ACID-BASE BALANCE AND IMBALANCE: A REVISED APPROACH
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(Of innovations)...when a thing was new people said “It is not true.” Later, when its truth became obvious, people said, “Anyway, it is not important”, and when its importance could not be denied, people said, “Anyway, it is not new.” — William James (1842-1910)

Traditionally, the clinical evaluation of acid-base balance of blood focused on the relationship between pH or hydrogen ion concentration ([H⁻]), carbon dioxide tension (PCO₂), and bicarbonate concentration ([HCO₃⁻], as described by the Henderson-Hasselbach equation. The relationship of these variables to one another being described by the CO₂ hydration or carbonic acid equation (H₂O + CO₂ = H₂CO₃ = H⁺ + HCO₃⁻). In 1981 Peter Stewart applied physiochemical principles to provide a quantitative analysis of acid-base balance in biological fluids. Since its introduction into clinical medicine, Stewart’s approach has been adapted by almost everyone that evaluates acid-base abnormalities in patients. The basis for Stewart’s approach to acid-base balance centers on three fundamental laws: 1) the dissociation constants of all weak electrolytes in a solution must be satisfied simultaneously; 2) electroneutrality must be maintained; and 3) mass must be conserved. With these laws firmly in mind the second and most important concept of Stewart’s approach to acid-base balance can be stated: H⁺ and HCO₃⁻ are dependent variables in biological fluids. There are three primary independent variables in acid base physiology which determine H⁺, HCO₃⁻ and PCO₂. All other variables (e.g., [H⁺], pH, [HCO₃⁻], concentration of non-volatile weak acids in dissociated form [A⁻]) are dependent variables. They cannot change primarily or individually. They all will change simultaneously if one or more of the independent variables changes. At any given time, knowledge of the independent variables allows one to calculate the dependent variables. The independent variables are: the PCO₂ which can be changed by changes in alveolar ventilation; the strong ion difference ([SID]), the difference between all fully dissociated (strong) cations and anions; and the total concentration of non-volatile weak acids ([ATOT]). This last independent variable represents the sum of the dissociated and non-dissociated forms of the weak acids ([ATOT] = [A⁻] + [HA]). In plasma, the main components of [ATOT] are plasma proteins (>90% under normal circumstances) and inorganic phosphate.

By definition, strong ions are completely dissociated in water. The most important strong ions in determining acid-base balance are sodium, potassium, magnesium, chloride, sulfate, lactate, B-hydroxybutyrate and acetoacetate. The net effect of the presence of strong ions can always be expressed in terms of the difference between the total concentration of strong cations and strong anions [SID], and consequently [HCO₃⁻] can change as a result of changes in free water (as indicated by Na⁺), chloride, or unmeasured strong anions (UA⁻).

Using the Stewart approach, several insights can be gained concerning acid-base regulation in body fluids. First, [H⁺] and [HCO₃⁻] change only if PCO₂, [SID] or [ATOT] change. Since protein and inorganic phosphate concentrations in plasma ([ATOT]) normally are constant, even in the face of an acid-base disturbance, long-term acid-base homeostasis acutely controlled by changes in PCO₂ (mediated by the lungs) and changes in [SID] (mediated by the kidneys). Furthermore, the exchange of H⁺ and HCO₃⁻ between fluids separated by membranes (e.g., extracellular and intracellular fluid) is dependent upon the exchange of strong ions. [ATOT] is comprised mainly of proteins that do not cross cellular membranes, and therefore, do not participate in transmembrane exchange. Carbon dioxide is highly permeable in all membranes of the body. The local PCO₂ in a fluid compartment therefore is determined mainly by arterial PCO₂ and local CO₂ production, which in turn is a function of local tissue perfusion. Hydrogen ion concentration and [HCO₃⁻] are dependent variables, and transport of HCO₃⁻ or H⁺ across cell membranes cannot result in changes in [HCO₃⁻] or [H⁺] unless these ions are accompanied by strong ions. The effects of transported strong ions on [SID] in the individual fluid compartments are what determine the new [HCO₃⁻] and [H⁺] in body fluid compartments.

Clinical Application
The clinical application of Stewart’s concepts has been articulated at many continuing education seminars and never more clearly than by Dr. David Leath. In summary these concepts are:
1. Acid-base balance is determined by 3 independent variables: SID, A$_{\text{TOT}}$ and PCO$_2$
2. Evaluation of acid-base balance requires the evaluation of SID, A$_{\text{TOT}}$ and PCO$_2$
3. All acid-base abnormalities occur because of derangement’s in SID, A$_{\text{TOT}}$ and PCO$_2$
4. Clinically A$_{\text{TOT}}$ (total protein) in infrequently manipulated in order to correct acid-base imbalance, therefore, most if not all acid-base disturbances are corrected by manipulating the SID and PCO$_2$. It is important to realize that the correction of all nonrespiratory acid-base disturbances requires the correction of SID only!

Respiratory Acid-Base Balance: Disorders of PCO$_2$
Alterations in PCO$_2$ (breathing) can change [H$^+$] and [HCO$_3^-$]. An increase in PCO$_2$ (respiratory acidosis) or decrease in PCO$_2$ (respiratory alkalosis) are considered as a change in an independent variable in the traditional and “new” approach to acid-base balance. One important relationship to remember is that for every increase in PCO$_2$ of 10 mmHg the pH decreases by 0.05 units; and for every decrease of PCO$_2$ by 10 mmHg the pH increases 0.1 units. A PCO$_2$ of 70 mmHg therefore would be expected to decrease the pH from normal (7.40) to approximately 7.25. If the measured pH were 7.25, then the patient can be assumed to have a primary respiratory acidosis.

Non-respiratory Acid-Base Balance
A. Disorders of A$_{\text{TOT}}$
Changes in [A$_{\text{TOT}}$] will change [HCO$_3^-$]. Disorders of [A$_{\text{TOT}}$] include hypoproteinemic alkalosis, hyperproteinemia acidosis and hyperphosphatemic acidosis.

Disorders of plasma protein concentration: Plasma proteins are nonvolatile weak acids. Consequently, changes in total protein and albumin concentrations will change [H$^+$]. A decrease in albumin and total protein concentration will lead to hypoproteinemic alkalosis. Hypoproteinemia decreases [A$_{\text{TOT}}$] and causes alkalosis without changing [SID]. Although uncommon, an increase in protein concentration is expected to cause acidosis due to an increase in [A$_{\text{TOT}}$].

Disorders of Phosphate Concentration: Phosphate is a potentially important component of [A$_{\text{TOT}}$]. At normal serum phosphorus concentration, it accounts for only 5% of [A$_{\text{TOT}}$]; therefore, hypophosphatemia is not expected to cause a non-respiratory alkalosis. Severe hyperphosphatemia, however, can cause [A$_{\text{TOT}}$] to change resulting in non-respiratory acidosis. Changes in serum phosphorus concentration have been observed in renal failure, after the administration of a hypertonic sodium phosphate enema to cats or in cats receiving phosphate-containing urinary acidifiers.

Treatment of hyperphosphatemic acidosis, hyperproteinemia acidosis and hypoproteinemic alkalosis should be directed at the underlying disease process. When mixed acid-base disorders occur such as hyperchloremic acidosis with hypoproteinemic alkalosis, hypoproteinemia (or hypo-albuminemia) may limit (compensate for) changes in plasma [H$^+$]. Correction of one variable, therefore, without considering the changes caused by the other, could allow acidosis or alkalosis to emerge unopposed.

B. Disorders of [SID]
Changes in [SID] usually are recognized by changes in [HCO$_3^-$] or BE. There are three general mechanisms by which [SID] changes: changing the water content of plasma (contraction alkalosis and dilutional acidosis), changing the [Cl] (hyperchloremic acidosis and hypochloremic alkalosis), and increasing the concentration of UA (organic acidosis).

Disorders of plasma free water content: Changing the water content of plasma without any change in the content of strong ions will dilute or concentrate both strong anions and strong cations. Consequently, [SID] will change by the same proportion (e.g. if [X$^+$] – [Y$^-$] = [SID], then k[X$^+$] – k[Y$^-$] = k[SID]). If all strong ions increase, for example by 15%, [SID] also will increase by 15%. The new [SID] will change all dependent variables ([H$^+$], [HCO$_3^-$]) resulting in an increase in [HCO$_3^-$]. This alteration classically has been called “contraction alkalosis.” The same rational is used for addition of water to plasma so-called “dilutional acidosis.” The resultant non-respiratory acid-base disturbance is detected by the presence of hyponatremia or hypernatremia.
Disorders of [Cl\(^{-}\)]: When water balance is normal and does not change the [SID] only changes as a result of changes in strong anions. Chloride is the only strong anion present in sufficient quantities (concentration) to cause a significant change in [SID]. If [Na\(^{+}\)] remains constant, changes in [Cl\(^{-}\)] can substantially increase or decrease [SID]. A decrease in [Cl\(^{-}\)] (relative to Na\(^{+}\)) in extracellular fluid is referred to as hypochloremic alkalosis, whereas an increase in [Cl\(^{-}\)] (relative to Na\(^{+}\)) is called hyperchloremic acidosis. In clinical patients the [SID] increases causing hypochloremic alkalosis when [Cl\(^{-}\)] decreases. On the other hand, and increase in the strong anion concentration and resultant decrease in [SID] can be caused by increases in [Cl\(^{-}\)] (hyperchloremic acidosis) and by increases in organic anions and sulfates.

Treatment of hypochloremic alkalosis should be directed at correction of [SID]. In cases where expansion of extracellular volume is desired, intravenous infusion of 0.9% NaCl (addition of extra chloride) is the treatment of choice. This solution has an [SID] of 0 and will decrease plasma [SID]. If hypokalemia is present, KCl should be added to the fluid. If volume expansion is not necessary, Cl\(^{-}\) can be administered using salts without Na\(^{+}\) (e.g. KCl, CaCl\(_{2}\), MgCl\(_{2}\)). Potassium chloride is the salt of choice for most clinical situations. Ammonium chloride and acetazolamide can be given orally to decrease [SID] and correct hypochloremic alkalosis. Treatment of hyperchloremic acidosis is based on administration of solutions with an elevated Na\(^{+}\) concentration (elevate [SID]; sodium bicarbonate).

Disorders of [UA\(^{-}\)]: Accumulation of metabolically produced organic anions (e.g. lactate, acetoacetate and B-hydroxybutyrate) will produce non-respiratory acidosis because they behave as strong anions at body pH, thus decreasing [SID] and causing an increase in [H\(^{+}\)] in order to maintain electroneutrality. Organic alkalosis does not occur because there is no organic base present in plasma at sufficiently great enough concentrations to influence (increase) [SID]. The addition of exogenous anions such as salicylate or glycolate (e.g. ethylene glycol poisoning) or an increase in serum sulfate concentration will mimic organic acidosis because these substances behave as strong anions.

Organic acidosis in small animal medicine is usually due to hypoxemia-ischemia (lactic acid accumulation) or diabetic ketoacidosis (e.g., (B-hydroxybutyrate). An increase in inorganic strong anions can contribute to acidosis in uremia (e.g. sulfates). Treatment should be directed at the underlying cause of the organic acidosis. When the underlying cause cannot be corrected and the pH is <7.2 alkali (NaHCO\(_{3}\)) therapy should be considered. It should be remembered that organic anions can be metabolized, reestablishing normal [SID]. Therefore, the administration of NaHCO\(_{3}\) (a solution with a high [SID]) may result in an increase in [SID] after the organic acids have been metabolized causing a non-respiratory alkalosis.

Quantitation of Nonrespiratory Acid-Base Disorders:
1. Determine the serum Na\(^{+}\), Cl\(^{-}\) and total protein (TP)
2. Calculate the free water, chloride and TP abnormalities
3. Sum the values of the free water, chloride and TP abnormalities and compare that sum with the observed base excess (BE). A BE less than the summed values indicates the presence of unmeasured anions in equal magnitude to the difference.

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\text{Free water abnormalities: } 0.3 \ (\text{[Na}^+\text{]} - 140) = \_
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\text{Chloride abnormalities: } 102 - \text{[Cl}^{-}\text{]} \text{ corr} = \_
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\text{Hypoproteinemia: } 3 \ (6.5 - \text{TP}) = \_
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\text{Unidentified anions make the balance: } \_ = \_
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Total is the observed (reported) BE: \_ = \_

Note: [Cl\(^{-}\)] corr is = [Cl\(^{-}\)] obs – 140/[Na\(^{+}\)].
Note: For [Albumin] instead of [TP], use 3.7 (4.5 – [Albumin]).

The concepts expressed by Stewart have changed our view of acid base physiology in health and disease, have provided a more mechanistic and quantitative approach to the pathophysiology of acid-base disorders, and permit a more complete understanding of electrolyte and plasma protein imbalances.
in relation to changes in blood $[\text{H}^+]$. Changes in $[\text{HCO}_3^-]$ can be explained by changes in $[\text{SID}]$, $\text{PCO}_2$ and $[\text{A}_\text{TOT}]$, and quantification of the individual roles of these variables should be routine in veterinary patients.