Impact of chloride balance in acidosis control: the Stewart approach in hemodialysis critically ill patients

Alexandre Braga Libório MDa, Cristianne da Silva Alexandre MDa, Danilo Teixeira Noritomi MDb, Lúcia Andrade MD, PhDa, Antonio Carlos Seguro MD, PhDa,*

aDepartment of Nephrology, University of São Paulo School of Medicine, Hospital das Clínicas, São Paulo 01246-903, Brazil
bEmergency Department, University of São Paulo School of Medicine, Hospital das Clínicas, São Paulo 01246-903, Brazil

Received 8 July 2005; revised 12 December 2005; accepted 28 March 2006

Abstract

Background: Metabolic acidosis is highly prevalent in critically ill patients with acute renal failure. Little is known about the mechanisms by which renal replacement therapy intervenes in such cases. The objective of this study is to analyze the role of hemodialysis in acidosis correction in intensive care unit patients, with an emphasis on chloride levels in plasma and dialysate.

Methods: We studied 19 intermittent hemodialysis procedures in 17 acidotic patients. The patients were grouped by procedure type (conventional or sustained low-efficiency dialysis) and by predialysis plasma chloride level (higher or lower than the dialysate chloride concentration). Immediately before and after each procedure, blood samples were collected for biochemical analysis. The Stewart method was used to calculate the strong ion difference and strong ion gap.

Results: The patients presented acidosis related to hyperchloremia, hyperphosphatemia, and high unmeasured anions. Hypoalbuminemia had an alkalinizing effect. Hemodialysis corrected acidosis mainly by reducing phosphate and unmeasured anions. In the group as a whole, chloride levels did not change after dialysis. However, when analyzed according to predialysis plasma chloride, the high-chloride group presented a reduction in plasma chloride, resulting in better base excess improvement (ΔSBE) than in the low-chloride group. Among the determinants of acid-base status, the only factors correlating with ΔSBE were Δ strong ion gap and Δ chloride.

Conclusion: The serum chloride/dialysate chloride relationship during hemodialysis has an important impact on acidosis control.

© 2006 Elsevier Inc. All rights reserved.

Keywords:
- Chloride balance;
- Stewart approach;
- Hemodialysis

1. Introduction

Acid-base disorders continue to be a challenge in clinical practice, especially in the treatment of severely ill patients, in whom these disorders can be quite complex. Metabolic acidosis is one of the most common acid-base disorders...
occurring in the intensive care unit (ICU) [1], mainly when acute renal failure (ARF) is also present [2].

In the early 1980s, Peter Stewart [3] proposed an alternative approach to acid-base physiology and disorders. The Stewart approach has evolved through modifications made by Watson [4], Fencl and Rosiing [5], Figge et al [6], and Kellum et al [7]. In this approach, plasma pH is determined by 3 independent variables: arterial carbon dioxide tension (PaCO₂); strong ion difference (SID), which is the difference in charge between the strong cations and strong anions in plasma; and total plasma concentration of nonvolatile weak acids, mainly albumin and inorganic phosphate. Using this approach, bicarbonate is considered a dependent variable.

Rocktaeschel et al [8] showed that patients with ARF present severe metabolic acidosis because of increased strong ion gap (SIG), determined by calculating levels of unmeasured anions, phosphate, and lactate. Continuous venovenous hemofiltration has been shown to reverse acidosis by decreasing the SIG and the levels of phosphate and chloride [9]. In 2 recent reviews, Leblanc [10,11] suggested that intermittent hemodialysis corrects metabolic acidosis by restoring normal SID apparent (SIDa) and decreasing SIG.

Another important aspect of hemodialysis management is the composition of the dialysate and replacement fluid. In particular, the choice of buffer has elicited a considerable amount of interest. Surprisingly, fewer data are available on chloride concentration. Most commercially available hemodialysis solutions contain supraphysiological concentrations of chloride [12].

Because the chloride ion is an etiologic factor in acidosis, we decided to use the Stewart method of assessing acid-base status to evaluate a prospective cohort of critically ill patients with ARF or chronic renal failure (CRF). All patients were on intermittent classic hemodialysis or intermittent sustained low-efficiency dialysis (SLED), and the chloride level of the dialysate was 109.5 mEq/L.

2. Methods

We conducted a prospective study of 19 consecutive critically ill patients. Two patients presented hemodynamic instability, resulting in the discontinuation of the procedure, and were therefore excluded. We analyzed 19 sessions of intermittent hemodialysis performed during June and July of 2004. Inclusion criteria were renal failure, metabolic acidosis, standard base excess (SBE) less than −5 mEq/L, and a need for dialysis therapy. Exclusion criteria included severe hyponatremia (Na⁺ <125 mEq/L) and severe hypernatremia (Na⁺ >155 mEq/L). Only 1 patient was excluded. The decision to perform dialysis was made by an attending nephrologist, who also selected the dialysis method. Demographic data were obtained from the ICU staff. Because the study protocol did not alter the course of treatment in any way (blood sample is routinely drawn by the ICU staff to assess Kt/V), it was unnecessary to obtain written informed consent from the participants. The local ethics committee of the institution approved the study design.

2.1. Description of hemodialysis techniques

Patients were submitted to conventional hemodialysis or SLED. Vascular access was obtained by insertion of a 12-gauge double-lumen central venous catheter. In conventional hemodialysis sessions, blood flow and dialysate flow were set to 250 to 300 and 500 mL/min, respectively, and the duration was 4 hours. In SLED sessions, blood flow and dialysate flow were set to 170 to 250 and 300 mL/min, respectively, and the duration was 8 hours. For both methods, the ultrafiltration rate was determined by an attending nephrologist. When feasible, heparin (1000 IU/h) was used to prevent clotting in the extracorporeal circuit.

Dialysate composition was fixed: sodium, 138 mEq/L; potassium, 2.0 mEq/L; calcium, 3.5 mEq/L; magnesium, 1.0 mEq/L; chloride, 109.5 mEq/L; acetate, 3 mEq/L; and bicarbonate, 32 mEq/L. None of the patients required potassium supplementation in the dialysate. Dialysis was performed using a Fresenius 4008S (Fresenius, Bad Homburg, Germany). A low-flux filter with a surface area of 1.5 m² (CA-150; Baxter Healthcare, Deerfield, Ill) was used in all procedures.

2.2. Blood samples

Blood samples were collected immediately before and 3 minutes after the procedure. Therefore, in the biochemical analyses, the rebound phenomenon was not taken into account. All samples were analyzed at the on-site central laboratory. Samples were not stored on ice. A Cobas Integra 700 biochemical analyzer (Roche Diagnostics GmbH, Mannheim, Germany) and standard reagents were used to measure multiple biochemical variables, including urea, sodium, potassium, calcium, phosphate, magnesium, chloride, and albumin. Arterial blood gases and lactate were analyzed using an AVL OMNI blood gas analyzer (Roche). Bicarbonate and SBE were determined according to the Henderson-Kasselbach and Van Slyke equations, respectively.

2.3. Interpretation of quantitative acid-base analysis

Quantitative physicochemical analysis of the results was performed using the Stewart model. This model involves the following principles:

1. SIDa = [Na⁺] + [K⁺] + [Ca²⁺] + [Mg²⁺] − [Cl⁻] − [lactate⁻], where all concentrations are expressed in milliequivalent per liter;
2. SID effective (SIDe), representing the effect of weak acid on the balance of electrical charges in plasma: SIDe = (2.46 × 10⁻³) × (PaCO₂/10⁻¹⁸) + (albumin...
\[
\text{pH} = 0.631 + (\text{phosphate} \times 0.309 \times [\text{pH} - 0.469]),
\]
where \(P_{\text{aCO}_2}\) is expressed in millimeter mercury, albumin in grams per liter, and phosphate in millimoles per liter;

3. \(\text{SIG} = \text{SIDa} - \text{SIDe},\) the product representing the unmeasured anions (sulfate, ketoacids, citrate, pyruvate, acetate, and others);

4. Anion gap: \([\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-].\)

### 3. Results

#### 3.1. Demographic features

As shown in Table 1, the median age was 67 years (interquartile range, 50-72 years). Only 3 patients were under treatment with vasopressors during the study period. Before the study onset, 5 patients were on continuous renal replacement therapy because of hemodynamic instability, although they had not recently undergone dialysis (at least 24 hours). In all cases, dialysis was indicated because of uremia or hypervolemia (or both), and was in no cases because of acidosis alone. All patients were oliguric (diuresis <400 mL per 24 hours) on the day of the hemodialysis treatment. The overall 28-day mortality was 47.36%.

#### 3.2. Characterization of acidosis

Before receiving hemodialysis, all patients presented metabolic acidosis. Analysis according to the Stewart methodology revealed that the main underlying mechanisms of metabolic acidosis were hyperchloremia, hyperphosphatemia, and additional unmeasured anions (high SIG) (Table 2). Considering the fact that the normal plasma level of albumin is 3.5 mg/dL, the hypoalbuminemia presented by the patients contributed to a median alkalinizing effect of 3 mEq/L. The predialysis level of serum lactate was only slightly elevated (Table 2).

#### 3.3. Conventional hemodialysis vs SLED

There was no significant difference between conventional hemodialysis and SLED dialysis in terms of the

### Table 1

<table>
<thead>
<tr>
<th>Demographic features and diagnosis in the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>APACHE II score</td>
</tr>
<tr>
<td>Urea reduction rate (%)</td>
</tr>
<tr>
<td>28-day mortality</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Metabolic determinants of predialysis and postdialysis pH in all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Bicarbonate</td>
</tr>
<tr>
<td>Sodium</td>
</tr>
<tr>
<td>Chloride</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Lactate</td>
</tr>
<tr>
<td>SIG</td>
</tr>
<tr>
<td>Phosphate</td>
</tr>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>SBE</td>
</tr>
<tr>
<td>to −7.0</td>
</tr>
<tr>
<td>Anion gap</td>
</tr>
</tbody>
</table>

Data are expressed as median and interquartile range at milliequivalent per liter. Albumin data were transformed into milliequivalent per liter according to the following formula: \(10 \times \text{albumin (g/dL)} \times (0.123 \times \text{pH} - 0.631).\) ns indicates not significant.
predialysis and postdialysis features of acid-base status (data not shown).

3.4. Effects of intermittent dialysis on acid-base status

As shown in Table 2, hemodialysis corrected acidemia, as evidenced by the difference between predialysis and postdialysis median pH. The median SBE level also increased after hemodialysis. The improvement in the SBE levels was accompanied by a decrease in SIG and a decrease in serum phosphate concentration. Median serum levels of calcium also increased after hemodialysis, and this increase could have an alkalinizing effect. The changes in SIDa and its other determinants (sodium, magnesium, chloride, and lactate) were not statistically significant. With intermittent hemodialysis, there was a measurable, although less than statistically significant, difference between predialysis and postdialysis median serum chloride levels. However, serum levels of chloride before and after hemodialysis were heterogeneous among individual patients.

Intermittent saline flushes were used during the hemodialysis procedure. The median total amount of saline used was 900 mL (interquartile range, 600-1300 mL), with no differences between SLED and conventional dialysis or between the High-Cl and Low-Cl groups. The median ultrafiltration per hemodialysis procedure was 950 mL (interquartile range, 600-1400 mL), and there were no differences between SLED and conventional dialysis or between the High-Cl and Low-Cl groups (data not shown).

3.5. Influence of serum chloride level balance on metabolic acidosis

When we compared the High-Cl group to the Low-Cl group, we observed that the median delta (Δ) increase in SBE levels was greater in the High-Cl group (n = 8) than in the Low-Cl group (n = 11): 9.49 mEq/L (interquartile range, 6.9-10.8 mEq/L) vs 4.73 mEq/L (interquartile range, 2.8-8.47 mEq/L), \( P = .0006 \) (Fig. 1). The predialysis degree of metabolic acidosis was comparable between the 2 groups (Fig. 1).

Analyzing the factors responsible for this difference, the only statistically different alkalinizing factor was the Δ chloride level (Fig. 2). The Spearman correlation analysis was used to describe the relationship between the Δ SBE and the Δ of each of the pH determinants (sodium, chloride, potassium, calcium, phosphate, magnesium, lactate, and SIG). We found Δ SBE to correlate most

![Graph expressing changes during dialysis that favor acidosis correction. Data are shown in mEq/L and express predialysis and postdialysis values (Δ). Difference is significant only for chloride levels (\( P = 0.01 \))](image)

**Fig. 1** Predialysis SBE and Δ SBE in the Low-Cl and High-Cl groups.

![Comparison of alkalinizing factors during intermittent dialysis in the Low-Cl and High-Cl groups.](image)

**Fig. 2** Comparison of alkalinizing factors during intermittent dialysis in the Low-Cl and High-Cl groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation (Spearman)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Sodium</td>
<td>−0.2737</td>
</tr>
<tr>
<td>Δ Chloride</td>
<td>−0.7621*</td>
</tr>
<tr>
<td>Δ Potassium</td>
<td>−0.2208</td>
</tr>
<tr>
<td>Δ Calcium</td>
<td>0.2887</td>
</tr>
<tr>
<td>Δ Magnesium</td>
<td>0.0960</td>
</tr>
<tr>
<td>Δ Lactate</td>
<td>0.1318</td>
</tr>
<tr>
<td>Δ SIDa</td>
<td>0.3877</td>
</tr>
<tr>
<td>Δ SIG</td>
<td>−0.4842**</td>
</tr>
<tr>
<td>Δ Phosphate</td>
<td>−0.0570</td>
</tr>
</tbody>
</table>

* \( P < .0001 \).
** \( P = .01 \).
closely with $\Delta$ chloride and $\Delta$ SIG (Table 3, Fig. 3). Fig. 4 shows individual chloride values as well as the dialysis procedure for each single patients before and after the dialysis procedure.

4. Discussion

Our data demonstrate that acidosis correction after dialysis can differ depending on predialysis levels of serum chloride and their relationship to the chloride concentration of the dialysate. We found that serum chloride concentrations lower than that of the dialysate can actually perpetuate acidosis. It is widely accepted that dialysis plays an important role in correcting acidosis. Until recently, however, it was difficult to determine which of the factors affected by the dialysis had the most influence on acidosis. The Stewart approach provides better understanding and allows quantitative analysis of the role of dialysis in controlling the acid-base balance. In this modern approach, 3 factors are considered important for acidosis control in dialysis: unmeasured anion and phosphate clearance, as well as the restoration of normal SIDa.

In our study, we found that intermittent hemodialysis provides reasonable control of SIG and hyperphosphatemia. According to the Stewart approach, these 2 factors are, together, 70% responsible for acidosis. A high-flux dialyzer can provide better phosphate removal and, consequently, better acidosis control. Although the acidosis seen in the patients studied had a significant hyperchloremia component, the improvement in SBE was comparable to the reduction in anion gap, that is, hemodialysis corrected only the high-anion gap component of the acidosis. In fact, some patients (the Low-Cl group patients) presented an increase in serum chloride levels, and dialysis failed to restore normal serum chloride levels in these patients. Therefore, in these cases, the hemodialysis corrected normochloremic acidosis, with high SIG, and induced hyperchloremic acidosis. Surprisingly, hyperchloremia occurred after hemodialysis in 12 of the 19 procedures performed. Hyperchloremia must therefore be seen as an etiologic factor in perpetuating acidosis, rather than simply a mechanism to compensate for hypoubluminemia, because patients continue to present metabolic acidosis after dialysis. Postdialysis acidosis can be related to causes other than the dialysate chloride concentration. Such causes may include dialysis efficiency and the high production of unmeasured ions in critically ill patients. The last 2 factors are probably responsible for the high SIG.

4.1. Variations in dialysate chloride levels

The strong correlation between better control of metabolic acidosis and the serum chloride/dialysate chloride relationship prompted us to give special attention to the dialysate composition. In reviewing the literature, we found that dialysate chloride concentrations ranged from 90 to 125 mEq/L [10]. This wide range can account for the heterogeneous results in acidosis control seen among these studies, especially in those comparing lactate to bicarbonate buffers [12-16].

The most suitable approach would probably be to individualize dialysate SID and chloride based on patient’s SID and chloride and albumin levels. Reducing chloride in dialysate involves augmenting another anion, principally bicarbonate. Although further studies are warranted, this approach could avoid the negative effects of a low serum chloride/high dialysate chloride relationship, the reduction in serum SIDa, and the perpetuation of acidosis. The relationship between plasma and dialysate must also take account the Gibbs-Donnan equilibrium condition, which predicts a greater loss of exchangeable anions (such as chloride) in plasma due to the presence of albumin (an unexchangeable anion in plasma) [17].

One limitation of the present study was that it did not randomize. More importantly, dialysates with different chloride concentrations were not evaluated. In addition, we used only intermittent hemodialysis, which, unlike continuous renal replacement therapy, is not sustained over a 24-hour period. Furthermore, we were unable to determine whether there was any rebound effect related to unmeasured...
anions, phosphate, and acetate. Such a rebound effect might have affected acid-base status.

5. Conclusion

Hyperchloremic acidosis is a common and significant risk factor for morbidity and mortality in critically ill patients with ARF. In the present study, we have shown, for the first time, the effect that chloride ion concentrations in dialysate have on such acidosis. Our results demonstrate that serum chloride levels play a heterogeneous and important role in determining the effects of dialysis on acid-base status, and that the relationship between serum chloride and dialysate chloride concentration is strongly correlated with the correction of metabolic acidosis.

Acknowledgments

Dr Alexandre Braga Libório and Dr Cristianne da Silva Alexandre received financial support from the Fundação do Desenvolvimento Administrativo do Estado de São Paulo (FUNDAP, Foundation for Administrative Development in the State of São Paulo). The authors would like to thank the intensive care unit staff for their excellent assistance.

References