

consistent with it goes against all we know about numerous cell-membrane transporters that use  $H^+$ ,  $HCO_3^-$ , or  $CO_3^{2-}$  as coions or counterions with  $Na^+$ ,  $K^+$ , and  $Cl^-$  (3). There has been no identification of a  $Na^+/Cl^-$  antiporter or an electrogenic  $Na^+-Cl^-$  cotransporter that will alter local electroneutrality to create or consume the supposed dependent variables. Simply because one can electro dialyze chloride by brute force, as Zanella and colleagues (4) report, does not mean it happens *in vivo* at the microscopic level. Clinical adoption of the Stewart approach has shown no superiority to conventional approaches (4–6), and the measurement of all the strong ions repeatedly is wasteful and costly, risks measurement errors that beget more testing, contributes to anemia in many patients, contributes to more transfusions, and is very difficult to teach to trainees and even seasoned clinicians. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## Reply by Cove and Kellum to Swenson

From the Editorialists:

We thank Prof. Swenson for his well-articulated letter. We conceded in our editorial that the Stewart approach doesn't provide a strong mechanistic explanation (1), and therefore we also agree it doesn't eliminate a mechanistic role of bicarbonate. Rather, the Stewart

approach provides a unifying explanation of the factors determining plasma pH by incorporating the role of electrolytes, plasma proteins, and carbon dioxide in all forms, including bicarbonate. Whether one considers bicarbonate to be dependent and  $PCO_2$  independent, or vice versa, depends on the system under examination. Thus, we do not think this a useful classification and avoided the terms in our editorial because we've shown  $PCO_2$  behaves like a dependent molecule under some circumstances (2). However, the classification does serve the purpose of drawing attention to the fact that  $PCO_2$  and  $HCO_3^-$  are not independent of each other. Furthermore, the Stewart approach is not at odds with our understanding of membrane ion transporters; instead, it provides a more complete understanding of their function (3).

In the paper by Zanella and colleagues, normal pH was restored after induction of acidosis by removing chloride to increase the strong ion difference; this also led to an increased bicarbonate level (4). Both of these changes can be easily understood with the Stewart approach, whereas a bicarbonate-centric approach focuses only on the bicarbonate change that occurred. Therefore, if we simply considered the information on the blood gas, we could only classify the acid-base changes in the Zanella experiments as metabolic, respiratory, or mixed, but we would be unable to describe what had caused the observed changes. Similarly, in clinical practice, a bicarbonate-centered approach allows us to identify the presence of an acid-base derangement as effectively as the Stewart approach. However, the Stewart approach provides a more precise classification of the acid-base changes, even in the studies referenced by Prof. Swenson (5). Such precision is important in clinical practice where, for example, the impact of choice of resuscitation fluids on acid-base status needs to be considered. We flatly reject the assertion that teaching the Stewart approach is difficult or that it leads to increased costs and blood loss. In fact, the variables needed to apply the approach are routinely measured already (6). The value of the approach comes from the ability to understand the relative contributing effects of simultaneous abnormalities on the final observed pH, such as elevated lactate, hypoalbuminemia, and electrolyte abnormalities, in a way that bicarbonate-centric understanding cannot (7). ■

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## Reply by Zanella et al. to Swenson

From the Authors:

We thank Dr. Swenson for the interest in our experimental study, in which we employed electro dialysis to reduce the plasma chloride concentration and correct acidemia in healthy piglets with either metabolic or respiratory acidosis (1). By selectively removing chloride, the main extracellular negatively charged ion, we were able to increase the plasma strong ion difference (SID), thus effectively correcting the experimentally induced acidemia. Of note, removing chloride to increase the SID is exactly what healthy kidneys do during acidemia, especially acidemia of respiratory origin (2, 3). This occurs, among other mechanisms, through the downregulation of pendrin, the renal Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger (4). Electro dialysis, despite its complexity, has the advantage of being faster and independent from renal function. Furthermore, as correctly pointed out, chloride removal has the straightforward advantage of correcting acidemia without changing natremia or osmolality, as opposed to what happens with the administration of sodium bicarbonate.

Acid-base balance is undoubtedly a complex topic that has also had polarized opinions in the past, with the well-known trans-Atlantic debate between the Boston and Copenhagen schools (5). It is therefore not surprising that this is somehow happening again, although the current clash is between enthusiasts of the physicochemical approach (i.e., the Stewart approach) and the rest of the world.

The Stewart approach has the advantage of combining the following two very important aspects of medicine: the acid-base and the hydroelectrolyte equilibrium (6).

It is based on the principle that the pH of a biological solution can be varied independently by three variables: 1) P<sub>CO<sub>2</sub></sub>, 2) the SID,

and 3) the total amount of noncarbonic weak acids, which in the extracellular space are mainly constituted by albumin and phosphates. The claim made by Dr. Swenson that only the strong ions determine pH and bicarbonate of a biological solution is, therefore, partially incorrect because it does not take into account P<sub>CO<sub>2</sub></sub> and total amount of noncarbonic weak acids. Furthermore, it is important to underline that these variables are not completely independent from each other. Indeed, a certain degree of interdependence is certainly present (7).

Technology is improving quickly, and modern blood gas analyzers provide reliable measurements of blood gases and pH, requiring only microliters of whole blood. In addition, they reliably measure, through direct ion-selective electrodes, the concentration of the major extracellular electrolytes, namely, sodium, potassium, ionized calcium, chloride, and lactate. Currently, blood gas analyzers do not measure albumin and phosphate concentration. However, these variables can be at first guessed and, in case of complex acid-base disorders, easily measured. We therefore believe that Dr. Swenson overstates the economic and biological costs (anemia and transfusion) related to a single blood gas analysis.

In conclusion, we respectfully do not believe that teaching and understanding the physicochemical approach to acid-base equilibrium is difficult. What matters is to comprehend that the physicochemical approach is the base to integrate electrolytes and acid-base balance rationally. Stewart's and Van Slyke's approaches are two faces of the same medal; as such, trying to demonstrate the superiority of one over the other may not be worth the effort. The medal is always the same. Similarly to what happens during language learning, it is on the one hand difficult to learn a new language (approach) if one has spoken (applied) another one for decades. On the other, children (trainees) learn the language (approach) they grow in, without even noticing. Of note, if more languages are spoken together, both can be learned with a reasonable effort. Given the reasonable advantages of bilingualism, one wonders why both methods cannot be applied in the near future, without necessarily trying to demonstrate the superiority of one over the other. ■

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