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Regular paper

Ionic homeostasis, acid-base balance and the risk of citrate accumulation in patients after cardiovascular surgery treated with continuous veno-venous haemofiltration with post-dilution regional citrate anticoagulation – An observational case-control study

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Background: Patients after cardiovascular surgery, requiring renal replacement therapy, can benefit from adequate non-heparin circuit anticoagulation. Simplified regional citrate anticoagulation (RCA) protocol proposes the use of citric acid dextrose formula A (ACD-A) during post-dilutional continuous veno-venous hemofiltration (CVVH) with standard bicarbonate buffered calcium containing replacement solution. Citrate accumulation diagnosed upon total to ionized calcium ratio (tCa/iCa) and low ionized calcium (iCa) are considered as the biggest risks related to regional citrate accumulation. Methods: This prospective observational case-control study evaluated electrolyte and acid-base homeostasis in cardiovascular surgery patients treated with post-dilution CVVH with a simplified RCA protocol with ACD-A. In total, 50 consecutive cardiovascular surgery patients were evaluated. Base excess, pH, bicarbonate, lactate, Na^+, Cl^-, Mg^{++}, and inorganic phosphate concentrations, the total to ionized calcium ratio (tCa/iCa), and high anion gap metabolic acidosis were assessed during haemofiltration treatment in survivors and non-survivors. Results: Thirty-three (66%) patients died. The therapies were very well balanced in sodium and chloride homeostasis. The lactate concentration and anion gap decreased during CVVH sessions lasting longer than 72 hours, but no inter-group difference was observed. The tCa/iCa ratio exceeded 2.5 in 4.5% of measurements and was significantly higher in non-survivors (p=0.037). Initial lactate concentration did not correlate with tCa/iCa ratio during haemofiltration. Magnesium and phosphate concentrations decreased and additional supplementation with magnesium was necessary. The magnesium concentration was lower in the non-survivors. Conclusions: The incidence of citrate accumulation exceeded 4% and was significantly higher in non-survivors. Supplementation with magnesium and phosphate ions is needed in CVVH with RCA.

Keywords: citrate; calcium; acidosis; alkalosis; cardiac surgery; haemofiltration; acute kidney injury.

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Abbreviations: ACD-A, acid dextrose formula A; AKI, acute kidney injury; ASA, acetylsalicylic acid (ASA); BUN, blood urea nitrogen; CA, citrate accumulation; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; CVVH, continuous veno-venous haemofiltration; ECMO, extracorporeal membrane oxygenation; ESRF, end-stage renal failure; HAGMA, high anion gap metabolic acidosis; iCa, ionized calcium (in blood); INR, international normalized ratio; IQR, interquartile range; LMWH, low molecular weight heparin; OPCABG, off-pump coronary artery bypass graft; PM, pacemaker; RCA, regional citrate anticoagulation; tCa, total calcium (in blood); tCa/iCa, total to ionized calcium ratio; UFH, unfractionated heparin; VAD, ventricular assist device.

INTRODUCTION

Acute kidney injury (AKI) after cardiac surgery affects 2–5% of patients and has a mortality rate between 36 and 78% (Pickering *et al.*, 2015). According to the KDIGO guidelines, even with a lack of a contraindication for heparin, RCA should be selected rather than heparin anticoagulation, as it is related to increased filter life span, a lower incidence of bleeding, and better metabolic control (Kellum, 2012; Stucker *et al.*, 2015). Although citrate anticoagulation is considered superior for preventing filter clotting and clogging, it carries the risk of several complications, including acid-base abnormalities, hypocalcaemia, hypernatremia, and hypomagnesemia (Schilder *et al.*, 2014; Schneider *et al.*, 2017).

Tissue hypoperfusion, as manifested by increased lactate levels, is common in cardiac surgery patients, rendering citrate metabolism less predictable than in the non-cardiac surgical intensive care setting. Hypocalcaemia might more readily exacerbate heart failure after cardiac surgery than in the general ICU population (Sanaie *et al.*, 2017). Decreased citrate metabolism in tissues can result in its accumulation (CA). In contrast, an overdose of citrate in the case of unaffected citrate metabolism may lead to the development of metabolic alkalosis (Schneider *et al.*, 2017).

Citrate exerts its anticoagulation effect by chelating calcium ions, which should decrease their concentration below 0.4 mmol/L in the CRRT circuit. A great deal of calcium ions bound to citrate are filtered out and must be replaced by the continuous calcium infusion before the blood is returned to the patient. Due to the lack of commercially available tests of the serum citrate concentration, the assessment of the ratio of the total to ionized calcium concentrations (tCa/iCa) and high anion

gap metabolic acidosis (HAGMA) remain the only feasible methods for the clinical assessment of CA (Monchi *et al.*, 2017). An increase in the tCa/iCa ratio exceeding 2.5 is related to a high risk of citrate accumulation, and if this ratio exceeds 3.0, CA can be diagnosed (Honore *et al.*, 2015).

In most studies on CRRT in ICU patients, the assessment of the safety of the therapy is limited to the incidences of bleeding, arrhythmia, and haemodynamic instability. We strongly believe that the currently available blood purification protocols should also be evaluated with respect to their influence on pH and electrolyte balance, which are known risk factors for mortality and morbidity in the intensive care setting (Upala *et al.*, 2016; Wang *et al.*, 2019). Limited number of studies have focused on the incidence of acid-base imbalance and dyselectrolytaemia during CRRT with RCA (Cassina *et al.*, 2008; Khadzhynov *et al.*, 2014; Tan *et al.*, 2019).

The risk of electrolyte disorders and acid-base imbalance should be clinically evaluated for every novel protocol proposed for clinical practice. To the best of our knowledge, the simplified citrate anticoagulation protocol for post-dilution continuous veno-venous (CVVH) haemofiltration described by Kirwan and others (Kirwan *et al.*, 2016) has not been evaluated with respect to ion and acid-base homeostasis in cardiovascular surgery patients with acute renal failure.

MATERIALS AND METHODS

The primary objective of this study was to compare the incidence of electrolyte and acid-base disorders between survivors and non-survivors during post-dilution CVVH treatment with a simplified RCA protocol in cardiovascular surgery patients. The secondary aim was to monitor the risk of CA during RCA haemofiltration treatment.

We conducted a prospective single-centre observational case-control study on consecutive cardiovascular surgery patients, including patients with end-stage renal failure on chronic haemodialysis treatment, who were treated with CVVH RCA between September 2015 and November 2017. The study protocol conformed to the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, was approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (https://structure.mug.edu.pl/178; approval No.: NKBBN/539/2016-17) and was retrospectively registered in the ClinicalTrials database (NCT03836742). Due to the observational nature of the study, the institutional review board waived the need to obtain patient consent. The decision to start renal replacement therapy was based on oliguria/anuria, volume overload, azotaemia, and dyselectrolytaemia (Oudemans-van Straaten *et al.*, 2012). Contraindications to RCA were blood lactate concentration above 8 mmol/L and liver failure with international normalized ratio (INR)>2. The most recent serum creatinine concentration before surgery was considered the baseline value. The recorded CRRT parameters included blood and filtrate flows, citrate and calcium chloride solution flows and filter life span.

Haemofiltration and RCA protocol

CVVH was performed with the Aquarius+ CRRT device with 6.02.14/15 software (Aquarius system, NIKKISO Europe GmbH, Desbrocksriede 1, 30855 Langenhagen, Germany) and Citraset RCA for therapies with regional citrate anticoagulation comprising Aqualine RCA (Haemotronic S.p. A, Via Carreri 16, 41037 Mirandola, Italy) and the Aquamax haemofilter (Nikkiso Belgium bvba, Industriepark 6, 3300 Tienen, Belgium). Filter size (either Aquamax 1.2 m^2 or Aquamax 1.9 m^2) was determined by the treating clinician, based on the patient actual body weight (>90 kg) and symptoms of distributive shock requiring noradrenaline infusion over 0.1 μg/kg/hour, where Aquamax 1.9m^2 filter was used. In all patients, glucose-free Accusol 35 K0 (Nikkiso, Belgium Industriepark 6 B-3300 Tienen; Belgium) was used as the post-dilution replacement fluid. The composition of the Accusol35 K0 was as follows: Na^+ 140 mmol/L, Cl^- 109,3 mmol/L, K^+ 0 mmol/L, Ca^{++} 1,75 mmol/L, Mg^{++} 0,5 mmol/L, HCO_3^- 35 mmol/L, glucose 0 mg/dL, osmolality: 287 mOsm/L.

All substitution solution bags were supplemented with potassium in order to reach 4 mEq/L concentration. Anticoagulant citrate dextrose solution A (ACD-A, Macopharma, 5003F Rue Lorthiois, 59420 Mouvaux, France) was used as the source of citrate.

The haemofiltration setting and its modifications in response to metabolic alkalosis were adopted from the CVVH RCA protocol published by Kirwan et al.; however, the renal dose was calculated for the actual body weight (Kirwan *et al.*, 2016). The prescribed starting dose of CRRT was 35 ml/kg/h and was adjusted according to the desired urea clearance. Ultrafiltration was titrated by the treating physician according to clinical indications and haemodynamic status.

Besides calcium supplementation from postdilution replacement solution, the plasma concentration of ionized calcium (iCa) was augmented with additional calcium infusion using initially a dose of 10 mL of 10% Calcium Chloride (WZF Polfa, Karolkowa Str. 22/24, Warsaw, Poland) added to 1 L of normal saline which resulted in Ca^{++} concentration of 4.6 mmol/L. Due to observed high requirement for calcium solution, after the first 10 patients its concentration was increased to 20 mL 10% calcium chloride, and after the following 10 patients it was further increased to 40 mL 10% calcium chloride, equivalent to Ca^{++} concentration of 18.4 mmol/L. The target calcium concentration in plasma was increased from 0.9-1.2 range of the original Kirvan protocol to 1.0–1.2 range. The original protocol was also modified by adding routine infusion of magnesium sulfate 0.2 g/hour.

Details of the anticoagulation therapy

Three thousand units of UFH were added to 1000 mL 0.9% NaCl solution for CRRT circuit priming in all but 7 patients who had a suspicion of heparin induced thrombocytopenia.

Six patients received no antithrombotic medication or acetylsalicylic acid (ASA) alone, 15 patients received a prophylactic dose of low molecular weight heparin (LMWH) or fondaparinux, with or without ASA, twenty-eight patients received a therapeutic dose of LMWH or fondaparinux with or without ASA, and 3 patients were treated with continuous UFH infusion. The detailed analysis of filter life span in patients treated with CVVH RCA, depending on systemic anticoagulation administered for cardiac surgical indications in the subgroup of patients who were not administered UFH infusion was published elsewhere (Koška *et al.*, 2020).

Outcome measures

According to the reference values used by the hospital laboratory, the following parameters were adopted

for the diagnosis of electrolyte disorders: hyponatraemia Na^+<135 mEq/L, hypernatraemia Na^+>145 mEq/L, hypochloraemia Cl^-<98 mEq/L, hyperchloraemia Cl^->112 mEq/L, hypocalcaemia iCa<0.98 mmol/L, hypercalcaemia iCa>1.21 mmol/L, hypomagnesaemia Mg^{++}<1.5 mg/dL, and hypophosphataemia PO_4^{3+}<2.3 mg/dL. Severe hypernatraemia was diagnosed when Na^+>150 mEq/L, severe hypochloraemia when Cl^-<92 mEq/L, severe hypocalcaemia when iCa< 0.9 mmol/L, and severe hypercalcaemia when iCa>1.32 mmol/L. The incidence of tCa/iCa> 2.5, as the parameter indicating the risk of CA, was reported. Ionized calcium was not corrected for the albumin concentration (Zheng *et al.*, 2017). Metabolic alkalosis was diagnosed based on a pH>7.45 and HCO_3^- concentration >26 mmol/L. HAGMA was reported if the high anion gap (calculated as $Na^+ – (Cl^- + HCO_3^-)$) exceeded 12 and the bicarbonate concentration was lower than 20 mmol/L. CA was diagnosed when at least three out of the following four systemic metabolic diagnostic criteria were present: 1) a decrease in systemic ionized calcium to a value below 1.1 mmol/L, 2) an increase of tCa/iCa to a value >2.25, 3) metabolic acidosis (pH<7.2 or BE<–5 mmol/L) and 4) an anion gap greater than 12 mmol/L.

Laboratory analyses

Creatinine, blood urea nitrogen (BUN), magnesium, tCa, and phosphate were measured once a day. Arterial blood gas analysis, sodium, potassium, chloride, iCa, bicarbonate, base excess, anion gap, lactate and haemoglobin were assessed every 6 hours. Arterial blood gas analyses were performed on an ABL800 Flex 835 blood analyser (Radiometer, Copenhagen, Denmark). According to recent opinions, the blood gas analyser was placed inside the intensive care department where patients were treated (Krzych *et al.,* 2020). The total calcium concentration was assessed with the Arsenazo III method (Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA). The magnesium ion concentration was assessed with the isothiocyanate dehydrogenase enzymatic method (Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA). The inorganic phosphate serum concentration was assessed by a colorimetric method based on phosphomolybdic acid reduction to molybdenum blue. Magnesium, tCa and inorganic phosphate concentrations were used for the analysis if the time span between blood sampling and the time point of the study (which was related to the beginning of CVVH treatment) was less than 6 hours. For the assessment of changes in sodium, chloride, magnesium, phosphate, ionized calcium, pH, bicarbonate, and lactate concentrations during CVVH, exclusively data from sessions lasting more than 72 hours were used.

Statistical analysis

Data were tested for normal distribution with Shapiro-Wilk test. All baseline variables are presented using descriptive summary statistics including the means ± standard deviation (S.D.) or medians with quartiles and 25th and 75th interquartile ranges (IQR), as appropriate. Normally distributed data were compared using Student's *t*-tests; nonnormally distributed data were compared with the Mann-Whitney U test. Categorical variables are expressed as proportions and were compared between groups using the χ^2 test or Fisher's two-tailed exact test, depending on the sample size. Comparisons between multiple sets of measured parameters were performed with repeated-measures ANOVA and are presented as the means ±S.Ds. Statistical analyses were performed with Statistica 10 software (StatSoft Inc., Tulsa, USA). Statistical significance was set at the 0.05 level.

RESULTS

Patient characteristics

During the study period, 54 cardiovascular surgery patients were treated with CVVH RCA. Four patients were excluded from the analysis due to reasons presented in the patient flow chart (Fig. 1). Fifty patients underwent a total of 233 haemofiltration treatment sessions with RCA. The median circuit life span was 57 hours (range: 1–117, Q_1=27, Q_3=83), and it did not differ between survivors and non-survivors. The following CVVH parameters were recorded at the beginning of the CVVH session: blood flow 187.4±34.8 mL/min (80-300), replacement fluid flow 2213±383 mL/h (1300-2700), ultrafiltration 234±90 mL/h (10-500), citrate flow 279±53.1 mL/h (104-350), calcium flow 78.5±44.5 mL/h (0-200), and dialysis dose 32.1±5.4 ml/kg/h (18.4-50). Patient characteristics and cardiovascular surgical procedures are detailed in Table 1.

Of the 50 analysed patients, 33 (66.0%) died before hospital discharge. Patient age was significantly higher in non-survivors than in survivors. The incidence of hyperthyroidism was higher among survivors. No other significant difference in preoperative parameters was observed between the groups. Among 48 patients who were not treated with intermittent haemodialysis before surgery, renal function recovered in 14 patients (29.1%) including 10 survivors (66.7%) and four who eventually died (12.1%).

Ionic homeostasis

Any kind of dyselectrolytaemia before the beginning of the haemofiltration session was observed in 248 of a total of 946 (26.2%) electrolyte analyses. Out of 233 haemofiltration sessions, 94 (40%) lasted longer than

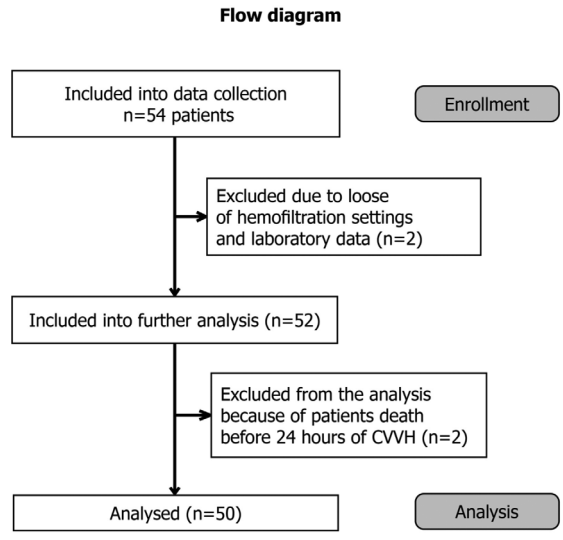

Figure 1. Flow chart of the study population

Table 1. Patient characteristics and type of surgical procedures in n=52 patients after cardiovascular surgery who were treated with renal replacement therapy with regional citrate anticoagulation.

Patient characteristics/type of surgery	Total	Survivors N=17	Non-survivors N=35	*p*
Age, years	70 (Q_1=62, Q_3=74; Range: 37-84)	64 (Q_1=57.2, Q_3=70; Range: 37-78)	72 (Q_1=65, Q_3=76; Range: 48-84)	0.029
BMI, kg/m^2	27.9 (Q_1=24.2, Q_3=31.6; Range: 17-31.6)	27.5 (Q_1=23.6, Q_3=31.2; Range: 20-36)	28 (Q_1=25.7, Q_3=33.4; Range: 17-45)	0.161
Sex (male)	28	9 (53 %)	19 (54 %)	0.93
Pre-existing renal disease	25	7 (41 %)	18 (51 %)	0.488
Chronic dialysis treatment	4	2 (12 %)	2 (6 %)	0.589
Diabetes mellitus	12	3 (18%)	9 (26 %)	0.729
Arterial hypertension	33	9 (53 %)	24 (69 %)	0.272
COPD	4	1 (6 %)	3 (9 %)	1
Hyperthyroidism	3	3 (18 %)	0 (0 %)	0.031
Hypothyroidism	4	1 (6 %)	3 (9 %)	1
Chronic atrial fibrillation	11	2 (12 %)	9 (26 %)	0.304
Pre-operative haemoglobin [g/dL]	11.3 (Q_1=9.8, Q_3=12.5; Range: 7.2-16.3)	11.7 (Q_1=10.5, Q_3=13.6; Range: 9.0-16.3)	10.9 (Q_1=9.4, Q_3=12.2; Range: 7.2-13.9)	0.11
Pre-operative haemoglobin <10 [g/dL]	16	3 (18 %)	13 (37 %)	0.208
Pre-operative creatinine concentration [mg/dL]	1.49 (Q_1=1.04, Q_3=2.10; Range 0.62-9.31)	1.49 (Q_1=1.02, Q_3=2.02; Range 0.61-6.15)	1.5 (Q_1=0.89, Q_3=2.5; Range 0.69-9.3)	0.923
Type of surgery				
Valvular surgery	21	6	15	0.60
Revascularization surgery (CABG and OPCABG)	7	4	3	0.20
Valvular + revascularization	7	1	6	0.40
Other cardiac surgery	2	0	2	1.00
Vascular surgery including thoracic aorta surgery	10	3	7	1.00
Extracorporeal support (ECMO/VAD)	2	1	1	1.00
Heart transplant	1	1	0	0.32
Pericardial drainage	1	0	1	1.00
PM electrodes removal	1	1	0	0.32

Legend: CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ESRF, end-stage renal failure; PM, pacemaker; OPCABG, off-pump coronary artery bypass graft; VAD, ventricular assist device.

72 hours. The incidence of specific electrolytic and acid-base disorders in survivors and non-survivors is presented in Table 2.

After 24, 48 and 72 hours of haemofiltration, dyselectrolytaemia was observed in 136 of 804 (16.9%), 121 of 601 (20.1%), and 79 of 400 (19.8%) readings, respectively. The only difference between groups in the incidence of electrolyte disorders was that hyperchloraemia before the commencement of CVVH treatment was more common in survivors than in non-survivors. Hypernatraemia during CVVH was observed in 10 out of 424 measurements (2.4%). The incidences of hyponatraemia, hypernatraemia, severe hypernatraemia, hypochloraemia and hyperchloraemia were significantly lower after 24, 48 and 72 hours of CVVH treatment than at baseline. Post-dilution haemofiltration with the RCA protocol provided stable sodium and chloride concentrations, with their median values approaching the mid-reference values, and decreased ranges throughout the course of treatment (Fig. 2).

Calcium balance and citrate accumulation

The incidences of hypercalcaemia and severe hypercalcaemia during haemofiltration were 5.2% and 0.7%, respectively. The incidence of hypercalcaemia was significantly lower after 24 and 72 hours of CVVH than at baseline. The incidences of hypocalcaemia and severe hypocalcaemia during haemofiltration treatment were 17.9% and 0.7%, respectively. The incidence of hypocalcaemia was significantly higher after 24 hours of haemofiltration than at baseline. The incidence of hypocalcaemia was higher in survivors before the beginning and after 24, 48 and 72 hours of haemofiltration (Table 2).

Altogether, out of 246 time points at which data for the calculation of the tCa/iCa ratio were complete after the initiation of haemofiltration treatment, its value exceeded 2.5 at 11 time-points (4.5%), including two at which 3< tCa/iCa ≤3.5 and one at which it exceeded 3.5. All episodes in which tCa/iCa exceeded 2.5 were observed in 10 patients from the non-surviving group.

Table 2. The incidences of electrolytic and acid-base disorders during n=232 haemofiltration sessions performed in n=50 patients.
Data are presented as cases/all blood tests at the time-point. (#$p<0.01$ for difference between groups, ##$p<0.05$ for difference between groups, *$p<0.01$ for difference from the value before CVVH, **$p<0.05$ for difference from the value before CVVH)

	Start HF			24 hours HF			48 hours HF			72 hours HF		
	Survivors	Non-survivors	All	Survivors	Non-survivors	All	Survivors	Non-survivors	All	Survivors	Non-survivors	All
Hyponatremia (Na<135 mEq/L)	12/54 (22.2%)	45/178 (25.3%)	57/232 (24.6%)	6/41 (14.6%)	10/148 (6.8%)	16/189* (8.5%)	1/29 (3.4%)	4/112 (3.6%)	5/141* (3.5%)	1/22 (4.5%)	1/72 (1.4%)	2/94* (2.1%)
Hypernatremia (Na>145 mEq/L)	10/54## (18.5%)	13/178## (7.3%)	23/232 (9.9%)	2/41 (4.9%)	2/148 (1.4%)	4/189* (2.1%)	1/29 (3.4%)	3/112 (2.7%)	4/141** (2.8%)	1/22 (4.5%)	1/72 (1.4%)	2/94** (2.1%)
Severe hypernatremia (Na>150 mEq/L)	4/54 (7.4%)	7/178 (3.9%)	11/232 (4.7%)	1/41 (2.4%)	0/148 (0%)	1/189** (0.5%)	0/29 (0%)	1/112 (0.9%)	1/141** (0.7%)	0/22 (0%)	0/72 (0%)	0/94** (0%)
Hypochloremia (Cl<98 mEq/L)	10/54 (18.5%)	24/177 (13.6%)	34/231 (14.7%)	8/41# (19.5%)	8/148# (5.4%)	16/189** (8.5%)	3/29 (10.3%)	8/111 (7.2%)	11/140** (7.9%)	4/22 (18.1%)	6/72 (8.3%)	10/94 (10.6%)
Severe hypochloremia (Cl<92 mEq/L)	2/54 (3.7%)	3/177 (1.7%)	5/231 (2.2%)	0/41 (0%)	0/148 (0%)	0/189 (0%)	0/29 (0%)	0/111 (0%)	0/140 (0%)	0/22 (0%)	0/72 (0%)	0/94 (0%)
Hyperchloremia (Cl>107 mEq/L)	16/54# (29.6%)	15/177# (8.5%)	31/231 (13.4%)	1/41 (7.1%)	4/148 (2.7%)	5/189* (2.6%)	3/29 (10.3%)	4/111 (3.6%)	7/140* (5%)	1/22 (4.5%)	2/72 (2.8%)	3/94* (3.2%)
Hypomagnesemia (Mg<1.5 mg/dL)	7/27 (25.9%)	15/111 (13.5%)	22/138 (15.9%)	8/28## (28.6%)	13/101## (12.9%)	21/129 (16.3%)	9/21 (42.9%)	18/73 (24.6%)	27/94** (28.7%)	6/14 (42.9%)	10/50 (20%)	16/64 (25%)
Hypophosphatemia (Pi<2.3mg/dL)	3/19 (15.8%)	14/94 (14.9%)	17/113 (15%)	13/24# (54.2%)	14/84# (16.7%)	27/108 (25%)	11/18# (61.1%)	18/67# (26.7%)	29/85* (34.1%)	13/14# (92.9%)	16/40# (40%)	29/54* (53.7%)
Hypocalcemia (iCa<0.98 mmol/L)	13/54## (24.1%)	19/178## (10.7%)	32/232 (13.8%)	16/41# (9%)	26/148# (17.6%)	42/189** (22.2%)	12/29# (41.4%)	14/112# (12.5%)	26/141 (18.4%)	6/22## (27.3%)	6/72## (8.3%)	12/94 (12.8%)
Severe hypocalcemia (iCa<0.9 mmol/L)	4/54 (7.4%)	8/178 (4.5%)	12/232 (5.2%)	5/41 (12.2%)	8/148 (5.4%)	13/189 (6.9%)	2/29 (6.9%)	4/112 (3.6%)	6/141 (4.2%)	2/22 (9.1%)	0/72 (0%)	2/94 (2.1%)
Hypercalcemia (iCa>1.21 mmol/L)	9/54 (16.7%)	23/178 (12.9%)	32/232 (13.8%)	3/41 (7.3%)	2/148 (1.6%)	5/189* (2.6%)	3/29 (10.3%)	9/112 (8%)	12/141 (8.5%)	0/22 (0%)	5/72 (6.9%)	5/94** (5.3%)
Severe hypercalcemia (iCa>1.32 mmol/L)	2/54 (3.7%)	2/178 (1.1%)	4/232 (1.7%)	0/41 (0%)	1/148 (0.7%)	1/189 (0.5%)	0/29 (0%)	1/112 (0.9%)	1/141 (0.7%)	0/22 (0%)	1/72 (1.4%)	1/94 (1.1%)
Metabolic alkalosis (pH>7.45 and HCO_3^->26 mmol/L)	8/67 (11.9%)	29/165 (17.6%)	37/232 (15.9%)	11/53 (20.7%)	33/136 (24.3%)	44/189 (23.3%)	13/37 (35.1%)	26/104 (25%)	39/141* (27.7%)	8/26 (30.8%)	16/68 (23.6%)	24/94** (25.5%)
HAGMA	9/66## (13.6%)	9/165## (5.5%)	18/231 (7.8%)	1/53 (1.97%)	4/136 (2.9%)	5/189** (2.6%)	0/37 (0%)	2/104 (1.9%)	2/141* (1.4%)	0/26 (0%)	0/68 (0%)	0/94* (0%)
tCa/iCa>2,5	0/27 (0%)	2/89 (2.2%)	2/116 (1.7%)	0/30 (0%)	4/80 (5%)	4/110 (3.6%)	0/19 (0%)	7/62 (11.3%)	7/81** (8.6%)	0/14 (0%)	0/36 (0%)	0/50 (0%)
Citrate accumulation	1/27 (3.7%)	4/89 (4.5%)	5/116 (4.3%)	1/30 (3.3%)	5/80 (6.2%)	6/110 (5.5%)	0/19 (0%)	2/61 (3.3%)	2/80 (2.5%)	1/14 (7.1%)	0/36 (0%)	1/50 (2%)

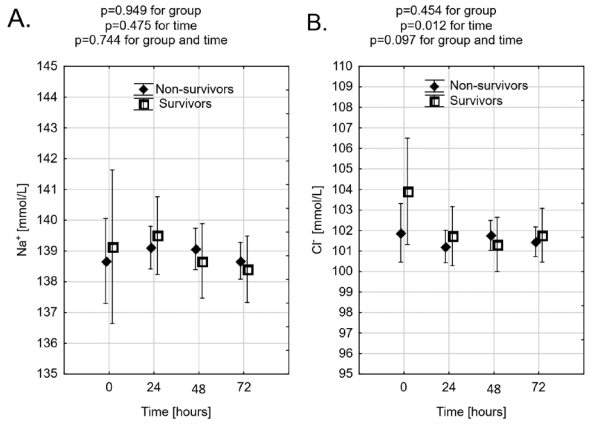

Figure 2. Sodium (A) and chloride (B) concentrations during haemofiltration treatment in survivors (n=17) and non-survivors (n=33) in sessions lasting >72 hours (means ± S.D.).

The incidence of a tCa/iCa ratio higher than 2.5 was significantly higher after 48 hours of haemofiltration than at baseline, and no significant inter-group difference was observed. The incidence of CA did not differ over the course of haemofiltration treatment, and no inter-group difference was observed.

Magnesium and phosphate

Magnesium and phosphate concentrations significantly decreased during haemofiltration, but no significant difference between the outcome groups was observed (Fig. 4.A and B) Moreover, hypomagnesaemia was reported in 64/287 (20.6%) blood samples during CVVH. The incidence of hypomagnesaemia was significantly higher after 48 hours of haemofiltration than at baseline. After 24 hours of haemofiltration, the incidence of hypomagnesaemia was higher in survivors than in non-survivors.

Hypophosphataemia was reported in 77/247 blood samples (31%) over the course of haemofiltration treatment. The incidence of hypophosphataemia was significantly higher after 48 and 72 hours of haemofiltration than at baseline. The incidences of hypophosphataemia

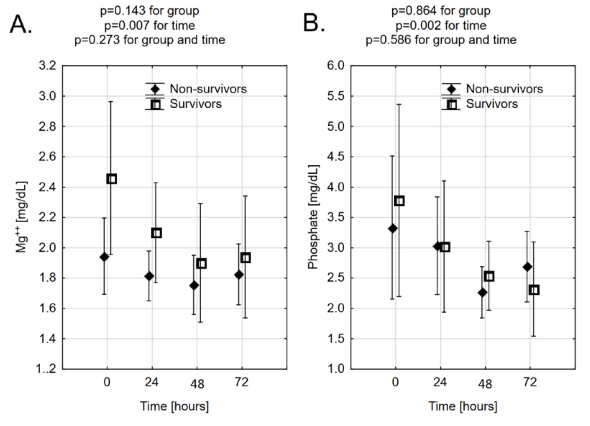

Figure 4. Magnesium (A) and phosphate (B) concentrations during sessions lasting longer than 72 hours in survivors and non-survivors.
Complete data on magnesium and phosphate concentrations were available from 25 and 15 haemofiltration sessions, respectively.

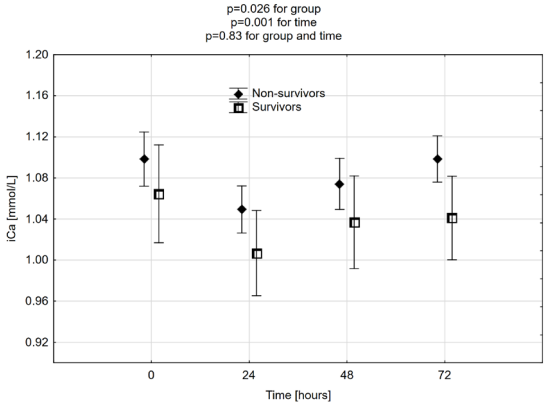

Figure 3. Ionized calcium concentration during haemofiltration treatment in survivors (n=17) and non-survivors (n=33) in sessions lasting >72 hours (means ± S.D.).

after 24, 48 and 72 hours of haemofiltration were significantly higher in survivors than in non-survivors.

Acid-base balance

The pH value and HCO_3^- concentration increased significantly during haemofiltration, and the pH was significantly higher in survivors than in non-survivors (Fig. 5).

During haemofiltration treatment, metabolic alkalosis (pH>7.45 and HCO_3^->26mmol/L) was observed in 107 of 424 blood samples (25.2%). The incidence of metabolic alkalosis was significantly higher after 48 and 72 hours of CVVH than at baseline, and the pH value as well as bicarbonate concentration increased significantly over time.

Altogether, out of 637 measurements, high anion gap metabolic acidosis (HAGMA) was observed at 25 time points (3.9%). The incidence of HAGMA during haemofiltration treatment did not differ between survivors and non-survivors, but it was significantly higher in survivors than in non-survivors before the beginning of haemofiltration. However, the incidence of HAGMA was significantly lower after 24, 48 and 72 hours of haemofiltration than at baseline.

Lactate

Both blood lactate and anion gap changed significantly during treatment (p=0.001 and p=0.026, respectively) (Fig. 6).

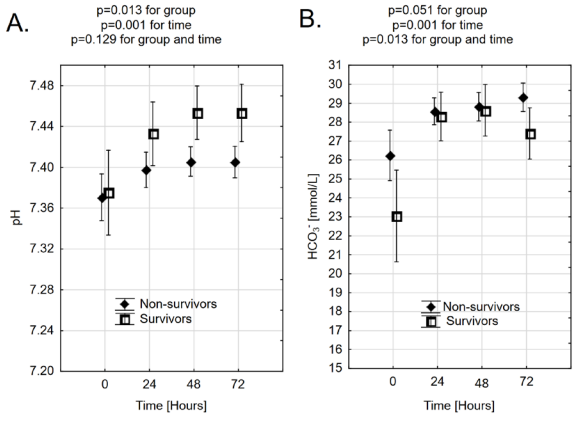

Figure 5. The pH values (A) and HCO_3^- concentrations (B) during sessions longer than 72 hours in survivors and non-survivors (means ± S.D.).

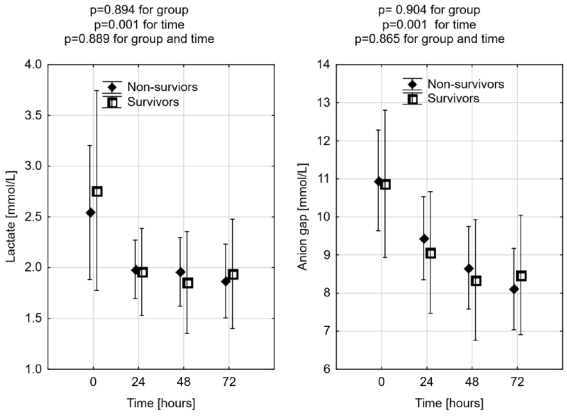

Figure 6. Lactate concentrations (A) and anion gaps (calculated as $Na^+ - (Cl^- + HCO_3^-)$) (B) during sessions longer than 72 hours in survivors and non-survivors (means ± S.D.).

Out of 23 sessions that started with lactate levels equal to or greater than 4 mmol/L, the tCa/iCa ratio was tracked in 17 sessions. Within these sessions, the tCa/iCa ratio exceeded 2.5 in 3 sessions, but during further CVVH treatment, it felt below 2.5 in one session and decreased from 2.58 to 2.52 in another session.

We did not find a significant correlation between the lactate concentration before the beginning of the haemofiltration session and the tCa/iCa ratio after 24, 48 and 72 hours of haemofiltration in linear regression (Fig. 7).

DISCUSSION

The filter life span in our group compares well with the results from multicentre trial by Zarbock group who observed median filter life span of 47 hours (IQR 19-70) (Zarbock *et al.*, 2020). We attribute longer filter life span in our group to additional prophylactic or therapeutic dose LMWH administered to most of our patients for cardiac surgical indications.

Citrate, when administered as tri-sodium, can induce hypernatraemia (Oudemans-van Straaten *et al.*, 2009). However, previous studies on CVVHDF with RCA also reported a significant decrease in sodium levels after treatment, which was not observed in our group (Khadzhynov *et al.*, 2014). The use of ACD-A solution for RCA is related to a lower sodium load than the use of tri-sodium citrate-based RCA (Schneider *et al.*, 2017). Therefore, with the ACD-A solution-based RCA protocol, low-sodium substitution fluid is not required to prevent hypernatraemia. The 2.4% incidence of hypernatraemia observed in our group during CRRT treatment was lower than observed with protocols based on tri-sodium citrate solutions used for CVVHD (Costa *et al.*, 2018).

In our study, the incidence of hypocalcaemia was higher than in the previous studies on RCA for continuous veno-venous haemodialysis (CVVHD) and continuous veno-venous hemodiafiltration (CVVHDF) (2.8–13%), but this may result from using different diagnostic criteria (Monchi *et al.*, 2004; Durao *et al.*, 2008; Oudemans-van Straaten *et al.*, 2009; Hetzel *et al.*, 2011; Khadzhynov *et al.*, 2017). Khadzhynov group observed that during RCA haemodiafiltration, up to 66% of the measured iCa concentrations were outside of the normal range, leading to a 67.5% incidence of hypocalcaemia (<1.1 mmol/L) (Khadzhynov *et al.*, 2017). The incidence of moderate hypocalcaemia (<1 mmol/L) reported in his study (13.3%) was lower than that observed in our patients (18.9%) based on similar criteria (Khadzhynov *et al.*, 2017). He also reported severe hypocalcaemia (<0.9 mmol/L) in three patients (20%), while in our group, we reported severe hypocalcaemia in 11 patients (22%), which was equal to 4.9% of all readings. Hypercalcaemia was observed more often before than during haemofiltration in the present cohort (4.9% of all readings during CVVH), and the incidence was higher than those previously reported from CVVHD and CVVHDF studies (2–2.5%) (Costa *et* al., 2018; Khadzhynov *et al.*, 2017). The incidence of severe hypercalcaemia (0.7%) in our group was, however, lower than the 2% incidence observed by Khadzhynov and others (Khadzhynov *et al.*, 2017).

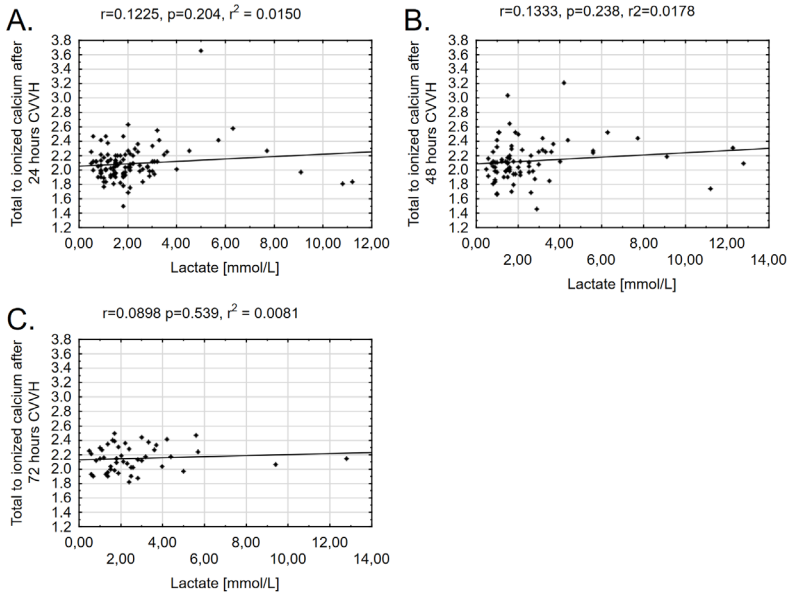

Figure 7. Correlation between the lactate concentration before the beginning of the haemofiltration session and the total to ionized calcium ratio after 24 (A), 48 (B), and 72 (C) hours of haemofiltration.

The incidence of electrolyte imbalance is difficult to compare between studies, not only due to different threshold values adopted for their identification but also due to the variance in reference values between laboratories and methods of analysis. A change in the calcium chloride concentration used for supplementation, which took place in our study protocol, should not have significantly influenced the results, as with initially lower concentrations, higher calcium chloride solution flows were used. Although the authors increased the target ionized calcium concentration range from the original RCA protocol, a substantial number of iCa readings were below the normal range, which indicates that the original protocol for the adjustment of calcium substitution was inadequate (Kirwan *et al*., 2016). This might be of importance in cardiac surgery patients, in whom low iCa can exacerbate heart failure.

It has been suggested that each new CRRT RCA protocol should be assessed with respect to the incidence of CA and electrolytic disorders to enable clinicians to predict and possibly prevent potentially dangerous ion shifts and their complications (Khadzhynov *et al*., 2014). The measurement of the citrate concentration in the plasma is still not feasible or timely (Monchi *et al*., 2004). An increased tCa/iCa ratio is a reliable indicator of CA (Schneider *et al*., 2017). A tCa/iCa threshold of 2.5 is commonly used as an indication of CA; however, it has high specificity but low sensitivity as a risk factor for mortality (Tan *et al*., 2019). Some authors have proposed that this threshold should be decreased to 2.3, while others claim that it may be a poor indicator of ongoing accumulation (Bakker *et al*., 2006; Link *et al*., 2012; Schneider *et al*., 2017).

Impaired citrate metabolism causes the build-up of calcium-citrate complexes, resulting in impaired free calcium recuperation. In fact, low iCa is the only known effect of citrate toxicity. Clinical symptoms in humans appear when the Ca^{++} concentration falls below 0.8 mmol/L (Khadzhynov *et al*., 2014). In our study, the case of low iCa was observed in a patient with severe lactic acidosis, who should be excluded from citrate anticoagulation. In the studied patients, other indirect features of CA, such as escalating calcium requirements and the development of HAGMA, were rarely observed, making the diagnosis of citrate toxicity questionable. In the present study, the incidence of a high tCa/iCa ratio during haemofiltration treatment (4.6%) was higher than that observed during RCA for CVVHD, when it did not exceed 2.3 in any patient (Costa *et al*., 2018).

It is still a matter of debate whether RCA can be used in patients with high lactate levels before the initiation of CRRT. In our group, the 3.8% incidence of CA was similar to that reported by Khadzhynov and others (Khadzhynov *et al*., 2017) in a study on general ICU patients treated with CVVHD. The authors of this study concluded that the risk of CA during RCA is low even in cases of initial severe hyperlactataemia. During CVVH with RCA, the incidence of CA may be as high as 8–23%, depending on the CRRT dose (Schilder *et* al., 2014; Tan *et al*., 2019). It should be emphasized that in our group, at three measurements, the tCa/iCa ratio exceeded 3.0, which indicated a high risk of citrate toxicity. A tCa/iCa ratio up to 3.4 was previously reported in studies on RCA with high-dose haemofiltration (35–45 ml/kg/h) (Tan *et al*., 2019). In our group, a higher incidence of CA was expected as a result of higher blood flows during CVVH, which required higher citrate doses than in most CVVHD protocols. Tan and others (Tan *et al*., 2019) observed citrate intolerance in 22.7% of patients treated with RCA haemofiltration. Data from the literature on the incidence of CA in patients with hyperlactataemia treated with RCA CRRT are limited, and questions arise regarding whether refusing these patients the benefits of RCA is reasonable (Khadzhynov *et al*., 2017). Our study is not exceptional in using RCA CRRT in patients with hyperlactataemia. In a previously described group of 1049 patients, CRRT was started in 221 ICU patients with lactate levels exceeding 4 mmol/L, in whom the reported incidence of CA was 6.3% (Khadzhynov *et al*., 2017).

In addition to calcium, citrate chelates magnesium ions and moves them to the filtrate. This can lead to hypomagnesaemia if magnesium substitution is not adequate. It was observed that post-filter magnesium concentrations decrease in a manner similar to the concentrations of calcium ions under RCA (Zakcharchenko *et al*., 2016). When using substitution fluid containing 0.5 mmol/L magnesium, a tendency towards a decreased magnesium concentration was observed during haemofiltration treatment. In our group, the magnesium level in the serum decreased over time during treatment with CVVH with A-CDA RCA and significant hypomagnesaemia developed after 48 hours of CVVH, despite routine magnesium sulfate supplementation at a rate of 0.81 mmol/hour. In this study hypomagnesaemia was more common (22.3%) than previously reported from the CVVHD RCA study in cancer patients with AKI (2.3%) (Costa *et al*., 2018). It was proposed that the magnesium concentration in substitution fluids used in ICU patients should be supra-normal rather than subnormal to compensate for increased losses due to its chelation by citrate (Zakcharchenko *et al*., 2016). Previously, supra-normal values of magnesium were observed in 54% of samples during haemodiafiltration treatment (Khadzhynov *et al*., 2014).

The incidence of hypophosphataemia in ICU patients treated with CRRT without replacement solutions containing phosphate can reach up to 80% and is related to increased mortality (Pistolesi *et al*., 2017). The 34.4% incidence of hypophosphataemia in our study is comparable to other reported results when no-phosphate-containing substitution fluids were administered, but it is much higher than the 3% incidence reported from the study on CVVHDF with phosphate-containing fluids (Yang *et al*., 2013). The observed increase in the incidence of hypophosphataemia over the course of CVVH treatment could have deleterious effects on patient outcomes and should be corrected in future work to determine an optimal CVVH RCA protocol based on a phosphate-containing solution. The higher incidence of hypophosphataemia in survivors than in non-survivors might be attributed to their better general condition and lower need for parenteral nutrition. In our study group phosphate was routinely intravenously supplemented in patients with parenteral nutrition, while it was administered only sporadically in patients who were fed enterally. The reported protocol might be improved by starting with higher supplementation doses of magnesium and inorganic phosphate than those used in the authors' department.

Metabolic alkalosis during CRRT was more common in our study (25.2%) than in earlier studies on RCA for CVVHD: 14% observed in cancer patients (Costa *et al*., 2018) and 5% observed in ICU patients (Borg *et* al., 2017; Khadzhynov *et al*., 2017). However, this overcompensation of metabolic acidosis with the simplified CVVH RCA protocol might be beneficial in patients who were acidotic at the beginning of CRRT.

In a previous study on CVVH with isosmotic citrate anticoagulation, Cassina and others (Casina *et al*., 2008)

reported alkalosis (pH>7.48) mostly of the respiratory type in only 4% of patients. In contrast to our results, Khadzhynov and others (Khadzhynov *et al.*, 2014) found that the bicarbonate concentration and base excess were below the normal ranges (69.9% and 84.6%, respectively) during RCA haemodiafiltration. Jacobs et al. reported metabolic alkalosis (pH >7.5) in 10% of patients treated with pre-dilution CVVH RCA in the group of patients treated with Prismocitrate 18 solution in contrast to its absence in patients treated with Prismocitrate 10/2 solution (Jacobs *et al.*, 2016). Since our data collection, the protocol recommended by Nikkiso changed the starting dose from 35 ml/kg/h to 25 ml/kg/h, which results in decreased citrate dose and might lead to lower incidence of both metabolic alkalosis and hypocalcaemia.

HAGMA is frequently observed in conjunction with CA (Schneider *et al.*, 2017). HAGMA and increased lactate concentrations are believed to appear not secondary to CA itself but rather to the shared primary problem of an impaired Krebs cycle, which reduces both citrate and lactate metabolism (Schneider *et al.*, 2017). Low incidence of HAGMA reported in this study, despite the high incidence of high anion gap, might result from trends towards a higher pH and a higher bicarbonate concentration. It was previously concluded that the risk of CA during RCA is low even in cases of severe hyperlactataemia and that lactate kinetics rather than its concentration should be considered in the assessment of the risk of CA (Khadzhynov *et al.*, 2017).

Main findings

To the best of our knowledge, this is the first study to evaluate electrolytic homeostasis and metabolic control during the simplified ACD-A RCA protocol for CVVH on the Aquarius platform. In this prospective study, we found that CVVH with a simplified RCA protocol provides very good sodium and chloride balance, but it is related to significant incidences of magnesium and phosphate deficiency. We also found that the incidence of CA can be significant in cardiovascular surgery patients. Interestingly, the tCa/iCa ratio did not increase in many patients in whom CVVH was started at a high lactate level. Except for magnesium and phosphate, which should be supplemented during CVVH, the RCA protocol was found to be safe and associated with satisfactory ion homeostasis, but it was related to the development of metabolic alkalosis.

During CRRT with RCA, acid-base status can be affected by excess citrate, leading to metabolic alkalosis or its impaired metabolism, which can result in an exacerbation of metabolic acidosis. The ACD-A solution used for RCA in our study had some advantages over the most commonly used tri-sodium citrate solution. Its use is related to the generation of 1/3 less bicarbonate after metabolism. A target citrate concentration in the filter compartment equal to 2.8 mmol/L should decrease the iCa concentration to 0.35 mmol/L on average (Kirwan *et al.*, 2014) and provide effective anticoagulation (Kośka *et al.*, 2020). According to the protocol, citrate flow was reduced stepwise when a trend towards alkalosis was observed, although this did not sufficiently counteract the development of metabolic alkalosis. On the other hand, the episodes of metabolic acidosis were most common at the beginning of CRRT therapy.

The lack of correlation between the lactate concentration before the beginning of the haemofiltration session and the tCa/iCa ratio after 24, 48 and 72 hours of haemofiltration in our study is in contrast to the results of Tan and others who found that hyperlactataemia predicted citrate intolerance (Tan *et al.*, 2013).

Strengths and limitations

The strengths of our study include the prospective evaluation of a considerable number of CVVH procedures in cardiovascular surgery patients using a novel simplified RCA protocol. Our study evaluated acid-base imbalance and electrolyte disorders with different blood flow settings and CRRT doses, thus representing real-life clinical practice.

Our study shares the limitations of all single-centre studies. An additional limitation was that the analysis was not restricted to only the first CVVH session per patient. Therefore, subsequently analysed sessions in the same patient may have serious confounding factors and were not truly independent. Another drawback of this study was that in a substantial number of patients, data on magnesium, phosphate and tCa were not available, which limited the assessment of certain imbalances in patient subgroups.

CONCLUSIONS

The present study showed that the simplified RCA protocol for CVVH on the Aquarius platform in cardiovascular surgery patients provides excellent sodium and chloride balance. Losses of magnesium and phosphate during CVVH therapy can lead to the depletion of these ions. The simplified RCA protocol with starting hemofiltration dose of 35 ml/kg/h provided insufficient control of the acid-base balance, causing over-compensation for metabolic acidosis and leading to metabolic alkalosis. The evaluated protocol might be related to significant incidences of hypocalcaemia and CA. Whether these are higher than those associated with other RCA protocols should be clarified in a comparative study.

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Authors contribution: AK had the initial conception of the study, collected and analysed the vast parts of data, drafted partially the methods, results and discussion; MMK collected partially the data, drafted and critically reviewed the manuscript and drew the graphical abstract; ALM collected and analyzed the data, drafted partially the methods, results, and discussion; WK and DJ took part in study design, reviewed the analyses and drafted partially the introduction, results and discussion; RL developed the conception and designed the study, performed the analyses and prepared the figures, drafted partially the introduction, results and discussion. All authors added substantially to the intellectual content, have revised and finally approved the submitted version.

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