Original Article

Determinants of Calcium Infusion Rate During Continuous Veno-venous Hemofiltration with Regional Citrate Anticoagulation in Critically Ill Patients with Acute Kidney Injury

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Abstract

Background: It is unclear that how to decide the calcium infusion rate during continuous veno-venous hemofiltration (CVVH) with regional citrate anticoagulation (RCA). This study aimed to assess the determinants of calcium infusion rate during CVVH with RCA in critically ill patients with acute kidney injury (AKI).

Methods: A total of 18 patients with AKI requiring CVVH were prospectively analyzed. Postdilution CVVH was performed with a fixed blood flow rate of 150 ml/min and a replacement fluid flow rate of 2000 ml/h for each new circuit. The infusion of 4% trisodium citrate was started at a rate of 29.9 mmol/h prefilter and adjusted according to postfilter ionized calcium. The infusion of 10% calcium gluconate was initiated at a rate of 5.5 mmol/h and adjusted according to systemic ionized calcium. The infusion rate of trisodium citrate and calcium gluconate as well as ultrafiltrate flow rate were recorded at 1, 2, 4, 6, 12, and 24 h after starting CVVH, respectively. The calcium loss rate by CVVH was also calculated.

Results: Fifty-seven sessions of CVVH were performed in 18 AKI patients. The citrate infusion rate, calcium loss rate by CVVH, and calcium infusion rate were 31.30 (interquartile range: 2.70), 4.60 ± 0.48, and 5.50 ± 0.35 mmol/h, respectively. The calcium infusion rate was significantly higher than that of calcium loss rate by CVVH ($P < 0.01$). The correlation coefficient between the calcium and citrate infusion rates, and calcium infusion and calcium loss rates by CVVH was −0.031 ($P > 0.05$) and 0.932 ($P < 0.01$), respectively. In addition, calcium infusion rate (mmol/h) = 1.77 + 0.8 × (calcium loss rate by CVVH, mmol/h).

Conclusions: The calcium infusion rate correlates significantly with the calcium loss rate by CVVH but not with the citrate infusion rate in a fixed blood flow rate during CVVH with RCA.

Key words: Anticoagulation; Calcium; Citrate; Hemofiltration

Introduction

Continuous veno-venous hemofiltration (CVVH) is the most common modality of continuous renal replacement therapy (CRRT) in critically ill patients with acute kidney injury (AKI). Anticoagulation of the extracorporeal circuit is generally required. However, systemic anticoagulation might increase bleeding risk;[1] in addition, 1–5% of patients treated with heparin anticoagulation develop heparin-induced thrombocytopenia.[2,3] Anticoagulation with citrate has been recommended as the most suitable form of CRRT regional circuit anticoagulation.[4] Calcium is a necessary element in blood coagulation. Regional citrate use in the extracorporeal circuit provides anticoagulation by chelating calcium. Regional anticoagulation can be achieved by the citrate infusion prefilter. Citrate chelates calcium, decreasing

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ionized calcium in the extracorporeal circuit. This effect is reversed by calcium infusion into the systemic circulation.[5]

Recent studies have shown that regional citrate anticoagulation (RCA) is superior to regional heparin/protamine anticoagulant for the prolongation of circuit life during CRRT and is associated with fewer adverse events.[6-9] Actually, the rate of calcium infusion into the systemic circulation differs depending on the parameters of CRRT or other factors in different studies.[10-12] Therefore, it is unclear that which factors affect the calcium infusion rate during CRRT with RCA. The aim of the present study was to assess the determinants of calcium infusion rate during CVVH with RCA in critically ill patients with AKI.

Methods

Study population

The local ethics committee stated that its permission was not necessary as CVVH with RCA was used to treat patients with AKI in the Intensive Care Unit (ICU) of the Beijing Chaoyang Hospital on a routine basis. The study was carried out in accordance with the *Declaration of Helsinki*. All consecutive patients with AKI treated with CVVH in the 20-bed surgical ICU from November 2014 to May 2015 were enrolled in the study. Overall, 18 patients were included: 11 males and seven females (mean age 59.5 ± 17.0 years). AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[4] Patients were excluded if they were younger than 18 years, had hypercalcemia (>1.35 mmol/L) or hypocalcemia (<0.9 mmol/L) before starting CVVH, had hepatic failure, had active bleeding, required prolonged systemic heparin anticoagulation, were pregnant, or were moribund.

Continuous veno-venous hemofiltration protocol

Vascular access was obtained using an 11.5-F double-lumen catheter (Teleflex, Arrow, IN, USA). Postdilution CVVH was performed with a fixed blood flow rate of 150 ml/min and a replacement fluid flow rate of 2000 ml/h for each new circuit. A 1.4-m^2 polysulfone membrane filter (AV600S, Fresenius, Bad Homburg, Germany) and CRRT device (Multifiltrate, Fresenius, Bad Homburg, Germany) were used. The replacement fluids were heated to 39°C, and a combination of buffer-free fluids, containing 113 mmol/L Na^+, 3.0 mmol/L K^+, 0.797 mmol/L Mg^{2+}, 118 mmol/L Cl^-, 10.6 mmol/L anhydrous dextrose, and bicarbonate-buffer were used postfilter, adjusted by plasma bicarbonate and pH according to the results of blood gas analysis. The circuits were disconnected at a high prefilter pressure (>280 mmHg, 1 mmHg=0.133kPa) or transmembrane pressure (>280 mmHg). After disconnection, a new circuit was initiated immediately if the patients still needed CVVH. A session of CVVH was defined as the survival time of the individual filter.

The infusion of 4% trisodium citrate was started at a rate of 220 ml/h (29.9 mmol/h). The goal of the treatment was to maintain postfilter ionized calcium between 0.25 and 0.35 mmol/L. The infusion rate of 4% trisodium citrate was adjusted according to postfilter ionized calcium [Table 1].[10] The infusion of 10% calcium gluconate postfilter was initiated at a rate of 25 ml/h (5.5 mmol/h). The goal of the treatment was to maintain the systemic ionized calcium between 1.00 and 1.35 mmol/L.[10] The infusion rate of 10% calcium gluconate was adjusted according to the systemic ionized calcium [Table 2].[10]

The ultrafiltrate flow rate was the sum of the dehydration rate by CVVH and the infusion rate of replacement fluid, bicarbonate-buffered fluids, citrate, and calcium. The dehydration rate by CVVH was adjusted by attending physicians according to the patients' clinical condition.

Data collection

Age, gender, weight, length of stay in the ICU, cause of AKI, baseline serum blood urea nitrogen, serum creatinine and potassium, urine output, renal function, severity of illness, and organ failure of each patient were recorded before initiating the first session of CVVH. The renal function was classified according to the KDIGO criteria.[4] The severity of illness and organ failure were scored using the Acute Physiology and Chronic Health Evaluation II systems[13] and the Sequential Organ Failure Assessment score.[14] The baseline values of the systemic total calcium and ionized calcium were recorded

Table 1: Adjustment of citrate infusion rate in the prefilter

Postfilter ionized Ca^{2+} (mmol/L)	Change in citrate infusion rate		Repeat postfilter ionized Ca^{2+}
	mmol/h	ml/h	
<0.25	↓1.32	20	In 1 h
0.25–0.35	No change		In 4 h
0.36–0.40	↑1.32	10	In 1 h
0.41–0.45	↑2.64	20	In 1 h
>0.45	↑3.97	30	In 1 h

The infusion of 4% trisodium citrate prefilter was started at a rate of 29.9 mmol/h; the goal of the treatment was to maintain postfilter ionized calcium between 0.25 and 0.35 mmol/L; the infusion rate was adjusted according to the postfilter ionized calcium.↑: Increase; ↓: Decrease.

Table 2: Adjustment of Ca^{2+} infusion rate in the postfilter

Systemic ionized Ca^{2+} (mmol/L)	Change in Ca^{2+} infusion rate		Repeat systemic ionized Ca^{2+}
	mmol/h	ml/h	
<0.75	↑2.20	10.0	In 2 h
0.75–0.85	↑1.65	7.5	In 2 h
0.86–0.90	↑1.10	5.0	In 4 h
0.91–0.99	↑0.50	2.3	In 6 h
1.00–1.35	No change		In 6 h
>1.35	↓1.10	5.0	In 4 h

The infusion of 10% calcium gluconate postfilter was initiated at a rate of 5.5 mmol/h; the goal of the treatment was to maintain the systemic ionized calcium between 1.00 and 1.35 mmol/L; the infusion rate was adjusted according to the systemic ionized calcium. ↑: Increase; ↓: Decrease.

before initiating each session of CVVH. The postfilter ionized calcium, systemic total calcium and ionized calcium, and ultrafiltrate total calcium and ionized calcium were measured at 1, 2, 4, 6, 12, and 24 h after starting CVVH for each new circuit, respectively. The systemic and ultrafiltrate total calcium was detected by the arsenazo III method, and the systemic and ultrafiltrate ionized calcium was detected using an electrolyte analyzer (GEM Premier 3000, Lexington, MA, USA). Simultaneously, the infusion rate of citrate and calcium as well as the ultrafiltrate flow rate was also recorded during CVVH. The calcium loss rate by CVVH was calculated as (ultrafiltrate flow rate, L/h) × (ultrafiltrate total calcium concentration, mmol/L). The pH, anion gap, lactate, HCO_3^-, K^+, and Na^+ of arterial blood were monitored at least 4 times daily. The first measurement was done 1 h after initiation of each session of CVVH. Routine daily laboratory measurements included acid-base balance, electrolytes, hemoglobin, and white blood cell and platelet counts. The survival time of the individual filter was also recorded. All data were collected prospectively by a specialized doctor who did not participate in patient care.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]). Categorical variables were presented as number and percentage. The variables were compared using the Student's *t*-test or Chi-square test (two-sided) as appropriate. Linear regression analysis was used to calculate the correlation coefficient between the calcium infusion rate and the citrate infusion rate, and the calcium loss rate by CVVH. A two-sided $P < 0.05$ was considered statistically significant. SPSS 20.0 (SPSS, Chicago, IL, USA) was used for analysis.

Results

A total of 57 sessions of CVVH were performed in 18 patients with AKI. The mean survival time of filters was 24.5 ± 13.0 h. Patient characteristics and baseline data at the start of initial CVVH are shown in Table 3. The mean ultrafiltrate flow rate at the start of initial CVVH was 29.63 ± 5.00 ml·kg^{-1}·h^{-1}.

Metabolic control

Metabolic derangements before the start of CVVH and at the end of each session of CVVH are shown in Table 4. Metabolic acidosis was corrected at the end of CVVH. The systemic total calcium/systemic ionized calcium <2.25 was found in 1 of 57 sessions of CVVH.

Data of measurements

The baseline values of systemic total calcium and ionized calcium were 2.01 ± 0.28 mmol/L and 1.04 ± 0.17 mmol/L, respectively, before starting CVVH. The concentration of the systemic total calcium and ionized calcium, and ultrafiltrate total calcium and ionized calcium at 1, 2, 4, 6, 12, and 24 h during CVVH are shown in Table 5. The overall concentrations of the systemic total calcium and ionized calcium, and ultrafiltrate total calcium and ionized calcium during CVVH were 2.13 ± 0.24 mmol/L, 1.08 ± 0.11 mmol/L, 1.87 ± 0.18 mmol/L, and 0.47 ± 0.10 mmol/L, respectively [Table 5]. The ultrafiltrate total calcium was significantly lower than the systemic total calcium ($P < 0.01$), but significantly higher

Table 3: Patient characteristics and baseline data at the start of initial CVVH

Characteristics	All patients (n = 18)
Age (mean ± SD, years)	59.5 ± 17.0
Male (n)	11
Weight (mean ± SD, kg)	70.56 ± 11.97
Cause of AKI (n)	
Sepsis	10
Ischemic	6
Other	2
Classification of AKI at initial CVVH (n)	
KDIGO I	0
KDIGO II	3
KDIGO III	15
Oliguria	12
At the start of initial CVVH	
APACHE II (mean ± SD)	21.56 ± 5.05
SOFA (mean ± SD)	7.67 ± 3.48
Length of stay in ICU prior to CVVH (mean ± SD, days)	2.89 ± 1.64
Diuresis in 24 h prior to CVVH (median [IQR], ml)	300 (1527.50)
Creatinine (mean ± SD, μmol/L)	424.89 ± 70.91
Urea (mean ± SD, mmol/L)	30.72 ± 6.25
Potassium (mean ± SD, mmol/L)	4.88 ± 0.79
Serum ionized calcium (mean ± SD, mmol/L)	1.04 ± 0.17
Serum total calcium (mean ± SD, mmol/L)	2.01 ± 0.28
Ultrafiltrate flow rate (mean ± SD, ml·kg^{-1}·h^{-1})	29.63 ± 5.00

AKI: Acute kidney injury; CVVH: Continuous veno-venous hemofiltration; KDIGO: Kidney Disease: Improving Global Outcomes; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential organ failure assessment; IQR: Interquartile range; SD: Standard deviation.

Table 4: Metabolic derangements at the start and end of individual hemofiltration sessions, n (%)

Metabolic derangements	Start of HF sessions (n = 57)	End of HF sessions (n = 57)	χ^2	P
Metabolic event (mmol/L)				
Plasma sodium <130	6 (10.5)	4 (7.0)	0.298	0.74
Plasma sodium >150	4 (7.0)	3 (5.3)	0.117	0.69
Plasma bicarbonate <20	14 (24.6)	3 (5.3)	4.119	0.01
Plasma bicarbonate >30	4 (7.0)	2 (3.5)	0.563	0.67
Plasma pH <7.30	16 (28.1)	9 (15.8)	0.791	0.17
Plasma pH >7.50	1 (1.8)	3 (5.3)	0.896	0.61
Plasma lactate >2	18 (31.6)	16 (28.1)	0.027	0.84
Systemic ionized calcium (mmol/L)				
<1.0	3 (5.3)	4 (7.0)	0.117	0.69
>1.35	0 (0)	1 (1.8)	0.974	0.32
totCa/iCa >2.25	0 (0)	1 (1.8)	0.974	0.32

HF: Hemofiltration; totCa: Systemic total calcium; iCa: Systemic ionized calcium.

than the systemic ionized calcium ($P < 0.01$). The ultrafiltrate ionized calcium was significantly lower than the systemic ionized calcium ($P < 0.01$).

The citrate infusion rate, calcium loss rate by CVVH, and calcium infusion rate at 1, 2, 4, 6, 12, and 24 h during CVVH are shown in Table 6. The overall citrate infusion rate, calcium loss rate by CVVH, and calcium infusion rate during CVVH were 31.3 (IQR: 2.7), 4.60 ± 0.48, and 5.50 ± 0.35 mmol/h, respectively [Table 6]. The calcium infusion rate was significantly higher than the calcium loss rate by CVVH ($P < 0.01$). The correlation coefficient of the calcium infusion rate and the citrate infusion rate was −0.031 ($P > 0.05$) while the correlation coefficient of the calcium infusion rate and the calcium loss rate by CVVH was 0.932 ($P < 0.01$). Furthermore, the calcium infusion rate (mmol/h) = 1.77 + 0.8 × (calcium loss rate by CVVH, mmol/h) [Figure 1].

Discussion

The 2012 KDIGO Clinical Practice Guidelines for AKI suggested RCA as the first choice of anticoagulant in patients with AKI undergoing CRRT, regardless of the patient's bleeding risk and coagulation status.[4] The citrate infused prefilter is partially removed by convection or diffusion and enters the systemic circulation. The chelated calcium in the systemic circulation is liberated when citrate is completely metabolized in the Krebs cycle, mainly in the liver but also in the skeletal muscle and the renal cortex. Therefore, the calcium infusion rate depends mainly on the calcium loss rate by CRRT in the absence of citrate accumulation.[15,16] In the present study, citrate was infused upstream in the extracorporeal circuit of CVVH at an initial infusion rate of 29.9 mmol/h with a fixed blood flow rate of 150 ml/min and a fixed calcium-free replacement fluid flow rate of 2000 ml/h postfilter, the citrate infusion rate was adjusted according to postfilter ionized calcium, which was maintained between 0.25 and 0.35 mmol/L. Simultaneously, the calcium infusion was initiated at 5.5 mmol/h through a central venous line and adjusted according to the systemic ionized calcium, which was maintained between 1.00 and 1.35 mmol/L. A strong positive correlation was found between the calcium infusion rate and the calcium loss rate by CVVH ($P < 0.01$). Furthermore, the calcium infusion rate can be calculated if the ultrafiltrate flow rate and the ultrafiltrate total calcium concentration are known, and the calcium infusion rate (mmol/h) = 1.77 + 0.8 × (calcium loss rate by CVVH, mmol/h) [Figure 1]. This means that the calcium infusion rate might be determined as soon as possible if the calcium loss rate by CVVH is monitored at an early stage of CVVH.

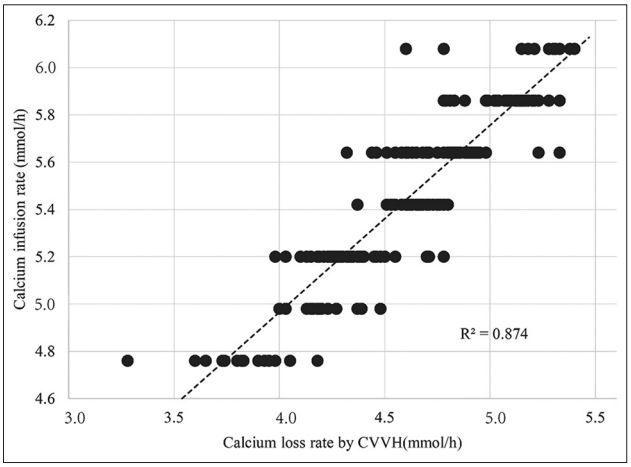

Figure 1: Correlation between calcium infusion rate and calcium loss rate by CVVH. Calcium infusion rate (mmol/h) = 1.77 + 0.8 × (calcium loss rate by CVVH, mmol/h). CVVH: Continuous veno-venous hemofiltration.

Table 5: Systemic total calcium and ionized calcium, and ultrafiltrate total calcium and ionized calcium at different time during CVVH, mean ± SD

Concentration (mmol/L)	1 h (n = 57)	2 h (n = 57)	4 h (n = 55)	6 h (n = 55)	12 h (n = 52)	24 h (n = 37)	Total (1–24 h) (n = 313)
Systemic total calcium	2.09 ± 0.23	2.14 ± 0.22	2.17 ± 0.20	2.18 ± 0.20	2.19 ± 0.19	2.19 ± 0.22	2.13 ± 0.24
Systemic ionized calcium	1.04 ± 0.12	1.07 ± 0.10	1.10 ± 0.08	1.11 ± 0.07	1.11 ± 0.07	1.12 ± 0.07	1.08 ± 0.11
Ultrafiltrate total calcium	1.86 ± 0.20	1.87 ± 0.19	1.89 ± 0.19	1.88 ± 0.19	1.87 ± 0.19	1.88 ± 0.14	1.87 ± 0.18*
Ultrafiltrate ionized calcium	0.45 ± 0.11	0.46 ± 0.09	0.47 ± 0.09	0.46 ± 0.10	0.51 ± 0.10	0.53 ± 0.10	0.47 ± 0.10†

*Ultrafiltrate total calcium versus systemic ionized calcium ($t = 66.33$; $P<0.01$); †Ultrafiltrate ionized calcium versus systemic ionized calcium ($t = 81.12$, $P<0.01$); CVVH: Continuous veno-venous hemofiltration; SD: Standard deviation.

Table 6: Citrate infusion rate, calcium loss rate by CVVH, and calcium infusion rate at different time during CVVH

Variables (mmol/h)	1 h (n = 57)	2 h (n = 57)	4 h (n = 55)	6 h (n = 55)	12 h (n = 52)	24 h (n = 37)	Total (1–24 h) (n = 313)
Citrate infusion rate	29.9 (29.9–32.6)	31.3 (29.9–32.6)	32.6 (29.9–32.6)	32.6 (31.3–34.0)	32.6 (31.3–32.6)	32.6 (31.3–32.6)	31.3 (29.9–32.6)*
Calcium loss rate by CVVH	4.49 ± 0.55	4.7 (4.3–4.9)	4.67 ± 0.46	4.72 ± 0.41	4.8 (4.3–5.1)	4.7 (4.3–4.9)	4.60 ± 0.48†
Calcium infusion rate	5.46 ± 0.32	5.49 ± 0.33	5.49 ± 0.349	5.49 ± 0.36	5.48 ± 0.35	5.48 ± 0.32	5.50 ± 0.35

*Correlation coefficient of calcium infusion rate and citrate infusion rate was –0.031($P>0.05$); †Correlation coefficient of calcium infusion rate and calcium loss rate by CVVH was 0.932 ($P<0.01$); Continuous variables in symmetric distribution or in skewed distribution are presented as mean ± SD or median (IQRs). CVVH: Continuous veno-venous hemofiltration; SD: Standard deviation; IQRs: Interquartile ranges.

About 50% of the total calcium in the plasma exists in the ionized form. The remainder is either bound to the plasma proteins (about 40%) or complexed in the nonionized form with anions such as phosphate and citrate (about 10%). Because calcium bound to the plasma proteins cannot be filtered by CVVH, about 60% of the systemic total calcium is filterable in CVVH[17] and the sieving coefficient of calcium unbound to the plasma proteins is close to 1.0.[15] Theoretically, the concentration of the ultrafiltrate total calcium should be slightly higher than the concentration of the systemic ionized calcium. Actually, this study found the ultrafiltrate total calcium to be significantly higher than the systemic ionized calcium ($P < 0.01$), and the ultrafiltrate ionized calcium to be significantly lower than the systemic ionized calcium ($P < 0.01$). This phenomenon can be interpreted as follows. When citrate flows through the filter during RCA, citrate chelates the ionized calcium and decreases the concentration of the ionized calcium in the extracorporeal circuit. Calcium bound to plasma proteins is partially dissociated with a decrease in the concentration of ionized calcium and filtered mainly in the form of a calcium-citrate complex by CVVH.

Usually, the citrate infusion rate is adjusted with the change in extracorporeal blood flow rate to maintain the concentration of postfilter ionized calcium between 0.25 and 0.35 mmol/L during RCA. This study did not find any correlation between the calcium infusion rate and the citrate infusion rate in a fixed blood flow rate (150 ml/min). Further studies are warranted to investigate the correlation between the calcium infusion rate and the citrate infusion rate when the blood flow rate changes.

Almost 99% of all the calcium in the body is stored in the bone, with only about 1% in the extracellular fluid and 0.1% in the intracellular fluid. One of the most important regulators of bone uptake and release of calcium is parathyroid hormone (PTH). When the extracellular fluid calcium concentration falls below normal, the parathyroid glands are directly stimulated by the low calcium levels to promote the increased secretion of PTH.[18] PTH then acts directly on the bones to release large amounts of calcium into the extracellular fluid, thereby bringing the calcium levels back to normal.[19] When the calcium ion concentration is elevated, PTH secretion decreases and excess calcium is deposited in the bones. Under certain conditions, calcium can be secreted into the intestinal lumen and excreted in the feces. Calcium can also be excreted by kidney. An increase in plasma phosphate stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion. The opposite occurs with a reduction in plasma phosphate concentration.[20] The present study found the calcium infusion rate to be significantly higher than the calcium loss rate by CVVH ($P < 0.01$), which suggests that the calcium infusion rate postfilter is affected by calcium excretion via non-CVVH routes or redistribution of calcium in the body.

The study had several limitations. First, PTH was not monitored during CVVH; hence, the effect of PTH on the calcium infusion rate was uncertain. Second, the excretion of calcium in the urine was not measured. Third, albumin infusion, hemodilution, or hemoconcentration might affect the level of plasma proteins. Unfortunately, as the dynamic change in plasma proteins was not monitored, it is unclear whether plasma proteins correlate with the calcium infusion rate. Fourth, the replacement fluid flow rate (2000 ml/h) was constant in this study. Therefore, the study results cannot be extrapolated as the replacement fluid flow rate changes, but a fixed replacement fluid flow rate of 2000 ml/h is suitable for most of the adult patients requiring CVVH.

In conclusion, the calcium infusion rate correlates significantly with the calcium loss rate by CVVH, but not with the citrate infusion rate in a fixed blood flow rate of extracorporeal circuit during CVVH with RCA. The ultrafiltrate total calcium is significantly higher than the systemic total calcium while the ultrafiltrate ionized calcium is significantly lower than the systemic ionized calcium, which indicates CVVH removes calcium mainly in the form of a citrate-calcium complex. The calcium infusion rate is significantly higher than the calcium loss rate by CVVH, which suggests that the calcium infusion rate is also affected by calcium excretion via non-CVVH routes or redistribution of calcium in the body.

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Conflicts of interest

There are no conflicts of interest.

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