

Calcium flux in continuous venovenous haemodiafiltration with heparin and citrate anticoagulation

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Renal replacement therapy (RRT) with continuous venovenous haemodiafiltration (CVVHD-F) is commonly used in the care of the critically ill for a variety of indications, including acute renal failure of various aetiologies, management of severe electrolyte and acid–base disturbances, and detoxification. Anticoagulation of the circuit is implemented to increase circuit life and minimise therapy downtime. This is usually achieved by either systemic heparinisation of the patient or regional heparinisation of the circuit, with or without protamine reversal on return to the patient.¹

Contraindications to heparin are common among critically ill patients, and regional circuit anticoagulation with citrate is used as an alternative. A recent trial demonstrated that citrate had similar efficacy for circuit anticoagulation to nadroparin, a low-molecular-weight heparin, and appeared to offer a survival benefit in post-hoc subgroup analysis.²

Citrate exerts its anticoagulant effect by chelating calcium, an essential cofactor to clotting.³ Both ionised calcium (iCa^{2+}) and calcium bound to diffusible solutes, such as citrate, can traverse dialyser membranes to equilibrate with the dialysis solution.⁴ Standard dialysis and replacement solutions contain calcium; however, to avoid reversal of anticoagulation within the circuit, calcium is omitted from some commercial solutions designed for citrate anticoagulation.⁵ Consequently, significant amounts of calcium may shift to the effluent, necessitating systemic calcium supplementation to avoid hypocalcaemia.⁶

Hypocalcaemia may also result from the fraction of citrate not cleared by CVVHD-F being returned to the systemic circulation. Citrate is predominantly metabolised by hepatocytes with release of chelated ions and bicarbonate. Significant hepatic dysfunction is a contraindication to citrate anticoagulation, as it can result in citrate accumulation and severe ionised hypocalcaemia.⁷

Systemic hypocalcaemia is prevented by monitoring the arterial iCa^{2+} and continuous intravenous calcium replacement. The rate of replacement has largely been empirical, using infusion protocols that specify target ranges for the extracorporeal iCa^{2+} (achieved by adjusting the citrate dose) and the arterial iCa^{2+} (achieved by adjusting the calcium replacement dose).⁶ Physiological defences against hypocalcaemia are also likely to operate,⁸ and the degree to which calcium supplementation towards a target arterial iCa^{2+} actually replaces the calcium lost from the patient is unknown.

ABSTRACT

Background: Calcium chelation with citrate is an effective alternative to heparin for anticoagulation of the extracorporeal circuit during continuous venovenous haemodiafiltration (CVVHD-F). Calcium release occurs upon citrate metabolism; however, ultrafiltration of citrate-bound and free ions also occurs.

Objective: To quantify calcium loss and improve understanding of calcium homeostasis in CVVHD-F.

Methods: Calcium loss was prospectively quantified from heparinised and citrated circuits in consecutive intensive care patients requiring CVVHD-F. CVVHD-F prescription and anticoagulation choice was by the treating intensivist using commercial solutions (Gambro, Lundia, Sweden). Sample sets comprising arterial, prefilter and postfilter blood and an effluent sample were analysed for ionised total calcium (iCa^{2+}) and magnesium levels. Flow rates were then used to calculate calcium flux. Citrate dose (predilution rate) and calcium replacement followed unit protocols to maintain a circuit iCa^{2+} concentration of 0.3–0.5 mmol/L and an arterial iCa^{2+} concentration of 0.8–1.1 mmol/L.

Results: 26 heparinised circuits and 22 citrated circuits in 13 patients were included; 334 sample sets were tested. For target extracorporeal blood flows of 200 mL/min, mean predilution Prismocitrate 10/2 flows were 1660 mL/h, delivering 2.42 mmol citrate per litre of blood. For heparin, mean predilution flows of Hemosol B0 were 2058 mL/h. Mean calcium loss was 4.01 mmol/h from citrate anticoagulated circuits versus a gain of 0.24 mmol/h from heparinised circuits ($P < 0.001$). Despite calcium replacement, citrate patients experienced a mean calcium loss of 1.12 mmol/h (SD, 0.70; 95% CI 1.0–1.22 mmol/h; $P < 0.001$). Calculated effective diffusion volume (Q_E) for calcium was closer to total blood water volume in heparin circuits and closer to plasma water volume in citrate circuits.

Conclusions: Despite supplementation to maintain arterial iCa^{2+} levels, citrate anticoagulation results in a net calcium deficit. An equation for estimating required citrate dose may allow revision of citrate dosing protocols.

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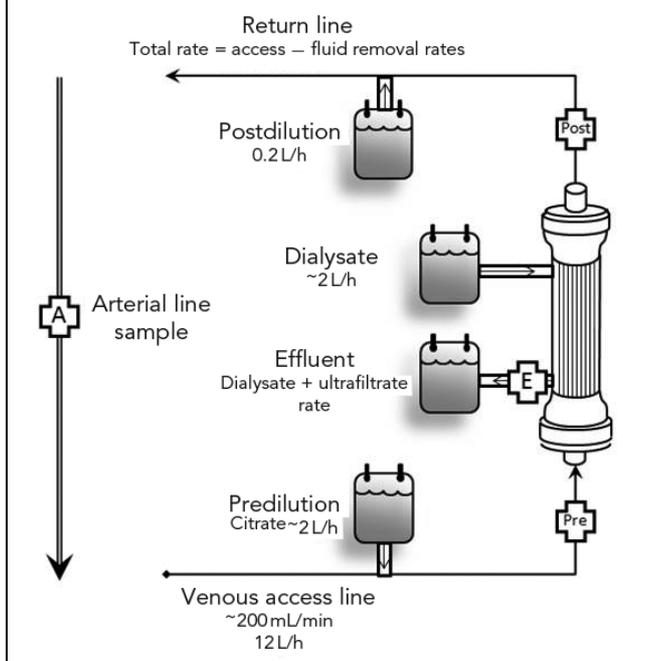
Table 1. Composition of commercial dialysis and replacement fluids*

Prismocitrate 10/2	Concentration (mmol/L)	Prismocal	Concentration (mmol/L)	Hemosol B0	Concentration (mmol/L)
Trisodium citrate [†]	10	Magnesium	0.5	Calcium	1.75
Citric acid [†]	2	Sodium	140	Magnesium	0.5
Sodium	136	Chloride	106	Sodium	140
Chloride	106	Lactate	3	Chloride	109
		Bicarbonate	32	Lactate	3
				Bicarbonate	32

* Data from product packaging. † In all calculations, the citrate concentration of Prismocitrate 10/2 is considered to be 12 mmol/L. The ratio of citric acid to trisodium citrate has been determined by the manufacturer to lessen the incidence of alkalosis that occurs with trisodium citrate alone.¹⁰

Widespread implementation of regional citrate anticoagulation in the intensive care unit has been limited by the complexity of less integrated delivery systems and increased monitoring required to deliver the therapy safely.⁹

In this study, we aimed to quantify net calcium loss and replacement from critically ill patients treated with CVVHD-F who were anticoagulated with either citrate or heparin using commercially available solutions, and to define relationships that may improve delivery of citrate anticoagulation.

Figure 1. Schematic diagram of circuit and sampling points for continuous venovenous haemodiafiltration

Crosses mark ports where study samples were taken from: A (arterial line), Pre (prefilter port where blood enters haemofilter after predilution), E (effluent sample line) and Post (posthaemofilter port). For illustration, "typical" starting flow rates are included. For clarity, blood and solution pumps are not shown. The access line is the afferent limb of the circuit taking blood from the patient. The return line is the efferent limb returning blood to patient. Fluid removal rate is the measured volume of plasma removed each hour. Ultrafiltrate rate = predilution rate + postdilution rate + fluid removal rate.

Methods

Patients

Consecutively admitted adult patients to our ICU who required RRT for at least 12 hours were included in the study. Two eligible patients were excluded due to high demand for resources. The study protocol was approved by the Human Research Ethics Committee (Tasmania) Network and included waiving of informed consent. This prospective study was purely observational and all data were available to treating clinicians.

Haemodiafiltration method

The duty intensive care physician was responsible for all decisions involving patient care, including the decision to initiate or withdraw haemodiafiltration, method of circuit anticoagulation, and prescription of CVVHD-F flow rates. Therapy was implemented by critical care nurses following unit protocols for monitoring and adjustment of therapy. Vascular access was by a 12 French double lumen haemodialysis catheter (Arrow International, Diegem, Belgium) inserted into either a femoral or internal jugular vein.

Haemodiafiltration was carried out using Prismaflex machines with a Prismaflex ST100 set containing AN69 ST membranes (Gambro, Lundia, Sweden). Figure 1 demonstrates a circuit schematic with approximated "typical" flow rates. In citrated circuits, the predilution rate was adjusted according to protocols detailed below. Hourly flow rates for these parameters and fluid removal rate were recorded, along with transmembrane pressures and clinical parameters.

Box 1. Citrate prescription protocol**Calcium chloride (CaCl) infusion (100 mg/mL)**

Commence at 4 mL/h 15 minutes before initiating continuous renal replacement therapy. Adjust rate according to the following nomogram:

If serum ionised calcium (iCa^{2+}) > 1.1 mmol/L, reduce CaCl infusion rate by 1 mL/h — review in 1 hour.

If serum iCa^{2+} = 0.8–1.1 mmol/L, maintain current rate. Reassess in 2 hours if a rate change had been made in the previous 2 hours, or if there is an identified trend toward the upper or lower limit.

Otherwise, reassess in 4 hours.

If serum iCa^{2+} < 0.8 mmol/L, increase CaCl infusion rate by 1 mL/h — review in 1 hour.

Citrate dose (Prismacitrate 10/2)*

Commence between 2000 and 2500 mL/h (24–30 mmol/h of citrate).

Adjust rate according to the following nomogram.

If prefilter iCa^{2+} > 0.5 mmol/L, increase rate by 250–500 mL/h (3–6 mmol/h of citrate) — reassess in 1 hour.

If prefilter iCa^{2+} = 0.3–0.5 mmol/L, maintain rate. Reassess in 2 hours if a rate change had been made in the previous 2 hours, or if there is an identified trend towards the upper or lower limit.

Otherwise, reassess in 4 hours.

If prefilter iCa^{2+} < 0.3 mmol/L, reduce rate by 250–500 mL/h (3–6 mmol/h of citrate) — reassess in 1 hour.

If a significant trend towards either limit is identified, the operator may adjust the infusion rates abiding by the principles of the protocol and reassess in 1 hour.

* Gambro recently introduced a citrate module for the Prismaflex where the citrate dose is specified per litre of blood and the Prismaflex software then determines the prefilter flow rate to maintain that dose for selected blood flow. For a blood flow rate of 200 mL/min (12 L/h), 2000–2500 mL/h of Prismacitrate 10/2 is equivalent to a citrate dose of 2–2.5 mmol per litre of blood.

Compositions of commercial solutions used are shown in Table 1. CVVHD-F for citrate patients was performed with Prismocitrate 10/2 (Gambro) as predilution and Prismocal (Gambro) as the dialysate and post-blood-pump replacement solution. For non-citrate patients, Hemosol B0 (Gambro) was used for dialysis, predilution and postfilter replacement. Potassium was added to the dialysate according to a protocol (Appendix 1). We routinely use 200 mL/h of dialysate for postfilter replacement to minimise negative pressure in the return line and occurrences of an air–blood interface in the circuit air-trap.

Anticoagulation method — heparin

Heparin was administered based on one of two protocols. Regional anticoagulation of the circuit was achieved using the Prismaflex controlled syringe driver to add heparin to the access line of the circuit using a dose of 5 units/kg/h, with activated partial thromboplastin time monitoring to detect any inadvertent systemic anticoagulation. When a

concurrent indication for full systemic anticoagulation existed, heparin dosing and monitoring followed a well described weight-based protocol.¹¹

Anticoagulation method — citrate

Regional citrate anticoagulation was achieved by adjusting the predilution rate of Prismocitrate 10/2. This was started at 2000 mL/h (equivalent to 2 mmol citrate per litre of blood for a blood flow rate of 200 mL/min) and adjusted to maintain a prefilter circuit iCa^{2+} between 0.3 and 0.5 mmol/L. A 10% calcium chloride infusion was started at 4 mL/h (2.72 mmol/h) 15 minutes before therapy via a central venous catheter, and was targeted to maintain serum arterial iCa^{2+} concentration between 0.8 and 1.1 mmol/L, as described in Box 1. Parenteral nutrition was administered to four patients in the citrate group and one patient in the heparin group. At maximum rate, our parenteral nutrition delivers 0.283 mmol/h of calcium; we elected not to include this in results for net calcium balance. No attempt was made to estimate calcium absorption from enteral nutrition administration.

Laboratory samples

Sample sets were collected from the sites shown in Figure 1 within the first 2 hours of starting CVVHD-F, 2-hourly for the first 12 hours and 4-hourly thereafter. One-millilitre blood samples were collected into a RAPIDLyte 3 mL blood gas syringe (Siemens, Deerfield, Ill, USA) and a CAPIJECT 0.5 mL blood tube (Terumo Medical Corporation, Somerset, NJ, USA). Twenty-millilitre effluent samples were collected in a preservative-free container. Ionised Ca^{2+} was determined by blood gas analyser (GEM Premier 4000, Instrument Laboratory, Bedford, Mass, USA) and total calcium analysis of blood and effluent by spectrophotometric dye binding (Architect c8000, Abbott Diagnostics, Abbott Park, Ill, USA); dye for calcium was arsenazo III, analysed at 660 nm.

Blood collected daily or twice daily as part of routine patient care was analysed in the hospital laboratory for haematocrit and total protein and serum albumin levels. There was no significant difference between haematocrit results using the laboratory haematology analyser (Coulter LH 500, Beckman Coulter, Brea, Calif, USA) and results from the blood gas analyser for samples collected simultaneously ($n=78$ sample pairs; respective means, 29.28% and 29.69%; Pearson's $r=0.915$; $P<0.001$).

Calculations and statistical analysis

Equations and calculations, including those for calculating calcium flux from conservation of mass across the haemofilter, are included in Appendix 2. Although not in our primary design, we were also able to derive values for the effective diffusion volume flow rates for calcium that may be useful in designing future kinetic studies.

Table 2. Characteristics of patients who underwent CVVHD-F

Patient no.*	Anticoagulation [†]	Hours/filters [‡]	Age/sex	Diagnosis	Indication for RRT	APACHE II/III score	Outcome
5	Citrate	101/3	75/M	Intra-abdominal sepsis	MODS, ARF	22/96	Died
6	Citrate	125/7	58/M	Necrotising pancreatitis	MODS	17/71	Survived
7	Citrate	76/3	50/M	Sepsis	ARF, CRF	29/89	Survived
12	Citrate	46/2	66/M	GI loss, acidosis	ARF, acidosis	27/96	Survived
13	Citrate	14/1	55/F	Cardiac failure, sepsis	Fluid removal	22/88	Survived
8 [§]	LDH, citrate	13/2, 142/5	74/F	Ruptured AAA	ARF	30/113	Survived
9 [§]	LDH, citrate	20/1, 15/1	60/M	Sepsis	ARF	29/126	Survived
1 [¶]	LDH, nil	197/5	47/M	Intra-abdominal sepsis	MODS, ARF	46/176	Survived
2	LDH	12/1	60/M	Overdose	MODS, ARF	23/64	Died
3	LDH	23/1	71/M	Cardiac failure	Fluid removal, ARF	29/62	Survived
4	WBH, LDH	161/5	72/M	AMI, APO	CRF, fluid removal	32/103	Survived
10 [¶]	LDH, nil	140/10	30/M	Drug overdose	MODS	45/152	Died
11	LDH	22/1	59/M	Hepatic failure, CCF	Fluid removal	31/149	Died

CVVHD-F = continuous venovenous haemodiafiltration. LDH = low-dose heparin. nil = anticoagulation was ceased for a proportion of therapy. WBH = weight-based heparin. GI = gastrointestinal. AAA = abdominal aortic aneurysm. AMI = acute myocardial infarction. APO = acute pulmonary oedema. CCF = congestive cardiac failure. RRT = renal replacement therapy. MODS = multiorgan dysfunction. ARF = acute renal failure. CRF = chronic renal failure. APACHE = Acute Physiology, Age and Chronic Health Evaluation.

* Patient number refers to the sequential order of enrolment in the study. † When two anticoagulation methods are listed, they were performed sequentially and filter hours are divided respectively. ‡ Hours refers to total time of CVVHD-F (in hours). Filters refers to the total number of haemofilters used over therapy course. § Patients 8 and 9 received LDH initially and were later changed to citrate; their data were divided and analysed in each group. ¶ Patients 1 and 10 had periods without any circuit anticoagulation due to coagulopathy, during this time their CVVHD-F treatment otherwise continued according to our LDH protocols with Hemosol B0 as described in the methods.

Table 3. Continuous venovenous haemodiafiltration parameters by anticoagulation method

	Heparin protocol	Citrate protocol
No. of sample sets*	182	152
No. of filters	26	22
Mean circuit life, hours (SD); <i>P</i> v heparin	22.6 (18.1)	23.6 (16.6); <i>P</i> = 0.85
Mean circuit blood flow, mL/min (SD)	199 (11.3)	194 (18.9)
Mean predilution rate, [†] mL/h	2069 (654)	1660 (320)
Mean citrate dose, mmol per litre of blood	na	2.42 (SD, 0.43; range, 1.41–3.79)
Mean dialysate rate, mL/h	1853 (910)	1743 (325)
Initial pH (range)	7.32 (7.02–7.44)	7.38 (7.18–7.40)
Systemic pH change/h (95%CI); <i>P</i> [‡]	0.0011 (0.0009–0.0013); <i>P</i> = 0.004	0.0009 (0.0006–0.0012); <i>P</i> = 0.002
Mean haematocrit, % (SD)	29 (0.04)	29 (0.04)
Mean total protein, g/L	47.7	50.3

na = not applicable. * Each set comprised arterial blood, prefilter blood, postfilter blood and effluent samples. † For citrate patients, the predilution rate is adjusted according to a protocol to maintain a prefilter iCa^{2+} between 0.3 and 0.5 mmol/L. ‡ Versus zero effect.

Differences in mean analyte values between patient circuits anticoagulated with heparin or citrate (intercept), and the strength of associations with time (slope) were estimated using mixed-methods linear regression corrected for repeated measures. *P* values were corrected for multiple comparisons where appropriate by the Holm method. All statistical analyses were performed using Stata/SE 11.0 (StataCorp, College Station, Tex, USA).

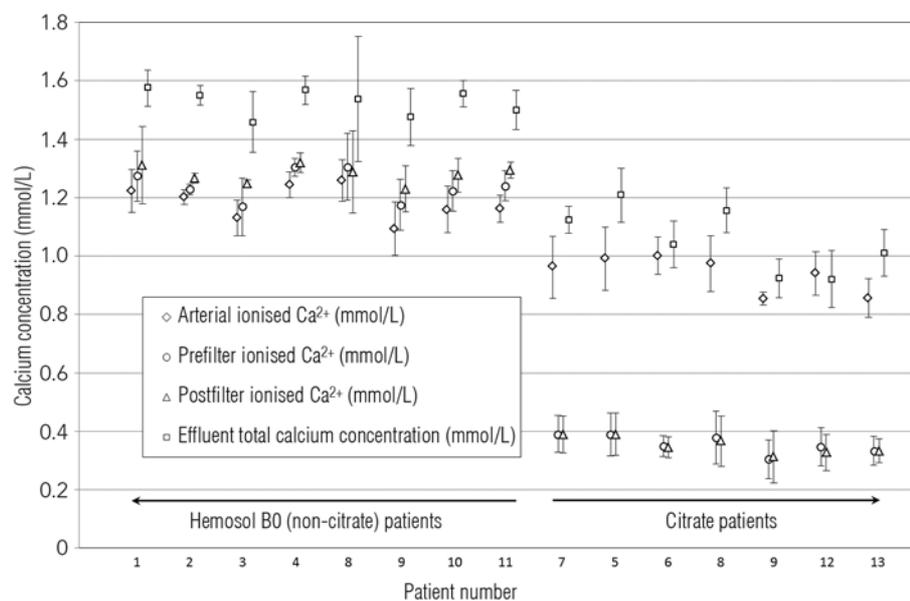
Results

Clinical characteristics of included patients are summarised in Table 2.

Patient parameters and outcomes

Five patients received citrate anticoagulation only, six received heparin only, and two received heparin followed by citrate anticoagulation. In two patients, continuous RRT

Figure 2. Mean and standard deviation calcium concentration by patient and collection site



Compared with Hemosol B0 predilution with citrate results in a consistent fall in ionised calcium (iCa^{2+}) levels from the arterial to the prefilter sampling site. Arterial and circuit measurements reflect iCa^{2+} concentrations, whereas effluent calcium concentrations are higher, reflecting both free calcium and calcium bound to diffusible solutes, such as phosphate, lactate, citrate, bicarbonate and sulphate. Unlike citrated circuits, where effluent calcium can only come from the patient, patients managed with heparin receive 1.75 mmol/L calcium from Hemosol B0 used for filtration and in the dialysate (mean citrate arterial–effluent difference, 0.10 mmol/L [SD, 0.089]; heparin mean difference, 0.37 mmol/L [SD, 0.027]; difference heparin v citrate mean, 0.27; 95% CI, 0.21–0.33; $P < 0.001$).

measurements). The mean arterial iCa^{2+} level among heparinised patients was 1.21 mmol/L. Figure 2 demonstrates the mean iCa^{2+} and effluent total calcium concentrations.

Predilution with Hemosol B0 raises the prefilter iCa^{2+} concentration above the arterial iCa^{2+} concentration; the mean ratio of prefilter to arterial iCa^{2+} concentration was 1.05 (95% CI, 0.99–1.12; P v zero effect < 0.001). In contrast, the mean prefilter iCa^{2+} to arterial iCa^{2+} concentration ratio in the citrate group was 0.43 (95% CI, 0.34–0.52; P v zero effect < 0.001 ; P v heparin < 0.001). Treatment duration did not have a significant effect on the ratio in either group (slope for heparin, -0.011 mmol/h; P v zero effect, 0.89; slope for citrate, -0.001 mmol/h; P v zero effect > 0.9).

For citrated patients, the ratio of prefilter–arterial iCa^{2+} concentration was inversely related to citrate dose (mmol per litre of blood) by Equation 8,

$$iCa_{pre}/iCa_{art} = 0.54 - 0.093 \times \text{citrate dose}$$

The 95% confidence interval for the intercept coefficient (0.54) was 0.48 to 0.60 ($P < 0.001$) and for the slope coefficient -0.059 to -0.127 ($P < 0.001$). Adjusting for haematocrit did not significantly alter the relationship.

Model validation

Calculation of calcium balance depends on the assumption of conservation of mass over the haemofilter (Equation 3, Appendix 2). Figure 3 plots total amount of calcium leaving the haemofilter (in the postfilter bloodstream and the effluent) on the y axis against the amount entering the haemofilter (via the prefilter bloodstream and the dialysate) on the x axis and demonstrates good correlation ($R^2 = 0.962$) over the range of calcium values studied.

Total extracorporeal circuit calcium flux and net calcium balance

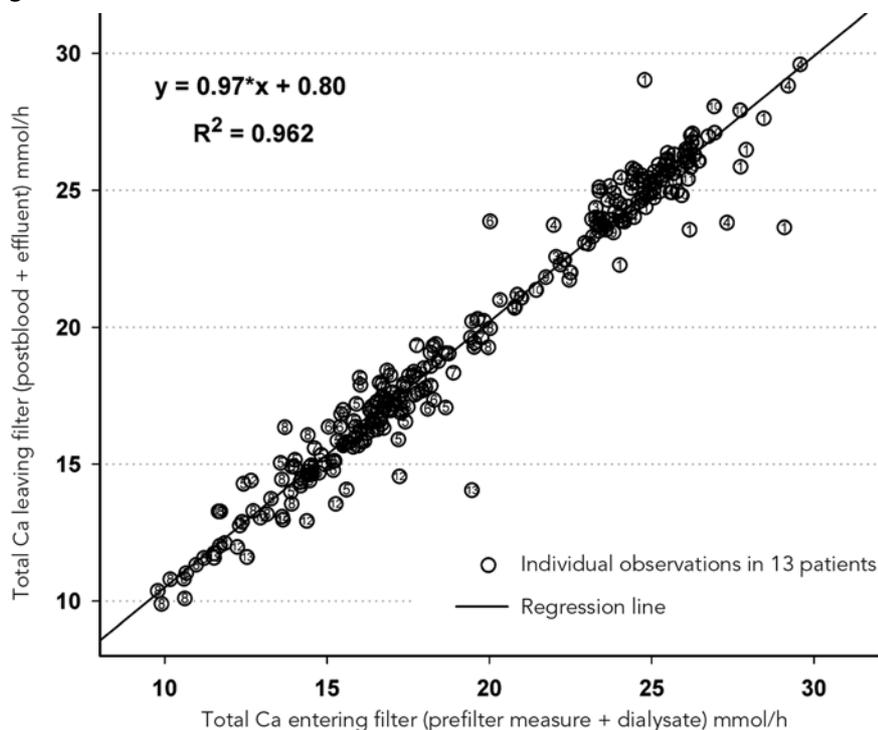
For citrate-anticoagulated patients the mean loss of calcium across the extracorporeal circuit (from Equation 2) was 4.01 mmol/h (95% CI, 3.67–4.34). Heparinised patients had a mean calcium gain from calcium in the extracorporeal

was performed without any anticoagulation until a coagulopathy resolved. In all other respects, their therapy was the same as for heparinised patients and their data are included with this group.

Mean APACHE (Acute Physiology and Chronic Health Evaluation) II and III scores were 27 and 104, respectively, for citrate anticoagulated patients, and 33 and 118, respectively, for heparinised patients. One patient who received citrate died compared with three who received heparin; all deaths were considered due to the underlying pathological process. Treatment parameters are outlined in Table 3.

Citrate dose response and circuit calcium levels

For patients anticoagulated with citrate the mean citrate dose was 2.42 mmol per litre of blood (SD, 0.43; range, 1.41–3.79). The mean prefilter iCa^{2+} level was 0.37 mmol/L and no measurements were greater than 0.5 mmol/L. On 17 measurements (11.2%), the prefilter iCa^{2+} level fell below 0.3 mmol/L. The mean arterial iCa^{2+} level in the citrate group was 0.97 mmol/L (SD, 0.094 mmol/L; mode, 0.99 mmol/L; range 0.77–1.18 mmol/L). The arterial iCa^{2+} level fell below 0.8 mmol/L on six occasions (3.95% of

Figure 3. Conservation of mass of total calcium across the haemofilter

The amount of calcium entering the haemofilter per hour via the prefilter bloodstream and the dialysate intake is plotted on the x axis. The amount of calcium leaving the haemofilter per hour in the effluent plus the postfilter bloodstream is on the y axis (Equation 3, Appendix 2).

circuit of 0.24 mmol/h (95% CI, 0.17–0.31; P v citrate <0.001). There was no statistically significant relationship between calcium net balance and calcium concentration (plasma or prefilter, total or ionised).

Figure 4 shows net calcium balance over time since beginning of each new haemofilter for both groups calculated as calcium replaced minus calcium lost for that hour. Mean calcium replacement for citrate patients was 2.93 mmol/h (SD, 0.62 mmol/h; range, 2.04–4.08). The overall mean difference between calcium lost and replaced using our citrate protocol was 1.12 mmol/h (SD, 0.696; 95% CI, 0.999–1.22 mmol/h; P <0.001). This difference was time-dependent, with a mean deficit to the patient at first measurement of 1.42 mmol/h (95% CI, 1.89–0.96 mmol/h deficit; P v zero effect, <0.001; P v heparin, <0.001), which lessened with time by 0.061 mmol/h (95% CI, 0.014–0.108; P v zero effect, <0.001; P v heparin, <0.001).

When adjusted for time since starting a new haemofilter, heparinised patients had a mean initial calcium gain of 0.84 mmol/h (95% CI, 0.47–1.21), which changed with time by –0.021 mmol/h (95% CI, 0.056–0.014); this fall was not statistically significant (P v zero effect, 0.25), with

some participants demonstrating a positive slope. When adjusted for haematocrit (P =0.68), transmembrane pressure (P =0.28), and $iCa_{pre}-iCa_{art}$ ratio (P =0.58), the effect size estimates were not significantly changed. When adjusted for citrate dose, calcium difference was strongly associated with citrate dose (P <0.001), and the difference between initial calcium difference in the citrate and heparin groups was greatly diminished (P for difference, 0.46), but the patterns of change (slopes) in calcium difference in the citrate and heparin groups were not substantially changed and both remained significant (P <0.001).

Effective diffusion volume for calcium

Geometric means of log transformation of values for the ratios Q_{ECa}/Q_{BWpre} and Q_{ECa}/Q_{PWpre} are shown in Table 4, where Q_{BWpre} and Q_{PWpre} represent the calculated prefilter blood and plasma water flows, respectively. In cir-

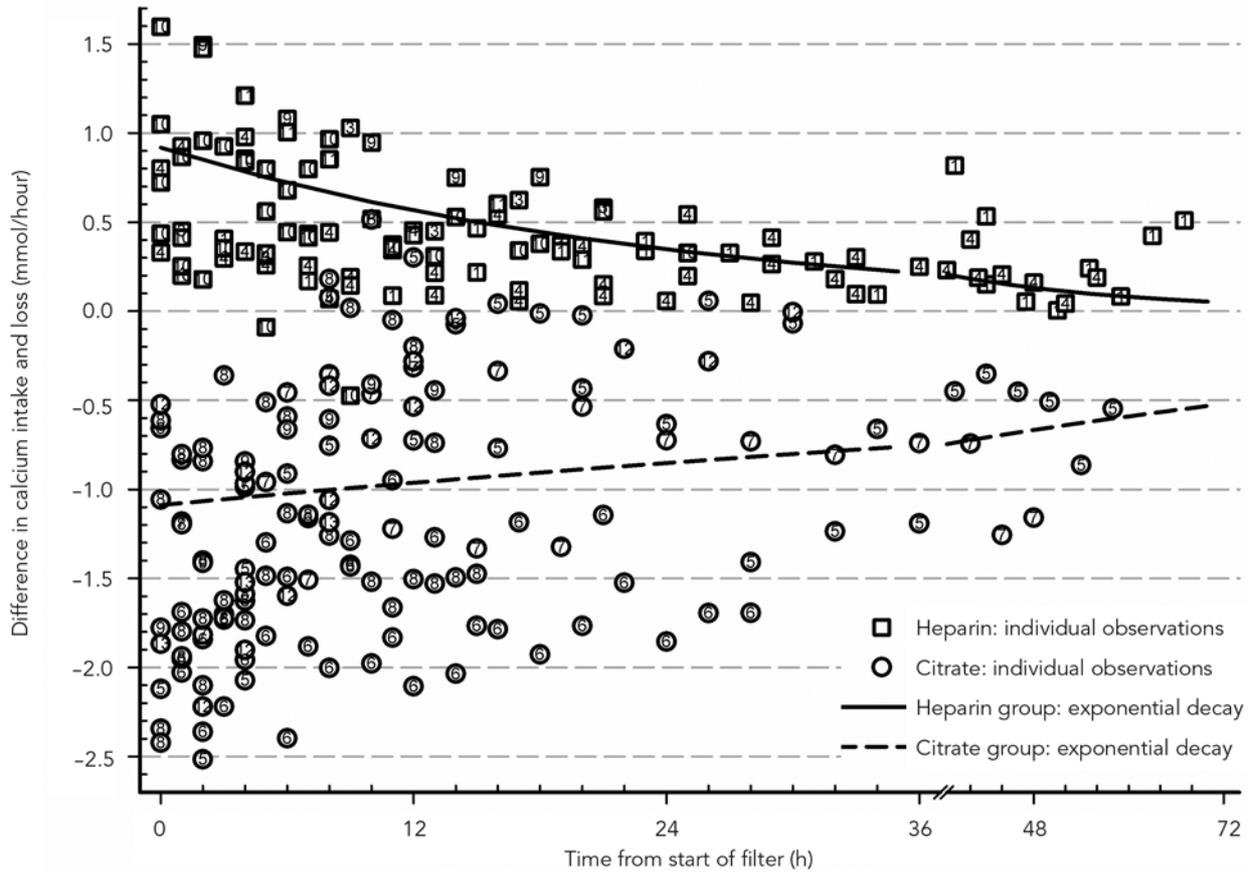
cuits using Hemosol B0, the Q_{ECa} is not significantly different to prefilter blood water flow, whereas for citrated circuits, Q_{ECa} is not significantly different from plasma water flow.

Discussion

Regional citrate anticoagulation offers a useful alternative to heparin in CVVHD-F for the critically ill. Like heparin, citrate anticoagulation has adverse effects that are consequent to its physiology. Hypocalcaemia can be expected due to haemodiafiltration without calcium in the replacement and dialysis solutions, and chelation of the ion by citrate, which is then lost to the circuit effluent.¹² The possibility of a reduction in total body calcium concentration has been less well studied.

The adverse effects of chronic calcium depletion and associated secondary hyperparathyroidism are well described in chronic kidney disease. Hypocalcaemia and elevated parathyroid hormone (PTH) have also been associated with increased mortality in critically ill patients.¹³ Our finding of an average calcium loss of 4.01 mmol/h in patients anticoagulated with citrate reinforces the need for

Figure 4. Relationship between calcium balance and time from start of each new filter for 13 patients receiving heparin and citrate anticoagulation



Relationship between calcium balance (calcium replaced in hour – calcium lost) and time from start of each new filter. Numbers in data points represent individual patient number (Table 1). Note distribution is skewed by 2-hourly sampling for the first 12 hours and 4-hourly thereafter. The overall mean difference between calcium lost and replaced using our citrate protocol was 1.12 mmol/h. This difference was time-dependent, with a mean deficit to the patient at therapy initiation of 1.42 mmol/h (95% CI, 1.89–0.96 mmol/h deficit; P v zero effect < 0.001; P v heparin < 0.001) which lessened with time by 0.061 mmol/h (95% CI, 0.014–0.108; P v zero effect < 0.001; P v heparin < 0.001). Heparinised patients had an overall mean calcium gain from calcium in the extracorporeal circuit of 0.24 mmol/h (95% CI, 0.17–0.31). Overall time dependence was not statistically significant (P value v zero effect = 0.25) with an increase in some patients and fall in others as therapy progressed.

Comparison by mixed-methods linear regression

		<i>P</i> v zero effect	<i>P</i> v heparin
Heparin			
Mean at first measurement (95% CI)	0.84 (0.47–1.21)	< 0.001	
Slope, mmol/h (95% CI)	– 0.021 (– 0.056 to 0.014)	0.25	
Citrate			
Mean at first measurement (95% CI)	– 1.42 (– 1.89 to – 0.96)	< 0.001	< 0.001
Slope, mmol/h (95% CI)	0.061 (0.014–0.108)	< 0.001	0.001

calcium supplementation. This level of calcium loss equates to 97 mmol/day, which represents 0.4% of total body calcium. Although our calcium replacement protocol maintained the arterial iCa^{2+} concentration within our specified range of 0.8 to 1.1 mmol/L, we found a mean calcium deficit of 1.12 mmol/h for a mean citrate dose of 2.42 mmol

per litre of blood. Such a loss could be expected to drive PTH release and mobilisation of body calcium stores. This was demonstrated by Apsner and colleagues in intermittent haemodialysis using citrate anticoagulation with a mean citrate dose of 3.74 mmol per litre of blood.⁸ Over 4 hours of therapy, arterial iCa^{2+} levels increased from 1.1 mmol/L

Table 4. Effective diffusion volume for calcium

Ratio	Mean Q_{BWpre} (SD), mL/min	Mean Q_{PWpre} (SD), mL/min	Geometric mean Q_{ECa}/Q_{BWpre} (95% CI)	P^*	Geometric mean Q_{ECa}/Q_{PWpre} (95% CI)	P^*
Citrate	199.6 (19.2)	158.9 (18.9)	0.72 (0.60–0.85)	< 0.001	0.91 (0.78–1.06)	ns
Heparin	209.4 (17.5)	167.3 (17.6)	1.13 (0.89–1.44)	ns	1.46 (1.13–1.89)	< 0.004

Q_{BWpre} = prefilter blood water flow. Q_{PWpre} = prefilter plasma water flow. ns = not significant. * P of $\log_{10}(Q_E/Q_B/Q_{PWpre})$ v $\log_{10}1$.

(SD, 0.16 mmol/L) to 1.17 mmol/L (SD, 0.10 mmol/L) and PTH secretion fell by 25.4% in response to high-dose (15 mmol/h) calcium replacement. In response to low-dose (5 mmol/h) replacement, iCa^{2+} concentration decreased from 1.12 mmol/L (SD, 0.13 mmol/L) to 0.89 mmol/L (SD, 0.10 mmol/L) and PTH rose by 121.4%.

Oudemans-van Straaten and colleagues' study of continuous venovenous haemofiltration (CVVH) with citrate or nadroparin demonstrated similar efficacy and a trend towards lower mortality rates with citrate in post-hoc subgroup analysis.² They used a citrate dose of 3.0 mmol per litre of blood and an arterial iCa^{2+} target of 0.9–1.0 mmol/L. At the end of haemofiltration sessions, 6% of citrate patients had an arterial iCa^{2+} less than 0.9 mmol/L, with 80% between 0.9 and 1.19 mmol/L. Apart from the use of CVVH with postdilution instead of CVVHD-F, this study differed from ours in using calcium containing filtration solutions and did not appear to measure circuit iCa^{2+} , but rather relied on a fixed ratio of citrate to blood flow. Advantages of this approach include simplicity of operation, ability to maintain a fixed haemofiltration dose, and lower systemic calcium replacement requirement. However, our anecdotal experience suggests maintaining the extracorporeal iCa^{2+} levels between 0.3 and 0.5 mmol/L requires higher citrate doses (around 4.0 mmol per litre of blood) when calcium-containing replacement solutions are used. If we had maintained a higher systemic iCa^{2+} level by systemic calcium infusion, it may have necessitated higher citrate doses and as there is significant citrate clearance across the extracorporeal circuit,¹² calcium balance could have still been negative. This requires further evaluation, as to our knowledge no one else has quantified total calcium loss in CVVHD-F.

Rearranging Equation 8 to solve for citrate dose (mmol per litre of blood) and a target extracorporeal prefilter iCa^{2+} of 0.30 mmol/L yields Equation 9,

$$\text{Citrate dose} = 5.81 - 3.23/iCa^{2+}_{art}$$

Equation 9 may allow more precise targeting of initial citrate dose; however, it should be highlighted that it has not been prospectively validated and is derived from 152 sample sets from seven patients anticoagulated with citrate using the protocols described; confidence intervals have been omitted for clarity.

We had expected that haematocrit would also affect Equations 8 and 9, as Whitfield and Levy demonstrated that the impermeability of erythrocytes to citrate resulted in variable plasma citrate concentrations when whole blood and citrate were mixed in fixed ratios.¹⁴ The relatively narrow range of haematocrit values in our citrate patients, or a cancelling-out effect from Q_{ECa} being close to plasma water, may have masked such an effect. Describing such a relationship is important as delivery systems that allow the citrate dose to be specified in a fixed ratio to extracorporeal blood flow are now available (see footnote to Table 3).

Limitations of this study include the small number of participants and the possibility of the results being disproportionately influenced by those who received CVVHD-F for longer periods, had a greater number of filters or, for time-dependent results, those who achieved longer filter life. This was a real-world study performed during the fluctuating course of critically ill patients, some of whom died, so it is unlikely that any individual factors were constant over the collection period. As the analysis was primarily of the behaviour of calcium in the extracorporeal circuit, we believe our sample size was adequate. To the best of our knowledge, no participants had been exposed to bisphosphonate therapy. We hypothesise that such therapy could reduce buffering of serum calcium levels by bone and require higher calcium replacement doses to maintain normocalcaemia. An increased number of participants may have allowed us to explore this.

Limitations of our model of conservation of mass include compounding of multiple measurement imprecision errors in equations and that postfilter blood flow is not reported by the Prismaflex machine, but must be calculated from other flow rates (see Equations 1 and 3 in Appendix 2). This introduces potential mathematical linkage and eliminates machine imprecision, so it is possible that the correlation coefficient reported under model validation would be lower if actual flows were available. Measurement imprecision affects the calcium flux result for heparin to a greater extent than citrate as calcium enters the circuit at multiple points in the heparin circuit; however, postfilter blood flow is not a component of the flux calculations (Equation 2).

Calculation of effective diffusion volume is important for design of future kinetic models and has been performed for creatinine, urea and phosphate.¹⁰ It has been suggested, but not shown experimentally, that the effective diffusion volume for total calcium would be equivalent to plasma water.¹⁵ Our result suggests that predilution with Hemosol B0 results in Q_E being closer to blood water volume, but that citrate predilution results in a Q_E closer to plasma water volume. Unlike creatinine and urea, diffusible calcium is significantly affected by complex pH-dependent equilibria with several complexes.^{4,16} It is thus unlikely that a single value for Q_E exists, particularly among critically ill patients, in whom protein and hydrogen concentrations are frequently outside the normal range. Our Q_E result requires confirmation in kinetic studies specifically designed to assess this. Imprecision in our result may result from small concentration differences across the haemofilter significantly affecting the denominator of Equation 5 (Appendix 2). Suggested experimental methods to overcome this include creating a closed-loop system where the blood is recycled through a reservoir and where solute accumulation can be measured over time.¹⁴

In summary, our results contribute to the understanding of calcium haemostasis in CVVHD-F. The most significant finding of this study is a substantial net calcium loss from patients dialysed with citrate anticoagulation when calcium-free solutions are used. Potential adverse effects of calcium loss include parathyroid activation, and bone calcium loss; however, overall effect on patient outcome is not clear and requires further study. Current practice is to supplement calcium to avoid hypocalcaemia and its consequences; thought should also be given to the total calcium deficit that the therapy can produce. The development of a formula for estimating the required citrate dose to achieve anticoagulation may allow development of alternative citrate dosing protocols and, if validated, could be implemented into the haemodialyser software.

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Appendix 1. Potassium replacement protocol

Target serum potassium ion (K⁺) level is 4.0–4.8 mmol/L unless otherwise specified.

Potassium chloride may be added to the dialysate solution as serum potassium will equilibrate with dialysate potassium concentration. Refer to the table below.

Additional potassium may need to be administered intravenously.

Protocol for addition of potassium to dialysate (Hemosol B0/Prism0cal)

Serum ionised K ⁺	Target dialysate K ⁺	Volume KCl (10 mmol/10 mL) to add to each 5 L bag
< 4.8 mmol/L	4 mmol/L	20 mL
4.8–5.4 mmol/L	3 mmol/L	15 mL
5.4–6.0 mmol/L	2 mmol/L	10 mL
> 6 mmol/L	1 mmol/L	5 mL

Appendix 2. Calculations and equations

Equation 1 describes conservation of solute mass across the extracorporeal circuit.

$$\begin{aligned} \text{Solute mass entering haemofilter} &= \text{Solute mass lost to effluent + mass returned to patient} \\ \text{Plasma/serum Ca}^{2+} &+ \text{Predilution} + \text{Dialysate} = \text{Effluent} + \text{Postfilter flow} + \text{Postdilution} \\ (Q_{Bi} \times C_{Bi}) &+ (Q_{PBP} \times C_{PBP}) + (Q_{Di} \times C_{Di}) = (C_{Eff} \times Q_{Eff}) + (C_{Bo} \times Q_{Bo}) + (Q_{Post} \times C_{Post}) \end{aligned}$$

Where Q = flow, C = concentration of solute (total calcium), and the quantity Q × C (mmol/h) represents the amount of material in the flowing stream. Q_{Bi} and Q_{Bo} represent blood flow in and out of extracorporeal circuit, respectively. Arterial total calcium concentration was used for C_{Bi}. PBP = predilution. Di = inlet dialysate concentration. Eff = effluent. Post = postfilter dilution. The postfilter blood flow (Q_{Bo}) is calculated from Q_{Bi} – Q_{UF}. The ultrafiltration rate (Q_{UF}) is equal to the fluid removal rate + postdilution flow rate + preblood-pump flow rate.

Inspection of Equation 1 reveals that the calcium flux (loss or gain to the patient) over the entire extracorporeal circuit is determined by the amount lost to the effluent minus any added in the extracorporeal circuit. Total calcium flux (J_T [mmol/h]) across the circuit is shown in

$$\text{Equation 2: } J_T = Q_{Eff} \times C_{Eff} - Q_{Di} \times C_{Di} - Q_{PBP} \times C_{PBP} - Q_{Post} \times C_{Post}$$

For citrate, Equation 2 simplifies to J_T = Q_{Eff} × C_{Eff} = J_d, as any calcium in the effluent must have come from the patient, as the predilution, dialysate and postdilution are all calcium-free; this also represents calcium flux across the haemofilter, J_d. For circuits using Hemosol B0, J_d will be greater due to the additional calcium added as predilution.

For any solute, there will be an effective volumetric blood flow rate from which the solute can participate in concentration-driven flux across the haemodialyser. Published values suggest that for urea this equals the total blood water volume, for creatinine it is plasma water plus 60% of red cell water volume, and inorganic phosphorus is limited to plasma water volume.¹⁵ It has been suggested, but not demonstrated, that the effective blood diffusion volume flow rate (Q_E) for calcium is equal to plasma water flow rate;¹⁴ however, this has not been verified in experimental studies. Although our study was not designed to study this, we were able to derive values for Q_E that may aid design of future kinetic studies and suggest that Q_E is altered by the addition of citrate (which does not enter red cells). Equation 3 describes conservation of mass across the haemofilter alone and can be rearranged to express balance of solute flux, Equation 4. In continuous venovenous haemodiafiltration, the term Q_E at the haemofilter includes predilution added to the bloodstream.

Equation 3:¹⁷ Solute mass entering haemofilter = solute mass leaving haemofilter

$$(Q_E \times C_{Bi}) + (Q_{Di} \times C_{Di}) = (C_{Eff} \times [Q_{Di} + Q_{UF}]) + (C_{Bo} \times [Q_E - Q_{UF}])$$

Equation 4:¹⁰ Solute flux out of blood (J_b) = solute flux into dialysate (J_d)

$$Q_E(C_{Bi} - C_{Bo}) + Q_{UF} \times C_{Bo} = Q_{Di}(C_{Eff} - C_{Di}) + Q_{UF} \times C_{Eff}$$

Note that C_{Bi} here is the solute concentration immediately before the haemofilter (after predilution) unlike in Equation 1, where it represents blood entering the extracorporeal circuit.

We used the methods described by Gotch and colleagues¹⁰ to calculate effective diffusion volume of calcium by rearrangement of Equation 4 to solve for Q_E and then expressing this as a ratio of total blood water flow rate (Q_{BW}) and plasma water flow rate (Q_{PW}).

$$\text{Equation 5: } Q_E = \frac{Q_{Di}(C_{Eff} - C_{Di}) + Q_{UF}(C_{Eff} - C_{Bo})}{(C_{Bi} - C_{Bo})}$$

The total blood water flow rate (Q_{BW}) and plasma water flow rate (Q_{PW}) at the haemodialyser were calculated from the whole blood flow rate (Q_B), haematocrit (Hct [%]), published values for red cell water fraction of 72%^{10,17} and calculation of plasma water fraction, F_P as:

$$F_P = 0.989 - 0.0074 \times C_{\text{total protein}}$$

where the total protein concentration is expressed in g/dL.¹⁷

Values for the ratios Q_{ECa}/Q_{BWpre} and Q_{ECa}/Q_{PWpre} for the two anticoagulant groups were calculated, where Q_{BWpre} and Q_{PWpre} represent the calculated prefilter blood and plasma water flows, respectively.

$$\text{Equation 6:}^{17} Q_{BW} = Q_B([F_P - \text{Hct}/100] \times [F_P - F_R])$$

$$\text{Equation 7:}^{17} Q_{PW} = Q_B(1 - \text{Hct}/100) \times F_P$$

$$\text{Equation 6a: } Q_{BWpre} = Q_B(F_P - [\text{Hct}/100] \times [F_P - F_R]) + Q_{PBP}$$

$$\text{Equation 7a: } Q_{PWpre} = Q_B(1 - \text{Hct}/100) \times F_P + Q_{PBP}$$

When the difference C_{Bi} – C_{Bo} in the denominator of Equation 5 is small, as in the case of our data, measurement imprecision becomes proportionally great. This led to some large and impossible values for Q_E and a skewed deviation. Accordingly, log transformation of the values for Q_E was performed to make the data more symmetric and homoscedastic, and the results are reported as geometric means.



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