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Strong ion gap and outcome after cardiac arrest: another nail in the coffin of traditional acid–base quantification

Received: 15 August 2008
Accepted: 17 September 2008
Published online: 14 October 2008
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This editorial refers to the article available at:
doi:[10.1007/s00134-008-1315-1](https://doi.org/10.1007/s00134-008-1315-1).

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The role of unmeasured anions in critical care patients remains a controversial issue. Recent data demonstrate that circulating anions can be quantified and that this might have prognostic value. An alternative approach to acid–base balance, based more squarely on chemical and physical principles, was proposed by Peter Stewart more than 25 years ago [1]. The strong ion difference as later modified by Figge and Fencel [2] corresponds with the net charge balance of all strong ions present in a given solution (the “Fencel–Stewart” approach) [3]. Whilst striving for more accuracy and bedside practicality, Kellum [4] proposed using the strong ion gap (SIG) which corresponds with the difference between the apparent strong ion difference and the effective strong ion difference. In comparison to the traditional anion gap, the SIG

is calculated from all charged blood constituents and is now the gold standard for the quantification of unmeasured anions [5]. The origin of these circulating anions remains unclear though clinicians are inclined to believe that those anions are released from ischemic or hypoxic tissue and that quantification of these anions could be more sensitive for prognosis than lactate in these conditions. An elevated SIG has been associated with increased mortality in critically ill children [3] as well in patients undergoing major surgery [6]. No study till now has sought to describe a possible association between outcome after cardiac arrest and SIG. This question is addressed by the study of Funk et al. published in this issue of *Intensive Care Medicine* [7]. For almost two decades, the Stewart approach, though commendable theoretically, seemed to lack usefulness as a tool for the clinician at the bedside. Recognition of the fact that utilization of the traditional anion gap, especially in critically ill patients, was highly unsatisfactory [8], renewed interest for the use of the more accurate SIG, which takes into account all the ions present in a given solution [9]. In this issue, Funk et al. [7] compare SIG versus lactate as a determinant of outcome after cardiac arrest, whereby outcome is described in survivors in terms of neurological performance. An association is indeed demonstrated, independent of time to return of spontaneous circulation, epinephrine dose, age or other acid–base variables. It is asserted that the anions constituting SIG may be surrogates for tissue damage. Additionally, as an association between SIG and cerebral performance category is found, it is postulated that the brain may be a potential source of unmeasured anions after cardiac arrest and arising even before lactate levels increase. While these findings and their exciting explanations remain to be demonstrated in further controlled studies, it is important to point out a number of pitfalls in this study. By far the most important is the retrospective nature of the study design, representing an obvious and serious drawback to

the validity of the conclusions. Nevertheless, although retrospective, this is a well conducted study, both in terms of methodology and in terms of adjustment for confounding factors. A further drawback of the study is the selective use of bicarbonate in some patients, albeit according to strict criteria, thereby creating, for some at least, a bias in the study. The long period over which the study was conducted is a major concern: it took 12 years to complete the study, a period in which profound changes in treatment of the intensive care patient will have taken place which impacts on the strength of this retrospective study, though the size of the cohort (288 patients in cardiac arrest who were successfully resuscitated) works to the study's advantage. Funk's study highlights the fact that more and more studies are currently evaluating SIG as a possible tool not only for measurement of anions but also as a surrogate marker for tissue damage (sometimes very locally) and as an early and more specific predictor of outcome when compared to traditional acid-base quantification and lactate. Indeed, studies have recently shown that in a general intensive care population, SIG was an independent prognostic factor for mortality even in the presence of a normal acid-base status as traditionally described using the Henderson-Hasselbach equation [10]. The SIG has the theoretical advantage when compared to traditional anion gap (AG) that it remains stable and reliable, even in cases of extremes in PCO_2 and pH, further enhancing its utility in acid-base disturbances in those circumstances [11]. Another potential advantage is the detection of metabolic acidosis that has been offset by a greater metabolic alkalosis especially after liver transplantation [12], thereby facilitating interpretation of complex acid-base changes [12]. The same phenomenon has been described is sepsis too, a situation in which metabolic acidosis maybe offset by concurrent respiratory alkalosis [13]. The relationship between metabolic acidosis, unmeasured anions and mediators released remains unclear [14] especially during

special procedures like cardiopulmonary bypass and haemofiltration procedures [14]. In a recently conducted study, an elevated SIG presaged mortality after injury better than admission pH, bicarbonate level and even lactate [15]. Along the same lines, in children after cardiopulmonary bypass, an elevated SIG appears to be superior to lactate as mortality predictor [16]. Nonetheless, controversy persists in particular to what constitutes a normal range of SIG and where abnormal SIG with adverse outcome starts. Indeed, this is reflected in what one could term a transatlantic acid-base debate as American studies describe abnormal values at around 5 mEq/L [17, 18] while studies from Europe and Australasia found far higher values [19]. In this study, the mean SIG from healthy controls was 3.6 mmol/L and an elevated SIG was described when values were above 8.9 mmol/L [7]. Some authors claim that this difference was due to the use of gelatins as an exogenous source of unmeasured anions used in resuscitation [20] but the use of gelatins has diminished in these countries as they can induce hyperoncotic acute kidney injury [21]. Recent work has demonstrated that up to 50% of endogenous low molecular weight anions are sourced from the intermediate metabolism [22]. In conclusion, the study from Funk et al. [7], although retrospective in nature, sheds new light upon the role of SIG after cardiac arrest as a marker of outcome and especially neurological outcome. SIG proved to be a better marker of outcome after cardiac arrest than epinephrine dose, age and other acid-base variables including traditional anion gap and even lactate. They subsequently concluded that the anions constituting SIG may be surrogates of tissue damage that occurred mostly in the brain. However, these conclusions needs to be challenged in further controlled and well-conducted studies. A new era of change in which SIG replaces traditional acid-base quantification is upon us. The speed of this change will remain an area of uncertainty for the near future.

References

1. Stewart PA (1983) Modern quantitative acid-base chemistry: applications in biology and medicine. *Can J physiol Pharmacol* 61:1444-1461
2. Figge J, Mydosh T, Fencel V (1992) Serum proteins and acid-base equilibria: a follow-up. *J Lab clin Med* 120:713-719
3. Balasubramanian N, Havens PL, Hoffman GM (1999) Unmeasured anions identified by the Fencel-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Crit Care Med* 27:1577-1581
4. Kellum JA, Kramer DJ, Pinsky MR (1995) Strong ion gap: a methodology for exploring unexplained anions. *J Crit Care* 10:51-55
5. Gunnerson KJ (2005) Clinical review: the meaning of acid-base abnormalities in the intensive care unit part 1-epidemiology. *Crit Care* 9:508-516
6. Kaplan LJ, Kellum JA (2004) Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med* 32:1120-1124
7. Funk GC, Doberer D, Richling N, Kneidinger N, Lindner G, Scheeweiss B, Eisenburger P (2008) The strong ion gap and outcome after cardiac arrest in patients treated with therapeutic hypothermia. *Intensive Care Med*. doi: 10.1007/s00134-008-1315-1
8. Levraut L, Bounatirou T, Ichai C, Ciais JF, Jambou P, Hechemia R, Grimaud D (1997) Reliability of anion gap as an indicator of blood lactate in critically ill patients. *Intensive Care Med* 23:417-422

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9. Leblanc M (1999) The acid–base effects of acute hemodialysis. *Curr Opin Crit Care* 5:468–478
 10. Antonini B, Piva S, Paltenghi M, Candiani A, Latronico N (2008) The early phase of critical illness is a progressive acidotic state due to unmeasured anions. *Eur J Anaesthesiol* 25:566–577
 11. Morgan TJ, Cowley DM, Weier SL, Venkatesh B (2007) Stability of the strong ion gap over extremes of PCO_2 and pH. *Anaesth Intensive Care* 35:370–373
 12. Story DA, Vaja R, Poustie SJ, McNicol L (2008) FencI–Stewart analysis of acid–base changes immediately after liver transplantation. *Crit Care Resusc* 10:23–26
 13. Leisewitz AL, Jacobson LS, de Moraes HS, Reyers F (2001) The mixed acid–base disturbances of severe canine babesiosis. *J Vet Intern Med* 15:445–452
 14. Honoré PM, Matson JR (2002) Hemofiltration, adsorption, sieving and the challenge of sepsis therapy design. *Crit Care* 6:394–396
 15. Kaplan LJ, Kellum JA (2008) Comparison of acid base models for prediction of hospital mortality following trauma. *Shock* 29:662–666
 16. Durward A, Tibby SM, Skellett S, Austin C, Anderson D, Murdoch IA (2005) The strong ion gap predicts mortality in children following bypass surgery. *Pediatr Crit Care Med* 6:281–285
 17. Gunnerson KJ, Roberts G, Kellum JA (2003) What is normal strong ion gap (sIG) in healthy subjects and critically ill patients without acid–base abnormalities. *Crit Care Med* 31:A11
 18. Kellum JA (2007) Acid–base disorders and strong ion gap. *Contrib Nephrol* 156:158–166
 19. Cusack RJ, Rhodes A, Lochhead P, Jordan B, Perry S, Ball JA, Grounds RM, Bennett ED (2002) The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. *Intensive Care Med* 28:864–869
 20. Kellum JA (2003) Closing the gap on unmeasured anions. *Crit Care* 7:219–220
 21. Honoré PM, Joannes-Boyau O, Boer W (2008) Hyperoncotic colloids in shock and risk of renal injury: enough evidence for a banning order? *Intensive Care Med* 34 (published online). doi: [10.1007/s00134-008-1225-2](https://doi.org/10.1007/s00134-008-1225-2)
 22. Forni LG, McKinnon W, Lord GA, Treacher DF, Peron JM, Hilton PJ (2005) Circulating anions usually associated with the krebs cycle in patients with metabolic acidosis. *Crit Care* 9:591–595