systemic half-life to further limit any potential for systemic adverse effects.

The apparent inconsistency between the previously published data and pharmacological data generated using potent and selective TMEM16A potentiators may reflect *1*) the imperfect translation of genetically manipulated models, *2*) the limitations of using nonselective pharmacological inhibitors to characterize ion channel function, and *3*) concluding that positive modulation will deliver the opposite phenotype to inhibition. For example, data reported from pulmonary arterial hypertension models using a Tmem16a knockout and supported by pharmacological studies using the nonselective TMEM16A blocker benzbromarone failed to translate into clinical efficacy (3). In this study, a paradoxical increase in mean pulmonary artery pressure was reported in benzbromarone-treated patients with pulmonary arterial hypertension (3). In addition, although some Tmem16a knockdown studies have reported a reduction in blood pressure, overexpression of the channel did not cause an increase in pressure (4).

Dr. Olschewski and colleagues correctly note the failure of the inhaled P2Y2 agonist, denufosol, to demonstrate clinical benefit in patients with cystic fibrosis. The reasons for this are likely multifactorial and may include poor pulmonary pharmacokinetics, rapid degradation by ectonucleotidases, potential receptor desensitization, and emptying of intracellular calcium stores (5, 6). It should be noted that contrary to Dr. Olschewski's letter, cough and sputum production did not differ between the placebo and denufosol-treated cohorts in the TIGER2 (Transport of Ions to Generate Epithelial Rehydration 2) study. In contrast to P2Y2 agonists, which act indirectly through elevation of intracellular calcium, compounds such as ETX001 selectively enhance the activity of TMEM16A in response to physiologically regulated changes in intracellular calcium (1).

ETD002, a first-in-class TMEM16A potentiator, has successfully completed its Investigational New Drug enabling safety studies with clinical studies expected to commence in 2020. As with all drug candidates in clinical development, the potential for adverse events will be carefully monitored. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Whither the Bicarbonate Era

*To the Editor*:

For metabolic acidosis, beyond treating the underlying cause, correcting hypoxemia, and establishing good perfusion, sodium bicarbonate is often given at variable arbitrary thresholds of depressed blood pH. Recently, Zanella and colleagues (1) employed extracorporeal removal of chloride by electrodialysis in healthy pigs made acidemic by either lactic acid infusion or hypoventilation ($CO_2$ retention). By physically drawing off chloride and establishing a local separation of charge, blood electroneutrality at the membrane is immediately reestablished by the hydrolysis of water to yield a hydroxyl ion that instantly combines with $CO_2$ to form bicarbonate. The authors show the feasibility of quantitatively increasing bicarbonate in this fashion for both forms of acidosis without the associated and unwanted hypernatremia and volume loading that can occur with intravenous sodium bicarbonate administration. The accompanying editorialists (2) proclaim the postbicarbonate era with this study that illustrates a major tenet of the Stewart approach to acid–base chemistry and its superiority over other approaches to understanding acid–base physiology and pathophysiology. In Stewart's paradigm, $H^+$, $OH^-$, $HCO_3^-$, and $CO_3^{2-}$ are relegated to the status of dependent variables; that is, they can only be formed from the differential movements and exchanges of independent strong ions ($Na^+$, $K^+$, and $Cl^-$) that disturb electroneutrality, which is immediately corrected by the hydrolysis of water and reaction with $CO_2$. Although the heuristics of the Stewart analysis are valid, I remain unconvinced by the claim that what the mathematics of this approach reveal demands that physiology must follow these rules and conclusions. The assumption that only strong ions and their differential movement from one space to another alters $H^+$ and $HCO_3^-$ concentrations because the math is



Originally Published in Press as DOI: 10.1164/rccm.202005-1544LE on May 27, 2020

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 electrodialyze 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. ■

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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 $P_{CO_2}$ 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 $P_{CO_2}$ behaves like a dependent molecule under some circumstances (2). However, the classification does serve the purpose of drawing attention to the fact that $P_{CO_2}$ 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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Originally Published in Press as DOI: 10.1164/rccm.202005-1747LE on May 27, 2020