DOI: 10.1111/apha.13622

EDITORIAL

ACTA PHYSIOLOGICA

Stewart's approach: Just a heresy or another lens into acid-base physiology?

We thank Prof. Bie for his interest in our article[1] as well as for his criticisms,[2] which gave us the opportunity to, more extensively, address an issue which still concerns the international scientific community, and which has both ardent supporters and fierce opponents.

On the whole, our Editorial[1] did not intend to take a stand in favour of one or the other view regarding the renal response in compensating acid-base disorders, but to present, in addition to the conventional view about renal acid excretion in the form of NH_4^+, the Stewart's physicochemical approach[3] on the subject. Also, we had no intention to present exact numerical values but to make clear the conceptual difference between the two pathophysiological views.

1 | DEVIATION FROM ELECTRONEUTRALITY

This is clearly a misunderstanding. The misunderstanding stems from our use of the term *net electrical charge*, which we borrowed from the cited article by Gattinoni et al[4] and is meant to represent only the *electrical charge difference of the strong ions*. The concept becomes clear in the explanatory figure of the Editorial.

2 | RIEMANN-STIELTJES INTEGRAL

Applications do not need to repeat the mathematical theory behind the tools used. Besides, Calculus has a physical importance, which is utilized by the first-year students of the respective faculties (physics, chemistry, engineering sciences, etc), without knowing the corresponding mathematical formalism.

As for the integral, we rewrite it

$$\int_a^b d\left([\mathrm{SID}]_{\mathrm{ECV}}(t)\cdot V(t)-[\mathrm{SID}]_u(t)\cdot V(t)\right)$$

without an asterisk (*)!

Dropping the formal requirements of the validity of such an expression (eg functions of bounded variation etc), this is a Riemann-Stieltjes integral

$$\int_a^b f(t)\,\mathrm{d}g(t),$$

where $f(t)=1$ and $g(t)=[\mathrm{SID}]_{\mathrm{ECV}}(t)\cdot V(t)-[\mathrm{SID}]_u(t)\cdot V(t)$, for $t\epsilon\,[a,b]$.

It arises as a consequence of the application of Stewart's approach. One can apply the equation proposed by Gattinoni et al[4] for the calculation of the $[\mathrm{SID}]_{\mathrm{ECV}}$ value at any given time, based on: its previous (basal) value, the production of strong ions during metabolism, the possible administration of solutions containing strong ions and the excretion of strong ions in the urine. In particular,

$$[\mathrm{SID}]_{\mathrm{ECV}}\ t\cdot V\,t=[\mathrm{SID}]_{\mathrm{ECV}}\ a\cdot V\,a+\int_a^t \mathrm{EPR}\ s\ \mathrm{d}s$$
$$+\int_a^t \mathrm{IR}\ s\cdot[\mathrm{SID}]_{\mathrm{infusion}}\ s\ \mathrm{d}s-\int_a^t \mathrm{UPR}\ s\cdot[\mathrm{SID}]_u\ s\ \mathrm{d}s$$

where EPR is the endogenous production rate, IR is the infusion rate and UPR is the urine production rate.

3 | NH_4^+ EXCRETION AND UAG ($[SID]_U$)

Regarding the question, whether the 'renal proton excretion rate is properly quantified by [UAG] (or $[SID]_U$)', we emphasize that the purpose of the Editorial was not to make an accurate estimate of the quantitative correlation between [UAG] (or $[SID]_U$) and NH_4^+ elimination, although we have briefly addressed the issue. Anyway, [UAG] has been used as a rough estimation of urine NH_4^+ excretion in the evaluation of hyperchloremic metabolic acidosis; as it actually reflects the difference between all unmeasured anions and

cations, if urine contains non-usually existing anionic or cationic compounds, the correlation between [UAG] and urine NH_4^+ excretion will be disturbed.[5] In particular, in chronic kidney disease, [UAG] has been shown to be a poor surrogate of [NH_4] in urine; the correlation observed was partly restored when urine phosphate and sulphate were included in the calculation.[6]

4 | THE 'STEWART'S CONCEPT'

Bie has been critical of the Stewart's point of view.[2] However, a scientific theory can in no way be debunked with aphorisms of the type 'The promotion of the SID to the position of an important variable of body-fluid control is wrong mainly because it is a variable without sensor and leads to untenable conclusions'. The only way a theory's falseness or hollowness to be exposed is to definitely prove that it contradicts common sense (not fixed assumptions) or fundamental physicochemical principles (which, however, provide the basis for this theory), that it is not confirmed/is refuted by experimental or in vivo data or that it is incomplete; that is, if another important factor—in addition to what Stewart mentions—that played a key role in regulating acid-base balance in the body was identified. Disagreeing with a different view regarding the organism's physiology, just because it does not present it the way we are used to perceiving it, does not offer any constructive criticism. Moreover, a period of several decades cannot be considered sufficient for a particular scientific theory not to 'pass the test of time'. If the above reasons are not met, it would be better to follow its 'evolution' over time. One such development, as reported by many researchers, is the concept of SID, which is considered to be synonymous with the concept of Buffer Base shaped by Singer and Hastings (1948)[7] (as also Bie notes), and which Stewart incorporated in his comprehensive view of the regulation of acid-base disorders. While Bie, following Siggaard-Andersen,[8] focuses on the 'inside' of the Singer and Hastings structure, Stewart focuses on the 'outer' skeleton.

In an analytical approach to physiological acid-base parameters in plasma, Wooten[9] arrives at the following equation, which demonstrates the quantitative identity of the above mentioned quantities:

$$\mathrm{SID} = C - \sum_i c_i \times \overset{!!}{z}_i - D$$

where C is the concentration of proton acceptor cites of the carbonate buffers, C_i is the concentration of the non-carbonate buffer ion (i), $\overset{!!}{z}_i$ is the average charge per molecule for species (i) and D is Ricci's difference function ($D = [\mathrm{H+}] - [\mathrm{OH^-}]$).

Stewart[3] suggests that Strong Ion Difference (SID) difference, together with the total concentration of non-volatile, weak acids ([A_{TOT}]) and PCO_2 are three independent variables that determine the acid-base status of the organism. Stewart also defined the way these variables interact, which obeys three fundamental physicochemical principles: (a) the principle of mass conservation, (b) the principle of electrical neutrality in aqueous solutions and, for the dissociation of weak electrolytes, (c) the Guldberg-Waage mass action law. The fundamental merit of Stewart's view is that it integrates acid-base balance into the overall charge balance between water and electrolytes.

Criticism on Stewart's point of view essentially stems from the Brønsted-Lowry approach,[10] which defined as acidic substances that can and do dissociate in an aqueous solution and donate a proton (hydrogen cation). However, this does not prove that the previous approach (recognizing that acids and bases were synonyms for anions and cations), or that of Stewart, is wrong. In addition, with the focus of researchers/physiologists on the Henderson-Hasselbalch equation, special emphasis was placed on bicarbonate (HCO_3^-) concentration, which was considered not only an indicator of the body's acid-base status but also an independent determinant.

5 | PROTON (H^+)/HCO_3^- TRANSPORT AND CONCENTRATION CHANGE

According to Stewart,[3] H^+/HCO_3^- are dependent variables, without the ability to change their concentration themselves, with a hypothetical movement through membranes. The reference to the specific molecular structure of H^+ (in aqueous solutions) was beyond the scope of this treatise. Readers understand what we are talking about and, by simply symbolizing protons as H^+, no harm is done on the pathophysiology described. For Stewart, the way fluids interact in the body's various compartments to compensate for acid-base aberrations is primarily through the exchange of strong ions. To cause a [H^+] change in a compartment, one of the three independent variables must theoretically be changed: [SID], PCO_2 or [A_{TOT}]. [A_{TOT}] is mainly represented by proteins, which, under normal conditions, cannot move freely through membranes, while their concentration is not usually subject to short-term changes. Also, CO_2 circulates between the body's compartment fluids, following the partial pressure gradients created by the balance of CO_2 production, diffusion, transport and elimination from the lungs. Thus, PCO_2 in the body's fluids is 'imposed' in some way by organism's operational circumstances; PCO_2 certainly affects [H^+] and pH, but this is not primarily a regulatory interaction. Therefore, the change in [SID] is the only available mechanism by which the various compartments of the organism can regulate each other's [H^+] (pH).[11]

In Stewart's treatise, in an example regarding ion movements between two compartments, taking place through a

semipermeable membrane, while maintaining a constant PCO_2, it becomes obvious that when $[HCO_3^-]$ is changed in a compartment, one cannot say with certainty whether HCO_3^- has been transported or not. What matters is the transport of CO_2 being highly permeable through membranes, which does not have to happen as HCO_3^-.[12] As also Bie says, 'at the molecular level, transmembrane transport of the carbon atom may take place as diffusion of carbon dioxide'.

As for the body fluids acidity: 1. For Stewart, the increase in gastric acidity[13] (high HCl concentration that can reach 0.1 N, ie, $[H^+] = 1.0 \times 10^{-1}$ Eq/L, pH = 1.0) is not caused by H^+ transport from the cells of the gastric mucosa in the gastric lumen. What these cells do is transfer Cl^- (but not Na^+ or any other strong cation) from the interstitial fluid to the gastric fluid. Because the electrolytes in the interstitial fluid are in equilibrium with the plasma, the Cl^- in the interstitial fluid is constantly renewed by the plasma. Whether some weak ions accompany this movement of Cl^-, for example, OH^- or HCO_3^-, in the opposite direction or H^+ in the same direction or any combination thereof is not relevant and cannot be checked. Importantly, this movement of Cl^- is not accompanied by other strong ions. Thus, it is the Cl^- transport and change of $[Cl^-]$ that lead to a change in the pH of the gastric fluid. Plasma [SID], in the blood removed from the stomach, will increase as a result of a decrease in $[Cl^-]$. This change has been observed and is called the 'alkaline tide'. 2. With similar reasoning, regarding renal function,[14] in case of a metabolic acidosis, when the [SID] of the plasma reaching the kidney is lower than normal, the kidneys react by reabsorbing less Cl^- to increase the plasma [SID], increasing excretion of Cl^- in the urine (where the [SID] is reduced). This is exactly what our Editorial describes.

6 | IS [SID], ACCORDING TO STEWART'S CONCEPT, 'A NON-REGULATED VARIABLE, THAT MAY CHANGE FOR REASONS OTHER THAN ACID-BASE DEVIATIONS WITHOUT CONSEQUENCES FOR ACID-BASE CONTROL'?

It is not true that in Stewart's view [SID] is 'not a regulated variable' and cannot participate in 'feedback systems driven by fluctuations in regulated variables'. Stewart describes an interaction and co-dependency between the supposedly independent variables within the multi-compartmented system of whole body physiology. Thus, for example, the Donnan equilibrium is reported,[15,16] in which the concentration of the freely permeable strong ions (hence [SID]), in two compartments separated by a semipermeable membrane, is determined by the presence of the non-permeable, partially dissociated proteins in one of them, so that the tendency of the permeable ions, for example, Na^+ and Cl^-, to move through the semipermeable membrane according to the difference in their concentration to be balanced by the electric forces (electric potential) that resist this movement (Nernst equation). However, in each individual compartment, [SID] acts as an independent determinant of $[H^+]$. Also, when PCO_2 is abnormal, the kidneys react by altering the plasma [SID] to limit its $[H^+]$ aberration.[17] Conventional views consider $[HCO_3^-]$ instead of [SID] as the compensatory variable. Overall, Stewart recognizes that the clinical assessment of acid-base disorders essentially coincides with the interpretation of $[H^+]$ changes in plasma 'in terms of the ionic effects of lungs, kidneys and gastrointestinal tract and interactions with other body fluids'.[18] Thus, for the overall regulation of acid-base balance in the body, Stewart presents a $[H^+]$ versus $[PCO_2]$ diagram for the plasma, using lines of constant [SID] instead of constant $[HCO_3^-]$ (Figure 1).

7 | ON THE PARTICULAR IMPORTANCE ATTACHED TO HCO_3^-

The 'misperception' probably results from ignoring the fact that the various biochemical/redox reactions in the body take place in a common space (milieu), that is, water. Water is the substance with the highest concentration in the human body (55.3 M) and has a very small dissociation constant (of the order of 10^{-16} Eq/L). These two properties make it an infinite supplier and unsaturated acceptor of proton charge. In chemical terms, the ionic product of water ($[H^+] \times [OH^-]$) does not appreciably change.

The addition/increase of the concentration of any strong ion (eg Cl^-) in aqueous solution will lead to a change in the dissociation of the water molecules and therefore to a change in the $[H^+]$ in the solution. At the same time, the equilibrium point of the partial dissociation reaction of the weak acids that are present in this solution will also change. According to the isohydric principle, when more than one weak acid (buffers) are present together in an aqueous solution, all are exposed/are in equilibrium with the same $[H^+]$, the same as the water molecules. H^+ are not distinct, as belonging to or derived from a specific electrolyte (acid) that has dissociated, the water molecules not excluded. The pKa of each weak acid, together with its total mass (ie the amount of acid that is in dissociated form, that is, in the form of an anion, and the amount that is in non-dissociated form) will dictate the ratio between its concentration in the un-dissociated form to the concentration of its anion—in accordance with the Henderson-Hasselbalch equation, which is used to describe the acid-base status of the organism. In fact, any of these weak acids could be used to calculate the pH, from Henderson-Hasselbalch type equations, which are essentially derived from the application of

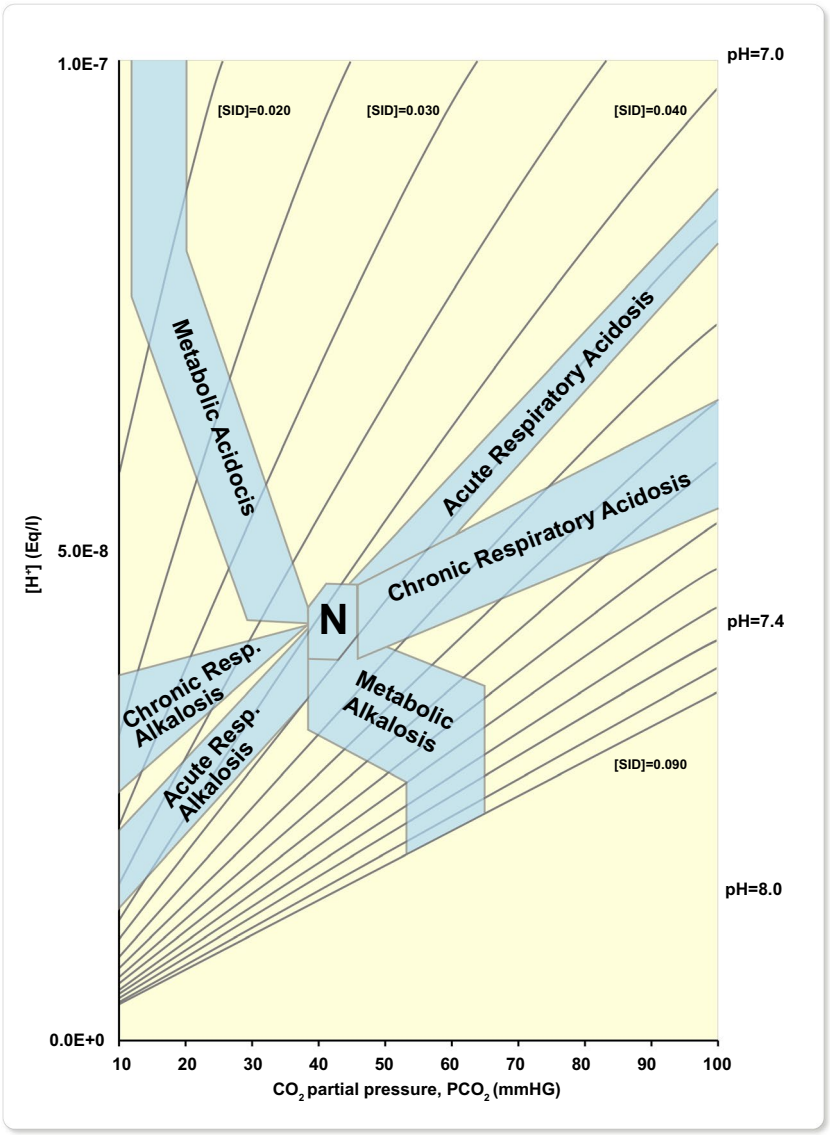

FIGURE 1 The $[H^+]$-PCO_2 diagram for plasma with lines of constant [SID]. Figure summarizes the changes in the body's acid-base balance in a simple way. Superimposed areas indicate normal values (N), and common ranges of values for patients with [SID] abnormalities, labelled metabolic acidosis and alkalosis, as well as with PCO_2 abnormalities for acute/chronic respiratory acidosis and alkalosis. Normal state (N) corresponds to plasma [SID] 40-45 Eq/L and PCO_2 36-44 mmHg. Therefore, the limits of normal $[H^+]$ are $3.6\text{-}4.4 \times 10^{-8}$ Eq/L (pH: 7.36-7.44). If $[H^+]$ is outside these limits, then either [SID] (metabolic disorder), PCO_2 (respiratory disorder) or both (mixed disorder) must be differentiated from their baseline values. In the event of a primary change of one variable ([SID] or PCO_2), the other variable also changes to compensate for (limit) $[H^+]$ (pH) deviation from normal. Reproduced with permission. Copyright © 2009 by AcidBase.org

the fundamental physicochemical principle of the Guldberg-Waage law of mass action ($[H^+] \times [HCO_3^-] = K \times PCO_2$ [$K = 2.6 \times 10^{-11}$ $(Eq/L)^2$ /mmHg]).

Note here that: (a) While HCO_3^- is considered the major alkaline reserve of the body, H_2CO_3 (formed by the reaction of CO_2 with water) has pKa = 6.1. Therefore, it is not considered an effective buffer for plasma conditions since, as is well known, only buffers with pKa values within 1 pH unit of that in a solution can effectively participate in the buffering of the solution pH. Alternatively, HCO_3^- as a weak ion cannot affect the regulation of the body's acid-base balance. Thus, the alkaline effect of $NaHCO_3$ solution administration is not caused by the administration of HCO_3^- but by the very high Na^+ concentration (1 mEq/mL for the 8.4% solution), which increases the [SID] in plasma. (b) Van Slyke, in his memorable treatise on acid-base buffering,[19] finally attributes the special buffering ability of HCO_3^-, not so much to chemical but to physiological causes. That is, while the buffering capacity of weak acids is by definition attributed to their much smaller dissociation in aqueous solutions compared to the (almost) complete dissociation of strong acids (the quantitative relationships that calculate the buffering capacity result from the application of the Guldberg-Waage mass action law for the weak acid dissociation reaction), van Slyke notes that the buffering capacity of HCO_3^- is mainly a consequence of the volatility of CO_2 (formed during the neutralization of acids by HCO_3^-) and its elimination by the lungs with respiration.

8 | ABOUT H^+ GENERATED BY BIOCHEMICAL REACTIONS

Serious objections have been raised by researchers, who claim that H^+ are not produced/consumed during biochemical reactions. Thus, responding to a debate about the origin of H^+ during glycolysis and lactate production in contracting muscles, Lindinger et al[20] suggest: (a) Biochemical reactions during glycolytic ATP production

produce pyruvate (not pyruvic acid) and lactate (not lactic acid), because, for example, the pKa of lactic acid is equal to 3.87 (37°C) ($Ka > 10^{-4}$ Eq/L). Thus, lactic acid is a strong acid, existing only as an anion (in the dissociated form) in aqueous solutions (plasma), thereby reducing plasma [SID]. (b) Similarly, phosphocreatine (PCr^{2-}) is a strong anion (pKa = 4.5) and therefore, being hydrolysed at the beginning of muscle contraction, its concentration decreases inside muscle cells (producing electroneutral creatine), resulting in increased [SID] that contributes to the observed reduction of [H^+]. (c) When the very important contribution of water to the charge balance during biochemical reactions is not taken into account (together with other metabolic reactants/products), the principle of electrical neutrality is violated. (d) Finally, following Stewart's view, they report that at any given time, even very small charge imbalances, resulting in large electrical forces, are restored instantaneously, with appropriate displacement of the equilibrium point of the dissociation reactions of the weak acids (and water) and a corresponding change in [H^+]. These changes are made in such a way that all physicochemical constraints are satisfied. So it may not make sense to try to trace the origin of H^+ in space-time during the biochemical reactions of the various metabolic pathways, as the acid-base status changes instantaneously.

Regarding, particularly, the association of diet with acid-base balance in the body, from Stewart's point of view, to our knowledge, there are insufficient data in the literature. One could possibly focus on the 'input and output quantity of SID'.[4] Interestingly, a study has investigated the effect of dietary cation-anion difference on the acid-base status in dry cows, that is, cows fed a diet that contained anionic salts (dietary cation-anion difference = −63 to −40 mEq/kg of dry matter) were compared with cows fed a control diet, without anionic salts (dietary cation-anion difference = 203 mEq/kg of dry matter). Mean ruminal pH decreased 0.12 units in cows fed diet with anionic salts, possibly because, as authors note, of the reduced [SID] in ruminal fluid. Also, [SID] in urine was decreased because of the relatively greater excretions of Cl^- and S^{2-} (sulphide anion) versus Na^+ and K^+ by cows fed this diet.[21]

9 | REGARDING THE MOBILITY OF H^+

Central to classical approaches regarding the interpretation of acid-base disorders is the transfer of H^+ between the various compartments of the body. As mentioned in the Editorial, H^+ conventional diffusion is disputed because of their low concentration in body fluids ($\approx 10^{-7}$ Eq/L) (it would be very slow as it depends on concentration gradients) but also of their fleeting presence in solutions (on the order of picoseconds). Instead of bulk transfer of H^+, a special mechanism has been proposed, the Grotthuss mechanism[22] (or structural diffusion) accounting for proton conductance not only in water solutions but also through ionic channels. This unique 'transport' process transfers proton charge without diffusive movement of either individual H^+ or oxygen atoms (Figure 2). Charge distribution in a hydrogen bond network, being highly polarizable, may be altered and charge delocalization may occur by the application of an external electric field, as could possibly be the case with [SID] change. Water, in fact, seems to play a very important role in this type of transfer of H^+ (and electrons), allowing distant communication without the need for diffusion processes to occur.[23]

10 | PHYSICOCHEMICAL APPROACH AND ACID-BASE DISORDERS IN CLINICAL STUDIES

Strong ions, although not considered acids (strong anions) or bases (strong cations) according to the classic definition of acids and bases (they are called aprotes), can nevertheless cause acid-base disorders. Metabolic (hyperchloremic) acidosis resulting from Normal Saline (NS 0.9%) administration has long been documented.[24] The cause, following Stewart's viewpoint, would be the significantly higher Cl^- concentration (154 mEq/L) compared to plasma and the 'zero' [SID], which results in a decrease in plasma [SID]. Hyperchloremic/low [SID] acidosis has been studied in critically ill patients. Accordingly, in a study conducted in our Intensive Care Unit (ICU), to identify the main causes of metabolic acidosis in 85 critically ill septic patients, the most common cause was hyperchloremic/low [SID] acidosis, identified by the ratio [Cl^-]/[Na^+] (>0.75).[25] Also, in determining the cause of a metabolic acidosis disorder, it is extremely important to investigate whether there are increased amounts of non-volatile acid anions other than hydrochloric acid (called unmeasured anions). These anions are traditionally quantified by the anion gap ([AG]) calculation, ideally corrected for albumin, that is, $AG = [Na^+] - ([Cl^-] + [HCO_3^-]) + 2.5\times\{4.5 - [\text{albumin(g/dL)}]\}$. Following the Stewart's approach, the strong ion gap ([SIG] can be used instead, derived from the difference between apparent and effective [SID][26]:

$$[SIG] = [SIDa] - [SIDe].$$

$$[SIDa] = \left[Na^+\right] + \left[K^+\right] - [Cl^-].$$

$$[SIDe] = 2.46\times 10^{pH-8}\times PCO_2\,(mmHg) + \left[\text{albumin}\,(g/l)\right] \times (0.123\times pH - 0.631) + \left[\text{phosphate}\,(mmol/l)\right]\times(0.309\times pH - 0.469).$$

Including lactate anion in the [SIDa] calculation, the resulting value will refer to the other unmeasured anions (other than lactate).

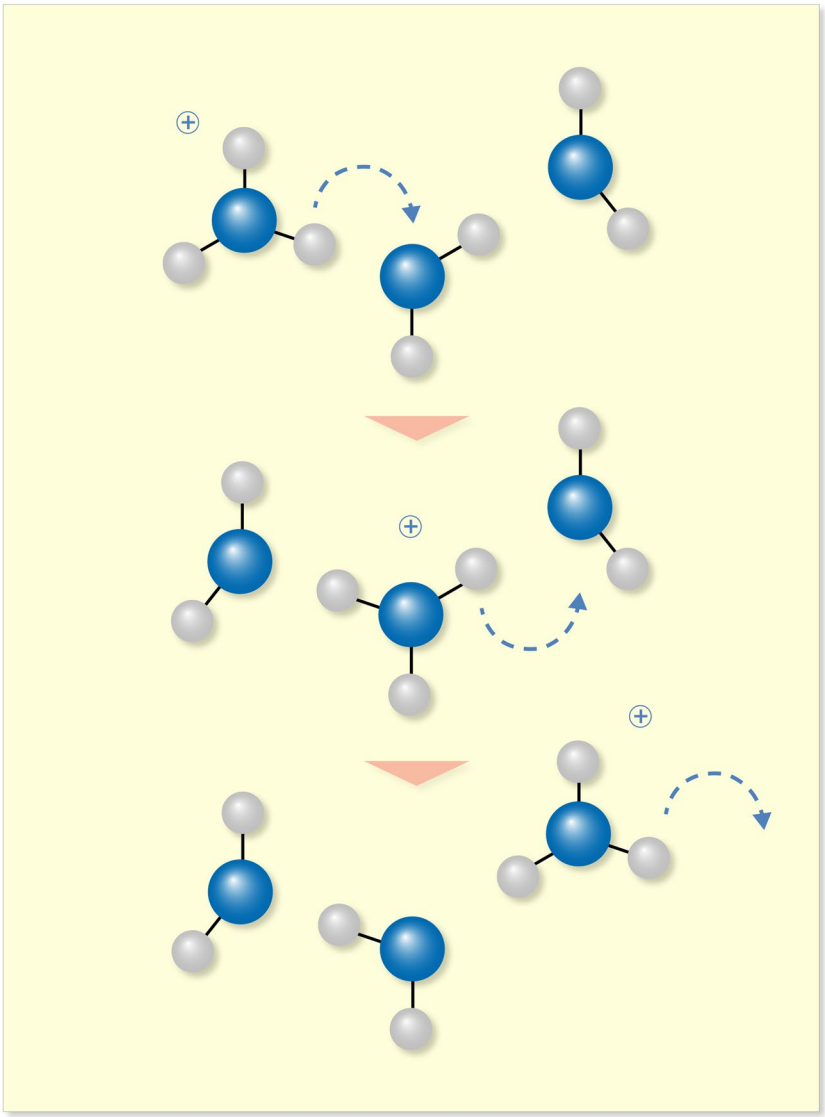

FIGURE 2 Simplified, schematic illustration of Grotthuss mechanism. Blue circles depict oxygen atoms and grey circles depict hydrogen atoms in water molecules. According to this mechanism, an excess proton *hops* between adjacent water molecules in a stepwise manner, through successive covalent bond formation and cleavage (proton charge transfer). More precisely, it has been suggested that Grotthuss shuttling occurs via the interconversion between the Eigen and Zundel solvation structures (Eigen cation: $H_9O_4^+ = (H_2O)_3H_3O^+$, Zundel cation: $H_5O_2^+ = H_2O\text{-}H^+\text{-}OH_2$)

In a study by Moviat et al,[27] an excellent relation between the strong ion gap and the albumin-corrected and lactate-corrected anion gap was found ($r^2 = .934$), proving the two methods comparable for the investigation of metabolic acid-base disorders in clinical practice—in fact, their conceptual basis is common, that of electrical neutrality. Finally, the point at which Stewart's approach is radically different is the concept of buffering.[28,29] Stewart questions the buffering ability attributed to weak acids. With his analytical approach, he concludes that the presence of a weak acid (HA) in a solution of strong ions—when [SID] has a positive sign, as is normally the case in the body, and in the range from 0 to [A_{TOT}]—results in [H^+] that is greater and varies more for a given change in [SID] than if the weak acid was not present. Thus, in a solution such as plasma, the presence of the weak acid changes the value of [H^+] and pH, for a given [SID] value, to the most acidic side. For Stewart, the buffering capacity of the organism can be estimated by the ratio of the change of each of the independent variables to the corresponding change of pH (or [H^+]). In a study[30] evaluating tissue buffering capacity in severely ill, septic patients, Vasileiadis et al calculated the ratio of central venous-arterial gradients of [SID] (and PCO_2) with the corresponding pH (and [H^+]) gradients, upon ICU admission and at either clinical improvement or severe deterioration. Lower values on admission and higher values at reassessment of certain PCO_2 buffer indices were independently associated with a reduced risk of death in the ICU. The lack of a consistent interpretation of a given buffering index change found in the study led to pathophysiological conclusions with reference to the activation of mitochondrial metabolism (in which CO_2 is produced) during sepsis, in relation to the severity of acid load, that is, the change in pH/[H^+]; indeed, authors deal with protons produced by metabolism(!), 'unbending', somehow, 'in honest defeat'. It should be noted that Stewart's view has been criticized that while it is physicochemically correct, it nevertheless ignores physiology. Indeed, his approach looks mostly mechanistic in nature, interpreting the acid-base

disorders in terms of the surrounding circumstances, that is, the underlying physicochemical forces (approximating a physicochemical determinism), while paying no special attention to a possible teleological element of physiological functions. Whether this will be verified or not will be shown by further studies. Finally, studies confirm the alkaline effect of hypoalbuminaemia, for which a subsequent reduction in [SID] is considered normal compensation.[31,32]

11 | COMMENTS ON THE OCCASION OF THE RECOMMENDED BY BIE ARTICLE BY SIGGAARD-ANDERSEN AND FOGH-ANDERSEN

In the article proposed by Bie (by Siggaard-Andersen and Fogh-Andersen),[8] the authors describe suggested indices (measures) of a non-respiratory acid-base disturbance (in particular, total CO_2, actual bicarbonate, standard bicarbonate, standard pH, buffer base, whole blood base excess and extracellular base excess), culminating in a critique of Stewart's approach. However, throughout the article, there is no conclusive evidence that Stewart's theory is incorrect. Commenting on the concept of buffer base of Singer and Hastings, trying in some way 'to attack evil at the root', they state that the distinction between the so-called aprote (ie strong) ions and buffer (ie weak) ions 'is somewhat arbitrary, depending upon the actual pH interval', and bring as an example the lactate ion, which is considered as an aprote anion at a pH around 7.4, being, however, a buffer ion when the pH is around 3.6. This is of course true; however, at pH around 3.6, the human body would not be alive, so as the lactate anion could act as a weak anion buffer. What is mainly of interest from a physiological point of view is not generally the chemical behaviour of, for example, acids, but their chemical behaviour in the context of the physiological conditions of the organism. Wilkes,[33] utilizing the physicochemical approach, refers to the 'relativity' of the term 'strong ion', providing the following interpretation for the acidic pH (5.5) of NaCl 0.9% solution. Considering that it contains only aprote ions in equimolar concentrations, it should be neutral. Also, the physiochemical approach, superficially viewed, predicts that the [SID] of the solution would be equal to zero. Thus, from the formula that calculates the pH in a solution of strong ions,

$$\left[H^+\right] = \sqrt{K_w' + \frac{[SID]^2}{4}} + \frac{[SID]}{2}$$

Since SID = 0, then $\left[H^+\right] = \sqrt{K_w'}$. So the solution should have pH = 7 (25°C). However, because hydrochloric acid (HCl) is more 'strong' than sodium hydroxide (NaOH) ($K_{HCl} > K_{NaOH}$), the affinity of Na^+ for OH^- will be greater than that of Cl^- for H^+. Therefore, an H^+ 'excess' will be created in relation to the OH^-. This H^+ excess creates the acidic pH. That is, [SID] is not actually zero. For this solution, $[SID] + [H^+] - [OH^-] = 0$, and since $[H^+] - [OH^-] > 0$, [SID] <0. The value of [SID] can be calculated as follows:

Ionic product of water: $[H^+] \times [OH^-] = K_w' \leftrightarrow [OH^-] = K_w'/[H^+]$

Electrical neutrality law: $[SID] + [H^+] - [OH^-] = 0 \leftrightarrow [SID] = [OH^-] - [H^+] \leftrightarrow [SID] = (K_w'/[H^+]) - [H^+]$

$K_w' = 1 \times 10^{-14}$ (Eq/L)^2, $[H^+] = 3.16 \times 10^{-6}$ Eq/L (corresponding to pH = 5.5)

Therefore, $[SID] = -3.1 \times 10^{-6}$ Eq/L

Thus, a very small [SID] creates a very large difference in pH. This is a consequence of the fact that the aqueous NaCl solution has a very low buffering capacity, and for a [SID] value range close to zero a very large change in pH is observed. Wilkes[33] refers to the difference between the 'concentration' of an ion and its 'activity', which actually determines its chemical behaviour.

Authors also refer to the concept of 'anaemic alkalosis with metabolic acidosis' (which they obviously reject and, as they say, would not be used by Singer and Hastings). This is mentioned in obvious analogy to the concept of hypoalbuminaemic alkalosis, which is accompanied by, as predicted by Stewart, compensatory reduction of [SID] and metabolic acidosis. In fact, it is like a logical leap, since in Stewart's book, there is no such reference relating haemoglobin (Hb) anywhere. Hb (in red blood cell intracellular fluid, RBC-ICF) is not considered by Stewart to be an effective buffer for the entire extracellular space buffering. Nevertheless, he accepts that ion movements may occur between RBC-ICF and plasma as a result of changes in Hb concentration, but for Stewart, these ion movements affect the plasma [SID] to a very small extent.[34] Elsewhere, the authors refer to hyperchloremic acidosis as a 'relic of time when chloride was considered an acid', rejecting without strong arguments other than the 'anachronism' of following an 'older' definition for acids, a pathophysiological view that has been one of the main topics of medical research recently, mainly in the field of intensive care.[35] Finally, in their last clinical example of a patient with pH = 7.00, PCO_2 = 16.5 kPa (=123.75 mmHg), extracellular base excess = 0.0 mmol/L, plasma base excess = 3.0 mmol/L, [SID] = 43 mmol/L, $[Cl^-]$ = 102 mmol/L, normal plasma albumin concentration and albumin anion concentration ($[Alb^-]$) = 9 mmol/L, they conclude that following their approach, the patient has pure respiratory acidosis (which is correct since the change in pH is not clearly outside the expected limits for a pure respiratory disorder), noting that Stewart would add that there is also slight metabolic alkalosis. However, since [SID] = 43 mmol/L (normal), a metabolic disorder (relating to a change in [SID]) is not documented. Certainly, one would expect a subsequent

increase in [SID], to compensate for the severe respiratory disorder. In addition, 'to illustrate the unfamiliar and inept terminology resulting from the Stewart approach', authors state that the low [Alb^-] according to Jabor and Kazda[36] would have been interpreted as hypoalbuminic alkalosis, inconsistent with Stewart's approach. The misinterpretation of the physicochemical approach, however, is not evidence of inherent inconsistencies of the approach itself. Indeed, according to Stewart, the independent variable affecting [H^+] is the total concentration ([A_{TOT}] = [HA] + [A^-]) of non-volatile (non-carbonate) weak acids (including albumin) and not the reduced, by an independent change (decrease) of pH, anion concentration ([A^-]). Explicating the issue of [Alb^-] reduction, we could simply refer to the effect of pH change on albumin charge, that is, because of its isoelectric point of 4.7, albumin has a net negative charge at physiological pH; with reduced pH, its negative charge will decrease. Instead, we will approach it in an apparently 'simplistic' way that, however, makes the conceptual difference clear.

Following the physicochemical approach, when albumin concentration (and therefore its weak anion concentration) is reduced, PCO_2 and [SID] being stable, the deficit created in the negative charge space occupied by the weak acid anions will be covered by increasing the concentration of the remaining weak anions (shift of the equilibrium point of the dissociation reactions towards a greater dissociation of the corresponding weak acids). Among these anions are HCO_3^- and OH^-. However, as the ionic product of water ([H^+] × [OH^-]) remains constant, [H^+] changes reciprocally (it decreases), resulting in metabolic alkalosis.

In the case mentioned in the article, with increasing PCO_2, [HCO_3^-] will also significantly increase. If the [SID] does not change, the 'space' occupied by the other weak anions will be reduced, hence the [Alb^-] as well as the [OH^-] will decrease. Following the above reasoning, this will lead to an increase in [H^+] and acidosis. In the first case, the decrease in total albumin concentration (with the consequent decrease in [Alb^-]) was the primary disorder leading to metabolic alkalosis. In the second case, the decrease in [Alb^-] occurs secondarily, as a result of acidosis (by another cause), while the total albumin concentration is constant. Therefore, the reduction of the negative charge of albumin in this case cannot be considered as producing an alkalinizing effect. Interestingly, however, it has been suggested that pH variations in plasma may induce recruitment or de-recruitment of protein-bound strong ions, altering [SID] and buffering the acid-base disturbances.[37] Thus, reduced pH (as a result of increased PCO_2) may lead to release of sodium and calcium, which are electrostatically bound to the negatively charged albumin, increasing [SID]; increased [SID], with its alkalinizing effect, compensates partially for the pH reduction caused by the increased PCO_2.[38]

The authors ultimately 'choose' base excess (especially as calculated for the total extracellular space, ie, the standard base excess, SBE) as the most appropriate indicator for the metabolic component of acid-base disorders. To note, in an attempt to embed the physicochemical approach to acid-base physiology in the SBE concept, the partitioning of SBE into four distinct components has been proposed: (a) Free water effect: $0.3 \times ([Na^+] - 140)$, (b) Chloride effect (corrected for sodium): $104\text{-}[Cl^-] \times (140 \div [Na^+])$, (c) Albumin effect: $(0.148 \times pH - 0.818) \times (40 - [Alb]$ in g/L) and (d) Unmeasured anions: $SBE\text{-}SBE_{FW}\text{-}SBE_{Cl}\text{-}SBE_{Alb}$.[39]

Note that, in this formula, the contribution of albumin to base excess is calculated from the product of *the albumin mass concentration difference from its normal value* and *the value of a parameter, which depends on the pH:* $(0.148 \times pH - 0.818) \times (40 - [Alb]$ in g/L). Thus, if the albumin concentration is normal, the albumin component is eliminated (equals zero). Calculating the difference of the *albumin's anion concentration* (albumin charge, CAlb), based on its actual mass concentration and pH, from *the value that is considered normal* (CAlb°, derived from the normal mass concentration and pH values) is by no means the same thing [$\Delta CAlb = CAlb° - CAlb$, where $CAlb = Alb/10 \cdot (1.23 \cdot pH - 6.31)$]![36]

12 | CONCLUSION

Stewart's approach is by no means the holy grail of acid-base balance and we did not claim that it stands clearly above all others; nevertheless, it surely offers an integrated view, based on a simple but fundamental background. This gives a confidence that is definitely appealing to a scholar. For, in any case, one wants to stand on solid ground. That is fair enough, as long as one has his eyes open for the upcoming refutation, every moment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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