Commentary

Closing the gap on unmeasured anions

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Abstract

Many critically ill and injured patients, especially those with metabolic acidosis, have abnormally high levels of unmeasured anions in their blood. At the same time, such patients are prone to hypoalbuminemia, which makes the traditional anion gap calculation inaccurate. Thus, little is known about the epidemiology and clinical consequences of an excess in unmeasured anions in the blood. Indeed, even the etiology of these "missing ions" is often unclear. Unfortunately, more precise means of quantifying unmeasured anions, such as the strong ion gap (SIG), are cumbersome to use clinically. However, a simple means of correcting the anion gap can be used to estimate SIG and may provide additional insight into this common clinical problem.

Keywords acid–base balance, anion gap, metabolic acidosis, pH, strong ion difference, strong ion gap

Acid–base balance is among the most tightly regulated variables in human physiology. Acute changes in blood pH induce powerful regulatory effects at the level of the cell, the organ and the organism [1]. Yet the mechanisms responsible for local, regional and systemic acid–base control are incompletely understood, and controversy exists in the literature regarding what methods should be used to understand them [2]. The use of physical chemical principles to analyze clinical acid–base disorders has been advocated by some workers [3–5], and not by others [6,7]. One difficulty with the physical chemical approach is that it cumbersome to apply clinically. For example, to calculate the strong ion gap (SIG) requires, at the very least, a programmable calculator [8]. In addition, some investigators have found that the pH and the standard base excess are better outcome predictors than the SIG [9]. Other investigators have found, however, that the SIG is a powerful predictor of outcome in acutely ill or injured patients [10,11] and that other, more traditional, variables performed less well.

In the present issue of *Critical Care*, Moviat and colleagues report an analysis of 50 critically ill patients with metabolic acidosis [12]. The majority of their patients had multiple underlying mechanisms explaining their metabolic acidosis, and unmeasured strong anions were present in 98% (defined by SIG > 0). In keeping with previous studies [4,5,13], Moviat and colleagues found that while the uncorrected anion gap was of little value in detecting unmeasured ions, there was an excellent agreement between the SIG and the corrected anion gap. They thus demonstrated that the corrected anion gap could be used in place of the more cumbersome SIG.

However, the study of Moviat and colleagues raises some other fundamental questions. What is the normal SIG in critically ill patients? And what are the unmeasured anions? We unfortunately do not have the answer to either of these questions. An increased SIG appears to be common in acidotic patients such that even if one accepts a level of < 2 mEq as 'normal', then more than 75% of Moviat and colleagues' patients had an elevated level. The SIG was much higher in similar studies from the United Kingdom [9] and from Australia [13]; however, the use of gelatin in this population may have contributed. An exogenous source of unmeasured anions (e.g. gelatin) may also explain why some studies have not found a strong correlation between the SIG and outcome, whereas other studies, in which gelatins were not used, have shown that the SIG is associated with increased mortality [10,11].

SIG = strong ion gap.

As regards the source of unmeasured anions, we can only speculate. An increased SIG appears to occur in patients with renal [12] and hepatic [8] impairment, and unexplained anions have been shown experimentally to arise from the liver in animals challenged with bolus intravenous endotoxin [14]. However, the precise identity or, more probably, identities remain unknown. Given their rapid appearance in the circulation in experimental models [14] and in patients sustaining vascular injury [10], it seems probable that these ions are acute phase proteins but this has not yet been satisfactorily explored.

Whatever the source of the SIG, it is easily estimated from the corrected anion gap and would appear to be frequently elevated in critically ill patients with metabolic acidosis. Preliminary data from our institution suggest that SIG > 2 mEq is independently associated with mortality in critically ill patients with metabolic acidosis [15]. Further studies are needed both to establish the true 'normal range' for the SIG and to determine its etiology.

Competing interests

None declared.

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