Early Acid-Base and Blood Pressure Effects of Continuous Renal Replacement Therapy Intensity in Patients with Metabolic Acidosis

Rinaldo Bellomo, MD, Miklos Lipcsey, MD, Paolo Calzavacca, MD, Michael Haase, MD, Anjia Haase-Fielitz, BMedSc (Hons), PharmD, Elisa Licari, MD, Augustine Tee, MD, Louise Cole, M.B., B.S., PhD, Alan Cass M.B., B.S., PhD, Simon Finfer M.B., B.S., Martin Gallagher M.B, B.S., Joanne Lee, BMedSc (Hons), Serigne Lo, PhD, Colin McArthur M.B.B.S., Shay McGuinness, M.B.B.S., John Myburgh, M.B., B.S., PhD, Carlos Scheinkestel M.B., B.S., the RENAL Study Investigators and the ANZICS Clinical Trials Group

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Address reprint requests to Prof. Rinaldo Bellomo at ANZICS CTG, Level 3, 10 levers St, Carlton, Vic 3053, Australia or at ctg@anzics.com.au

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The names and affiliations of the RENAL Replacement Therapy Study Investigators are listed in the Appendix*

Key words: acidosis, acid-base, acidemia, norepinephrine, alkalosis, base excess, bicarbonate, pH, continuous renal replacement therapy, hemodialysis, strong ion difference

Abstract

Purpose: In acute kidney injury (AKI) patients, metabolic acidosis is common. Its severity, duration and associated changes in mean arterial pressure (MAP) and vasopressor therapy may be affected by the intensity of continuous renal replacement therapy (CRRT).

We aimed to compare key aspects of acidosis and MAP and vasopressor therapy in patients treated with two different CRRT intensities.

Methods: We studied a nested cohort of 115 patients from two tertiary ICU's within a large multicenter randomized controlled trial treated with lower intensity (LI) or higher intensity (HI) CRRT.

Results: Levels of metabolic acidosis at randomization were similar (base excess (BE) of -8 ± 8 vs. -8 ± 7 mEq/L; $p=0.76$). Speed of BE correction did not differ between the two groups. However, the HI group had a greater increase in MAP from baseline to 24 hours (7 ± 3 mmHg vs. 0 ± 3 ; $p<0.01$) and a greater decrease in norepinephrine dose (from 12.5 to 3.5 vs. 5 to 2.5 $\mu\text{g}/\text{min}$; $p<0.05$). The correlation (r) coefficients between absolute change in MAP and NA dose vs. change in BE were 0.05 and -0.37 respectively.

Conclusions: Overall, LI and HI CRRT have similar acid-base effects in patients with acidosis. However, HI was associated with greater improvements in MAP and vasopressor requirements. (Clinical Trial No: NCT00221013)

Introduction

Acid base homeostasis is a key therapeutic target in critically ill patients [1, 2]. Yet, acidosis is common in the critically ill [3]. Such acidosis is an independent predictor of unfavourable outcome in this population [4, 5]. In patients with acute kidney injury (AKI), metabolic acidosis is especially common [6]. Although the exact mechanisms of metabolic acidosis in AKI are complex, excess of retained metabolic acids is likely to contribute, together with other general acid-base disorders of critical illness (hyperlactatemia and/or hyperchloremia) [7, 8]. Depending on its severity, correction may require different levels of intervention including renal replacement therapy RRT [9].

Despite the logical expectation that RRT should improve metabolic acidosis, studies have reported that its effect on acid-base status is likely dependent on the nature of acidosis (anion gap positive vs. non-anion gap acidosis) its intensity, choice of buffer, ability of the body to metabolise buffer to bicarbonate, site of delivery of the buffer, and quantity of the buffer delivered [10-12]. In addition, the plasma concentration of solutes available for ultrafiltration, and the rate of ultrafiltration also appear to determine the effect of RRT on acid-base status [13, 14]. In this regard, although under most circumstances other buffers are adequate, bicarbonate based replacement or dialysis solutions more predictably and consistently reverse metabolic acidosis [11]. However, once bicarbonate is used as replacement fluid and dialysate fluid, little is known about the impact of CRRT intensity on the speed and extent of correction of the metabolic acidosis of advanced AKI. In particular, it is unknown whether applying more intensive CRRT would lead to faster and/or greater

resolution of acidosis in the early (first 24 hours) treatment period. Also given concerns that acidosis and/or acidemia might lower MAP and increase vasopressor requirements, it is unknown whether such correction would be accompanied by an effect on mean arterial pressure.

We hypothesized that, in the first 24 hours, higher intensity CRRT (HI CRRT) would reverse metabolic acidosis at a faster rate and to a greater degree than lower intensity CRRT (LI CRRT) and thus had correction of acidosis in the first 24 hours as our primary endpoint. We also hypothesized that such changes would be accompanied by a greater increase in MAP, and therefore had improved MAP at 24 hours as our secondary endpoint. We tested these hypotheses by conducting a nested cohort study within the Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Study, a multicentre randomized controlled study comparing two levels of CRRT intensity [15].

METHODS

The study involved a nested cohort of patients from two centres within the RENAL study in whom detailed data on acid-base status was obtained during the first 24 hours of CRRT treatment. The RENAL study was a multicenter, prospective, randomized trial of two levels of intensity of continuous renal replacement therapy (CRRT) originally in 1508 critically ill patients with acute kidney injury conducted in 35 ICUs in Australia and New Zealand [15]. The study was approved by the Human Research Ethics Committees of the University of Sydney and all participating institutions.

The methodological details of the RENAL study were recently reported [15]. In brief, patients were eligible for enrolment if they were critically ill adults who had AKI, were deemed to require RRT by the treating clinician and fulfilled predefined criteria [15]. Eligible patients were randomly assigned to continuous veno-venous hemodiafiltration (CVVHDF) with effluent flow at 25 ml/kg/hr (lower intensity, LI) or 40 ml/kg/hr (higher intensity, HI). Replacement fluid was delivered into the extracorporeal circuit after the filter (i.e., postdilution), with a ratio of dialysate to replacement fluid of 1:1. Blood flow was kept above 150 ml per minute. Fluid was removed by decreasing the flow of the replacement fluid and of the dialysate in equal proportion, so that effluent exceeded them by any amount prescribed by the clinician.

Filters with the AN69 membrane (Gambro) were used. Hemosol BO fluid (Gambro) was used as the dialysate and replacement fluid. Hemosol contains sodium ion (Na^+) ($140 \text{ mmol} \times \text{L}^{-1}$), chloride ion (Cl^-) ($109.5 \text{ mmol} \times \text{L}^{-1}$), bicarbonate (HCO_3^-) ($32 \text{ mmol} \times \text{L}^{-1}$), lactate ($3 \text{ mmol} \times \text{L}^{-1}$), calcium ion (Ca^{++}) ($1.75 \text{ mmol} \times \text{L}^{-1}$) and magnesium ion (Mg^{++}) ($0.5 \text{ mmol} \times \text{L}^{-1}$).

All patients were anticoagulated with unfractionated heparin with target at the attending clinicians discretion.

The intensive care management of the patients including carbon dioxide tension in arterial blood (PaCO_2) and MAP aims were set by the treating physicians. Study treatment was discontinued on death, discharge from ICU, or recovery of renal function.

Measurements

In all patients arterial blood pH, plasma lactate, PaCO_2 , K, Na, Mg, ionized Ca (iCa), Cl, phosphate (Phos), albumin (alb), creatinine and urea levels, MAP and dose of norepinephrine in $\mu\text{g}/\text{min}$, were recorded two hourly for 24 hours.

Calculations

Plasma standard HCO_3^- levels and BE values were calculated by blood gas machines.

The strong ion gap (SIG) [16] was calculated as the difference between the apparent (SIDa) and effective (SIDe) strong ion difference [17, 18], where

$$\text{SIDa} = [\text{Na}^+] + [\text{K}^+] + 2 \times [\text{Ca}^{++}] + 2 \times [\text{Mg}^{++}] - [\text{Cl}^-] - [\text{L-lactate}]$$

and

$$\text{SIDe} = 1000 \times 2.46 \times 10^{-11} \times \text{PaCO}_2 / 10^{-\text{pH}} + \text{Alb} \times (0.123 \times \text{pH} - 0.631) + \text{Phos} \times (0.309 \times \text{pH} - 0.469) \text{ [16].}$$

Statistical analysis

Data are expressed as means with standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables.

To adjust for the effect of any missing data, calculations were made with and without imputations for missing data. Imputations were done by calculating the mean of the value immediately before and after the missing value. If a value was missing at the end of the observational period the “last value carry forward” method was used. The calculations with the two data sets corresponded well to one another, thus only analysis based on original data without imputations is reported, unless otherwise stated.

Comparisons were made using the z-test for dichotomous variables, t-test or ANOVA as appropriate for repeated measurements for variables with normal distribution and the Mann-Whitney test or Wilcoxon matched pairs test for variables with non-normal distribution. Spearman ranks test was used for calculating correlation coefficients. A $p < 0.05$

was considered significant. Statistical analyses were performed by STATISTICA™ software, version 10 (StatSoft, Tulsa, OK, USA).

RESULTS

Patient characteristics

We studied 115 patients, of whom 59 (51%) were randomized into the lower intensity (LI) group and 56 (49%) into the higher intensity (HI) group. The two groups were comparable in terms of age, mortality, severity of illness and organ failure and delivered CRRT time (Table 1). All but one patient had an abnormal anion gap and 28 of the 115 patients (24%) had plasma lactate over $4 \text{ mmol} \times \text{L}^{-1}$. Discharge diagnosis groups are provided in Table 2.

At 28 days, 45 (39%) patients were dead: 24 (41%) in the LI group and 21 (38%) in the HI group. The most common ICU admission diagnosis was sepsis with AKI ($n=43$, 37% of total), followed by postoperative AKI ($n=21$, 18% of total), AKI due to primary renal disease ($n=19$, 17% of total) and AKI secondary to other medical conditions ($n=32$, 28% of total).

Acid-base effects

Biochemical, acid-base and MAP values at baseline and 24 hours are given in Table 3. Overall, acidosis improves similarly in both groups. In particular, BE increased similarly from 0 to 24 hours in both groups (Figure 1).

A normal BE between $-2 \text{ mmol} \times \text{L}^{-1}$ to $+2 \text{ mmol} \times \text{L}^{-1}$ at 24 hours was achieved in 29 (49%) LI patients and 29 (52%) HI patients.

Effect on mean arterial pressure and norepinephrine dose

The MAP was higher in the LI group at baseline compared with the HI group (78 ± 12 mmHg vs. 73 ± 11 ; $p < 0.05$) in the overall population. However, the absolute change in MAP from baseline to 24 hours was greater in the HI group ($p < 0.001$) (Figure 2). The absolute change in MAP did not correlate with the absolute change in BE ($r = 0.05$).

The dose of norepinephrine differed between the groups at baseline ($p < 0.05$, Table 3). The absolute change in dose norepinephrine dose from baseline to 24 hours (Figure 3), was greater in the HI group (-7 ± 5 vs. $0 \pm 5 \mu\text{g} \times \text{min}^{-1}$; $p < 0.05$) than in the LI group. This difference in dose remained significant even when patients without baseline norepinephrine treatment were excluded (25 out of 59 patients in the LI Group and 15 out of 52 patients in the HI Group). The correlation between absolute change in noradrenaline dose and the absolute change in BE was weak ($r = -0.37$).

Discussion

Key findings

We conducted a nested cohort study within the RENAL trial to test whether HI CRRT would result in faster and/or greater early correction of acidosis and whether it would also affect MAP and NE treatment. Overall, we found that HI-CRRT achieved a similar rate and magnitude of acidosis correction compared with LI-CRRT. However, HI-CRRT resulted in a greater increase in blood pressure and a greater decrease in norepinephrine requirements. These changes did not correlate with changes in pH or BE.

Relationship to previous studies

The effect of CRRT on acid base balance appears determined by the plasma concentration of solutes available for ultrafiltration, the composition of the dialysis or replacement fluid, the

intensity of ultrafiltration and body weight [13, 14]. Our study showed, as expected, that bicarbonate based CRRT attenuates metabolic acidosis [10-12]. Although the effects of bicarbonate-based CRRT on acid-base disorders have been investigated previously [19], our study is the largest study of the acid base effect of CRRT intensity within a randomized trial.

The overall reversal of acidosis was similar in the LI and HI groups in terms of pH change and change in HCO_3^- levels and BE.

Despite the similar effects on BE, HI and LI had a different effect on SIG, which decreased more in the HI group. This effect could be consistent with the view that the removal of unmeasured organic anions by CRRT is increased with greater intensity [7, 20]. However, since SIG decreased similarly in both HI and LI groups in the severe acidosis subgroup, this effect may not entirely be related to CRRT intensity or only operate at less severe acid base disturbances. In contrast, there were no or minimal effects of CRRT on the SID, a major determinant of acid-base status [16]. However, one ion (potassium) was affected by CRRT intensity. Such decrease in plasma potassium levels appears due to direct clearance by CRRT rather than a pH effect [21].

CRRT has been previously associated with improved MAP in animal models of sepsis and in humans [22-25]. However, no controlled studies have compared two intensities of CRRT in terms of their effect on MAP and vasopressor requirements [26]. We found that MAP increased and vasopressor requirements decreased with HI CRRT. Although decreased norepinephrine requirements could be attributed to normalisation of pH, this was not different between the two groups and cannot be logically used to explain our findings [27,

28]. Cooling by CRRT at higher intensity may also explain changes in MAP, However, in all cases fluids were warmed to 37 degrees or more making this mechanisms somewhat unlikely. A potential alternative mechanism could be more efficient removal of biologic mediators responsible for hypotension and/or vasodilatation [23, 29-31]. Some of these mediators may have contributed to the changes in SIG as well as inducing hypotension. Our study, however, cannot provide a mechanistic analysis of the physiological effects observed.

Implications

Our study suggests that acidemia is generally effectively reversed during CRRT after 24 hours of therapy. This information could be of interesting to clinicians wishing to correct metabolic acidosis in patients with severe AKI, but it is not clear if it actually would change the management of these patients. Additionally, the findings that higher intensity CRRT improves MAP and reduces vasopressor doses may assist clinicians dealing with patients with the combination of acidosis, severe hypotension and vasopressor requirements during early CRRT. Although, bicarbonate buffer was used in this study, other buffers may have similar effects on acid-base balance.

Strengths and limitations

This study is the largest investigating the effect of CRRT dialysate and replacement fluid flow on acid-base status within a randomised controlled trial, data collection was extensive, numerical, based on blood gas machine output or independently recorded by the bedside nurse. These aspects of the study make bias unlikely. As this is a nested cohort study of the RENAL trial, thus a sub-study, the selection bias introduced by studying a subpopulation can influence results. However, patients included in this study

were recruited by including *all* patients from two centres of the RENAL study, their age and illness severity are similar to those reported for the whole population of RENAL trial patients [15], and the cohort represents a mixture of patients typically seen in general intensive care units. Others have reported that nested cohort studies have a design that preserves the validity of the original population when selection bias can be avoided [32].

Another consequence of our methodology is that our patients were not recruited and randomized to test the specific hypothesis of this study. However, since a majority of study patients had metabolic acidosis, this population was particularly useful to investigate the acid-base effects of CRRT in this setting. This study investigated a specific CRRT set up (bicarbonate based continuous veno-venous hemodiafiltration, with a fixed blood flow and post-filter replacement), conclusions from this study, therefore, may not apply to other CRRT techniques.

Finally, our study was only conducted for 24 hours, thus we cannot comment on the later effects associated with CRRT [33]. However, most acid-base disturbances are reversed within this time period and if CRRT fails to restore acid-base homeostasis by 24 hours, clinicians may choose additional therapies [34].

Future research

Further studies of CRRT intensity with other buffers (e.g. citrate) may be of interest given the evolution of therapy in toward greater use of citrate as anticoagulant [35]. In addition, investigation of the mechanism by which HI CRRT improves MAP might provide insights into future therapeutic interventions.

Conclusions

In this nested cohort study within a large RCT, HI CRRT did not affect acid-base differently from LI CRRT overall. In addition, HI CRRT increased MAP and decreased norepinephrine requirements compared to LI CRRT. These physiological observations may be helpful to clinicians faced with the treatment of patients with combined AKI, metabolic acidosis, hypotension and vasopressor therapy.

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Writing Committee (in alphabetical order): Rinaldo Bellomo (Chair), Alan Cass, Louise Cole, Simon Finfer, Martin Gallagher, Serigne N Lo, Colin McArthur, Shay McGuinness, John Myburgh, Robyn Norton, Carlos Scheinkestel and Steve Su.

Management Committee: (in alphabetical order): Rinaldo Bellomo (Chair), David Ali, Alan Cass, Louise Cole, Simon Finfer, Martin Gallagher, Donna Goldsmith, Joanne Lee, John Myburgh, Robyn Norton and Carlos Scheinkestel.

Steering Committee: Rinaldo Bellomo (Chair), Ashoke Banerjee Deepak Bhonagiri, David Blythe, John Botha, John Cade, Louise Cole, Geoff Dobb, John Eddington, Simon Finfer, Arthas Flabouris, Craig French, Peter Garrett, Seton Henderson, Benno Ihle, Chris Joyce, Michael Kalkoff, Jeff Lipman, Colin McArthur, Shay McGuinness, David Milliss, Imogen Mitchell, John Morgan, John Myburgh, Priya Nair, Neil Orford, Asif Raza, Carlos Scheinkestel, Yahya Shehabi, Antony Tobin, Richard Totaro, Andrew Turner and Christopher Wright.

Project Management Team (in alphabetical order): David Ali, Joanne Lee, Lorraine Little, Alana Morrison, Giovanna Regaglia and Ravi Shukla

Data Safety and Monitoring Committee (in alphabetical order):: Colin Baigent (Chair), Jonathan Emberson, David Wheeler and Duncan Young,

Statistics Committee (in alphabetical order): Laurent Billot, Severine Bompont, Stephane Heritier, Serigne N Lo, Avinesh Pillai, Steve Su.

Data management and IT/Programming (in alphabetical order): Sameer Pandey, Suzanne Ryan, Manuela Schmidt, Gemma Starzec and Bala Vijayan

Site Investigators and Research Co-ordinators (in alphabetical order):

Australian Capital Territory:

Canberra Hospital: Imogen Mitchell, Rebecca Ashley, Jelena Gissane, Katya Malchukova and Jamie Ranse

New South Wales:

Blacktown Hospital: Asif Raza, Kiran Nand and Treena Sara

Concord Hospital: David Millis, Jeff Tan and Helen Wong

John Hunter Hospital: Peter Harrigan, Elise Crowfoot and Miranda Hardie

Liverpool Hospital: Deepak Bhonagiri and Sharon Micallef

Mater Calvary Hospital, Newcastle: Jorge Brieva and Melissa Lintott

Nepean Hospital: Louise Cole, Rebecca Gresham, Maria Nikas and Leonie Weisbrodt

Prince of Wales Hospital: Yahya Shehabi, Frances Bass, Michelle Campbell and Victoria Stockdale

Royal North Shore Hospital: Simon Finfer, Susan Ankers, Anne O'Connor and Julie Potter

Royal Prince Alfred Hospital: Richard Totaro and Dorrilyn Rajbhandari

St George Hospital: John Myburgh, Vanessa Dhiacou, Alina Jovanovska and Francesca Munster

St Vincent's Hospital: Priya Nair, Jeff Breeding and Claire Burns

Westmead Hospital: Ashoke Banerjee, Maridy Morrison, Caroline Pfeffercorn and Anne Ritchie

New Zealand:

Auckland City Hospital/CVICU: Shay McGuinness, Heidi Buhr, Michelle Eccleston and Rachael Parke

Auckland City Hospital/DCCM: Colin McArthur, Jeanette Bell and Lynette Newby

Christchurch Hospital: Seton Henderson and Jan Mehrrens

Whangarei Hospital: Michael Kalkoff and Cathy West

Queensland:

Mater Adult and Mater Private Hospital: John Morgan, Lorraine Rudder and Joanne Sutton

Nambour General Hospital: Peter Garrett, Nicole Groves, Shona McDonald, and Jennifer Palmer

Princess Alexandra Hospital: Chris Joyce, Meg Harwood, Jean Helyar and Benjamin Mackie

Royal Brisbane Hospital: Jeff Lipman, Robert Boots, Claire Bertenshaw, Renae Deans, Cheryl Fourie and Melissa Lassig-Smith

South Australia:

Royal Adelaide Hospital: Arthas Flabouris, Jason Edwards, Stephanie O'Connor, and Justine Rivett

Tasmania:

Royal Hobart Hospital: Andrew Turner, Tanya Field and Kathryn Marsden

Victoria:

Austin Hospital: Rinaldo Bellomo, Claire Mathlin, Donna Goldsmith, Inga Mercer and Kim O'Sullivan

Bendigo Hospital: John Edington, Catherine Boschert and Julie Smith

Epworth Hospital: Benno Ihle, Michael Graan and Samuel Ho

Frankston Hospital: John Botha, Nina Fowler, Jodi McInness and Naomi Pratt

Geelong Hospital: Neil Orford, Tania Elderkin, Melissa Fraser and Anne Kinmonth

Monash Medical Centre: Christopher Wright, Sue Burton, Carly Culhane, Pauline Galt and Rebecca Rutzou

Royal Melbourne: Megan Roberston, Deborah Barge, Tania Caf, Belinda Howe and Patzy Low

St Vincent's Hospital Melbourne: Antony Tobin, Nicole Groves, Jennifer Holmes and Roger Smith

The Alfred Hospital: Carlos Scheinkestel, Andrew Davies, Lynne Murray, Rachael Nevill, Shirley Vallance, Sue Varley and Vickie White

Western Hospital: Craig French, Lorraine Little and Heike Raunow

Western Australia:

Fremantle Hospital: David Blythe and Anna Palermo

Royal Perth Hospital: Geoff Dobb, Melanie Boardman, Jenny Chamberlain, Andree Gould, Geraldine McEntaggart, Samantha Perryman and Linda Thomas

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Figure legends

Figure 1: Changes in base excess (BE) levels in the first 24 hours of treatment in patients receiving lower intensity and higher intensity CRRT. (Mean $\pm$ SE)

Figure 2: Absolute changes in mean arterial pressure (MAP) from baseline in the first 24 hours of treatment in patients receiving lower intensity and higher intensity CRRT. (Mean $\pm$ SE)

Figure 3: Absolute changes in the infusion rate of norepinephrine from baseline in the first 24 hours of treatment in patients receiving lower intensity and higher intensity CRRT. (Mean $\pm$ SE).

Table 1: Characteristics of the study population according to treatment allocation

	Overall population	LI group	HI group	p-value
Sex (% male)	83/115 (72%)	41/59 (70%)	42/56 (75%)	0.51
Day 28 mortality (% dead)	45/115 (39%)	24/59 (41%)	21/56 (38%)	0.70
Age (IQR)	67 (19)	66 (18)	69 (19)	0.24
APACHE III (IQR)	103 (30)	100 (35)	107 (33)	0.09
SOFA (IQR)	11 (6)	11 (6)	11 (6)	0.43
Hrs on CRRT (IQR)	21 (6)	21 (7)	22 (6)	0.46

LI=lower intensity; HI=high intensity;

APACHE=acute physiology and chronic health evaluation score

CRRT=continuous renal replacement therapy; SOFA=sequential organ failure assessment score

p-values refer to intergroup differences.

Table 2: ICU discharge diagnosis groups for cohort (n=115).

	n	% of total
Medical diagnoses	89	77
Infectious conditions	34	30
Cardiac conditions	6	5
Respiratory conditions	2	2
Genitourinary conditions	25	22
Hepatic conditions	8	7
Other medical conditions	14	12
Surgical diagnoses	26	23
General surgical conditions	13	11
Cardiac surgical conditions	9	8
Vascular surgical conditions	3	3
Trauma	1	1

Table 3: Change in Biochemical and physiologic data in the two study groups from Baseline to 24 hours

Change from baseline to 24 hrs of CRRT	Lower intensity CRRT			Higher intensity CRRT		
	0	24	p-value	0	24	p-value
pH	7.30±0.12	7.36±0.12	<0.001	7.29 ± 0.11	7.38 ± 0.07	<0.001
HCO ₃ ⁻ (mmol x L ⁻¹)	18 ± 6	22±4	<0.001	18 ± 6	23 ± 6	<0.001
BE (mEq x L ⁻¹)	-8 ± 8	-3±6	<0.001	-8 ± 7	-2 ± 4	<0.001
SIDa (mmol x L ⁻¹)	38 ± 6	38±5	0.38	38 ± 6	37 ± 4	0.17
SIG (mmol x L ⁻¹)	10 ± 4	8±14	0.30	10 ± 5	5 ± 4	<0.001
Lactate (mmol x L ⁻¹)	2.4 (1.3-4.6)	1.8 (1.4-2.9)	0.83	2.2 (1.6-3.8)	1.4 (1.1-2.5)	<0.01
Chloride (mmol x L ⁻¹)	104 ± 7	103 ± 4	0.24	103 ± 8	103 ± 3	0.97
MAP (mmHg)	78 ± 11	78±12	0.93	73 ± 11	81 ± 15	<0.001
Norepinephrine dose (µg x min ⁻¹)	5 (0-14)	3 (0-11)	0.53	13 (0-22)	4 (0-14)	<0.001

Values are given at 0 hours (at the start of CRRT) and at 24 hours of CRRT. Data are given as mean ± standard deviation or median (interquartile range). p-values refer to intragroup difference from 0 to 24 hours.

Figure 1

Figure 2

Figure 3