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WHAT'S NEW IN INTENSIVE CARE

The Janus faces of bicarbonate therapy in the ICU: con

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Metabolic acidosis is common in critically ill patients and is associated with worse outcomes [1, 2]. Acidemia may lead to decreased myocardial contractility, decreased potency of catecholamine vasopressors and decreased blood pressure [3], although the clinical significance of these effects may be variable. The role of sodium bicarbonate in treating metabolic acidosis, however, has been controversial [4].

Most medical textbooks state or imply that among the buffer systems, the bicarbonate buffer system is dominant.

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-.$$

Because two components in this system are independently acted on by the lungs (excreting CO_2) and the kidneys (filtering and reclaiming bicarbonate), clinicians often assume that these species are independently regulated and that we can affect changes in one without the other. However, these species are in equilibrium and in the presence of carbonic anhydrase, conversion between CO_2 and H_2CO_3 occurs rapidly. Given that an average person exhales about 900 g of CO_2 per day (corresponding to about 850 mmol/h), any administered bicarbonate is rapidly exhaled as CO_2.

How then does sodium bicarbonate result in a change in bicarbonate concentration when the bicarbonate is rapidly converted to CO_2 and excreted by the lungs? The answer is that it is not bicarbonate but Na^+ (or more often lack of Cl^-) that matters. This is because the total concentration of strong cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) exceeds the total concentration of strong anions (Cl^-, $Lactate^-$) in blood plasma (Fig. 1). To preserve electroneutrality, the strong ion difference (SID) is balanced by weak acids (predominantly bicarbonate, albumin and phosphate) [5]. Normal SID is approximately 40 mEq/L. In the open system, rather than bicarbonate dictating pH, both are determined by a combination of SID, pCO_2 and total concentration of non-volatile weak acids. Any decrease in SID decreases pH and an increase in SID increases pH. The most common way, at least in North America, to administer bicarbonate is by mixing three ampules of sodium bicarbonate (50 mmol each) in 1 L D5 W solution. The resultant solution contains 150 mmol of Na in 1150 mL of water or 130 mmol/L and no Cl. The effect of administering this solution is to increase the SID—although there is a small decrease in Na, there is a much larger decrease in Cl.

However, the efficacy of bicarbonate infusions for improving physiological outcomes has been unclear in both experimental and clinical studies. Pigs receiving L-lactic acid infusion to induce metabolic acidosis failed to demonstrate any benefit of sodium bicarbonate administration in increasing myocardial contractility [6]. Similarly, patients with metabolic acidosis (pH 7.22) in a surgical ICU showed no benefit of sodium bicarbonate over saline in improving cardiac output [7]. Infusion of sodium bicarbonate has also been shown to increase lactate production in experimental models due to stimulation of glycolysis [8].

However, renal replacement therapy is frequently initiated to correct refractory acidemia using high bicarbonate dialysate solutions (e.g. 40 mmol/L). Concern has been raised about the potential to worsen hypercapnea in patients with limited ventilation [9], but this effect is rather modest. For example, during CRRT net bicarbonate gain is only 90–100 mmol/h. Even if minute ventilation is fixed this additional load represents < 10% of CO_2

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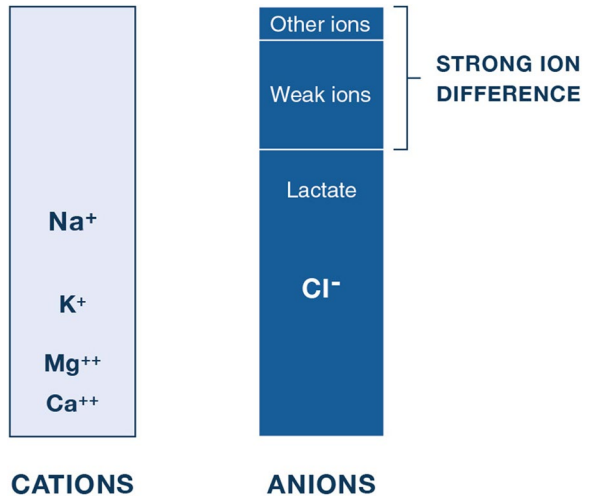

Fig. 1 Strong ion difference

production. Of course, there are clinical scenarios where even this amount would be undesirable—for example, a patient on the brink of respiratory failure.

As such the key to correcting acidemia in critically ill patients is to identify and treat the underlying cause. For example, improving tissue perfusion and treating sepsis with antibiotics and source control for lactic acidosis [10]. The use of bicarbonate infusions or even renal replacement therapy are, at best, adjunct therapies to buy time for the underlying condition to be treated. Although carefully selected patients may benefit from such therapy, the average patient will not. Finally, increasing SID can lead to alkalemia (overshoot alkalosis) once the underlying cause of acidosis is corrected. If this happens rapidly, it can precipitate seizures.

Given these considerations and the troubled history of bicarbonate therapy, the secondary outcomes of a recent multicenter trial were surprising [11]. In this trial, hypertonic (4.2%) sodium bicarbonate solution was administered to critically ill patients to keep arterial pH > 7.30. There was no difference in the primary outcome, a composite of all-cause mortality and presence organ failure (71% vs 66%, $p = 0.24$). However, initiation of renal replacement therapy (RRT) during the ICU stay was lower among patients in the interventional arm (35% vs 52%, $p < 0.001$). In addition, there was a marginal benefit in a predefined subgroup of patients with AKI stage 2 or higher on admission (70% vs 82%, $p = 0.0462$).

These results should be interpreted in light of some significant limitations. First, the trial was unblinded, and did not have a placebo or control intravenous solution for patients randomized to the control group. Lack of blinding particularly complicates the use of RRT, which was left to clinical discretion. Second, the trial size was based on the entire population and was powered to include an interim analysis with a split p value (0.03 in the final analysis). Neither of these conditions were imposed on the AKI subgroup. As always, secondary endpoints in even "pre-defined" subgroups should be treated with caution and are more hypothesis generating than definitive.

Finally, unlike the 1.1–1.3% solutions used in the US, the trial used a 4.2% concentration (500 mmol/L) in 125–250 mL infusions given over 30 min up to 1 L per day which is a common practice style in France [2]. For context, a 250 mL infusion of a 4.2% sodium bicarbonate (or 1 L of 1.3%) would be expected to increase the SID (equivalent to a change in base deficit) by 3 mEq/L. This rather small effect has limited plausibility as a "life-saving" therapy. Indeed, a recent observational study including 3406 patients with 836 receiving bicarbonate therapy, after adjusting for potential confounders, found no evidence that IV sodium bicarbonate was beneficial for patients with acute kidney injury and acidosis [12]. Although again, even this study suggested potential beneficial effects in some highly selected subgroups. Thus, we can likely expect further experimental trials in this area.

In conclusion, the debate for using sodium bicarbonate therapy in patients with metabolic acidosis continues. The physiologic rationale for using sodium bicarbonate is influenced by multiple factors including the etiology of the acid–base disorder, the ability to control the underlying disease process and the patients' ability to cope with the fluid and carbon dioxide load delivered with sodium bicarbonate therapy. Our recommendation is to use sodium bicarbonate in the absence of renal replacement therapy selectively, if at all, and only with consideration of the above factors.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

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