

Review

Science review: Quantitative acid–base physiology using the Stewart model

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Abstract

There has been renewed interest in quantifying acid–base disorders in the intensive care unit. One of the methods that has become increasingly used to calculate acid–base balance is the Stewart model. This model is briefly discussed in terms of its origin, its relationship to other methods such as the base excess approach, and the information it provides for the assessment and treatment of acid–base disorders in critically ill patients.

Keywords acid–base, base excess, Stewart model

Introduction

Acid–base derangements are commonly encountered in the critical care unit [1], and there is renewed interest in the precise description of these disorders in critically ill patients [2–5]. This new interest has led to a renovation of the quantitative assessment of physiological acid–base balance, with increasing use of the Stewart model (strong ion difference [SID] theory) to calculate acid–base balance in the critically ill [2,3,6,7]. This method is discussed, particularly as it pertains to the metabolic component of acid–base derangements, as one of several approaches that may be used in the intensive care unit for quantitative evaluation. As with any mathematical model, a basic understanding of its principles is useful for proper application and interpretation.

Stewart model

All equilibrium models of acid–base balance utilize the same basic concept. Under the assumption of equilibrium or a steady-state approximation to equilibrium, some property of the system (e.g. proton number, proton binding sites, or charge, among other possible properties) is enumerated from the distribution of that property over the various species comprising the system, according to the energetics of the system manifested through the relevant equilibrium constants

of the various species under a given set of conditions [5,8–12]. This function is calculated at the normal values and then the abnormal values; from these the degree of change is obtained to give information about the clinical acid–base status of the patient. All of the apparently 'different' methods for assessing acid–base balance arise from this common framework [5,12].

In the Stewart method, charge is taken as the property of interest [7,11,13]. Using this property, acid–base status may be expressed for a single physiologic compartment, such as separated plasma, as follows [7,10,11,13]:

$$\text{SID} = - C_1 \bar{z}_1 - C_2 \bar{z}_2 - \dots C_n \bar{z}_n \quad (1)$$

Strong ions are those that do not participate in proton transfer reactions, and the SID is defined as the difference between the sum of positive charge concentrations and the sum of negative charge concentrations for those ions that do not participate in proton transfer reactions. C_n are the analytical concentrations of the various buffer species also in the compartment (e.g. of the buffer amino acid groups on albumin), and \bar{z}_n are the average charges of those various species. The \bar{z}_n can be expressed as functions of pH and

BE = base excess; C_{Alb} = albumin concentration; C_{Phos} = phosphate concentration; P_{CO_2} = partial CO_2 tension; SBE = standard base excess; SID = strong ion difference; SIG = strong ion gap.

equilibrium constants [11,12], and it is therefore convenient to calculate SID using Eqn 1 from the pH and the concentrations of relatively few buffer species, as opposed to a direct calculation from a measurement of all of the various strong ion species. In many implementations of the Stewart method, contributions from the water equilibrium and from carbonate species other than bicarbonate are neglected, because these are small under physiologic conditions [11,14,15]. The first term in Eqn 1 may then be equated with the bicarbonate concentration, with the remaining terms referring to other buffer species [11,14].

Plasma physiologic pH is then determined by the simultaneous solution of Eqn 1 and the Henderson-Hasselbalch Equation:

$$\text{pH} = \text{pK}' + \log \frac{[\text{HCO}_3^-]}{S \cdot P_{\text{CO}_2}} \quad (2)$$

Where for human plasma $\text{pK}' = 6.103$. $S = 0.0306$ is the equilibrium constant between aqueous and gas phase CO_2 [16,17]. $[\text{HCO}_3^-]$ is the concentration of plasma bicarbonate in mmol/l, and P_{CO_2} is the partial CO_2 tension in Torr.

The standard technique for acid–base assessment [1,18] may be recognized as a subset of the Stewart model [14], in which the series in Eqn 1 is truncated at the first term to give the following:

$$\text{SID} = [\text{HCO}_3^-] \quad (3)$$

In this approach the metabolic component of an acid–base disorder is quantified as the change in plasma bicarbonate concentration ($\Delta[\text{HCO}_3^-]$) [18], which by Eqn 3 is also equal to ΔSID . This method is often sufficient and has been used successfully to diagnose and treat countless patients, but it has also been criticized as not strictly quantitative [19,20]. $[\text{HCO}_3^-]$ depends upon the P_{CO_2} and does not provide complete enumeration of all species, because albumin and phosphate also participate in plasma acid–base reactions [15,17,20,21].

A more complete calculation may be undertaken for better approximation by including more terms in the series in Eqn 1. In addition, although \bar{z}_n is a nonlinear function of pH, it can be approximated over the physiologic range by a more computationally convenient linear form, such that for plasma the following explicit expression is obtained [11,12,15]:

$$\text{SID} = [\text{HCO}_3^-] + C_{\text{Alb}} (8.0\text{pH} - 41) + C_{\text{Phos}} (0.30\text{pH} - 0.4) \quad (4)$$

Where C_{Alb} and C_{Phos} are plasma albumin and phosphate concentrations, respectively. All concentrations are in mmol/l. One may multiply albumin in g/dl by 0.15 to obtain albumin in mmol/l, and phosphate in mg/dl by 0.322 to get phosphate in mmol/l. The factors 8.0 and 0.30 are the molar buffer values

of albumin and phosphate, respectively. The buffer value is the change in \bar{z}_n of a species for a one unit change in pH [5,11,17]. Note that the ability of a system to resist pH change also increases with C_{Alb} and C_{Phos} [11].

Equation 4 was obtained via a term by term summation over all of the buffer groups in albumin and of phosphoric acid, as performed by Figge and coworkers [15,21]. The theoretical basis for the validity of this approach is well established [8], and Eqn 4 has been shown to reproduce experimental data well [11,12,15,21,22]. Some authors have argued that the effects of plasma globulins should also be considered for better approximation [17,20,23,24], although other calculations suggest that the consideration of globulins would be of little clinical significance in humans [22].

Consideration of the change in SID using Eqn 4 between normal and abnormal states at constant albumin and phosphate concentrations gives the following:

$$\Delta\text{SID} = \Delta[\text{HCO}_3^-] + (8.0C_{\text{Alb}} + 0.30C_{\text{Phos}})\Delta\text{pH} \quad (5)$$

Which is recognized to be of the same form and numerically equivalent to the familiar Van Slyke equation for plasma, yielding the plasma base excess (BE) [5,11,17,25]. Furthermore, Eqn 4 is of the same form as the CO_2 equilibration curve of the BE theory presented by Siggaard-Andersen [11,17,20,25]. The BE approach and the Stewart method are equivalent at the same level of approximation [11,12,26].

Strong ion gap

A widely used concept arising from the Stewart approach is the strong ion gap (SIG), which was popularized by Kellum [27] and Constable [28]. This relies upon a direct calculation of the SID as, for example, the following:

$$\text{SID}_m = [\text{Na}^+] + [\text{K}^+] + 2[\text{Mg}^{2+}] + 2[\text{Ca}^{2+}] - [\text{Cl}^-] - [\text{lactate}^-] - [\text{urate}^-] \quad (6)$$

Where SID_m is the measured SID [27]. This direct measurement is then compared with that generated via Eqn 4:

$$\text{SIG} = \text{SID}_m - \text{SID} \quad (7)$$

This gives a higher level version of the familiar plasma anion gap [1,18]. Some publications have used the notation SID_a (for SID apparent) to refer to the variable SID_m calculated using Eq. 6, and SID_e (SID effective) to refer to that calculated using Eqn 4 [2,3,15,27]. SIG has been shown to predict the presence of unmeasured ions better than the conventional anion gap [28], as might be expected, given that more variables are taken into account. Some unmeasured ions that are expected to contribute to the SIG are β -hydroxybutyrate, acetoacetate, sulfates, and anions associated with uremia [6].

Table 1

Acid-base parameters for a normal and two abnormal cases

Case	pH	[HCO ₃ ⁻] (mmol/l)	C _{Alb} (mmol/l)	C _{Phos} (mmol/l)	PCO ₂ (Torr)	SID (mmol/l)
1 (normal)	7.40	24.25	0.67	1.16	40.0	39
2	7.30	15.27	0.67	1.16	31.7	29
3	7.40	24.25	0.15	1.16	40.0	29

Case 1 is for a normal individual, case 2 is for a metabolic acidosis at constant noncarbonate buffer concentrations, and case 3 is for hypoproteinemia. C_{Alb}, albumin concentration; C_{Phos}, phosphate concentration; PCO₂, partial CO₂ tension; SID, strong ion difference.

Changes in noncarbonate buffer concentration

Δ SID expressed through the relationship of Eqn 5 unambiguously quantifies the nonrespiratory component of an acid-base disturbance in separated plasma [11,17], with the total concentrations of amphoteric species such as albumin and phosphate remaining constant [11,12,17]. An amphoteric substance is one that can act as both an acid and a base. Stewart and other investigators [4,7,29–33], though, have emphasized the role played by changes in the noncarbonate buffer concentrations in acid-base disorders. When the noncarbonate buffer concentrations change, the situation becomes more complex, and in general a single parameter such as Δ SID no longer necessarily quantifies the metabolic component of an acid-base disorder, and enough variables must be examined to characterize the disorder unambiguously. Examples below demonstrate this point when the concentrations of noncarbonate buffers change, through a pathologic process or through resuscitation.

Table 1 gives several examples for separated human plasma, including the normal values of case 1. Case 2 demonstrates a metabolic acidosis with constant noncarbonate buffer concentrations, in which the Δ SID of -10 mmol/l quantifies the metabolic component of the acid-base disorder [11], which has been described as a strong ion acidosis [4]. Case 3 gives values for the fairly common occurrence of isolated hypoproteinemia. This too gives a Δ SID of -10 mmol/l, although the total weak acid and weak base concentrations have both decreased [11]. The physiological interpretation of this condition in terms of acid-base pathology is the subject of debate [3,6,12,20,31,34]. Considering this to be an acid-base disorder, some authors would classify this case as hypoproteinemic alkalosis with a compensating SID acidosis [4,6,30–32]. More generally, this has been termed a buffer ion alkalosis with compensating strong ion acidosis [4]. If the mechanism of hypoalbuminemia is *en bloc* loss of charged albumin with counterions in tow, for example in nephrotic syndrome, then it seems dubious to describe this process as compensation in the usual physiologic sense. Also, note that both cases 2 and 3 have the same decrease

in SID, but the individual in case 2 is expected to be quite sick with acidemia whereas the patient in case 3 is probably not acutely ill, except for the effects of low oncotic pressure.

Although it has been suggested that alkalosis can result from hypoproteinemia, with patients without adequate compensation becoming alkalemic [29,32], the idea of alterations in protein concentration as acid-base disorders *per se* has been questioned [3,20]. The concept of the normal SID changing as a function of protein concentration has been suggested [3,11,12]. In such an instance, Δ SID again quantifies the metabolic component of an acid-base disturbance, essentially renormalizing the noncarbonate buffer concentrations to the abnormal values [11,12]. This is basically what has been advocated in the past for BE [20,34], in which Eqn 5 uses the abnormal protein and phosphate concentrations for C_{Alb} and C_{Phos} [11]. Thus, the SID of 29 mmol/l in case 3 is said to be normal for the decreased albumin concentration [3], giving a Δ SID of 0 mmol/l. This individual will, however, be more susceptible to acidemia or alkalemia for a given derangement, as expressed through the molar buffer values and noncarbonate buffer concentrations, than would a normal individual [5]. If SID is not renormalized as described above, then BE and Δ SID differ by an added constant [11,12].

Another interesting issue is raised in the treatment of patients with intravenous albumin or other amphoteric species. Kellum previously pointed out that, based on the SID, one might think that albumin solutions with a SID of 40–50 mmol/l would be alkalinizing to the blood, even though their pH is close to 6.0 [35]. This apparent paradox is resolved by again realizing that, for amphoteric substances, one is not only changing the SID but also increasing both the total weak acid and weak base concentrations by increasing the total protein concentration [9,11]. This highlights the point made by Stewart concerning the necessity of considering all variables in assessing acid-base balance [7,13]. A complete calculation yields what is intuitively predicted – that such a solution is in fact acidifying to blood (unpublished data). One might further speculate that the administration of ‘unbuffered’ albumin to patients may contribute to the reason why this treatment has not been more successful in the critically ill

[36]. Extensive quantitative discussions regarding the acid–base balance of administered fluids have typically not been given in publications on resuscitation with amphoteric colloids [36–39], although this is an issue that should be examined. Constable [40] recently gave a brief quantitative discussion of acid–base effects of giving various crystalloids.

Model for whole blood

Several points arise in the comparison of SID with BE, as has been performed in a number of studies [33,38,41–44]. This is in some respects a misplaced comparison, because BE represents a difference whereas SID does not [11,26]. The corresponding variable to SID in the BE formalism is the concentration of total proton binding sites, while the BE represents the change in this quantity from the normal value, and corresponds to Δ SID [11,12,17,26]. More significant, clinical studies using Stewart theory have calculated the separated plasma SID, while making comparison with the BE for whole blood or the standard base excess (SBE) [33,38,41,42], rather than the corresponding plasma BE. Furthermore, consideration of only the plasma compartment creates a potential source of error, because separated plasma versions of the Stewart method quantify only a portion of the acid–base disorder [12,17,45]. An equation for the SID of whole blood has recently been derived, partly to address this issue [12].

$$\begin{aligned} \text{SID(B)} = & \left\{ 1 - 0.49\phi(\text{E}) \right\} [\text{HCO}_3^-]_p \\ & + \left\{ 1 - \phi(\text{E}) \right\} \left\{ C_{\text{Alb}}(\text{P})(8.0 \text{ pH(P)} - 4.1) + C_{\text{Phos}}(\text{P})(0.30 \text{ pH(P)} - 0.4) \right\} \\ & + C_{\text{Hgb}}(\text{B}) \left\{ 0.2(\text{pH(P)} - 0.21) - 71.5 \right\} + \phi(\text{E}) C_{\text{DPG}}(\text{E}) \left\{ 0.70(\text{pH(P)} - 0.21) - 0.4 \right\} \end{aligned} \quad (8)$$

Where $\phi(\text{E})$ is the hematocrit, $C_{\text{Hgb}}(\text{B})$ is the hemoglobin concentration of whole blood, and $C_{\text{DPG}}(\text{E})$ is the 2,3-diphosphoglycerate concentration in the erythrocyte. Again, concentrations are in mmol/l, and one may multiply hemoglobin in g/dl by 0.155 to obtain hemoglobin in mmol/l. The normal 2,3-diphosphoglycerate concentration in the erythrocyte is 6.0 mmol/l [12]. The 'P', 'B', and 'E' designations stand for plasma, whole blood, and erythrocyte fluid, respectively. The corresponding Van Slyke form has also been obtained, and is numerically identical to BE for whole blood [12].

The SBE, as mentioned above, is also widely used [3,17,20,25]. This parameter reflects the extracellular acid–base status and approximates the *in vivo* BE for the organism [17,20,25]. The Van Slyke equation for SBE approximates this situation via a 2:1 dilution of whole blood in its own plasma [17,20,25]. It should be borne in mind, therefore, that Eqn 4 may prove more concordant with clinical data than Eqn 8, since the plasma expression may produce values closer to the *in vivo* condition because of the distribution functions of various species across the whole organism [17].

Stewart theory and mechanism

Finally, the Stewart model is taken by some to be a mechanistic description of acid–base chemistry in which changes only occur by alteration in PCO_2 , SID, or noncarbonate buffer concentrations because these are the only true independent variables; changes never occur by addition or removal of H^+ to the system or by changes in $[\text{HCO}_3^-]$ because these are dependent variables [7,13]. It is said that because the Stewart theory provides mechanistic information, it is superior to the BE approach [3,35,46,47]. Support for this point of view is offered in the form of philosophic arguments regarding the nature of independence [7,13], as well as studies showing that the Stewart model accurately predicts what is observed experimentally [30,42,44,48]. However, like the BE approach and like any other method derived from considerations involving the calculation of interval change via the assessment of initial and final equilibrium states, the Stewart method does not produce mechanistic information [8,35]. These are basically bookkeeping methods. To believe otherwise risks falling prey to the *computo, ergo est* (I calculate it, therefore it is) fallacy. What is thus required for mechanistic understanding is the collection of actual mechanistic data, perhaps obtainable through isotopic labeling and kinetics experiments.

Conclusion

Both experimental and theoretical data have shown that the Stewart method is accurate for describing physiological acid–base status, and the use of the SIG potentially offers an improvement over the traditional anion gap, but because the Stewart method proceeds from the same common framework as the BE approach, it theoretically offers no quantitative advantage over BE at corresponding levels of approximation [11,12,26,35,49]. As such, it remains to be seen whether the renovation of acid–base assessment afforded by the Stewart approach constitutes a radical new architecture for understanding acid–base physiology, or whether it is simply a new façade.

Competing interests

The author(s) declare that they have no competing interests.

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