

Alterations in urinary strong ion difference in critically ill patients with metabolic acidosis: a prospective observational study

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Acid–base disturbances are frequently present in critically ill patients. The understanding of their pathophysiological mechanisms is a key point for correct diagnosis and treatment. The kidney has a fundamental role regulating acid–base status. However, when its function is altered, it can behave as an amplifier of the initial acid–base disturbance.¹ Despite this, the evaluation of urine is not routinely considered as an initial step in managing patients with acid–base alterations.

Proton balance is the basis of the traditional concept of renal compensation for acid–base disorders, which emphasises the importance of the $\text{NH}_3/\text{NH}_4^+$ system as a vehicle for urinary elimination of protons.² Madison and Seldin showed that the increase in ammonium excretion constitutes the appropriate renal response to exogenous or endogenous acid loading.³ Goldstein et al proposed the use of the urinary anion gap ($[\text{AG}]_{\text{urinary}} = [\text{Na}^+]_{\text{urinary}} + [\text{K}^+]_{\text{urinary}} - [\text{Cl}^-]_{\text{urinary}}$) as an indirect index of ammonium excretion.⁴ As the increase in ammonium excretion is accomplished by an increased excretion of $[\text{Cl}^-]$, the $[\text{AG}]_{\text{urinary}}$ should become negative. Battle et al used the $[\text{AG}]_{\text{urinary}}$ for the diagnosis of different types of hyperchloraemic metabolic acidosis.⁵ They concluded that $[\text{AG}]_{\text{urinary}}$ is positive in patients with distal acidification disorders (such as renal tubular acidosis) and negative in patients with hyperchloraemic metabolic acidosis of extrarenal causes.

In the Stewart approach, the concept of $[\text{AG}]_{\text{urinary}}$ is replaced by the urinary strong ion difference ($[\text{SID}]_{\text{urinary}}$).⁶ The kidney is the organ responsible for the excretion of strong ions. For this purpose, variable quantities of $[\text{Na}^+]$, $[\text{K}^+]$ and $[\text{Cl}^-]$ are eliminated in the urine. The excretion of $[\text{Na}^+]$ and $[\text{K}^+]$ has other priorities, such as the regulation of

ABSTRACT

Background and objective: The correct renal response to metabolic acidosis should be a negative shift in the urinary strong ion difference ($[\text{SID}]_{\text{urinary}} = [\text{Na}^+]_{\text{urinary}} + [\text{K}^+]_{\text{urinary}} - [\text{Cl}^-]_{\text{urinary}}$). Our hypothesis was that the failure to decrease the $[\text{SID}]_{\text{urinary}}$ is frequently present and leads to a more severe metabolic acidosis.

Design, setting and participants: Prospective observational study conducted in the medical/surgical intensive care unit of a teaching hospital between 1 January 2006 and 30 April 2007. Participants were 98 patients with metabolic acidosis on ICU admission and 10 healthy volunteers.

Interventions: None.

Main outcome measures: Severity of metabolic acidosis; behaviour of acid–base variables according to positive or negative $[\text{SID}]_{\text{urinary}}$.

Results: Twelve patients (12%) had negative $[\text{SID}]_{\text{urinary}}$ and 86 (88%) had positive $[\text{SID}]_{\text{urinary}}$. Compared with patients with positive $[\text{SID}]_{\text{urinary}}$, those with negative $[\text{SID}]_{\text{urinary}}$ had higher $[\text{HCO}_3^-]$ (20 ± 2 v 18 ± 3 mmol/L), base excess ($[\text{BE}]$) (-5 ± 2 v -7 ± 2 mmol/L), anion gap ($[\text{AG}]$) (21 ± 5 v 17 ± 4 mmol/L), $\Delta[\text{AG}] - \Delta[\text{HCO}_3^-]$ (1 ± 5 v -3 ± 3 mmol/L) and lower $[\text{Cl}^-]$ (105 ± 5 v 111 ± 3 mmol/L).

Conclusions: Most of the critically ill patients with metabolic acidosis showed inappropriate renal compensation, as evidenced by positive $[\text{SID}]_{\text{urinary}}$ and higher plasma $[\text{Cl}^-]$. These patients had more severe metabolic acidosis. On the other hand, patients with adequate renal response and negative $[\text{SID}]_{\text{urinary}}$ had positive $\Delta[\text{AG}] - \Delta[\text{HCO}_3^-]$. These findings, usually considered as a diagnosis of associated metabolic alkalosis, might be interpreted as the proper renal response to metabolic acidosis.

Abbreviations

AG	Anion gap
APACHE	Acute Physiology and Chronic Health Evaluation
BE	Base excess
Pi	Phosphate
SID	Strong ion difference
SIG	Strong ion gap
SOFA	Sepsis-related Organ Failure Assessment

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the intravascular volume. On the other hand, the balance of $[\text{Cl}^-]$ is strictly related to acid–base regulation.⁷

Kellum stated that the proper renal response to nonrenal metabolic acidosis should be a negative $[\text{SID}]_{\text{urinary}}$.⁷

When a strong anion (eg, $[\text{Cl}^-]$ or lactate) is added to plasma, plasma $[\text{SID}]$ decreases, and metabolic acidosis is generated. The kidney reaction to this event is to increase NH_4Cl excretion. Excretion of NH_4Cl allows the elimination of $[\text{Cl}^-]$ accompanied by a weak cation in the absence of $[\text{Na}^+]$ and $[\text{K}^+]$.^{7,8} In this way, the $[\text{SID}]_{\text{urinary}}$ becomes negative, and this compensatory response increases plasma $[\text{SID}]$ (an alkalinising effect).

Our objective was to evaluate the behaviour of $[\text{SID}]_{\text{urinary}}$ in critically ill patients with metabolic acidosis on admission to the intensive care unit. Our hypothesis was that failure to increase the urinary elimination of $[\text{Cl}^-]$ and reduce the $[\text{SID}]_{\text{urinary}}$ is a frequent expression of renal dysfunction. Consequently, this failure should produce a more severe metabolic acidosis than that seen in patients with negative $[\text{SID}]_{\text{urinary}}$.

Methods

Study design and sample selection

We conducted a prospective observational study in the medical/surgical ICU of a teaching hospital. From 1 January 2006 to 30 April 2007, we screened every patient admitted to the ICU. We included patients with simple (pure) metabolic acidosis, as identified by a base excess ($[\text{BE}] < -3$ mmol/L and an appropriate respiratory response:

$$\text{PCO}_2 \text{ in mmHg} = ([\text{HCO}_3^-] \text{ in mmol/L} \times 1.5) + 8 \pm 2.^9$$

We excluded patients with associated respiratory acid–base disturbances, surgical urinary procedures, diuretic use, and/or renal insufficiency (serum creatinine level > 1.7 mg%). This left 98 patients in our sample. In addition, 10 normal volunteers were studied.

Measurements

On admission to the ICU, patients' demographic data (age, sex) and the type of admission (surgical or medical) were recorded. The APACHE (Acute Physiology and Chronic Health Evaluation) II score,¹⁰ SOFA (Sepsis-related Organ Failure Assessment) score,¹¹ McCabe score¹² and predicted risk of mortality were calculated. Arterial blood samples were analysed for gases (AVL OMNI 9, Roche Diagnostics, Graz, Austria); $[\text{Na}^+]$, $[\text{K}^+]$ and $[\text{Cl}^-]$ (selective electrode ion, AEROSSET, Abbott Laboratories, Abbott Park, Ill, USA); $[\text{Ca}^{++}]$ (selective electrode ion, AVL OMNI 9); $[\text{Mg}^{++}]$ (Arsenazo dye/Mg complex); [albumin] (bromocresol–sulfonphthaleinyl), [phosphate] ($[\text{Pi}]$) (molybdate–vanadate); and [lactate] (selective electrode ion, AVL OMNI 9). $[\text{Na}^+]$, $[\text{K}^+]$ and $[\text{Cl}^-]$ were also measured in urine.

Calculated variables

- $[\text{HCO}_3^-]$ and $[\text{BE}]$ (extracellular) were calculated using the Henderson–Hasselbalch equation^{13,14} and van Slyke equation.^{15,16}
- $[\text{AG}]$ was calculated from the equation:¹⁷

$$[\text{AG}] = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]).$$
- $[\text{AG}]$ was corrected for the effect of abnormal albumin concentration, using the equation:¹⁸

$$[\text{AG}]_{\text{corrected}} \text{ (mmol/L)} = [\text{AG}]_{\text{observed}} + \{0.25 \times ([\text{normal albumin}] - [\text{observed albumin}]) \text{ (in g/L)}\}.$$
- Differences between the changes in $[\text{AG}]_{\text{corrected}}$ and $[\text{HCO}_3^-]$ ($\Delta[\text{AG}]_{\text{corrected}} - \Delta[\text{HCO}_3^-]$) and between the changes in $[\text{AG}]_{\text{corrected}}$ and $[\text{BE}]$ ($\Delta[\text{AG}]_{\text{corrected}} - \Delta[\text{BE}]$) were calculated.
- $[\text{SID}]_{\text{urinary}}$ was calculated from the equation:⁵

$$[\text{SID}]_{\text{urinary}} = [\text{Na}^+]_{\text{urinary}} + [\text{K}^+]_{\text{urinary}} - [\text{Cl}^-]_{\text{urinary}}.$$
- Effective $[\text{SID}]$ was calculated from the equation:¹⁹

$$[\text{SID}]_{\text{effective}} = [\text{HCO}_3^-] + [\text{albumin}^-] + [\text{Pi}^-].$$
- $[\text{albumin}^-]$ and $[\text{Pi}^-]$ (mmol/L) were calculated from the measured [albumin] (g/L), $[\text{Pi}]$ (mmol/L) and pH using the equations:¹⁹

$$[\text{albumin}^-] = [\text{albumin}] \times (0.123 \times \text{pH} - 0.631) \text{ and}$$

$$[\text{Pi}^-] = [\text{Pi}] \times (0.309 \times \text{pH} - 0.469).$$
- Apparent $[\text{SID}]$ was calculated from the equation:¹⁹

$$[\text{SID}]_{\text{apparent}} = [\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{++}] + [\text{Mg}^{++}] - [\text{Cl}^-].$$
- The strong ion gap ($[\text{SIG}]$) is based on strong anions other than $[\text{Cl}^-]$ (lactate, sulfate, ketoacids and other organic anions) and was calculated from the equation:¹⁹

$$[\text{SIG}] = [\text{SID}]_{\text{apparent}} - [\text{SID}]_{\text{effective}}.$$
- $[\text{Cl}^-]$ and $[\text{SIG}]$ were adjusted for water excess or deficit by multiplying the observed value by a correcting factor $([\text{Na}^+]_{\text{normal}}/[\text{Na}^+]_{\text{observed}})$.¹⁹

Data analysis

Patients were grouped according to positive or negative $[\text{SID}]_{\text{urinary}}$. Acid–base variables (mean \pm SD) were analysed by the one-way analysis of variance and Newman–Keuls tests. Epidemiological data, expressed as mean \pm SD, median (interquartile range [IQR]) and percentages, were analysed by the unpaired Student *t* test, Mann–Whitney *U* test, and χ^2 test, respectively.

Ethics approval and patient consent

Our study was approved by the institutional review board. As standard procedures were applied in the diagnosis, only permission to use the data was requested from patients or

relatives. Written consent was obtained from the normal volunteers.

Results

Of 590 critically ill patients evaluated, 98 met the inclusion criteria for our study. Twelve (12%) had negative $[SID]_{urinary}$ and 86 (88%) had positive $[SID]_{urinary}$. Their clinical and epidemiological characteristics are summarised in Table 1. There were nonsignificant trends towards longer ICU and hospital stays and higher mortality in the positive $[SID]_{urinary}$ group. These patients also had higher APACHE II and SOFA scores. Figure 1 compares the $[SID]_{urinary}$ in critically ill patients with that of normal volunteers. There were no significant differences between patients with positive and negative $[SID]_{urinary}$ in pH or PCO_2 , but $[HCO_3^-]$ and $[BE]$ were lower in patients with positive $[SID]_{urinary}$ (Figure 2). Accordingly, $[SID]_{effective}$ and $[SID]_{apparent}$ were lower in this group (Figure 3).

Patients with negative $[SID]_{urinary}$ had higher $[AG]_{corrected}$ and $[SIG]_{corrected}$, and lower plasma $[Cl^-]$ (Figure 4). They also had higher $\Delta[AG]_{corrected} - \Delta[HCO_3^-]$, and $\Delta[AG]_{corrected} - \Delta[BE]$ (Figure 5). Values of lactate, albumin, and other electrolytes are shown in Table 2. There were no significant differences between patients with positive or negative $[SID]_{urinary}$ in urea levels (29 ± 13 v 37 ± 23 mg%; $P=0.25$) and creatinine levels (0.9 ± 0.2 v 0.9 ± 0.3 mg%; $P=0.68$) on admission, or at the moment of hospital discharge (30 ± 21 v 28 ± 13 mg%; $P=0.71$ [urea]; and 0.8 ± 0.2 v 0.8 ± 0.3 mg%; $P=0.75$ [creatinine]).

As an $[SID]_{urinary}$ lower than the plasma $[SID]_{effective}$, rather than a negative $[SID]_{urinary}$, would be needed to improve $[SID]_{effective}$, we also grouped the patients according to the difference between $[SID]_{urinary}$ and $[SID]_{effective}$. Only 36 patients (37%) had $[SID]_{urinary}$ lower than $[SID]_{effective}$. On the other hand, 62 patients (63%) had $[SID]_{urinary}$ higher than $[SID]_{effective}$. Patients with $[SID]_{urinary}$ lower than $[SID]_{effective}$ presented higher $[HCO_3^-]$ (19 ± 2 v 17 ± 3 mmol/L), higher $[BE]$ (-6 ± 2 v -7 ± 3 mmol/L), and lower plasma $[Cl^-]$ (109 ± 5 v 111 ± 3 mmol/L).

Discussion

The main results of our study were that only 12% of critically ill patients with metabolic acidosis had negative $[SID]_{urinary}$ on ICU admission, and 37% of them also had $[SID]_{urinary}$ lower than $[SID]_{effective}$. These findings suggest that critically ill patients may frequently show a type of renal dysfunction that has not been previously described.

Quantitative acid–base chemistry allows a more comprehensive understanding of the mechanisms of metabolic acid–base disorders.⁶ The difference between the sum of all strong cations and all strong anions (those completely

dissociated at physiological pH) is known as the $[SID]$. Although not based on experimental data, this approach states that $[SID]$ has a powerful electrochemical effect on water dissociation, and hence on $[H^+]$ concentration. Decreases in $[SID]$ determine acidosis, and increases in $[SID]$ produce alkalosis.^{6,19}

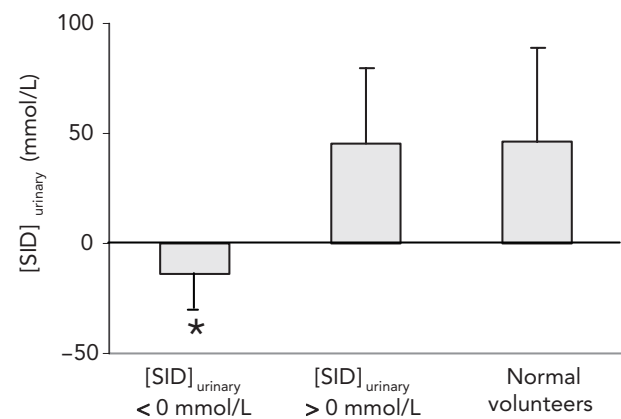
The $[SID]$ can change because of (i) addition of strong ions to the system, as occurs with the infusion of fluids with an $[SID]$ different from that of plasma (isotonic saline

Table 1. Clinical and epidemiological characteristics*

Characteristic	$[SID]_{urinary}$ negative	$[SID]_{urinary}$ positive
Number of patients (%)	12 (12%)	86 (88%)
Age (years)	54 ± 21	61 ± 20
Sex, male (%)	58%	45%
APACHE II score	4.5 ± 2.8	8.0 ± 6.1 [†]
SOFA score	0.8 ± 0.9	2.2 ± 2.5 [†]
McCabe score	1.0 ± 0.0	1.3 ± 0.6
APACHE II predicted mortality (%)	5.8 ± 2.3%	11.3 ± 12.6%
Actual mortality (%)	0	6%
Medical/surgical diagnosis (%)	17%	31%
ICU length of stay (days)	2.0 (1.5–3.0)	3.0 (2.0–5.0)
Hospital length of stay (days)	6.0 (4.0–10.5)	7.0 (5.0–12.0)

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. SID = strong ion difference. SOFA = Sepsis-related Organ Failure Assessment. * Values are number (%), mean ± SD or median (interquartile range). † $P < 0.05$ compared with the other group.

Figure 1. Values of $[SID]_{urinary}$ in patients with metabolic acidosis with negative and positive $[SID]_{urinary}$ and in normal volunteers



SID = strong ion difference. * $P < 0.05$ compared with the other groups.

solution); (ii) endogenous production of strong ions (lactate, sulfate, phosphates, ketoacids and others); (iii) redistribution of strong ions within different compartments; and (iv) loss of fluids with [SID]s different from that of plasma (such as in urine or in fistulas).⁷

To maintain plasma [SID] within normal limits, a strict balance between the input and output of strong ions, as well as the volume in which they are distributed, is required. The kidney plays an important role in reaching this equilibrium.^{7,20} Animal studies have shown that addition of anions to the diet causes systemic metabolic acidosis followed by reductions in [SID]_{urinary}.^{21,22}

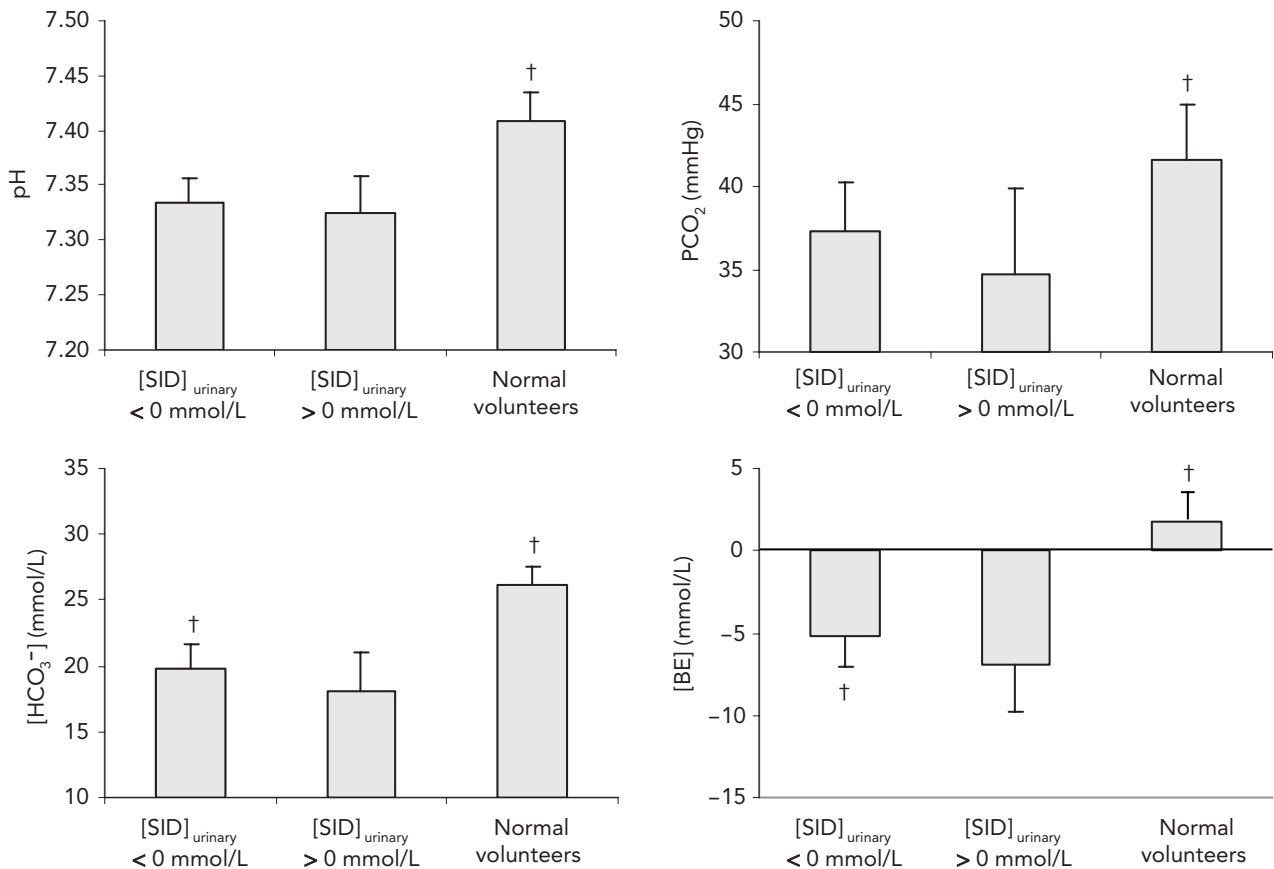
Many investigators have used the Stewart approach to explain metabolic acidosis secondary to increases in strong ions, such as in hyperchloraemic metabolic acidosis, which results from saline-solution expansion,²³ or lactic acidosis secondary to endogenous production of lactate.¹⁹ On the other hand, few studies have evaluated the excretion of strong ions.^{24,25} In the only study performed on critically ill patients, Moviat et al showed that acetazolamide-mediated

correction of metabolic alkalosis was related to changes in [SID]_{urinary}.²⁴ This effect was completely accounted for by the increase in the renal excretion ratio of sodium to chloride, which results in an increased serum chloride concentration.²⁴

Unfortunately, [SID]_{urinary} is not easy to measure ($[SID]_{urinary} = [Na^+]_{urinary} + [K^+]_{urinary} + [nonmeasured\ cations] - [Cl^-]_{urinary} - [nonmeasured\ anions]_{urinary}$). The most abundant non-measured cation in urine is ammonium, produced by ammonogenesis, while the principal anion is sulfate, from sulfated amino acids.²⁰ However, the traditional concept of [AG]_{urinary} provides an equivalent assessment of renal response to acid-base disorders to that of [SID]_{urinary}.²⁴ As the cations usually measured in urine are [Na⁺] and [K⁺], and the principal anion is [Cl⁻], [AG]_{urinary} is $[Na^+]_{urinary} + [K^+]_{urinary} - [Cl^-]_{urinary}$. Battle et al reported that, in healthy volunteers, [AG]_{urinary} is 41 ± 9 mmol/L (mean \pm SEM).⁵ This figure is similar to the values of 42 ± 13 mmol/L that we found in our volunteers.

Kellum proposed that the adequate response to nonrenal metabolic acidosis should be a negative [SID]_{urinary}.⁷ When a

Figure 2. Values of pH, PCO₂, [HCO₃⁻] and [BE] in patients with metabolic acidosis with negative and positive [SID]_{urinary} and in normal volunteers*



BE = base excess. SID = strong ion difference. * Patients with positive [SID]_{urinary} had lower levels of [HCO₃⁻] and [BE]. † P < 0.05 compared with the other groups.

strong acid is added to plasma, plasma [SID] decreases and metabolic acidosis is produced. The kidney response is to increase NH_4Cl excretion, which allows the elimination of $[\text{Cl}^-]$ concurrently with a weak cation in the absence of $[\text{Na}^+]$ and $[\text{K}^+]$. Consequently, $[\text{SID}]_{\text{urinary}}$ becomes negative and thus increases the plasma [SID] (an alkalinising effect).

Conversely, the renal response to metabolic alkalosis should be a decrease in $[\text{Cl}^-]$ excretion and an increase in $[\text{Na}^+]$ and $[\text{K}^+]$ elimination. Therefore, $[\text{SID}]_{\text{urinary}}$ becomes positive and plasma [SID] is decreased (an acidifying effect).

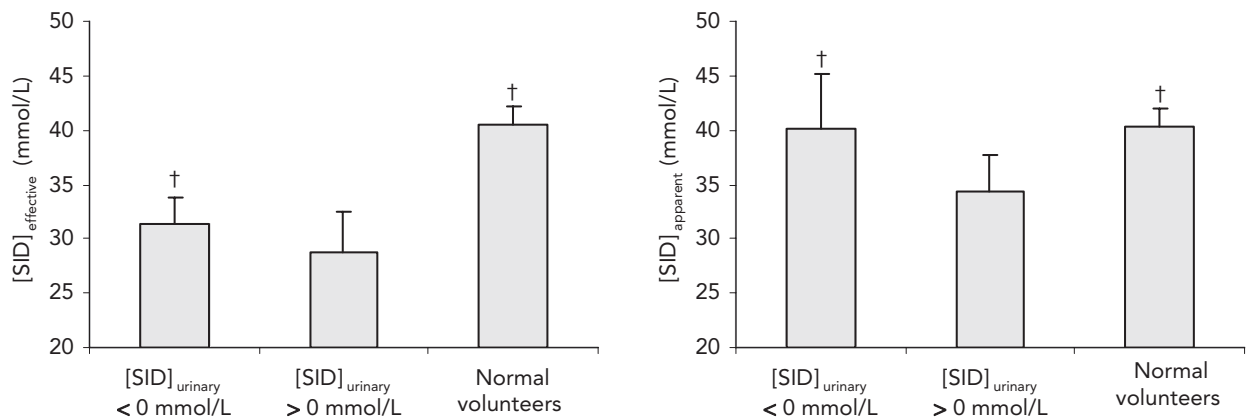
This compensatory renal response is not restricted to metabolic disturbances. In chronic respiratory acidosis, tubular resorption of $[\text{Cl}^-]$ is also diminished, leading to hypochloraemia and increased plasma [SID].²⁶

Our study includes $[\text{SID}]_{\text{urinary}}$ as an initial step in evaluating metabolic acidosis in critically ill patients. Only 12% of the patients had negative $[\text{SID}]_{\text{urinary}}$ on ICU admission, whereas

88% had positive $[\text{SID}]_{\text{urinary}}$. Patients with negative $[\text{SID}]_{\text{urinary}}$ had lower plasma $[\text{Cl}^-]$ and higher [SID] compared with patients with positive $[\text{SID}]_{\text{urinary}}$. The accompanying increase in the elimination of $[\text{Cl}^-]_{\text{urinary}}$ is a compensatory response that enhances plasma [SID] (an alkalinising effect).

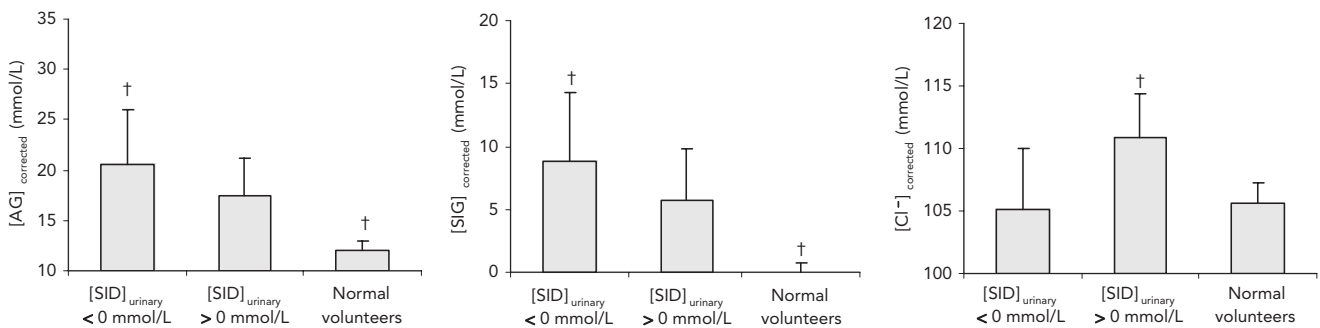
Correct management of $[\text{Cl}^-]$ by the kidney is essential to compensate for metabolic acidosis. The presence of positive $[\text{SID}]_{\text{urinary}}$ in patients with metabolic acidosis may be an expression of tubular dysfunction. The creatinine and urea values, however, were comparable in both groups of patients. In acute renal failure, acid-base alterations can occur before changes in creatinine and urea levels. In chronic renal failure, the urine acidification process can continue up to an advanced stage.²⁷ Although patients with overt renal failure were excluded from our study, some of the included patients probably had some alteration in renal function. Despite the presence of normal glomerular filtration, patients with renal

Figure 3. Values of $[\text{SID}]_{\text{effective}}$ and $[\text{SID}]_{\text{apparent}}$ in patients with metabolic acidosis with negative and positive $[\text{SID}]_{\text{urinary}}$ and in normal volunteers*



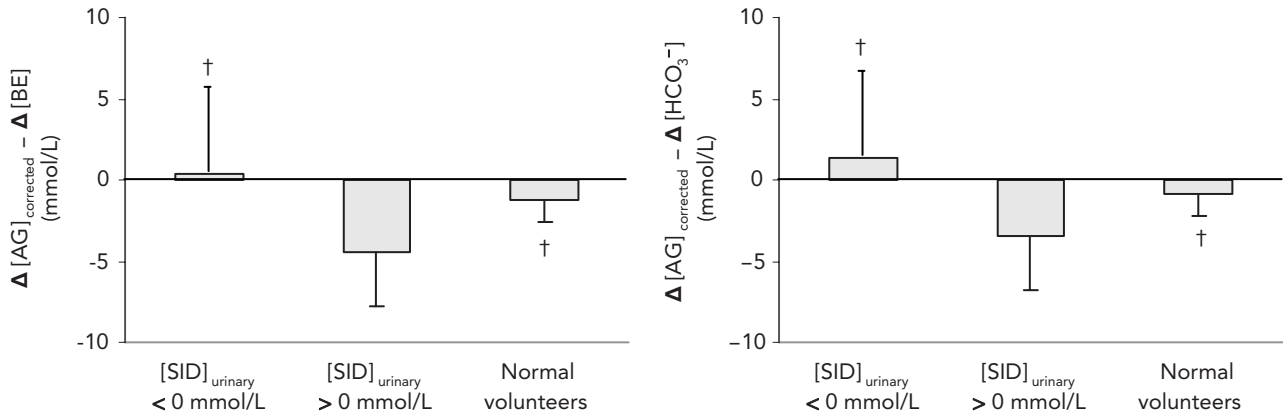
SID = strong ion difference. * Patients with positive $[\text{SID}]_{\text{urinary}}$ had lower $[\text{SID}]_{\text{effective}}$ and $[\text{SID}]_{\text{apparent}}$. † $P < 0.05$ compared with the other groups.

Figure 4. Values of $[\text{AG}]_{\text{corrected}}$, $[\text{SIG}]$ and $[\text{Cl}^-]_{\text{corrected}}$ in patients with metabolic acidosis with negative and positive $[\text{SID}]_{\text{urinary}}$ and in normal volunteers*



AG = anion gap. SID = strong ion difference. SIG = strong ion gap. * Patients with positive $[\text{SID}]_{\text{urinary}}$ had lower $[\text{AG}]_{\text{corrected}}$ and $[\text{SIG}]$ and higher $[\text{Cl}^-]_{\text{corrected}}$. † $P < 0.05$ compared with the other groups.

Figure 5. Values of $\Delta[AG] - \Delta[HCO_3^-]$ and $\Delta[AG]_{corrected} - \Delta[BE]$ in patients with metabolic acidosis with negative and positive $[SID]_{urinary}$ and in normal volunteers*



AG = anion gap. BE = base excess. SID = strong ion difference.

* Patients with negative $[SID]_{urinary}$ had higher $\Delta[AG]_{corrected} - \Delta[HCO_3^-]$ and $\Delta[AG]_{corrected} - \Delta[BE]$. † $P < 0.05$ compared with the other groups.

tubular acidosis syndromes,²⁸ hepatic diseases,²⁹ drug toxicity³⁰ and other conditions may have different kinds of tubular dysfunction. For example, patients with chronic alcoholism have a variety of tubular abnormalities that include impaired renal acidification. These alterations are transient, improve with alcohol withdrawal, and are not associated with progressive renal disease.³¹ This may explain why, in our study, creatinine and urea values remained similar in both groups at the time of hospital discharge. Furthermore, the patients with positive $[SID]_{urinary}$ had higher APACHE II and SOFA scores, as expressions of more severe organ dysfunction and critical illness. In addition, they showed a nonsignificant trend toward longer stays and higher mortality.

In patients with metabolic acidosis, some conditions may alter the renal ability to reduce $[SID]_{urinary}$. Volume-depleted patients exhibit reduced chloride excretion because of their increased tubular avidity for NaCl. These patients usually have a low urinary sodium concentration. In our series, however, only 6/86 patients in the positive $[SID]_{urinary}$ group and 1/12 patients in the negative $[SID]_{urinary}$ group had $[Na^+]_{urinary} < 20$ mmol/L.

Another situation in which $[SID]_{urinary}$ may fail to decrease is when patients with a high-anion-gap metabolic acidosis lose organic anions in the urine, such as ketoacids, salicylic acid or carbenicillin, along with strong cations, such as sodium or potassium. In these circumstances, there is a loss of cations in excess of anions and the chloride excretion should be lower than that seen in a pure hyperchloraemic metabolic acidosis, in which it is easier for the kidney to excrete the chloride. Nevertheless, plasma unmeasured anions were lower in the positive $[SID]_{urinary}$ group than the negative $[SID]_{urinary}$ group in our study, suggesting that this mechanism was not significant in our patients.

Hyperchloraemia is a frequent finding in ICU patients, often associated with the infusion of large volumes of saline solution.²³ However, other mechanisms may be involved. Although there is no evidence that endogenous hyperchloraemia can occur in patients with metabolic acidosis, this mechanism has been suggested in experimental endotoxaemia.³² Capillary lesions and resulting increased permeability might generate the loss of the Donnan equilibrium because of albumin migration from the intravascular compartment into the interstitial space. To maintain balance, chloride is displaced in the opposite direction.

Table 2. Haemoglobin, albumin, lactate and other electrolytes*

	$[SID]_{urinary}$ negative	$[SID]_{urinary}$ positive	Normal volunteers
Haemoglobin (g%)	11.3 ± 1.7	10.9 ± 2.3	14.3 ± 1.4 [†]
Lactate (mmol/L)	3.1 ± 2.5	2.8 ± 2.1	1.1 ± 0.4 [†]
[albumin] (g/L)	3.6 ± 0.4 [†]	3.2 ± 0.6	4.4 ± 0.1 [†]
$[Na^+]$ (mmol/L)	137 ± 2	137 ± 4	140 ± 1 [†]
$[K^+]$ (mmol/L)	3.9 ± 0.6	3.9 ± 0.5	3.9 ± 0.4
$[Ca^{++}]$ (mmol/L)	1.0 ± 0.2	1.0 ± 0.2	1.2 ± 0.1 [†]
$[Mg^{++}]$ (mmol/L)	1.7 ± 0.4	1.8 ± 0.4	1.8 ± 0.2
$[Cl^-]$ (mmol/L)	103 ± 4 [†]	108 ± 5	106 ± 2
[Pi] (mg%)	3.2 ± 0.9	3.5 ± 0.9	3.6 ± 0.4
$[Na^+]_{urinary}$ (mmol/L)	99 ± 67	108 ± 59	104 ± 48
$[K^+]_{urinary}$ (mmol/L)	31 ± 25	49 ± 45	58 ± 43
$[Cl^-]_{urinary}$ (mmol/L)	144 ± 65	111 ± 61	115 ± 49

Pi = phosphate. SID = strong ion difference. * Values are mean ± SD. † $P < 0.05$ compared with the other groups.

Finally, the results of our study suggest that the lack of adequate renal response, transitory or permanent, as indicated by a positive $[SID]_{\text{urinary}}$, may be another mechanism contributing to the development of hyperchloraemia.

A positive $\Delta[AG]_{\text{corrected}} - \Delta[HCO_3^-]$ and $\Delta[AG]_{\text{corrected}} - \Delta[BE]$ in metabolic acidosis is usually considered to indicate associated metabolic alkalosis.⁹ However, these gradients have a wide range, and should be used cautiously for this purpose.³³ On the other hand, it is possible to speculate from our findings that these positive gradients are, in fact, not an expression of a complex metabolic disorder but rather a normal compensatory renal response to metabolic acidosis.

Our study has limitations: the renal compensation for acid–base disorders is a slow process that requires hours to be completed. Our patients were studied on ICU admission and had no temporal follow-up. Thus some patients may have had an inadequate response that was merely transient. Furthermore, we can not completely rule out the possibility that drugs that directly modify the $[SID]_{\text{urinary}}$ (eg, loop diuretics, mannitol) were administered to patients before their admission to the ICU. Finally, as fluid therapy before patients' enrolment was not quantified, we can not rule out the possibility that different kinds of solutions may have a particular effect on $[SID]_{\text{urinary}}$.

Conclusion

Most of the patients with metabolic acidosis on ICU admission showed an inappropriate renal response, as evidenced by a positive $[SID]_{\text{urinary}}$ and higher plasma $[Cl^-]$. These findings may be an expression of a form of renal dysfunction as yet unreported in critically ill patients that produces a more severe degree of metabolic acidosis.

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