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Impaired renal function is associated with greater urinary strong ion differences in critically ill patients with metabolic acidosis

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Abstract

Purpose: Urinary excretion of chloride corrects metabolic acidosis, but this may be hampered in patients with impaired renal function. We explored the effects of renal function on acid-base characteristics and urinary strong ion excretion using the Stewart approach in critically ill patients with metabolic acidosis.

Materials and Methods: We examined the plasma and urine chemistry in 65 critically ill (mixed medical and surgical) patients with metabolic acidosis. The apparent strong ion difference, effective strong ion difference, strong ion gap, and urinary simplified strong ion difference (urinary SID) were calculated. Linear regression analyses were used (1) to assess whether plasma creatinine concentrations were related to urinary SIDs values, adjusted for blood pH levels, and (2) to determine whether urinary SID values were associated with blood pH levels.

Results: Creatinine concentrations were positively and significantly ($P < .001$) associated with urinary SIDs values, adjusted for pH levels. Urinary simplified strong ion difference values were inversely and significantly ($P < .001$) related to pH levels.

Conclusions: In critically ill patients with metabolic acidosis, impaired renal function was associated with greater urinary SIDs. Subsequently, the higher urinary SIDs values were related to lower pH levels, illustrating the importance of renal chloride excretion to correct for acidosis.

1. Introduction

Metabolic acidosis is a frequent disorder in intensive care unit (ICU) patients that contributes to mortality [1]. The quantitative physicochemical approach to acid-base disorders originally described by Stewart [2] states that ionic charge equivalence influences acid-base chemistry. The apparent strong ion difference (SIDa) is the difference between the main strong cations and anions concentrations measured in plasma. The effective strong ion difference (SIDe) is determined by the contribution of weak acids to the electrical charge equilibrium in plasma. The difference between the SIDa and SIDe, the strong ion gap (SIG), should equal zero. A positive value for the SIG indicates the presence of unmeasured strong anions.

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According to the Stewart approach, only 3 factors independently influence pH, namely, the SIDa value, P_{CO_2}, and the concentration of weak acids [3,4].

The factors that contribute to metabolic acidosis and are specific for acute renal failure (ARF) in ICU patients are lower SIDa values, higher SIG values, and higher concentrations of the weak acid phosphate [4]. Applying the physicochemical principles of Stewart, the primary defense mechanism against acidosis in healthy subjects is increasing their SIDa values by renal excretion of chloride without a strong cation [4,5].

The importance of this mechanism and how it is influenced by renal function in critically ill patients is unknown. We hypothesized that, in critically ill patients with renal dysfunction and metabolic acidosis, impaired urinary excretion of the strong anion chloride contributes to acidosis.

2. Methods

2.1. Study population

This prospective observational study was conducted in a multidisciplinary ICU. The local medical ethical committee waived the need for informed consent. Sixty-five consecutive, adult, critically ill patients with a metabolic acidosis defined as pH less than 7.35 and base excess (BE) of −5 or less, present at admission or developed during their stay, were enrolled. Acute Physiology and Chronic Health Evaluation (APACHE) II data were collected for the first 24 hours after admission. Fluid resuscitation was performed by discretion of the treating physician with isotonic saline or short-acting starch products (sodium and chloride concentration 154 mmol/L).

2.2. Measurements

In each patient, a single arterial blood sample was collected. In this sample, pH, partial pressures of oxygen and carbon dioxide (Pa_{O_2} and Pa_{CO_2}), and plasma concentrations of ionized calcium and lactate were measured on a blood gas analyzer (RapidLab; Bayer Diagnostics, Breda, The Netherlands). Plasma concentrations of sodium, potassium, and chloride were analyzed using an ion-selective electrode on an Aeroset (Abbott Diagnostics, Hoofddorp, The Netherlands); and plasma concentrations of magnesium, creatinine (in micromole per liter), urea, phosphate, and albumin were measured on an Aeroset. Bicarbonate was calculated using the Henderson-Hasselbalch equation $\{pH = 6.1 + \log [(HCO_3^-)/0.0301\ Pa_{CO_2}]\}$ and the standard base excess using the Siggaard-Andersen formula. The SIDa $[SIDa = (Na^+) + (K^+) + (Ca^{2+}) + (Mg^{2+}) - (Cl^-) - (lactate^-)]$ and SIDe $[SIDe = 12.2 \times PCO_2/(10^{pH}) + (albumin) \times (0.123 \times pH - 0.631) + (phosphate) \times (0.309 \times pH - 0.469)]$, and SIG (SIG = SIDa − SIDe) were calculated. In addition, the plasma SID (plasma SID) was calculated: $(Na^+) - (Cl^-)$ in plasma. All mentioned concentrations are expressed in milliequivalent per liter, except for the concentrations of albumin (gram per liter), phosphate (millimole per liter) and P_{CO_2} (millimeters of mercury).

The main urinary strong ions sodium and chloride were measured in a single urine sample on an Aeroset at the time of blood gas analysis. Subsequently, the urinary simplified strong ion difference (urinary SID) (milliequivalent per liter) was calculated: $(Na^+) - (Cl^-)$.

2.3. Statistical analysis

Continuous variables were described by the mean and SD or the median and interquartile range (IQR) for variables with skewed distributions. Logistic regression was used to estimate the association between plasma creatinine concentrations and sepsis status.

Multivariate linear regression analysis was performed to determine whether plasma creatinine concentrations (the independent variable as a measure of renal function) were related to urinary SID values (as a measure of the net urinary charge excretion of the main strong ions sodium and chloride). The model was adjusted for the potential confounder blood pH level. We hypothesized lower pH levels to be related to declined renal function and, second, to increase renal chloride excretion to elevate the plasma SIDa value and normalize the pH level [6]. To satisfy the statistical assumptions of the regression model, both independent variables were natural log transformed to achieve normal distributions using the *lnskew0* function in Stata. This yielded the following equations: (*a*) the log-transformed plasma creatinine concentration = ln(plasma creatinine concentration − 34.0) and (*b*) the log-transformed blood pH level = −ln(−blood pH level + 7.35). (See the electronic supplement for a more detailed description.) In addition, we further adjusted the model for the potential confounders plasma SIDa, plasma simplified SID, and plasma SIG values separately because they may be related to renal function and the urinary excretion of chloride.

To assess whether urinary SIDs values were related to blood pH levels, simple linear regression analysis was applied. The urinary SIDs values were natural log transformed to achieve a normal distribution using the *lnskew0* function in Stata: −ln(−urinary SIDs value + 42.5). To characterize the relation between plasma creatinine concentrations and determinants of blood pH levels, the Spearman rank correlation (r_S) was used. The relations were presented by box plots with plasma creatinine cutoff values of 100, 200, and 300 μmol/L, which we defined before conducting the analysis. In addition, multivariate linear regression analyses were used to examine whether creatinine concentrations were associated with SIDa values independently of pH levels and, second, to assess whether creatinine concentrations were related to SIG values independently of the presence of sepsis.

All analyses were performed with the use of Stata software, version 10.1 (StataCorp LP, College Station, Tex).

Table 1 Demographic, clinical, and outcome data of ICU patients with metabolic acidosis

Variable	n	%
N	65	
Age (y) [a]	70	(57-75)
Sex (male)	35	(54%)
APACHE II score [a]	19	(16-26)
Mortality	21	(32%)
Diagnosis		
Sepsis	24	(37%)
Trauma/bleeding	10	(15%)
Cardiogenic shock	14	(22%)
Surgical	10	(15%)
Other	7	(11%)

[a] Results of this variable are presented as median (IQR).

$P < .05$ was considered statistically significant, and 2-sided tests of hypotheses were used throughout.

3. Results

The characteristics of the ICU patients, with metabolic acidosis, are summarized in Table 1. Patients were aged between 17 and 90 years, and APACHE II scores ranged from 7 to 43. Patients were predominantly diagnosed with sepsis. In Table 2, the laboratory parameters are presented. The difference between the 25th and 75th percentiles of the creatinine concentrations was approximately 140 μmol/L. In the logistic regression analysis, concentrations of plasma creatinine were a positive predictor of sepsis (odds ratio per 140 μmol/L increase in creatinine values, 2.87; 95% confidence interval [CI], 1.36-6.07; $P < .01$).

Table 2 Laboratory parameters in ICU patients with metabolic acidosis

Variable	Median	IQR	Range
Creatinine (μmol/L)	153	92-234	50-602
pH	7.28	7.21-7.31	6.91-7.34
SBE (mmol/L)	−9	−11 to −6	−25 to −5
P_{CO_2} (mm Hg)	39	35-43	22-74
Sodium (mmol/L or mEq/L) [a]	138	±5	124-149
Potassium (mmol/L or mEq/L) [a]	4.2	±0.7	1.7-6.0
Chloride (mmol/L or mEq/L)	113	110-117	93-124
Lactate (mmol/L or mEq/L)	2.1	1.4-3.0	0.8-11.8
SIDa (mEq/L)	29	27-33	20-44
Albumin (g/L)	16	13-18	6-34
Phosphate (mmol/L)	1.12	0.98-1.72	0.40-2.72
SIDe (mEq/L)	25	21-27	11-30
SIG (mEq/L)	5.6	3.7-8.0	−1.9 to 16.1
Urinary sodium (mmol/L or mEq/L)	51	20-85	5-168
Urinary chloride (mmol/L or mEq/L)	75	32-110	14-192
Urinary SIDs (mEq/L)	−12	−29 to −3	−152 to 29

SBE indicates standard base excess.
[a] Results of this variable are presented as mean ± SD and range.

3.1. Association between renal function and urinary SID values

In the linear regression model of the urinary SID, the log-transformed plasma creatinine concentrations (β coefficient, 16.6; 95% CI, 7.7-25.5; $P < .001$) were positively and significantly associated with urinary SIDs values, adjusted for log-transformed blood pH levels. The correlation between the independent variables in the regression model did not reach statistical significance ($P = .06$). Fig. 1 illustrates the relation between the measured creatinine and urinary SIDs values and the estimated relation between these variables according to the regression model. After further adjusting the regression model for plasma SIDa and plasma simplified SID values separately, the log-transformed creatinine concentrations remained positively and significantly related to urinary SIDs values. Adjustment for plasma SIG values

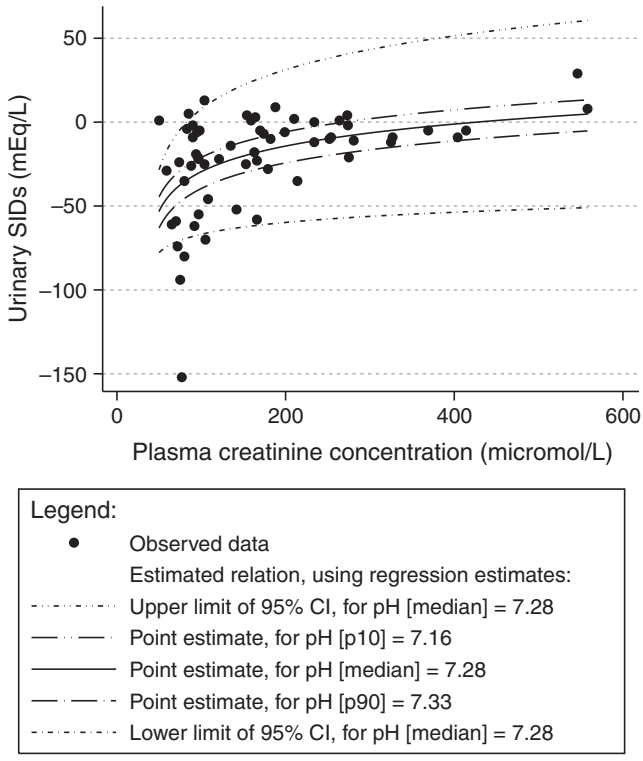

Fig. 1 Scatterplot of the measured plasma creatinine concentrations and urinary SIDs overlayed with the estimated relation between these variables according to the linear regression model, for blood pH levels of 7.16, 7.28, and 7.33, which are the 10th percentile, median, and 90th percentile of the pH distribution, respectively. The point estimates of the associations and, for the median pH value, also the 95% CI of the point estimate are presented.

resulted in a borderline significant ($P = .07$) positive association between log-transformed creatinine concentrations and urinary SIDs values.

3.2. Association between urinary SID values and pH levels

In the linear regression model of blood pH, the log-transformed urinary SIDs values (−0.090; 95% CI, −0.134 to −0.046; $P < .001$) were inversely and significantly related to pH levels. Fig. 2 shows the relation between the measured urinary SIDs and pH values and the estimated relation between these variables according to the regression model.

3.3. Associations between creatinine concentrations and determinants of pH levels

Creatinine concentrations were positively associated with plasma SIDa values ($r_S = 0.36$; $P < .01$), concentrations of the weak acid phosphate ($r_S = 0.57$; $P < .0001$), and plasma SIG values ($r_S = 0.50$; $P < .0001$; all in milliequivalent per liter). Box plots of these relations are shown in Fig. 3. After adjusting for blood pH levels, creatinine concentrations remained positively and significantly related to SIDa values, as estimated by the linear regression model. In the linear regression model of the plasma SIG, creatinine concentrations remained positively associated with SIG values ($P < .001$), after adjustment for sepsis status ($P = .92$). Furthermore, creatinine concentrations were inversely related to concentrations of plasma chloride ($r_S = -0.59$; $P < .0001$; millimole per liter).

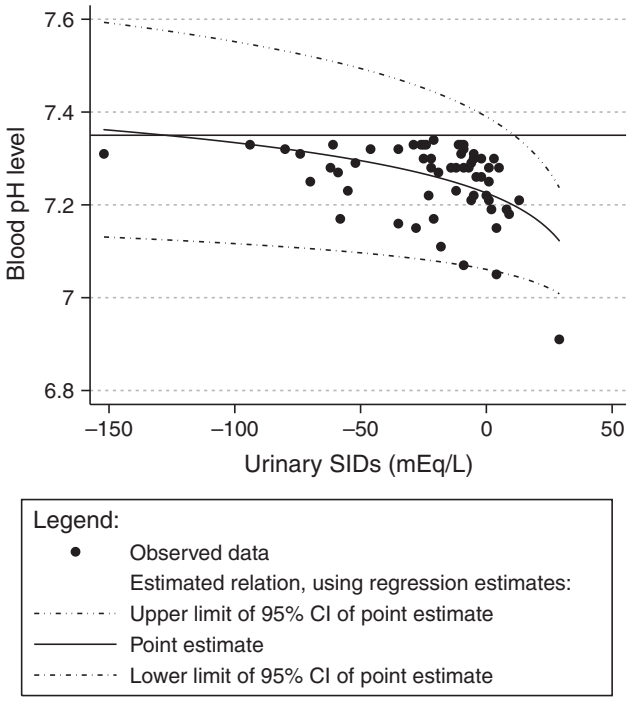

Fig. 2 Scatterplot of the measured urinary SIDs and blood pH levels, overlayed with the estimated relation between these variables according to the linear regression model. The relation is presented by the point estimate and its 95% CI. Only ICU patients with pH levels lower than 7.35 (see reference line) were included in the study.

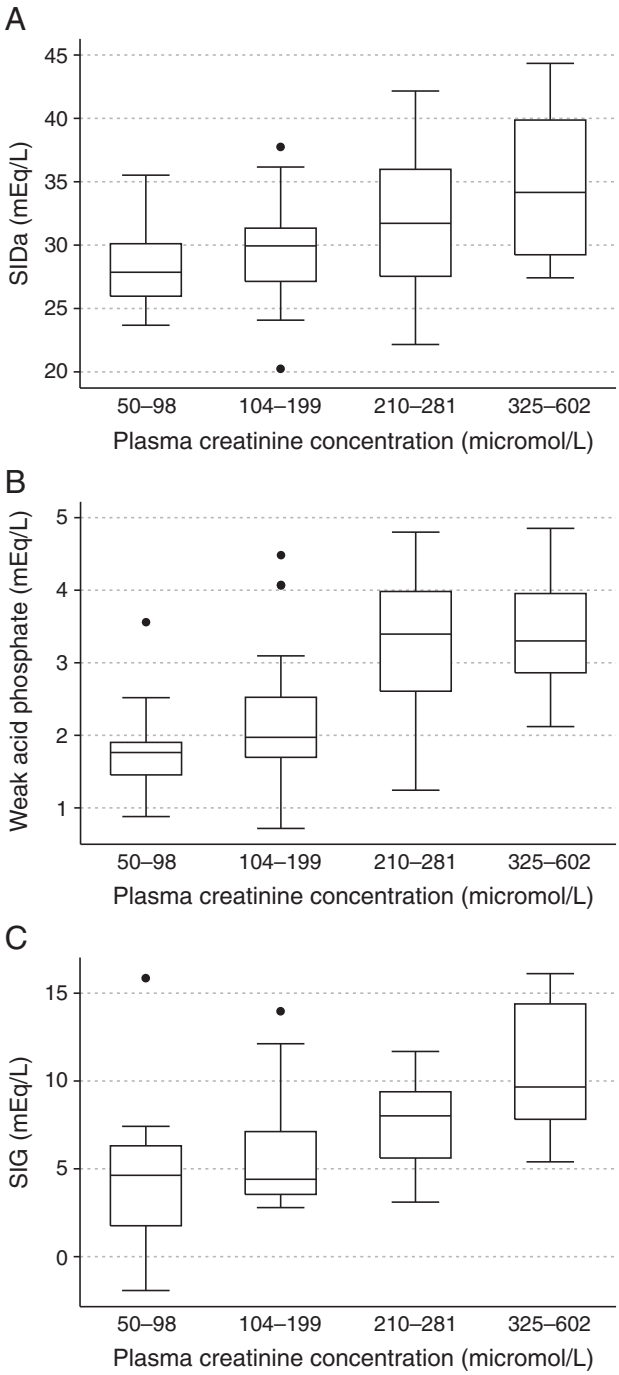

Fig. 3 Box plots of plasma SIDa values (A), concentrations of the weak acid phosphate (B), and plasma SIG values (C) (all in milliequivalent per liter) for plasma creatinine concentration groups with cutoff values of 100, 200, and 300 μmol/L, respectively.

4. Discussion

In this study, we examined the effect of renal function on urinary strong ion excretion and plasma acid-base status in critically ill patients with metabolic acidosis. In these patients, higher plasma creatinine concentrations were significantly associated with greater urinary SID values. Subsequently, greater urinary SIDs values were significantly related to lower blood pH levels. Therefore, less urinary strong anion excretion during impaired renal function appears to represent a determinant of the metabolic acidosis in these patients.

The kidney plays a central role in the body's handling of chloride and sodium. In normal subjects, 80% of the sodium filtered by the glomerulus is resorbed with chloride; and 20% is exchanged for potassium and hydrogen, which allows chloride clearance [7]. During metabolic acidosis, the absolute renal chloride clearance (by coexcretion with NH_4^+ produced by metabolism of glutamine) should increase [6]. In this way, every chloride ion filtered but not reabsorbed increases the plasma SID [3] and, subsequently, corrects acidosis. Accordingly, in our sample, less strong anion excretion during impaired renal function is probably caused by impaired NH_4^+ generation from glutamine metabolism. Thus, this probably reflects an inadequate renal chloride excretion in response to acidosis. This was previously described in patients with chronic renal failure and distal renal tubular acidosis [8] but, to our knowledge, not in critically ill patients in relation to renal function.

Theoretically, the significantly greater urinary SIDs values in relation to declined renal function in our study may also partly reflect greater renal excretion of unmeasured anions, as higher plasma SIG values (as a result of extra renal causes such as sepsis or ketoacidosis) may result in more negatively charged glomerular filtrates because of filtered unmeasured anions. As a result, the excretion of chloride ions may be hampered for a given renal function. However, our observation of higher SIG values in association with impaired renal function is most likely the consequence of an attenuated urinary excretion of unmeasured anions. Therefore, it appears unlikely that unmeasured anions in the urine account for the impaired urinary excretion of chloride in patients with impaired renal function. In addition, the confounding effect of the plasma SIG was assessed and only slightly attenuated the estimated effect of renal function on the urinary SIDs in our sample.

Quantitative plasma analysis of the variables that independently determine the pH level revealed 2 other points. First, the significantly higher SIG and weak acid phosphate values in patients with higher creatinine concentrations accounted for a greater acidifying effect. This finding is consistent with a previous report that compared ICU patients with ARF with ICU controls without ARF [4]. As discussed above, the significantly greater SIG values in association with declined renal function in our study may be explained by a decreased renal clearance of unmeasured anions. A possible candidate is sulphate, as described in prior studies [9,10]. Although sepsis has been associated with the appearance of strong ions in several reports [11,12], in our study, the presence of sepsis was not associated with higher SIG values for a given creatinine concentration. This may indicate that increased plasma SIG values in ICU patients with sepsis are primarily caused by impaired renal function.

Second, plasma SIDa values were significantly higher in patients with declined renal function. Still, the SIDa values in our study sample (range, 20-44 mEq/L) were lower than SIDa values reported in nonacidotic ICU controls (mean ± SD, 45 ± 4 mEq/L) [4] and SIDa values in normal subjects (42 ± 2 mEq/L) [12]. As higher levels of plasma SIDa and simplified SID may in itself increase the urinary SIDs value, the relation between plasma creatinine and urinary SID values was adjusted for the plasma apparent and simplified SID values separately, in addition to the adjustment for pH levels. The correction for plasma SIDs values only slightly attenuated the estimated effect of renal function on urinary SIDs values. However, adjustment for SIDa values did not alter the relation to a relevant extent.

Our observation of significantly higher plasma SIDa values and significantly lower plasma chloride concentrations in relation to declined renal function can only be explained by a less liberal fluid policy in patients with elevated creatinine concentrations, given their impaired chloride excretion. No specific protocol for fluid treatment was prescribed, and balanced solutions were not used at the time. Our study was not aimed at addressing the effects of volume and composition of fluid therapy on acid-base chemistry in relation to renal function. Therefore, data on fluid, sodium, and chloride intake and output were not recorded.

Two other limitations of our study should be addressed. First, we defined renal function as a single measurement of the plasma creatinine concentration and not as the actual glomerular filtration rate (GFR). However, the logarithmic relation between urinary SID values and creatinine concentrations resembles the relation between GFR and creatinine concentrations. This suggests a linear relation between GFR and the renal capacity to excrete strong anions. Second, we defined the urinary SID as the difference between urinary sodium and chloride concentrations, not taking into account other electrolytes in the urine. We feel this simplification is justified because sodium and chloride are the most abundant strong ions in the extracellular compartment and, therefore, the most important determinants of the strong ion difference [13,14]. Because plasma sodium controls intravascular volume and osmolality and given that plasma potassium is important for cardiac and neuromuscular function, plasma chloride appears to represent the strong ion that the kidney uses to regulate acid-base status without interfering with other important homeostatic processes. In accordance, using urinary chloride alone instead of the urinary SID in examining the effect of renal function on urinary chloride excretion yielded similar results (data not shown). Despite these limitations, to our knowledge, our study is the first to

examine urinary strong ion excretion and acid-base status in relation to renal function in critically ill patients.

In conclusion, declined renal function was associated with greater urinary SIDs in critically ill patients with metabolic acidosis. Subsequently, higher urinary SID values were associated with lower blood pH levels. This may suggest that, in critically ill patients with metabolic acidosis, impaired renal function is related to the urinary excretion of inadequate amounts of plasma chloride to correct for acidosis. Accordingly, chloride loading by means of massive unbalanced volume resuscitation may lead to more pronounced acidosis in these patients.

Supplementary materials related to this article can be found online at doi:10.1016/j.jcrc.2011.05.028.

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