The End of the Bicarbonate Era? A Therapeutic Application of the Stewart Approach

Critically ill patients frequently present with disorders of acid–base homeostasis (1), making arterial blood gas interpretation a cornerstone activity in the clinical assessment of patients by intensivists. Many of us are unaware that we've been taught to interpret acid–base homeostasis in the "bicarbonate era" (2), where a focus on the Henderson-Hasselbalch equation for dissociation of carbon dioxide has led us to believe that bicarbonate is a major determinant of acid–base status (3). However, when we try to understand some of the commonly encountered acid–base abnormalities in critical illness, such as hyperchloremia (4), the Henderson-Hasselbalch equation leaves us yearning for a better explanation.

Forty years ago, the Canadian physiologist Peter Stewart provided a better explanation. He described an approach to understanding acid–base in which bicarbonate is not the major determinant of acid–base status (5). Although it is referred to as the "modern" approach (2), Stewart's explanation incorporated time-tested concepts of physical chemistry, such as conservation of mass, dissociation of electrolytes, and electroneutrality, some of which date back to the 18th century (6). Therefore, it is perhaps more accurate to refer to Stewart's work as the physicochemical approach. Stewart applied these physicochemical principles by using simple algebra to demonstrate that plasma pH (and bicarbonate concentration) is determined by the P_{CO_2}, the strong ion difference, and the concentration of weak acids (primarily albumin and phosphate).

The strong ion difference in plasma is determined by the relatively higher concentration of sodium compared with chloride, and the difference is typically about 40 mEq/L (5). The electroneutrality of plasma is maintained because the charge gap between these two strong ions is made up by the dissociation of weak acids into their respective anions, including the dissociation of dissolved carbon dioxide into bicarbonate. By showing that plasma proteins (weak acids) and dissolved strong ions also participate in acid–base homeostasis, the physicochemical approach provides an explanation for acid–base disorders commonly encountered in critical illness, such as hypoalbuminemia and hyperchloremia. However, although this approach is mathematically accurate (7), it oversimplifies some of the mechanistic insights (8), which is perhaps why reception has been mixed, ranging from full embracement at the bedside (9) to outright hostility (10).

Unfortunately, the controversy has left many of us wondering whether it is truly important to learn the physicochemical approach. After all, intensivists really have access to only two tools for rapid manipulation of plasma pH in the setting of acidosis: *1*) hyperventilation to lower P_{CO_2} and *2*) administration of sodium bicarbonate. Nonetheless, our understanding of these interventions may be improved with the physicochemical approach. For example, although the Henderson-Hasselbalch equation predicts that hyperventilation will lower pH, it doesn't allow us to understand that hyperventilation does this by removing carbon dioxide without changing the strong ion difference, and it doesn't predict the effect that remaining weak acids will have on the final observed pH.

Similarly, the physicochemical approach helps us understand that administration of sodium bicarbonate increases pH by increasing the concentration of plasma sodium relative to chloride, rather than simply by adding a bicarbonate buffer to the system. This is because sodium fully dissociates in solution, whereas bicarbonate exists in equilibrium with dissolved carbon dioxide (P_{CO_2}) (i.e., it behaves like a weak acid). In fact, the physicochemical approach helps us understand the potential harmful effects of a rapid bolus of sodium bicarbonate, because it predicts an increase in the local P_{CO_2}. This may rapidly increase intracellular P_{CO_2}, worsening intracellular acidosis, because carbon dioxide rapidly diffuses across cellular membranes (11).

In this issue of the *Journal*, Zanella and colleagues (pp. 799–813) report their ingenious alternative method for therapeutically increasing the strong ion difference in plasma (12). The authors used electrodialysis cell technology to defy the principles of electroneutrality and remove chloride ions from plasma while maintaining the concentration of sodium ions. As a result, they increased the strong ion difference and raised the pH back to normal levels. They tested this technology in animal models of both metabolic and respiratory acidosis and showed that the effect was maintained even after the electrodialysis was discontinued. Their work not only validates a direct therapeutic application of the physicochemical approach, it also provides fascinating insights into acid–base homeostasis. Before electrodialysis was initiated, renal chloride excretion was increased in response to both metabolic and respiratory acidosis. Once the pH was restored by lowering plasma chloride with electrodialysis, renal chloride excretion was reduced. Homeostatic mechanisms involving chloride shifts have previously been shown to play an important role in the maintenance of pH through mechanisms involving circulating red blood cells (13) as well as the kidney (14). This leads one to conclude that lowering plasma chloride with electrodialysis augments the natural homeostatic response to acidosis, unlike the administration of concentrated sodium bicarbonate, which also increases plasma sodium.

However, we should be cautiously enthusiastic. Modifying pH by removing chloride and manipulating the strong ion difference will not treat the underlying cause of the acid–base disorder any more than lowering P_{CO_2} or administering sodium bicarbonate does, unless of course the primary derangement is hyperchloremia, elevated P_{CO_2}, or hyponatremia. Although acidosis with hyperchloremia is quite common in critical illness (4), preventing hyperchloremia by using the physicochemical approach to guide the choice and composition of fluids is perhaps a simpler and wiser alternative. Furthermore, hyperventilation, sodium bicarbonate administration, and chloride electrodialysis do not directly treat elevated lactate levels, the most common cause of acidosis in critical illness (1). However, Zanella and colleagues make no such claims. They simply use the physicochemical approach to elegantly show that increasing the strong ion difference restores pH to normal levels. It's

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conceivable that the same result could be more easily obtained by conventional dialysis, where the dialysate solutions are engineered to target a given strong ion difference. Either way, the manipulation of strong ion difference to achieve specific therapeutic effects is slowly gaining traction, and similar approaches have recently been shown to enhance respiratory support (15, 16). Whatever the future holds for these therapies, it behooves us to start teaching the physicochemical approach to our medical students and junior colleagues sooner rather than later. ■

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Mounting Clarity on Enteral Feeding in Critically Ill Patients

Like many questions in the ICU, best practices for provision of nutrition remain unclear. Several factors contribute to the relative lack of robust ICU nutrition research. Critical care clinical research is immensely difficult for a variety of reasons, not the least of which are extraordinary clinical heterogeneity and multiple overlapping interventions. Furthermore, our understanding of specific nutritional needs during severe physiologic and metabolic stress is poor. Finally, the field is historically fraught with strong opinions on all sides and heavy influence from industry. Despite important questions that remain unanswered, we are fortunate that several large investigator- or network-initiated randomized controlled trials (RCTs) studying enteral calorie delivery in critically ill patients have been published over the past 8 years. In this issue of the *Journal* (pp. 814–822), Deane and colleagues (1) report the 6-month outcomes of nearly 4,000 participants in the TARGET RCT (The Augmented versus Routine Approach to Giving Energy Trial) that investigated delivery of 70% versus 100% caloric requirements in mechanically ventilated critically ill adults.

How Does 100% versus 70% Caloric Intake Affect Critically Ill Patients 6 Months after Study Enrollment?

In the large, initial TARGET trial, the full- and reduced-calorie groups received 103% and 67% of calculated caloric needs, respectively (2). Average age and body mass index (BMI) were 57 years and 29 kg/m^2, respectively. The amount of protein delivered to both groups was similar. Neither 90-day mortality (the primary outcome) nor additional secondary outcomes were significantly different between the two arms. However, recovery does not stop at 90 days, and in their current work, Deane and colleagues (1) undertook telephone contact of over 2,700 survivors 180 days after randomization. The

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