Kidney360

The Δ Anion Gap/Δ Bicarbonate Ratio in Early Lactic Acidosis: Time for Another Delta?

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Abstract

Background The ratio of Δ anion gap and Δ bicarbonate ($\Delta AG/\Delta HCO_3$) is used to detect coexisting acid-base disorders in patients with high anion gap metabolic acidosis. Classic teaching holds that, in lactic acidosis, the $\Delta AG/\Delta HCO_3$ is 1:1 within the first few hours of onset and subsequently rises to 1.8:1. However, this classic 1:1 stoichiometry in early lactic acidosis was derived primarily from animal models and only limited human data. The objective of this study was to examine the $\Delta AG/\Delta HCO_3$ within the first hours of the development of lactic acidosis.

Methods Data were obtained prospectively from a convenience sample of adult (age >18 years) trauma-designated patients at a single level-1 trauma center. Venous samples, including a chemistry panel and serum lactate, were drawn before initiation of intravenous fluid resuscitation.

Results A total of 108 patients were included. Of these, 63 patients had normal serum lactate levels (≤2.1 mmol/L) with a mean AG of 7.1 mEq/L, the value used to calculate subsequent ΔAG values. $\Delta AG/\Delta HCO_3$ was calculated for 45 patients who had elevated serum lactate levels (>2.1 mmol/L). The mean $\Delta AG/\Delta HCO_3$ for all patients with elevated serum lactate levels was 1.86 (SD, 1.40).

Conclusions The mean $\Delta AG/\Delta HCO_3$ was 1.86 within the first hours of the development of lactic acidosis due to hypovolemic shock, confirming a small prior human study. This contradicts the traditional belief that, in lactic acidosis, the $\Delta AG/\Delta HCO_3$ is 1:1 within the first several hours. The classic 1:1 stoichiometry was determined on the basis of animal models in which lactic acid is infused into the extracellular space, facilitating extracellular buffering of protons by bicarbonate. In contrast, our results demonstrate a higher initial $\Delta AG/\Delta HCO_3$ ratio in early endogenous lactic acidosis in humans. Our analysis indicates this is likely due to unmeasured anions contributing to an elevation in AG.

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Introduction

The Δ anion gap (ΔAG) and Δ bicarbonate (ΔHCO_3) ratio ($\Delta AG/\Delta HCO_3$) is used to detect coexisting acid-base disorders in patients with high AG metabolic acidosis. In general, the ΔHCO_3 accompanies an equivalent change in the ΔAG, and this apparent 1:1 stoichiometry has been used to identify concurrent acid-base disorders, such as metabolic alkalosis or normal AG metabolic acidosis; a $\Delta AG/\Delta HCO_3$ below one suggests a coexisting normal AG metabolic acidosis, whereas a $\Delta AG/\Delta HCO_3$ more than one to two suggests a coexisting metabolic alkalosis (1).

In lactic acidosis, traditional belief holds that lactate anions tend to remain in the extracellular (EC) fluid compartment, whereas protons that accompany the lactate are buffered outside of the EC fluid, in cells and bone. Additionally, lactate excretion by the kidney is usually decreased because of lactate absorption by sodium-lactate transporters, hypoperfusion, and acute renal dysfunction. Regardless of the explanation, the net result is a $\Delta AG/\Delta HCO_3$ of more than one in lactic acidosis, usually approximately 1.6–1.8.

Notably, the duration of the lactic acidosis is thought to affect the $\Delta AG/\Delta HCO_3$. The $\Delta AG/\Delta HCO_3$ of 1.6–1.8:1 is thought to occur after the acidosis persists for several hours (1). Within the first 60 minutes of onset of lactic acidosis, classic teaching holds that the $\Delta AG/\Delta HCO_3$ is initially 1:1, increasing with time over several hours (1). However, this classic 1:1 stoichiometry described early in the development of lactic acidosis is derived primarily from animal models (2,3), and only limited human data has investigated the $\Delta AG/\Delta HCO_3$ in early lactic acidosis (4,5). The objective of this study was to examine the $\Delta AG/\Delta HCO_3$ within the first hours of the development of lactic acidosis. A secondary objective was to examine potential pathophysiologic explanations for the observed $\Delta AG/\Delta HCO_3$.

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Materials and Methods

The study was a reanalysis of data by Rudkin *et al.* (6), which examined the correlation between arterial and peripheral venous pH and base excess in patients who experienced trauma. They concluded that venous blood gas (VBG) pH and base excess cannot be used interchangeably with the corresponding arterial blood gas (ABG) measurements. The study was a prospective study that enrolled a convenience sample of adult (age >18 years) trauma-designated patients from a single level-1 trauma center. The study enrolled 385 patients. When an ABG was obtained for clinical purposes, a peripheral VBG was drawn as soon as possible. Venous samples, including a chemistry panel and serum lactate, were drawn before initiation of intravenous fluid resuscitation. Data collected included collection times of the ABG and VBG, physiologic data including BP, and indicators of patient severity (Glasgow Coma Scale score, Trauma and Injury Severity scores).

Statistical Analyses

The association between duration of lactic acidosis and the $\Delta AG/\Delta HCO_3$, Δlactate and ΔAG, arterial pH and the $\Delta AG/\Delta HCO_3$, and serum chloride and the $\Delta AG/\Delta HCO_3$ were examined using Pearson correlation, and linear regression models were constructed. Least-squares regression lines were calculated and plotted. Additionally, the association between ΔHCO_3 and ΔAG was examined using Pearson correlation, a linear regression model was constructed, and 95% prediction intervals were computed.

Results

The reanalysis included 108 patients. A total of 63 patients had normal serum lactate levels (≤2.1 mmol/L), and 45 patients had elevated serum lactate levels (>2.1 mmol/L). The final sample of the original study included 346 patients. In the reanalysis, 148 patients were excluded because they were missing serum lactate or serum HCO_3 values, and five patients were excluded because of clerical errors, leaving 193 patients remaining. To determine the group with the elevated serum lactate measurements (>2.1 mmol/L), 67 patients with an AG <7.1 mEq/L were excluded, 68 patients with a serum HCO_3 >24 mEq/L were excluded, and 13 patients with a serum lactate <2.1 mmol/L were excluded, resulting in 45 patients in the elevated serum lactate group. To determine the group with normal serum lactate measurements (<2.1 mmol/L), of the 193 patients remaining, 63 patients were found to have serum lactate measurements of <2.1 mmol/L.

The patients with normal serum lactate levels had a mean AG of 7.1 mEq/L and a mean lactate level of 1.5 mmol/L; these values were used to calculate subsequent ΔAG and Δlactate values in the patients with elevated serum lactate levels. The mean lactate for the elevated lactate group was 4.89 mmol/L, with an SD of 2.36 mmol/L and range between 2.2 and 11.1 mmol/L. $\Delta AG/\Delta HCO_3$ and Δlactate/ΔHCO_3 were then calculated for the 45 patients who had elevated serum lactate levels (>2.1 mmol/L). In the group with the normal serum lactate levels, the mean serum potassium was 3.82 mEq/L with an SD of 0.42 mEq/L and a range of 2.9–5.0 mEq/L; the mean serum creatinine was 0.95 mg/dl, with an SD of 0.32 mg/dl and a range of 0.3–2.3 mg/dl. The elevated serum lactate group had a mean serum potassium of 3.6 mEq/L, with an SD of 0.48 mEq/L and a range of 2.5–4.7 mEq/L; the mean serum creatinine was 1.04 mg/dl, with an SD of 0.37 and a range of 0.4–2.8 mg/dl. Table 1 shows the patient characteristics. For the patients with elevated lactate levels, the average (±SD) patient age was 38.6±18.8 years old, with a preponderance of males (71%). The mechanism of injury was predominantly blunt trauma (71%).

The mean $\Delta AG/\Delta HCO_3$ was 1.86, with an SD of 1.40; the mean Δlactate/ΔHCO_3 was 1.21, with an SD of 1.06. The mean Δlactate/ΔHCO_3 was also calculated using the reported upper range of normal for serum lactate (2.1 mmol/L), yielding a value of 0.95 with an SD of 0.91.

Figure 1 shows the linear regression model examining duration of lactic acidosis and $\Delta AG/\Delta HCO_3$. The $r=-0.14$, with a P value of 0.37. The duration of lactic acidosis was estimated by determining the period of time that elapsed between the time from activation of emergency medical services to the draw time of venous blood in the emergency department. This time ranged from 25.0 to 166.0 minutes, with a mean time of 81.5 minutes (SD, 31.4).

Figure 2 shows the linear regression model examining Δlactate and ΔAG. $r=0.50$ with $P=0.001$. The R^2 is 0.25. Figure 3 shows the linear regression model examining arterial pH and $\Delta AG/\Delta HCO_3$. The $r=0.10$ with $P=0.52$. Figure 4 shows the linear regression model between serum chloride and $\Delta AG/\Delta HCO_3$. The $r=-0.15$ with $P=0.33$. Supplemental Figure 1 shows the linear regression model between ΔHCO_3 and ΔAG. The $r=0.70$, with $P<0.001$. Dashed lines represent the 95% prediction interval.

Discussion

The relationship between the ΔAG, which reflects changes in the concentration of unmeasured anions, and ΔHCO_3 has been used to evaluate for complex acid-base disorders in patients with underlying high AG metabolic acidosis (1). The accumulation of a nonchloride-containing acid, such as lactic acid, in the blood results in a reduction in serum HCO_3. The accompanying anion, such as lactate, is retained to maintain electroneutrality, resulting in a rise in the serum AG. Theoretically, the reduction in serum HCO_3 corresponds to an equivalent increase in the AG, resulting in a $\Delta AG/\Delta HCO_3$ of one. Hence, any deviation from this 1:1 stoichiometry may reflect a coexisting acid-base disorder in addition to the AG metabolic acidosis.

The existing literature reveals there is variable stoichiometry of $\Delta AG/\Delta HCO_3$, depending on the specific type of organic acidosis. In lactic acidosis, the traditional belief is that, in the first few hours, the $\Delta AG/\Delta HCO_3$ is approximately 1:1 (1). However, as the lactic acidosis persists beyond a few hours, the mean $\Delta AG/\Delta HCO_3$ ratio is approximately 1.6–1.8 (1); the increased $\Delta AG/\Delta HCO_3$ has most commonly been ascribed to the theory that, after a few hours, hydrogen ion buffering in cells and bone reach completion, while only a small fraction of the lactate remains in the intracellular fluid space, preferentially residing within the EC fluid compartment.

Only limited human data have investigated the $\Delta AG/\Delta HCO_3$ in early lactic acidosis. The main objective of this study was to specifically examine the $\Delta AG/\Delta HCO_3$ within

Table 1. Patient characteristics

Characteristics	Normal Lactate (≤2.1 mmol/L)	Elevated Lactate (>2.1 mmol/l)
N	63	45
Age (yr), mean±SD	43.6±21.0	38.6±18.8
Male, *n/N* (%)	44/63 (70)	32/45 (71)
Intubated, *n/N* (%)	6/63 (10)	10/45 (22)
Hypotensive (systolic BP ≤90 mm Hg), *n/N* (%)	3/63 (5)	8/45 (18)
Mechanism of injury, *n/N* (%)		
Blunt trauma	49/63 (78)	32/45 (71)
Penetrating trauma	6/63 (10)	8/45 (18)
Burns	5/63 (8)	3/45 (7)

the first hours of the development of lactic acidosis. Patients in this study had undergone trauma and, therefore, the lactic acidosis was a result of hypovolemic shock. The patient characteristics, including the relatively young mean age (38.6 years) and male predominance (71%), are consistent with the demographics typically seen in patients who have experienced trauma. The mean $\Delta AG/\Delta HCO_3$ was 1.86 within the first hours of the development of lactic acidosis due to hypovolemic shock, and was not associated with duration of lactic acidosis (Figure 1). This contradicts the traditional belief that, in lactic acidosis, the $\Delta AG/\Delta HCO_3$ is 1:1 within the first few hours, subsequently increasing to approximately 1.6–1.8 as hydrogen ion buffering in cells and bone reach completion (while the lactate preferentially resides in the EC fluid compartment) (1). Notably, of the 45 patients that had elevated serum lactate levels (>2.1 mmol/L), 19 patients had a pH >7.4 and respiratory alkalosis, which, in the setting of trauma, was likely related to factors such as pain, anxiety, and head injury. Of these 19 patients, seven also had a concurrent metabolic alkalosis, likely related to factors such as vomiting.

Although reviews of the literature have concluded that both animal and human studies indicate that the $\Delta AG/\Delta HCO_3$ is 1:1 early in the course of lactic acidosis (1), a more detailed re-evaluation of the literature reveals divergent results in animal and human studies. Oster *et al.* (2) and Madias *et al.* (3) both conducted animal studies in dogs and rats, respectively. The mean $\Delta AG/\Delta HCO_3$ in the first hour of lactic acidosis in these studies ranged from 1.00 to 1.25. Notably, in these animal models, lactic acidosis was produced *via* a lactic-acid infusion. Therefore, the lactic acid directly enters the EC space, presumably facilitating EC buffering of protons by HCO_3. Concurrently, the lactate remains in the same compartment, resulting in a 1:1 stoichiometry and the $\Delta AG/\Delta HCO_3$ of approximately one observed in these animal studies.

In contrast, two small human studies have yielded more conflicting results (4,5). Orringer *et al.* (4) found that, in early lactic acidosis, the mean $\Delta AG/\Delta HCO_3$ ranged from 1.5 to 1.86 within the first 30 minutes after grand-mal seizures. A second study by Brivet *et al.* (5) also examined patients after grand-mal seizures and determined that the mean $\Delta AG/\Delta HCO_3$ was 1.28, with 33% of patients exhibiting a ratio of <0.8. The mean $\Delta AG/\Delta HCO_3$ of 1.86 in early lactic acidosis in our study serves to confirm the findings by Orringer *et al.* It is worth highlighting that both Orringer and Brivet examined lactic acidosis occurring after grand-mal seizures, with pathophysiology resulting from enhanced metabolic rate and accelerated aerobic glycolysis. In contrast, to our knowledge, this is the first study to evaluate early lactic acidosis from shock in humans, with pathophysiology resulting from hypoperfusion and decreased oxygen delivery.

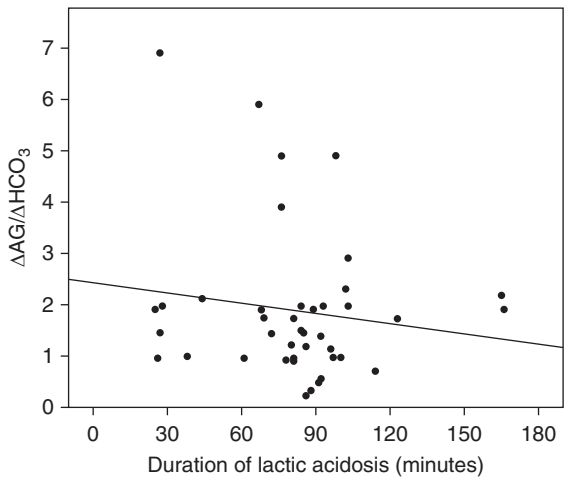

Figure 1. | Pearson correlation between duration of lactic acidosis and the ratio of Δ anion gap to Δ bicarbonate ($\Delta AG/\Delta HCO_3$). There is no association between $\Delta AG/\Delta HCO_3$ and duration of lactic acidosis. $r=-0.14$, $P=0.37$.

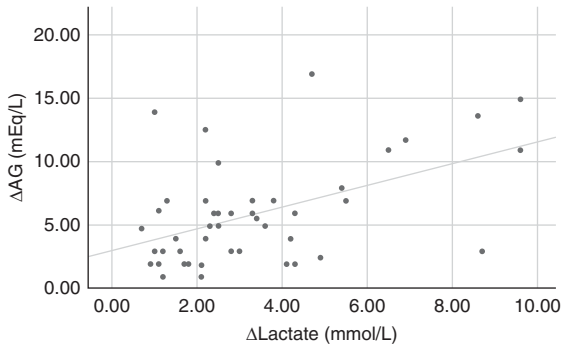

Figure 2. | Pearson correlation between Δlactate and Δ anion gap (ΔAG). The Δlactate explains 25% of the observed variance in the ΔAG. $r=0.50$, $P=0.001$.

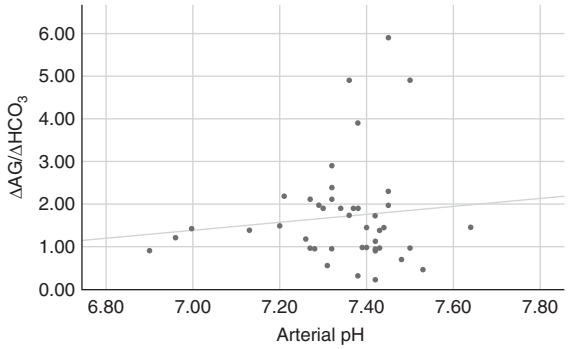

Figure 3. | Pearson correlation between arterial pH and ΔAG/ΔHCO$_3$. There is no association between arterial pH and ΔAG/ΔHCO$_3$. r=0.10, P 0.52.

As discussed above, in animal models of early lactic acidosis, the mean ΔAG/ΔHCO$_3$ was approximately one in the first hour of lactic acidosis, attributable to the lactic acid infusion directly entering the EC space and facilitating EC buffering of protons by HCO$_3$. In contrast, our results indicate that, in humans, endogenous lactic acidosis manifests a mean ΔAG/ΔHCO$_3$ of approximately 1.8 within the first few hours, a ratio which does not appear to change as the acidosis persists beyond a few hours (7–9). In distinction to animal models of lactic acidosis, which are initiated in the EC space, early endogenous human lactic acidosis originates intracellularly. This has been postulated by some to result in intracellular buffering of protons while lactate is predominantly distributed in the EC fluid, resulting in a mean ΔAG/ΔHCO$_3$ approaching 1.8 as the acidosis persists beyond a few hours. The ΔAG/ΔHCO$_3$ of one reported early in the course of lactic acidosis has been theorized to occur because the hydrogen ion buffering in cells and bone takes a few hours to reach completion. Our findings that the mean ΔAG/ΔHCO$_3$ early in the course of lactic acidosis is 1.86 suggest that, if this elevated ratio is indeed related to the differing distribution spaces of lactate and hydrogen ions, the hydrogen buffering in cells and bone occurs much more rapidly than previously described.

In addition to establishing that the mean ΔAG/ΔHCO$_3$ in lactic acidosis during the first few hours is approximately 1.8, our study helps elucidate the reasons for the high ΔAG/ΔHCO$_3$. Four possible explanations for the deviation in 1:1 stoichiometry have been proposed. First, it has been suggested that only a small fraction of lactate generated by cellular metabolism remains in the intracellular space, which, combined with decreased urinary excretion of lactate anion because of reduced renal function, results in lactate retention in the EC fluid compartment; in contrast, a significant proportion of hydrogen ions that accompany the lactate are buffered in cells and bone. The disparity between space of distribution of hydrogen ions compared with lactate has been proposed to result in a ΔAG/ΔHCO$_3$ of more than one, usually approximating 1.6–1.8. The assumption underlying this theory is that the increase in AG relative to the decrement in ΔHCO$_3$ reflects an increase in EC lactate. Our data demonstrates a mean ΔAG/ΔHCO$_3$ of 1.86, consistent with prior studies of lactic acidosis in humans (4,7–9). By contrast, the mean Δlactate/ΔHCO$_3$ ranged between 0.95 and 1.21, depending on the baseline lactate value. Additionally, Figure 2 demonstrates that the Δlactate can only explain 25% of the observed variance in the ΔAG. Taken together, these data suggest the high ΔAG that results in an increased ΔAG/ΔHCO$_3$ does not appear to be primarily a result of increased EC lactate, as this proposed model would suggest. Second, in theory, organic or inorganic anions or cations may exhibit a pH-dependent contribution to the AG as the pH decreases. For example, the albumin concentration, which is the main contributor to the AG, increases with a rise in pH, resulting in an elevated AG in metabolic alkalosis. Conversely, a drop in pH may change the degree to which certain anions and cations contribute to the AG, resulting in a high AG and an elevated ΔAG/ΔHCO$_3$. However, Figure 3 demonstrates there is no statistically significant association between arterial pH and ΔAG/ΔHCO$_3$, with a P value of 0.52. Therefore, the pH-dependent contribution of anions or cations does not explain the increased ΔAG/ΔHCO$_3$ observed in lactic acidosis. Third, Madias *et al.* (3) suggested that, on the basis of an animal model, hypochloremia may account for 30%–50% of the increment in AG seen in lactic acidosis, explaining the deviation from 1:1 stoichiometry and elevated ΔAG/ΔHCO$_3$. The decrement in serum chloride results from extrusion of cellular cations and resultant expansion of the EC compartment during the buffering process in lactic acidosis. However, there is not a significant correlation between serum chloride and ΔAG/ΔHCO$_3$ (Figure 4), arguing that hypochloremia does not play a significant role in the elevated ΔAG/ΔHCO$_3$ observed in lactic acidosis in humans. Fourth, it is likely that the increase in AG that results in an elevated ΔAG/ΔHCO$_3$ is caused by unknown organic anions (or, less likely, due to a decrease in unmeasured cations). Our data, consistent with previous literature, show that, in lactic acidosis, up to 75% of the observed variance in the AG is not explained by blood lactate and, therefore, lactic acid does not entirely account for the AG metabolic acidosis (10–12). Although attempts to identify specific unknown organic anions in lactic acidosis have not been uniformly successful, some studies have identified increased concentrations of Krebs cycle intermediates, including citrate, isocitrate, α-ketoglutarate, succinate, malate, and D-lactate (13,14). Importantly, these unmeasured anions may better predict clinical outcomes than serum lactate

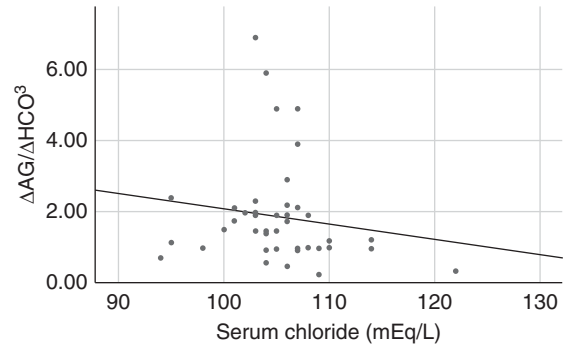

Figure 4. | Pearson correlation between serum chloride and ΔAG/ΔHCO$_3$. There is no association between serum chloride and ΔAG/ΔHCO$_3$. r=−0.15, P=0.33.

levels (15,16). Given that our data argue against other possible explanations of the high $\Delta AG/\Delta HCO_3$ seen in lactic acidosis, these unmeasured anions are the most likely cause and further work to identify them needs to be carried out.

Although ongoing research attempts to identify the unmeasured anions in lactic acidosis and better explain its pathophysiology, the $\Delta AG/\Delta HCO_3$ remains a widely used tool to detect coexisting acid-base disorders in patients with lactic acidosis and other high AG metabolic acidosis. The wide 95% prediction interval suggests that $\Delta AG/\Delta HCO_3$ should be used cautiously in the diagnosis of mixed acid-base disorders (Supplemental Figure 1). For example, although the mean $\Delta AG/\Delta HCO_3$ was 1.86, which is consistent with prior studies, the SD was 1.40 and 15 of 45 patients had a $\Delta AG/\Delta HCO_3$ of less than one. Additionally, it should be recognized that the AG is an insensitive screening tool for elevated blood lactate (10,17).

To our knowledge, our study was the first to evaluate the $\Delta AG/\Delta HCO_3$ in early lactic acidosis from shock in humans. However, the study does have some limitations. This study was a reanalysis of data from a prior study, which prospectively enrolled a convenience sample of adult, trauma-designated patients. Although the patient selection did not involve formal random sampling, this is unlikely to have resulted in systematic bias, because our demographics are similar to a typical population of patients with trauma seen in the emergency department, and the ranges of laboratory values (including serum lactate, serum HCO_3, pH, and AG) span the clinically important range. Because most forms of type-A lactic acidosis are due to marked tissue hypoperfusion, it is likely that the results of this study will apply not just to hypovolemia, but also to other pathophysiologic states characterized by tissue hypoperfusion, including sepsis, cardiac failure, or cardiopulmonary arrest.

Secondly, this study used mean normal values for serum AG and plasma HCO_3. In the past, the normal range for the AG has been 12 ± 4 mEq/L, with variations depending on the specific blood gas analyzer used. More recently, new technology and use of ion-selective electrodes has resulted in reporting of higher serum chloride concentrations and, consequently, lower AGs (18). In fact, several studies have reported the normal range for AG to be 6 ± 3 mEq/L (19,20). Given that the AG will vary among different laboratories, the mean AG (7.1 mEq/L) from the patients with normal serum lactate levels was used as an approximation of the true normal values for the specific study patient population in the study center. There is clearly a wide interindividual variability in AG, and use of the actual normal baseline values of individual patients would ideally be used for calculation of $\Delta AG/\Delta HCO_3$, although this was not feasible in our population of patients experiencing acute trauma and in most study settings. In addition to our study, virtually all prior clinical studies examining $\Delta AG/\Delta HCO_3$ used mean normal values for AG and HCO_3. Regardless, it is important to note that the practice of using mean normal values likely has an important effect on the calculation of the ratio and subsequent conclusions about the underlying pathophysiology. For example, in this study, patients with an AG $\leq$7.1 mEq/L were excluded because the mean AG of 7.1 mEq/L was the value used to calculate subsequent ΔAG values. It is important to note that this mirrors what occurs in clinical practice when using a normal value for AG; some patients invariably have an AG that falls below the normal value used, precluding calculation of the ΔAG. To avoid this, the actual normal baseline values of individual patients, if known, should be used.

Thirdly, the dataset did not include some pertinent parameters. It did not include serum albumin, so it was not possible to correct the AG for albumin level. The dataset also did not include serum phosphorus, although, due to its low concentration in the EC fluid, the buffering by inorganic phosphate in the EC fluid is likely negligible compared with that of HCO_3. The dataset also lacked information about comorbidities.

Lastly, this reanalysis had a relatively small sample size. Only 45 patients had elevated serum lactate levels. However, the prior human studies of lactic acidosis after grand-mal seizures by Orringer *et al.* (4) and Brivet *et al.* (5) only included eight and 35 patients, respectively. Therefore, to date, this is the largest human study investigating the $\Delta AG/\Delta HCO_3$ in early lactic acidosis.

The mean $\Delta AG/\Delta HCO_3$ was 1.86:1 within the first hours of the development of lactic acidosis due to hypovolemic shock, not 1:1 as previously thought. The traditional belief is that this deviation in 1:1 stoichiometry results from intracellular buffering of protons while lactate is predominantly distributed in the EC fluid, although our study implicates unmeasured anions as the cause.

Disclosures

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Author Contributions

T.R. Grogan and S.E. Rudkin were responsible for project administration; T.R. Grogan, S.E. Rudkin, and R.M. Treger were responsible for data curation; T.R. Grogan and R.M. Treger were responsible for formal analysis; S.E. Rudkin and T.R. Grogan were responsible for funding acquisition; and R.M. Treger conceptualized the study, was responsible for investigation and methodology, provided supervision, and wrote the original draft.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000842019/-/DCSupplemental.

Supplemental Figure 1. Pearson correlation between ΔHCO_3 and ΔAG. r=0.689, $P<0.001$. Dashed lines are the 95% prediction interval.

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