

Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients

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Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients.

Background. We determined the effect of regional citrate versus systemic heparin anticoagulation for continuous renal replacement therapy in critically ill subjects suffering from acute renal failure who were not at high risk for hemorrhagic complications.

Methods. Between April 1999 and June 2002, 30 critically ill subjects requiring continuous renal replacement therapy and using 79 hemofilters were randomly assigned to receive regional citrate or systemic heparin anticoagulation.

Results. The median hemofilter survival time was 124.5 hours (95% CI 95.3 to 157.4) in the citrate group, which was significantly longer than the 38.3 hours (95% CI 24.8 to 61.9) in the heparin group ($P < 0.001$). Increasing illness severity score, male gender, and decreasing antithrombin-III levels were independent predictors of an increased relative hazard of hemofilter failure. After adjustment for illness severity, antithrombin-III levels increased significantly more over the period of study in the citrate as compared to the heparin group ($P = 0.038$). Moreover, after adjustment for antithrombin-III levels and illness severity score, the relative risk of hemorrhage with citrate anticoagulation was significantly lower than that with heparin (relative risk of 0.14; 95% CI 0.02 to 0.96, $P = 0.05$).

Conclusion. Compared with systemic heparin anticoagulation, regional citrate anticoagulation significantly increases hemofilter survival time, and significantly decreases bleeding risk in critically ill patients suffering from acute renal failure and requiring continuous renal replacement therapy.

Acute renal failure (ARF) is a common complication of critically ill patients with mortality rates in excess of 40% [1–6]. The use of continuous renal replacement therapy (CRRT) in the management of acute renal failure in critically ill patients has become accepted, and based on two North American surveys, it has been estimated that one

quarter of all patients in the United States and Canada with acute renal failure are treated with CRRT [6–8].

The requirement for continuous systemic anticoagulation is a major drawback to the use of CRRT. Systemic anticoagulation with unfractionated heparin has been the anticoagulant of choice, with regional citrate anticoagulation being used as the method of choice in only 13% of patients in Canada [8, 9]. The use of regional citrate anticoagulation has been described in the setting of CRRT, and one randomized trial has suggested its superiority over that of heparin [10–12]. However, a recent conference on CRRT failed to provide a consensus on the preferred anticoagulant for most CRRT patients, offering a recommendation to avoid systemic anticoagulation with heparin in patients at high risk for hemorrhage [7].

We have previously described an algorithm for regional citrate anticoagulation in CRRT [11]. The objective of this study was to compare the hemofilter survival times and bleeding risks in critically ill patients undergoing CRRT for ARF. Patients were randomized to receive either systemic unfractionated heparin or regional citrate anticoagulation.

METHODS

Study design and population

Eligible patients were 18 years old or older and suffering from ARF using a standard definition, and were admitted to either of two tertiary care intensive care units (ICUs) or one community hospital ICU [5]. Patients were excluded if they had a contraindication to the use of systemic heparin or trisodium citrate or if they were anticipated to require systemic heparin for medical reasons. Contraindications to the use of heparin included a prior history of heparin-induced thrombocytopenia or heparin allergy, intracranial hemorrhage within three months, gastrointestinal hemorrhage requiring a transfusion of greater than two units of blood within three months, active bleeding within three days or significant trauma within three days, a platelet count $< 40,000$ per mm^3 , and evidence of a irreversible coagulopathy

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(INR >2.5, PTT >65, or fibrinogen <1.00 g/L) as a result of liver failure, disseminated intravascular coagulation, or a coagulation factor deficiency. Contraindication to the use of trisodium citrate included a serum ionized calcium level of <0.70 mmol/L, a serum pH of >7.60, and a serum sodium of >160 mmol/L. Pregnant females were also excluded from the study. Ethics approval was obtained from regional ethics boards, and written informed consent was obtained for all subjects prior to randomization.

Randomization and interventions

Consecutive eligible patients were randomized to anticoagulation with either heparin or citrate within variable block sizes of 4 and 8. Treatment assignment was not blinded given the requirement of following levels of PTT and INR. Subjects randomized to the heparin group received an initial bolus of 50 U/kg of heparin for a PTT \leq 35 seconds (no heparin bolus if the PTT was >35 seconds), followed by an algorithm titrated to maintain a systemic PTT between 45 and 65 seconds. Subjects randomized to receive citrate received trisodium citrate titrated to maintain posthemofilter ionized calcium levels between 0.25 and 0.35 mmol/L. Details of the trisodium citrate algorithm have been previously described [11]. In the heparin treatment group, INR and PTT levels were performed at least every four hours according to a standardized dosing nomogram. In the citrate group, post-hemofilter and serum ionized and total calcium levels were monitored one hour after initiation of regional citrate anticoagulation, at four-hour intervals thereafter for 24 hours, followed by monitoring every eight hours. The hemofilters in both treatment groups were primed with 10,000 U of heparin in 1 L of normal saline prior to the initiation of CRRT. CRRT was performed as continuous-veno-venous hemodiafiltration using the PRISMA CFM system (Gambro Renal Products, Montreal, Canada) with a standard PRISMA M-100 AN69 (polyacrylonitrile) hemofilter. Unfractionated heparin has previously been demonstrated to bind to both AN69 and the newer AN69ST hemofilter membranes, and to provide an anticoagulant effect with a simultaneous reduction of systemic anticoagulation requirements [13]. Blood flow rates were maintained at 125 mL/min, with dialysate flow rates of 1000 mL/hr and hemofiltration rates (prehemofilter) of 1000 mL/hr. Fluid removal rates were left to the discretion of the attending physician in order to achieve optimal hemodynamic balance; however, these rates were not permitted to exceed a net negative balance of 300 mL/hour by protocol. The dialysis and replacement solution used was produced either by the regional pharmacy of the participating centers, or provided as an equivalent preformulated solution (Gambro Dasco SpA, Medolla, Italy), and consisted of Na⁺ 117 mmol/L, Mg⁺⁺ 0.70 mmol/L, and

Cl⁻ 117 mmol/L. The attending physician dictated the concentration of KCl and HCO₃⁻ to be used in the dialysis/replacement fluid solution. Doses of HCO₃⁻ used in the replacement fluid of both treatment groups varied between 33.3 mmol/L and 50 mmol/L, and in the patients randomized to the heparin group, HCO₃⁻ was also permitted to be included at similar concentrations in the dialysis solution.

The logistic organ dysfunction (LOD) score, which included the platelet count and INR in its composite score, was measured during the 24-hour period after ICU admission [14]. Protein C levels (using a clot-based assay STA instrument), antithrombin III (AT-III) levels (using a chromogenic method STA instrument), and the LOD score were measured just prior to initiation of CRRT, day 4 and 7 after CRRT initiation, and weekly thereafter until day 21.

Follow-up and outcome measures

All patients were followed to hospital discharge or death. Hemofilter failure was defined as hemofilter clotting or persistent transmembrane pressures greater than 200 mm Hg, resulting in repeatedly triggering the "high pressure" alarm and subsequently prohibiting continuation of CRRT at the prescribed dose. Definite bleeding was defined when a site of gross bleeding had been witnessed, and at least one of the following criteria was met: (1) a spontaneous drop of \geq 20 mm Hg in systolic or diastolic blood pressure within 24 hours; (2) an increase in heart rate of 20 bpm and a drop in systolic blood pressure of 10 mm Hg on assuming an upright position; (3) transfusion of \geq 2 U packed red blood cells within 24 hours; (4) failure of the hemoglobin concentration (in g/dL) to increase after transfusion by at least the number of units transfused minus 2; or (5) a decrease in hemoglobin of \geq 2 g/dL within 24 hours. Occult bleeding was defined in the absence of observed blood loss and when either of the two criteria were met: (1) a decrease in hemoglobin of \geq 2 g/dL within a 24-hour period on CRRT; or (2) failure of the hemoglobin concentration (in g/dL) to increase after transfusion by at least the number of units transfused minus 2. During the study, the transfusion threshold guideline utilized was 7.0 g/dL [15]. Clinically significant metabolic alkalosis or hypocalcemia was defined as an adverse event when a threshold of pH >7.50 or serum ionized calcium of <0.70 mmol/L was met within a consecutive 24-hour period.

Statistical analysis

Patient survival proportion and the reasons for hemofilter termination was compared between groups using Fisher exact test and the chi-square test. Hemofilter survival times were compared using the Kaplan-Meier method and the log-rank test [16]. An extension

of the Cox proportional hazard model that accounted for the correlation within each individual to clot sequential hemofilters and adjusted for potential confounding variables was used to compare the relative hazard of hemofilter failure between treatment groups [17]. Potential confounding variables included age, gender, and treatment effect as fixed covariates and LOD score, protein C, and AT-III, as time-dependent covariates. First-order interaction terms for protein C and AT-III by treatment assignment were also evaluated. The temporal change in AT-III levels over time was modeled using random effects linear regression and adjusting for the effect of anticoagulant treatment assignment, age, and gender as fixed covariates, and LOD score as a time-dependent covariate with interaction terms between treatment and LOD score [18]. Definite and occult hemorrhage was used as a composite end point, and comparisons of absolute rates and relative rates of hemorrhage between treatment groups were described using a Poisson distribution [19]. Multivariable adjustment for variables including age, gender, etiology of renal failure, LOD score, protein C, and AT-III levels was performed using a Poisson regression model. For the extended Cox proportional hazard model, the random effects linear regression model, and the Poisson regression model, backward selection of covariates was performed, and covariates were deemed to be significant in the final model if they obtained a significance level of $P < 0.05$.

For the study to have a statistical power of 90% with a two-sided alpha level of 0.05 to detect an absolute difference of 10% in hemofilter survival from 1% to 11% on day 8 after hemofilter initiation, and assuming a rate of hemofilter censoring of 63%, a total sample size of 96 hemofilters was required [20]. The sample size was increased to 120 hemofilters to account for previously observed inpatient correlation. For the statistical component of the interim analysis, the use function of O'Brien and Fleming was adopted with one interim analysis at the study midpoint of approximately 30 patients assuming an average of 2 hemofilters per patient [21]. For analytic purposes, hemofilters were the unit of analysis, and only those hemofilters consecutively receiving the assigned anticoagulant were included in the analysis. The analysis was performed using SAS 8.02 and S-Plus 2000 (Cary, NC, USA) and conducted according to the intention-to-treat principle.

RESULTS

Randomization

Recruitment began in April 1999 and ended in June 2002. A total of 285 patients were screened; 33 were eligible but not randomized (consent refused in 29 and physician refusal in 4) and 221 patients met exclusion criteria. The remaining 31 patients were randomized into

Table 1. Characteristics of the 30 randomized subjects^a

Characteristic	Citrate group (N = 16)	Heparin group (N = 14)
Male gender No. (%)	7 (43.8)	8 (57.1)
Age years	66.5 ± 14.5	63.9 ± 21.2
Logistic organ dysfunction score ^b	7.75 ± 3.53	9.42 ± 2.31
Etiology of renal failure		
Surgical acute tubular necrosis No. (%)	3 (18.8)	1 (7.1)
Nephrotoxic acute tubular necrosis No. (%)	3 (18.8)	4 (28.6)
Septic acute tubular necrosis No. (%)	5 (31.3)	6 (42.9)
Medical acute tubular necrosis No. (%)	4 (25)	1 (7.1)
Acute glomerulopathies No. (%)	0 (0)	1 (7.1)
Other No. (%)	1 (6.3)	1 (7.1)
Oliguric (<400 mL/24 hours) No. (%)	9 (56.3)	5 (35.7)
Highest urea mmol/L ^c	22.8 ± 6.5	22.4 ± 13.1
Highest creatinine μmol/L ^c	335 ± 100	297 ± 195
Urine output mL ^c	986 ± 1347	919 ± 867
Lowest platelet count × 10 ⁹ /L ^c	131 ± 38	126 ± 98
Highest INR ^c	1.4 ± 0.2	1.6 ± 0.8
Protein C μg/mL ^c	0.65 ± 0.37	0.47 ± 0.29
AT-III μg/mL ^c	0.78 ± 0.18	0.56 ± 0.21

^aPlus-minus values are mean ± SD.

^bValues obtained within the first 24 hours after ICU admission.

^cValues obtained within the 24 hour period preceding CRRT initiation.

the clinical trial. One patient was excluded after randomization because he had suffered significant abdominal trauma within three days prior to randomization. The intention-to-treat analysis was based on 30 patients, 16 randomized to receive heparin and 14 randomized to receive citrate. All 30 patients were followed to hospital discharge or death. Two patients crossed over from citrate to heparin, and two patients crossed over from heparin to citrate treatment. The trial stopped early because of an advantage using citrate anticoagulation. There was no significant difference between the groups in any of the baseline characteristics (Table 1). Patient survival to ICU and hospital discharge was three of 16 patients (19%) in the citrate group compared to four of 14 patients (29%) in the heparin group ($P = 0.69$).

Outcomes

A total of 79 hemofilters were included in the analysis, 43 receiving heparin and 36 receiving citrate. Within the heparin and citrate groups, 25 (58%) and 12 (33%) of hemofilters, respectively, clotted or were terminated because of high hemofilter pressures. The most frequent reason for hemofilter censoring was for patient transport in both the citrate (22.2%) and in the heparin groups (18.6%). The reasons for terminating a hemofilter in the citrate group were significantly different from those in the heparin group ($P = 0.05$; Table 2). The median hemofilter survival time was 124.5 hours (95% CI 95.3 to 157.4) in the citrate group, which was significantly longer than

Table 2. Reason for terminating hemofilter by treatment group

Reason for hemofilter termination	Citrate (N = 36)	Heparin (N = 43)
Circuit clotting	6 (16.7%)	23 (53.5%)
Switching to intermittent hemodialysis	1 (2.8%)	0
Vascular access malfunction	2 (5.6%)	0
Circuit break/leak	1 (2.8%)	0
Circuit kinking	1 (2.8%)	0
Transport to radiology/operating theatre	8 (22.2%)	8 (18.6%)
High hemofilter pressures	1 (2.8%)	2 (4.7%)
Other reasons	16 (44.4%)	10 (23.3%)

Comparison between groups, chi-square = 12.8764, $P = 0.045$.

the 38.3 hours (95% CI 24.8 to 61.9) in the heparin group ($P < 0.001$) (Fig. 1).

The Cox proportional hazard model included the effects of treatment, gender, LOD score, and AT-III levels (Table 3). The relative hazard of hemofilter clotting in the citrate group was significantly less than in the heparin group (hazard ratio, 0.37; 95% CI 0.20 to 0.70; $P = 0.002$). Increasing LOD score, male gender, and decreasing AT-III levels were independent predictors of hemofilter failure (Table 3). Neither protein C levels nor the interaction between AT-III levels and treatment assignment were significant predictors of hemofilter survival. When considering temporal changes in AT-III levels over the entire period under study, patients receiving citrate had a significantly greater rise in their AT-III levels over time compared to those receiving heparin after adjusting for illness severity as measured by the LOD score ($P = 0.038$). Age and gender were not found to be significantly predictive of temporal changes in AT-III levels during the period under study.

Adverse events

The duration of time where patients randomized to the citrate or the heparin group received their assigned anticoagulation was 2079 hours and 1444 hours, respectively. Hemofilters were significantly more often terminated because of clotting in the heparin (53.5%) compared to the citrate (16.7%) group, and the resultant "down time" off renal replacement therapy accounted in large part for the shorter duration of time on continuous renal replacement therapy in the heparin group (Table 2). Definite hemorrhage did not occur in the citrate group, and occurred in seven instances in the heparin group. Occult hemorrhage occurred once in both the citrate and heparin group. Patients randomized to receive citrate trended toward a reduced rate of hemorrhage (relative risk of 0.17; 95% CI 0.03 to 1.04, $P = 0.06$; Table 4). After adjustment for AT-III levels and LOD score, the relative risk of hemorrhage with citrate anticoagulation was significantly lower than that with heparin (relative risk of 0.14; 95% CI 0.02 to 0.96, $P = 0.05$; Table 5). In the multivariable model, AT-

III levels trended toward a positive association with the risk of hemorrhage. Patient age, gender, LOD score, the etiology of renal failure, and protein C levels were not significant predictors of hemorrhage. A total of 15 units and 20 units of red blood cells were transfused, respectively, in the citrate and heparin groups. The relative risk of red blood cell transfusion was lower in the citrate group, but was not statistically significant (relative risk 0.53, 95% CI 0.24 to 1.20; $P = 0.13$; Table 4). A total of 35 units and 5 units of plasma were transfused, respectively, in the citrate and heparin groups. The relative risk of plasma transfusion was also not statistically significant between citrate and heparin groups (relative risk 4.95, 95% CI 0.47 to 52.30; $P = 0.18$; Table 4).

Three episodes of metabolic alkalosis occurred in one patient receiving citrate, and no episodes of alkalosis occurred in any of the patients receiving heparin. Likewise, two episodes of hypocalcemia occurred in one patient receiving citrate, and no episodes of hypocalcemia occurred in any of the patients receiving heparin. None of the episodes of metabolic alkalosis or hypocalcemia were deemed to be life threatening.

DISCUSSION

Continuous renal replacement therapy is an important component in the treatment of ARF because it offers better hemodynamic tolerance, improved delivered doses of dialysis, and the ability to provide adequate parenteral nutrition [7, 22, 23]. For intermittent hemodialysis, problems with clotting continue to be the most important limits to dialysis adequacy aside from dialysis prescription [24]. Continuous anticoagulation has remained a major obstacle to CRRT, and a recent study utilizing either heparin or no anticoagulation in critically ill patients receiving CRRT demonstrated a median time of three hours per day where CRRT was not applied because of circuit disruption. This disruption was correlated with a lower percentage reduction in urea and creatinine [25]. Frequent hemofilter clotting may limit achieving an adequate dialysis dose, and efficient dialysis to specified end points has been associated with improved mortality in patients with ARF receiving either intermittent hemodialysis or CRRT [22, 26].

Our findings are consistent with previous findings demonstrating the superiority of citrate anticoagulation compared to unfractionated heparin or low-molecular-weight heparin with respect to hemofilter thrombus formation seen by electron microscopy [27]. The superiority of citrate over heparin is also consistent with the only previously published small randomized trial comparing the two anticoagulants, with median hemofilter survival times of 70 hours and 40 hours, respectively, in the citrate and heparin groups [12]. However, the previous trial did not adjust for illness severity, gender, and AT-III levels,

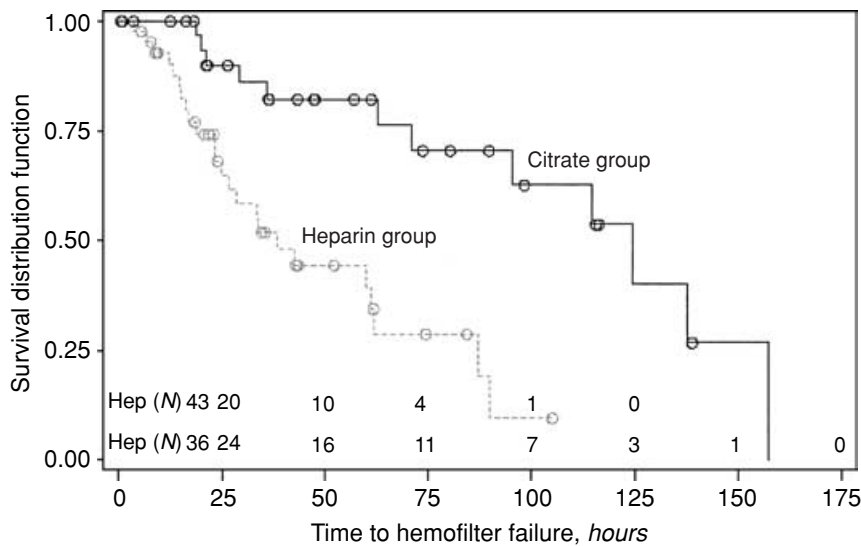


Fig. 1. Kaplan-Meier survival function indicating hemofilter survival times between heparin and citrate treatment groups.

Table 3. Extended Cox proportional hazard model for hemofilter survival

Variable	Coefficient (β)	Robust Standard error	Wald χ^2	<i>P</i> value	Hazard ratio	95% CI
Citrate ^a	-0.992	0.323	-3.07	0.002	0.371	0.197-0.699
LOD score ^b	0.237	0.055	4.30	< 0.001	1.267	1.138-1.411
Female ^c	-0.646	0.261	-2.47	0.01	0.524	0.314-0.874
AT-III ^d	-1.541	0.612	-2.52	0.01	0.214	0.065-0.712

^aHeparin as reference.

^bLogistic organ dysfunction score.

^cMale as reference.

^dPer-unit increase in AT-III level.

Table 4. Incidence of definite or occult hemorrhage and transfusion requirements

	Citrate ^{a,b}	Heparin ^{a,b}	Relative risk ^b	<i>P</i> value
Definite or occult hemorrhage	0.01 (0-0.04)	0.13 (0.04-0.23)	0.17 (0.03-1.04)	0.06
Red blood cell transfusion <i>U</i>	0.17 (0.10-0.25)	0.33 (0.18-0.49)	0.53 (0.24-1.20)	0.13
Plasma transfusion <i>U</i>	0.40 (0.29-0.52)	0.08 (0.01-0.16)	4.95 (0.47-52.30)	0.18

^aIncident rates are defined as the rate of definite or occult hemorrhage per 24-hour period at risk (on CRRT) or units of red blood cells or plasma transfused per 24-hour period at risk (on CRRT).

^bThe numbers in brackets indicate the 95% CIs.

all of which significantly influenced hemofilter survival in this study. In an observational study of regional citrate anticoagulation, median hemofilter survival time was only 24.2 hours, and this may have been attributable to inadequate experience with regional citrate anticoagulation [28]. The median hemofilter survival of 38 hours in our heparin group is comparable with previously described median times using unfractionated heparin or no anticoagulation (15 to 51.7 hours), dalteparin (46.8 hours), and hirudin (22 hours) [12, 29-32]. Significantly fewer units of red blood cells (0.17 per day at risk) were transfused in the citrate group compared to the heparin group (0.33 per day at risk), and both of these rates compare favor-

ably to previously published rates of 1.1 units and 1 unit per day using unfractionated heparin [12, 33].

Hemofilter clotting is thought to be associated with low baseline levels of AT-III, heparin cofactor II, and tissue factor pathway inhibitor, and a rise in thrombin-antithrombin complexes, implicating thrombin generation as a major factor [34, 35]. Our finding that AT-III, in a time-dependent fashion, was a strong predictor of hemofilter clotting confirms these findings. Acquired AT-III deficiency has been well described as an etiologic factor in the microvascular thrombosis of sepsis, as have the natural anticoagulant and anti-inflammatory properties of AT-III [36-38]. However, a recent randomized trial

Table 5. Multivariable Poisson regression model of relative risk of definite or occult hemorrhage during CRRT

Variable	Relative risk	Chi-square	P value	95% CI
Intercept	0.001	7.10	0.008	0.00001–0.174
Citrate ^a	0.137	4.01	0.05	0.020–0.959
AT-III	6.647	3.03	0.08	0.789–56.003
LOD Score ^b	0.924	0.10	0.75	0.571–1.494

^aSystemic heparin anticoagulation as reference.

^bLogistic organ dysfunction score.

using AT-III in sepsis failed to demonstrate a mortality benefit [39]. The generation of clot by artificial membranes depends on the activation of surface factor XII, which subsequently initiates the clotting cascade, culminating in the generation of thrombin and fibrin [27]. AT-III's ability to inhibit almost all coagulation factors renders it the most important serpin in the formation of clot, and this may explain its independent effect on hemofilter survival compared with the lack of effect of protein C observed in this study [36]. This study also demonstrated a significantly greater increase in AT-III levels over time in the citrate group compared to the heparin group after adjustment for temporal changes in illness severity. We hypothesize that heparin binding to AT-III may account for the delayed increase in AT-III levels in those patients anticoagulated with heparin. However, despite these temporal differences in AT-III levels between groups, citrate anticoagulation remained an independent predictor of improved hemofilter survival after adjustment for these temporal differences in AT-III levels.

This study was limited because treatment assignments were randomized but unblinded. However, every effort was made to reduce bias with respect to the provision of CRRT and administration of blood products by using a transfusion threshold of 7.0 g/dL [15]. Our study was undertaken within a single geographic region with extensive familiarity with regional citrate anticoagulation and may not be generalizable. Other less experienced centers have noted both hypocalcemia and metabolic alkalosis with poorer hemofilter survival when initiating their program [28]. Every effort was made to monitor the effects of either heparin or regional citrate anticoagulation in a timely manner at least every four hours, and this was outlined in protocol form a priori. Despite this, more frequent anticoagulant monitoring in the form of INR, PTT, and posthemofilter ionized calcium measurements were permitted, and, if performed unevenly between treatment groups, may have accounted for some of the differences demonstrated in hemofilter survival. Although this study population was not at a high risk of bleeding, one could assume that the rates of bleeding would have been proportionately higher with heparin if a high bleeding risk population were studied. No significant difference in ICU or hospital mortality was found; how-

ever, the study was not powered to determine differences in mortality end points.

CONCLUSION

Our findings demonstrate the superiority of regional citrate anticoagulation over systemic heparin anticoagulation in a population of critically ill patients suffering from ARF. Given the results of this study, regional citrate anticoagulation should be advocated as the anticoagulation mode of choice in patients receiving CRRT, who are at both high risk and non-high risk for hemorrhage. Moreover, both the degree of illness severity and serum AT-III levels predict hemofilter survival time, and provide further insights into the importance of known and unknown hematologic factors in the pathophysiology of critical illness.

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