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## Physicochemical characterization of metabolic acidosis induced by normal saline resuscitation of patients with severe sepsis and septic shock

*Caracterização físico-química da acidose metabólica induzida pela expansão volêmica inicial com solução salina a 0,9% em pacientes com sepse grave e choque séptico*

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### ABSTRACT

**Objective:** The aim of this study was to characterize and quantify metabolic acidosis that was caused by initial volume expansion during the reanimation of patients with severe sepsis and septic shock.

**Methods:** A blood sample was drawn for physicochemical characterization of the patient's acid-base equilibrium both before and after volume expansion using 30 mL/kg 0.9% saline solution. The diagnosis and quantification of metabolic acidosis were based on the standard base excess (SBE).

**Results:** Eight patients with a mean age of  $58 \pm 13$  years and mean APACHE II scores of  $20 \pm 4$  were expanded using  $2,000 \pm 370$  mL of 0.9% saline solution. Blood pH dropped from  $7.404 \pm 0.080$  to  $7.367 \pm 0.086$  ( $p=0.018$ ), and  $PCO_2$  increased from  $30 \pm 5$  to  $32 \pm 2$  mmHg ( $p=0.215$ ); SBE dropped from  $-4.4 \pm 5.6$  to  $-6.0 \pm 5.7$  mEq/L ( $p=0.039$ ). The drop in SBE was associated with the acidifying

power of two factors, namely, a significant increase in the strong ion gap (SIG) from  $6.1 \pm 3.4$  to  $7.7 \pm 4.0$  mEq/L ( $p = 0.134$ ) and a non-significant drop in the apparent inorganic strong ion differences (SIDai) from  $40 \pm 5$  to  $38 \pm 4$  mEq/L ( $p = 0.318$ ). Conversely, the serum albumin levels decreased from  $3.1 \pm 1.0$  to  $2.6 \pm 0.8$  mEq/L ( $p = 0.003$ ) with an alkalinizing effect on SBE. Increased serum chloride levels from  $103 \pm 10$  to  $106 \pm 7$  mEq/L ( $p < 0.001$ ) led to a drop in SIDai.

**Conclusion:** Initial resuscitation using 30 mL/kg of 0.9% saline solution for patients with severe sepsis and septic shock is associated with worsened metabolic acidosis, as measured by SBE. This worsened SBE can be ascribed to a serum increase in the levels of unmeasurable anions and chloride.

**Keywords:** Ketosis; Intensive care units; Sepsis; Shock, septic/therapy; Acid-base equilibrium; Saline solution, hypertonic/therapeutic use

This study was conducted at the Emergency Department – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – USP – São Paulo (SP), Brazil.

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**Conflicts of interest:** None.

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### INTRODUCTION

In Brazil, approximately 26% of patients who are admitted to the intensive care unit (ICU) are diagnosed with sepsis or severe sepsis.<sup>(1)</sup> Antibiotics and volume expansion are often the first-line therapies for these patients.<sup>(2)</sup> Crystalloids, particularly 0.9% saline solution (normal saline), are commonly used for volume expansion.<sup>(3)</sup> Although 0.9% saline solution is considered to be a “physiological solution”, infusing large volumes can cause metabolic disorders, particularly hyperchloremia-associated acidosis.<sup>(4-6)</sup>

The actual implications of metabolic acidosis in patients with severe sepsis and septic shock is currently uncertain;<sup>(7)</sup> however, metabolic acidosis and hyperchloremia at admission and unimproved metabolic acidosis that are associated with lactate and unmeasurable anions within 5 days of admission are related to an increased mortality rate.<sup>(8)</sup> Overall, in septic patients, improving metabolic acidosis as measured by

standard base excess (SBE) is associated with less severe organ dysfunction<sup>(9)</sup> and a decreased risk of death.<sup>(10)</sup>

Acid-base equilibrium can be analyzed using various approaches with slightly different points of view showing the very same changes.<sup>(11)</sup> The physicochemical technique provides a quantification of the influence of both organic and non-organic components on pH.<sup>(12)</sup> In this method, strong ions (e.g., sodium, potassium, magnesium, calcium and chloride), unmeasurable anions, lactate, albumin and phosphates act to regulate metabolic pH control,<sup>(9,12)</sup> whereas the partial pressure of carbon dioxide modulates respiratory pH control.<sup>(12)</sup>

Therefore, considering the widespread use of volume expansion with 30 mL/kg normal saline solution in patients with severe sepsis and septic shock,<sup>(2)</sup> we hypothesized that significant metabolic acidosis occurs after infusion of normal saline. Accordingly, the aim of this study was to perform a physicochemical characterization and quantification of metabolic acidosis caused by initial volume expansion in patients with severe sepsis and septic shock.

## METHODS

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, and all of the patients provided signed and informed consent. The study was conducted at the emergency department of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. The patients were sequentially selected according to the criteria of the Sepsis, Severe Sepsis and Septic Shock Consensus Conference.<sup>(13)</sup> Therefore, patients who presented at the emergency department with two out of four diagnostic features, as defined by the American College of Chest Physicians consensus, together with one out of two organ dysfunction criteria (lactate  $\geq 2$  mEq/L or systolic blood pressure  $< 90$  mmHg), were admitted to the study. The following exclusion criteria were applied: 1) pregnant women; 2) patients younger than 18 years; and 3) patients with severe hypotension requiring the immediate use of vasopressor drugs.

Brief medical histories and physical examinations (including body weights) were obtained. All of the patients who met the criteria for sepsis underwent a peripheral venous puncture for blood culture, blood chemistry, blood counts and coagulogram and an arterial puncture for measuring blood gas with lactate. In addition, a urine sample was obtained for urinalysis and culture, a chest radiograph was taken, and other cultures were performed as necessary. Via the venous puncture and at the emergency department physician's discretion, the patients were given their first antibiotic dose

within one hour of the sepsis diagnosis. Patients with systolic blood pressure that was lower than 90 mmHg underwent immediate volume expansion with 30 mL/kg 0.9% saline solution within 30 minutes. For non-hypotensive patients, the venous puncture was maintained with normal saline for volume expansion (similar to the above-described method) at a later time if their plasma lactate levels exceeded 2 mEq/L. Within 10 minutes of the completion of the volume expansion procedure, a fresh arterial blood sample was drawn for blood gas and blood chemistry analysis.

## Physicochemical analysis

We used the following standard equations to calculate the following physicochemical parameters:<sup>(12,14,15)</sup>

1. Standard base excess (SBE van Slyke equation; mEq/L) =  $0.9287 \times (\text{HCO}_3^- \text{ (mEq/L)} - 24.4 + 14.83 \times [\text{pH} - 7.4])$

2. Strong ion difference apparent inorganic (SIDai; mEq/L) =  $\text{Na}^+ \text{ (mEq/L)} + \text{K}^+ \text{ (mEq/L)} + \text{Ca}^{2+} \text{ (mEq/L)} + \text{Mg}^{2+} \text{ (mEq/L)} - \text{Cl}^- \text{ (mEq/L)}$

3. Effective strong ion difference (SIDE; mEq/L) =  $2.46 \times 10^{-8} \times \text{PCO}_2 \text{ (mmHg)} / 10^{\text{pH}} + (\text{albumin (g/dL)}) \times (0.123 \times \text{pH} - 0.631) + (\text{phosphate (mg/dL)} / 3 \times \text{pH} - 0.469)$

4. Strong ion gap (SIG; mEq/L) =  $\text{SIDai} - \text{SIDE} - \text{lactate}$

5. Ionic albumin (mEq/L) =  $10 \times \text{albumin (g/dL)} \times (0.123 \times \text{pH} - 0.631)$

6. Ionic phosphorus (Pi) (mEq/L) =  $(\text{PO}_4 \text{ (mg/dL)} \times 10 / 30.97) \times (0.309 \times \text{pH} - 0.469)$

Through the physicochemical interpretation of the metabolic component of acid-base equilibrium, changes in SBE can be explained by changes in lactate, SIG, SIDai, SIG, albumin and phosphate levels.<sup>(8,9,16-18)</sup> Based on this premise, any change in SBE between the two measurements can be explained by changes in these components; therefore, the SBE change that is ascribable to lactate, SIG, SIDai, albumin and phosphate is the difference between these ionic forms at the two evaluation times. The magnitude of the difference is related to the influence of each variable in relation to the final SBE.<sup>(16,19)</sup> Thus:

1. SBE ascribable to lactate = initial – normal lactate
2. SBE ascribable to SIG = initial – normal SIG
3. SBE ascribable to SIDai = initial – normal SIDai
4. SBE ascribable to albumin = initial – normal ionic albumin
5. SBE ascribable to phosphate = initial – normal ionic phosphorus  
with all of the units in mEq/L.

## Statistical analysis

The number of patients that were needed to find a significant decrease in SBE of at least 4 mEq/L between

the measurements was based on a mean admission SBE of 8 mEq/L with a 3.5 mEq/L standard deviation.<sup>(8)</sup> Based on an alpha of 5% and a power of 80%, a sample size of 8 patients was required. A normal distribution was confirmed with the Shapiro-Silk test, and the data are presented as means  $\pm$  standard deviation. The categorical data are presented as occurrences and percentages. The analysis of the variation between the measured values was performed with the paired Student's *t*-test. The equality of the variance was confirmed by the Levene test.<sup>(20)</sup> The software SPSS 17.0 for Windows (Chicago, Illinois, USA) was used for the calculations.

## RESULTS

Eight patients were studied, and their clinical characteristics, required support and outcomes are shown in table 1. With regard to comorbidity, only one of the patients had systemic arterial hypertension, and the remaining 7 patients were healthy. At admission, the hemoglobin level was  $12 \pm 2$  g/dL, and the white blood cell count was  $15,590 \pm 6,600$  cells/mL. The patients were given a mean volume of  $2,000 \pm 370$  mL of 0.9% saline solution over 30 minutes, as had been predetermined based on their weights.

Table 2 shows the pre- and post-volume expansion vital

**Table 1 – Patient characteristics**

Variable (N = 8)	
Overall characteristics	
Age (years)	58 $\pm$ 13
Gender (M/F)	6 (75) / 2 (25)
APACHE II score	20 $\pm$ 4
Syndrome	
Severe sepsis	5 (63)
Septic shock	3 (37)
Primary infection site	
Respiratory	7 (88)
Urinary	1 (12)
ICU support and outcome	
Mechanical ventilation	3 (38)
Renal replacement	1 (12)
Vasopressors	4 (50)
Inotropes	2 (25)
Antibiotics	8 (100)
ICU length of stay (days)	11 $\pm$ 3
Death	1 (12)

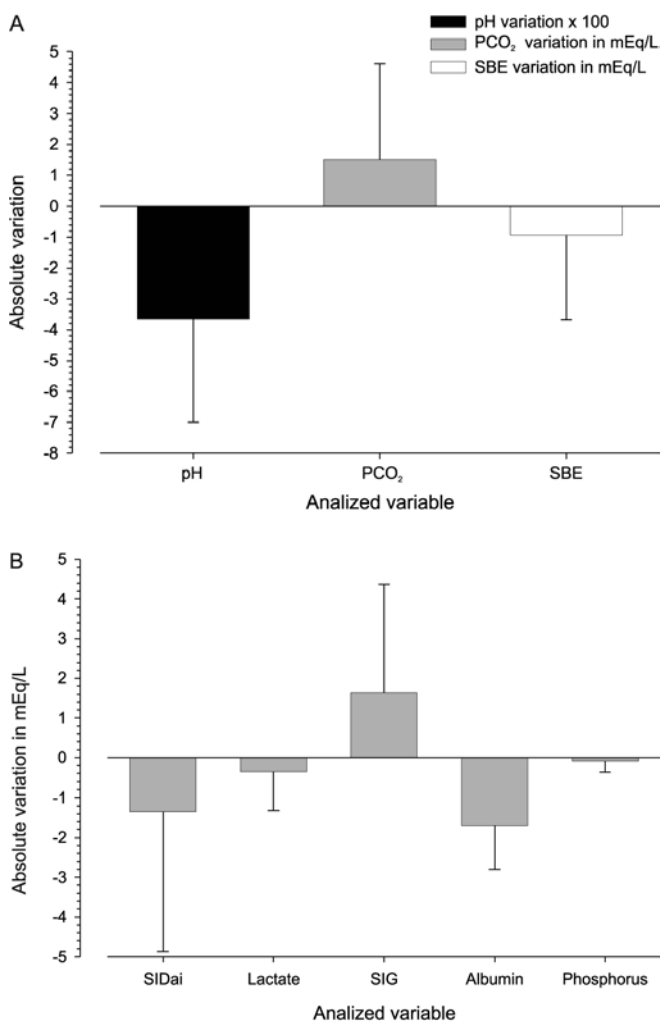
ICU – intensive care unit; APACHE - Acute Physiological and Chronic Health Evaluation. Results are expressed as mean  $\pm$  standard deviation or number of patients (percentage).

**Table 2 – Pre- and post-volume expansion vital signs, blood gas and physicochemical data**

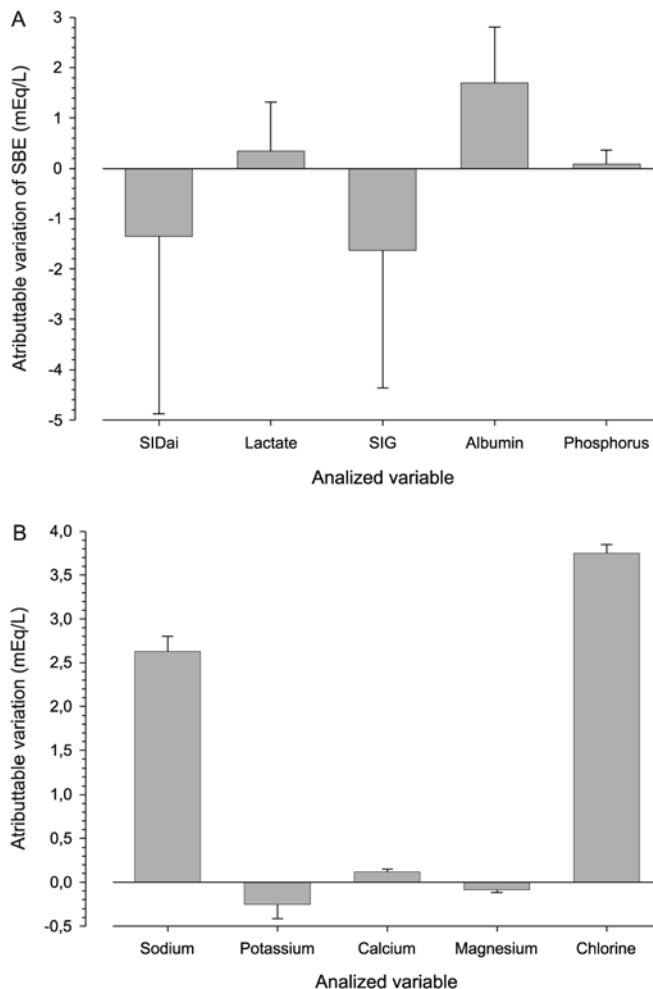
	Pre-volume expansion	Post-volume expansion	p value
Medical data			
Respiratory rate (inspirations/min)	23 $\pm$ 4	25 $\pm$ 7	0.191
Heart rate (beats/min)	107 $\pm$ 17	98 $\pm$ 16	0.014
Mean blood pressure (mmHg)	69 $\pm$ 17	80 $\pm$ 18	0.035
Systolic blood pressure (mmHg)	94 $\pm$ 19	108 $\pm$ 25	0.020
Diastolic blood pressure (mmHg)	57 $\pm$ 16	65 $\pm$ 14	0.077
Axillary temperature (°C)	37.5 $\pm$ 1.4	36.6 $\pm$ 0.6	0.219
Blood chemistry data			
Sodium - mEq/L	135 $\pm$ 6	138 $\pm$ 6	< 0.001
Potassium - mEq/L	4.2 $\pm$ 0.6	3.9 $\pm$ 0.4	0.210
Magnesium - mEq/L	1.80 $\pm$ 0.40	1.78 $\pm$ 0.32	0.485
Calcium - mEq/L	2.46 $\pm$ 0.32	2.70 $\pm$ 0.40	< 0.001
Chloride - mEq/L	103 $\pm$ 10	106 $\pm$ 7	< 0.001
Blood glucose – mg/dL	95 $\pm$ 16	89 $\pm$ 16	0.018
Arterial blood gas			
pH	7.404 $\pm$ 0.080	7.367 $\pm$ 0.086	0.018
PCO <sub>2</sub> – mmHg	30 $\pm$ 5	32 $\pm$ 6	0.215
PO <sub>2</sub> – mmHg	72 $\pm$ 14	73 $\pm$ 13	0.708
O <sub>2</sub> saturation - %	93 $\pm$ 5	91 $\pm$ 5	0.154
SBE - mEq/L	-4.4 $\pm$ 5.6	-6.0 $\pm$ 5.7	0.039
HCO <sub>3</sub> - mEq/L	19 $\pm$ 5	18 $\pm$ 4	0.349
Physicochemical data			
SIDai - mEq/L	40 $\pm$ 5	38 $\pm$ 4	0.318
Lactate - mEq/L	2.4 $\pm$ 1.2	2.1 $\pm$ 0.8	0.347
SIDe - mEq/L	30 $\pm$ 7	27 $\pm$ 7	0.032
SIG - mEq/L	6.1 $\pm$ 3.4	7.7 $\pm$ 4.0	0.134
Albumin – g/dL	3.1 $\pm$ 1.0	2.6 $\pm$ 0.8	0.003
Phosphate – g/dL	3.7 $\pm$ 0.9	3.6 $\pm$ 0.6	0.480

SIDai - strong ion difference apparent, only inorganic component; SIDe - strong ion difference effective; SIG - strong ion gap; SBE - standard base excess. Results are expressed as mean  $\pm$  standard deviation.

signs, blood chemistry, blood gas and physicochemical data. Given the pH drop and SBE drop in association with a non-significant increase in PCO<sub>2</sub> (Table 2 and Figure 1-A) together with changes in several electrolyte and serum albumin levels, figure 1-B was generated to show the mEq/L variation of several SBE components. The influence of each SBE component is illustrated more clearly in figure 2-A in which several components are presented separately (for each determinant, the bar shows the mean SBE that is ascribable to that component). Finally, as the SIDai was highly relevant to pre- and post-volume expansion SBE, Figure 2-B shows the variation of the individual SIDai components.



**Figure 1 – Change in acid-base and physicochemical components between baseline and post-volume expansion.** Panel A shows the absolute change in pH and PCO<sub>2</sub> and Standard Base Excess (SBE). Panel B shows the absolute change in SBE components.



**Figure 2 – Change in metabolic physicochemical components between baseline and post-volume expansion.**

Panel A shows change in the indicated components of the Standard Base Excess (SBE). Panel B shows the change in the indicated components of the apparent inorganic strong ion difference (SIDai).

## DISCUSSION

In this study, a drop in pH was observed in association with an increased PCO<sub>2</sub> and a drop in SBE following normal saline administration (Figure 1-A). This drop in SBE was ascribed to the acidifying power of the SIDai drop and SIG increase, which were counteracted by the alkalinizing effect of the drop in albumin (Figures 1-B and 2-A). Despite the numerical changes in the parameters, only SBE and albumin differed significantly (Table 2). With regard to the non-significant SIDai drop, several electrolyte levels were significantly different between the two assessment times (Table 2); however, as shown in figure 2-B, this variation

was primarily due to significant increases in chloride, sodium and calcium with only slight changes in potassium and magnesium (Table 2).

A drop in pH during the course of severe sepsis and septic shock is common in patients.<sup>(7,8)</sup> Within days, an increase in arterial PCO<sub>2</sub> often occurs.<sup>(8)</sup> In our patient sample, PCO<sub>2</sub> was increased by about 2 mmHg during initial resuscitation (within 30 minutes) despite a stable respiratory rate (Table 2). This finding can be explained, at least in part, by a reduction in anxiety, improved blood pressure (which was significantly increased between the two assessment times; see Table 2) and improved systemic perfusion (which may have optimized the removal of CO<sub>2</sub> from the tissues and, thereby, increased its partial blood pressure).

As measured by SBE, metabolic acidosis worsened significantly; however, as shown in figure 2-A, this drop in SBE could be ascribed to a combination of the SIDai acidifying component and SIG, which were counteracted by the alkalinizing effect of the drop in albumin levels. This drop in SIDai components is classically described as being produced by an increase in serum chloride as a result of volume expansion.<sup>(4-6)</sup> However, in endotoxemic rats, volume expansion explains only 30% of the increase in serum chloride levels, and the remaining increase is probably the result of a compartmental shift from intracellular into extracellular and extravascular into intravascular.<sup>(21)</sup> The lower change in sodium levels may be due to its large volume of distribution and concentration.<sup>(22)</sup> Interestingly, in our patients, we noted an increase in ionic calcium levels that may be explained by the drop in both serum albumin concentration and pH, which would promote a reduction in albumin's affinity for calcium. With regard to ionic calcium, despite its significant change between the two assessment times, this change had little influence on SBE (Figure 2-B).

The increase in unmeasurable anions that was measured with SIG apparently also contributed to the drop in SBE. This finding is difficult to explain but is consistent with the findings of Marques et al.<sup>(23)</sup> in which a chloride reduction from 111 to 107 mEq/L in the dialysis fluid of chronic renal patients was associated with improved SBE because of reduced SIG with no change in SIDai. The authors hypothesized that this finding was due to a compartmental redistribution of chloride and unmeasurable anions, thus causing a Gibbs-Donnan effect, in which weak acids that are composed of macromolecules drive inter-molecular repulsion and prevent their passage through biological membranes.

Another interesting finding in our study was the drop in albumin levels after the initial resuscitation. In previous case studies of critically ill patients in general and in septic patients in particular, albumin levels changed little in the days

following the initial resuscitation.<sup>(7,8,17)</sup> Considering the brief interval between our measurement, the most important factor in generating hypoalbuminemia was likely dilution, although hypoalbuminemia in septic patients has other recognized causes, including a possible imbalance between liver albumin synthesis and loss into the interstitial space due to increased capillary permeability,<sup>(24)</sup> particularly during the acute phase of sepsis,<sup>(25)</sup> in association with reduced lymphatic albumin clearance.

Metabolic acidosis in association with hyperchloremia is common in critically ill patients and is associated with poorer prognosis in critically ill patients in general<sup>(26)</sup> and in septic patients in particular.<sup>(8)</sup> Recently, an interesting notion was proposed in which hyperchloremic acidosis renders the kidneys at least partially incapable of eliminating SIDai (i.e., chloride).<sup>(27)</sup>

Our findings should be interpreted as an explanation of the acid-base changes that follow volume resuscitation. This finding adds no negative ideas related to volume expansion or related to the use of 0.9% saline solution; these results merely concern how the changes should be interpreted and, in the future, how the organ dysfunction responsible for these changes should be addressed.

There were some limitations to this study, including 1) a lack of a control group, 2) a lack of long-term follow-up and 3) a relatively small sample size. However, our primary focus was the physicochemical characterization of volume expansion using normal saline in septic patients, and this goal was met with this study.

## CONCLUSIONS

The initial resuscitation of patients with severe sepsis and septic shock using 30 mL/kg 0.9% saline solution is associated with worsened metabolic acidosis, as assessed with SBE. This worsened SBE is physicochemically complex and may be ascribed to an increase in the levels of unmeasurable anions and chloride with the latter being responsible for the drop in SIDai. The rapid decrease in serum albumin concentration apparently mitigates the acidifying effects of expansion with normal saline.

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## RESUMO

**Objetivo:** O objetivo deste estudo foi caracterizar e quantificar a acidose metabólica causada pela expansão volêmica inicial na reanimação de pacientes com sepse grave e choque séptico.

**Métodos:** Uma coleta de sangue para caracterização físico-química do equilíbrio ácido-básico antes e após a expansão volêmica.

mica com 30 mL/kg de solução salina a 0,9%. O diagnóstico e a quantificação da acidose metabólica foram feitas com o uso do "standard base excess" (SBE).

**Resultados:** Oito pacientes com  $58 \pm 13$  anos e APACHE II de  $20 \pm 4$  foram expandidos com  $2000 \pm 370$  mL de solução salina a 0,9%. Houve queda do pH de  $7,404 \pm 0,080$  para  $7,367 \pm 0,086$  ( $P=0,018$ ) associada a elevação da  $PCO_2$  de  $30 \pm 5$  mmHg para  $32 \pm 2$  mmHg ( $P=0,215$ ) e queda do SBE de  $-4,4 \pm 5,6$  para  $-6,0 \pm 5,7$  mEq/L ( $P=0,039$ ). Esta queda do SBE foi associada ao poder acidificante de dois fatores: elevação não significativa do "strong ion gap" (SIG) de  $6,1 \pm 3,4$  para  $7,7 \pm 4,0$  mEq/L ( $P=0,134$ ) e queda não significativa do "strong ion difference" aparente inorgânico (SIDai) de  $40 \pm 5$  para  $38 \pm 4$  mEq/L

( $P=0,318$ ). Em contraposição, houve queda da albumina sérica de  $3,1 \pm 1,0$  para  $2,6 \pm 0,8$  mEq/L ( $P=0,003$ ), que teve um poder alcalinizante sobre o SBE. A elevação do cloro sérico de  $103 \pm 10$  para  $106 \pm 7$  mEq/L ( $P<0,001$ ) gerou a queda do SIDai.

**Conclusão:** A reanimação inicial de pacientes com sepse grave e choque séptico com 30 mL/Kg de solução salina a 0,9% é associada a piora da acidose metabólica aferida pelo SBE. Esta piora do SBE pode ser atribuída a uma elevação dos ânions não mensuráveis e do cloro sérico.

**Descritores:** Cetose; Unidades de terapia intensiva; Sepse; Cloro; Choque séptico/terapia; Equilíbrio ácido-base; Solução salina hipertônica/uso terapêutico

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