Andrew Davenport

Dilutional acidosis or uncovered cellular metabolism?

Received: 28 August 2009

Accepted: 23 September 2009

Published online: 23 October 2009

© Copyright jointly hold by Springer and ESICM 2009

This editorial refers to the articles available at:

doi:[10.1007/s00134-009-1528-y](https://doi.org/10.1007/s00134-009-1528-y) and [10.1007/s00134-009-1653-7](https://doi.org/10.1007/s00134-009-1653-7).

A. Davenport (✉)

Center for Nephrology, University College London Medical School, Royal Free Campus, Rowland Hill Street, London NW3 2PF, UK

e-mail: andrew.davenport@royalfree.nhs.uk

Commentary

Metabolic acidosis is common in critically ill patients admitted with hypovolaemic and/or septic shock. Following resuscitation with appropriate parenteral fluids, although the patient may be clinically improving, in terms of changes in blood pressure and urine output, repeat blood gas analysis may show a fall in arterial pH [1]. Similarly patients undergoing general anaesthesia may develop a metabolic acidosis intra- or postoperatively that spontaneously resolves within 24 h [2]. This fall in arterial pH may appear somewhat paradoxical compared to the clinical state. It was initially suggested that the administration of intravenous fluids produced a dilutional acidosis, because of a dilution of plasma bicarbonate, with continued tissue respiration and carbon dioxide generation [3].

For optimal cell function, it is important to maintain intracellular homeostasis. Although blood plasma and interstitial fluid typically have a pH of 7.2–7.4, intracellular pH is usually lower: 6.1 for skeletal muscle and 6.9 for hepatocytes. The maintenance of intracellular pH depends upon both intracellular buffering involving proteins, organic and inorganic acids (phosphate, citrate,

lactate moieties), and changing intracellular electrolyte composition via a number of cell membrane channels and transporters, including the Na^+/H^+ and $\text{Cl}^-/\text{HCO}_3^-$ exchangers. The maintenance of intracellular pH homeostasis is outside the scope of this commentary, but is dynamic and affected by the extracellular environment. As the electrolyte and protein composition differs between the intracellular and extracellular environment, then the relative importance of different buffering systems varies.

Several organ systems are involved in regulating extracellular pH. As bicarbonate is predominantly extracellular, the traditional approach to acid–base has centered on the Henderson–Hasselbalch equation [4], relating pH to the relative concentrations of HCO_3^- to H_2CO_3 . The lungs therefore play a pivotal role in controlling blood pH by regulating arterial gas CO_2 tensions, whereas the kidney and to a lesser extent bone matrix can regulate plasma bicarbonate concentrations.

Protein catabolism in healthy individuals produces around 1 mmol/kg of non-volatile and organic acids each day. The kidney secretes hydrogen ions into the urine where they are buffered by titratable buffers and/or ammonia, and so are excreted. The liver also has a major role in maintaining acid–base homeostasis by responding to metabolic acidosis by increasing glutamine and reducing urea synthesis, and to alkalosis by conversely increasing urea and reducing glutamine synthesis. Although a significant amount of volatile and organic acids and lactate are produced daily in the body, they are not accounted for in the Henderson–Hasselbalch equation. The importance of noncarbonated buffers was recognised by Van Slyke, and then by Siggard-Anderson and colleagues [5], who developed the concept of base excess, which is now established in routine clinical practice.

More recently, Stewart proposed a different approach to acid–base disorders, based upon the laws of mass action and the conservation of both mass and electrical charge

[6]. He introduced two novel variables into the acid–base equation: the strong ion difference ($SID = Na^+ + K^+ - Cl^- - Lactate - \text{other strong anions}$) and the total weak acids (A_{Tot}) [7]. A simplified version of the Stewart equation:

$$[SID] = [HCO_3^-] + [A^-],$$

where $[A^-]$ is the concentration of weak noncarbonic acids, predominantly albumin and phosphate in normal healthy patients.

For example, using the Stewart model a metabolic acidosis would either have a low SID and high strong ion gap (SIG), including ketoacids, lactic acid, salicylate, formate, methanol, or a low SID and low SIG, such as renal tubular acidosis, total parenteral nutrition, saline infusions, anion exchange resins, diarrhoea and pancreatic losses. Conversely, using the Stewart approach a metabolic alkalosis will occur in cases of low albumin, such as nephrotic syndrome and hepatic cirrhosis and high SID due to chloride losses (vomiting, gastric drainage, diuretics, post-hypercapnoea, chloridorrhoea, mineralocorticoid excess, hyperaldosteronism, Cushing's syndrome, Liddle's syndrome, Bartter syndrome, exogenous corticosteroids, liquorice) or due to a sodium load with a weak base, including sodium acetate, citrate or lactate, such as Ringer's solution, haemofiltration/dialysate substitution/replacement fluids, blood products and total parenteral nutrition [8]. Lactate, acetate and citrate are predominantly metabolised by the liver and kidney, but also muscle, and can be indirectly converted through to bicarbonate. Haemofiltration and/or dialysates with low lactate and high chloride concentrations used for continuous renal replacement therapies [9] predispose to metabolic acidosis and vice versa [10].

The advent of balanced solutions, containing less chloride with either lactate or acetate to maintain neutrality has led to an increased interest in the metabolic acidosis following intravenous fluid resuscitation [11]. As the addition of 0.9% saline would provide equal amounts of sodium and chloride, then both Doberer [12] and Gattinoni [13] have suggested that according to the

Stewart approach there should be no change in SID, and as such this would not explain the acidosis observed post fluid resuscitation. Doberer and colleagues conducted a number of in vitro physico-chemical laboratory experiments, predominantly diluting alkaline solutions with a more neutral solution under either closed (constant PCO_2) or open (variable PCO_2) conditions, and showed that a dilutional acidosis was associated with a reduced SID, but this was a reflection of the dilutional effect per se and did not mechanistically explain the acidosis. The predominant cause of dilutional acidosis in their laboratory experiments was dilution of the bicarbonate buffer capacity, with continued carbon dioxide generation [14]. Gattinoni used an in vitro model of fresh frozen plasma diluted with distilled water, 0.9% saline and Ringer's lactate, and confirmed Doberer's result that in a closed system, pH did not fall with dilution.

Both Doberer and Gattinoni used in vitro experiments, but the situation in human plasma is somewhat more complex, as strong ions have a plasma water concentration, but also undergo electrochemical binding, depending upon fluid composition, pH and temperature, so that activity of the ion is less than the absolute concentration. For example, sodium has a plasma water concentration around 155 mmol/l, but an activity 142 mmol/l. Sodium has other key effects, in terms of anion transport, for example, exogenous sodium bicarbonate can reverse intracellular acidosis, whereas choline bicarbonate does not [15].

In clinical practice appropriate fluid resuscitation leads to improved blood flow to perfusion dependent organs and tissues, such as muscle. This is typified in the management of diabetic ketoacidosis, when patients initially display insulin insensitivity or resistance, which then resolves as muscle blood supply improves. However, the improved tissue blood supply also leads to a "wash out" of lactate, organic acids and other intermediary metabolites of metabolism, increasing $[A^-]$. This probably accounts for the paradoxical fall in arterial pH in patients who are clinically improving following appropriate fluid resuscitation.

References

1. The SAFE Study Investigators (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 30:1356–1360
2. Bruegger D, Bauer A, Rehm M, Niklas M, Jacob M, Irlback M, Becker PF, Christ F (2005) Effect of hypertonic saline dextran on acid–base balance in patients undergoing surgery of abdominal aortic aneurysm. *Crit Care Med* 33:556–563
3. Shires GT, Tolman J (1948) Dilution acidosis. *Ann Intern Med* 28:557–559
4. Henderson LJ (1908) The theory of neutrality regulation in the animal organism. *Am J Physiol* 21:427–448
5. Severinghaus JW (1985) History of blood gas analysis. II. pH and acid base balance measurements. *J Clin Monit* 4:259–277
6. Stewart PA (1981) How to understand acid–base. A quantitative acid–base primer for biology and medicine. Elsevier, New York
7. Figge J, Mydosh T, Fencl (1992) Serum proteins and acid base equilibria: a follow up. *J Lab Clin Med* 120:713–719
8. Corey H (2003) Stewart and beyond: new models of acid base balance. *Kidney Int* 64:777–787

-
9. Davenport A (2008) Potential adverse effects of replacing high volume hemofiltration exchanges on electrolyte balance and acid–base status using the current commercially available replacement solutions in patients with acute renal failure. *Int J Artif Organs* 31:3–5
 10. Davenport A (2002) Replacement and dialysate fluids for patients with acute renal failure treated by continuous veno-venous haemofiltration and/or haemodiafiltration. *Contrib Nephrol* 144:317–328
 11. Scheingraber S, Markus R, Sehisch C, Finsterer U (1999) Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecological surgery. *Anesthesiology* 90:1265–1270
 12. Doberer D, Funk GC, Spital OW, Kirchner K, Schneeweiss B (2009) A critique of Stewart's approach: the chemical mechanism of dilutional acidosis. *Intensive Care Med.* doi: [10.1007/s00134-009-1528-y](https://doi.org/10.1007/s00134-009-1528-y)
 13. Gattinoni L, Carlesso E, Maiocchi G, Polli F, Cadringer P (2009) Dilutional acidosis: where do the protons come from. *Intensive Care Med.* doi: [10.1007/s00134-009-1653-7](https://doi.org/10.1007/s00134-009-1653-7)
 14. Garella S, Chang BS, Kahn SI (1983) Dilution acidosis and contraction alkalosis: review of concept. *Kidney Int* 8:279–283
 15. Goldsmith DJ, Forni LG, Hilton PJ (1997) Bicarbonate therapy and intracellular acidosis. *Clin Sci* 93:593–595