltrator.

into erythrocytes at high concentrations and after prolonged administration (15). Therefore, if there is a concentrating effect of EACA during ultrafiltration, there may be red blood cell distribution.

A major concern with the use of an ultrafiltrator is whether there is a concentrating or eliminating effect on circulating drugs. The clinical significance of concentrations above the therapeutic level of 0.130 mg mL^{-1} blood has been well documented. The adverse effects of EACA include: thrombus formation, acute renal failure, and anaphylactic reactions (17–22). Prolonged exposure to EACA may also lead to myopathy and rhabdomyolysis (23, 24). A concentration of EACA below therapeutic level may lead to an ineffective dose. However, it is imperative to note that patients presenting with impaired renal function should need a lower EACA dose (14).

The development of the qualitative TEG fibrinolytic assay was initially attributable to an extraordinary financial and professional expense. However, the value of the fibrinolytic assay for EACA determination proved informative. The therapeutic dose for EACA is 0.130 mg mL^{-1} blood. Concentrations above and below this value were studied. There was a significant decline in the TEG profiles as the concentration of EACA was reduced. The first significant change in the fibrinolytic TEG assay was discovered from 0.065 mg to $0.0325 \text{ mg mL}^{-1}$ blood. Therefore, an initial dose of 0.065 mg was used during ultrafiltration. It was then postulated that if the EACA were significantly eliminated during ultrafiltration, the postultrafiltration sample would demonstrate fibrinolysis similar to a dose of 0.0325 mg.

Ultrafiltration resulted in prolongation of the R and K times. The R time represents whole blood clotting, as previously stated. We chose not to use heparin in our study because of the linear concentrating effect that was found by Groom et al. (7). Even with the use of heparinase cups and pins the possibility of a TEG tracing consistent with

Table 2. Ultrafiltration samples using the fibrinolytic assay for EACA determination.

	Baseline	5 min Pre	5 min Post	10 min Pre	10 min Post
R time	1.9 ± 0.2 ^{a,c}	1.8 ± 0.3 ^{a,c}	2.5 ± 0.5 ^c	2.3 ± 0.8 ^c	3.3 ± 1.0
K time	1.0 ± 0.0 ^{b,c}	1.0 ± 0.0 ^{b,c}	1.2 ± 0.3 ^c	1.4 ± 0.7	1.7 ± 0.4
α	73.7 ± 1.1	74.6 ± 5.2	73.2 ± 1.9	71.6 ± 6.2	70.4 ± 7.1
MA	68.2 ± 3.0 ^c	69.7 ± 4.2 ^c	72.4 ± 3.8	71.4 ± 6.6	75.8 ± 10.0
TI	4.5 ± 0.3	4.8 ± 1.9	4.6 ± 0.5	4.3 ± 1.9	4.2 ± 2.3
Lys 30	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

α = alpha angle; Lys 30 = percentage lysis at 30 min; MA = maximum amplitude; TI = TEG index. a = $p < .05$ vs. 5 min postultrafiltrator; b = $p < .05$ vs. 10 min preultrafiltrator; c = $p < .05$ vs. 10 min postultrafiltrator.

an anticoagulant on board would deem the fibrinolytic assay for EACA determination ineffective. However, the increase in R time may be attributable to several factors. The soft-shell reservoir used was heparin coated. Heparin leaching would cause the clotting times to be prolonged. Another hypothesis is that ultrafiltration concentrated natural anticoagulants. A third proposal involves EACA. Glock et al. have stated that high doses of EACA may prolong bleeding times (25).

Ultrafiltration also resulted in a widened MA. Two factors may have contributed to an increase in MA. Ultrafiltration concentrates proteins; of these, a major contributor may include coagulation factors (9). Another possibility is that ultrafiltration did, indeed, concentrate EACA that was bound to plasminogen and, therefore, heightened coagulation.

Limitations of this study include the study being performed in vitro with the use of bovine blood. In addition, the fibrinolytic assay for EACA determination was more sensitive with lower concentrations of EACA. Therefore, a dose of 0.065 mg opposed to the standard of 0.130 mg was used. Further investigations may include the plasma concentration measurements from pre- and postultrafiltrator in vivo.

In conclusion, this study demonstrates that the antifibrinolytic properties of EACA are maintained during ultrafiltration and is not appreciably removed after a 25% reduction in total circulating volume.

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