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# THE STANDARD STRONG ION DIFFERENCE, STANDARD TOTAL TITRATABLE BASE, AND THEIR RELATIONSHIP TO THE BOSTON COMPENSATION RULES AND THE VAN SLYKE EQUATION FOR EXTRACELLULAR FLUID

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**ABSTRACT.** A general formalism for calculating physiological acid–base balance in multiple compartments is extended to the combined interstitial, plasma, and erythrocyte multicompartment system in humans using the Siggaard-Andersen approximation for interstitial fluid. The resulting equations for total titratable base and strong ion difference reproduce the experimental in vivo carbon dioxide titration curve as well as the experimental strong ion difference value of the interstitial, plasma, and erythrocyte system in normal man. The ''Boston rules'' for compensation in acute respiratory acidosis and alkalosis are then derived analytically from the model. The Van Slyke equation for the interstitial, plasma, and erythrocyte system is also derived and shown to approximate the Van Slyke equation for standard base excess.

**KEY WORDS.** strong ion difference, Stewart method, base excess, Van Slyke equation, respiratory acidosis, respiratory alkalosis, Boston rules.

## INTRODUCTION

The quantitative description of physiological acid–base balance continues to generate both interest and controversy [1–3]. One of the most widely used methods to calculate the metabolic component of an acid–base disorder is the base excess approach developed by Siggaard-Andersen et al. [4]. The base excess was originally calculated from nomograms [4], but today is usually calculated by the Van Slyke equation, also derived by Siggaard-Andersen [4–6]. Van Slyke equations have been developed for plasma, whole blood, and the interstitial, plasma, and erythrocyte system, which Siggaard-Andersen referred to as the extracellular fluid [4–6]. A different strategy for the calculation and assessment of acid–base balance is the strong ion difference theory or Stewart method [7–14]. In addition, using a more general approach, encompassing both the base excess and Stewart methodologies, equations have previously been derived for the total titratable base and strong ion difference of plasma and whole blood [7, 8]. In what follows, this general formalism is used to develop equations for the total titratable base and strong ion difference of the interstitial, plasma, and erythrocyte system and are shown to reproduce in vivo data. The relationship of the equations for this system to the existing base excess and Stewart equations as well as to the bicarbonate based ''Boston

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approach'' [1, 15–18] is also discussed. The development of the Van Slyke equation is first reviewed by way of introduction.

The Van Slyke equation was initially obtained for human separated plasma as

$$\mathrm{BE(P)} = \Delta[\mathrm{HCO_3}^-]_\mathrm{P} + \beta(\mathrm{P})\Delta\mathrm{pH(P)} \quad (1)$$

where BE(P) is the base excess of plasma, $\beta$(P) is the buffer value of plasma, and $\Delta[\mathrm{HCO_3}^-]_\mathrm{P}$ and $\Delta$pH(P) are the changes in the plasma bicarbonate concentration and plasma pH, respectively [4, 5, 7, 8].

Because it was recognized that the plasma compartment is in equilibrium with the intracellular compartment of the erythrocytes, and that the buffering capacity of erythrocytes is substantial [4, 5], the Van Slyke equation was derived semiempirically for human whole blood in the form [4–6, 8]

$$\mathrm{BE(B)} = \left\{1 - \frac{\mathrm{C}_{Hgb}(\mathrm{B})}{\mathrm{C}^{\mathrm{o}}_{Hgb}}\right\}\left\{\Delta[\mathrm{HCO_3^-}] + \beta'_\mathrm{B}(\mathrm{B})\Delta\mathrm{pH(P)}\right\} \quad (2)$$

where BE(B) is the base excess of whole blood, $\mathrm{C}_{Hgb}$(B) is the hemoglobin concentration of whole blood, $\mathrm{C}^{\mathrm{o}}_{Hgb}$ is a value assumed to be constant which depends upon the erythrocyte fluid hemoglobin concentration and the bicarbonate Donnan ratio between the plasma and erythrocyte compartments, and $\beta'_\mathrm{B}$(B) is the effective buffer value of whole blood given by [5, 6, 8]

$$\beta'_\mathrm{B}(\mathrm{B}) = \mathrm{C}_{Hgb}(\mathrm{B}) \cdot \beta'_\mathrm{B}(\mathrm{E}) + \beta'_\mathrm{B}(\mathrm{P}) \quad (3)$$

$\beta'_\mathrm{B}$(E) is described as an apparent molar buffer value for the hemoglobin monomer [5, 6, 8]. There is some discrepancy regarding $\beta'_\mathrm{B}$(P), which has been described as both equivalent to the buffer value of plasma [5, 6] and as an effective buffer value for plasma [8].

While Equations 1 and 2 reproduce experimental data for separated plasma and whole blood in vitro, neither is able to reproduce the experimental in vivo carbon dioxide titration curve in humans [4, 6]. The reason for this is thought to be that just as the plasma compartment is in equilibrium with the erythrocyte compartment, the true plasma of whole blood is in equilibrium with the interstitial fluid compartment. To account for this, Siggaard-Andersen proposed that $\mathrm{C}_{Hgb}$(B) be replaced with one-third of its value, $\mathrm{C}_{Hgb}$(B)/3, in Equations 2 and 3 [4, 6]. This approximation was found to reproduce the in vivo carbon dioxide titration curve [4], and has also been described as diluting whole blood in its own plasma 2:1 [4, 6]. Siggaard-Andersen called this calculated base excess the base excess of extracellular fluid or standard base excess [4, 6] and has asserted that this is the most relevant measure of the metabolic component of an acid–base disorder [4, 6].

Siggaard-Andersen derived the Van Slyke equation by seeking an expression for the change in total titratable base directly [4, 5]. A different approach, which encompasses both the base excess [4, 7, 8] and Stewart [7–14] approaches to physiological acid–base balance, calculates the total titratable base, in the case of base excess, or the strong ion difference, in the case of the Stewart method [7, 8]. The advantage is that this more general approach has more general applications, for example in resuscitation [19–21]. The calculated strong ion difference can also be compared to the value determined from ion concentrations to obtain the strong ion gap to assess for unmeasured ions [22]. The previously derived total titratable base and strong ion difference equations reproduce experimental data well for both separated plasma [7] and whole blood in vitro [8], but like the corresponding Van Slyke equations, do not reproduce the experimental human in vivo $\mathrm{CO_2}$ titration curve.

An alternate method to the base excess and Stewart methods for the clinical evaluation of acid–base status is the bicarbonate based ''Boston approach'' [1, 15–18]. This method uses an empirical set of rules, sometimes called the ''Boston rules'', which examine values for plasma arterial proton or bicarbonate concentration, together with carbon dioxide partial pressure, to determine the type of acid–base disorder present and the degree of compensation [16, 17]. The Boston approach has been at least implied by some authors to be entirely separate from the base excess method [1, 15], although similar rules have been empirically determined in terms of standard base excess [18].

The Siggaard-Andersen approximation for the interstitium is applied to the general multicompartment model developed previously [8] to obtain equations for the total titratable base and the strong ion difference of the combined human interstitial, plasma, and erythrocyte system. It is then shown that the empirical Boston rules for pure respiratory disturbances can be derived analytically from the theory. Using the same model, the Van Slyke form for the interstitial, plasma, and erythrocyte system is derived, approximating the equation obtained semiempirically by Siggaard-Andersen for the standard base excess.

## THEORY

The acute response to plasma $\mathrm{P_{CO_2}}$ changes in vivo can be calculated by considering the oxygenated arterial plasma compartment in equilibrium with the erythrocyte compartment and the interstitial fluid compartment [4]. Intracellular and bone buffering occurs over a longer time course, and so may be neglected in the consideration of the acute response to changes in $\mathrm{P_{CO_2}}$ [4]. As discussed previously [8], the relevant generalized acid–base parameter is

$$P(IPE) = \sum_{\chi} \phi_{IPE}(\chi) P(\chi) \tag{4}$$

where $P(IPE)$ is an acid–base concentration parameter, in this case either total titratable base or strong ion difference, for the total plasma, erythrocyte, and interstitial fluid system denoted by *IPE*. Siggaard-Andersen refers to this system as the extracellular fluid [4, 6], but since it includes red blood cells, the label is somewhat misleading. The $P(\chi)$ are the parameters for the single compartment $\chi$ for plasma ($\chi$ = P), erythrocyte fluid ($\chi$ = E), and interstitial fluid ($\chi$ = I). The volume fractions $\phi_{IPE}(\chi)$ refer to the fraction of the total *IPE* system, as opposed, for example, to the hematocrit $\phi_B(E)$ for whole blood described before [8]. The nonlinear and linear models for separated plasma $P(P)$, the erythrocyte compartment $P(E)$, and whole blood $P(B)$ have been described previously in detail [7, 8]. The present problem reduces to finding an expression for $P(I)$, which represents either the total titratable base $C_B(I)$ or the strong ion difference SID(I) of the interstitial compartment.

In the previous models, the $P(\chi)$ could be calculated from the chemical structure, equilibrium constants, and analytical concentrations of the noncarbonate buffer species in compartment $\chi$, together with the proton and bicarbonate concentrations in compartment $\chi$ [8]. When one considers the heterogeneity of the interstitial fluid compartment and the extracellular matrix across multiple different organs and tissues [23–27], with multiple types of collagen and proteoglycans, the enormity and difficulty of formulating a similar solution for $P(I)$ becomes immediately apparent. Siggaard-Andersen's approximation to the Van Slyke equation to solve this problem is applied to the previously developed theory for plasma, erythrocyte fluid, and whole blood in order to obtain similar equations for the *IPE* system as detailed below.

### *The Siggaard-Andersen approximation*

Siggaard-Andersen modeled the base excess of the *IPE* system by diluting blood in its own plasma, under the assumption that the interstitial fluid is identical to plasma [4]. That this is a workable assumption derives from the fact that the experimental strong ion composition and buffer value of interstitial fluid are basically the same as plasma [4, 25, 27].

Under this approximation using Equation 4

$$P(IPE) = \frac{V_B P(B) + V_I P(P)}{V_B + V_I} \tag{5}$$

$V_B$ and $V_I$ are the volumes of blood and the interstitial fluid, respectively, which together make up the total volume of the *IPE* system. Since $V_I$ is approximately twice $V_B$ for normal fluid status, Equation 5 shows that this amounts to diluting whole blood 2:1 in its own plasma as asserted by Siggaard-Andersen [4, 6].

Using the results obtained previously [7, 8] in Equation 5 gives

$$P(IPE) = \frac{\lambda \phi_B(E) V_B}{V_B + V_I} P(E) + \left\{ 1 - \frac{(\lambda \phi_B(E) V_B)}{V_B + V_I} \right\} P(P) \tag{6}$$

where $\phi_B(E)$is the whole blood hematocrit, and $\lambda$ is a factor which accounts for trapped plasma between the erythrocytes in the vessels. $\lambda\phi_B(E)$ is referred to as the whole body hematocrit [4, 27]. The calculation of $P(P)$ and $P(E)$ have been described previously for both the nonlinear and linear approximation cases [7, 8]. The linear forms are more easily manipulated and have been shown to be good approximations to the complete nonlinear cases [7, 8]. The linear approximations are therefore used in the subsequent derivations. After substitution of the linear equations from references 7 and 8 into Equation 6, the resulting total titratable base and strong ion difference for the *IPE* system with fully oxygenated erythrocyte fluid are stated explicitly as

$$\begin{aligned} C_B(IPE) = & \left\{ 1 - \frac{(1 - r_c(E))\lambda \phi_B(E) V_B}{V_B + V_I} \right\} [HCO_3^-]_P \\ & + \left( 1 - \frac{\lambda \phi_B(E) V_B}{V_B + V_I} \right) \{ C_{Alb}(P)(8.0\text{pH}(P) + 53) \\ & + C_{Phos}(P)(0.30\text{pH}(P) - 0.4) \} \\ & + \frac{\lambda V_B}{V_B + V_I} C_{Hgb}(B)\{10.2\text{pH}(P) + 12.4\} \\ & + \frac{\lambda \phi_B(E) V_B}{V_B + V_I} C_{DPG}(E)\{0.70\text{pH}(P) - 0.5\} \end{aligned} \tag{7}$$

and

$$\begin{aligned} \text{SID}(IPE) = & \left\{ 1 - \frac{(1 - r_c(E))\lambda \phi_B(E) V_B}{V_B + V_I} \right\} [HCO_3^-]_P \\ & + \left( 1 - \frac{\lambda \phi_B(E) V_B}{V_B + V_I} \right) \{ C_{Alb}(P)(8.0\text{pH}(P) - 41) \\ & + C_{Phos}(P)(0.30\text{pH}(P) - 0.4) \} \\ & + \frac{\lambda V_B}{V_B + V_I} C_{Hgb}(B)\{10.2\text{pH}(P) - 73.6\} \\ & + \frac{\lambda \phi_B(E) V_B}{V_B + V_I} C_{DPG}(E)\{0.70\text{pH}(P) - 0.5\} \end{aligned} \tag{8}$$

with $C_B(IPE)$ and SID($IPE$) indicating the total titratable base and strong ion difference, respectively, of the interstitial, plasma, and erythrocyte system. $C_{Alb}(P)$ and $C_{Phos}(P)$ are the albumin and phosphate concentrations of plasma, respectively. $C_{Hgb}(B)$ is the hemoglobin concentration of whole blood, $C_{DPG}(E)$ is the 2,3-diphosphoglycerate

concentration in the erythrocyte, pH(P) is the plasma pH, and $[HCO_3^-]_P$ is the plasma bicarbonate concentration. $r_c(E)$ is the bicarbonate Donnan ratio between the plasma and erythrocyte compartments. All concentrations are in millimoles per liter. Plasma albumin in g/dL may be multiplied by 0.15 to obtain mM, and phosphate in mg/dL by 0.322 to obtain mM [28]. Hemoglobin in g/dL may be multiplied by 0.155 to obtain mM [28].

Using the normal values for blood volume $V_B = 5$ and interstitial fluid volume $V_I = 10$ L along with $r_c(E) = 0.51$ [4, 5, 8], Equations 7 and 8 become for normal volume status

$$\begin{aligned} C_B(IPE) &= (1 - 0.17\phi_B(E))[HCO_3^-]_P \\ &+ (1 - 0.33\phi_B(E))\{C_{Alb}(P)(8.0pH(P) + 53) \\ &+ C_{Phos}(P)(0.30pH(P) - 0.4)\} \\ &+ 0.33C_{Hgb}(B)\{10.2pH + 12.4\} \\ &+ 0.33\phi_B(E)C_{DPG}(E)\{0.70pH(P) - 0.5\} \end{aligned} \quad (9)$$

and

$$\begin{aligned} SID(IPE) &= (1 - 0.17\phi_B(E))[HCO_3^-]_P \\ &+ (1 - 0.33\phi_B(E))\{C_{Alb}(P)(8.0pH(P) - 41) \\ &+ C_{Phos}(P)(0.30pH(P) - 0.4)\} \\ &+ 0.33C_{Hgb}(B)\{10.2pH(P) - 73.6\} \\ &+ 0.33\phi_B(E)C_{DPG}(E)\{0.70pH(P) - 0.5\} \end{aligned} \quad (10)$$

As the normal $\lambda = 0.96$ does not have a significant effect on the final value, it has been set to unity. Physiological pH is then determined by the simultaneous solution of Equations 9 or 10 and the well known equilibrium relationship [4, 8, 17]

$$K' = \frac{[H^+]_P[HCO_3^-]_P}{S \cdot P_{CO_2}(P)} \quad (11)$$

For human plasma $pK' = 6.103$ [4, 17]. S is the equilibrium constant between aqueous dissolved $CO_2$ and $CO_2$ in the gas phase and equals 0.0306 at 37°C, when the proton plasma concentration $[H^+]_P$ is in moles per liter, $[HCO_3^-]_P$ is in millimoles per liter, and the partial pressure of carbon dioxide $P_{CO_2}(P)$is in Torr [17].

### *Relationship to the Boston rules for acute respiratory acid–base disorders*

The acute in vivo carbon dioxide titration curve represents a pure respiratory acid–base disorder, for which $\Delta C_B(IPE) = \Delta SID(IPE) = 0$ mM, even though $\Delta[HCO_3^-]_P \neq 0$ mM. As an alternate method of analysis to the base excess and strong ion difference approaches, the Boston rules can also be used to determine whether a given set of $[H^+]_P$, $[HCO_3^-]_P$, and $P_{CO_2}(P)$ represents a pure respiratory acidosis or alkalosis [16, 17]. The compensation equations are empirical [16, 29], but it is possible to derive the empirical rules theoretically for acute respiratory disorders from the above model. The derivation of the bicarbonate based Boston rules for acute respiratory acidosis and alkalosis from Equation 10 is given below using the strong ion difference parameter. Equation 11 is substituted into Equation 10 with substitution of the normal values for the noncarbonate buffer concentrations and constants [7, 8] to give

$$\begin{aligned} [H^+]_P SID(IPE) &= -81[H^+]_P - 5.8[H^+]_P Ln[H^+]_P \\ &+ 0.925K'SP_{CO_2}(P) \end{aligned} \quad (12)$$

where the definition of pH

$$pH(P) = \frac{Ln[H^+]_P}{Ln10} \quad (13)$$

has been utilized. *Ln* denotes the natural logarithm. The second term on the right side of Equation 12 involving $[H^+]_P Ln[H^+]_P$ is now expanded to first order in a power series in $[H^+]_P$ about an arbitrary nonzero concentration point $[H^+]_o$, and the resulting equation rearranged to give

$$[H^+]_P = \frac{5.8[H^+]_o + 0.925K'SP_{CO_2}(P)}{86.8 + 5.8Ln[H^+]_o + SID(IPE)} \quad (14)$$

Taking the derivative of $[H^+]_P$ with respect to $P_{CO_2}(P)$ gives

$$\frac{\partial[H^+]_P}{\partial P_{CO_2}(P)} = \frac{0.925K'S}{86.8 + 5.8Ln[H^+]_o + SID(IPE)} \quad (15)$$

The analogous equation for plasma bicarbonate may be obtained similarly starting with Equation 10 and inserting normal values for noncarbonate buffer concentrations and constants [7, 8] to give

$$SID(IPE) = -81 - 5.8Ln[H^+]_P + 0.925[HCO_3^-]_P \quad (16)$$

The analogous power series expansion of the second term in Equation 16 on the right to first order is then performed and the result rearranged to yield

$$\begin{aligned} [H^+]_P &= -13[H^+]_o + 0.16[H^+]_o[HCO_3^-]_P \\ &- [H^+]_o Ln[H^+]_o - 0.17[H^+]_o SID(IPE) \end{aligned} \quad (17)$$

Substituting Equation 17 into Equation 14, rearranging, and taking the derivative as before provides

$$\frac{\partial[\mathrm{HCO_3^-}]_\mathrm{P}}{\partial \mathrm{P_{CO_2}(P)}} = \frac{5.8K'\mathrm{S}}{[\mathrm{H^+}]_\mathrm{o}\{86.8 + 5.8Ln[\mathrm{H^+}]_\mathrm{o} + \mathrm{SID}(IPE)\}} \quad (18)$$

which gives the analogous relationship to Equation 15 in terms of bicarbonate.

*Relationship to the Van Slyke equation for standard base excess*

Using the derivation described in detail previously [8], the equations for $\mathrm{C_B}(IPE)$ and $\mathrm{SID}(IPE)$ may be recast with constant noncarbonate buffer concentrations (normal or abnormal) in the form of the Van Slyke equation [4–6, 8]

$$\mathrm{SBE} = \mathrm{BE(ECF)} = \Delta\mathrm{C_B}(IPE) = \Delta\mathrm{SID}(IPE) = \left\{V^* - \frac{\mathrm{C}_{Hgb}(\mathrm{B})}{\mathrm{C}^*_{Hgb}}\right\}\{\Delta[\mathrm{HCO_3^-}]_\mathrm{P} + \beta'(IPE)\Delta\mathrm{pH(P)}\} \quad (19)$$

where SBE is the standard base excess, which is equal to BE(ECF), the base excess of the extracellular fluid, which is equivalent to both $\Delta\mathrm{C_B}(IPE)$ and $\Delta\mathrm{SID}(IPE)$, the changes in the total titratable base and the strong ion difference, respectively, of the interstitial, plasma, and erythrocyte system for constant noncarbonate buffer concentrations [7, 8].

The $\mathrm{C}^*_{Hgb}$ is given by

$$\mathrm{C}^*_{Hgb} = \frac{\mathrm{C}_{Hgb}(\mathrm{E})(V_\mathrm{B} + V_\mathrm{I})}{V_\mathrm{B}(1 - r_c(\mathrm{E}))} \quad (20)$$

with $\mathrm{C}_{Hgb}(\mathrm{E})$ representing the erythrocyte fluid hemoglobin concentration with the other variables as given above. The $V^*$ term is

$$V^* = \frac{V_\mathrm{B} + V_\mathrm{I} r_c(\mathrm{I})}{V_\mathrm{B} + V_\mathrm{I}} \quad (21)$$

where $r_c$ (I) is the bicarbonate Donnan ratio between the plasma and interstitial fluid compartments.

$$\beta'(IPE) = \mathrm{C}_{Hgb}(\mathrm{B}) \cdot \beta'_{IPE}(\mathrm{E}) + \beta'_{IPE}(\mathrm{P}) + \beta'_{IPE}(\mathrm{I}) \quad (22)$$

with effective buffer values for plasma in the erythrocyte, plasma, and interstitial compartments of $\beta'_{IPE}(\mathrm{E})$, $\beta'_{IPE}(\mathrm{P})$, and $\beta'_{IPE}(\mathrm{I})$, respectively.

$$\beta'_{IPE}(\mathrm{E}) = \frac{V_\mathrm{B}\{\mathrm{pH'(E)}\beta(\mathrm{E}) - \beta(\mathrm{P})\}}{V_\mathrm{B}\{\mathrm{C}_{Hgb}(\mathrm{E}) - (1 - r_c(\mathrm{E}))\mathrm{C}_{Hgb}(\mathrm{B})\} + V_\mathrm{I} r_c(\mathrm{I})\mathrm{C}_{Hgb}(\mathrm{E})} \quad (23)$$

$$\beta'_{IPE}(\mathrm{P}) = \frac{\beta(\mathrm{P})V_\mathrm{B}\mathrm{C}_{Hgb}(\mathrm{E})}{V_\mathrm{B}\{\mathrm{C}_{Hgb}(\mathrm{E}) - (1 - r_c(\mathrm{E}))\mathrm{C}_{Hgb}(\mathrm{B})\} + V_\mathrm{I} r_c(\mathrm{I})\mathrm{C}_{Hgb}(\mathrm{E})} \quad (24)$$

$$\beta'_{IPE}(\mathrm{I}) = \frac{\beta(\mathrm{I})V_\mathrm{I}\mathrm{pH'(I)}\mathrm{C}_{Hgb}(\mathrm{E})}{V_\mathrm{B}\{\mathrm{C}_{Hgb}(\mathrm{E}) - (1 - r_c(\mathrm{E}))\mathrm{C}_{Hgb}(\mathrm{B})\} + V_\mathrm{I} r_c(\mathrm{I})\mathrm{C}_{Hgb}(\mathrm{E})} \quad (25)$$

where pH′(E) and pH′(I) are the partial derivatives of pH in the erythrocyte and interstitial compartments, respectively, with respect to the plasma compartment pH [4, 8]. $\beta$(E), $\beta$(P), and $\beta$(I) are the true molar buffer values in the erythrocyte, plasma, and interstitial compartments, respectively. Again, $\lambda$ is assumed to be unity.

There are several features to note regarding Equations 19–25. The first is that if $V_\mathrm{I}$ is set to zero, then the equations collapse to the case for whole blood derived previously [8]. If the Siggaard-Andersen approximation for interstitial fluid is applied, in which $\beta$(I) = $\beta$(P), pH′(I) = 1, and $r_c$ (I) = 1, Equations 19–25 become

$$\mathrm{SBE} = \mathrm{BE(ECF)} = \Delta\mathrm{C_B}(IPE) = \Delta\mathrm{SID}(IPE) = \left\{1 - \frac{V_\mathrm{B}\mathrm{C}_{Hgb}(\mathrm{B})}{(V_\mathrm{B} + V_\mathrm{I})\mathrm{C}^*_{Hgb}}\right\}\{\Delta[\mathrm{HCO_3^-}]_\mathrm{P} + \beta'_{SA}(IPE)\Delta\mathrm{pH(P)}\} \quad (26)$$

where

$$\beta'_{SA}(IPE) = \frac{V_\mathrm{B}\mathrm{C}_{Hgb}(\mathrm{B})}{(V_\mathrm{B} + V_\mathrm{I})}\beta'_{SA}(\mathrm{E}) + \beta'_{SA}(\mathrm{P}) \quad (27)$$

and

$$\beta'_{SA}(\mathrm{E}) = \frac{\{\mathrm{pH'(E)}\beta(\mathrm{E}) - \beta(\mathrm{P})\}}{\mathrm{C}_{Hgb}(\mathrm{E}) - \dfrac{(1 - r_c(\mathrm{E}))V_\mathrm{B}\mathrm{C}_{Hgb}(\mathrm{B})}{(V_\mathrm{B} + V_\mathrm{I})}} \quad (28)$$

and

$$\beta'_{SA}(\mathrm{P}) = \frac{\beta(\mathrm{P})\mathrm{C}_{Hgb}(\mathrm{E})}{\mathrm{C}_{Hgb}(\mathrm{E}) - \dfrac{(1 - r_c(\mathrm{E}))V_\mathrm{B}\mathrm{C}_{Hgb}(\mathrm{B})}{(V_\mathrm{B} + V_\mathrm{I})}} \quad (29)$$

analogous to the form for whole blood in vitro [4–6, 8]. The values $\beta'_{SA}(IPE)$, $\beta'_{SA}$(E), and $\beta'_{SA}$(P), denote the effective buffer values using the Siggaard-Andersen approximation, analogous to those in Equations 2 and 3. For the normal values of $V_\mathrm{B}$ = 5 L and $V_\mathrm{I}$ = 10 L, it is seen that this approximation amounts to replacing $\mathrm{C}_{Hgb}$(B) in the

equation for whole blood with one-third of its value, $C_{Hgb}(B)/3$ [4, 6, 8]. Note, however, that $C_{Hgb}(B)$ must be replaced wherever it occurs, and not just where it appears in Equations 2 and 3. Also of note, Siggaard-Andersen defined the hemoglobin concentrations $C_{Hgb}(B)$ and $C_{Hgb}(E)$ and hence $\beta'_{SA}(E)$ in terms of the hemoglobin monomer concentration, which is four times that of the conventionally reported tetramer concentration [4, 5]. Either can be used, provided that the definition is consistent throughout [8].

## METHODS

Calculations were performed on an HP Pavilion computer equipped with a 2.19 GHz Athlon AM 64 dual core processor running Mathematica 6.0 (Wolfram Research) and Excel 2003 (Microsoft). Calculations performed using Mathematica were exported to Excel for graphical display. The pH(P) was stepped in 0.01 increments to calculate $P_{CO_2}(P)$ or $[HCO_3^-]_P$. The calculations employed the constants and methods used previously except where otherwise specified below [8]. The designations "normal plasma" and "normal whole blood" used the normal values given in reference 8. The designation "normal interstitial, plasma, and erythrocyte system" used these same values together with $V_B$ = 5 L and $V_I$ = 10 L.

For theoretical graphs of plasma $P_{CO_2}(P)$ vs. pH(P) from Equation 10, constant SID(*IPE*) was assumed, and Equation 11 or the Henderson–Hasselbalch equation [4, 8, 17] was used to convert plasma bicarbonate concentration to plasma $P_{CO_2}$. Similar calculations were performed for the linear approximations for plasma and whole blood as before [8]. The corresponding $[HCO_3^-]_P$ vs. pH(P) graph from Equation 10 was also calculated together with the associated plasma and whole blood graphs as before [7, 8]. Experimental data for $P_{CO_2}(P)$ vs. pH(P) were obtained from Brackett et al. [29], with the experimental $[HCO_3^-]_P$ vs. pH(P) curves generated from the Henderson–Hasselbalch equation. In addition, $P_{CO_2}(P)$ vs. pH(P) and $[HCO_3^-]_P$ vs. pH(P) assuming constant normal plasma bicarbonate at 24.25 mM were also calculated from the Henderson–Hasselbalch equation [4, 8, 17].

The theoretical in vivo carbon dioxide titration curves $P_{CO_2}(P)$ vs. pH(P) and $[HCO_3^-]_P$ vs. pH(P) were also calculated using the Van Slyke equation for extracellular fluid [6], assuming constant base excess and normal parameters with the explicit form [6]

$$\begin{aligned} SBE &= BE(ECF) \\ &= \left\{1 - 0.00775C_{Hgb}(B)\right\}\left\{\left([HCO_3^-]_P - 24.25\right)\right. \\ &\quad \left. + \left(0.77C_{Hgb}(B) + 7.7\right)\left(pH(P) - 7.40\right)\right\} \end{aligned} \tag{30}$$

which is defined in terms of hemoglobin monomer concentration in mM [4–6]. The Henderson–Hasselbalch equation was used to obtain Equation 30 in terms of $P_{CO_2}(P)$. The $P_{CO_2}(P)$ vs. pH(P) and $[HCO_3^-]_P$ vs. pH(P) curves were additionally calculated using Equations 26-29 assuming normal parameters for the *IPE* system. Equations 26–30 were also used to obtain graphs of $[HCO_3^-]_P$ vs. pH(P) at constant SID(*IPE*) for both normal and half normal whole blood hemoglobin values.

## RESULTS

The strong ion difference calculated from the model of Equation 10 for the normal interstitial, erythrocyte, and plasma system is 40 mM, which agrees well with the value of 39.5 mM calculated from the strong ion concentration values and compartment volumes given by reference 27. In addition, the normal calculated slope of the $[HCO_3^-]_P$ vs. pH(P) curve at constant SID(*IPE*) obtained from differentiation of Equation 10 is

$$\frac{\partial\left[HCO_3^-\right]_P}{\partial pH(P)} = -14 \tag{31}$$

This value is consistent with the previously measured values of −12.2 [29], −16.2 [4], and −21 [30].

The theoretical $P_{CO_2}(P)$ vs. pH(P) curves for the *IPE* system, whole blood in vitro, and separated plasma are shown in Figure 1. The experimental values obtained by Brackett et al. [29] are also shown. $P_{CO_2}(P)$ vs. pH(P) assuming constant bicarbonate alone is provided for comparison. These same relationships are also plotted for plasma bicarbonate vs. plasma pH in Figure 2 as a Davenport diagram [31].

The strong ion difference theory, or Stewart formalism, was used to compute the Boston rules for pure respiratory disturbances as shown in Equations 15 and 18. For $pK' = 6.103$, $S = 0.0306$, constant SID(*IPE*) = 40 mM, and $[H^+]_o$ corresponding to either a mildly physiologically acid pH of 7.3 or a mildly alkaline pH of 7.5 Equation 15 gives

$$\frac{\Delta[H^+]_P}{\Delta P_{CO_2}(P)} = \frac{0.8\,\text{nM}}{\text{Torr}} \tag{32}$$

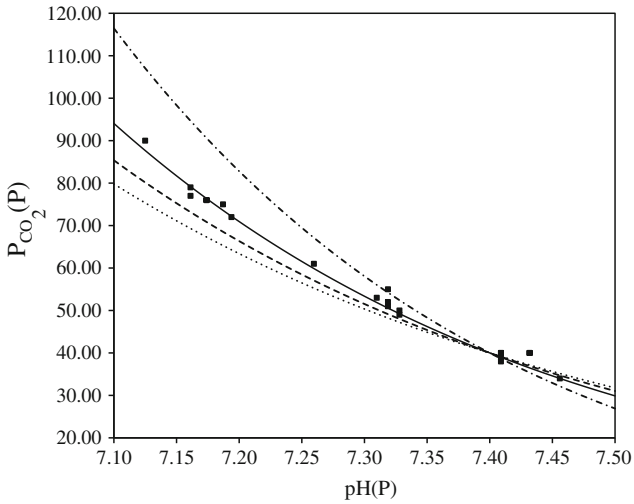


*Fig. 1. $P_{CO_2}(P)$ vs. pH(P) at constant strong ion difference for the normal IPE system (solid curve), whole blood in vitro (dot dashed curve), and separated plasma (dashed curve) together with the $P_{CO_2}(P)$ vs. pH(P) curve calculated from the Henderson–Hasselbalch relationship at constant normal $[HCO_3^-]_P$ (dotted curve). Experimental data from reference 29 is also shown (squares).*

which is the result obtained empirically for acute respiratory acidosis and alkalosis [16, 17, 29].

For the constants above and $[H^+]_o$ corresponding to a mildly acid pH of 7.3, Equation 18 gives

$$\frac{\Delta[HCO_3^-]_P}{\Delta P_{CO_2}(P)} = \frac{0.1\,\text{nM}}{\text{Torr}} \tag{33}$$

for a pure respiratory acidosis. An $[H^+]_o$ corresponding to a mildly alkaline pH of 7.5 gives

$$\frac{\Delta[HCO_3^-]_P}{\Delta P_{CO_2}(P)} = \frac{0.2\,\text{mM}}{\text{Torr}} \tag{34}$$

for a pure respiratory alkalosis. The values derived here equal the previously published empirical values [16, 17, 29].

Figure 3 shows calculated in vivo carbon dioxide titration curves from the Van Slyke forms of Equations 26 and 30 together with the experimental curve of Brackett et al. [29]. The curve calculated from Equation 10 is also shown. Analogous graphs for plasma bicarbonate vs. plasma pH are shown in Figure 4. The effects of hemoglobin concentration are shown for normal hemoglobin

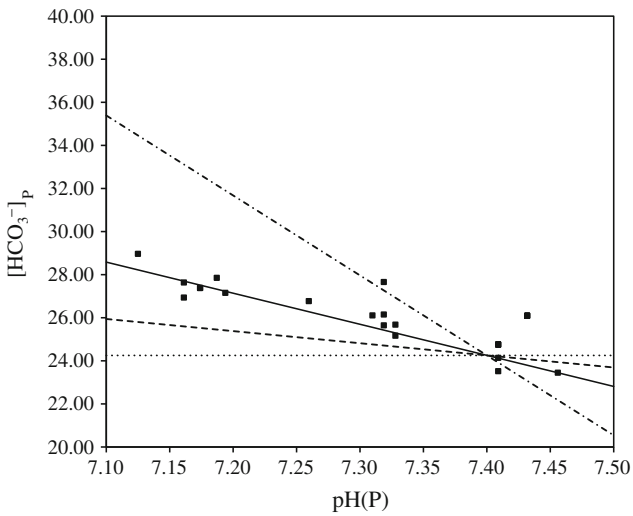


*Fig. 2. $[HCO_3^-]_P$ vs. pH(P) at constant strong ion difference for the normal IPE system (solid curve), whole blood in vitro (dot dashed curve), and separated plasma (dashed curve), together with the $[HCO_3^-]_P$ vs. pH(P) line for the Henderson–Hasselbalch relationship at constant normal $[HCO_3^-]_P$ (dotted line). Experimental data from reference 29 is also shown (squares).*

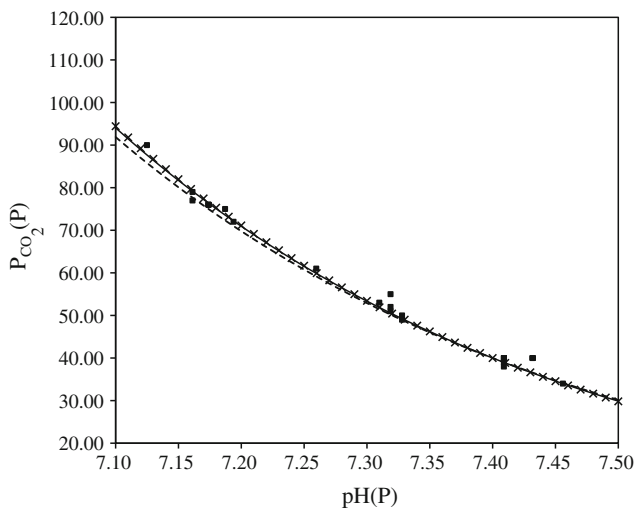


*Fig. 3. $P_{CO_2}(P)$ vs. pH(P) at constant strong ion difference for the normal IPE system calculated from Equation 10 (solid curve), the Van Slyke equation of Equation 30 (x), and the Van Slyke form of Equation 26 (dashed curve), together with experimental data from reference 29 (squares).*

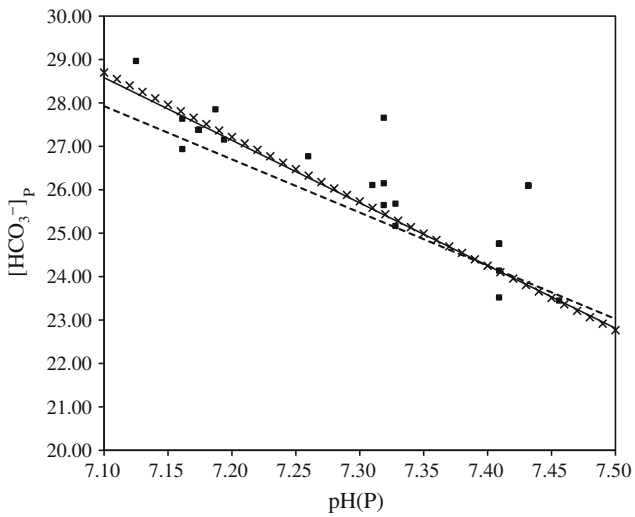


*Fig. 4. $[HCO_3^-]_P$ vs. pH(P) at constant strong ion difference for the normal IPE system calculated from Equation 10 (solid curve), the Van Slyke equation of Equation 30 (x), and the Van Slyke form of Equation 26 (dashed curve) together with experimental data from reference 29 (squares).*

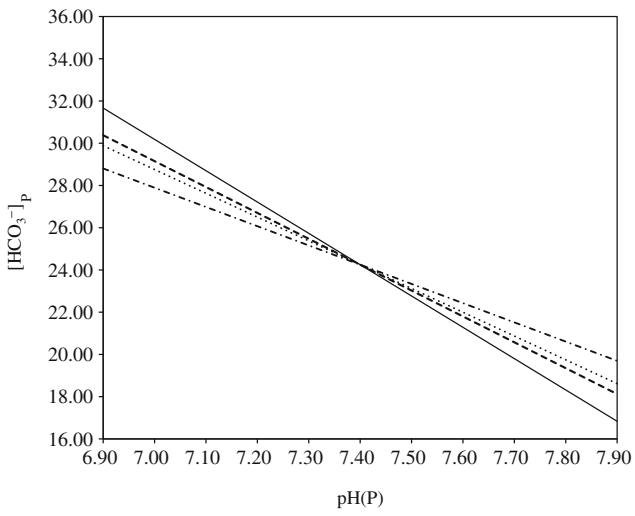


*Fig. 5. $[HCO_3^-]_P$ vs. pH(P) at constant strong ion difference for the Van Slyke equation calculated from Equation 30 using normal (solid curve) and half normal (dotted curve) $C_{Hgb}(B)$, together with the Van Slyke equation of Equation 26 using normal (dashed curve) and half normal (dot dashed curve) $C_{Hgb}(B)$.*

concentration and half normal concentration for both Equations 26 and 30 plotted as a Davenport diagram [31] in Figure 5.

## DISCUSSION

The use of the Stewart method continues to be reported for analysis of clinical acid–base balance with largely acceptable results [32–37]. These studies have usually employed the Stewart strong ion difference equations for plasma [7, 9–13], although as previously noted, plasma is in equilibrium with the erythrocyte phase, and therefore an equation for whole blood was derived [8], which also gives clinically concordant results [38]. In addition, Rees et al. [39, 40] have developed a sophisticated optimized numerical model for simulating acid–base physiology which can accurately calculate arterial blood gas parameters from venous values. The previously developed generalized model for total titratable base and strong ion difference has also been shown to replicate the results of the Van Slyke equations for plasma and whole blood [7, 8], but like the Van Slyke equations for plasma and whole blood, do not reproduce the in vivo carbon dioxide titration curve of normal man [29]. Experimental results have suggested that the acute in vivo $CO_2$ titration curve depends upon equilibration between the plasma, erythrocyte, and interstitial fluid compartments of the total *IPE* system [4], and therefore the interstitial compartment must be included in the model. To circumvent the problem of obtaining a precise model for the complex interstitial compartment, Siggaard-Andersen proposed the approximation of assuming that the interstitial compartment has the same composition and properties as plasma to calculate the extracellular base excess [4, 6]. As formally demonstrated in Equations 4 and 5, this approximation amounts to diluting whole blood in its own plasma, which produces the linear approximations given in Equations 9 and 10 for total titratable base and strong ion difference, respectively. Since Siggaard-Andersen referred to the extracellular base excess as the standard base excess, one could therefore by analogy consider the variables of $C_B(IPE)$ and $SID(IPE)$ the standard total titratable base and standard strong ion difference, respectively. As previously derived for the general case, the extracellular base excess BE(ECF), $\Delta C_B(IPE)$, and $\Delta SID(IPE)$ are equivalent for constant noncarbonate buffer concentrations at the same level of approximation [8].

Figure 1 demonstrates a comparison of $P_{CO_2}(P)$ vs. pH(P) curves using the linear approximations for the strong ion difference of plasma, whole blood in vitro, and the *IPE* system. The *IPE* curve reproduces the in vivo titration curve surprisingly well, particularly considering that the average normal values for the noncarbonate buffer concentrations were used, as the actual values were not measured in the classic experimental study of Brackett et al. [29]. It should be noted that Dell and Winter [41]

developed a model to predict the slope of the in vivo curve and argued that intracellular buffers must be included in the acute carbon dioxide titration curve to reproduce the slope, although they assumed a much lower value for the buffer value of interstitial fluid, which may be the reason that their model for the *IPE* system was insufficient to predict the slope of the experimental in vivo curve [41].

As demonstrated in Figure 1, the whole blood equation overestimates the slope of the experimental $CO_2$ titration curve data more than the plasma curve underestimates it. The curve for the Henderson–Hasselbalch equation is also graphed for comparison at constant $[HCO_3^-]_P$ = 24.25 mM, demonstrating that the bicarbonate equilibrium alone is insufficient for prediction of the human in vivo carbon dioxide titration curve. Figure 2 shows the same relationships plotted in a Davenport diagram format as plasma bicarbonate versus plasma pH for the acute $CO_2$ titration curve, showing similar findings. The slope of the theoretical $[HCO_3^-]_P$ vs. pH(P) curve for the *IPE* curve of Figure 2 is −14, concordant with previous results [4, 29, 30], and the theoretical normal SID(*IPE*) is 40 mM, also in agreement with previously published data [27]. The normal value for SID(*IPE*) is noted to be close to that for the SID(P) of 39 mM determined before [7, 8].

As with the base excess of Siggaard-Andersen, the multicompartment model used in the present work may be regarded as a correction to bicarbonate for respiratory effects in order to obtain the metabolic component of an acid–base disorder [4, 6–8, 31]. Equation 10 for the *IPE* system together with the plasma and whole blood models developed previously [7, 8] may therefore be used to assess the relative discrepancies in the respective models for a ΔSID = 0 mM. One deduces that for a pH(P) of 6.9 (ΔpH(P) of −0.5), the calculated $\Delta[HCO_3^-]_P$ for a pure respiratory disturbance will be 7.2 mM for the *IPE* system, 18.6 mM for whole blood, and 2.8 mM for plasma, so that at a plasma pH of 6.9 the plasma curve bicarbonate value is 4.4 mM from the *IPE* curve, while whole blood is 11.4 mM from it. These discrepancies, particularly for whole blood, could be large enough to produce erroneous results in clinical applications for sufficiently large ΔpH(P). These results do suggest, however, that the Stewart equation for separated plasma, even though it does not exactly reproduce the in vivo titration curve, could give qualitatively acceptable clinical results, since the overall buffer value and SID for plasma are relatively close to that for the *IPE* system, and this may in fact be the reason for the clinical utility of the plasma Stewart equations found in clinical studies [32–37].

As noted above and demonstrated graphically in Figure 2, for a pure respiratory disturbance, the straight line for the Henderson–Hasselbalch equation assuming constant bicarbonate is insufficient to precisely calculate the metabolic component of an acid–base disorder. In the example above, for a pH(P) = 6.9, although the ΔSID(*IPE*) for the *IPE* system gives a metabolic component of zero, the bicarbonate approach using the Boston rules would need to be applied to the bicarbonate concentration to deduce that the $[HCO_3^-]_P$ = 31.46 mM ($\Delta[HCO_3^-]_P$ = 7.2 mM) represents a pure respiratory acidosis without a metabolic component [16, 17]. As shown in Equations 12–18 and Equations 32–34, the Boston rules for acute respiratory acidosis and alkalosis can be derived from first principles using the multicompartment model, reproducing the experimental values exactly [16, 17, 29]. The Boston rules for acute respiratory acidosis and alkalosis are thus not only compatible with the Copenhagen base excess method and the Stewart approach, but can be derived analytically from them. This result is consistent with the corresponding empirical compensation rules in terms of standard base excess found by Schlichtig et al. [18]. While the rules are derived here for the case of normal noncarbonate buffer concentration and compartmental volumes, one could use the model for the *IPE* system to take into account the effects of fluid status and changes in noncarbonate buffer concentration. It should also be pointed out that although these rules are sometimes referred to as compensation rules, in the case of the acute respiratory abnormalities this does not represent physiological compensation, but is simply a reflection of LeChatlier's principle in the setting of a chemical equilibrium.

The results obtained and summarized in Figures 1 and 2 demonstrate that the linear approximation for the total titratable base and strong difference *IPE* models reproduce the in vivo titration curve and therefore may be regarded, as stated by Siggaard-Andersen for the corresponding extracellular base excess model [6], as the most relevant of the three compartmental models. Equations 9 and 10 are therefore expected to produce the best agreement with clinical data and have the most prognostic value.

It is also noted, despite the claim of a recent publication [42], that Equations 9 and 10 may be solved and used in a variety of ways. The usual clinical scenario relates to knowing the plasma pH, plasma bicarbonate, and noncarbonate buffer concentrations, and the $C_B$, SID, $\Delta C_B$, or ΔSID are used to estimate the metabolic component of an acid–base disorder [28]. Alternatively, if one knows the $C_B$ or SID, together with the bicarbonate and noncarbonate buffer concentrations, one could calculate the final pH. This could theoretically be important, for example, in calculating the effects of resuscitation [19–21].

For over 40 years the Van Slyke equations have been available to calculate the metabolic component of an acid–base derangement [4–6], and have been used for

calculation in blood gas analyzers [43]. As shown previously for plasma and whole blood in vitro, Van Slyke equations may be derived from first principles [7, 8], and Equations 19-29 demonstrate that the formalism can be extended to the *IPE* system and formally demonstrate Siggaard-Andersen's previous assertions regarding standard base excess as detailed below [4, 6]. Figures 3 and 4 compare the *IPE* multicompartment model (Equation 10), the standard base excess of Siggaard-Andersen (Equation 30), and the Van Slyke equation derived from the multicompartment model (Equation 26) for the prediction of the curves for $P_{CO_2}(P)$ vs. pH(P) and $[HCO_3^-]_P$ vs. pH(P) compared to the data of Brackett et al. [29].

It is appropriate at this point to review several features and observations regarding the Van Slyke equations and Figures 3 and 4. First, as mentioned above, there is a different Van Slyke form for plasma, whole blood, and extracellular fluid, where extracellular fluid is equal to the *IPE* system. In many publications, the exact form being calculated varies or is not specified [44]. Second, for the extracellular base excess, also known as the standard base excess, the interstitial compartment is considered to have the same properties as the plasma compartment, which is shown formally by Equation 5 to amount to diluting whole blood 2:1 in its own plasma as asserted by Siggaard-Andersen [4, 6]. An equivalent statement, also previously asserted by Siggaard-Andersen, and formally shown in Equations 26–29, is that this same result may be achieved by replacing $C_{Hgb}(B)$ by one-third of its value in the Van Slyke equation for whole blood [6].

Third, the Siggaard-Andersen derivation of the Van Slyke equation expresses the hemoglobin concentration in the erythrocyte, $C_{Hgb}(E)$, as well as the hemoglobin concentration of whole blood $C_{Hgb}(B)$, which is the product $\phi_B(E)\ C_{Hgb}(E)$, in terms of hemoglobin monomer concentration [4–6]. Thus, for normal human whole blood, the appropriate monomer value in the Van Slyke equation for $C_{Hgb}(E)$ is 21.2 mM, and for $C_{Hgb}(B)$ is 9.3 mM [4, 5]. For extracellular fluid the $C_{Hgb}(B)$ is divided by 3, or 3.1 mM for one-third the monomer concentration [4, 5]. As an aside, if the corresponding whole blood hemoglobin tetramer concentration of 2.3 mM were incorrectly used in the whole blood equation, this approximates the monomer concentration divided by 3, and the error would actually approximate the extracellular base excess.

In addition, in the development of the Van Slyke equation, Siggaard-Andersen provided the form of Equation 2, but indicated that $\beta'_B(P)$ in Equation 3 equals the true plasma buffer value $\beta(P)$, which as noted previously [8], and evident in Equations 19–29, does not appear to be correct for the Van Slyke form. This remains true even if a different grouping of terms for $\beta'_{SA}(IPE)$ in Equations 27–29 is chosen. Furthermore, based on the present and previous [8] derivation of the buffer values in the Van Slyke form, the effective buffer values are also not independent of $C_{Hgb}(B)$, as shown by Equations 19–29. It turns out, however, that the dependence is rather weak as shown in the Davenport diagram of Figure 5. For a pure respiratory disturbance, the $[HCO_3^-]_P$ calculated using the Van Slyke form of Siggaard-Andersen in Equation 30 differs from the calculation of Equation 26 by approximately 1 mM for a $\Delta pH(P)$ of $-0.5$ for both normal and abnormal hemoglobin values, while decreasing the blood hemoglobin concentration by half results in a difference of approximately 2 mM between normal and abnormal values for both Equations 26 and 30 at a $\Delta pH(P)$ of $-0.5$. Nonetheless, the standard base excess of Equation 30 and the SID(*IPE*) of Equation 10 reproduce the experimental data slightly better than the Van Slyke form of Equation 26. This discrepancy is a consequence of both the dependence of the buffer values on $C_{Hgb}(B)$ as well as the fact that $pH'(E) = 0.77$ is used in both Equations 26 and 30 [4, 5, 8], while a $pH'(E) = 1$ is implicit in Equation 10.

At this point it is worth discussing the validity of the Siggaard-Andersen approximation. It is, of course, manifestly nonphysical as the albumin and phosphate concentrations in interstitial fluid do not approach those of plasma, and the collagen and proteoglycans supply both charge and buffer capacity [4, 24]. Furthermore, the assumption of aqueous equilibrium behavior for the gel-like interstitium may be invalid [23, 26, 27]. Nonetheless, such an approximation provides reasonable results and is attractive for several reasons. First, the strong ion difference and buffer capacity of plasma and interstitial fluid are experimentally similar [4, 25, 27]. Second, the Nernst potential across the endothelial membrane is low, and the Donnan ratios for protons and bicarbonate concentrations are close to unity [25]. Third, the approximation allows one to link interstitial acid–base and electrolyte behavior to clinically measured variables such as serum albumin concentration. Although one could derive a monoprotic model with a $pK_a$ and normal concentration parameter $A_{Tot}$ for the interstitium [9, 12, 39], it is difficult to see how to apply that to an abnormal case in which there is an abnormal $A_{Tot}$. In cases of hypoalbuminemia, which are often associated with peripheral edema, the low albumin is expected to be associated with dilution of the interstitium as edema fluid builds up in the interstitium, thereby tying the decreased albumin concentration to a decrease in the noncarbonate buffer concentrations of the interstitial fluid [27]. Consequently, there is reason to expect that the Siggaard-Andersen approximation would continue to hold at least to some degree in such cases. This conjecture is supported by the utility found for standard base excess for a wide application of clinical studies [18, 35, 38, 44].

In summary, the approximation used by Siggaard-Andersen to obtain the standard base excess has been applied to the previously developed multicompartment model to obtain the analogous standard total titratable base, $C_B(IPE)$, and standard strong ion difference, $SID(IPE)$, as linear closed form equations as a function of plasma pH, plasma bicarbonate, and noncarbonate buffer concentrations for the interstitial, plasma, and erythrocyte (*IPE*) system. This model for the *IPE* system reproduces the in vivo carbon dioxide titration curve in normal man. The associated $\Delta C_B(IPE)$ and $\Delta SID(IPE)$ are equivalent to the extracellular base excess of Siggaard-Andersen at constant noncarbonate buffer concentrations. The multicompartment model for the *IPE* system in the Siggaard-Andersen approximation was then used to derive from first principles the Boston rules for acute respiratory acid–base disorders, demonstrating that the Boston approach is entirely compatible with the base excess and Stewart approaches. Next, from the multicompartment model, the Van Slyke equation for the *IPE* system was derived, giving similar results to the Van Slyke equation for standard base excess obtained by Siggaard-Andersen. In addition, Siggaard-Andersen's assertion that the extracellular base excess can be obtained by replacing the blood hemoglobin concentration with one-third its value in the whole blood Van Slyke equation was formally demonstrated.

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