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STRONG ION DIFFERENCE EXCESS AND CORRECTED STRONG ION DIFFERENCE MODEL INCORPORATING THE VARIATIONS IN APPARENT DISSOCIATION CONSTANT FOR HUMAN BLOOD PLASMA ELECTRO-NEUTRALITY EQUILIBRIA

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Abstract : We introduce computed value of the corrected Strong Ion Difference (SID) by including the large variability of the apparent dissociation constant pK' in non-logarithmic form on SID in Henderson-Hasselbach bicarbonate ion aqueous equilibria thereby resulting in a significant correction of up to 27% in SID. We further introduce a new concept of Strong Ion Difference Excess (SIDE) as the change in SID from the reference value at pH = 7.4, pCO2 = 5.33 Kpa (or 40 torr). The SIDE is a particularly useful quick measure when one can rule out the effects of hemoglobin, weak proteins and unidentified components for human blood plasma.

Key words : albumin bicarbonate blood gases dissociation constant pH, SID strong-ion-difference

INTRODUCTION

Almost a century ago, Henderson (1) used an equilibrium theory of carbonate species to suggest a physio-chemical approach to acid-base balance in human blood. Later, Hasselbach (2) provided a simple formula (the Henderson-Hasselbach Equation) to describe those equilibria. Thereafter, Van Slyke realized the importance of non-carbonate buffers, principally hemoglobin and proteins, in the regulation of acid-base behavior (3).

From these early observations, Siggaard-Anderson and others have developed the standard (base excess) model of acid-base balance in common use today (4). This model has enjoyed much success as is used widely. The model is relatively easy to understand, based on experimental correlations, and relies on easy-to-measure variables.

However, the standard approach to acid-base balance is not without its detractors. Base excess is derived by titration of the blood with acid or base in vitro. Since base

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excess is measured in a “closed” apparatus, some investigators have criticized base excess as artificially derived, physiologically unregulated, and otherwise irrelevant to an “open” in vivo system. Others have criticized base excess (BE) for merely quantifying rather than truly explaining acid-base disturbances. The BE is based on experimental correlations with curve fitting equations which were named as Van Slyke equation by Siggaard-Andersen (7) thereby lacking usage of electro-neutrality and laws of mass action in the 21st century.

In 1981, Stewart (5, 6), a Canadian physiologist, proposed a radically different approach to acid-base balance. He started by discarding many of the features of the traditional model, including the standard notions of acids and bases. Based upon the laws of mass action, the conservation of mass and the conservation of charge, he derived relatively complex mathematical formulas to describe acid-base balance, while introducing two new variables, the strong ion difference (SID) and the total weak acids (A_{tot}).

The reaction from defenders of the “standard model” was vitriolic. To Siggaard-Anderson and Fogh-Andersen (7) and their followers, the “Stewart approach is absurd and anachronistic”. Partly as a result of this criticism, Stewart’s equations are largely unknown outside a small group of anesthesiologists and intensivists. In the intensive care unit, however, new models of acid-base behavior have become important to describe complex acid-base derangements.

Although differing conceptually, the primary goal of traditional or the Stewart approach are similar : (1) the measurement of the acid-base disturbance; (2) the elucidation of the mechanism of the disturbance; (3) the classification of the disturbance as “metabolic” or “respiratory”; and (4) the enumeration of the principle that govern the disturbance. To determine how well each of these models meets these objectives, we will first briefly describe the traditional model. Then, we will review the salient features of Stewart’s work. Finally we will show that corrected SID which incorporates the large variability of the apparent dissociation constant pK’ in non-logarithmic form on SID and “Strong Ion Difference Excess” theory may provide a firmer foundation.

Although aware of the buffering power of noncarbonated species, Henderson (1) emphasized the significance of bicarbonate as a reserve of alkali in excess of acids other than carbonic acid. In his now famous monograph, he wrote the law of mass action for carbonate species (the “Henderson equation”) as :

$$[H^+] = K_1 * [CO_2] / [HCO_3^-] \quad \text{(Eq. 1)}$$

where $[CO_2]$ is the total concentration of dissolved CO_2 gas and aqueous H_2CO_3 in plasma, $[H^+]$ and $[HCO_3^-]$ are the concentrations of hydronium and bicarbonate in plasma, and K_1’ is the equilibrium constant for the association reaction.

Subsequently, Hasselbach and Gammeltoft (8) and Hasselbach (2) adopted the Sorenson convention (where $[H^+]$ is expressed by pH), and rewrote equation 1 (“the Henderson-Hasselbach equation”) as :

$$pH = pK' + \log[HC0_3^-] / (Sco_2 * Pco_2) \quad \text{(Eq. 2)}$$

where the total CO_2 concentration is expressed as Henry's law $[CO_2] = Sco_2 * Pco_2$ where Sco_2 (the solubility coefficient of CO_2 in plasma) and Pco_2 (the partial pressure of CO_2 in plasma). Equation 2 can also be expressed as in equation 2A where $K_1' = Sco_2 * 10^{-pK'}$

$$[HCO_3] = K_1' * [Pco_2] / [H^+] \quad \text{(Eq. 2A)}$$

METHODS

The Stewart model : SID, A_{tot} and Pco_2

The traditional approach is often successful in clinical practice. However, the model appears to break down at physiologic extremes. For example, the buffer curve (equation 2) indicates that the plot of log Pco_2 vs. pH should be linear with an slope equal to –1 (9). However, experimental data cannot be fitted to the equation 2. The plot of pH vs. Pco_2 is in fact displaced by changes in protein concentration or the addition of sodium or chloride and becomes nonlinear in markedly acid plasma (9).

Stewart, a Canadian physiologist put forth a novel approach of acid-base balance (5, 6) with the following features (1) the quantity of H^+ added or removed from a physiologic system is not relevant to the final pH, since $[H^+]$ is a "dependent" variable; (2) human plasma consists of fully dissociated ions ("strong ions" such as sodium, potassium, chloride, and lactate), partially dissociated "weak" acids (such as albumin and phosphate), and volatile buffers (carbonate species); (3) an evaluation of nonvolatile buffers equilibrium is important to the description of acid-base balance; (4) the weak acids of plasma can be described as a pseudomonoprotic acid, HA; and (5) plasma membranes may be permeable to strong ions, which constitute the "independent" variable SID, the strong ion difference. Thus transport of strong ions across cell membranes may influence $[H^+]$.

With these assumptions, Stewart wrote equations based upon the laws of mass action, the conservation of mass, and the conversation of charge.

Water Dissociation Equilibrium

$$[H^+] * [OH^-] = K_W' \quad \text{(Eq. 3)}$$

where K_W' is the autoionization constant of water

Electrical Neutrality Equation

$$[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{-2}] - [OH^-] = 0 \quad \text{(Eq. 4)}$$

where SID is the "strong ion difference" ($[Na^+] + [K^+] - [Cl^-] -$ [lactate]) and $[A^-]$ is the concentration of dissociated weak acids.

Weak Acid Dissociation Equilibrium

$$[H^+] * [A^-] = K_a * [HA] \quad \text{(Eq.5)}$$

where K_a is the weak acid dissociation constant of weak acids. Thus, in our case K_1' in equation 1 for bicarbonate ion equilibria does not include weak acids contribution as it has been addressed by equations 5 and 6. Further,

$$[HA] + [A^-] = [A_{tot}] \quad \text{(Eq. 6)}$$

The three independent variables in Stewart's model are SID, A_{tot} and Pco_2 and determine pH. In addition, one may vary the temperature and any of the rate constants. Physiologically, the kidney, intestine and tissue each contribute to SID while lever mainly determines $[A_{tot}]$ and the lungs Pco_2. Acidosis results from an increase in Pco_2, $[A_{tot}]$ or temperature, or a decrease in [SID]. Metabolic acidosis may be due to overproduction of organic acids (e.g. lactic acids, ketoacids, formic acid, salicylate, and sulphate), loss of cations (e.g. diarrhea), mishandling of ions (e.g. RTA) or administration of exogenous anions (e.g. poisoning). These all result in low SID. Alkalosis results from a decrease in Pco_2, $[A_{tot}]$, or temperature, or an increase in [SID]. For example, metabolic alkalosis (e.g. due to vomiting) may be due to chloride loss resulting in high SID. We would like to stress here that it is ultimately, the Electrical Neutrality Equation (equation 4) which provides the balance of all the variables irrespective of whichever variable may emerge to be independent or dependent depending on more accurate future research on mechanisms involved.

Bicarbonate Ion Formation Equilibrium

While both Sco_2 and pK' in equation 2 are not constants and vary with ionic strength, temperature, pH and protein concentration, the variation of pK' is much more significant in non-logarithmic form of equation 1 when temperature is fixed at 37°C (10). We find that $K_1' = 0.03 * 10^{-pK'}$ where Sco_2 is taken to be reasonably constant 0.03 mmol/L * Hg at 37°C. Once the temperature is fixed, at 37°C, pK' varies strongly with ionic strength (11, 12). Abnormal plasma Na-levels fluctuations over hours and days in a given patient are not uncommon (11). The variation in pK' with ionic strength is particularly evident if logarithmic scale is not used. Hyponatraemia or hypernatraemia i.e. variation in Plasma Na levels (and thus Strong Ion Difference in general) contributes significantly to variations in K_1'. Such large corrections are very obvious when applied to Strong Ion Difference model which does not utilize logarithmic scale (calculation of bicarbonate from equation 2 even in Base Excess approach (4, 7) also includes taking the antilog and thus is confronted by same high level of variations due to pK'). We converted the data in the literature (12) from pK' versus ionic strength to K_1' Versus SID when only bicarbonate and strong ions are present (as contributions to SID by weak acids are accounted for separately by utilizing equations 5 and 6) utilizing equations 1 and 4 and find it to be:

$$K_1' = 2.3 * 10^{-11} + 0.0355778 * 10^{-11} * SID \quad \text{(Eq. 7)}$$

Carbonate Ion Formation Equilibrium

$$[H^+] * [CO_3^{-2}] = K_3 * [HCO_3^-] \quad \text{(Eq. 8)}$$

where K_3 is the apparent equilibrium dissociation constant for bicarbonate.

Combining the above equations and $K_3 = 6 * 10^{-11}$ equiv/L, $Kw' = 4.4 * 10^{-14}$ $(equiv/L)^2$, we obtain the "Corrected Stewart Equation" :

$$[SID] + [H^+] - [2.3 * 10^{-11} + 0.0355778 * 10^{-11} * SID] * Pco_2/[H^+] - K_a * [A_{tot}]/(K_a + [H^+]) - K_3 * (2.3 * 10^{-11} + 0.0355778 * 10^{-11} * SID)\ Pco_2/[H^+]^2 - K_w'/[H^+] = 0 \quad \text{(Eq. 9)}$$

Figge et al (13) further refined A_{tot} to Albumin, [Alb] in g/dL and Phosphates, [Phos] in nmol/L and with equation 9 results in corrected SID :

$$SID = (2.3 * 10^{-11} * Pco_2/[H^+] + 10\,[Alb]\,(0.12 * pH - 0.631) + [Phos]\,(0.309 * pH - 0.469) + 2.3 * 10^{-22} * 6 * Pco_2/[H^+]^2 + K_w'/[H^+] - [H^+])/(1 - 0.0355778 * 10^{-11} * Pco_2/[H^+] - 0.0355778 * 6 * 10^{-22} * Pco_2/[H^+]^2) \quad \text{(Eq. 10)}$$

It may be also be noted that A_{tot}/Albumin do provide a fair share to the value of corrected SID and there is no doubt about the contributions due to variations in Pco_2.

RESULTS AND DISCUSSION

Figure 1 shows the fixed-SID for pK' = 6.1 (or K_1' = 2.46 * 10^{-11} (equiv/L)^2/mmHg, assumed constant), exact-SID for the measured data points by utilizing the exact pK' values (12) and corrected-SID, corrected for pK' variability by absorbing pK' (or K_1') versus exact-SID (equation 7) into the corrected-SID calculations (equation 10). Note the improvement in the corrected-SID being closer to exact-SID values than the fixed-SID values without having resort to costly and error prone measurements of the ionic strength, etc. there by reducing health care costs. The x-axis reflects various data points shown as pK' values (12).

The Stewart's model may prompt reexamination of the role of transepithelial chloride conductance in the regulation of acid-base balance. For example, mutations of the genes encoding the $Na^+ - HCO_3^-$ cotransporter (NBC-1), the B1 subunit of the H^+ - adenosine triphosphatase (ATPase) and

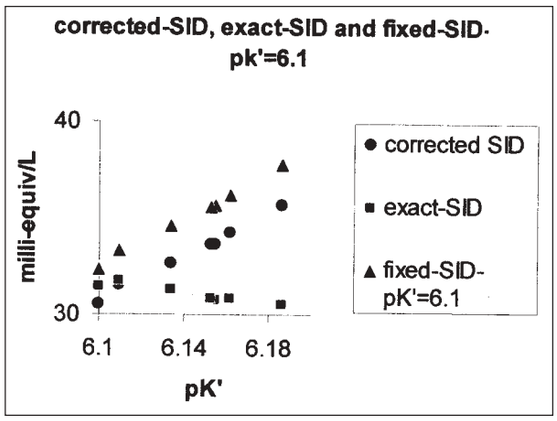

Fig. 1 : Show the fixed-SID for pK' = 6.1 ((or K_1' = 2.46 * 10^{-11} (equiv/L)^2/mmHg, assumed constant), exact-SID for the measured data points (12) and corrected-SID, corrected for pK' variability by absorbing pK' (or K_1') versus exact-SID into the corrected-SID calculations. Note the improvement of corrected-SID without having resort to costly and error prone measurements of the ionic strength, etc. there by reducing health care costs. The x-axis reflects various data points shown as pK' values.

the $Cl^- : [HCO_3^-]$ exchanger (AE1) are collectively referred to as renal tubular acidosis (RTA) (14). In the traditional model, the resulting hyperchloremic metabolic acidosis is attributed to low net acid excretion. In the Stewart model, acidosis is due to hyperchloremia and the retention of chloride by the renal tubule. For example, mutations in the WNK1 and WNK4 genes are associated with pseudohypoaldosteronism type II (PHA II). Recently, Choate et al (15) have linked these mutations with a high transtubular chloride flux. This observation suggests that the acidosis of PHA II may be due to high reabsorption of chloride, as predicted by the Stewart model. We would like to stress here that it is ultimately, the Electrical Neutrality Equation (equation 4) which provides the balance of all the variables irrespective of whichever variable

may be emerge to be independent or dependent depending on more accurate future research on mechanistic details.

To measure SID requires, depending upon the precision to which one aspires, the measurement of strong ion concentrations including Na^+, Cl^-, K^+, Ca^{++}, Mg^{++}, sulfate, urate, and lactate with their attendant costs. The problem of cumulative random assay error with so many measured parameters is not trivial and may compromise the very precision the Stewart's independent variable SID approach seeks, especially in more difficult cases of extreme acidosis or alkalosis, thereby reducing its utility and precision in spite of its mathematically rigorous model. The experimental proof of SID has been established by comparing experimental measurements with computations (16, 17). The measurement of total ionic strength would also be susceptible to similar inaccuracies and added cost. We therefore suggest that computation of corrected SID as in equation 10 incorporating the variability of K_1' (along with $[H^+]$/pH, Pco_2) and A_{tot}/Albumin contribution (and additional testing of keto acids in diabetics and other species where warranted) is an integrated and a more accurate and complete measure of respiratory/non-respiratory equilibria of blood plasma. Thus computation of corrected SID, rather than its experimental measurement is a fair pragmatic approach with a sound biological, chemical and mathematical basis.

We attempt to further introduce "Strong Ion Difference Excess" (SIDE) as the change in corrected SID from the reference value of 23.2 milli-equiv/L at pH = 7.4, pCO2 = 5.33 Kpa (or 40 torr or 40 mm Hg) and independent of hemoglobin and weak proteins and unidentified components. The SIDE is particularly a quick useful measure when one can rule out the effects of hemoglobin and weak proteins and unidentified components. Thus, ignoring weak proteins, albumin and smaller terms from equation 10, we obtain:

$$SIDE = (((2.3 * 10^{-11} * Pco_2/[H^+])/(1 - (0.0355778 * 10^{-11} * Pco_2/[H^+] - 0.0355778 * 6 * 10^{-22} * Pco_2/[H^+]^2)) - 0.0232) \quad \text{(Eq. 11)}$$

According to our definition SIDE is zero for values of Pco_2 = 40 Torr and for pH = 7.4.

We hope that future K_1' versus SID values will be available experimentally spanning the wide physiological range for healthy individuals and also under critical care conditions. Direct accurate $[HCO_3^-]$ measurements free of all interfering ions in the future is also a good solution to improve the accuracy of the SID approach.

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