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Rising serum sodium levels are associated with a concurrent development of metabolic alkalosis in critically ill patients

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Abstract *Purpose:* Changes in electrolyte homeostasis are important causes of acid–base disorders. While the effects of chloride are well studied, only little is known of the potential contributions of sodium to metabolic acid–base state. Thus, we investigated the effects of intensive care unit (ICU)-acquired hypernatremia on acid–base state.
Methods: We included critically ill patients who developed hypernatremia, defined as a serum sodium concentration exceeding 149 mmol/L, after ICU admission in this retrospective study. Data on electrolyte and acid–base state in all included patients were gathered in order to analyze the effects of hypernatremia on metabolic acid–base state by use of the physical–chemical approach.
Results: A total of 51 patients were included in the study. The time of rising serum sodium and hypernatremia was accompanied by metabolic alkalosis. A transient increase in total base excess (standard base excess from 0.1 to 5.5 mmol/L) paralleled by a transient increase in the base excess due to sodium (base excess sodium from 0.7 to 4.1 mmol/L) could be observed. The other determinants of metabolic acid–base state remained stable. The increase in base excess was accompanied by a slight increase in overall pH (from 7.392 to 7.429, standard base excess from 0.1 to 5.5 mmol/L). *Conclusions:* Hypernatremia is accompanied by metabolic alkalosis and an increase in pH. Given the high prevalence of hypernatremia, especially in critically ill patients, hypernatremic alkalosis should be part of the differential diagnosis of metabolic acid–base disorders.

Keywords Acid–base ·
Stewart's approach · Hypernatremia ·
Critically ill

Introduction

Hypernatremia is defined as a serum sodium concentration exceeding 145 mmol/L [1]. Usually, the development of thirst protects us against the development of hypernatremia, which is always associated with hyperosmolality [2]. Thus, individuals with a disturbed sensation of thirst, unconscious people, or those with no access to free water are prone to develop hypernatremia [1]. Consequently, hypernatremia is mainly a problem in persons living in nursing homes or critically ill patients who are mechanically ventilated and whose fluid intake is managed by the physician [3, 4].

Despite the fact that hypernatremia was described to be an independent predictor of mortality, only few publications can be found in the literature investigating the effects of an increased serum sodium level on physiologic functions [5–7]. Some older studies found that hypernatremia and concurrent hyperosmolality lead to an increase in peripheral insulin resistance or an impaired left ventricular contractility [8–11]. While the physical–chemical acid–base approach postulates that metabolic alkalosis is a consequence of hypernatremia [12, 13], only one small study investigated the acid–base state during hypernatremia [14]. In our study we wanted to investigate the impact of rising serum sodium levels prior to hypernatremia and of hypernatremia per se on human acid–base state.

Methods

In this retrospective study we screened a prospectively collected database of medical critically ill patients from a large university hospital. From all patients with an admission date between 1 June 2001 and 30 April 2004, those who experienced hypernatremia for at least 1 day were included in the study. All laboratory values including serum sodium concentration were measured once daily at 05:00 a.m. Hypernatremia was defined as a serum sodium concentration exceeding 149 mmol/L [5, 15, 16]. We excluded patients who were hypernatremic on admission to the ICU. One episode of hypernatremia was defined by the number of consecutive days with hypernatremia. When patients experienced more than one episode of hypernatremia, only the first episode was analyzed. Maximum serum sodium concentration was defined as the highest value within one episode. When the highest value was measured more than once, the value measured on the first occasion was chosen as the maximum serum sodium concentration. The last day before and the first day after an episode of hypernatremia were defined as the last day with normonatremia before an episode of hypernatremia and the first day with normonatremia after one episode of hypernatremia, respectively. In order to assess acid–base values while sodium rose or decreased we also looked at the values on a day in the middle between the last normonatremic day and the day with maximum serum sodium concentration as well as on a day in the middle between the day with maximum serum sodium concentration and the first day with normonatremia.

From all these patients we gathered data on patients' characteristics such as age, gender, admission diagnosis, and outcome. Additionally, all relevant acid–base data were included in the database (pH, partial pressure of carbon dioxide, sodium, chloride, potassium, magnesium, ionized calcium, albumin, lactate, hemoglobin).

Acid–base analysis

Arterial blood samples were collected from the radial or femoral artery on admission, and every day at 05:00 a.m. The parameters used for assessment of acid–base status were instantly measured in the same blood sample. Partial pressure of carbon dioxide ($PaCO_2$), pH, and ionized calcium (Ca) were measured with a blood gas analyzer (ABL 725, Radiometer®, Copenhagen, Denmark). Samples of separated plasma were analyzed for concentrations of sodium (Na), potassium (K), chloride (Cl), magnesium (Mg), inorganic phosphate (Pi), and albumin by a fully automated analyzer (Hitachi 917, Roche Diagnostics® GmbH, Mannheim, Germany). Na and Cl were measured using ion-selective electrodes. Lactate was measured with an amperometric electrode. Lactate was measured by the ABL 725. All measurements were performed at 37 °C and derivative variables were calculated using constants for 37 °C. Acid–base variables are reported without correction for actual patient temperature.

HCO_3^- (bicarbonate) was calculated from the measured pH and $PaCO_2$ using the Henderson–Hasselbalch equation [17]. Standard base excess (SBE) was calculated according to the formula by Siggaard-Andersen [17].

Quantitative physical–chemical analysis of the results was performed using Stewart's quantitative biophysical methods [13], as modified by Figge and colleagues, to acknowledge the effects of plasma proteins [18]. The apparent strong ion difference (SIDa) was calculated:

$$SID_a = Na + K + 2 \times Mg^{2+} + 2 \times Ca^{2+} - Cl - lactate$$

(all concentrations in mmol/l).

In order to account for the role of weak acids (CO_2, albumin, and phosphate) in the balance of plasma electrical charges, the effective strong ion difference (SIDe) was calculated:

$$SIDe = 1000 \times 2.46 \times 10 - 11 \\ \times PaCO_2/(10 - pH+)Alb \\ \times (0.123 \times pH - 0.631) + Pi \\ \times (0.309 \times pH - 0.469)$$

($PaCO_2$ in mmHg, Alb in g/L, and Pi in mmol/L).

SIDe considers the contribution of weak acids to the electrical charge equilibrium in plasma. In the absence of unmeasured charges the SIDa to SIDe difference equals zero. Such charges are described by the strong ion gap:

$$Strong\ ion\ gap = SIDa - SIDe.$$

In order to compare the effects of sodium, chloride, and albumin the base excess compounds according to Gilfix were calculated [19] as shown below (all values in mmol/L, if not otherwise indicated).

Excess of free water causes hyponatremia and dilutional acidosis, whereas a lack of free water causes hypernatremia and concentrational alkalosis. Na^+ as the regulated variable that controls the extracellular fluid volume is used to assess the effect of dilution.

BE caused by free water effect(BE_{Na})
$$= 0.3 \times \left(Na^+ - Na^+_{Normal}\right).$$

The constant 0.3 derives from $BE_{Na} = 42 \times (Na^+ - 140)/140$ with $Na^+_{normal} = 140$ mmol/L.

Hyperchloremia and hypochloremia lead to hyperchloremic acidosis and hypochloremic alkalosis, respectively. The effect of changes in Cl^- can be obtained by first correcting Cl^- for changes in free water: $Cl^-_{Na^+ corrected} = Cl^- \times \left(Na^+_{normal}/Na^+\right)$, and second: BE caused by changes in Cl^-: $BE_{Cl} = Cl^-_{normal} - Cl^-_{Na^+ corrected}$.

Albumin is a weak non-volatile acid. Thus, hypoalbuminemia is a lack of acid and results in hypoalbuminemic alkalosis. The BE effect due to albumin (BE_{Alb}) can be calculated: $BE_{Alb} = (0.148 \times pH - 0.818) \times (Alb_{normal} - Alb_{observed})$.

The two constants in the equation account for albumin being a weak acid, i.e., possessing variable charges dependent on pH [18].

$$ABE = BE_{Na} + BE_{Cl} + BE_{Alb} + BE_{Lac} + BE_{UMA}.$$

Reference values were obtained from a sample of healthy volunteers ($n = 14$; 8 males, 6 females; mean age 39 ± 12 years).

Statistical analysis

Data are presented as means and standard deviations, or as median and 1st to 3rd quartiles (Q1 to Q3). Continuous variables were compared using the Student's t test or by ANOVA with Tamhane's T2 test for post hoc testing. Proportions were compared using the χ^2 test. When the expected count for cells was lower than five, Fisher's exact test or the exact test module by SPSS was used.

In order to study whether the components of the metabolic acid–base state changed between observations (last normal sodium, rising sodium, peak sodium, declining sodium, sodium normal again) we used a generalized estimating equation. For this purpose we assumed an exchangeable correlation matrix for repeated observations within one patient [20]. The acid–base variable (e.g., base excess) was set as the dependent variable and the time of observation was set as the predictor using a backward difference coding. A p value of 0.05 or less was considered statistically significant. Statistical analysis was performed using SPSS (SPSS for Windows release 15.0, Chicago, IL).

Results

Patient characteristics

Fifty-one patients fulfilled the inclusion criteria and were included in the analysis. Twenty-eight patients (55 %) were male; the mean age was 58 ± 16 years. Length of stay was 15 (9 to 26) days (median, 1st to 3rd quartile). Thirty patients (59 %) survived to ICU discharge. Upon ICU admission 41 patients (80 %) had respiratory failure, 31 patients (61 %) had circulatory failure, 17 patients (33 %) had renal failure, 8 patients (16 %) had liver failure, and 17 patients (33 %) had cerebral failure. None of the patients included in the study received renal replacement therapy during their ICU stay.

During normonatremia, central venous pressure in patients was 14 cmH_2O (Q1 10, Q3 18) and mean arterial pressure was 79 mmHg (Q1 70, Q3 90) while central venous pressure was 13 cmH_2O (Q1 11, Q3 17) and mean arterial pressure was 78 mmHg (Q1 69, Q3 86) during hypernatremia. Total fluid balance during normonatremia was +804 mL (Q1 −141, Q3 2004) with a urine output of 2,075 mL (Q1 1,538, Q3 2,793). During hypernatremia total fluid balance was 1,607 mL (Q1 145, Q3 2,982) with a urine output of 1,720 mL (Q1 910, Q3 2,730). A detailed overview on fluid balances and infusion solutions administered during normo- and hypernatremia is given in Table 1.

Table 1 Fluid balances and administered infusion solutions during normo- and hypernatremia

	Normonatremia			Hypernatremia		
	Median	Quartile 1	Quartile 3	Median	Quartile 1	Quartile 3
Total fluid balance	804	−141	2,004	1,607	145	2,982
Total fluid input	3,684	2,510	5,329	3,179	2,427	4,298
Isotonic saline	400	100	1,200	313	100	700
Lactated Ringer's	1,650	995	2,513	1,200	600	2,400
Distilled water	1,075	213	1,975	1,100	325	1,650
Oral input	80	23	400	135	50	470

All data in milliliters

Table 2 Acid–base state during the course of hypernatremia

	Last normal [Na$^+$]	Rising [Na$^+$]	Peak [Na$^+$]	Declining [Na$^+$]	[Na$^+$] normal again
Number of patients	50	37	50	27	36
pH	7.392 ± 0.104	7.421 ± 0.083	7.429 ± 0.089	7.431 ± 0.076	7.424 ± 0.089
PaCO$_2$ (mmHg)	42.2 ± 13.8	44.3 ± 11.7	46.6 ± 12.1	45.0 ± 10.5	42.9 ± 11.6
Standard base excess	0.1 ± 4.9	3.4 ± 4.4	5.5 ± 5.6	4.7 ± 4.7	2.8 ± 4.1
HCO$_3^-$	24.6 ± 4.8	27.8 ± 4.6	30.0 ± 5.7	29.1 ± 4.8	27.0 ± 4.2
Sodium	142 ± 3	148 ± 2	154 ± 4	149 ± 2	142 ± 3
Potassium	4.01 ± 0.69	3.79 ± 0.48	3.68 ± 0.51	3.81 ± 0.54	3.85 ± 0.57
Chloride	106 ± 5	111 ± 5	114 ± 5	110 ± 5	107 ± 5
Chloride, corrected	105 ± 4	105 ± 4	104 ± 5	104 ± 4	106 ± 5
Magnesium	0.91 ± 0.25	0.97 ± 0.24	0.95 ± 0.26	0.99 ± 0.39	0.88 ± 0.22
Ionized calcium	1.11 ± 0.09	1.12 ± 0.11	1.12 ± 0.13	1.07 ± 0.12	1.10 ± 0.11
Inorganic phosphate	1.31 ± 0.52	1.05 ± 0.44	1.00 ± 0.47	1.19 ± 0.41	1.16 ± 0.55
Lactate	2.2 ± 1.6	1.8 ± 1.1	1.8 ± 1.4	1.7 ± 1.1	1.6 ± 1.6
Albumin (g/L)	23.7 ± 5.1	22.9 ± 3.3	22.9 ± 4.1	22.1 ± 4.6	21.6 ± 4.1
Base excess sodium	0.7 ± 0.9	2.5 ± 0.6	4.1 ± 1.2	2.7 ± 0.7	0.7 ± 0.9
Base excess chloride	−3.0 ± 4.5	−3.2 ± 4.3	−2.3 ± 4.5	−2.4 ± 4.5	−3.6 ± 4.6
Base excess albumin	5.8 ± 1.7	6.2 ± 0.9	6.2 ± 1.2	6.5 ± 1.3	6.6 ± 1.1
Apparent strong ion difference	40.4 ± 9.6	42.7 ± 8.8	43.2 ± 12.0	44.9 ± 5.1	38.4 ± 12.7
Effective strong ion difference	32.7 ± 8.4	36.6 ± 4.9	38.8 ± 5.6	37.9 ± 4.9	35.7 ± 4.5
Strong ion gap	7.3 ± 4.7	7.1 ± 4.5	6.7 ± 3.4	7.0 ± 5.1	5.5 ± 3.6

All variables in mmol/L unless otherwise indicated. Numbers are mean and standard deviations

Electrolytes and acid–base variables upon ICU admission

Measured immediately after admission to the ICU the overall acid–base state of the patients was almost normal. The acidifying effect of mildly elevated lactate and of a mild hyperchloremic acidosis was offset by the alkalinzing effect of hypoalbuminemia leaving the standard base excess normal.

Electrolytes and acid–base variables during hypernatremia

The last day with normal serum sodium was 2 (0 to 4) days after admission to the ICU. In 37 patients a rising serum sodium value could be recorded 1 (1–2) day after the last day with normal serum sodium. Peak serum sodium was recorded in all patients 3 (2–4) days after the last day with normal serum sodium. Five (3–8) days after the last day with normal serum sodium a declining serum sodium value was measured in 27 patients. In 36 patients normalization of serum sodium was recorded 5 (4–9) days after the last day with normal serum sodium.

Changes of the components of metabolic acid–base state during hypernatremia

The development and resolution of hypernatremia was accompanied by metabolic alkalosis. The observed transient increase in base excess was paralleled by a transient increase in the base excess due to sodium. The other
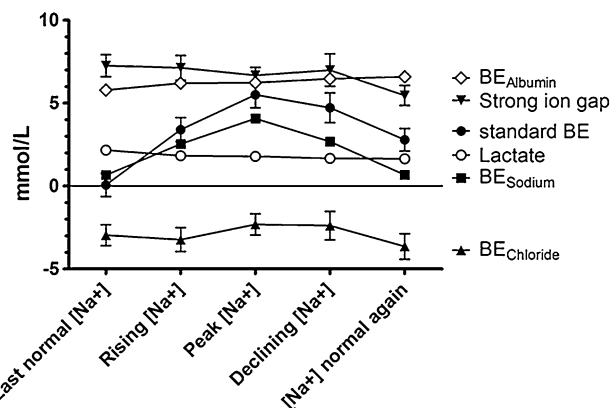

Fig. 1 Course of acid–base variables prior to, during, and after hypernatremia

determinants of metabolic acid–base state remained stable (Table 2 and Fig. 1).

The increase in base excess was accompanied by a slight increase in overall pH.

The components of overall metabolic acid–base state (assessed by standard base excess) are shown in the figure. p values for the changes are shown in Table 3.

Discussion

In the present study of 51 critically ill patients we showed that a rise in serum sodium during development of hypernatremia is accompanied by an increasing pH,

Table 3 p values for the changes of the components of metabolic acid–base state

	Change between last day with normal serum sodium and day with rising serum sodium	Change between day with rising serum sodium and peak serum sodium	Change between day with peak serum sodium and day with declining serum sodium	Change between day with declining serum sodium and first day on which serum sodium was normal again
Lactate	0.0873	0.1000	0.2756	0.5501
Base excess sodium	<0.0001	<0.0001	<0.0001	<0.0001
Base excess chloride	0.7417	0.5655	0.9879	0.2950
Base excess albumin	0.0131	0.0304	0.0541	0.0177
Strong ion gap	0.1629	0.1004	0.1042	0.0123

serum bicarbonate, and standard base excess defining "hypernatremic alkalosis".

Electrolyte disorders are an important cause of acid–base disorders as can be derived by looking at the physical–chemical approach to acid–base disorders [12]. But the classic approach also discusses electrolyte disorders as potential causes of acid–base disorders [2]. However, dyschloremia—especially hyperchloremia—as a cause of metabolic acidosis has been the focus of a multitude of acid–base research, primarily in critically ill patients [21–23]. On the other hand, when searching the literature for effects of hypernatremia on acid–base state, one will find only few studies on this issue, despite the fact that metabolic alkalosis is repeatedly discussed as an independent cause of increased mortality [14, 24]. The results presented in our study show that hypernatremic alkalosis should be part of the differential diagnosis of metabolic acid–base disorders.

The exact mechanisms leading to the development of hypernatremic alkalosis are not clear; however, certain mechanisms can be thought of: Although we do not have detailed information on the volume state of patients included in the present study, one can postulate that a certain degree of free water deficit relative to absolute sodium content as a consequence of hypertonic solution infusion, as often seen in critically ill patients, is essential in the development of hypernatremia [15, 25]. This in fact would support the classic concept of contraction alkalosis where a loss of free water leads to an absolute increase in bicarbonate concentration and thus an increase in pH [2]. However, recently, Luke and Galla [26] reviewed contraction alkalosis and stated that it should be named chloride depletion alkalosis for the following reason: it is an increase in the sodium to chloride ratio that leads to the development of metabolic alkalosis. Thus, diuretics, for example, providing a loss of more chloride than sodium lead to the development of metabolic alkalosis. Also, as the authors mention, correction of this type of metabolic alkalosis can only occur via the administration of chloride. From a pathophysiologic point of view a reduced bicarbonate elimination was made responsible for the development of metabolic alkalosis due to the relatively low appearance of chloride in the collecting duct of the nephron [26]. On the other hand, applying the physical–chemical approach the development of hypernatremia is accompanied by an increase in the subset of base excess for sodium, explaining the development of metabolic alkalosis.

The only previous study on the effects of hypernatremia on acid–base state found that the development of metabolic alkalosis correlated with the strong ion difference but not with the absolute serum sodium concentration [14]. This finding can be explained well by use of the physical–chemical approach: If a rise in serum sodium is accompanied by a concurrent rise in serum chloride concentration the effect of hypernatremia is counteracted by the developing hyperchloremic acidosis, resulting in no obvious change in metabolic acid–base state as measured by base excess.

It is very easy to imagine that the mechanism mentioned by Luke and Galla plays a central role in our critically ill patients: diuretics are the mainstay of therapy in critically ill patients; additionally, in our collective, balanced infusion solutions such as lactated Ringer's solution with a lower chloride content are preferred over isotonic sodium chloride solutions, mainly in order to avoid the development of hyperchloremic acidosis. This administration of infusion solutions with a reduced chloride content in addition to the administration of diuretics may be a crucial part of the mechanisms leading to hypernatremic alkalosis. Taken together, hypernatremic alkalosis can be considered a counterpart to dilutional acidosis.

Hypernatremia is a common event in critically ill patients with about 2 % of patients having it on presentation to the ICU and about 10 % developing it during ICU stay [5, 6, 27]. Only recently, hypernatremia was found to be an independent predictor of mortality in critically ill patients [5]. In the few studies on the mechanisms leading to ICU-acquired hypernatremia, a strong iatrogenic component could be identified [15, 25]. Having this fact in mind, it should be clear that a profound knowledge of the clinical implications of (in-hospital/ICU-acquired) hypernatremia is necessary. Nevertheless, despite the few studies which investigated the detrimental effects of hypernatremia and the

associated hyperosmolality, there is a lack of modern studies systematically studying the effects of hypernatremia on physiologic functions [8–10, 28, 29]. In the present study we were able to show that a rise in serum sodium is associated with a rising pH and serum bicarbonate, indicating an alkalinizing effect of hypernatremia. The significance of our findings for patient outcome remains unclear so far. On the other hand, metabolic alkalosis is the most common acid–base disturbance in critically ill patients [30]. Presence of metabolic alkalosis is associated with the occurrence of cardiac arrhythmias, which are often refractory [31]. Moreover, metabolic alkalosis leads to hypoventilation in patients with and without lung disease [32, 33]. Finally, studies have been published which found an increase in mortality in critically ill patients with compared to those without metabolic alkalosis [34, 35].

Our study is limited by its retrospective design. Additionally, we were not able to include all patients owing to a lack of data. Although there is some evidence that metabolic alkalosis per se has adverse effects on patient morbidity and mortality as discussed above, the definitive impact on a patient's course of disease remains uncertain.

In conclusion, the present results indicate that rising serum sodium levels/hypernatremia lead to an increase in pH, serum bicarbonate, and standard base excess indicating metabolic alkalosis. Hypernatremic alkalosis should considered to be an independent factor of metabolic acid–base disorders comparable to hyperchloremic acidosis and should be part of the differential diagnosis of metabolic acid–base disturbances.

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