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RESEARCH ARTICLE

Electrolyte profiles with induced hypothermia: A sub study of a clinical trial evaluating the duration of hypothermia after cardiac arrest

Hans Kirkegaard[1,2] | Anders M. Grejs[3,4] | Simon Gudbjerg[5] | Christophe Duez[3] | Anni Jeppesen[3] | Christian Hassager[6,7] | Timo Laitio[8] | Christian Storm[9] | Fabio Silvio Taccone[10] | Markus B. Skrifvars[11,12] | Eldar Søreide[13,14]

[1]Research Center for Emergency Medicine, Emergency Department, Aarhus University Hospital, Aarhus, Denmark

[2]Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[3]Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark

[4]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[5]Department of Anaesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark

[6]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark

[7]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[8]Division of Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital, University of Turku, Finland

[9]Department of Internal Medicine, Nephrology and Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany

[10]Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

[11]Department of Anaesthesiology, Intensive Care and Paine Medicine, University of Helsinki, Helsinki University Hospital, Helsinki, Finland

[12]Department of Emergency Care and Services, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[13]Critical Care and Anaesthesiology Research Group, Stavanger University Hospital, Stavanger, Norway

[14]Department of Clinical Medicine, University of Bergen, Bergen, Norway

Correspondence
Hans Kirkegaard, Research Center for Emergency Medicine, Aarhus University Hospital, Palle Juul-Jensens Boulevard 161, J103-252, 8200 Aarhus N. Denmark.
Email: hanskirkegaard@clin.au.dk

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Abstract

Background: Electrolyte disturbances can result from targeted temperature treatment (TTM) in out-of-hospital cardiac arrest (OHCA) patients. This study explores electrolyte changes in blood and urine in OHCA patients treated with TTM.

Methods: This is a sub-study of the TTH48 trial, with the inclusion of 310 unconscious OHCA patients treated with TTM at 33°C for 24 or 48 h. Over a three-day period, serum concentrations were obtained on sodium potassium, chloride, ionized calcium, magnesium and phosphate, as were results from a 24-h diuresis and urine electrolyte concentration and excretion. Changes over time were analysed with a mixed-model multivariate analysis of variance with repeated measurements.

Results: On admission, mean ± SD sodium concentration was 138 ± 3.5 mmol/l, which increased slightly but significantly ($p < .05$) during the first 24 h. Magnesium concentration stayed within the reference interval. Median ionized calcium concentration increased from 1.11 (IQR 1.1–1.2) mmol/l during the first 24 h ($p < .05$), whereas

median phosphate concentration dropped to 1.02 (IQR 0.8–1.2) mmol/l ($p < .05$) and stayed low. During rewarming, potassium concentrations increased, and magnesium and ionizes calcium concentration decreased ($p < .05$). Median 24-h diuresis results on days one and two were 2198 and 2048 ml respectively, and the electrolyte excretion mostly stayed low in the reference interval.

Conclusions: Electrolytes mostly remained within the reference interval. A temporal change occurred in potassium, magnesium and calcium concentrations with TTM's different phases. No hypothermia effect on diuresis was detected, and urine excretion of electrolytes mostly stayed low.

Editorial Comment

While there can be electrolyte abnormalities in cases after cardiac arrest and resuscitation, this secondary analysis from a trial with post-arrest temperature management assessed possible relations between temperature and serum electrolyte levels. No clear association between temperature change and electrolyte change was observed.

1 | INTRODUCTION

When induced hypothermia—now called targeted temperature management (TTM)—was introduced as standard post-cardiac arrest intensive care unit (ICU) treatment, several authors stressed the importance of avoiding electrolyte disturbances.[1,2] Earlier studies have demonstrated that induced mild hypothermia in brain-injured patients causes magnesium, calcium and phosphate depletion.[3,4] Particularly, the negative effects of hypopotassaemia and hypomagnesemia were highlighted. Hypopotassaemia has been linked to cardiac arrhythmia.[5-7] Magnesium plays an important role in many cellular functions, and hypomagnesemia may induce cardiac arrhythmias and interfere with vascular tone.[8] Hypomagnesaemia has also been associated with poor neurologic outcomes in patients suffering from post-cardiac arrest syndrome (PCAS).[9] Other electrolytes are also of importance in this context. Hypocalcaemia can cause reduced cardiac contractility and decreased vascular tone,[10] while hypophosphatemia can cause muscle weakness and reduced diaphragmatic contractility, leading to difficulties weaning from a ventilator.[3,11,12]

Part of the electrolyte disturbances may be due to so-called cold diuresis (increased hourly urine output), which leads to increased loss of electrolytes in the urine.[3,13,14,15] Some smaller studies of urine output and electrolyte losses during TTM exist,[16-20] but there is still a paucity of data on the interaction of serum electrolytes and urine output/excretion in out-of-hospital cardiac arrest (OHCA) patients undergoing TTM in the ICU, furthermore conclusions are largely based on data with a great risk of bias.

Hence, we decided to use the TTH48 trial cohort[21] to study changes in serum values of sodium, potassium, chloride, magnesium, calcium and phosphate, as well as urine output and electrolyte excretion, during TTM at 33°C of variable durations. Such information could help optimize ICU care in post-cardiac arrest patients.[22] We hypothesized that induction and maintenance of hypothermia, compared to re-warming to normothermia, would be associated with changes in serum and urinary electrolytes, and urinary volumes.

2 | METHODS

This is a pre-planned explorative sub-study of the TTH48 trial (NCT01689077).[21] The TTH48 trial was a multinational assessor-initiated, randomized, outcome-blinded pragmatic clinical trial where patients resuscitated from OHCA where randomized to TTM at 33°C for 24 or 48 h. The primary outcome was cerebral performance at six months. Inclusion criteria were as follows: OHCA with presumed cardiac cause, re-established spontaneous circulation for 20 min after resuscitation, Glasgow Coma Score (GCS) <8, and age ≥18 years and <80 years. The list of exclusion criteria can be seen in the protocol paper.[23] Patients were cooled as fast as possible; target temperature (TT) was obtained when the core temperature reached 34°C. After intervention, patients were rewarmed by a maximum temperature of 0.5°C per hour. The trial protocol included recommendations on supportive treatment but not on electrolyte treatment.

2.1 | Patient data

Prehospital cardiac arrest data were collected according to the Utstein guidelines. All clinical data were retrieved from the TTH48 database and merged with post hoc collected data from point-of-care analyses on full blood of sodium, potassium, chloride, ionized calcium and pH collected separately from the ICU chart of each patient. Reference values for serum concentrations and urine excretion in 24 h may vary between laboratories, hospitals and countries.

We used the following reference values retrieved from a Danish teaching book on laboratory medicine[24]: Serum concentrations for sodium: 135–145; potassium: 3.5–5.0; chloride: 98–108; magnesium: 0.67–0.93; ionized calcium: 1.15 –1.30; and phosphate: 0.8–1.5, all in mmol/l. For the 24-h urine excretion, the references values were as follows: sodium, 40–200; potassium: 30–130; magnesium: 2–12; ionised calcium: 2.5–8; phosphate: 20–60; and chloride: 50–150, all in mmol.

Blood samples for serum analyses of ionized calcium, magnesium and phosphate were collected at admission to the ICU and at days one, two and three. Point-of-care analyses on full blood were performed at the discretion of the clinical team and included electrolyte and blood gas measurements performed at 37°C. Twenty-four-hour urine output was measured on days one, two and three, and the concentrations of urine sodium, potassium, magnesium, ionized calcium and phosphate were measured at time 0, when TT was reached, and at 24, 48 and 72 h after TT. For practical reasons it was not possible to collect information about replacement therapy.

2.2 | Statistics

Intervention for the two TTM groups was identical for the first 24 h. TTM groups are therefore compared only beyond the first 24 h.

Categorical variables were given as numbers and percentages. Continuous variables were given as means with standard deviation (SD) and medians with inter-quartile ranges (IQR) as appropriate.

Normally distributed data were compared using an unpaired *t*-test, and non-normally distributed continuous variables were compared using the Mann–Whitney U-test. Electrolytes from point-of-care analyses were compared between the two groups at 40–43 h (T41) and 60–63 (T61) hours after TT. Values are mean and SD calculated from all measurements in each three-hour time interval. A mixed-model multivariate analysis of variance (MANOVA) with repeated measurements was used to analyse changes over time. A result of $p < .05$ was considered statistically significant.

2.3 | Ethics

The TTH48 study protocol was approved by the ethics committee in each centre or country, and the trial was carried out according to the Declaration of Helsinki. Written informed consent was obtained from next of kin and/or a legal representative.

3 | RESULTS

Of the 355 patients included in the main study, sufficient electrolyte data were available from 310 patients treated at eight different centres. In addition, we had urine samples collected in four centres from a total of 215 patients. Patient characteristics for the 310 included patients are shown in Table 1.

TABLE 1 Patient characteristics

	No. (%) of patients		
	24 h group ($n = 155$)	48 h group ($n = 155$)	*p*
Demographics			
Age, mean (SD), years	60 (12)	61 (12)	.49
Male sex, *n* (%)	132 (85)	128 (83)	.54
Weight, mean (SD), kg	86 (15)	86 (17)	.84
Medical history			
Previous myocardial infarction	21 (14)	25 (16)	.54
Previous PCI or CABG	24 (16)	23 (15)	.86
Previous cardiac arrest	3 (2)	0	.08
Chronic heart failure	7 (5)	3 (2)	.20
Chronic obstructive pulmonary disease	10 (6)	11 (7)	.82
Liver cirrhosis	0	3 (2)	.08
Chronic renal failure with dialysis	0	1 (<1)	.32
Diabetes mellitus	24 (15)	33 (21)	.19
Immunosuppression	1 (<1)	1 (<1)	1.00
Previous stroke	14 (9)	10 (6)	.40
Arrest witnessed			.40
Bystander	132 (85)	139 (90)	
Emergency medical services	11 (7)	6 (4)	
Unwitnessed	12 (8)	10 (6)	
Resuscitation factors			
Bystander-initiated CPR	131 (85)	134 (86)	.63
Shockable rhythm	136 (88)	143 (92)	.19
Time to basic life support, median (IQR), min	1 (0–1)	1 (0–1)	.52
Time to advanced life support, median (IQR), min	8 (5–11)	8 (5–11)	.80
Time to ROSC, median (IQR), min	20.5 (15–27)	20 (15–29)	1.00
Clinical status on ICU admission			
Temperature, mean (SD), °C	35 (1)	35 (1)	.98
Mean arterial blood pressure, mm Hg	79 (18)	80 (19)	.58
PaO_2, median (IQR) mm Hg	117 (90–173)	119 (91–183)	.73
$PaCO_2$, mean (SD) mm Hg	45 (10)	46 (10)	.65
Time from ROSC to achievement of target temperature, median (IQR), min	319.5 (241–400)	278 (201–346)	.003
TTM method used			
Surface cooling	68 (46)	59 (40)	.34
Invasive cooling catheter	89 (59)	100 (65)	.28
Cool fluid bolus	46 (37)	53 (41)	.45

(Continues)

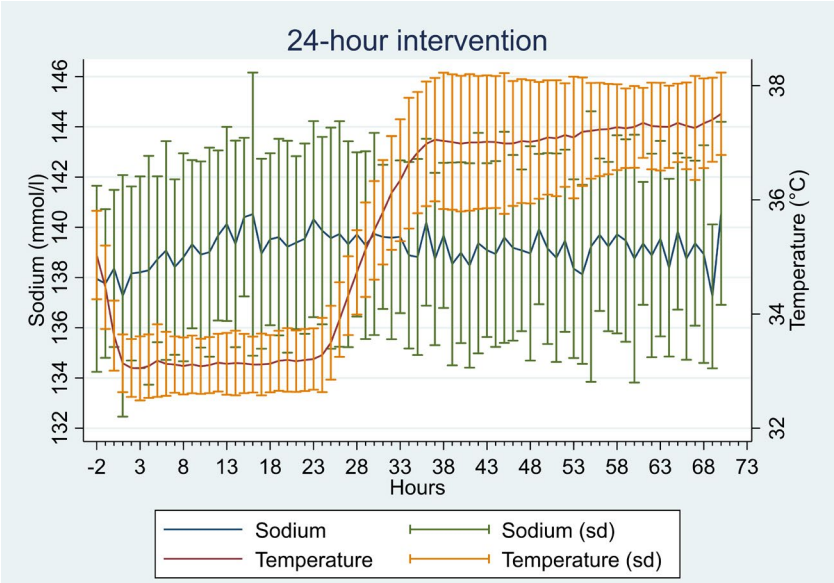
TABLE 1 (Continued)

	No. (%) of patients		
	24 h group ($n = 155$)	48 h group ($n = 155$)	p
Renal replacement therapy	14 (9)	12 (8)	.68
ICU length of stay, median (IQR), hours	96 (48–168)	120 (96–192)	.0002
Hospital length of stay, median (IQR), days	12 (6–19)	11 (6–17)	.35

Abbreviations: CABG, coronary artery bypass grafting; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; PCI, Percutaneous coronary intervention; ROSC, return of spontaneous circulation.

3.1 | Serum values of sodium, potassium and chloride

Temperature curves and sodium concentrations obtained during the first 72 h in the ICU by point-of-care analyses on arterial blood are depicted in Figure 1. Mean values stayed within the reference interval throughout the 72 h; there was no difference between the two hypothermia groups ($p > .05$). A significant increase was seen during the first 24 h ($p < .05$). Figure 1 revealed SDs beyond the reference interval, indicating a considerable inter-individual variation. This was noted for all other electrolytes measurements as well. The percentage of patients with concentrations above and below the reference interval is depicted in the supplemental material (Figure S1), as it is



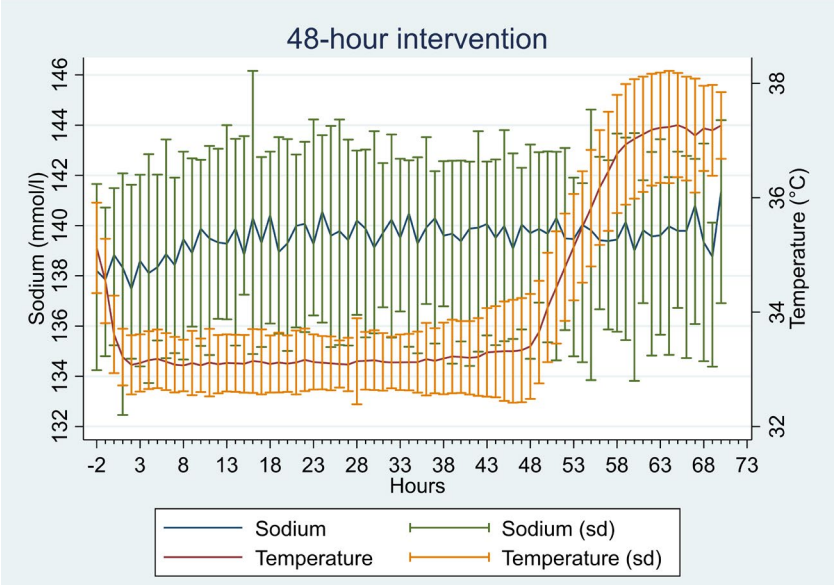


FIGURE 1 Sodium concentrations from point-of-care analyses in the two TTM groups and temperature during the first 72 h in the ICU. Values are mean ± SD

for potassium, chloride and ionized calcium measurements as well. To compare the two TTM groups visually, we present the sodium measurements without deviations and in the same graph in Figure S2, as we did for the other point-of-care measurements as well.

Concentrations of potassium are presented in Figure 2; Figures S3 and S4. No significant change was observed during cooling ($p > .05$). A significant increase in potassium during rewarming was seen on day two in the 24-h group and on day three in the 48-h group ($p < .05$).

The chloride concentrations are shown in Figure 3; Figures S5 and S6. At T41 there was a significant difference between the two hypothermia groups ($p < .05$). A corresponding significant decrease during rewarming was seen at day two in the 24-h group and at day three in the 48-h group ($p < .05$). Parallel to the decrease in chloride during rewarming, an increase in pH was observed (Figures S7 and S8).

3.2 | Serum values of magnesium, calcium and phosphate

In Table 2, the mean serum concentrations of magnesium, ionized calcium and phosphate during the first three days in the ICU are shown. Median magnesium concentrations stayed within the reference interval throughout the 72 h. There were significant differences between the TTM groups on days two and three ($p < .05$). S-magnesium decreased significantly over time ($p < .05$). There was a significant difference in S-calcium concentrations between the two hypothermia groups on day two ($p < .05$). The MANOVA showed a significant increase during the first day and a decrease the two following days ($p < .05$). The decrease was significant for the 24-h group on day two and for the 48-h group on day three ($p < .05$), the days of rewarming (Table 2). The

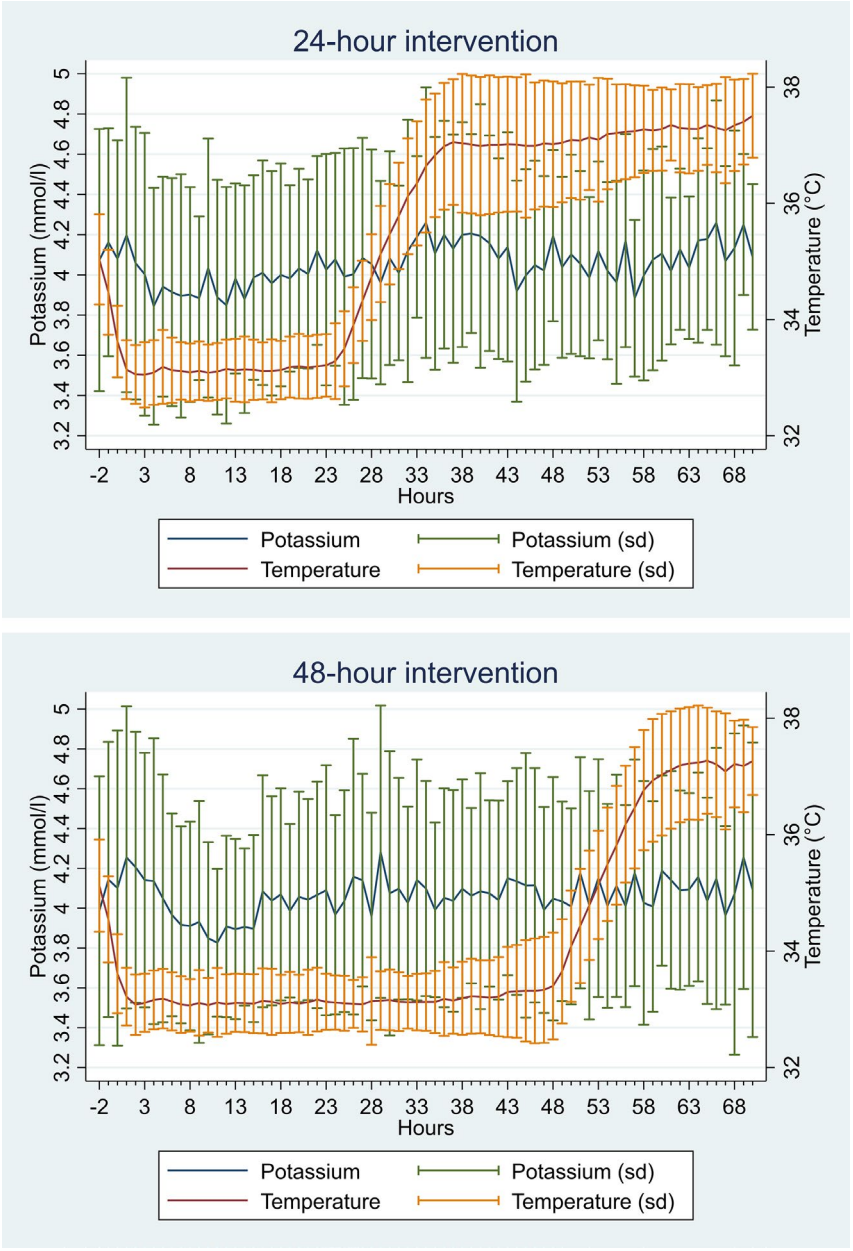


FIGURE 2 Potassium concentrations from point-of-care analyses in the two TTM groups and temperature during the first 72 h in the ICU. Values are mean ± SD

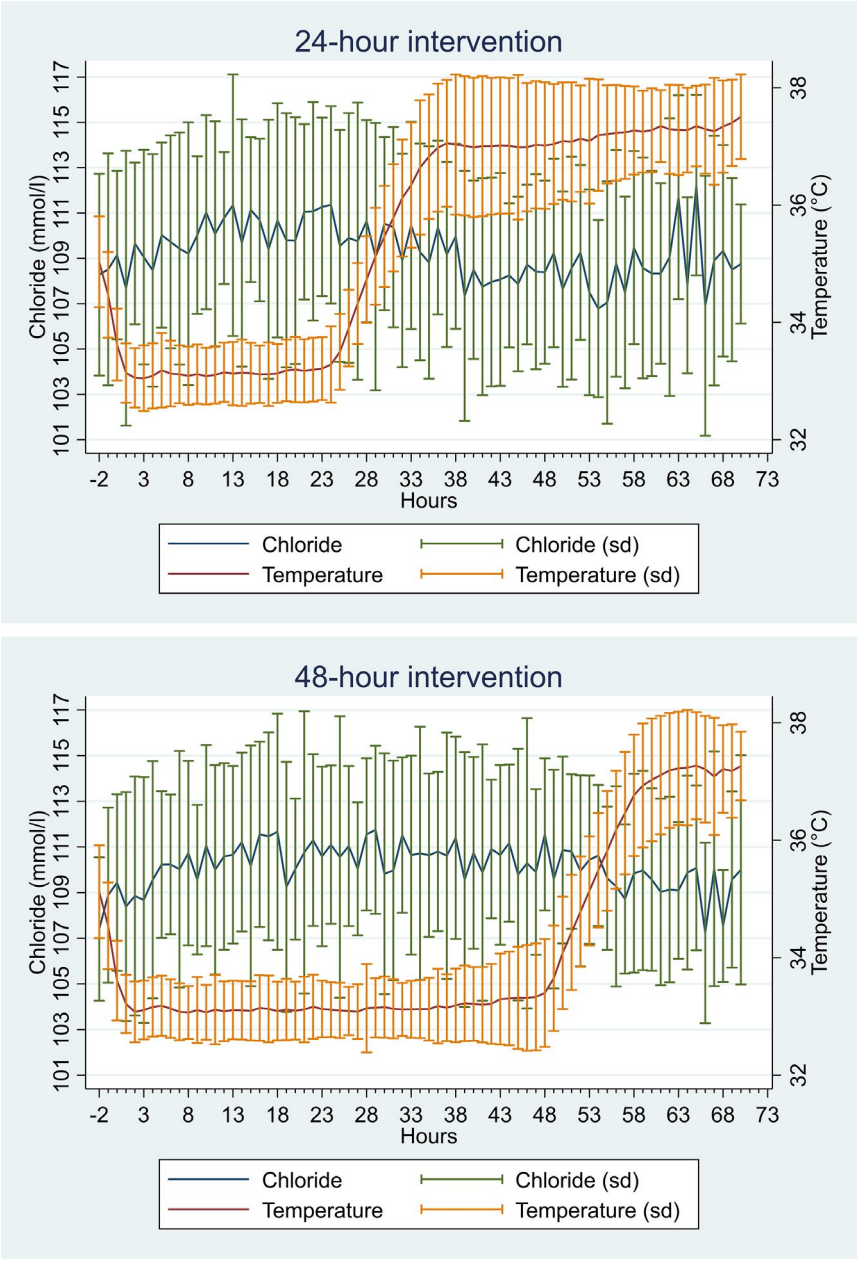


FIGURE 3 Chloride concentrations from point-of-care analyses in the two TTM groups and temperature during the first 72 h in the ICU. Values are mean ± SD

ionized calcium concentration from point-of-care analyses is depicted in Figures S9–S11, and showed the same trend ($p < .05$). Finally there was a significant difference in S-phosphate on day three between the two TTM groups ($p < .05$) (Table 2). During the first 24-h median, concentration dropped significantly from a value in the high end of the reference interval to a value low in the reference interval and stayed there ($p < .05$) (Table 2).

3.3 | Urinary output

The 24-h diuresis for the first 72 h is shown in Table 3. There was no difference between the two TTM groups at any time. The median diuresis at the time when TT (34°C) was reached was 350 ml, and the median 24-h diuresis measurements for the first 48 h were 2198 and 2048 ml respectively. On day 3, the MANOVA showed a significant increase in the 48-h group to 2640 ml ($p < .05$).

3.4 | Urinary excretion of sodium, potassium, magnesium, calcium and phosphate

For sodium there was no difference between the TTM groups. The MANOVA demonstrated a significant increase in excretion on day three ($p < .05$), but it was still well within the reference interval (Table 3). Potassium excretion increased on days two and three ($p < .05$), the days of rewarming, in the 24-h and 48-h groups respectively. The daily median magnesium excretion was unchanged over the 72 h. During all three days the excretion stayed in the lower end of the reference interval. There was no difference between the

TABLE 2 Serum concentrations of magnesium, ionized calcium (pH 7.4) and phosphate at the time of ICU admission and on days one, two and three. Measurements are given as median with IQR

	24-h group	48-h group
Magnesium mmol/l: median (IQR)	**	**
ICU admission	0.86 (0.78–0.93)	0.83 (0.78–0.93)
Day 1	0.82 (0.77–0.89)	0.84 (0.77–0.92)
Day 2*	0.77 (0.72–0.86)	0.82 (0.74–0.90)
Day 3*	0.83 (0.75–0.92)	0.77 (0.69–0.85)
Ca^{2+} mmol/l: median (IQR)	**	**
ICU admission	1.12 (1.04–1.18)	1.11 (1.05–1.15)
Day 1	1.20 (1.16–1.25)	1.19 (1.15–1.23)
Day 2*	1.16 (1.11–1.20)	1.19 (1.15–1.22)
Day 3	1.16 (1.12–1.21)	1.17 (1.13–1.20)
Phosphate mmol/l: median (IQR)	**	**
ICU admission	1.74 (1.16–2.25)	1.45 (0.97–2.04)
Day 1	1.03 (0.81–1.23)	1.00 (0.83–1.24)
Day 2	1.12 (0.91–1.35)	1.08 (0.86–1.37)
Day 3*	0.92 (0.73–1.11)	1.16 (0.96–1.55)

*$p < .05$ Mann-Whitney.; **$p < .05$ Mixed model for repeated measurements (MANOVA).

TTM groups beyond 24 h. Median ionized calcium excretion remained at the lower limit of the reference interval throughout the 72 h (Table 3). There was no difference between the TTM groups beyond 24 h. Median phosphate excretion was below the reference interval during the first two days and reached the lower level of the reference interval on day three in the 24-h group but stayed low in the 48-h group. The MANOVA showed that phosphate excretion decreased during cooling beyond 24 h in the 48-h group ($p < .05$) but increased significantly during rewarming in both groups ($p < .05$). Urine excretion was significantly higher in the 24-h TTM group on days two and three ($p < .05$).

Urine electrolyte concentrations for the first 72 h in the ICU are shown in the supplemental material (Table S1).

4 | DISCUSSION

The main finding in this exploratory study of electrolyte changes in post-cardiac arrest patients undergoing TTM at 33°C for 24 or 48 h was that serum and point-of-care concentrations as well as urine excretion and urine output remained within the reference interval in most patients. The clinical implications is that there will be no major washout of electrolytes due to increased diuresis. However, there were individual variations, with a certain number of patients showing values outside the reference interval, and also temporal changes with the different phases of TTM.

4.1 | Electrolyte changes

The noted increase in sodium and chloride concentration during the first 24 h, as well as the later increase in urine excretion, could partly be explained by infusion of cold saline for cooling purposes followed by a compensatory excretion.[25] As expected, potassium concentration decreased during cooling,[5-7] and excretion increased on the days of rewarming.

Serum magnesium decreased during rewarming, but both serum concentration and urine excretion were within the reference interval throughout the 72 h. Hypomagnesemia is often seen during post-resuscitation care in patients suffering from cardiac arrest. But as demonstrated in the present study, hypomagnesemia in these patients is not due to TTM. The beneficial effect of treating cardiac arrest patients with magnesium has been investigated in several randomized trials, but a favourable effect has not been demonstrated.

Ionized calcium increased during the first 24 h from a level below the lower reference limit at admission, Correspondingly, urine calcium loss for the first two days was below normal range. Animal studies have demonstrated a positive effect of calcium infusion,[20] but no clinical studies have demonstrated an effect. Furthermore, hypercalcemia may result in cell damage.[26] and routine treatment in post-arrest care is therefore not recommended.

Serum phosphate dropped during the first 24 h to a value low in the reference interval and stayed there. Correspondingly, phosphate excretion was below the lower reference limit for the first 48 h, indicating a phosphate consumption or redistribution and not a loss in the urine., however, the concerns regarding low serum concentrations persist.

Rewarming may mirror the effect of cooling. Interestingly, we observed several distinct although small and mostly clinically unimportant changes in electrolyte homeostasis. Chloride concentration dropped during rewarming in both groups but at different time points due to intervention. This observation had not been reported earlier, and we have no explanation for this finding. Another change during rewarming was observed in pH. With a higher temperature, a lower pH was expected, but the opposite occurred: pH increased. Ionized calcium and magnesium concentrations also decreased on the day of rewarming. As with pH we have no explanation for this change. Although distinct and statistically significant, the changes are small and probably without clinical importance. We also demonstrated a slight increase in diuresis during rewarming. This was also observed by Guluma et al.[27] and is in contrast to what was reported by Broman et al.,[28] who found a decrease in urine output during rewarming.

A considerable number of electrolyte measurements lay outside the reference interval. For sodium and chloride, this may be explained by the use of cold saline for cooling purposes, however the opposite is the case with ionized calcium, where measurements initially were below the reference interval, indication a redistribution of calcium.

TABLE 3 Diuresis and excretion of sodium, potassium, magnesium, ionized calcium and phosphate measured at target temperature and 24, 48 and 72 h after target temperature

		24-h group	48-h group[a]	Both TTM groups
Diuresis				
Target temperature	ml	363 (175–600)	320 (190–530)	350 (175–590)
24 h	ml	2230 (1500–3155)	2155 (1455–2860)	2198 (1475–2980)
48 h	ml	2105 (1420–2650)	2005 (1305–2668)	2048 (1373–2655)
72 h	ml	2225 (1500–3240)	2640 (1500–3350)	2508 (1500–3269)
		24-h group	**48-h group**	**Both TTM groups**
Sodium excretion median (IQR)				**
Target temperature	mmol	21 (8–41)	20 (10–36)	21 (9–39)
24 h	mmol/24 h	113 (60–197)	109 (54–214)	111 (56–210)
48 h	mmol/24 h	148 (68–220)	132 (62–193)	136 (64–204)
72 h	mmol/24 h	178 (101–334)	188 (73–306)	184 (79–307)
		24-h group	48-h group	
Potassium excretion median (IQR)		**	**	
Target temperature	mmol	15 (6–26)	13 (8–24)	
24 h	mmol/24 h	71 (53–90)	74 (50–98)	
48 h*	mmol/24 h	90 (60–126)	66 (47–95)	
72 h	mmol/24 h	114 (73–145)	110 (75–110)	
		24-h group	**48-h group**	**Both TTM groups**
Magnesium excretion median (IQR)				
Target temperature	mmol	0.8 (0.4–1.5)	0.6 (0.4–1.1)	0.7 (0.4–1.2)
24 h	mmol/24 h	3.4 (2.0–4.6)	3.4 (1.9–6.1)	3.4 (2.0–5.1)
48 h	mmol/24 h	3.6 (2.0–5.6)	3.8 (2.2–5.1)	3.7 (2.0–5.4)
72 h	mmol/24 h	3.8 (2.6–8.1)	4.1 (2.4–5.8)	4.0 (2.4–6.2)
		24-h group	**48-h group**	**Both TTM groups**
Calcium excretion median (IQR)				
Target temperature	mmol	0.8 (0.2–1.3)	0.5 (0.2–1.0)	0.5 (0.2–1.1)
24 h	mmol/24 h	2.2 (1.2–4.3)	2.4 (1.1–4.3)	2.4 (1.2–4.3)
48 h	mmol/24 h	2.3 (1.2–4.0)	2.3 (1.2–4.3)	2.3 (1.2–4.2)
72 h	mmol/24 h	2.7 (1.1–4.8)	2.9 (1.4–4.7)	2.9 (1.3–4.7)
		24-h group	**48-h group**	
Phosphate excretion median (IQR)		**	**	
Target temperature	mmol	6.1 (3.3–9.6)	5.4 (2.9–8.5)	
24 h	mmol/24 h	8.4 (6.3–18.0)	9.7 (5.1–18.8)	
48 h*	mmol/24 h	14.1 (7.0–27.0)	6.0 (4.0–12.1)	
72 h*	mmol/24 h	29.1 (18.2–47.5)	8.9 (4.3–18.6)	

There was no difference beyond 24 h between the two TTM groups except for phosphate. Measurements are given as a median (IQR). Data at target temperature is not for an entire 24-h period; data are therefore not included in the repeated measurement analyses. Pooled data for both groups is only shown if there were no difference between TTM groups.

[a]Indicate a significant difference between diuresis at 24, 48 and 72 h; $p < .05$ (MANOVA).

*$p < .05$; **$p < .05$ mixed model for repeated measurements (MANOVA).

4.2 | Urine output and electrolyte excretion

We did not observe any increased diuresis related to the hypothermia treatment. Our findings are in agreement with a prior study examining the hemodynamic consequences of mild therapeutic hypothermia in patients suffering from cardiac arrest.[29] They did not observe increased diuresis during ongoing hypothermia and concluded that cold diuresis does not pose a clinical challenge. In another study examining urine output changes during induced hypothermia in post-cardiac arrest treatment, the conclusion was

the same.[30] They found a modest increase in diuresis during induction of hypothermia but no changes during hypothermia maintenance or rewarming. In a third study that examined the effect of mild hypothermia in acute stroke patients,[27] it was demonstrated that mild hypothermia was associated with a decrease in urine output. This is in contrast to what was reported by Polderman et al.,[3] but the latter's observations were in neurotrauma patients, so there might have been an element of diabetes insipidus or treatment with mannitol in this patient population. Hypothermia in general does, however, increase urine output, but apparently these effects do not become significant until the temperature falls below 32°C.

4.3 | Strengths and limitations

The major strength of this study is that it was a preplanned substudy of an international, large multi-centre randomized controlled trial using granulated electrolyte data obtained throughout full intervention periods. This helps increase the external validity of our results. The trial design also made it possible to study the different TTM phases (induction, maintenance, rewarming).

There are also limitations. Even if the study was pre-planned, the primary aim of the TTH48 trial was not to investigate electrolyte changes. Not all centres were able to collect granulated data on electrolytes, and only four centres were able to collect data on urine. The urine output was not measured hourly; thus we were not able to detect minor changes during onset of hypothermia. Furthermore, repletion strategy was at the discretion of the clinical team and might have affected the results, particularly concerning potassium. For some of the electrolyte concentrations, we reported both serum concentrations and concentrations measured by point of care, and they may not be interchangeable. The results were reported as means or medians, but as can be noticed in the tables and figures and in the Supplementary material, they come with standard deviations and ranges that reach beyond the reference intervals. This informs us that the study population probably contains unstable patients demanding individual attention.

In patients resuscitated from OHCA there is a considerably individual variation in serum electrolyte concentration, however this variation is not caused by induced hypothermia. If these disturbances are due to PCAS, and can be used as markers of PCAS severity, and if a well-planned repletion policy will be of any benefit, is yet to be explored in future studies.

5 | CONCLUSION

In contrast to previous studies, we found that when comatose OHCA patients undergo TTM in the ICU, serum and point-of-care concentrations as well as urine excretion of electrolytes remain within the reference interval. An individual variation was, however, noted, and some temporal trends linked to the different phases of TTM appeared. Overall, electrolyte disturbances and hypothermia-induced diuresis in these ICU patients appear to be lesser problems than previously thought.

CONFLICT OF INTEREST

Fabio Taccone receive lecture fees from BD and ZOLL and Markus Skrifvars receive lecture fees and travel grants from BARD Medical (Ireland). The rest of the authors reports no conflict of interest.

AUTHOR CONTRIBUTIONS

HK, ES, MF, and FT designed this study. All authors contributed to data collection. HK, ES, MF and FT performed the data analysis and interpretation of data. HK wrote the manuscript, and all authors critically revised the manuscript. All authors approved the final manuscript.

ORCID

Hans Kirkegaard https://orcid.org/0000-0003-4853-8152
Anni Jeppesen https://orcid.org/0000-0003-2812-194X
Christian Storm https://orcid.org/0000-0002-8286-1650
Markus B. Skrifvars https://orcid.org/0000-0002-0341-0262

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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