Acid–base physiology: comments on 10 contentious assertions

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In the world of acid–base, models to explain observed phenomena tend to be adopted by particular "schools", and then fiercely defended, on an almost tribal basis.[1] Meanwhile, irrefutable truth (as distinct from debating positions) can remain elusive. In this context, we offer brief comments on 10 assertions which have had or still have currency. We regard these responses as consistent with available evidence, but acknowledge that all may require modification or even abandonment, subject to further discoveries.

1. The Stewart approach is sufficient to explain acid–base physiology

In the Stewart model,[2,3] three independent variables (PCO_2, the total concentration of non-volatile weak acid (Atot) and the strong ion difference [SID]) directly control plasma concentrations of several dependent variables, including pH and HCO_3^-. Six simultaneous equations (Table 1), separately or as a fourth-order polynomial, shed light on many areas of acid–base physiology (see below), but with several caveats. First, some prefer to characterise strong ions as mere "spectator" ions, their net charge a convenient inverse quantification of the "buffer base" concentration, which is the total concentration of bicarbonate and non-bicarbonate buffers.[4-6] This more traditional approach designates the buffer base as the site of all relevant molecular acid–base transactions. Stewart advocates have also been criticised for treating water as a limitless proton "reservoir" (Figure 1), ignoring the alternative viewpoint that it acts more as a proton conduit via excited-state "water bridges".[8] Hence, for some, the Stewart approach, while mathematically accurate, is mechanistically incorrect.[5,9] The debate continues.

Table 1. The six equations of Stewart*

- $[H^+] \times [OH^-] = K'w$
- $[H^+] \times [A^-] = Ka \times HA$
- $[HA] + [A^-] = Atot$
- $[H^+] \times [HCO_3^-] = Kc \times PCO_2$
- $[H^+] \times [CO_3^{2-}] = Kd \times [HCO_3^-]$
- $SID + [H^+] - [HCO_3^-] - [CO_3^{2-}] - [A^-] - [OH^-] = 0$

SID = strong ion difference (net charge concentration of fully dissociated ions). Atot = total concentration of non-volatile weak acids. * All K values are known dissociation constants.

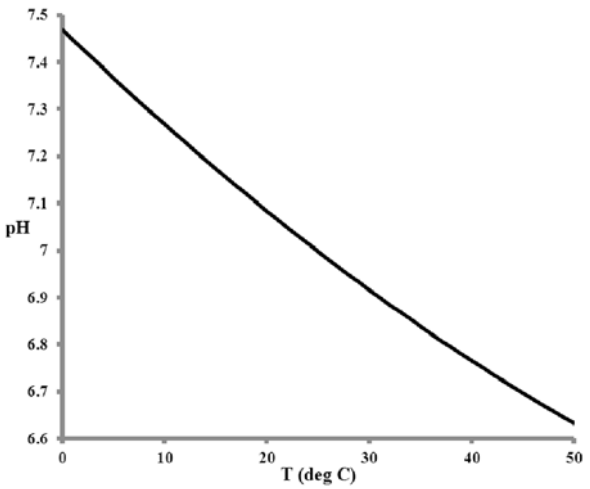
There is one genuine discrepancy in Stewart's original concept. Modelling plasma in isolation disregards ion and water traffic and associated Gibbs–Donnan phenomena in the interstitium–plasma–erythrocyte (IPE) complex.[10] Because of this, independent status cannot be claimed for plasma SID in vivo, since CO_2-driven traffic causes it to alter with PCO_2.[3,11] PCO_2 independence is retained by IPE SID, a more nebulous entity.

2. Acidosis stimulates renal bicarbonate reabsorption, new bicarbonate generation and proton excretion

These traditional concepts can be usefully reframed in Stewart terms as follows:[3,12,13]

- Tubular proton and bicarbonate transporters are simultaneous strong ion transporters, directly or indirectly, with immediate effects on urinary SID.
- At low urinary pH, NH_4^+ (pKa, 9.2) is a strong cation. However, in extracellular fluid, NH_4^+ is a weak cation, present in minute concentrations. It is therefore excluded from the urinary SID calculation.

Figure 1. The pH of pure water v temperature*



* Graph based on data from Harned and Owen,[7] showing that the pH of a water solution can be changed without adding any "acid". The implications are that water itself is a source of interactive hydrogen ions, and that it is impossible to identify the source of hydrogen ions with certainty in aqueous solutions such as plasma.

- Renal ionophore responses to acidosis decrease urinary SID.
- Upregulation of tubular NH_3 synthesis in acidosis supports urinary SID reduction, substituting NH_4^+ for sodium as a cationic partner of chloride.
- Decreasing urinary SID increases extracellular SID, restoring plasma pH and bicarbonate.

3. Hypoalbuminaemia does not affect acid–base physiology

Albumin acts as a weak acid.[2,3] Experiments using magnetic resonance and confirmed by modelling[14] quantify the titratable protein charge in plasma at physiological pH at 12–13 mEq/L,[15] mostly from histidine moieties on albumin.[16] Hypoalbuminaemia diminishes these acidifying effects and blood is alkalinised. The net negative charge of albumin necessitates an "albumin-corrected" anion gap to counteract albumin fluctuations.[16]

4. Acidosis in shock is from proton release generated by ATP hydrolysis[17]

No studies of clinical shock show proton release from ATP hydrolysis. In fact experimentally, net ATP hydrolysis implies zero perfusion (death or full ischaemia).[18] ATP depletion has never been shown in clinical septic, haemorrhagic, anaphylactic or cardiogenic shock or by magnetic resonance spectroscopy in extreme experimental septic shock.[19] A more elegant explanation is that tissues release L-lactate under physiological stress via adrenergically mediated accelerated glycolysis,[20] reducing SID and hence acidifying plasma.

5. Hyperlactataemia implies tissue hypoxia

The concept that tissue hypoxia underlies most hyperlactataemic states lacks any empirical basis.[21] With no gold standard to diagnose tissue hypoxia, its presence in septic shock, for example, can be challenged.[22] During maximal exercise, plasma lactate increases despite preserved intracellular oxygenation,[23] whereas in extreme hypoxaemia (eg, a person on Mount Everest) lactate is, at most, minimally elevated.[22] Lactate shuttles within cells and among tissues as a major biofuel.[23] Although it is an independent mortality predictor in shock, evidence suggests that hyperlactataemia is due to accelerated aerobic glycolysis driven by adrenergic stress,[24] facilitating bioenergetic efficiency in muscle, heart and brain cells. These characteristics best fit the notion of an adaptive survival response.

6. Lactate-balanced solutions contain "bicarbonate as lactate"

There is a belief that administered lactate is oxidised to bicarbonate, forming the rationale for "lactate buffered" solutions. In reality, manufacturers substitute organic anions for bicarbonate to avert bicarbonate degradation by CO_2 loss on autoclaving and storage. Administered L-lactate is metabolised to pyruvate and then predominantly to glucose (gluconeogenesis) and CO_2 (via the Krebs cycle). Its rapid metabolic "disappearance" means that the effective SID of a lactate-balanced solution is the difference between non-metabolised cations and anions. The effective SID of Hartmann's solution is therefore 29 mEq/L, slightly exceeding that required for exact balance (24 mEq/L).[25]

7. The bicarbonate in sodium bicarbonate corrects metabolic acidosis

In Stewart terms, the critical property of sodium bicarbonate is the presence of sodium, a strong cation, without a corresponding strong anion such as chloride.[26] Its SID is therefore its sodium concentration (1000 mEq/L in a 1 M solution), which increases extracellular SID on administration and antagonises metabolic acidosis. The bicarbonate component is rapidly exhaled as CO_2. The SID of NaOH 1 M is also 1000 mEq/L but with a pH of 14, it is unsuitable for intravenous use. Otherwise it would be equally effective in reversing metabolic acidosis, despite the absence of bicarbonate. Conversely, ammonium bicarbonate[27] contains no strong ions (its SID is zero). In sufficient quantity and despite the presence of bicarbonate, it will cause metabolic acidosis.[25]

8. Paradoxical intracellular acidosis from bicarbonate administration is a big problem

Tissue experiments confirm that the CO_2 content of added sodium bicarbonate generates marked respiratory acidosis.[28] The in-vivo situation differs for the following reasons.[26]

- There is massive haemodilution by cardiac output.
- Any intravenous CO_2 load immediately increases CO_2 excretion via mixed venous pulmonary transit.
- Modelling indicates that during acidosis correction, only a fraction of administered CO_2 in sodium bicarbonate requires subsequent excretion.[26]

In practice, large doses of sodium bicarbonate must be infused rapidly, for example, 1.5 mmol/kg in 5 minutes, to generate detectable $Paco_2$ and Vco_2 upswings.[29] Slower administration should prevent CO_2 surges, with possible exceptions being extreme pulmonary hypoperfusion states.

9. Fluid-induced acidosis is simple bicarbonate dilution

Bicarbonate is CO_2 in hydrated anionic form. Rapid CO_2–HCO_3^- transitions are facilitated by carbonic anhydrase, and body fluids are open to CO_2 ingress and egress. Hence, in living open systems during volume loading, there is no fixed bicarbonate mass to dilute. Concentrations continue to be

determined by P_{CO_2}, Atot and SID.[3] Saline haemodilution reduces both SID and Atot, with the net result being a fall in bicarbonate.[25]

10. Loop diuretics cause metabolic alkalosis because of "volume contraction"

Loop diuretics decrease urinary SID by competing for the chloride site on the NaK_2Cl cotransporter in the thick ascending limb.[30] The output of reduced-SID urine increases the extracellular SID, causing metabolic alkalosis. Although mineralocorticoid responses to diuretic-induced volume contraction also reduce urinary SID, they are readily overridden if the diuretic itself increases urinary SID, as does, for example, acetazolamide.[31]

Competing interests

None declared.

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