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Acid-base balance revisited: Stewart and strong ions

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Understanding acid-base physiology is a core requirement for anesthesiologists and intensivists and other physicians responsible for the care of critically ill and injured. Despite a long history, clinical acid-base physiology remains a confusing area for many clinicians and numerous misconceptions exist. The application of principles of physical chemistry to clinical acid-base physiology allows for a valuable new perspective on an old problem and may provide important insights.

"If the facts don't fit the theory, change the facts."
—Albert Einstein

The concentration of hydrogen ions (H^+) in blood plasma and various other body solutions is among the most tightly regulated variables in human physiology. In health, the free hydrogen ion concentration in arterial blood rarely deviates from 35-45 nmol/L—pH 7.45 to 7.35. Acute changes in blood pH induce powerful regulatory effects at the level of the cell, organ, and organism. Yet the mechanisms responsible for local, regional and systemic acid-base balance are incompletely understood and controversy exists in the literature as to what methods should be used to understand these mechanisms.[1] Much of this controversy exists only because the strict rules for causation (as opposed to association) have not often been applied to the understanding of acid-base balance and methods that are useful clinically have often been used to understand physiology without being subjected to appropriate scientific rigor. In other words "the facts" about acid-base are still in dispute. The use of various laboratory variables to diagnose an acid-base disorder is analogous to the use of the electrocardiogram (ECG) to diagnose a myocardial infarction. However, neither the changes in the ECG tracing nor the disturbances in electrical conduction that theses changes reflect were ever considered to be the cause of a myocardial infarction. In contrast, changes in bicarbonate (HCO_3^-) concentration, for example, have been assumed to be responsible for metabolic acidosis or alkalosis. Failure to establish causation has lead to numerous incorrect notions of acid-base physiology and has fueled years of, often heated, debate.[1,2] Thus, it is our intent to "revisit" acid-base balance in light of recent advances in the understanding of physiology and clinical epidemiology.

Acid-base: A brief history

During the 1950s there was a paradigm shift in the approach acid-base physiology and pathology.[3] Bicarbonate was promoted from being an important factor in acid-base balance[4] to being the central factor for control of the non-respiratory (metabolic) component of acid-base balance.[5-7] One reason for this shift was a desire among clinical chemists to define acids along the lines of the Bronsted-Lowry definition that

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had become popular with physical chemists: an acid is a hydrogen donor.[5,8,9] Using this new approach carbonic acid, and its conjugate base bicarbonate, assumed a central role.[9] A key feature of this bicarbonate-centered approach is to use the Henderson-Hasselbach equation (Equation 1) to describe acid-base status of the plasma. The Henderson-Hasselbach equation substitutes the concentration of carbonic acid with the partial pressure of carbon dioxide and its solubility coefficient.

$$pH = pKa + \log_{10} \frac{[HCO_3^-]}{\alpha pCO_2} \quad (1)$$

Where pH is the plasma pH, pKa is the pH at which the acid (carbonic acid) is 50% dissociated, $[HCO_3^-]$ is the plasma bicarbonate concentration; α is solubility of carbon dioxide in blood at 37°C, and pCO_2 is the partial pressure of carbon dioxide in blood.

The bicarbonate centered approach remains popular.[8,10,11] Many who use this approach, however, use bicarbonate "rules of thumb" to determine primary and mixed disorders without quantifying these disorders.[8,10,12] One advantage of using base-excess is that it quantifies non-respiratory changes in acid-base status.[13] Following on from this, the quantitative effects of acidifying factors such as lactate are poorly defined. Further, phenomena such as alkalosis associated with decreased plasma albumin concentration, and acidosis secondary to hyperphosphatemia are poorly explained using the bicarbonate centered approach.[14]

In the late 1970s and early 1980s, Peter Stewart, a Canadian-born physiologist working at Brown University, Rhode Island began to revisit acid-base balance.[15-18] Stewart was concerned about many issues in acid-base chemistry and felt that the bicarbonate centered approach to clinical acid-base chemistry was ". . .piecemeal, qualitative and confusing. . .."[17] Stewart's emphasis was on a quantitative approach, as highlighted in the title of his most widely cited paper "Modern quantitative acid-base chemistry."[16] Stewart examined the different roles of strong ions (ions that are completely dissociated in solutions), and weak acids that are only partly dissociated (Equation 2):

$$HA \quad H^+ + A^-. \quad (2)$$

Here HA is the undissociated weak acid, H^+ is the hydrogen ions, and A^- is the dissociated anion.

Stewart developed an acid-base framework that can be applied to any physiological solution.[18] However, in common with clinical acid-base work, he focused on plasma. In plasma, Stewart's three principal independent factors are: (1) the difference between the concentrations of strong cations and anions (particularly sodium and chloride); (2) the concentration of weak-acids (particularly albumin); and (3) the partial pressure of carbon dioxide.[16,17] Bicarbonate, while still a clinical marker, is but a minor electrolyte, dependent on the three independent variables.[17] A fourth component is the dissociation constants of weak-acids and water. The hydrogen ion concentration of plasma (or any physiological solution) will increase if there is an increase in the partial pressure of carbon dioxide, and increase in the concentration of weak acids, or a decrease in the strong-ion-difference.[16]

Water: A unique substance

While water is the solvent for physiological solutions, water also dissociates to produce hydrogen (H^+) ions and hydroxyl (OH^-) ions.[19] Under the Stewart approach, water is the principal source of hydrogen ions in physiological solutions.[16]

As temperature increases, the dissociation of water increases, which in turn increases the H^+ concentration. The dissociation of water can be expressed in terms of the law of mass action:

$$Kw = \frac{[H^+] \times [OH^-]}{[H_2O]} \quad (3)$$

Where Kw is the dissociation constant of water, $[H^+]$ the concentration of hydrogen ions, $[OH^-]$ the concentration of hydroxyl ions, and $[H_2O]$ the concentration of water. The concentration of "water" in water is 55 mol/l. The Stewart approach assumes that because the concentration of water is thousands of times the concentrations of H^+ and OH^-, it can be used as a constant. Further, because the dissociation of water is temperature dependent the dissociation constant used in calculations should be temperature corrected. A modified dissociation constant for water (K'w) is calculated.[16]

$$K'w = [H^+] \times [OH^-] \quad (4)$$

This equation simplifies the understanding of Stewart's approach—that increased water dissociation increases the hydrogen ion concentration. Further, Equation 4 simplifies the underlying mathematics.[16] Importantly, while the hydrogen ion concentration is important for physiological mechanisms[8] from a quantitative perspective, hydrogen ions are unimportant because compared with the quantitatively significant ions in solutions (such as plasma), that are in millimolar concentrations, hydrogen ions are in nanomolar concentrations.[16]

Strong and weak acids

One question is how to determine when an acid is weak or strong. Stewart[16] noted that in general, lactic acid is regarded as a weak acid by chemists, compared to the many strong acids available in the laboratory. Stewart also noted that whether an acid is weak or strong is relative to the surrounding acid-base environment. At pH 7.40 lactic acid is more than 99.9% dissociated and can be thought of as a strong acid; that is, all the lactic acid is assumed to be in the lactate anion form. The operational pH range for a weak