OPEN

Chloride Ion Is Not the Enemy

Jesús Salvador Sánchez Díaz, MD, MSc[1]

Karla Gabriela Peniche Moguel, MD[1]

Jesús Emmanuel Betamcourt Vera, MD[2]

Luis del Carpio Orantes, MD[3]

Enrique Monares Zepeda, MD[4]

Orlando Rubén Perez Nieto, MD[5]

Eder Ivan Zamarron Lopez, MD[6]

Ernesto Deloya Tomas, MD[5]

Diego Escarraman Martinez, MD, MSc[7]

Manuel Alberto Guerrero Gutierrez, MD[8]

To the Editor:

We have read the article by Kimura et al (1) with exceptional interest published in the recent issue of *Critical Care Explorations*. It should be considered that not all anions and cations are measured in daily clinical practice in seriously ill patients, of the measured ions sodium (Na^+) represents the highest percentage of cations and chloride (Cl^-) of anions. The negative charge of Cl^- allows it to associate with Na^+ and be co-responsible for maintaining serum osmolality and Cl^- levels are usually regulated by those processes that affect Na^+, associating the changes of one to the modifications of the other (2), so these ions must be interpreted as a ratio and not as an absolute value. The Na^+/Cl^- ratio can be understood through Stewart's model, which refers to six main disorders of the acid-base state (3) (**Fig. 1**):

1) Acidosis due to increased Pco_2.
2) Acidosis due to a decrease in strong ion difference apparent: hyperchloremia, hyponatremia (increased water).
3) Acidosis due to increased total weak nonvolatile acids (ATOT): hyperphosphatemia, hyperalbuminemia.
4) Alkalosis due to decrease in Pco_2.
5) Alkalosis due to increased strong ion difference apparent (SIDa): hypochloremia, hypernatremia (decreased water).
6) Alkalosis due to reduction of ATOT: hypophosphatemia, hypoalbuminemia.

In this approach, the SID is considered as part of the evaluation of metabolic disorders, its increase can be interpreted as metabolic alkalosis and its decrease as metabolic acidosis.

The sodium-chloride difference (Na^+/Cl^-) can be used as a substitute for SIDa ($R = 0.973$) in critically ill patients with a cutoff point less than or equal to 34 mEq/L for the diagnosis of metabolic acidosis and greater than 38 mEq/L for alkalosis metabolic (4).

The chloride/sodium index (Cl^-/Na^+) can also replace SIDa ($R = 0.959$) with a cutoff point greater than 0.77 for metabolic acidosis and less than 0.75 for metabolic alkalosis (5).

In 2015 in our ICU, we used the Na^+/Cl^- difference to predict mortality in patients with septic shock, the cutoff point was less than 31 mEq/L with area under the curve (AUC) 0.83 (95% CI, 0.67–0.93; $p = 0.05$), sensitivity 87%, specificity 57%; the multivariate analysis showed relative risk 1.59 (95% CI, 1.07–2.36; $p = 0.02$); and the need for renal replacement therapy (RRT) was not statistically significant (6). Low and high values, compared with normal values (32–34 mEq/L) of the difference Na^+/Cl^- are associated with greater acute kidney injury (AKI) and greater mortality in critically ill patients. These findings suggest that the Na^+/Cl^- difference is a better predictor of ICU outcomes because it evaluates the "Cl^- ratio" and not an absolute value (1). Furthermore, the adverse effects of Cl^- also depend on the serum change (Δ) through time. In our ICU, we evaluated the chlorine delta (ΔCl^-) at 24 hours of admission, the cutoff point greater than

DOI: 10.1097/CCE.0000000000000339

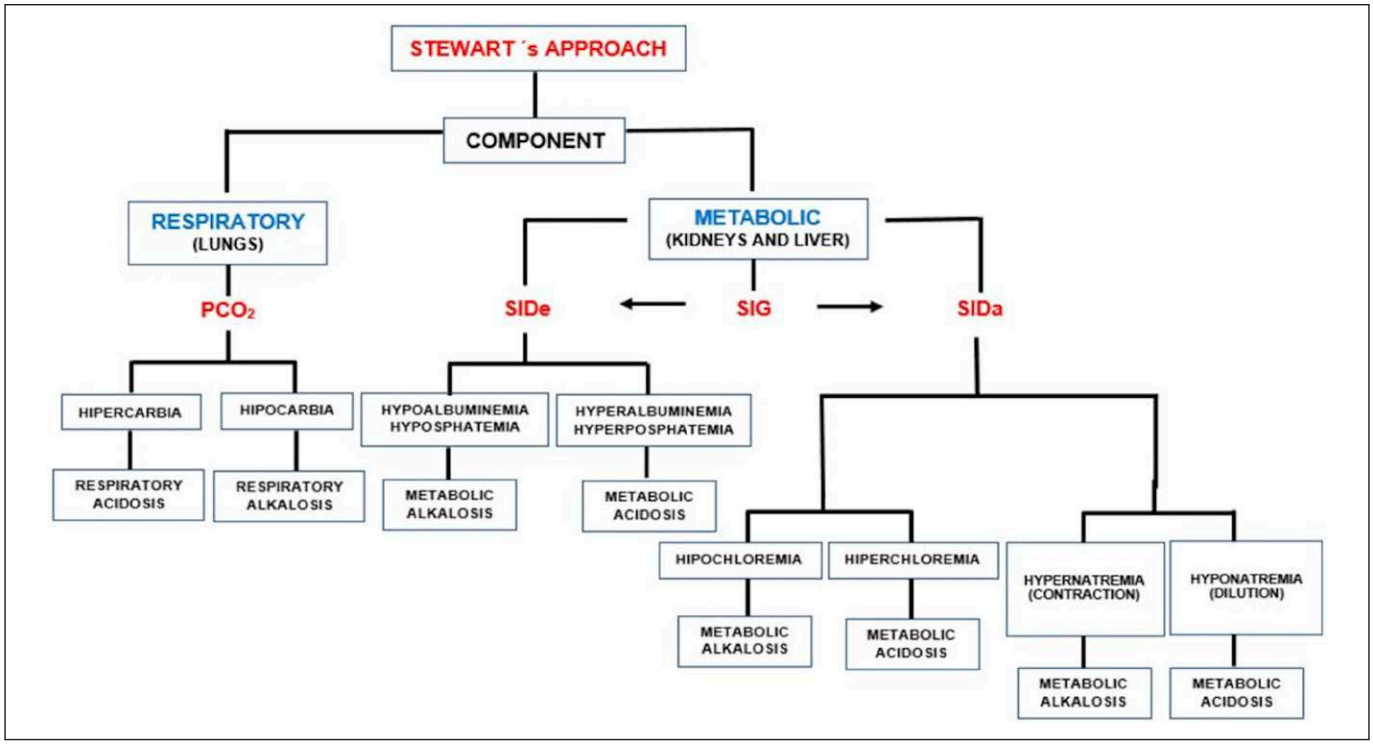

Figure 1. Stewart's approach for acid-base disorders. SIDa = strong ion difference apparent, SIDe = strong ion difference effective, SIG = strong ion gap.

or equal to 4 mEq/L with AUC 0.681 (95% CI, 0.557–0.805; $p = 0.009$), sensitivity 56%, specificity 74%, positive predictive value 64%, and negative predictive value 67%; increasing the risk of death 3.6 times (7).

The difference Na^+/Cl^- high is consistently correlated with Cl^- low and metabolic alkalosis; on the other hand, the difference Na^+/Cl^- low correlates with Cl^- high and metabolic acidosis (8). This occurs because Cl^- is reabsorbed and excreted mainly in the proximal tubule in inverse proportion to bicarbonate (Hco_3^-): if there is hypochloremia, the kidneys retain Hco_3^- producing metabolic alkalosis, on the contrary, hyperchloremia leads to a metabolic acidosis due to renal elimination of Hco_3^-. Over time, we have seen Cl^- as a "villain," but today, we know that patients with hypochloremia (< 96 mEq/L) have a higher risk of AKI than patients with hyperchloremia (> 111 mEq/L) with odds ratio (OR), 2.74; 95% CI, 1.19–6.32; $p = 0.02$ and OR, 1.26; 95% CI, 0.53–3.01; $p = 0.60$, respectively. There is also a greater risk (OR, 5.12; 95% CI, 2.56–10.23; $p \leq 0.001$) of incomplete renal recovery after RRT compared with patients with hyperchloremia (OR, 2.53; 95% CI, 1.25–5.13; $p = 0.01$) (9). Hyperchloremia in most patients is iatrogenic and can be avoided, the reason for this is the increased risk of death (OR, 2.50; 95 CI, 2.01–3.12; $p \leq 0.001$) that this entails (10).

The understanding of the metabolic alterations caused by dyschloremia is limited when we use the Henderson-Hasselbalch model since it does not consider all the factors that influence acid-base alterations, being Hco_3^- a "simple" variable to explain such a complex problem. The principle of electroneutrality (relationship between Na^+ and Cl^-) of the Stewart model allows to better evaluate these alterations, but not only that, it could determine what type of solution we should use, for example, if the difference between positive and negative charges of the solution (Hartmann: Na^+ 131 + K^+ 5 + Ca^+ 2 – Cl^- 111 = 27) is greater than the standard bicarbonate (Hco_3^- std) of the blood gas, the pH and excess base (EB) of the patient will increase, but if the difference between the positive and negative charges of the solution (saline 0.9%: Na^+ 154/Cl^- 154 = 0) is less than the Hco_3^- std of the blood gas, the pH and EB will decrease; finally, if the difference between the positive and negative charges of the solution are similar to the Hco_3^- std of the blood gas and the patient's pH and EB will not change (this solution does not appear to exist). The Na^+/Cl^- index could be another option in making decisions regarding what

type of liquid to use, taking into account that the normal Na^+/Cl^- index in the blood is 1.3 (Na^+ 140/Cl^- 108 = 1.296), considering that solutions with Na^+/Cl^- index less than or equal to 1 tend to cause metabolic acidosis and those with Na^+/Cl^- index greater than or equal to 1 metabolic alkalosis (10). Finally, the adverse effects of dyschloremia can appear with normal or abnormal values of Cl^- depending on the relationship with Na^+. Metabolic acidosis or alkalosis can be present even with normal Cl^- values depending on the amount of Na^+.

1 *Department of Critical Care, Hospital General de PEMEX, Veracruz, México*

2 *Department of Critical Care, Hospital de Especialidades No. 14, UMAE 189, IMSS Veracruz, México*

3 *Department of Critical Care, Hospital General de Zona No. 71, IMSS Veracruz, México*

4 *Department of Critical Care, Medical Center ABC, Mexico City, Mexico*

5 *Department of Critical Care, Hospital General San Juan del Rio, San Juan del Rio, Mexico*

6 *Department of Critical Care, CEMAIN Hospital, Tampico, Mexico*

7 *Department of Anesthesiology, National Medical Center IMSS "La Raza," Mexico City, Mexico*

8 *Department of Critical Care, Instituto Nacional de Cancerologia, Mexico City, Mexico*

The authors have disclosed that they do not have any potential conflicts of interest.

REFERENCES

1. Kimura S, de la Hoz MAA, Raines NH, et al: Association of Chloride Ion and Sodium-Chloride Difference With Acute Kidney Injury and Mortality in Critically Ill Patients. *Crit Care Explor* 2020; 2:e0247
2. Bandak G, Kashani KB: Chloride in intensive care units: A key electrolyte. *F1000Res* 2017; 6:1930
3. Deutschman CS, Neligan PJ: *Evidence-Based Practice of Critical Care*. Third Edition. Elsevier, 2019, pp 408–417
4. Mallat J, Barrailler S, Lemyze M, et al: Use of sodium-chloride difference and corrected anion gap as surrogates of Stewart variables in critically ill patients. *PLoS One* 2013; 8:e56635
5. Thongprayoon C, Cheungpasitporn W, Cheng Z, et al: Chloride alterations in hospitalized patients: Prevalence and outcome significance. *PLoS One* 2017; 12:e0174430
6. Cortes-Roman JS, Sanchez-Diaz JS, Garcia-Mendez RC, et al: Diferencia sodio-cloro e indice cloro/sodio como predictores de mortalidad en choque septico. *Med interna Mex* 2017; 33:335–343
7. Kee YK, Jeon HJ, Oh J, et al: Dyschloremia is associated with failure to restore renal function in survivors with acute kidney injury: An observation retrospective study. *Sci Rep* 2020; 10:19623
8. Martinez-Rojas M, Sánchez-Díaz JS, Peniche-Moguel KG, et al: Delta de cloro (ΔCl-) serico como pronostico de mortalidad en pacientes con choque séptico. *Med Crit* 2019; 33:66–72
9. Thongprayoon C, Cheungpasitporn W, Petnak T, et al: Hospital-acquired serum chloride derangements and associated in-hospital mortality. *Medicines (Basel)* 2020; 7:38
10. Sanchez-Diaz JS, Monares-Zepeda E, Meneses-Olguin C, et al: Soluciones balanceadas: Cloro el «nuevo villano». *Med Crit* 2017; 31:152–158