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Association between Anion Gap and Strong Ion Gap in Commonly Encountered Acid-Base Disorders among Critically Ill Patients

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Abstract

Acid-base abnormalities, especially saying, metabolic acidosis (Mac) related to various disease conditions are common in the intensive care unit (ICU) and attributable to highest mortality among these patients. Although traditional Henderson and Hasselbalch approach based on the anion gap (AG) is widely used in all clinical settings, it underestimates a great portion of Mac in critically ill patients due to lack of consideration of other strong ions and albumin in the definition. After albumin correction, anion gap is found to nearly similar to the strong ion gap (SIG) defined by modified Stewart approach, though still another strong ions need to be considered in predicting morbidity and mortality among these critical ill patients. To provide more appropriate approaches in critically ill patients, we review the association and the interactions between the AG and SIG in different clinical situations commonly encountered in intensive care units.

Background

Metabolic acidosis is a challenging disorder among intensive care unit (ICU) patients, and contributes the majority of mortality in these patients. Traditionally, Henderson and Hasselbalch approach based on standard base excess (SBE), bicarbonate [HCO3-], and anion gap (AG) were used to determine acid-base status of these patients [1]. However, traditional approach often fails to identify specific acid-base disorders associated with electrolyte and protein abnormalities (e.g. hypoalbuminemia, sepsis) [2], which are commonly encountered in critical care units. An alternative evaluation was proposed by Stewart [3] and modified by Figge et al [4-6], which based on 3 independent variables: strong ion difference (SID, difference between fully dissociated anions and cations in plasma water), the PaCO2, and total weak acid concentration (consisting mainly of albumin and phosphate) which determine plasma pH and bicarbonate (HCO3-). Complex acid-base disorders which appear to be normal in traditional approach were identified by this approach. Moreover, this method also provides insight into basic

principles underlying pathogenesis and management [7]. Since the Stewart and Figge approach requires complicated calculations at the bedside, a simpler albumin adjusted anion gap might be used more frequently in clinical situations. Recently, many studies explain nature of metabolic acid-base disorders in these critically ill patients using Stewart approach [8,9]. Our previous study also revealed SIG value is a better predictor of overall mortality than the AG and CAG (corrected AG) values in critically ill acute kidney injury (AKI) patients [10].

Normal Renal Physiological Condition

Under normal physiologic condition, the kidneys maintain chloride and sodium balance. In normal subjects, 80% of the sodium filtered by the glomerulus is resorbed with chloride, and the remaining 20% is exchanged for potassium and hydrogen, thus allowing chloride clearance [11]. During metabolic acidosis, the absolute renal chloride clearance increases, and chloride is excreted with the NH4 produced by glutamine metabolism [11, 12]. In normal people with metabolic acidosis, every filtered and nonreabsorbed chloride ion increases the plasma strong ion difference (SID) and subsequently alleviates acidosis. In renal failure, NH4 generation is impaired, causing less strong anion excretion, leading to persistent metabolic acidosis according to physicochemical approach. A high plasma creatinine concentration is associated with high urinary SID values, low plasma SID values, and low blood pH levels [13].

Acid–base physiology was described by follows traditional approach, semi-quantitative approach or quantitative (physicochemical) approaches. Each approach has its limitations when apply to different clinical situations. The traditional approach based on anion gap (AG) and standard base excess/deficit (semi-quantitative approach) , is recently widely accepted, easier to calculate and quick detection of most acid-base disorders, although could underestimates complex metabolic acidosis in critical care settings [14]. The physicochemical approach, an alternative approach described by Stewart, is useful for quantifying metabolic acidosis using SID and total weak acids [15,16], is considered more complex and clinically less feasible, although can diagnose most complex acid-base disorders than traditional approach.

Traditional Approach and Anion gap (AG)

The traditional approach is based on the Henderson and Hasselbalch equation for calculating the pH level and proton concentration, in which the blood bicarbonate level is calculated using the Siggaard–Andersen formula (which is based on the Henderson-Hasselbalch equation): $pH = 6.1 + \log([HCO_3^-]/[CO_2])$, where $[CO_2] = 0.0301 \times PaCO_2$.

Metabolic acid–base disturbances are changes in the strong or weak ion concentrations. These ions can be classified into routinely measured ions (e.g., Cl^-) and unmeasured ions (e.g., ketones). The AG, calculated as the difference between the serum cations (Na+ and K+) and anions (Cl– and HCO_3–), detects the presence of unmeasured ions (e.g., ketones and salicylates). The AG is formed by two types of components: major components (anions, i.e., albumin and phosphate) and minor components (strong ions, i.e., sulfate and lactate), whose net contributions are usually >2 mEq/L. Furthermore, unmeasured cations (Ca2+ and Mg2+) may exist. Plasma proteins, except albumin, can be either positively or negatively charged; however, they tend to be neutral on aggregation, except in rare scenarios of abnormal paraproteins, such as those observed in multiple myeloma [17]. In practice, the AG is calculated as follows: AG = (Na+ + K+) − (Cl− + HCO3−).

The normal value for AG is 12 ± 4 mEq/L (if K^+ is considered) and 8 ± 4 mEq/L (if K^+ is not considered). Hypoalbuminemia may result in falsely low AG values. Some studies have suggested adjusting the normal range of the AG according to the patient's albumin and phosphate concentration because these anions are not strong anions and because their charges are altered by pH changes. Figge et al [18] proposed the corrected anion gap (AGc): ($[Na^+ + K^+]$-$[Cl^- + HCO_3$–$]$)-2.0 (albumin [g/dL])-0.5 (phosphate [mg/dL])-lactate (mEq/L). The AGc should approximate to zero for preventing falsely low AG values.

Semi-quantitative approach and Standard Base Excess (SBE)

Metabolic acidosis is defined as a standard base excess (SBE) <-2 mEq/L. The SBE calculation is not based on pH because of respiratory compensation. The SBE is measured semiquantitatively. Compared with strong ion difference (SID), SBE of the traditional approach is defined as the number of milliequivalents of acid or base required to titrate 1 L of blood to pH 7.40 at 37 °C at a constant carbon dioxide tension (PCO_2) of 40 mmHg [19]. The Van Slyke equation is the most commonly used formula for calculating SBE [20]. SBE quantifies the amount of strong acid or base required to change the SID value to a new equilibrium point at which the pH is 7.40 and PCO_2 is 40 mmHg. The increase in SBE is caused by the increase in lactate and SIG levels.

Quantitative Approach and Strong ion gap (SIG)

SIG, the difference between the values of strong ion difference apparent (SIDa) and strong ion difference effective (SIDe), is an accurate estimate of unmeasured ions. The alkalinizing effect of hypoalbuminemia may mask the presence of unmeasured anions, leading to a falsely normal AG. Therefore, SIG is a more favorable indicator of unmeasured anions than AG is.

The physicochemical approach, an alternative method also

called the quantitative approach, was originally devised by Stewart and modified by Figge et al [4]. The SIDa is calculated in the physicochemical approach and is defined as the difference between the main strong cations (Na^+, K^+, Mg^{2+}, and Ca^{2+}) and anions (Cl^-, lactate, and urate). The normal SIDa value is approximately 40 mEq/L. Values <40 mEq/L and >40 mEq/L indicate metabolic acidosis and alkalosis, respectively [21]. The SIDa is calculated as follows: SIDa = $[Na^+] + [K^+] + [Ca^{2+}]+[Mg^{2+}]-[Cl^-]-[lactate]$.

SIDe is indicative of the interactions among pH, CO2, phosphate, and protein. Therefore, SIDe is a measure of the remaining anions (i.e., normally -40 mEq/L); it is calculated using the formula reported by Figge et al: SIDe = $12.2 \times PaCO_2$ [(mmHg)/(10^{pH})] + {[albumin (g/L)] × [0.123 × pH-0.631] + [HPO42−(mmol/L)] × [0.309 × pH-0.469]}. SIDe accounts for the contribution of weak acids to the electrical charge equilibrium in the plasma. The effective strong ion difference is the effect of the corrected PCO_2 and the weak acids albumin and inorganic phosphate on electrical charge equilibrium in the plasma.

According to the quantitative approach, SIDa values, pCO_2 levels, and the total amount of weak acid concentration (Atot; mainly albumin and phosphate) are the three variables that influence the blood pH [3]. Ph varies markedly with small changes in pCO_2 and SIDa; however, it is barely affected by changes in Atot. SID, Atot, and pCO_2 are true biological variables physiologically regulated by transepithelial transport, ventilation, and metabolism [22]. These variables are regulated by the gastrointestinal tract, liver, kidneys, tissue circulation, and intracellular buffers.

The factors that contribute to metabolic acidosis are low SID a values (elevated chloride, lactate, or other strong anion levels), high SIG values, and high weak acid levels (mainly hyperphosphatemia). According to Stewart, the major defense mechanism against metabolic acidosis is the urinary excretion of strong anion chloride without a strong cation [3]. Metabolic acidosis may be caused by reduced renal excretion of strong anions, resulting in the accumulation of metabolic acids, such as orotic acid, oxalic acid, and kynurenic acid [23].

Comparison and Relationship between AG and SIG in Different Clinical Settings

The traditional AG approach has a wide range of normal values, whereas that of the SIG is narrower; in healthy humans, the SIG is zero (electrical charge neutrality). A positive or high SIG (>2 mEq/L) indicates the presence of unmeasured strong anions, such as sulfate, keto acids, citrate, pyruvate, acetate, and gluconate, whereas a negative SIG indicates that the number of cations exceeds that of anions [24]. The SIG value of critically ill patients varies across countries. Studies conducted in the US, the Netherlands, and Thailand have reported approximately SIG values of 5 mEq/L, whereas those in the UK and Australia have reported values of >8 mEq/L [25-27]. Medicine or fluid (e.g., gelatins) administration alters SIG values [28, 29].

A strong association exists between the SIG and the albumin- and lactate-AGc (corrected AG) [14]. Rarely, high concentrations of pyroglutamic acid cause SIG-related acidosis. Pyroglutamic acidemia was associated with acetaminophen and flucloxacillin administration, impaired liver function, reduced glutathione reserves, sepsis, and the female sex [30,31]. Balanced fluids used during cardiopulmonary bypass and colloids containing gelatin contribute to elevated SIG values [32]. No association has been reported between SIG and mortality in patients receiving gelatin-based resuscitation fluids, whereas studies on patient's not receiving gelatins have reported a positive association between SIG and mortality [24]. Recent studies have suggested that high SIG values are associated with poor outcomes [27, 33].

Recently, tricarboxylic acid cycle intermediates that accumulate through amino acid catabolism have been reported to contribute to elevated SIG levels and high AGc [34]. Kaplan and Kellum [33] evaluated the relationship between SIG and mortality before fluid resuscitation. An SIG value >5 mEq/L in patients with major vascular injury requiring surgery was an indicator of mortality. Dondorp et al [27] reported the association between SIG and mortality in critically ill severe malaria patients. Severe falciparum malaria is frequently associated with metabolic acidosis and hyperlactatemia; in this disease, the predominant form of metabolic acidosis was not lactate but SIG acidosis. Mean lactate levels were low in survivors and non-survivors, whereas SIG levels were elevated in both groups of patients [27].

Elevated SIG levels are caused by various factors, such as poisoning (e.g., salicylate and methanol) and accumulation of ketones and other organic acids (e.g., sulfates) [35]. However, sepsis and shock can increase SIG through unknown mechanisms [36]. Sepsis, hepatic dysfunction, cardiogenic shock, and renal failure were associated with elevated SIG or AGc [37]. Thus, these conditions are associated with an increased production or reduced clearance of unmeasured anions. Higher SIG values in impaired renal function may be caused by the reduced urinary excretion of unmeasured anions. Sepsis has been associated with high SIG values in intensive care patients with impaired renal function but not those with normal renal function [38,39]. From our previous study analyzing the metabolic acidosis in critical ill patients with acute kidney injury (AKI), we found that whether high or low SIG values determine mortality depends on other variables determining the SIG, including creatinine, chloride, albumin, and phosphate levels [10]. In these patients, impaired urinary excretion of chloride and

poor nutrition contributes to metabolic acidosis [8,10]. AG predicts short-term mortality and SIG value predicts both short- and long-term mortality among metabolic acidosis patients with acute kidney injury [10]. Intensive care nonsurvivors had higher urinary SID than did survivors because of low urinary sodium and chloride. Intensive care unit survivors had low urinary SID because of the increase in plasma SID values.

Renal failure associated acidosis is called uremic acidosis and results in a high anion gap (normochloremic acidosis) caused by the accumulation of sulfate, phosphate, and organic anions. However, the accumulation of these anions does not contribute to acidosis. Metabolic acidosis persist even with anion removal through dialysis. Reduction in renal acid excretion and accumulation of uremic anions equally contribute to reduced renal function; however, these events are not causally related to each other [40]. It is also described by physicochemical approach which explains that uremic compounds are responsible for elevated SIG. Uric acid is a water-soluble low-molecular weight solute and potent uremic toxin significantly elevated when SIG is high [41].

Hyperchloremic Acidosis among Critically Ill Patients

Hyperchloremic acidosis is diagnosed through exclusion (i.e., metabolic acidosis caused by factors other than lactate or unmeasured anions). Hyperchloremic acidosis and SIG acidosis are common in renal failure [8]. Such acidosis cases have a rather elevated absolute chloride value. In critically ill patients, a large volume of saline infusion during resuscitation from shock causes metabolic acidosis by increasing the plasma chloride concentration relative to the plasma sodium concentration. This results in reduced plasma SID values and subsequently increases free H+ ions to maintain electrical neutrality because SID is the difference between positively and negatively charged electrolytes [42-45]. These mechanisms are better explained by physiochemical approach than traditional approach.

Gunnerson proposed a metabolic acidosis classification system based on physicochemical principles. In this system, metabolic acidosis is defined as SBE <2 mEq/L, lactic acidosis as lactate accounting for >50% of the SBE, SIG acidosis as SIG (unmeasured ions) accounting for >50% of SBE in the absence of lactic acidosis, and hyperchloremic acidosis as SBE less than-2 mEq/L in the absence of lactate or SIG. If no single AG accounts for >50% of the SBE, the classification is mixed and considered concomitant ethylene glycol toxicity or other unmeasured anions with hyperchloremia [46,47]. Hyperchloremic acidosis after fluid resuscitation is common in intensive care patients [43,46,48]. Kellum reported that a balanced resuscitation fluid (hextend) resulted in more favorable short-term survival than isotonic saline in a rat sepsis model [49]. Wilkes et al [50] compared the acid–base balance on using hetastarch-based solutions prepared in saline and in balanced electrolyte solutions and reported poor results. Gan et al [51] reported similar findings in large volume resuscitation in major surgery on comparing hetastarch prepared in a balanced electrolyte solution and in saline. Waters et al compared isotonic saline with lactated Ringer's solution in patients who had undergone abdominal aortic aneurysm repair [52]. In all these studies, the use of saline solution was more harmful than was the use of balanced electrolyte solutions. Saline-induced acidosis has similar side effects as those of ammonium chloride acidosis, such as abdominal pain, nausea, vomiting, headache, thirst, hyperventilation, and delayed urination [53, 54].

Conclusion

In conclusion, although serum bicarbonate and CO2 levels are independent variables in the Henderson–Hassalbalch approach; are dependent on weak acids, albumin and inorganic phosphate in the Stewart approach. AG and SIG are inter-dependent variables which are needed to consider together for better diagnosis, management and prognosis of most acid–base imbalances. Although an albumin corrected AG is considered as nearly similar to SIG, most unexplained acid-base disorders in critically care units are needed to be explored using Stewart approach for a better understanding of underlying mechanisms and prognosis.

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