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

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ABSTRACT

Background: The ratio of delta anion gap and delta bicarbonate (ΔAG/ΔHCO₃) is used to detect co-existing acid-base disorders in patients with high anion gap metabolic acidosis. Classic teaching holds that in lactic acidosis, the ΔAG/ΔHCO₃ 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 ΔAG/ΔHCO₃ 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 prior to initiation of intravenous fluid resuscitation.

Results: 108 patients were included. 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. ΔAG/ΔHCO₃ was calculated for 45 patients who had elevated serum lactate levels (>2.1 mmol/L). The mean ΔAG/ΔHCO₃ for all patients with elevated serum lactate levels was 1.86 (SD 1.40).

Conclusions: The mean ΔAG/ΔHCO₃ 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 ΔAG/ΔHCO₃ is 1:1 within the first several hours. The classic 1:1 stoichiometry is based on 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 ΔAG/ΔHCO₃ ratio in early endogenous lactic acidosis in humans. Our analysis indicates that this is likely due to unmeasured anions contributing to an elevation in AG.
INTRODUCTION

The ratio of delta anion gap and delta bicarbonate (ΔAG/ΔHCO₃) is used to detect co-existing acid-base disorders in patients with high anion gap metabolic acidosis. In general, the ΔHCO₃ 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 anion gap metabolic acidosis; a ΔAG/ΔHCO₃ below 1 suggests a coexisting normal anion gap metabolic acidosis whereas a ΔAG/ΔHCO₃ > 1-2 suggests a co-existing metabolic alkalosis.¹

In lactic acidosis, traditional belief holds that lactate anions tend to remain in the extracellular fluid compartment, whereas protons that accompany the lactate are buffered outside of the extracellular 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 ΔAG/ΔHCO₃ ratio of greater than 1 in lactic acidosis, usually approximately 1.6 to 1.8.

Notably, the duration of the lactic acidosis is thought to affect the ΔAG/ΔHCO₃. The ΔAG/ΔHCO₃ ratio 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 ΔAG/ΔHCO₃ 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 models²,³ and only limited human data has investigated the ΔAG/ΔHCO₃ in early lactic acidosis.⁴,⁵ The objective of this study was to examine the ΔAG/ΔHCO₃ within the first hours of the development of lactic acidosis. A secondary objective was to examine potential pathophysiologic explanations for the observed ΔAG/ΔHCO₃ ratio.

MATERIALS AND METHODS

The study was a re-analysis of data by Rudkin et al⁶ which examined the correlation between arterial and peripheral venous pH and base excess (BE) in trauma patients and concluded that VBG pH and BE cannot be used interchangeably with the corresponding 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 soon as possible. Venous samples, including a chemistry panel and serum lactate, were drawn prior to initiation of intravenous fluid resuscitation. Data collected included collection times of the ABG and VBG, physiologic data including blood pressure, and indicators of patient severity (Glasgow Coma Scale score, trauma and injury severity scores).

Statistical analysis:

The association between duration of lactic acidosis and the $\Delta$AG/$\Delta$HCO$_3^-$, $\Delta$Lactate and $\Delta$AG, arterial pH and the $\Delta$AG/$\Delta$HCO$_3^-$, and serum chloride and the $\Delta$AG/$\Delta$HCO$_3^-$ were examined using Pearson’s correlation and linear regression models were constructed. Least squares regression lines were calculated and plotted. Additionally, the association between $\Delta$HCO$_3^-$ and $\Delta$AG was examined using Pearson’s correlation, a linear regression model was constructed, and 95% prediction intervals were computed.

RESULTS

The re-analysis included 108 patients. 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 re-analysis, 148 patients were excluded because they were missing serum lactate or serum bicarbonate values and 5 patients were excluded because of clerical errors, leaving 193 patients remaining. In order to determine the group with the elevated serum lactate measurements (> 2.1 mmol/L), 67 patients with an anion gap < 7.1 mEq/L were excluded, 68 patients with a serum bicarbonate > 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. In order 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, the values 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 a standard deviation of 2.36 mmol/L and range between 2.2 and 11.1 mmol/L. ΔAG/ΔHCO₃ and ΔLactate/ΔHCO₃ 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 a standard deviation of 0.42 mEq/L and a range of 2.9 to 5.0 mEq/L; the mean serum Cr was 0.95 mg/dL with a standard deviation of 0.32 mg/dL and a range of 0.3 mg/dL to 2.3 mg/dL. The elevated serum lactate group had a mean serum potassium of 3.6 mEq/L with a standard deviation of 0.48 mEq/L and a range of 2.5 to 4.7 mEq/L; the mean serum Cr was 1.04 mg/dL with a standard deviation of 0.37 and a range of 0.4 mg/dL to 2.8 mg/dL. Table 1 shows the patient characteristics. For the patients with elevated lactate levels, the average patient age was 38.6 years old (SD ± 18.8 years) with a preponderance of males (71.1%). The mechanism of injury was predominantly blunt trauma (71.1%).

The mean ΔAG/ΔHCO₃ was 1.86 with a standard deviation of 1.40, while the mean ΔLactate/ΔHCO₃ was 1.21 with a standard deviation of 1.06. The mean ΔLactate/ΔHCO₃ was also calculated using the reported upper range of normal for serum lactate (2.1 mmol/L), yielding a value of 0.95 with a standard deviation of 0.91.

Figure 1 shows the linear regression model examining duration of lactic acidosis and ΔAG/ΔHCO₃ ratio. 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 minutes 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. The $r = 0.496$ with a p value of 0.001. The $R^2$ is 0.246. Figure 3 shows the linear regression model examining arterial pH and the ΔAG/ΔHCO$_3$ ratio. The $r = 0.101$ with a p value of 0.52. Figure 4 shows the linear regression model between serum chloride and the ΔAG/ΔHCO$_3$ ratio. The $r = -0.150$ with a p value of 0.33. Figure S1 shows the linear regression model between ΔHCO$_3$ and ΔAG. The $r = 0.689$, with a p value of < 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 anion gap metabolic acidosis. The accumulation of a non-chloride 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 anion gap. Theoretically, the reduction in serum HCO$_3$ corresponds to an equivalent increase in the anion gap, resulting in a ΔAG/ΔHCO$_3$ of 1. Hence, any deviation from this 1:1 stoichiometry may reflect a co-existing acid-base disorder in addition to the anion gap metabolic acidosis.

The existing literature reveals that there is variable stoichiometry of ΔAG/ΔHCO$_3$, depending on the specific type of organic acidosis. In lactic acidosis, the traditional belief is that in the first few hours the ΔAG/ΔHCO$_3$ is approximately 1:1. However, as the lactic acidosis persists beyond a few hours, the mean ΔAG/ΔHCO$_3$ ratio is approximately 1.6-1.8; the increased ΔAG/ΔHCO$_3$ 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 extracellular fluid compartment.

Only limited human data has investigated the ΔAG/ΔHCO$_3$ in early lactic acidosis. The main objective of this study was to specifically examine the ΔAG/ΔHCO$_3$ within the first hours of
the development of lactic acidosis. Patients in this study were trauma patients and therefore the lactic acidosis was a result of hypovolemic shock. The patient characteristics, including relatively young mean age (38.6 years) and male predominance (71.1%) are consistent with the demographics typically seen in trauma patients. The mean ΔAG/ΔHCO$_3$ 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 ΔAG/ΔHCO$_3$ 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 extracellular fluid compartment). 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, 7 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 ΔAG/ΔHCO$_3$ is 1:1 early in the course of lactic acidosis, a more detailed re-evaluation of the literature reveals divergent results in animal and human studies. Oster et al and Madias et al both conducted animal studies in dogs and rats, respectively. The mean ΔAG/ΔHCO$_3$ in the first hour of lactic acidosis in these studies ranged from 1.00-1.25. Notably, in these animal models, lactic acidosis was produced via a lactic acid infusion. Therefore, the lactic acid directly enters the extracellular space, presumably facilitating EC buffering of protons by bicarbonate. Concurrently, the lactate remains in the same compartment, resulting in a 1:1 stoichiometry and the ΔAG/ΔHCO$_3$ of approximately 1 observed in these animal studies.

In contrast, 2 small human studies have yielded more conflicting results. Orringer et al found that in early lactic acidosis, the mean ΔAG/ΔHCO$_3$ ranged from 1.5-1.86 within the first 30 minutes after grand-mal seizures. A second study by Brivet et al also examined patients after grand-mal seizures and determined that the mean ΔAG/ΔHCO$_3$ was 1.28, with 33% of patients
exhibiting a ratio of <0.8. The mean $\Delta \text{AG}/\Delta \text{HCO}_3$ 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 in humans from shock, with pathophysiology resulting from hypoperfusion and decreased oxygen delivery.

As discussed above, in animal models of early lactic acidosis, the mean $\Delta \text{AG}/\Delta \text{HCO}_3$ was approximately 1 in the first hour of lactic acidosis, attributable to the lactic acid infusion directly entering the extracellular space and facilitating extracellular buffering of protons by bicarbonate. In contrast, our results indicate that in humans, endogenous lactic acidosis manifests a mean $\Delta \text{AG}/\Delta \text{HCO}_3$ 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. In distinction to animal models of lactic acidosis which are initiated in the extracellular 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 $\Delta \text{AG}/\Delta \text{HCO}_3$ approaching 1.8 as the acidosis persists beyond a few hours. The $\Delta \text{AG}/\Delta \text{HCO}_3$ of 1 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 $\Delta \text{AG}/\Delta \text{HCO}_3$ 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 $\Delta \text{AG}/\Delta \text{HCO}_3$ in lactic acidosis during the first few hours is approximately 1.8, our study helps elucidate the reasons for the high $\Delta \text{AG}/\Delta \text{HCO}_3$ ratio. 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 extracellular 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 \( \Delta AG/\Delta HCO_3 \) ratio of greater than 1, usually approximating 1.6-1.8. The assumption underlying this theory is that the increase in AG relative to the decrement in \( \Delta HCO_3 \) reflects an increase in extracellular lactate. Our data demonstrates a mean \( \Delta AG/\Delta HCO_3 \) of 1.86, consistent with prior studies of lactic acidosis in humans.\(^4,7,8,9\) By contrast, the mean \( \Delta \text{Lactate}/\Delta HCO_3 \) ranged between 0.95-1.21 depending on the baseline lactate value. Additionally, Figure 2 demonstrates that the delta lactate can only explain 24.6% of the observed variance in the delta AG. Taken together, this data suggests that the high \( \Delta AG \) that results in an increased \( \Delta AG/\Delta HCO_3 \) ratio does not appear to be primarily a result of increased extracellular lactate, as this proposed model would suggest. Second, in theory organic or inorganic anions or cations may exhibit a pH-dependent contribution to the anion gap as the pH decreases. For example, the albumin concentration, which is the main contributor to the anion gap, increases with a rise in pH, resulting in an elevated anion gap in metabolic alkalosis. Conversely, a drop in pH may change the degree to which certain anions and cations contribute to the anion gap, resulting in a high AG and an elevated \( \Delta AG/\Delta HCO_3 \) ratio. However, Figure 3 demonstrates that there is no statistically significant association between arterial pH and the \( \Delta AG/\Delta HCO_3 \) ratio, with a p value of 0.52. Therefore, the pH-dependent contribution of anions or cations does not explain the increased \( \Delta AG/\Delta HCO_3 \) ratio observed in lactic acidosis. Third, Madias et al\(^3\) suggested that based on an animal model hypochloremia may account for 30% to 50% of the increment in anion gap seen in lactic acidosis, explaining the deviation from 1:1 stoichiometry and elevated \( \Delta AG/\Delta HCO_3 \) ratio. The decrement in serum chloride results from extrusion of cellular cations and resultant expansion of the extracellular compartment during the buffering process in lactic acidosis. However, there is
not a significant correlation between serum chloride and ΔAG/ΔHCO₃ (Figure 4), arguing that hypochloremia does not play a significant role in the elevated ΔAG/ΔHCO₃ ratio observed in lactic acidosis in humans. Fourth, it is likely that the increase in AG that results in an elevated ΔAG/ΔHCO₃ ratio is comprised of unknown organic anions (or less likely due to decrease in unmeasured cations). Our data, consistent with previous literature, shows that in lactic acidosis up to 75% of the observed variance in the anion gap is not explained by blood lactate, and therefore lactic acid does not entirely account for the anion gap 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 levels.¹⁵,¹⁶ Given that our data argues against other possible explanations of the high ΔAG/ΔHCO₃ seen in lactic acidosis, these unmeasured anions are the most likely cause and further work to identify them needs to be carried out.

While ongoing research attempts to identify the unmeasured anions in lactic acidosis and better explain its pathophysiology, the ΔAG/ΔHCO₃ remains a widely used tool to detect co-existing acid-base disorders in patients with lactic acidosis and other high anion gap metabolic acidosis. The wide 95% prediction interval suggests that ΔAG/ΔHCO₃ should be used cautiously in the diagnosis of mixed acid-base disorders (Figure S1). For example, although the mean ΔAG/ΔHCO₃ was 1.86, which is consistent with prior studies, the standard deviation was 1.40 and 15/45 patients had a ΔAG/ΔHCO₃ < 1. 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 ΔAG/ΔHCO₃ in early lactic acidosis in humans from shock. However, the study does have some limitations. This study was a re-analysis 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 ED trauma patients and the ranges of laboratory values,
including serum lactate, serum HCO$_3^-$, pH, and AG span the clinically important range. Since
most forms of type A lactic acidosis are due to marked tissue hypoperfusion, it is likely that the
results of this study will apply to not just hypovolemia, but 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 anion gap 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 anion gaps. In fact several studies have reported the normal range for anion gap to be 6
+/- 3 mEq/L. Given that the anion gap will vary amongst different laboratories, the mean
anion gap (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 anion gap 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 acute trauma patients 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 impact on the calculation of the
ratio and subsequent conclusions about the underlying pathophysiology. For example, in this
study, patients with an anion gap $\leq$ 7.1 mEq/L were excluded because the mean AG of 7.1
mEq/L was the value used to calculate subsequent $\Delta$AG values. It is important to note that this
mirrors what occurs in clinical practice when using a normal value for anion gap; some patients
invariably have an anion gap that falls below the normal value used, precluding calculation of
the delta AG. In order to avoid this, the actual normal baseline values of individual patients, if known, should be used.

Thirdly, the data set did not include some pertinent parameters. It did not include serum albumin, so it was not possible to correct the anion gap for albumin level. The data set also did not include serum phosphorus, although due to its low concentration in the extracellular fluid, the buffering by inorganic phosphate in the extracellular fluid is likely negligible compared to that of bicarbonate. The data set also lacked information about co-morbidities.

Lastly, this re-analysis 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\textsuperscript{4} and Brivet et al\textsuperscript{5} only included 8 and 35 patients, respectively. Therefore, this is the largest human study to date investigating the $\Delta$AG/$\Delta$HCO\textsubscript{3} in early lactic acidosis.

CONCLUSIONS

The mean $\Delta$AG/$\Delta$HCO\textsubscript{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

All authors have nothing to disclose.

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AUTHOR CONTRIBUTIONS

S Rudkin: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing - original draft
T Grogan: Data curation; Formal analysis; Project administration
R Treger: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing - original draft

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Supplementary Figure 1. Pearson correlation between ΔHCO₃ and ΔAG. r = 0.689, p < 0.001. Dashed lines are the 95% prediction interval.
REFERENCES


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### Table 1. Patient characteristics

<table>
<thead>
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Figure 1. Pearson correlation between duration of lactic acidosis and ΔAG/ΔHCO$_3^-$ ratio. $r = -0.14$, $p = 0.37$.

Figure 2. Pearson correlation between ΔLactate and ΔAG. $r = 0.496$, $p = 0.001$.

Figure 3. Pearson correlation between arterial pH and ΔAG/ΔHCO$_3^-$ ratio. $r = 0.101$, $p = 0.52$.

Figure 4. Pearson correlation between Serum chloride and the ΔAG/ΔHCO$_3^-$ ratio. $r = -0.150$, $p = 0.33$. 
Figure 2
Figure 3

The graph shows the relationship between \( \Delta AG/\Delta HCO_3 \) and Arterial pH. The data points are scattered across the graph with a trend line indicating a positive correlation.
Figure 4

Graph showing the relationship between ΔAG/ΔHCO₃ and Serum chloride (mEq/L).