## Optimizing continuous renal replacement therapy in the ICU

Nurmohamed, S.A.

2012

# Chapter 10

# Continuous venovenous hemofiltration with citrate-buffered replacement solution is safe and efficacious in patients with high bleeding risk

**S.A. Nurmohamed**

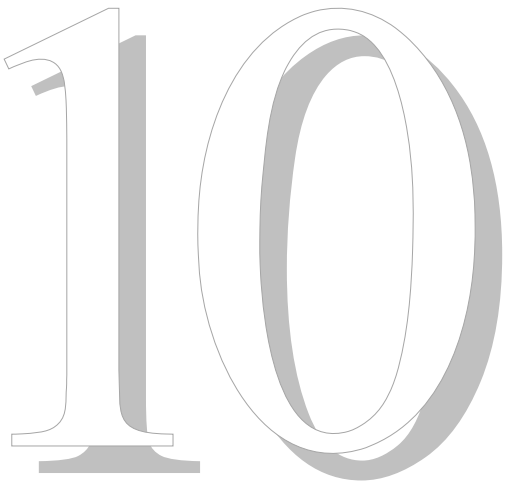
**B.P. Jallah**

**M.G. Vervloet**

**G. Yildirim**

**P.M. ter Wee**

**A.B.J. Groeneveld**



*Submitted*

## Abstract

**Objective.** Regional anticoagulation with citrate can be performed with a separate hypertonic citrate solution or with citrate added to the replacement fluid. We performed a study on the safety and efficacy of continuous venvenous hemofiltration (CVVH) with citrate-buffered replacement solution in predilution mode.

**Design.** A prospective observational study

**Setting and patients.** In 2005 a custom-made citrate-buffered replacement solution was introduced in our intensive care unit (ICU). All consecutive patients admitted in a 2-year period at the ICU with acute renal failure and a bleeding tendency treated by a protocol for CVVH with the solution were included.

**Interventions.** None

**Measurements.** Patient and CVVH characteristics, indicators and predictors of citrate accumulation, azotemic control and acid-base balance were evaluated in outcome groups in an attempt to analyse safety and efficacy. A standardized mortality rate was calculated using the simplified acute physiology score II and multivariable analysis was done to evaluate predictors and the role of citrate-buffered solution in outcome.

**Main results.** Ninety-seven patients were included and the hospital mortality after start of CVVH was 60% with a standardized mortality ratio of 1.1 (95% confidence interval 0.90-1.40). Citrate accumulation occurred in 9% and was timely identified. Patients accumulating citrate had higher plasma transaminases, higher CVVH dose and higher mortality. Azotemic control and calcium concentrations did not differ among survivors and non-survivors, whereas metabolic acidosis was more severe in non-survivors. Age rather than CVVH-characteristics and citrate accumulation predicted mortality in multivariable analysis.

**Conclusion.** In critically ill patients at increased bleeding risk with acute renal failure CVVH with citrate-containing replacement solution is safe and efficacious.

## Introduction

Despite major improvements in dialysis and supportive therapy, the mortality rate of intensive care patients with acute renal failure remains 50% or higher. Continuous renal replacement therapy (CRRT) is being used at increasing rates worldwide. One of the main disadvantages is the necessity of continuous anticoagulation for maintenance of patency of the extracorporeal circuit. Clotting of the filter may eventually contribute to blood loss. Excessive anticoagulation, however, may result in bleeding complications reported to occur in 5-26% of treatments.[1,2]. Many anticoagulation methods have been pursued including low dose heparin, low molecular weight heparin, prostanoids, mesilates and regional citrate anticoagulation.[3-5] Citrate offers an anticoagulant effect through its ability to chelate calcium. It acts regionally when administered pre-filter and thus reduces the risk of bleeding. Citrate is cleared by the tricarboxylic acid pathway in the liver, skeletal muscles and renal cortex producing bicarbonate. Citrate CRRT carries the potential risk of citrate accumulation (i.e. citrate toxicity). The main dangers are those of hypocalcemia.[6] Accumulation of calcium-citrate complexes will result in increase of the total to ionised calcium ratio; and if the metabolism of citrate fails a high anion gap acidosis.[7] Metabolic alkalosis may also develop when too much citrate enters the circulation and is adequately metabolised.[8,9] Citrate has been widely used for conventional hemodialysis and has been successfully adapted for use in continuous arteriovenous hemodialysis and filtration and continuous venovenous hemodiafiltration.[10-20] Two methods of regional citrate anticoagulation are currently being used.[5] The first and most frequently used method employs concentrated trisodium citrate together with the use of hypotonic low sodium alkali-free replacement solution or dialysate as reported by Mehta et al. and Kutsogiannis et al..[11,14] The second method employs citrate-containing replacement solution that is isotonic and has an adjusted concentration of citrate, so that the amount of bicarbonate equivalents is similar to that employed when lactate- or bicarbonate-buffered solutions are used.[13] Since 2005, patients at increased risk of bleeding are routinely treated by CVVH in our center using this method with citrate as anticoagulant and buffer in replacement solution.[13] For this prospective observational study we hypothesized its safety and efficacy. We therefore evaluated the occurrence and risk factors for citrate accumulation and the control of azotemia and acid-base balance and whether these contributed to hospital outcome.

## Patients and methods

**Patient population.** The citrate containing-replacement solution was introduced in our hospital in 2005. This solution contains citrate (13.3 mmol/L), sodium (140 mmol/L), chloride (104 mmol/L), potassium (3.0 mmol/L), glucose (5.0 mmol/L) and magnesium (0.5 mmol/L). All consecutive patients in a two year period admitted at the intensive care unit (ICU) of our university hospital with acute renal failure treated by CVVH with citrate-containing replacement solution for clinical reasons were included. The latter mostly included an increased risk of bleeding, arbitrarily defined as a platelet count below 40 $x10^9$/L, an activated partial thromboplastin time (aPTT) of more than 60 seconds or a prothrombin time test (PT-INR) of more than 2.0, a recent major bleeding or significant active bleeding. There were no exclusion criteria.

**Treatment**. Vascular access was secured by inserting an 11F double lumen catheter (GamCath. Gambro, Germany) into the jugular, femoral or subclavian vein. CVVH was carried out using a hemofiltration machine (DIAPACT, B.Braun, Germany). In all patients a 1.9 $m^2$ highly permeable cellulose triacetate hemofilter was used (NIPRO UF205, Nissho corporation, Japan). Filters were routinely changed after 72 hours. All patients were treated by CVVH in the predilution mode. A modified version of Palsson and Niles scheme was used.[13] The blood flow was set at 180 ml/min. With this blood flow, the citrate-containing replacement solution ran at a rate of 2400 ml/hr, since the rate of infusion of the citrate-based solution was continuously coupled to the blood flow. The replacement solution was infused after the blood pump in order to prevent backflow to the patient. Patients had a separate intravenous calcium drip for which we used calcium glubionate (Calcium Sandoz® containing calcium 0.225 mmol/ml, Novartis Consumer Health, The Netherlands). The rate of calcium administration depended on the systemic ionized calcium concentration. Calcium-levels in the extracorporeal circuit were not measured in order to keep the treatment simple.

**Safety monitoring and criteria to stop CVVH with citrate.** Total to ionized calcium concentration ratios, the anion gap, pH, bicarbonate and base excess were measured at least four times daily in blood samples, drawn from an arterial catheter to prevent complications such as low systemic ionized calcium, citrate accumulation and high anion gap acidosis or metabolic alkalosis if too much citrate enters the circulation. The first measurement was done one hour after initiation of CVVH. Afterwards, these measurements were done 6-hourly.

Lactate and transaminase plasma levels were measured at least once daily in the morning. The safety monitoring lasted for the duration of CVVH requirement. Citrate CVVH was stopped, if the patient fulfilled one of the following criteria: total to ionized calcium ratio of more than 2.5, persistent metabolic alkalosis with a base excess of more than 10 mmol/l, clinical signs of hypocalcemia (tetanic symptoms or prolonged QT interval) or progressive non-lactic acidosis (pH<7.20) combined with an increase in anion gap (>13 mmol/l), in the absence of endo- or exogenous acids other than citrate, suggesting citrate accumulation. If there were signs of citrate accumulation, predilution CVVH was continued using bicarbonate-based replacement solution without anticoagulation. A new episode of CVVH was defined as a period of at least 48 hours between the stop of CVVH treatment and the beginning of a new CVVH course. These were considered as new patients concerning baseline characteristics, azotemic control, calcium parameters and CVVH characteristics.

**Data collection**. We designed a predefined checklist for this prospective observational study focussing on safety and efficacy issues. Our ICU has an electronic patient file where patients' details are stored. Baseline characteristics were retrieved, including age, gender, weight, height, reason of admission and medical history. A severity of illness score at the time of ICU admission was generated by the Acute Physiology and Chronic Health Evaluation (APACHE II) score.[21] The sequential organ failure assessment (SOFA) score was obtained at admission, day 3 and at the day of start CVVH.[22] Data concerning safety were gathered: course of total and ionized calcium including the total to ionized ratio, frequency of change in calcium pump, frequency of citrate accumulation, bleeding complications and hospital mortality rate. A standardized mortality rate (SMR) to compare observed with expected mortality was calculated using the simplified acute physiology score II (SAPS II). Data concerning efficacy were retrieved such as filter life, reason of filter termination, azotemic control determined by daily plasma creatinine and urea levels, course of pH and bicarbonate during treatment and delivered dose. Delivered dose was defined as the total ultrafiltration volume delivered per kilogram preadmission body weight per hour; it was averaged per day and thus included downtime. As all patients were treated in the predilution mode, the ultrafiltration flow per hour (Quf) was adjusted by the following formula:[23,24]

$$\frac{[Qb \times 60 \times (1-Ht)]}{[(Qb \times 60 \times (1-Ht)) + Qs]} \times Quf$$

where Qb = blood flow per minute and Qs = substitution flow per hour.

**Statistical analysis**. Patients were grouped according to vital outcome during the hospital admission in an attempt to analyse whether or not CVVH-related characteristics were associated with mortality. To analyse which factor is associated with accumulation of citrate, patients were also grouped according to the occurrence of accumulation. The data were mostly normally distributed (Kolmogorov-Smirnov test $P>0.05$) and values are therefore summarized as mean±standard deviation. The independent sample t-test was test was used for continuous variables. For categorical data, the Fisher's exact test was used. Generalized estimating equations (GEE), taking repeated measurements in the same patients into account, were used to evaluate differences between outcome groups in azotemic and acid-base control, ionized and total calcium, total to ionized calcium ratio and citrate accumulation. We performed multiple logistic regression using backward elimination to assess the independent value of patient and CVVH characteristics to predict hospital mortality, including variables reaching statistical significance in univariate analyses ($P<0.05$). The odds ratio and its 95% confidence interval (CI) were calculated. The Hosmer-Lemeshow test was done to assess goodness-of-fit of the model. Citrate accumulation was included in the model. Exact P values are given and considered statistically significant if $<0.05$.

## Results

A total of 97 patients were treated by citrate-based CVVH during the study period. Five patients had two episodes of CVVH. Baseline characteristics of all patients are shown in Table 1.

**Safety.** In 11 (11%) patients treatment with citrate was withdrawn because of citrate accumulation. In retrospect, however, only 9 (9%) patients fulfilled the criteria of accumulation. In two patients citrate was withdrawn because of an increasing total to ionized calcium ratio, although the threshold of 2.5 was not reached. Accumulation usually occurred within a day after start of treatment (mean time to accumulation 13.0±8.7 h); after withdrawal of citrate the calcium parameters rapidly normalized (see supplemental figure 1; supplemental digital content 1). The characteristics of patients with or without accumulation are outlined in Table 2. Patients accumulating citrate were characterized by a greater disease severity at start of CVVH, lower body weight, higher transaminases concentrations in plasma and a higher prescribed CVVH dose. There were no complications due to citrate accumulation.

**Table 1.** Baseline characteristics.

| | Survivors n=39 | Non-survivors n=58 | P |
|---|---|---|---|
| Age (years) | 57 ± 16 | 66 ± 15 | 0.007 |
| Male (%) | 25 (64) | 42 (72) | 0.36 |
| Weight (kg) | 79 ± 14 | 76 ± 18 | 0.29 |
| APACHE II | 23 ± 5 | 24 ± 7 | 0.31 |
| SAPS II | 52 ± 9 | 57 ± 13 | 0.04 |
| SOFA day 1 | 12 ± 3 | 12 ± 4 | 0.74 |
| SOFA day 3 | 13 ± 4 | 14 ± 3 | 0.27 |
| SOFA at start CVVH | 13 ± 4 | 14 ± 3 | 0.27 |
| Manifest bleeding (%) | 18 (46) | 24 ± 41 | 0.65 |
| Blood transfusion (%) | 21 ( 54) | 32 ± 55 | 0.90 |
| Duration of ICU admission (days) | 22 ± 16 | 14 ± 14 | 0.02 |
| Reason of admission (%) | | | 0.27 |
| Postoperative | 18 (46) | 18 (31) | |
| Respiratory insufficiency | 10 ( 26) | 25 (43) | |
| Cardiogenic shock | 9 (23) | 10 (17) | |
| After CPR | 1 (3) | 3 (5) | |
| CVVH | 1 (3) | 2 (3) | |
| Sepsis at admission (%) | 13 (33) | 27 (47) | 0.19 |
| Reason of renal failure (%) | | | 0.10 |
| Sepsis | 8 (21) | 14 (24) | |
| Ischemic | 19 (49) | 35 (60) | |
| Toxic | 1 (3) | 0 | |
| Metabolic | 2 (5) | 0 | |
| Auto-immune | 2 (5) | 1 (2) | |
| Unknown | 3 (8) | 3 (5) | |
| History of CKD | 4 (10) | 5 (9) | |

Data are expressed as mean (±standard deviation) or number (percentage) of patients where appropriate. APACHE II Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiological Score; CVVH: continuous venovenous hemofiltration; ICU: intensive care unit; CPR: cardiopulmonary resuscitation; CKD: chronic kidney disease.

**Calcium homeostasis.** After initiating CVVH with citrate, ionized calcium decreased within a few hours and a gradually increasing total calcium concentration, irrespective of outcome (Figure 1). After adjustment of the calcium pump the ionized calcium concentration slowly increased. The total to ionized calcium ratio initially increased but stabilized in the first day. As demonstrated in Table 3, relatively more adjustments of the calcium pump were made in the first 48 hours of treatment as compared to the period thereafter; there were no differences in outcome groups.

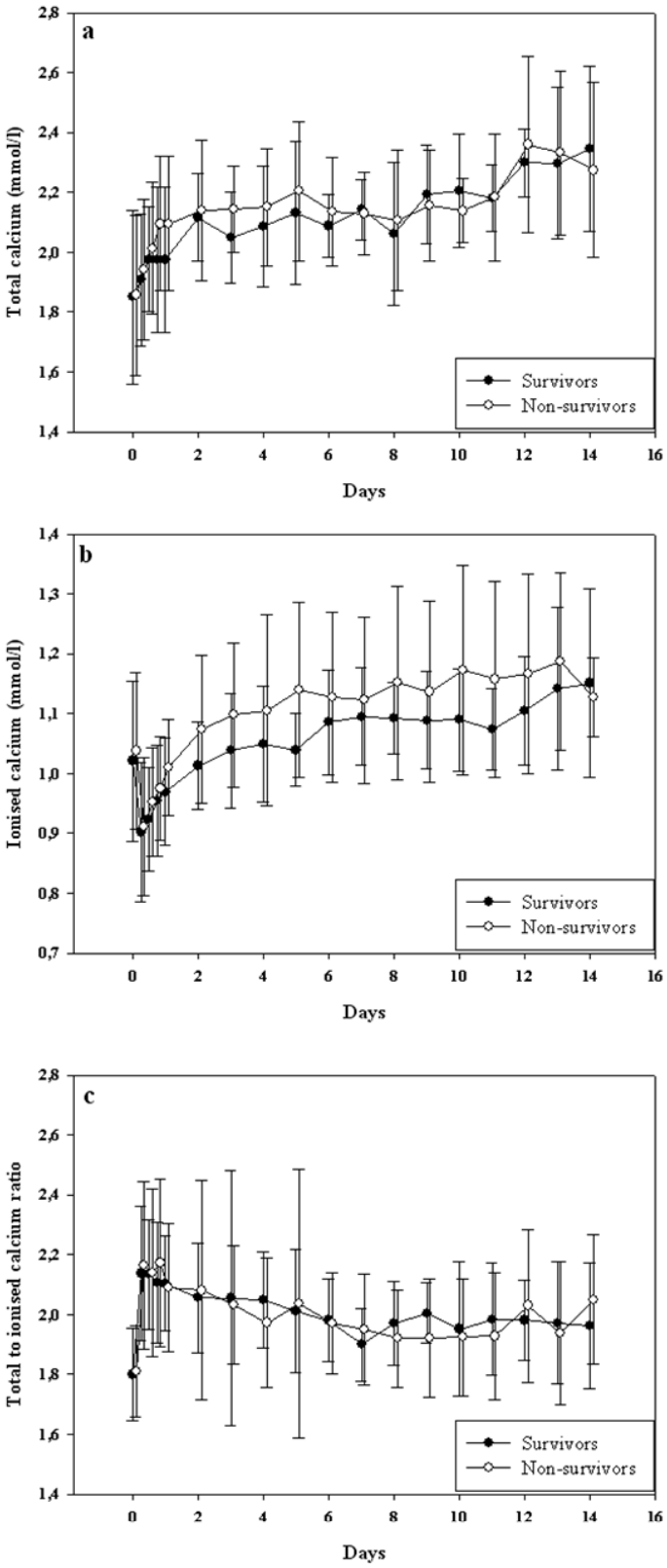



**Fig 1.** Course of total calcium (a), ionised calcium (b) and total to ionised calcium ratio (c) during treatment by continuous venovenous hemofiltration with trisodium citrate. The course of these calcium parameters was similar in survivors and non-survivors (P=0.45 for total calcium, P=0.38 for ionised calcium and P=0.83 for total to ionised calcium ratio, by GEE). Data presented as mean ± SD.

**Table 2.** Clinical and biochemical characteristics of patients with and without citrate accumulation.

| | Citrate accumulation n=9 | No citrate accumulation n=88 | P |
|---|---|---|---|
| Age (years) | 69 ± 14 | 62 ± 16 | 0.18 |
| Male (%) | 5 (56) | 62 (71) | 0.36 |
| Weight (kg) | 62 ± 8 | 79 ± 16 | 0.004 |
| APACHE II | 23 ± 4 | 24 ± 7 | 0.49 |
| SAPS II | 56 ± 8 | 55 ± 12 | 0.79 |
| SOFA day 1 | 13 ± 3 | 12 ± 4 | 0.11 |
| SOFA day 3 | 16 ± 3 | 13 ± 4 | 0.08 |
| SOFA at start CVVH | 16 ± 2 | 13 ± 4 | 0.01 |
| Duration of ICU admission (days) | 12 ± 9 | 18 ± 15 | 0.08 |
| Reason of admission (%) | | | 0.07 |
| Postoperative | 1 (11) | 35 (40) | |
| Respiratory insufficiency | 5 (56) | 30 (34) | |
| Cardiogenic shock | 3 (33) | 16 (18) | |
| After CPR | 0 | 4 (5) | |
| CVVH | 0 | 3 (3) | |
| Sepsis at admission (%) | 4 (44) | 36 (41) | 0.84 |
| Reason of renal failure (%) | | | 0.61 |
| Sepsis | 0 | 22 (25) | |
| Ischemic | 8 (89) | 46 (52) | |
| Toxic | 0 | 1 (1) | |
| Metabolic | 0 | 2 (2) | |
| Auto-immune | 0 | 3 (3) | |
| Unknown | 0 | 6 (7) | |
| History of CKD | 1 (11) | 8 (9) | |
| Filter life (h) | 12.4 ± 8.3 | 30.9 ± 23.1 | 0.0004 |
| Prescribed dose (ml/kg/h) | 30 ± 4 | 24 ± 5 | 0.001 |
| At start CVVH | | | |
| Alanine transaminase (U/l) | 652 ± 1031 | 227 ± 424 | 0.03 |
| Aspartate transaminase (U/l) | 1861 ± 3305 | 409 ± 942 | 0.01 |
| Gamma-glutamyl transferase | 86 ± 97 | 86 ± 113 | 0.99 |
| Alkaline phosphatase (U/l) | 123 ± 74 | 132 ± 154 | 0.80 |
| Bilirubin (µmol/l) | 133 ± 133 | 53 ± 106 | 0.21 |
| Lactate dehydrogenase (U/l) | 1396 ± 1088 | 1626 ± 3336 | 0.73 |
| PT-INR | 1.75 ± 0.38 | 1.78 ± 0.77 | 0.84 |
| Albumin (g/l) | 19 ± 4 | 17 ± 5 | 0.32 |
| Lactate (mmol/l) | 6.2 ± 3.6 | 3.5 ± 3.4 | 0.17 |
| Hospital mortality | 6 (86) | 50 (59) | 0.02 |

Data are expressed as mean (±standard deviation) or number (percentage) of patients where appropriate. APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiological Score; CVVH: continuous venovenous hemofiltration; ICU: intensive care unit; CPR: cardiopulmonary resuscitation; CKD: chronic kidney disease; PT-INR: prothrombin time–international normalized ratio.

**Table 3.** Continuous venovenous hemofiltration characteristics in survivors and non-non-survivors.

| | Survivors n=39 | Non-survivors n=58 | P |
|---|---|---|---|
| At start of CVVH | | | |
| Creatinine (µmol/l) | 364 ± 186 | 312 ± 233 | 0.28 |
| Urea (mmol/l) | 20.0 ± 7.2 | 21.1 ± 12.0 | 0.63 |
| Potassium (mmol/l) | 4.8 ± 0.8 | 4.5 ± 0.8 | 0.10 |
| pH | 7.33 ± 0.11 | 7.30 ± 0.10 | 0.12 |
| Bicarbonate (mmol/l) | 19.6 ± 3.9 | 18.6 ± 4.2 | 0.24 |
| Lactate (mmol/l) | 2.9 ± 2.2 | 4.3 ± 4.0 | 0.09 |
| Diuresis (ml/day) | 547 ± 709 | 601 ± 622 | 0.75 |
| aPTT (sec) | 50 ± 34 | 55 ± 30 | 0.51 |
| PT-INR | 1.63 ± 0.56 | 1.88 ± 0.82 | 0.14 |
| Blood flow (ml/min) | 180 ± 0 | 180 ± 0 | 1.00 |
| Substitution flow (ml/h) | 2403 ± 16 | 2397 ± 59 | 0.54 |
| Prescribed dose (ml/kg/min/h) | 24 ± 4 | 26 ± 6 | 0.13 |
| Filter life (hours) | 38 ± 24 | 23 ± 20 | 0.004 |
| Real citrate accumulation (n) | 1 (2.6%) | 8 (13.8%) | 0.04 |
| Calcium pump changes | | | |
| day 1 | 2.2 ± 1.3 | 2.2 ± 1.5 | 0.99 |
| day 2 | 1.6 ± 1.6 | 2.0 ± 2.0 | 0.37 |
| day 3 | 1.5 ± 1.4 | 1.6 ± 1.2 | 0.70 |
| day 5 | 1.6 ± 1.3 | 1.2 ± 1.1 | 0.99 |
| day 7 | 1.9 ± 1.5 | 1.1 ± 1.1 | 0.18 |
| Duration of CVVH (h) | 219 ± 237 | 223 ± 507 | 0.96 |

Data are expressed as mean (± standard deviation) or number of patients where appropriate; CVVH: continuous venovenous hemofiltration; aPTT: activated partial thrombplastin time; PT-INR: prothrombin time–international normalized ratio.

**Mortality.** The hospital mortality of all patients treated by citrate CVVH was 60%. The calculated expected mortality using the SAPS II score was 55%. With an overall standardized mortality ratio of 1.1 (95% confidence interval: 0.90-1.40), observed mortality in the studied group is comparable to what was expected. At initiation of CVVH, the lactate level was higher in the group of non-survivors (Table 3); during the course of treatment, the lactate levels remained higher at several time points and predicted mortality (β=-2.8 and P=0.0001 by GEE). Citrate accumulation predicted non-survival (P=0.03 by GEE). Multiple logistic regression using backward selection revealed that age was associated with hospital mortality, independently of CVVH characteristics or citrate accumulation (odds ratio 1.036; confidence interval 1.005-1.068, P=0.02). The Hosmer-Lemeshow test ($X^2$ 12.1, df8, P=0.15) indicated that the model calibrated reasonably.

**Efficacy.** CVVH with citrate resulted in adequate azotemic control (see supplemental figure 2; supplemental digital content 2), irrespective of outcome. Hypernatremia or severe metabolic alkalosis attributable to the CVVH treatment was not observed. Serum bicarbonate and pH levels normalized gradually after start of CVVH (see supplemental figure 3; supplemental digital content 3); these parameters, however, were lower in non-survivors than in survivors.

## Discussion

Treatment of patients in the ICU at increased bleeding risk with acute renal failure by CVVH with citrate-containing replacement solution appears to be safe and efficacious, since outcome was more related to patient than to CVVH characteristics, including citrate accumulation and azotemic control.

Although the use of citrate as a regional anticoagulant in CRRT is gradually increasing worldwide, the technique with citrate incorporated in the replacement solution is not applied frequently partly because of the limited availability of this fluid. Furthermore, many physicians are still reluctant to use citrate because of its potential hazards. However, the greatest risk of treatment with citrate consists of the uncontrolled infusion of hypertonic citrate causing severe hypocalcemia with adverse cardiovascular events or electrolyte and acid-base disturbances.[6-9,25] In our observational study in which we primarily focused on safety and efficacy issues, these hazards appeared to be rare with isotonic citrate-based replacement solution. Death attributable to treatment by citrate-containing replacement solution is indeed unlikely as the SMR was approximately one, with a hospital mortality that is comparable with other studies.[26,27] In one study treatment with hypertonic citrate and CVVH in postdilution mode reduced mortality when compared to nadroparin as systemic anticoagulant.[19] In a recent trial, however, CVVH with citrate-containing replacement solution was equivalent when compared to CVVH with heparin.[20] The results of a multicenter randomized trial comparing citrate-containing replacement fluid with bicarbonate-containing fluid and heparin are awaited (NCT 0209378). Some investigators have adopted the technique of regional anticoagulation with citrate added to the replacement fluid originally described elsewhere [13] and the results concerning safety and efficacy were promising.[28-32]

Citrate accumulation was observed in less than 10% of our patients. With our safety monitoring protocol accumulation was identified in time and after withdrawal of citrate the total to ionized calcium ratio normalized rapidly without side effects. The occurrence of

accumulation was associated with increased mortality, as the patients accumulating citrate were characterized by greater disease severity at initiation of CVVH, so that citrate accumulation did not independently contribute to mortality. Severe liver enzyme abnormalities (especially alanine transaminase, aspartate transaminase) and higher CVVH dose were major risk factors. However, minor liver enzyme abnormalities may not constitute a contra-indication for CVVH with citrate. Moreover, Kramer et al. demonstrated the feasibility of citrate anticoagulation in patients with advanced liver cirrhosis [33] and our study suggests that lower-dosed treatment may circumvent citrate accumulation; in this setting of treatment with citrate, CVVH dose is coupled to citrate dose. When accumulation occurs, CVVH is continued without anticoagulation; it is therefore not surprising that the filter life is reduced in this group. The current practice in our ICU is that CVVH and thus citrate dose is lowered in some cases of accumulation; if the total to ionised calcium ratio does not normalise within a few hours CVVH is continued with bicarbonate-buffered replacement fluid without anticoagulation.

Hypernatremia or severe metabolic alkalosis as a consequence of trisodium citrate overload, attributable to the treatment was not seen in our survey. This of course is explained by the isotonic composition of the replacement solution. These metabolic derangements are hazards of regional anticoagulation with hypertonic trisodium citrate.[8,9]

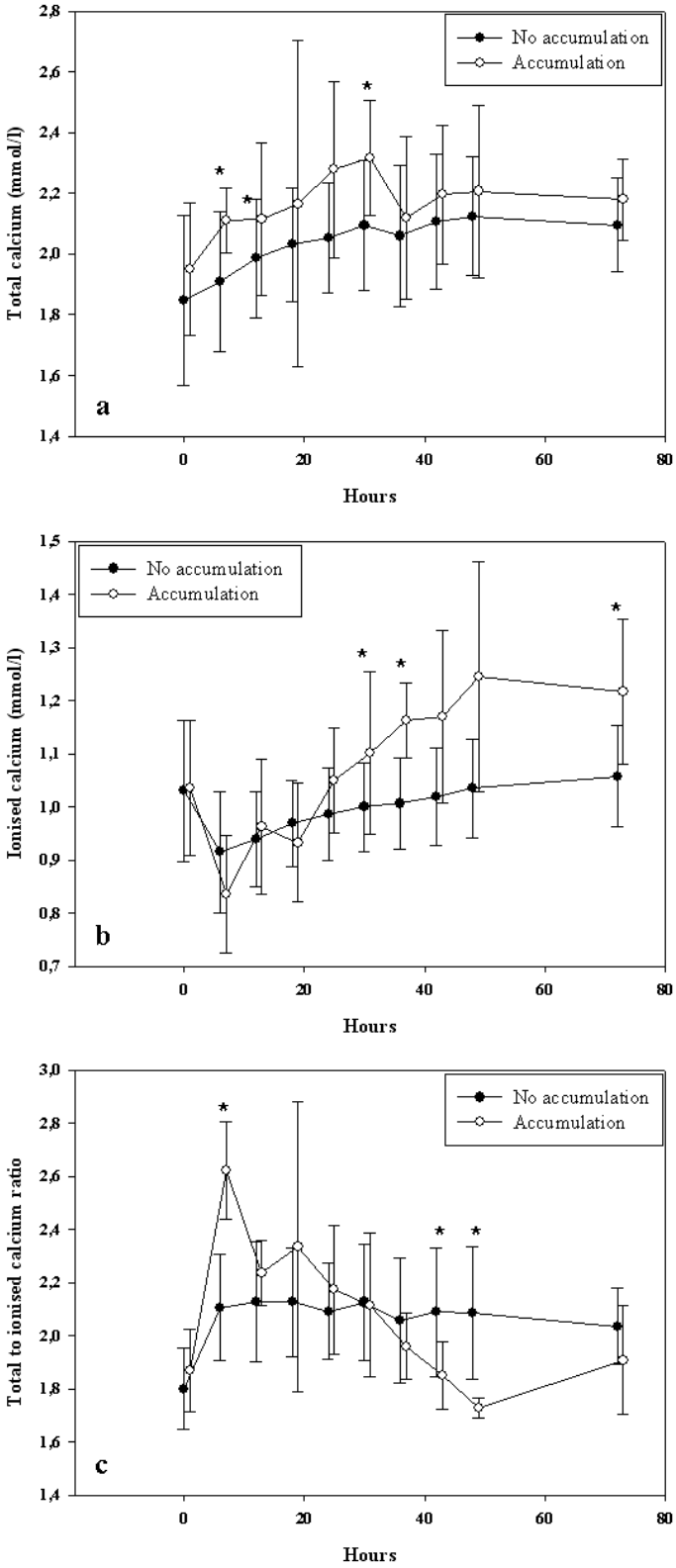
The calcium levels were kept within acceptable limits by only few calcium pump adjustments per day. The azotemic control was excellent with an acceptable decrease of serum creatinine and urea. The loss of efficiency because of delivery of the replacement solution in predilution mode is thus probably negligible, in line with previous studies.[34] After initiating CVVH there was an immediate and ultimately adequate recovery of metabolic acidosis. The lower serum pH and bicarbonate in the non-survivors may be explained by the higher lactate levels. The equivalence of citrate- with bicarbonate-buffered replacement solution was demonstrated earlier.[35]

The filter life of more than 30 hours for the entire study group was excellent and comparable with the filter life observed by others.[13,17,19,20] However, the filter life in non-survivors was approximately 15 hours shorter as compared to survivors reflecting the greater disease severity in the former group. This difference in filter life was observed earlier in patients with septic and non septic AKI.[34,36] This finding is in line with data suggesting that early circuit clotting is associated with more severe organ failure, prior systemic thrombin generation with consumptive coagulopathy, heparin resistance and elevated extracorporeal

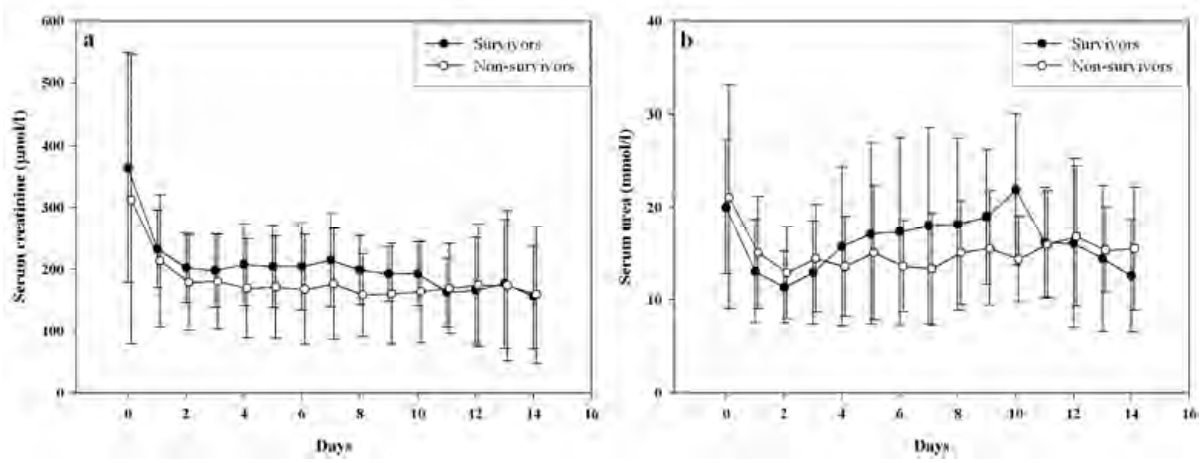
thrombin generation.[37] Our finding that advanced age is associated with increased mortality is not surprising as this represents a more vulnerable population.

Obviously, the limitations of our study include its observational nature with all inherent drawbacks such as the lack of randomisation. Our results should therefore be interpreted with caution. However, our data concerning a relatively large population provide important information on safety and efficacy with this form of CVVH treatment. These results may encourage centres to adopt the technique described here.

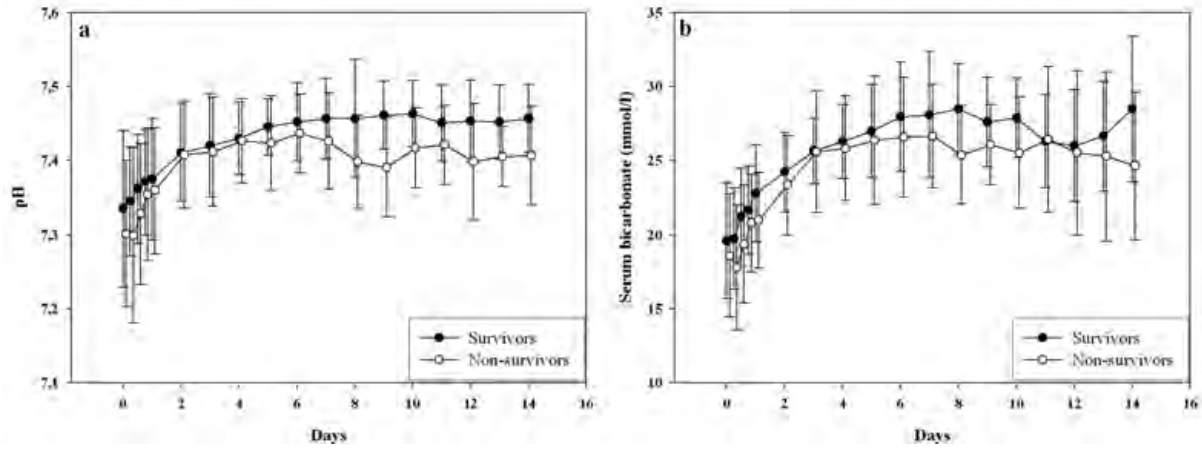
In conclusion, our results suggest that CVVH with citrate-containing replacement solution is safe and efficacious in patients with high bleeding risk, provided that the safety monitoring is strictly applied. The combination of elevated transaminases and high CVVH and thus citrate dose are risk factors for accumulation that may not contribute to mortality if timely recognized and followed by discontinuation of citrate. Patients with acute renal failure in need for CVVH and having a contra-indication for systemic anticoagulation may benefit from regional anticoagulation with citrate.




**Supplemental figure 1.** Course of total calcium (a), ionised calcium (b) and total to ionised calcium ratio (c) during treatment by continuous venovenous hemofiltration with trisodium citrate in patients with and without citrate accumulation. Patients with accumulation were converted to continuous venovenous hemofiltration with bicarbonate-based replacement solution without anticoagulation after a mean time of 13.0 ± 8.7 hr. Though at several time points there were some differences, the course of these calcium parameters was similar in both groups (P=0.21 for total calcium, P=0.92 for ionised calcium and P=0.08 for total to ionised calcium ratio, by GEE). Data presented as mean ± SD. *P < 0.05.




**Supplemental figure 2.** Course of serum creatinine (a) and urea (b) during treatment by continuous venovenous hemofiltration with trisodium citrate.The azotemic control was similar in survivors and non-survivors (P=0.22 for creatinine and P=0.97 for urea by GEE). Data presented as mean ± SD.




**Supplemental figure 3.** Course of pH (a) and serum bicarbonate (b) in survivors and non-survivors. Both parameters are higher in survivors by GEE (β=0.07, P=0.001 for pH and β=2.2, P=0.003 for bicarbonate). Data presented as mean ± SD.

**Acknowledgements**

We thank the staff of the intensive care and nephrology departments for their care of patients.

**Conflict of interest statement**

The results presented in this paper have not been published previously in whole or part.

## References


1. Ward DM, Mehta RL. Extracorporeal management of acute renal failure patients at high risk of bleeding. Kidney Int 1993; 43:S237-244.
2. Martin PY, Chevrolet JC, Suter P, Favre H. Anticoagulation in patients treated by continuous venovenous hemofiltration: a retrospective study. Am J Kidney Dis 1994; 24:806-812.
3. Mehta RL, Dobos GJ, Ward DM. Anticoagulation in continuous renal replacement procedures. Semin Dial 1992; 5:61-68.
4. Ronco C, Bellomo R, Kellum JA; Critical Care Nephrology; Saunders Elsevier Philadelphia 2009; Ch 244 Anticoagulation strategies for continuous renal replacement therapies, pp1342-1349.
5. Abramson S, Niles JL. Anticoagulation in continuous renal replacement therapy. Curr Opin Nephrol Hypertens 1999; 8:701-707.
6. Meier-Kriesche HU, Finkel KW, Gitomer JJ, DuBose TD. Unexpected severe hypocalcemia during continuous venovenous hemodialysis with regional citrate anticoagulation. Am J Kidney Dis 1999; 33:1-4.
7. Meier-Kriesche HU, Gitomer J, Finkel K, DuBose T. Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. Crit Care Med 2001; 29:748-752.
8. Kelleher SP, Schulman G. Severe Metabolic alkalosis complicating regional citrate hemodialysis. Am J Kidney Dis 1987; IX:235-236.
9. Silverstein FJ, Oster JR, Perez GO, Materson BJ, Lopez RA, Al-Reshaid K. Metabolic alkalosis induced by regional citrate hemodialysis. ASAIO Transactions 1989;35:22-25.
10. Lohr JW, Slusher S, Diederich D. Safety of regional citrate hemodialysis in acute renal failure. Am J Kidney Dis 1989; XIII:104-107.
11. Mehta RL, McDonald BR, Aguilar MM, Ward DM. Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. Kidney Int 1990; 38:976-981.
12. Mehta RL, McDonald BR, Ward DM. Regional citrate anticoagulation for continuous arteriovenous hemodialysis. Contrib Nephrol 1991; 93:210-214.
13. Palsson R, Niles JL. Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding. Kidney Int 1999; 55:1991-1997.
14. Kutsogiannis DJ, Mayers I, Chin WDN, Gibney RTN. Regional citrate anticoagulation in continuous venovenous hemodiafiltration. Am J Kidney Dis 2000; 35:802-811.
15. Tolwani AJ, Campbell RC, Schenk MB, Allon M, Warnock DG. Simplified citrate anticoagulation for continuous renal replacement therapy. Kidney Int 2001; 60:370-374.
16. Hofmann RM, Maloney C, Ward DM, Becker BN. A novel method for regional citrate anticoagulation in continuous venovenous hemofiltration (CVVHF). Ren Fail 2002; 24:325-335.
17. Gabutti L, Marone C, Colucci G, Duchini F, Schonholzer C. Citrate anticoagulation in continuous venovenous hemodiafiltration: a metabolic challenge. Intensive Care Med 2002; 28:1419-1425.
18. Mitchell A, Daul AE, Beiderlindr M et al. A new system for regional citrate anticoagulation in continuous venovenous hemodialysis (CVVHD). Clin Nephrol 2003; 59:106-114.
19. Oudemans-van Straaten HM, Bosman RJ, Koopmans M et al. Citrate anticoagulation for continuous venovenous hemofiltration. Crit Care Med. 2009; 37:545-552.

20. Hetzel GR, Schmitz M, Wissing H et al. Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrol Dial Transplant. 2011; 26:232-239.
21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985; 3:818-829.
22. De Mendonça A, Vincent JL, Suter PM et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000; 26:915-921.
23. Clark WR, Turk JE, Kraus MA Gao D. Dose determinants in continuous renal replacement therapy. Artificial Organs 2003; 27:815-820.
24. Marshall MR. Current status of dosing and quantification of acute renal replacement therapy. Part 2: Dosing paradigms and clinical implementation. Nephrology 2006; 1:181-191.
25. Ter Veldhuis SMJ, Wolthuis A, Bakker AJ, Van der Voort PHJ. Citrate, calcium, parathyroid hormone and aniongap in a patient with citrate intoxication during citrate based CVVH. Neth J Crit Care 2006; 10:74-76.
26. Nurmohamed SA, Jallah BP, Vervloet MG, Beishuizen A, Groeneveld AB. Predilution versus postdilution continuous venovenous hemofiltration: no effect on filter life and azotemic control in critically ill patients on heparin. ASAIO J 2011; 57:48-52.
27. Lines SW, Cherukuri A, Murdoch SD, Bellamy MC, Lewington AJ; The outcomes of critically ill patients with acute kidney injury receiving renal replacement therapy. Int J Artif Organs 2011; 34:2-9.
28. Thoenen M, Schmid ER, Binswanger U, Schuepbach R, Aerne D, Schmidlin D. Regional citrate anticoagulation using a citrate-based substitution solution for continuous venovenous hemofiltration in cardiac surgery patients. Wien Klin Wochenschr 2002; 114:108-114.
29. Naka T, Egi M, Bellomo R, et al. Low-dose citrate continuous veno-venous hemofiltration (CVVH) and acid-base balance. Int J Artif Organs. 2005; 28:222-228.
30. Bihorac A, Ross EA. Continuous venovenous hemofiltration with citrate-based replacement fluid: efficacy, safety, and impact on nutrition. Am J Kidney Dis 2005; 46:908-918.
31. Fealy N, Baldwin I, Johnstone M, Egi M, Bellomo R. A pilot randomized controlled crossover study comparing regional heparinization to regional citrate anticoagulation for continuous venovenous hemofiltration. Int J Artif Organs 2007; 30:301-307.
32. Schmitz M, Taskaya G, Plum J et al. Continuous venovenous haemofiltration using a citrate buffered substitution fluid. Anaesth Intensive Care 2007; 35:529-535.
33. Kramer L, Bauer E, Joukhadar C et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. Crit Care Med 2003; 31:2450-2455.
34. Nurmohamed SA, Koning MV, Vervloet MG, Groeneveld AB. Delivered dose of continuous venovenous hemofiltration predicts outcome in septic patients with acute kidney injury: a retrospective study. J Crit Care 2011; 26:213-220.
35. Aman J, Nurmohamed SA, Vervloet MG, Groeneveld AB. Metabolic effects of citrate- vs bicarbonate-based substitution fluid in continuous venovenous hemofiltration: a prospective sequential cohort study. J Crit Care 2010; 25:120-127.

36. Koning MV, Roest AA, Vervloet MG, Groeneveld ABJ, Nurmohamed SA. Determinants of outcome in non-septic critically ill patients with acute kidney injury on continuous venovenous hemofiltration. Nephron Extra 2011; 1:91-100.
37. Oudemans-van Straaten HM, Van Schilfgaarde M, Molenaar PJ, Wester JP, Leyte A. Hemostasis during low molecular weight heparin anticoagulation for continuous venovenous hemofiltration: a randomized cross-over trial comparing two hemofiltration rates. Crit Care 2009; 13:R193.