Commentary

Unmeasured anions: the unknown unknowns

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Abstract

Evidence is emerging that elevated concentrations of the intermediates of the citric acid cycle may contribute to unmeasured anions in critical illness. Both the anion gap and the strong ion gap are used as scanning tools for recognition of these anions. The mechanisms underlying these elevations and their significance require further clarification.

Unmeasured ions have long captured the imagination of intensivists. Potential candidates include L-lactate, β-hydroxybutyrate, D-lactate, salicylate, formate and oxalate in toxicological situations, pyroglutamate, semisynthetic penicillins, sulphate and hippurate in renal failure, and occasionally urate and amino acids with catabolic states and total parenteral nutrition. Reports of increased tricyclic acid (TCA) cycle anions in shock are now emerging [1,2].

Their presence is often inferred from the anion gap (AG), calculated as $[Na^+] + [K^+] - ([Cl^-] + [HCO_3^-])$. When its reference range is exceeded, a search for unmeasured anions should commence, irrespective of the overall metabolic acid-base status, because a competing metabolic alkalosis can mask their presence. Likely culprits vary with the clinical scenario, but the search usually starts with L-lactate and β-hydroxybutyrate. During this process, stoichiometry is tracked between ΔAG (measured AG - normal AG) and the summed concentrations of suspect anions (always in mEq/l, because we are dealing in electrical neutrality). If ΔAG - [suspect anions] exceeds 2 to 3 mEq/l, then the involvement of other unmeasured anions is likely.

Unfortunately, the AG is a flawed instrument. Both sensitivity and specificity are reduced by perturbations of albumin (remembering that albumin negative charge forms the bulk of the normal AG), pH, $[Ca^{2+}]$, $[Mg^{2+}]$ and [phosphate] [3]. The most promising alternative is the strong ion gap (SIG) [4,5] Like the AG, the SIG quantifies unmeasured anions minus unmeasured cations, but unlike its predecessor it is insulated from variations in [albumin], [phosphate], pH, [L-lactate], $[Ca^{2+}]$ and $[Mg^{2+}]$ [6].

In the previous issue of *Critical Care*, Bruegger and colleagues [1] combine SIG calculations with capillary electrophoresis, and report that anions associated with the TCA cycle, specifically citrate and acetate, contribute to the metabolic acidosis of canine haemorrhagic shock. Their data originate from an earlier experiment designed to investigate the benefits of a perflurocarbon-based oxygen carrier during resuscitation from a predefined oxygen debt [7]. Capillary electrophoresis on specimens before shock, during shock and on resuscitation revealed maximal citrate elevations of 1.9 mEq/l, whereas the peak acetate increase was 3.4 mEq/l after shock. Together, these accounted for around 60% of corresponding SIG increases. Minor increases were noted in fumarate, sulphate and α-ketoglutarate. L-lactate reached 5.6 mmol/l.

Although these findings fuel ongoing speculation concerning TCA anions in shock, several potential confounders are worthy of comment. During preparation, the animals acquired major metabolic perturbations, with severe baseline hypoalbuminaemia (1.5 g/dl) and impressive hyperchloraemia (130 mmol/l), but (from the parent study) only mild anaemia (11 g/dl) [7]. This suggests the administration of large fluid volumes during the surgical preparation phase. Most surprising in this context was a massive baseline plasma acetate (2.4 mEq/l), which is 40 times the level reported from a previous study in dogs (0.06 mmol/l) [8]. The postshock acetate peaked at 5.8 mEq/l, over 30 times that in the previous report (0.19 mmol/l).

To our knowledge such prodigious acetate levels are unprecedented outside the setting of exogenous administration

AG = anion gap; SIG = strong ion gap; TCA = tricyclic acid.

[9]. In the parent study [7], Ringer's solution 15 ml/kg per hour was documented as infused during all but the shock phase. If this was Ringer's acetate, and if the animals had received both saline (as stated by Bruegger and colleagues [1]) and Ringer's acetate, then this would explain much. Of relevance is a report that exogenous acetate can elevate hepatic citrate [10]. Although the authors acknowledge that they re-infused blood containing citrate phosphate dextrose solution during the shock phase, thus introducing exogenous citrate, they clearly stated that no acetate-containing solutions were administered. Hence, apart from possible assay problems, these acetate concentrations are unexplained. A final caveat is that charge and dissociation indices for human albumin used in this study differ from those for canine albumin [11,12], although the effect on SIG calculations is probably small.

Until now, talk of unmeasured ions in critical illness has largely been speculative, based on discrepancies in AG or SIG. Nonetheless, since the late 1960s reports have emerged of accumulating TCA cycle intermediates in shock and dysoxic states [13,14]. The pattern reported by Forni and colleagues [2] in human metabolic acidosis differed substantially from the findings reported by Bruegger and coworkers [1], with relatively small increases in isocitrate, α-ketoglutarate, malate and D-lactate, and in some cases citrate and succinate. Only on aggregate were these sufficient to inflate the AG. They did not measure acetate.

It is insufficient to invoke 'tissue stress' to explain such increases in TCA anions. Elevations must be considered within the context of anaplerosis and cataplerosis [15], which combine to maintain adequate concentrations of TCA intermediates. It is unclear how dysoxic states disturb this delicate balance.

So, do unmeasured anions appear in shock? It is highly likely. Do at least some have a mitochondrial source? This is very probable. Can there be massive acetate and citrate concentrations? We need more information.

Competing interests

The authors declare thay they have no competing interests.

References

1. Bruegger D, Kemming GI, Jacob M, Meisner FG, Wojtczyk CJ, Packert KB, Keipert PE, Faithfull S, Habler OP, Becker BF, Rehm M: **Causes of metabolic acidosis in canine hemorrhagic shock: role of unmeasured ions.** *Crit Care* 2007, **11:**R130.
2. Forni LG, Mc Kinnon W, Lord GA, Treacher DF, Peron JMR, Hilton PJ: **Circulating anions usually associated with the Krebs cycle in patients with metabolic acidosis.** *Crit Care* 2005, **9:** R591-R595.
3. Salem MM, Mujais SK: **Gaps in the anion gap.** *Arch Intern Med* 1992, **152:**1625-1629.
4. Morgan TJ: **What exactly is the strong ion gap, and does anybody care?** *Crit Care Resusc* 2004, **6:**155-159.
5. Kellum JA, Kramer DJ, Pinsky MR: **Strong ion gap: a methodology for exploring unexplained anions.** *J Crit Care* 1995, **10:**51-55.
6. Morgan TJ, Cowley DM, Weier SL, Venkatesh B: **Stability of the strong ion gap versus the anion gap over extremes of PCO_2 and pH.** *Anaesth Intensive Care* 2007, **35:**370-373.
7. Kemming GI, Meisner FG, Wojtczyk CJ, Packert KB, Minor T, Thiel M, Tillmans J, Meier J, Bottino D, Keipert PE, Faithful S, Habler OP: **Oxygent as a top load to colloid and hyperoxia is more effective in resuscitation from hemorrhagic shock than colloid and hyperoxia alone.** *Shock* 2005, **24:**245-254.
8. Kveim M, Nesbakken R, Bredesen JE: **Plasma acetate concentrations during canine haemorrhagic shock.** *Scand J Clin Lab Invest* 1979, **39:**645-652.
9. Veech RL: **The untoward effects of the anions of dialysis fluids.** *Kidney Int* 1988, **34:**587-597.
10. Veech RL, Gitomer WL: **The medical and metabolic consequences of administration of sodium acetate.** *Adv Enzyme Regul* 1988, **27:**313-343.
11. Staempfli HR, Constable PD: **Experimental determination of net protein charge and A(tot) and K(a) of non-volatile buffers in human plasma.** *J Appl Physiol* 2003, **95:**620-630.
12. Constable PD, Stampfl HR: **Experimental determination of net protein charge and A(tot) and K(a) of non-volatile buffers in canine plasma.** *J Vet Intern Med* 2005, **19:**507-514.
13. Barnett D, Cohen RD, Tassopoulos CN, Turtle JR, Dimitriadou A, Fraser TR: **A method for estimation of Krebs cycle and related intermediates in animal tissues by gas chromatography.** *Anal Biochem* 1968, **26:**68-84.
14. Iles RA, Barnett D, Strunin L, Strunin JM, Simpson BR, Cohen RD: **The effect of hypoxia on succinate metabolism in man and the isolated perfused canine liver.** *Br J Anaesth* 1972, **44:**223.
15. Owen OE, Kalhan SC, Hanson RW: **The key role of anaplerosis and cataplerosis for citric acid cycle function.** *J Biol Chem* 2002, **277:**30409-30412.