Acid–base physiology: new concepts

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Abstract

The traditional approach to acid–base physiology is based on the Henderson–Hasselbalch equation which is derived from the CO_2/HCO_3^- buffer system. However, it is becoming increasingly recognized that this is an incomplete analysis as it focuses on only one of the six reactions involving H^+ and can lead to the incorrect assumption that CO_2 and HCO_3^- are independently adjusted factors that ultimately determine pH. In 1983, Stewart, a Canadian physiologist, proposed that a fuller understanding of acid–base physiology required consideration of biological fluids as a complex dynamic system, taking into account the interactions of all the chemical species involved. He showed that the true independent variables controlling the pH of any given fluid compartment are: the difference in the concentration of 'strong ions'; the total concentration of 'weak acid'; and the PCO_2. Importantly, H^+ and HCO_3^- are dependent variables and it is incorrect to think of them as being specifically regulated to manipulate pH. This review will discuss the importance of pH homeostasis and highlight the implications of the Stewart approach in our understanding of acid–base control mechanisms and disorders. In particular, the true mechanisms by which the kidney regulates plasma pH will be discussed, emphasizing key misconceptions that have been propagated as a result of the traditional approach.

Keywords Acid–base physiology; acidosis; Stewart approach

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Importance of H^+

Maintenance of plasma pH ($-\log_{10}[H^+]$) within the range 7.35 to 7.45, which corresponds to an intracellular pH of neutrality (where $[H^+] = [OH^-]$; ~pH 6.8 at 37°C), is an essential requirement for life. But why should an ion that is only present in nanomolar concentrations be so critical? The answer is twofold: firstly, metabolic intermediates are completely ionized at neutral pH and therefore are maximally trapped within the cell; secondly, the activity of all proteins (including enzymes) is exquisitely sensitive to changes in H^+ concentration as their binding characteristics are determined by their net charge. Therefore the H^+ concentration is tightly regulated to provide conditions for optimal intracellular function.

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Problem

The main problem faced by the homeostatic control mechanisms is the defence against a massive daily acid load. The acid produced by the body can be thought of as either volatile or non-volatile:

Volatile acid is mainly carbonic acid (H_2CO_3) which is produced by the hydration of CO_2:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Therefore, although CO_2 is not itself an acid as it does not contain a hydrogen ion to donate, it can instead be thought of as representing a potential to create an equivalent amount of carbonic acid. At rest (with a CO_2 production of 200 ml/minute) the daily load of CO_2 is at least 15,000 mmol/day.

Non-volatile acids contribute much less to daily acid production with a net production of 1–1.5 mmol/kg/day or 70–100 mmol of H^+ per day in an adult. These acids are produced by the incomplete metabolism of carbohydrates (e.g. lactate), fats (e.g. acetoacetate, β-hydroxybutyrate) and proteins (e.g. sulphate, phosphate). Note that these are actually *bases* rather than acids. However, this terminology is common place because they have been formed by the liberation of an H^+ from their parent acid.

It is clear that these amounts are several orders of magnitude greater than the normal body H^+ concentration and thus robust defence mechanisms are essential for conditions compatible with life.

Defence mechanisms

The traditional approach to acid–base balance is that there are two component defence mechanisms:

- physicochemical buffering
- acid excretion from the lungs (as CO_2) and the kidneys.

In order to understand these mechanisms it is first necessary to understand the principles of buffer systems within the body.

Physicochemical buffering

A buffer is a solution that resists changes in pH when an acid or base is added to it. A buffer consists of an undissociated weak acid (HA) and its conjugate base (A^-) and can be represented by:

$$HA \rightleftharpoons H^+ + A^-$$

A buffer typically consists of a solution that contains a weak acid HA mixed with the salt of that acid (e.g. NaA). The principle is that the salt provides a reservoir of A^- to replenish $[A^-]$ when A^- is removed by reaction with H^+. The body has a huge buffering capacity and as this process happens instantaneously, physicochemical buffering provides a powerful first defence against acid–base perturbations.

The main buffer systems in the different fluid compartments of the body are as follows:

- blood
  - haemoglobin: $HHb \rightleftharpoons H^+ + Hb^-$
  - bicarbonate: $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

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- interstitial fluid
  - bicarbonate: $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
- intracellular fluid
  - proteins: $HPr \rightleftharpoons H^+ + Pr^-$
  - phosphate: $H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$

The main buffer system in the extracellular fluid is bicarbonate/carbonic acid:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Since the concentration of carbonic acid is very low compared to the other components, the acid moiety of the system is CO_2 and so the above equation can be simplified to:

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

Indeed, it is from this equation that the Henderson–Hasselbalch equation is derived:

$$pH = pK + \log\left[\left(HCO_3^-\right)/(\alpha PCO_2)\right]$$

$$\text{so, pH is a function of} \left[HCO_3^-\right]/PCO_2$$

The Henderson–Hasselbalch equation forms the basis of the traditional approach to acid–base balance: it is used to show that, for the CO_2/HCO_3^- buffer system to be sustainable, the body must ultimately regulate $[HCO_3^-]$ and PCO_2.

It has therefore been taught that the longer-term control of acid–base homeostasis is achieved by respiratory control of plasma PCO_2 through changes in alveolar ventilation (occurs over minutes), and by the control of HCO_3^- excretion by the kidneys (occurs over hours to days). Importantly, the traditional approach views these two variables as *independently* adjusted factors that ultimately determine pH.

Alternative approach: the Stewart method

However, in 1983, the Canadian physiologist Peter Stewart proposed an alternative approach to acid–base regulation. He proposed that a full understanding of acid–base physiology requires consideration of biological fluids as a complex dynamic system: one needs to consider all the chemical species involved and how they interact chemically with each other.

He made the argument that the traditional approach only focuses on one of six reactions that involves H^+ ions, and ignores the other five:

- water: $H_2O \rightleftharpoons H^+ + OH^-$
- 'weak' acids in water (mainly protein and inorganic phosphate): $HA \rightleftharpoons H^+ + A^-$
- carbonate: $CO_3^{2-} + H^+ \rightleftharpoons HCO_3^-$
- bicarbonate: $HCO_3^- + H^+ \rightleftharpoons CO_2$
- electrical neutrality equation: $[SID] + [H^+] = [HCO_3^-] + [A^-] + [CO_3^{2-}] + [OH^-]$
- conservation of mass for 'A': $[A_{TOT}] = [HA] + [A^-]$

Stewart employed the fundamental principles of physical chemistry to derive the factors that must determine $[H^+]$. He applied the principles of electroneutrality, conservation of mass, and the law of mass action (the requirement that all equilibriums must be simultaneously satisfied) to the various components which constitute body fluids:

- water
- weak ions – weak ions are produced from substrates that only partially dissociate when dissolved in water, and can be classified into two groups:
  - carbon dioxide and associated ions (volatile)
  - weak acids (non-volatile) which are mainly protein and inorganic phosphate
- strong ions – strong ions are ions which are fully dissociated in biological solutions (e.g. Na^+, K^+, Cl^-, lactate); that is their dissociation equilibria have a p*K* far removed from the local pH.

Stewart created a model of human solutions by adding each of these constituents in turn and solving simultaneous equations based on the dissociation equilibria of all the reactions involving H^+. In his analysis he emphasized that the concentrations of the various chemical species present are the variables of the system, which can be of two types:

Dependent variables have values that are determined *internally* by the system. They are determined by the equations (chemical equilibria) which determine the system and can be altered ***only*** by changes on the values of the independent variables.

Independent variables have values that are determined by processes or conditions which are *external* to the system; they are *imposed* on the system rather than being determined by it.

From his analysis, Stewart showed that that $[H^+]$ in a physiological solution is in fact a function of three independent variables:

- **The strong ion difference (SID)** → the total concentration of fully dissociated cations in solution minus the total concentration of fully dissociated anions in solution $= \{[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]\} - \{[Cl^-] + [\text{lactate}^-]\} \approx [Na^+] + [K^+] - [Cl^-]$ → controlled by the kidney. For the mathematical reader, proof of the dependency of $[H^+]$ on SID is shown in the Appendix.
- **Total concentration of weak acid ($[A_{TOT}]$)** → predominately phosphate and proteins such as albumin (controlled by the liver) and Hb (controlled by the haematopoietic system).
- **PCO_2** → controlled by the lung.

Therefore, in a given body fluid compartment, any changes in pH must be because of a change in one of more of these *independent* variables. Crucially, it is misleading of the traditional approach to think of HCO_3^- as being specifically regulated to manipulate pH as HCO_3^- *cannot* be individually or primarily altered. Stewart concluded that $[HCO_3^-]$ is a *marker* for acid–base disturbances rather than a causative factor.

The Stewart approach and the traditional approach both agree on the role of the lungs in regulating acid–base balance through CO_2 excretion and manipulation of arterial PCO_2. However, it is the role of the kidney that is disputed. Using the Stewart approach, we can discover the true mechanisms by which the kidney regulates plasma pH, and can appreciate key misconceptions that have been propagated as a result of the traditional approach.

Role of the kidneys in regulation of plasma pH

Conventionally, the kidney is viewed as regulating plasma pH by regenerating HCO_3^- with the net effect of excreting H^+.

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