

# Evaluation of acid–base disorders in dogs and cats presenting to an emergency room. Part 2: Comparison of anion gap, strong ion gap, and semiquantitative analysis

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## Abstract

**Objective** – To compare the diagnostic performance of the anion gap (AG) with 2 physicochemical approaches to identify unmeasured anions.

**Design** – Prospective cohort study.

**Setting** – University teaching hospital.

**Animals** – Eighty-four dogs and 14 cats presenting to a university teaching hospital emergency room.

**Interventions** – All dogs and cats in which venous blood samples for acid–base, lactate, and serum biochemical analysis were all collected within 60 minutes of each other, over a 5-month enrollment period. Unmeasured anions were quantified using each of three approaches: the anion gap (AG), strong ion gap (SIG), and a semiquantitative approach (XA).

**Measurements and Main Results** – An increased AG metabolic acidosis was evident in 34/98 of cases. The Stewart approach identified an increased SIG acidosis in 49/98 of cases. There was a strong correlation between SIG and AG ( $r = 0.89$ ;  $P < 0.001$ ). The semiquantitative approach identified increased unmeasured anions in 68/98 of cases. There was a moderate correlation between AG and XA ( $r = 0.68$ ;  $P < 0.001$ ) and a slightly stronger correlation between SIG and XA ( $r = 0.75$ ;  $P < 0.001$ ). Plasma lactate concentrations and AG were poorly correlated ( $r = 0.22$ ;  $P = 0.029$ ) and there was no correlation between lactate concentrations and BE ( $r = 0.19$ ;  $P = 0.069$ ).

**Conclusions** – Unmeasured anions occurred commonly in this sample of small animal emergency room patients and physicochemical approaches identified more animals with unmeasured anions than the traditional AG calculation. Further studies are needed to determine if the results of the physicochemical approach improves clinical management and warrants the associated increases in cost and complexity.

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**Keywords:** albumin, strong ion difference, stewart approach, unmeasured anions

## Introduction

Metabolic acidosis is a common acid–base disorder, reported to occur in 49% of all animals undergoing blood gas analysis for any reason at a veterinary teaching hospital.<sup>1</sup> Metabolic acidosis can be broadly

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## Abbreviations

AG	anion gap
BE	base excess
SIDapp	strong ion difference apparent
SIDeff	strong ion difference effective
A <sub>TOT</sub>	total quantity of weak acids
SIG	strong ion gap
XA	semiquantitative measure of unmeasured ions

categorized into those associated with an increase in unmeasured anions and those that are not. Recognizing the presence of unmeasured anions in a patient can aid

in understanding the cause of acid–base imbalance and may help direct the therapeutic approach. There are several methods available to estimate the quantity of unmeasured anions in the clinical patient. The relative diagnostic performance of these methods remains controversial in human medicine and has not been evaluated to date in veterinary medicine.<sup>2–9</sup>

The AG is the traditional measure of unmeasured anions. It is based on the principle of electroneutrality; the total number of cations in the system must equal the total number of anions. The majority of the cations in the blood are measured routinely, but the charge of several major anions is not easily quantified, particularly albumin and phosphorus. These anions contribute to the normal AG present in a healthy patient. The AG is increased by the accumulation of anions other than chloride or bicarbonate, many of which are conjugate bases of acids (eg, the sulfate ion from sulfuric acid accumulation in renal azotemia).<sup>10</sup>

The Stewart approach to acid–base analysis utilizes three variables:  $PCO_2$ , SID, and  $A_{TOT}$ , the total quantity of nonvolatile weak acids.<sup>11</sup> Strong ions are those that are fully dissociated at physiologic pH and SID is the difference in quantity between the strong cations and strong anions. The parameter  $A_{TOT}$  is a measure of the acid–base influence of weak acids, namely albumin and phosphorus. There are 2 methods by which the SID can be estimated, SIDapp based on measured cations and the anion chloride, and SIDeff based on bicarbonate and  $A_{TOT}$ . Several formulas have been proposed for the calculation of these two SID parameters.<sup>12,13</sup> In the normal healthy animal the values for SIDapp and SIDeff are very similar and the difference between them, a quantity known as SIG (Table 1), is close to zero.<sup>14,15</sup> Increases in unmeasured anions are identified by the associated increase in the SIG.

A third approach, developed by Fencl and colleagues, combines concepts from the Stewart physicochemical method with the BE, determined via traditional analysis.<sup>6,9</sup> This semiquantitative approach quantifies the influence of several individual acid–base processes on the patient's BE. These individual processes are marked by changes in albumin, phosphorus, chloride, sodium, and lactate concentration. Formulas are used to calculate the influence on BE for a given change in each parameter (Table 1). Unmeasured anions (XA) are then determined by calculating the difference between the sum total of the individual contributors and the patients measured BE (Table 1).<sup>9</sup>

Acid–base disorders in critically ill and injured human patients have been shown to have diagnostic and prognostic value and the quantity of unmeasured anions have frequently been reported to be one of the most useful acid–base parameters evaluated.<sup>3,5–7,16,17</sup> However, the

most accurate method to assess unmeasured anions in these studies varies. The aim of this study was to compare the diagnostic performance of three methods by which to quantify unmeasured anions in venous blood samples collected from dogs and cats on presentation to an emergency room. This is a companion study to a comparison of three methods of acid–base analysis (Part 1) using the same dataset.<sup>18</sup>

## Materials and Methods

This was a prospective, observational study. All dogs and cats presenting to a university teaching hospital in which venous blood samples for acid–base, lactate, and serum biochemical analysis were all collected within 60 minutes of each other, over a 5-month enrollment period, were included. The timing and choice of blood sample type and diagnostic tests performed was at the clinician's discretion. Patients that qualified for enrollment were recorded on a data sheet by the emergency room clinician or technician at the time of blood sample collection. The patient signalment and primary clinical diagnoses were recorded.

## Comparison values

Venous blood samples from 10 healthy dogs and 8 healthy cats were obtained for the purposes of comparison of acid–base, lactate, and electrolyte values (see Table 1 of the companion article)<sup>18</sup> on the ICU point-of-care machine with those obtained from clinical patients.<sup>a</sup> This range was derived from the mean  $\pm$  2 standard deviations. These animals were determined to be in good health on the basis of history, physical examination, packed cell volume, and total protein measurement. The standard reference values at the clinical pathological laboratories of the University of California-Davis were used for the phosphorus and albumin concentrations measured on a serum biochemistry panel. The formulas used to determine all calculated variables are provided in Table 1.<sup>10,12,13,19,20</sup>

## Measurements

Heparinized blood samples for acid–base, electrolyte, and lactate values were measured immediately following sample collection on a point-of-care analyzer.<sup>a</sup> The majority of samples were collected as whole blood and immediately transferred to 125  $\mu$ L heparinized clinitubes, purpose-made for the blood gas machine. Some of the samples were transferred to commercial heparinized tubes containing 50 units of heparin with a minimum volume of 1 mL of blood.

Blood samples for phosphorus and albumin concentrations were submitted to the hospital diagnostic

**Table 1:** Formulas for calculated acid base parameters<sup>10,12,13,18,19</sup>

Parameter	Formula
Anion gap	$([Na^+] + [K^+]) - ([HCO_3^-] + [Cl^-])$
SID apparent	$([Na^+] + [K^+] + [Ca^{2+}]) - [Cl^-]$
Albumin contribution	Measured albumin $\times ((0.123 \times pH) - 0.631) \times 10$
Phosphorus contribution	Measured phosphorus $\times 0.323 \times ((0.309 \times pH) - 0.469)$
A <sub>TOT</sub>	Albumin contribution + Phosphorus contribution
SID effective	$[HCO_3^-] + \text{Albumin contribution} + \text{Phosphorus contribution}$
Strong ion gap	SID apparent – SID effective
Free water effect	$0.25([Na^+] - \text{mid-normal } [Na^+])$
Dogs cats	$0.22([Na^+] - \text{mid-normal } [Na^+])$
Corrected chloride	Measured $[Cl^-] \times (\text{mid-normal } [Na^+]/\text{measured } [Na^+])$
Chloride effect	Mid-normal $[Cl^-] - \text{corrected } [Cl^-]$
Phosphate effect	$0.58 (\text{mid-normal } [\text{phosphorus}] - \text{measured } [\text{phosphorus}])$
Albumin effect	$3.7(\text{mid-normal albumin} - \text{measured } [\text{albumin}])$
Lactate effect	$-1 \times [\text{lactate}]$
Sum of effects	Free water effect + chloride effect + phosphate effect + albumin effect + lactate effect
Unmeasured anion effect	Base excess – sum of effects

Note: Mid-normal values were determined as the central value of the comparison range shown in Table 1 of the companion article. Albumin g/dL; Phosphorus mg/dL; Electrolytes and lactate mmol/L. SID, strong ion difference; A<sub>TOT</sub>, total weak acids.

laboratory for analysis.<sup>b</sup> The results of the blood gas, electrolyte, lactate, and serum biochemistry tests were imported from the computer-based laboratory data bank to a commercial spreadsheet application for analysis.<sup>c</sup>

### Calculated variables

Bicarbonate and BE were calculated by the analyzer using the Henderson–Hasselbalch and Van Slyke equations, respectively.<sup>21,22</sup> The BE equation used was that recommended by the Clinical Laboratory Standards Institute (C46-A2). Table 1 of the companion article lists the formulas used for all other calculated acid–base variables. The value for CO<sub>2</sub> solubility (S<sub>CO2</sub>) in plasma used by the blood gas machine<sup>a</sup> was 0.03 mmol/L/mmHg. The equation used for the determination of bicarbonate was:

$$HCO_3 = S_{CO_2} \times PCO_2 \times 10^{(pH - pK'_1)}$$

Where the pK'<sub>1</sub> used was derived from the formula:  $pK'_1 = 6.125 - \log[1 + 10^{(pH - 8.7)}]$

### Acid–base analysis

The metabolic acid–base diagnosis for each patient was determined using each of three approaches: the traditional approach, Stewart approach, and a semiquantitative approach, as described in the companion paper.<sup>18</sup>

### Statistics

Abnormal values for definitions of each acid–base disorder were considered as those that were two standard

deviations above or below the mean of the comparison values. A reference range for AG, SIDapp, SIDeff, and SIG was determined from the normal values collected, for dogs and cats, respectively. A reference range for the semiquantitative parameters of free water effect, chloride effect, albumin effect, and phosphorus effect was determined by using the high and low value of the normal range for each variable (provided in Table 1 of the companion article).<sup>18</sup>

Results are reported as median and range. Linear regression was used to evaluate the relationship between AG, albumin, SIG, and XA, as well as the relationship between lactate and BE and lactate and AG.<sup>d</sup> A *P*-value of < 0.05 was considered significant.

### Results

A total of 98 animals were enrolled with 84 dogs and 14 cats. The acid–base, electrolyte, lactate, albumin, phosphorus, and calculated acid–base values are shown in Table 3 of the companion article.<sup>18</sup> The clinical diagnoses and specific acid base diagnosis of these patients are provided in the companion article.

Traditional acid–base analysis identified metabolic acidosis in 53/98 of cases and an increased AG metabolic acidosis was evident in 34/98 of cases (Table 2). Hyperlactatemia was evident in 49/98 and hyperphosphatemia in 18/98 patients in this study. Regression analysis found no correlation between AG and serum albumin concentration ( $r = 0.07$ ;  $P = 0.5$ ).

The Stewart approach identified one or more acidotic processes in 34/98 of cases and coexisting alkalotic and acidotic processes in another 36/98 cases. An increased

**Table 2:** Comparison of values for unmeasured anion quantity using traditional, Stewart and a semiquantitative approach for metabolic acid–base diagnosis of 84 dogs and 14 cats presented to an emergency room

Unmeasured anion parameter	%
Elevated anion gap	35
Elevated strong ion gap	50
XA–Elevated unmeasured anions	73

SIG acidosis was present in 49/98 of cases (Table 2). There was a strong correlation between SIG and AG ( $r = 0.89$ ;  $P < 0.001$ ).

The semiquantitative approach identified one or more acidotic processes in 38/98 cases and coexisting alkalotic and acidotic processes in another 54/98 cases. Increased unmeasured anions (XA) were evident in 68/98 of cases (Table 2). Unmeasured cations (XA+) were present in 17/98 of cases (Table 7 of the companion article).<sup>18</sup>

There was a moderate correlation between AG and XA ( $r = 0.68$ ;  $P < 0.001$ ) and a strong correlation between SIG and XA ( $r = 0.75$ ;  $P < 0.001$ ) (Fig. 1). Plasma lactate concentrations and AG were poorly correlated ( $r = 0.22$ ;  $P = 0.029$ ) and there was no correlation between lactate concentrations and BE ( $r = 0.19$ ;  $P = 0.069$ ).

## Discussion

The identification of abnormal unmeasured anions in the cases evaluated in this study varied depending on the method used. The traditional acid–base parameter AG identified an increased level of unmeasured anions in 34/98 animals while the Stewart parameter SIG was increased in 49/98 cases and the semiquantitative entity XA was increased in 68/98 of cases. Previous human studies have also found the Stewart and semiquantitative approaches diagnose more abnormalities than the traditional approach.<sup>2,6–9</sup> This may suggest that the physicochemical approaches (Stewart and semiquantitative) have an increased sensitivity for detection of abnormal unmeasured anions. Alternatively, it is possible that the physicochemical approaches are more prone to error as they are based on calculations from a larger number of parameters.

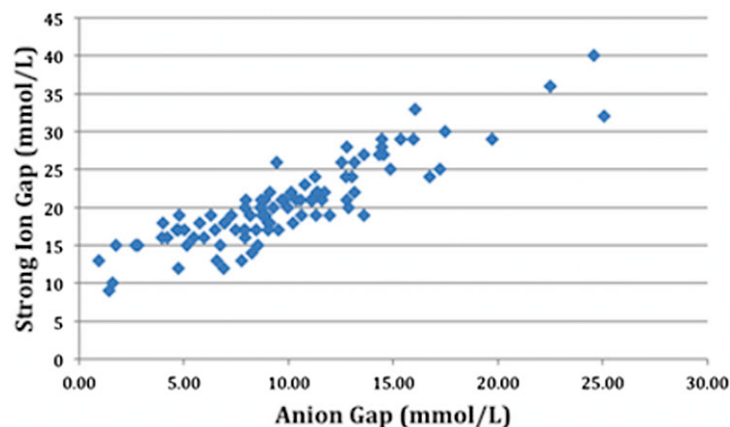
The AG is a common method used to identify unmeasured anions. The normal range for AG will depend on the normal values of electrolytes and bicarbonate for the analyzer used.<sup>23</sup> The normal range of AG for dogs and cats in the present study was within that previously reported.<sup>24</sup> The most common cause of an increase in AG is a metabolic acidosis due to the accumulation of endogenous acids such as lactic acid, uremic acids, and ketoacids or the intake of exogenous acids or acid precursors such as ethylene glycol. Hyperlactatemia was

evident in 49/98 of patients and hyperphosphatemia in 18/98 of patients in this study. None of the enrolled patients were diagnosed with ethylene glycol intoxication. Other potential sources of unmeasured anions may include substances such as D-lactate, acids associated with the Krebs cycle, or unidentified toxins.<sup>25</sup>

The negative charge of albumin constitutes the majority of the normal AG, as such a strong correlation between albumin concentration and AG would be expected. This is supported by a study in human patients with nephrotic syndrome, while Feldman and colleagues reported a moderate correlation ( $r = 0.5$ ) in a population of 5,328 human patients.<sup>26,27</sup> In contrast, the present study found no correlation between albumin and AG. This reflects the animals included in this study that had a high incidence of unmeasured anions and variable albumin concentrations. These changes are not unexpected in human critical illness or injury.<sup>2,3,28,29</sup> As albumin is the major contributor to the normal AG, the presence of hypoalbuminemia can confound interpretation of the AG, making it an unreliable predictor of the presence of unmeasured anions.<sup>27,29,30,e</sup> In human medicine, various formulas to correct the AG for changes in albumin concentration have been utilized to increase its sensitivity. The calculation of an albumin-corrected AG improves its diagnostic performance in the identification of unmeasured anions.<sup>7,27,29,31</sup> Formulas for the correction of the AG in dogs and cats have been proposed, but the diagnostic performance and clinical benefit of such calculations are yet to be investigated.<sup>24,e</sup>

Unlike the AG, the SIG is not impacted by changes in albumin concentration. In the normal patient the SIG should approach zero. The comparison values for SIG in the present study are similar to what has been reported previously for dogs and cats.<sup>14,32–34</sup> The SIG identified more patients with unmeasured anions than the AG in this study. Human studies have reported similar findings although there is little difference in performance if the AG is corrected for hypoalbuminemia.<sup>2,7,29,35</sup> The SIG was strongly correlated with the AG in the current study, and it is likely that the small difference in diagnostic performance between these parameters would be further reduced if the effect of hypoalbuminemia on AG were to be accounted for. The calculation of SIG requires measurement of anything from 5 to 9 variables, depending on the formula utilized. Although the SIG may perform better when abnormalities in albumin are present, it remains to be shown if the increased complexity and expense associated with its calculation provides substantial clinical benefit.

The parameter XA identified the presence of unmeasured anions in more patients than AG or SIG, a finding supported by previous studies.<sup>6,9</sup> There was a reasonably strong correlation between XA and both AG and



**Figure 1:** Correlation between strong ion gap and anion gap in 84 dogs and 14 cats presenting to an emergency room ( $R = 0.89$ ,  $P < 0.001$ ).

SIG, suggesting that all three parameters are identifying similar abnormalities in animals, with XA having greater sensitivity. A similar finding was reported in a study of critically ill human patients.<sup>36</sup> Determination of XA requires the sum of 5 calculations and the BE. With every calculation there is an inherent degree of error so a parameter utilizing multiple calculations is vulnerable to cumulative error, and it is possible this factor may contribute to the high rate of abnormal XA values in this study. The normal range for XA in this study was very small ( $-0.5$  to  $0.5$  mmol/L), as a consequence a small error could easily result in determination of an abnormal XA. Many of the abnormal XA values for dogs in this study were small in magnitude, as the median value of  $-1.5$  mmol/L indicates. The accuracy of this approach to acid–base analysis has not been validated *in vivo* and the clinical relevance of small abnormalities in XA remains unknown. The parameter XA has been associated with mortality in critically ill human patients in some, but not all investigations.<sup>5,6,36</sup>

Lactate is a useful diagnostic and monitoring tool in critically ill or injured patients.<sup>37,38</sup> When direct lactate measurement is unavailable, the BE and AG have been used to predict hyperlactatemia. Previous human and veterinary studies evaluating the reliability of this approach have provided contradictory results. Some studies have found poor correlation, while others have reported that AG or BE can be reliable surrogate measures of lactate concentration.<sup>6,36,39,40</sup> In the present study, there was poor correlation between lactate and both BE and the AG. Hypoalbuminemia and the presence of unmeasured anions other than lactate are the likely reasons for this finding. In small animal emergency room patients, direct measurement of lactate concentration is essential for ideal patient management.

The identification of increased unmeasured anions is generally assumed to indicate the presence of a metabolic

acidosis. This is true in many, but not all, clinical scenarios. The acidosis associated with lactate generation can be masked by the concurrent presence of alkalotic processes. In this study, concurrent metabolic alkalotic and acidotic processes were common, as identified by the Stewart and semiquantitative approaches in the companion study published elsewhere in this issue.<sup>18</sup> Similarly, mixed acid–base abnormalities associated with a normal pH and BE were evident in 20% of critically ill human patients with severe hyperlactatemia.<sup>41</sup> In addition, lactate generation is not always associated with acid production. Causes of hyperlactatemia such as increased glycolytic rate, as can happen in response to catecholamines or cytokine stimulation, will increase lactate concentration but will not change pH.<sup>42</sup> Blood samples contaminated with sodium lactate will also show an increase in unmeasured anions without an associated acidosis.<sup>43</sup> The interpretation of parameters such as AG, SIG, and XA should be integrated with the acid–base status of the patient and some understanding of the underlying disease processes present.

The semiquantitative approach identified the presence of unmeasured cations in 17/98 of the cases in this study. There are few reports of unmeasured cations in the literature; causes have included lithium intoxication and paraproteinemias.<sup>44,45</sup> Increased concentration of organic cations, primarily guanidines, have been described in human patients with chronic renal failure and may be a reason for the presence of unmeasured cations in some of the patients in this study.<sup>46</sup> Elevations in magnesium would also be represented as unmeasured cations in this study and could further contribute to this finding. As the formula used for the contribution of albumin to base excess was one determined for human albumin, it may well underestimate the true contribution of canine and feline albumin, and could result in the erroneous calculation of unmeasured cations. Low or

negative values for AG and SIG can also indicate the presence of unmeasured cations. Given the impact of hypoalbuminemia on AG, a low AG is an insensitive marker of unmeasured cations. A negative AG may be due to laboratory error, substances such as bromide or iodide interfering with measurement of chloride concentration, or the presence of unmeasured cations.<sup>44,45,47–49</sup> The causes of a low or negative (below the reference range) SIG would be similar. There were many patients in this study with low AG and SIG values; there were no negative values for either parameter. The impact of unmeasured cations on AG or SIG could not be determined in this study.

This study has several limitations. For accuracy, it would have been ideal to evaluate all the measured parameters on the same blood sample. In this study, we allowed a 60-minute time interval for blood sample collection so we cannot rule out the possibility that fluid therapy given during the sample collection period may have impacted our results. The majority of samples in this study were collected simultaneously so the effect of this issue is likely to be minimal. Another limitation is the small number of cats included in this study. As such, these results should be applied to cats with caution. This study was performed in a tertiary referral institution, so the nature of the emergency room population included may not be representative of general clinical practice. Another limitation is the small number of dogs and cats used to determine the comparison acid–base values for this study. Although not ideal, this was considered preferable to using previously published normal acid–base values measured on different blood gas machines, often on small numbers of animals.

The results of this study demonstrate that excess unmeasured anions were commonly found in dogs and cats presented to a university emergency service whose clinicians chose to obtain a venous blood gas, lactate, and serum biochemistry profile.

Physicochemical approaches identified more animals with unmeasured anions than the traditional AG calculation did. It is likely that parameters such as SIG and XA will be superior in identifying unmeasured anions in hypoalbuminemic patients. Further studies are needed to determine if the results of the physicochemical approaches can improve clinical management, and warrant the associated increases in cost and complexity in all patients or if they should be reserved for a subset of critically ill or injured patients.

### Footnotes

- <sup>a</sup> ABL 705, Radiometer Medical A/S, Copenhagen, Denmark.  
<sup>b</sup> Hitachi 717 chemistry analyzer, Roche Diagnostics, Indianapolis, IN.  
<sup>c</sup> Microsoft Excel 2008, Microsoft Corp, Santa Rosa, CA.  
<sup>d</sup> LogXact 8 for Windows, Cytel Software Corporation, Cambridge, MA.

<sup>e</sup> Hayes G, Mathews K, Bersenas A, Dewey C. (Abstract) *J Vet Emerg Crit Care* 2010; 20(S1):A4.

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