The assessment of acid-base analysis: comparison of the “traditional” and the “modern” approaches

Jasna Todorović, Jelena Nešović-Ostojić, Aleksandar Milovanović, Predrag Brkić, Mihailo Ille, Dušan Čemerikić

1Department of Pathological Physiology, 2Department of Occupational Health, 3Department of Medical Physiology, 4Department of Surgery; School of Medicine, University of Belgrade, Belgrade, Serbia

ABSTRACT

Three distinct approaches are currently used in assessing acid-base disorders: the traditional - physiological or bicarbonate-centered approach, the base-excess approach, and the “modern” physico-chemical approach proposed by Peter Stewart, which uses the strong ion difference (particularly the sodium chloride difference) and the concentration of nonvolatile weak acids (particularly albumin) and partial pressure of carbon dioxide (pCO₂) as independent variables in the assessment of acid-base status. The traditional approach developed from the pioneering work of Henderson and Hasselbalch and the base-excess are still most widely used in clinical practice, even though there are a number of problems identified with this approach. The approach works well clinically and is recommended for use whenever serum total protein, albumin and phosphate concentrations are normal. Although Stewart’s approach has been largely ignored by physiologists, it is increasingly used by anesthesiologists and intensive care specialists, and is recommended for use whenever serum’s total protein, albumin or phosphate concentrations are markedly abnormal, as in critically ill patients. Although different in their concepts, the traditional and modern approaches can be seen as complementary, giving in principle, the same information about the acid-base status.

Key words: acid-base balance, anion gap, strong ion difference, bicarbonate, base excess, nonvolatile weak acids, strong ion gap
INTRODUCTION

Historically, two different conceptual approaches have been evolved among clinicians and physiologists for interpreting acid-base phenomena. The “traditional” or bicarbonate-centered approach relies qualitatively on the Henderson-Hasselbalch equation, whereas the “modern” or strong ion approach utilizes either original Peter Stewart equations or its simplified version derived by Peter Constable (1,2). The strong ion and bicarbonate-centered approaches are qualitatively identical even in the presence of non-bicarbonate buffers. The “traditional” approach for interpreting acid-base disorders developed from the pioneering work of Henderson and Hasselbalch is still the most widely used in clinical practice. One of the advantages of this approach is that it is relatively easy to understand and to apply in clinical situations (3). The strong ion model offers a novel insight into the pathophysiology of mixed acid-base disorders and is mechanistic (4). The newest approach has steadily gained acceptance especially among critical-care physicians and anesthesiologists (5,6). In this review we will discuss the advantages and disadvantages of Stewart’s method of acid-base balance compared with traditional bicarbonate-based approach, what will help better understanding in the complexity of acid-base balance.

THE “TRADITIONAL” APPROACH

In the early 1900s sufficient laboratory and observational evidence had been accumulated to define the influence of carbon dioxide on pH and to suggest a role for serum bicarbonate in characterizing acid-base disorders. Henderson recognized that carbon dioxide and bicarbonate were key elements of carbonate mass action, as shown by his famous equilibrium equation (7). Hasselbalch reformulated this equation by introducing the negative logarithmic pH notation and by applying Henry’s law to generate the pCO2 term. A buffer is substance that has ability to bind or release hydrogen ions (H+) in solution, thus keeping the pH of the solution relatively constant despite the addition of considerable quantities of acid or bases (8). Bicarbonate is the most important buffer in biological system at constant pCO2, and Henderson-Hasselbalch equation provides a simple relationship among the respiratory parameter pCO2, the non-respiratory parameter bicarbonate, and overall acidity parameter, pH (9). But a change in bicarbonate concentration does not reflect the total amount of non-carbonic acid or base, because there are non-bicarbonate buffers, especially albumin and hemoglobin (10). Even more important is the fact that bicarbonate concentration is not independent of variation in pCO2. As pCO2 increases carbonic acid is buffered by non-bicarbonate buffers and the bicarbonate concentration increases. An elevated bicarbonate concentration may therefore erroneously be interpreted as a metabolic alkalosis when respiratory acidosis is the cause (11). So, this equation lists pCO2 and bicarbonate as independent predictors of pH while, in fact, these variables are interdependent. Consequently, this equation merely serves as a description of a patient’s acid-base state but does not provide insight into the mechanism of the patient’s acid base disorder (12,13).

The traditional approach to clinical acid-base interpretation (bicarbonate-centered approach) is based on Lowry-Bronsted theory, wherein acids are defined as substances capable of donating protons, and the centrality of the bicarbonate buffer system in whole body acid-base homeostasis, given that it is composed of a volatile and nonvolatile buffer pair. Two bicarbonate-centered approaches evolved: the comparative ∆HCO3-/∆pCO2 approach (14) and the base excess (BE) approach (15).

The comparative ∆HCO3-/∆pCO2 approach

Qualitatively, this approach starts with the assumption that the components of the HCO3-/CO2 equilibrium reaction are in equilibrium with non-bicarbonate buffers (albumin, phosphate, hemoglobin) (3). Two bicarbonate-centered approaches evolved: the comparative ∆HCO3-/∆pCO2 approach (14) and the base excess (BE) approach (15). The ∆HCO3-/∆pCO2 approach has been criticized (2,11) for being qualitative in nature and incapable of quantifying acid or base loads that result in metabolic acid-base disorders. In particular, because body compartments consist of multiple buffers, it is argued that HCO3 buffer is only one of several buffers that were protonated by an H+ load (16). Therefore, the ∆HCO3 would underestimate the actual total body acid bur-
den as, for example, in a patient with keto-acidosis (17). Additional criticism is the fact that a component of the change in the HCO$_3^-$ is due to a shift in the HCO$_3^-$-CO$_2$ equilibrium reaction as a result of the compensatory ventilatory response (altered pCO$_2$) that occurs in patients with metabolic acid-base disturbances (18). Moreover, the compensatory ventilatory induced alteration in the pCO$_2$ causes a change in renal NH$_4$ and HCO$_3^-$ and titratable acid excretion. This results in a further change of the [HCO$_3^-$] (which is independent of the acid-base load and independent of the change due to the shift in the HCO$_3^-$-CO$_2$ equilibrium reaction) (19, 20). Finally, a disadvantage is that the $\Delta$HCO$_3^-$/$\Delta$pCO$_2$ ratio expected in acute respiratory acid-base disorders depends on the number of proton binding sites on non-bicarbonate buffers (albumin, hemoglobin, phosphate) (2). Thus, the bicarbonate concentration may be used as a screening parameter of a non-respiratory acid-base disturbance when respiratory disturbances are taken into account (2).

One possibility to solve this problem is to measure the bicarbonate concentration at a standard condition (when pCO$_2$ is 40 mm Hg) - value that we call standard bicarbonate, or to use the sum of bicarbonate and non-bicarbonate buffer anions – value that we call buffer base (changes in pCO$_2$ would not affect the buffer base concentration as the rise in bicarbonate concentration associated with a rise in pCO$_2$ is matched with a fall in concentration of other buffer anions) (11). Disagreement about the best parameter to describe acid-base balance in the body has dominated this area of physiology for more than three decades (19). The Henderson-Hasselbalch equation does not satisfactorily explain why the apparent value of pK$_a$ in plasma depends on pH, protein concentration and Na$^+$ concentration as well as the fact that only a non-linear relationship exists between log pCO$_2$ and pH in vivo (markedly in acidic plasma) (2, 21). So, this equation (especially $\Delta$HCO$_3^-$/$\Delta$pCO$_2$ ratio) is criticized because of its qualitative nature and impossibility to quantify the acid or base excess that exists in acid base balance disorders (20). So, this approach can only be accurately applied to human plasma at approximately normal pH, protein concentration, and Na$^+$ concentration (22).

**Base excess (BE) approach**

Dissatisfactions with the Henderson-Hasselbalch approach prompted Singer and Hastings to propose in 1948 that plasma pH may be determined by two independent factors, pCO$_2$ and net strong ion charge as the difference between all of the cations (termed total base) and anions (termed total fixed acid). They introduced the concept of buffer base (BB), (23) as the sum of all plasma buffer anions, i.e. bicarbonate plus the non-volatile weak acid buffers (albumin, phosphate) (3,24). These parameters (standard bicarbonate and buffer base) suggested as measures of metabolic acid-base disturbance are now obsolete.

It is shown that a change in buffer base corresponds to a change in the metabolic component of acid-base balance, and yields the base excess (BE) methodology (25-28). Base excess is traditionally calculated from Van Slyke equation as developed by Siggard-Anderson (29). In the late 1950s, Sigggaard-Andersen and colleague, at a fixed temperature and partial pressure of carbon dioxide, measured the plasma bicarbonate concentration and compared the difference between this value and a reference (30). When corrected by a constant, this difference yields the base excess (BE) as a more sensitive measure of metabolic imbalance. Clinically, this base excess represents the amount of acid per unit volume that must be added to achieve a normal pH (27). Blood base excess was introduced to replace plasma [HCO$_3^-$] with a measure of the metabolic component that is independent from the respiratory component, and incorporates the effect of hemoglobin as a buffer (30). Base excess represents the amount of acid or alkali that must be added to 1l of oxygenated blood exposed in vitro to a pCO$_2$ of 40 mm Hg to achieve the average normal pH of 7.40 (30). Acid is required when blood pH is higher than 7.40 (positive BE or base excess), whereas alkali is needed when blood pH is lower than 7.40 (negative BE or base deficit). Under normal conditions, the average blood BE is zero (11). Criticism of this method followed soon (18, 31, 32). For example, the laboratory BE value represents the net effect of all metabolic acid-base abnormalities. Therefore, the effect of coexisting metabolic acidosis and alkalosis may lead to falsely suggest that no acid-base abnormality exists. Furthermore, this BE does not propose
an etiology for the acid-base disorder once an abnormality is discovered (33). During in vitro blood titration, any CO₂-induced increase in plasma concentration of bicarbonate is attended by an equivalent decrease in the anionic charge of non-bicarbonate buffers (mainly hemoglobin). This comes from the binding of H⁺ released from carbonic acid, and as a result blood base excess remains constant. Base excess becomes controversial because in vivo base excess is altered by purely respiratory changes. This occurs because blood freely exchanges ions with interstitial fluid, which contains little or no protein buffer. Therefore, as PaCO₂ changes in vivo, whole blood base excess changes measurably as bicarbonate and other ions equilibrate between blood and the interstitial space. Thus, primary PaCO₂ change in living organism causes base excess to move in the opposite direction, despite demonstrable in vitro CO₂ invariance. When the PaCO₂ is varied in vivo as a result of hypoventilation or hyperventilation, base blood excess does not remain constant because a concentration gradient for bicarbonate develops between blood and the extracellular compartment. Accordingly, bicarbonate is removed from the plasma into the interstitial fluid in hypocapnia resulting in a negative base excess, whereas bicarbonate is added to plasma from the interstitial fluid in hypocapnia causing positive base excess (1,5,34). When the pCO₂ is varied in vivo by CO₂ inhalation or hyperventilation, not only blood but all extracellular fluid is equilibrated with the new pCO₂. When pCO₂ increases pH tends to decrease more in the poorly buffered interstitial fluid than in the well buffered blood. H⁺ therefore tends to diffuse from the interstitial fluid into the blood where they are buffered in the erythrocytes. This addition of H⁺ to the blood is registered as a fall in whole blood base excess, while the plasma base excess rises slightly. The actual ionic movements involve a diffusion of bicarbonate ions from the erythrocytes to the plasma and interstitial fluid in exchange for chloride ions. However, the base excess of the total extracellular fluid remains constant, during acute pCO₂ changes in vivo. It is not possible to obtain a sample of average extracellular fluid (including erythrocytes). However, a blood sample diluted threefold (1 + 2) with its own plasma may serve as a model of extracellular fluid. This pitfall was addressed by introducing the extracellular base excess or standard base excess by Siggaard-Andersen (11), as a measure of the metabolic component that is modeled by diluting the blood sample threefold with its own plasma or estimated by using the blood base excess at a hemoglobin concentration of 50 g/l. Thus, standard base excess or extracellular base excess is modeled from the existing PaCO₂ and pH, at a hemoglobin concentration of approximately 50 g/l, to replicate the mean extracellular hemoglobin concentration and does appear to have acceptable CO₂ invariance in vivo, although it is less than perfect. The base excess equation was modified to standardize the effect of hemoglobin on CO₂ titration in order to improve the accuracy of the base excess in vivo. Base excess of such model of the extracellular fluid may be calculated using the Van Slyke equation and now it represents the most relevant measure of a metabolic acid-base disturbance. Standard base excess is therefore roughly the corrective dose of sodium bicarbonate in mmol per liter of extracellular fluid. Currently, many blood gas analyzers calculate standard base excess from measured pH, pCO₂ and hemoglobin. Modern pH-blood gas analyzers calculate the extracellular base excess and present the result with the same ease as they present the actual bicarbonate concentration. Determination requires an arterial blood sample and a modern pH blood gas analyzer. Total CO₂ (bicarbonate) measured in venous plasma using an electrolyte analyzer or multi-purpose chemical analyzer may be used as screening parameter in patients without respiratory disorders. Base excess is numerically identical with the delta buffer base of Singer and Hastings: the change in buffer base from the value at pH 7.4 and pCO₂ 40 mm Hg. However, standard base excess still yields results that are slightly unstable as pCO₂ changes. Furthermore, the equation assumes normal concentration of non-bicarbonate buffers (albumin and phosphate), and when albumin or phosphate is decreased, a common scenario in the critically ill patients, standard base excess will result in even more instability (4,11,23,35). Even that standard base excess became (and remains) an optional computation that could be printed by most commercial blood gas analyzers, Bill Schwartz and Arnold Relman in Boston 1967 continued to advocate for the use of the actual bicarbonate concentration in assessing a metabolic component of acid-
base status. Discussions in letters to the editors of several journals were called “the great trans-Atlantic acid-base debate” by John Bunker, and Boston and Copenhagen school were unreconciled (4,11,23,35). So, in a traditional approach the metabolic component of acid-base physiology is based on the analysis of plasma concentrations of bicarbonate and standard base excess. Both are usually used in clinical practice and their calculations are included in all blood gas analyzers. Despite these complexities, the comparative $\Delta$HCO$_3$/$\Delta$pCO$_2$ and BE approaches evolved historically as two alternative “bicarbonate-centered” approaches for diagnosing clinical acid-base disturbances (2,36).

The anion gap method
An additional diagnostic contribution in assessing metabolic component of acid-base analysis, the anion gap method, was eventually introduced. The anion gap is defined as the difference between unmeasured plasma anions and the unmeasured plasma cations. A normal anion gap is 12±4 mmol/l. Since normally the total unmeasured anions exceed the total unmeasured cations, there is an anion gap. Under normal conditions, the bulk of the serum anion gap (approximately 80%) is due to the sum of the anionic charges on circulatory proteins (albumin is the most abundant of circulating proteins). The charge on albumin at pH 7.4 contributes ~66% of the total net charge calculated by the anion gap, with the remainder composed of phosphate, urate, lactate, ketone bodies, and sulfate (37). Usually proteins behave as anions, contributing about 13 mmol/L to the unmeasured anion pool (pH-independent protein charge is 3.7 mmol/L, pH-dependent protein charge is 10.3 mmol/L, pH-dependent phosphate charge is 1.0 mmol/L, the net protein charge of human plasma = 3.7 + 10.3 – 1.0 = 13 mmol/L) (37). Therefore, changes in the concentration of serum albumin would be expected to alter the serum anion gap. For each 10 g/L decrement in the serum concentration of albumin, the serum anion gap was decreased by 2.5 mmol/L, and needed to be corrected to compensate for abnormal albumin concentrations (thus, for example, significant ketoacidosis, could be missed in a diabetic patient with hypoalbuminemia): corrected anion gap = observed anion gap – 0.25 x ([normal albumin g/L] - [abnormal albumin g/L]), (38). This corrected anion gap can unmask an organic acidosis that was previously undetected in the setting of hypoalbuminemia (33). So, changes in the anionic effect of albumin will alter both the anion gap and the base excess. The presence of organic acid (XAH), which dissociates to form the anionic species XA while consuming bicarbonate results in increased unmeasured anions (UA) and a subsequently increased anion gap. Therefore, an increase in the calculated anion gap compared to the institutional reference, suggests the presence of an organic metabolic acidosis. Thus, when anion gap acidosis exists, the increase in the anion gap should qualitatively mirror the fall in bicarbonate. Disruption of this expected relationship is indicative of certain mixed acid-base disorders (39). The small size of the anion gap is most likely to result from a reduced concentration of the normal “unmeasured anion” albumin in critically ill patients. Globulins do not have a significant charge contribution compared to albumin since their pKa is much greater than plasma pH (K$_a$ is the effective equilibrium dissociation constant for plasma weak acids). As myeloma proteins have isoelectric points >7.4 they become positively charged in the serum and behave as cations. In this way they may lead to a reduced anion gap by creating an excess of positively charges ions. That has to be counterbalanced by an increase in anions, mainly chloride. This explains why in about 30% of myeloma or gammapathies the anion gap could be <3 mmol/l (40). THE “MODERN” APPROACH

In late 70s and early 1980s Peter Stewart proposed that the generalized Arrhenius definition of acid (substance that, when dissolved in water, produces increased concentration of H$^+$) with Naunyn's ideas (acid-base status was partly determined by electrolytes, particularly sodium - base forming and chloride - acid forming), is more useful to outline physiology than the Bronsted-Lowry definition (acid-donate proton, base acceptor of proton), (41). In 1978 Stewart questioned the traditionally accepted approach used to analyze acid-base chemistry. He modeled a solution which contained a complex mixture of ions of constant charge over the physiologi-
cal pH range (Na⁺, K⁺, Ca²⁺), nonvolatile proton donors/acceptors which transfer H⁺ within the physiological pH range (albumin, phosphate, hemoglobin, metabolizable organic compounds), and the volatile bicarbonate-CO₂ buffer system composed of CO₃⁻, HCO₃⁻, H₂CO₃, and CO₂. According to requirements of electro neutrality, the law of conservation of mass and certain equilibrium constants, Stewart solved a fourth-order polynomial equation for calculating the H⁺ concentration. His analysis did not depart from the traditional approach to acid-base chemistry as a result of the equations that are derived. Pivotal to the Stewart formulation was the categorization of certain species as being dependent or independent variables in relationship to their purported role in determining and modifying the H⁺ concentration. At first, H⁺, OH⁻, HCO₃⁻, and CO₃²⁻ were categorized as dependent variables (the mass balance of these species in a solution or specific body fluid compartment could not per se affect the H⁺ concentration). Finally, he contended that H⁺ concentration was a function of three variables: strong ion difference (SID) (the difference in the net charge of fixed cations and anions fully dissociated in solution), partially dissociated weak acids (albumin, phosphate) (A_TOT), and the partial pressure of carbon dioxide (pCO₂) of the solution. According to the principle of electro neutrality, SID is balanced of the weak acids (albumin, phosphate) and CO₂. Therefore, SID can be defined either in terms of strong ions or in terms of the weak acids and CO₂ offsetting it. Of note, the SID defined in terms of weak acids and CO₂, termed as the effective SID and is identical to the buffer base term coined by Singer and Hastings over half a century ago. So, changes in standard base excess also represent changes in SID (42).

Stewart hypothesized that water dissociates into H⁺ and OH⁻ to a greater or a lesser extent when (SID), (A_TOT) or pCO₂ change. Aqueous solutions contain a virtually inexhaustible source of H⁺. Although pure water dissociates only slightly into H⁺ or OH⁻, electrolytes and CO₂ produce powerful electrochemical forces that influence water dissociation. SID has a powerful electrochemical effect on water dissociation, and hence on H⁺ concentration. As SID becomes more positive, H⁺, a “weak cation”, decreases - (and pH increases) in order to maintain electrical neutrality. Strong ions cannot be created or destroyed to satisfy electro neutrality but H⁺ ions are generated or consumed by changes in water dissociation (30). This method emphasizes the role of water dissociation as a proton source and the association of water to consume protons as the driving force behind changes in blood pH. The relative balance of plasma positive and negative charges, including those on serum proteins, most notably albumin, drives water dissociation and association by the law of mass action (43).

Stewart approach puts water dissociation at the center of the acid-base states of body fluids. pH of a body fluid is a function of water dissociation modified by pCO₂, other weak acids and certain electrolytes (5,44). To date there have been no empirical observations that confirm water dissociation as the mechanism whereby (SID), (A_TOT) or pCO₂ affect pH. Thus, the disadvantage of Siiggaard-Andersen approach is that it implies adding or introducing H⁺ to the solution, which is impossible. The more general Stewart’s approach explains the acid base variations over more valuable physical basis. This physicochemical approach can be helpful in understanding mechanisms barely understandable using traditional approach (45). The Stewart approach is a very general physicochemical method that uses charge and mass balance to deduce an expression for proton concentration. Similarly, the base excess method is another very general physicochemical approach, but one that uses proton balance to calculate changes in proton concentration by using the Van Slyke equation (46).

Thus, Stewart challenged the traditional bicarbonate-based method of diagnosis and treating acid-base disorders and proposed an approach based primarily on charge differences between strong cations and anions. He suggested that three independent factors, the pCO₂, the strong ion difference, and the total non-volatile weak acid concentration may be used to analyze the causes of acid-base disorders. These three factors control other variables including hydrogen ion concentration and bicarbonate concentration which are dependent variables. Increases in pCO₂ and total weak acid concentration increase acidity. Decreases in strong ion difference increase acidity. This approach may better explain the me-
chanism of acid-base physiology and disorders than the Henderson-Hasselbalch approach (44). On the basis of Stewart’s definition \(H^+\) and bicarbonate are dependent variables whose concentrations are determined by three independent variables, namely SID, \(pCO_2\), and \(A_{TON}\). SID therefore can be calculated as the difference between fully dissociated cations and anions which do not participate in proton transfer reactions (apore ions - neither donate or accept \(H^+\)) and by the principle of electro neutrality this difference is equal to the sum of bicarbonate and the non-bicarbonate anions, which represent total charges contributed of all non-bicarbonate buffers, primarily, albumin and phosphate, and in whole blood, hemoglobin. SID is, therefore, the same as buffer base concept introduced by Singer and Hastings more than 5 decades ago.

**“Apparent SID” and “effective SID”**

When abnormal anion is present, a gap will appear between SID calculated by the difference between strong ions (the so-called “apparent SID”) and calculated by the addition of bicarbonate and non-bicarbonate buffers (so called “effective SID”). This difference, named strong anion gap (SIG), is a marker for the presence of an abnormal anion (23). The SIG indicates the presence of unmeasured strong anions if its value is positive, the normal value of the SIG is zero. The SIG is similar in concept to the anion gap, once the latter has been corrected for anionic contribution of albumin and phosphate (3). A positive SIG value represents unmeasured anions (such as ketoads, urate, sulfate, citrate, pyruvate, acetate and gluconate) that are present in the blood.

Apparent SID is referred to as “apparent” (\(SID_{app}\)) with the understanding that some unmeasured ions might be also present. It represents the difference between the charge of measured strong cations (sodium, potassium, calcium, magnesium) and strong anions (chloride, lactate, sulfate, ketoacids, nonesterified fatty acids and many others) that are completely dissociated in biological solutions. Currently, (SID) is routinely measured from \([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [lactate]\). It is always positive in plasma and in healthy humans - its value is 40 to 42 mmol/L, while it is often quite different in critically ill patients.

The effective SID (\(SID_{eff}\)) represents the effect of the corrected \(pCO_2\) and the weak acids, albumin and inorganic phosphate, on the balance of electrical charge in plasma, where \(HCO_3^-\) is in mmol/L, albumin in g/L and phosphate in mmol/L. All the independent variables are present in millimolar concentrations and their interaction with water dictates the amount of free \(H^+\), the concentration of which is in order of nanomoles.

The difference between the calculated apparent SID and effective SID constitutes the strong ion gap, SIG. In healthy humans, the SIG should be “theoretically” equal to zero (electrical charge neutrality). If this is not the case, there must be unmeasured charges to explain this ion gap. A positive SIG value represents unmeasured anions (such as ketoads, urate, sulfate, citrate, pyruvate, acetate and gluconate) that are present in the blood and account for the measured pH, the measured levels of strong and weak ions, and the need to maintain electro neutrality (46). Unlike the classic parameters used to calculate the anion gap, in calculating SIG, the effect of albumin, phosphate and lactate is “subtracted out”. Therefore, SIG compared with the anion gap is caused by shorter list of unmeasured ions including ketone bodies, sulfate and uraemic anions (2).

Calculating the effective SID takes into account the role of weak acids (carbon dioxide, albumin and phosphate) in the balance of electrical charges of plasma water (47). Once weak acids are qualitatively taken into account, the difference between apparent and effective SID should be zero, unless there are unmeasured charges (anions). Such charges are then described by the strong ion gap, SIG (\(SIG = \text{apparent SID} - \text{effective SID}\)). Bicarbonate is considered separately because this buffer system is an open system in arterial plasma. Rapid changes in \(pCO_2\) and hence arterial bicarbonate concentration can be rapidly induced through alteration in respiratory activity. In contrast, the non-bicarbonate buffer system is a closed system containing relatively fixed quantity of buffers. Nonvolatile buffer ion (\(A^-\)) represents a diverse and heterogeneous group of plasma buffers consisting primarily of dissociable imidazole and \(\alpha\)-amino groups on plasma proteins with a smaller contribution from phosphate-containing weak acids and citrate.

On the basis of information stated above, plasma contains three types of charged entities: SID⁺,
HCO₃⁻ and A⁻. The requirement for electro neutrality dictates that at all times [SID⁺] equals the sum of [HCO₃⁻] and nonvolatile [A⁻], such that [SID⁺] - [HCO₃⁻] - [A⁻] = 0. (The dissociation reaction for a weak acid-conjugate base-pair, HA and A⁻, is HA =H⁺+A⁻) (48).

Partially dissociated weak acids (albumin, phosphate), (Aₜₒₜ) Plasma proteins provide the major contribution to Aₜₒₜ, and therefore, plasma protein concentration independently affects acid-base balance. One major departure from the traditional approach is classification of acid-base disorders as a result of alteration in Aₜₒₜ. Aₜₒₜ, representing all non-bicarbonate buffers pairs (HA + A⁻), is made up of charges contributed primarily by serum proteins (mainly albumin) with phosphate and other buffers playing a minor role. The sum of [HA] and [A⁻] (called Aₜₒₜ by Stewart) therefore remains constant through conservation of mass.

The normal value of the total negative charges on plasma non-bicarbonate buffers is [Aₜₒₜ] = [A⁻albumin] + [A⁻globulin] + [A⁻phosphate] = 16.6 mmol/L (49). On the basis of this classification, an increase in serum protein would result in metabolic acidosis while a decrease would cause metabolic alkalosis. Siggaard-Andersen and Fogh-Andersen have suggested that changes in protein concentration should not be considered as acid-base disorders, and have considered the Stewart approach problematic in that regard (11). Dissatisfaction with the Henderson-Hasselbalch approach prompted Singer and Hastings to propose in 1948, that plasma pH was determined by two independent factors, pCO₂ and net strong ion charge, equivalent to the strong ion difference (SID). Stewart later proposed that third variable, the total plasma concentration of nonvolatile weak acids (Aₜₒₜ), also, exerted an independent effect on plasma pH. Thus, by combining equations for conservation of charge, conservation of mass, and dissociation equilibrium reactions, Stewart developed a polynomial equation, relating H⁺ concentration [H⁺] to three independent variables (pCO₂, [SID⁺] and [Aₜₒₜ]) and five constants (48). These three independent variables may change the hydrogen concentration in water (i.e. the acid-base equilibrium). The strong ion difference is regulated by the kidney, weak acid concentration primarily by liver, and pCO₂ by lung (48). An independent variable is defined as one that influences the system but is not influenced by the system. The term system refers to any single aqueous compartment (i.e. plasma).

The Stewart's approach states that pH is primarily determined by several “independent variables” (which change primarily and independently of one another: by pCO₂, strong ion difference (SID) and nonvolatile weak acids). This physicochemical approach might identify altered individual component of complex acid-base abnormalities and provide insights to their underlying mechanisms (35).

The relation between strong ion difference (SID) and standard base excess (SBE) The SID must be counterbalanced by an equal and opposing charge termed the effective strong ion difference (SIDₑ) (normal approximately -40 to -42 mmol/L). The SIDₑ negative charge principally stems from the dissociated moieties of plasma proteins (-78% albumin) and phosphate (-20%). The sum of these weak acids is known as Aₜₒₜ since they exist in a dissociated form (A⁻), as well as an associated form (AH). When the SIDₑ and SIDₑ are equal the plasma pH is exactly 7.4 at a pCO₂ of 40 mm Hg. Bicarbonate is dependent variable and does not determine the pH (47). According to the principle of electro neutrality, SIDₑ is balanced of the weak acids and CO₂, such that SID can be defined either in terms of strong ions (SIDₑ) or in terms of the weak acids and CO₂ (SIDₑ) offsetting it. Of note, the SID defined in terms of weak acids and CO₂, which has been subsequently termed the effective SID is identical to the buffer base term coined of Singer and Hastings over half a century ago. So, changes in the standard base excess also represent changes in SID. The difference in electrical charge between strong cations and strong anions is called strong ion difference. In normal plasma this amount is about 42 mmol/L. Indeed, to reach the electro neutrality, 42 mmol/l of negative charged ions, are required. These are basically the bicarbonate (HCO₃⁻) and negative charged form of weak acids (A⁻), primarily albumin plus an extremely small amount of hydroxyl (OH⁻).
later by Siggaard-Andersen. Indeed, a big difference between the traditional approach (SBE) and the Stewart’s approach is that the first considers what happens inside buffer base domain. As an example, in the traditional model (SBE) the normal buffer base (42 mmol/l, as the normal [SID]) may decrease for 10 mmol/L if the (A-) and (HCO3) are consumed by adding 10 mmol/L of H+. In this case the actual buffer base is 32 mmol/L and the difference between the actual buffer base and the ideal buffer base is equal to -10 mmol/L, and is called base excess.

In the Stewart model the same problem is considered from another point of view. If a strong ion is added to the system the ratio between strong cations and strong anions will change. As an example, by adding 10 mmol/l of lactate the strong ion difference decreases from 42 mmol/L to 32 mmol/L. The “space” available for A- and HCO3 and OH- decreases, indeed part of A- will become AH, part of HCO3 will become H2CO3 and part of OH- will become H2O. As the product of H+ and OH- is constant, a decrease of OH- will correspond to an increase of H+, i.e. acidosis (45).

So, the disadvantage of standard base excess approach is that it implies adding or introducing H+ to the solution, which is impossible. The more general Stewart’s approach explains the acid-base variations on a more valuable physical basis. So, the physicochemical Stewart’s approach can be helpful in understanding mechanisms barely understandable using traditional approach.

“The mystery” of dilutional acidosis during repletion of extracellular fluid deficit can be better explained by the modern approach. The mechanism is obviously not bicarbonate dilution as explained by the traditional approach (otherwise why would the proton donors not be diluted at the same time?). Therefore, from Stewart’s perspective an alternative explanation for dilutional acidosis needed to be developed. His mechanistic explanation is based on strong ions and the maintenance of electro neutrality. It was believed that positive or negative changes (i.e. changes of the concentrations of strong ions) influence the dissociation of water (50). In the context of dilutional acidosis, this means dilution of plasma (which has a positive SID of 39 mmol/l) by water or another solution with SID of zero decreases the SID, i.e. diminishes the surplus of positive charges. However, the decrease in SID demands compensation by a positive charge. This is suggested by increased water dissociation with generation of a positively charged H+. This newly generated H+ then causes acidification of the solution, i.e. dilutional acidosis (50). Interestingly, hypertonicity makes solutions more acidifying, as more water is drained from the intracellular space, which ultimately contributes to the final equilibrium (51).

Changes in SID, SIG and A_{TOT} in acid base disorders

Respiratory disorders, in the modern approach as in the traditional approach, are due to change in pCO2, whereas metabolic disorders are due to alterations in either SID or A_{TOT}. SID is decreased in metabolic acidosis and increased in metabolic alkalosis. By calculating SIG, one can further classify metabolic acidosis. In hyperchloremic metabolic acidosis both effective and apparent SID decreases equally, as the increase in chloride is counterbalanced by an equal decrease in the bicarbonate concentration. SIG therefore remains at or near zero. In anion gap metabolic acidosis, apparent SID does not change (as chloride concentration is unchanged), but effective SID decreases (as a result of a decrease in bicarbonate concentration) and SIG therefore becomes positive, reflecting high levels of unmeasured anions such as lactate and ketoanions (52). One major departure from the traditional approach is classification of acid-base disorders as a result of alteration in A_{TOT}. On the basis of this classification, an increase in serum protein would result in metabolic acidosis and a decrease, metabolic alkalosis (23).

CONCLUSION

Three distinct approaches are currently used in assessing acid-base disorders, the traditional or physiological approach pioneered by Van Slyke, the base-excess method, developed by Astrup, and the physicochemical approach, proposed by Stewart. The last and newest approach has steadily gained acceptance especially among critical-care physicians and anesthesiologists (5).

The “traditional” approach to interpreting acid-base disorders developed from the pioneering work of Henderson and Hasselbalch and is still most widely used in clinical practice. An advantage of this approach is that it is relatively easy to understand and to apply in common clinical situations (3).
We conclude that the physiological or traditional approach remains the simplest, most rigorous, and most serviceable approach to assessing acid-base disorders. Clinically, the traditional approach is intuitive in nature and is supported by a large body of robust empirical observations. The true relevant acid-base quantities are the arterial pH, the arterial pCO₂, and the extracellular base excess. Determination requires an arterial blood sample and a modern pH blood gas analyzer. Total CO₂ (bicarbonate) measured in venous plasma using an electrolyte analyzer or multipurpose chemical analyzer may be used as screening parameter in patients without respiratory disorders (101). The strong ion model offers a novel insight into the pathophysiology of a mixed acid-base disorders and is mechanistic (4). The traditional approach should be abandoned only if proponents of Stewart’s approach could provide clear empirical observations supporting its superiority as a clinical tool in diagnosis and treating patients with acid-base disorders. The dependence of pK’, (carbonic acid) on pH and protein concentration is a major anomaly for the Henderson-Hasselbalch equation because the dissociation constant for equilibrium reactions should not be influenced by changes in reactants (hydrogen ion activity = pH) or by anything else (including protein) except temperature and ionic strength, the latter being determined primarily by the sodium concentration. The change in [SID+] from normal is equivalent to the base excess value assuming a normal, nonvolatile buffer ion concentration (normal albumin, globulin and phosphate concentrations) (1). If serum total protein, albumin and phosphate concentrations are approximately normal, then acid-base status should be evaluated using blood pH, pCO₂ and extracellular base excess concentration, which is the traditional Henderson-Hasselbalch approach. The presence of unidentified anions should be investigated by calculating anion gap. If albumin concentration is abnormal, the anion gap can be corrected based on the albumin concentration, as this corrected anion gap can unmask an organic acidosis that was previously undetected in the setting of hypoalbuminemia. However, if serum total protein, albumin and phosphate concentrations are markedly abnormal, as in critically ill patients, then acid-base status should be evaluated using blood pH, pCO₂, measured [SID+] and A_toT. The presence of unidentified strong ions should be investigated by calculating the SIG. Traditional approach works well clinically and is recommended for use whenever serum total protein, albumin and phosphate concentrations are normal. Although Stewart’s approach has been largely ignored by physiologists, it is increasingly used by anesthesiologists and intensive care specialists, and is recommended for use whenever serum total protein, albumin or phosphate concentrations are markedly abnormal, as in critically ill patients. Although different in their concept, the traditional and modern approaches can be seen complementary giving, in principle, the same information about the acid-base status.

**FUNDING**

This work was supported by grants 175081 from the Ministry of Education, Science and Technological Development of the Republic of Serbia.

**TRANSPARENCY DECLARATION**

Competing interests: None to declare.

**REFERENCES**

Acido-bazne analize: poređenje „tradicionalnog“ i „modernog“ pristupa

Jasna Todorović, Jelena Nešović-Ostojić, Aleksandar Milovanović, Predrag Brkić, Mihailo Ille, Dušan Čemerikić

1Institut za patološku fiziologiju, 2Institut za medicinu rada, 3Institut za fiziologiju, 4Hirurgija; Medicinski fakultet Univerziteta u Beogradu, Beograd, Srbija

SAŽETAK

Danas se koriste tri posebna pristupa u proceni acido-baznih poremećaja: tradicionalni ili fiziološki ili bikarbonatni pristup, metoda baznog ekcesa i „moderni“ fizikalno-hemijski pristup predložen od Stewarta koji koristi razliku glavnih jona (naročito natrija i hlorida), koncentraciju neisparljivih slabih kiselina (osobito albumina) i parcijalni pritisak ugljen dioksida (pCO₂) kao nezavisne varijable u analizi acido-baznog statusa. Tradicionalni pristup kojeg su predložili Henderson i Hasselbalch i metoda baznog ekcesa, uprkos brojnim nedostacima, još uvek su najšire korišćeni u kliničkoj praksi. Ovaj pristup se naročito preporučuje u kliničkoj praksi kada su koncentracije ukupnih proteina, albumina i fosfata u serumu normalne. Iako je Stewartova metoda bila uglavnom ignorisana od strane fiziologa, nju sve više primenjuju anesteziolozi i lekari intenzivne nege prilikom lečenja teško bolesnih pacijenata kod kojih su koncentracije ukupnih proteina, albumina i fosfata u serumu poremećene. Iako različite u svom konceptu, tradicionalna i moderna metoda mogu se posmatrati kao komplementarni pristupi koji upotpunjuju informisanost o acido-baznom statusu.

Ključne reči: acido-bazna ravnoteža, anjonski zjap, razlika glavnih jona, bikarbonati, bazni ekces, neisparljive slabe kiseline, zjap glavnih jona