FOCUS ON: MEDICAL UPDATE

Acid–base balance: Stewart’s physicochemical approach

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Summary The traditional approach to acid–base balance allows explanation and quantification of many disorders of acid–base physiology and is still widely used in clinical practice. However, complex metabolic disorders, such as those present in critically ill patients, can be difficult to define and treat using this approach. Peter Stewart proposed a radically different approach to acid–base physiology based upon physicochemical principles. In this second article, the main features of Stewart’s complex but powerful model are described and illustrated by clinical examples. © 2005 Elsevier Ltd. All rights reserved.

The ‘traditional’ approach to acid–base balance using the Henderson–Hasselbalch equation fails to consider all the factors influencing hydrogen ion concentration and is insufficient to explain complex metabolic abnormalities of acid–base physiology. It assumes $\text{HCO}_3^-$ behaves as an independent variable whose concentration determines the metabolic component of pH balance. This concept was challenged by Peter Stewart in the late 1970s.\textsuperscript{1} His mathematical approach to acid–base physiology treats body fluids as physicochemical systems, governed by the following fundamental principles:

1. Electrochemical neutrality: In an aqueous solution, positively charged ions must be balanced by an equal number of negatively charged ions. Net charge within a compartment is zero.
2. Conservation of mass: For substances that may simultaneously exist in different forms within a solution, such as dissociated and undissociated forms, the total amount remains constant unless added to or removed from a system.
3. Law of mass action: Equilibrium constraints on dissociation reactions must be satisfied.

According to Stewart, the concentration of $\text{H}^+$ in any aqueous solution depends upon the degree of dissociation of water into $\text{H}^+$ and $\text{OH}^-$.

Just three independent variables are $p\text{CO}_2$, total concentration of weak acids $[\text{ATOT}]$ and 'strong ion difference' (SID). Although several other variables are linked to...
the dissociation of water and [H⁺], they do not directly influence it, and are termed dependent variables. They include [H⁺], [OH⁻], [HA], [A⁻], [HCO₃⁻] and [CO₃²⁻], where square brackets indicate concentration. Dependent variables cannot directly influence any other variable. Therefore, only changes in independent variables can account for [H⁺] or pH changes in a biological solution. Note that bicarbonate, being a dependent variable, cannot exert direct control over [H⁺] (or pH).²

**pCO₂**

Manipulation of pCO₂ by adjusting alveolar ventilation causes rapid [H⁺] changes in aqueous solutions due to the reversible dissociation of carbonic acid. Small size and high solubility allow CO₂ to pass easily between compartments and alter [H⁺] in all body fluids.

**Total weak acid concentration [A_TOT]**

This is the next independent variable. Weak acids do not fully dissociate in biological solutions. Proteins are the main weak acids in plasma and their concentration is largely controlled by the liver, with changes occurring over days. Phosphates also contribute to [A_TOT] becoming particularly significant during hypoalbuminaemia.

**Strong ion difference**

Strong ions (the final independent variable) completely dissociate in aqueous solutions. The most important strong ions are sodium, potassium, magnesium, calcium, chloride and lactate. Strong ion difference is the amount by which strong cations exceed strong anions, measured in milliequivalents per litre. So, for plasma,

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\text{SID} = (\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+}) - (\text{Cl}^- + \text{Lactate}).
\]

In plasma, there is normally an excess of cations over anions, giving the SID a positive value of 40–48 meq l⁻¹. Milliequivalent concentrations represent the charge as well as the quantity of ions present. Since electrochemical neutrality must be maintained, SID has a powerful influence on the dissociation of water, and therefore [H⁺]. Concentrations of strong ions in the body are determined by gut absorption and renal excretion so changes in SID only occur over hours. This calculated value for SID, termed the apparent SID (SIDa), is based upon easily measured strong ions (Fig. 1). Another method for calculating SID makes no assumptions about which strong ions constitute the SID in plasma. The SID calculated in this manner is known as the effective SID (SIDe) and is based upon the concentration of bicarbonate and the charge contributions from inorganic phosphate and albumin ([A⁻]) in plasma. SIDa and SIDe should be equal. Any difference between SIDa and SIDe is termed the strong ion gap (SIG) which represents unmeasured anions. Unmeasured anions and lactate are normally insignificant (see text).

**The Stewart approach in action**

An important principle of this theory is that dependent variables only change in response to changes in one or more of the independent variables. Therefore, to explain variations in [H⁺] or pH, we only need to consider pCO₂, [A_TOT] and
As SID increases (becomes more positive), there is less dissociation of water and hydrogen ion concentration is reduced (pH increases), in order to maintain electrical neutrality. Conversely, as SID falls (becomes less positive) H+ concentration increases (pH falls).

Several clinical examples illustrate the effect of [SID] changes on acid–base balance. Prolonged vomiting with loss of gastric hydrochloric acid (HCl) reduces the plasma concentration of chloride relative to sodium. Consequently, the SID increases and alkalosis results. According to Stewart’s hypothesis the alkalosis is not caused by loss of H+ since the dissociation of water provides an inexhaustible supply of H+. Changes in SID also explain the metabolic acidosis caused by large volume infusions of ‘normal saline’. Hyperchloremia develops due to the relatively high chloride concentration of saline (150 mmol l⁻¹) compared to the chloride concentration of normal plasma (100 mmol l⁻¹). The resulting reduction in SID increases water dissociation and [H⁺]. The administration of sodium bicarbonate to treat acidosis may also be explained in physicochemical terms. The sodium load accompanying an infusion of sodium bicarbonate increases plasma [Na⁺] and increases SID. The dissociation of plasma water falls in order to maintain electroneutrality and the concentration of free H⁺ is reduced. The bicarbonate therefore appears to act as a buffer. However, the HCO₃⁻ in sodium bicarbonate cannot influence plasma pH as [HCO₃⁻] is a dependent variable.

Stewart’s model clarifies the role of the kidneys, liver and gut in acid–base control. Renal control of plasma electrolytes, particularly chloride, allows manipulation of SID and therefore plasma pH. Liver and gut function influence [ATOT]. The metabolic alkalosis resulting from chronic hypoalbuminaemia in critically ill patients is explained by a low [ATOT].

Different body fluids or compartments do not have the same pH. Adjacent compartments generate pH differences by manipulation of SID. It is the movement of strong ions across membranes, rather than movement of H⁺ or HCO₃⁻, which alters pH. CO₂ passes so freely across lipid membranes that its partial pressure is virtually the same in adjacent compartments. Therefore changes in pCO₂ enable rapid but similar changes in [H⁺] throughout all compartments. Proteins are practically bound by membranes due to their molecular size so cannot be used to regulate pH between compartments, despite exerting a strong influence on [H⁺] within a compartment.

All solutions must satisfy the constraints of equilibrium, mass conservation and electrical neutrality. Therefore, several equations describing these principles must be satisfied simultaneously for any complex biological solution. Calculating the value of a dependent variable, such as [H⁺], requires the clinician to solve a 4th-order polynomial algebraic expression. This perhaps explains why the Stewart approach has been slow to catch on in clinical practice and why the use of the ‘traditional’ approach has persisted. Nonetheless, the Stewart approach is particularly useful for analysis of metabolic acid–base disturbances, i.e. those caused by changes in either [SID] or [ATOT], or both. Unmeasured anions such as lactic acid and keto-acids, occurring in pathological states, may be detected and quantified. Classifying acid–base disorders according to derangements of the independent variables provides a clearer understanding of the primary clinical problem in order to direct corrective therapy.

References


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