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A comparison of traditional and quantitative analysis of acid–base imbalances in hypoalbuminemic dogs

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Abstract

Objective – To compare the traditional (HH) and quantitative approaches used for the evaluation of the acid–base balance in hypoalbuminemic dogs.
Design – Prospective observational study.
Setting – ICU of a veterinary teaching hospital.
Animals – One hundred and five client-owned dogs.
Measurements and Main Results – Jugular venous blood samples were collected from each patient on admission to determine: total plasma protein (TP), albumin (Alb), blood urea nitrogen (BUN), glucose (Glu), hematocrit (HCT), Na^+, Cl^-, K^+, phosphate (P_i), pH, $PvCO_2$, bicarbonate (HCO_3^-), anion gap (AG), adjusted anion gap for albumin (AG_{alb}) or phosphate ($AG_{alb\text{-}phos}$), standardized base excess (SBE), strong ion difference (SID), concentration of nonvolatile weak buffers (A_{tot}), and strong ion gap (SIG). Patients were divided in 2 groups according to the severity of the hypoalbuminemia: mild (Alb = 21–25 g/L) and severe (Alb ≤20 g/L). All parameters were compared among groups. Patients with severe hypoalbuminemia showed significant decrease in TP ($P = 0.011$), A_{tot} ($P = 0.050$), and a significant increase in adjusted AG ($P = 0.048$) and the magnitude of SIG ($P = 0.011$) compared to animals with mild hypoalbuminemia.
According to the HH approach, the most frequent imbalances were simple disorders (51.4%), primarily metabolic acidosis (84.7%) associated with a high AG acidosis. However, when using the quantitative method, 58.1% of patients had complex disorders, with SIG acidosis (74.3%) and A_{tot} alkalosis (33.3%) as the most frequent acid–base imbalances. Agreement between methods only matched in 32 cases (kappa < 0.20).
Conclusions – The agreement between the HH and quantitative methods for interpretation of acid–base balance was poor and many imbalances detected using the quantitative approach were missed using the HH approach. Further studies are necessary to confirm the clinical utility of using the quantitative approach in the decision-making process of the severely ill hypoalbuminemic patients.

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Keywords: albumin, anion gap, metabolic acidosis, strong ion gap

Abbreviations

AG	anion gap
AG_{alb}	adjusted anion gap for albumin
$AG_{alb\text{-}phos}$	adjusted anion gap for albumin and phosphate
A_{tot}	concentration of non-volatile weak buffers
BE	base excess
Glu	glucose
HCO_3^-	bicarbonate
HH	henderson-hasselbach
SBE	standardized base excess
SID	strong ion difference
SIG	strong ion gap
SIRS	systemic inflammatory response syndrome
TP	total plasma protein

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Introduction

Acid–base disturbances and electrolyte disorders have been widely reported in the veterinary intensive care

literature.[1–5] Such disorders have diagnostic, therapeutic, and prognostic implications in terms of morbidity and mortality, both in small animal[6,7] and human medicine.[8–12] Thus, proper assessment, monitoring, and guided treatment of these disorders may be crucial for the successful management of critically ill patients. Different approaches to acid–base analysis have been developed, such as the traditional and the quantitative approaches. The traditional approach is based on the Henderson–Hasselbach (HH) equation and uses pH, partial pressure of carbon dioxide (PCO_2), bicarbonate (HCO_3^-), base excess (BE), and anion gap (AG), and the quantitative approach or simplified strong ion model[13] uses pH, PCO_2, strong ion difference (SID), total concentration of weak acids (A_{tot}), and strong ion gap (SIG).

The HH approach describes the blood pH as the result of a respiratory component, represented by PCO_2, and a metabolic component, expressed by HCO_3^- concentration using the following formula: $pH = 6.11 + \log([HCO_3^-] / (0.03 \times PCO_2))$.[14] This approach indicates which system is responsible for the initial change in pH and defines four primary acid–base abnormalities: respiratory acidosis or alkalosis, and metabolic acidosis or alkalosis. When only one of these components is primarily altered it is referred to as a ''simple acid–base disorder.'' In these situations, there is a compensatory response by the opposing component of acid–base to moderate the change in pH to some extent. By inputting certain physiological variables obtained on a blood gas, this compensatory response can be calculated.[3] When the actual compensatory response does not match the expected response, more than one component of acid–base must be altered and this is termed a ''mixed acid–base disorder.'' The HH approach further characterizes the metabolic disturbances by the AG calculation to detect an increase in the concentration of unmeasured anions. Normally, the AG is made up of the net negative charge on sulfates, phosphates, plasma proteins, and organic anions (eg, lactate, citrate). Thus, metabolic acidosis is categorized as either associated with a high AG or a normal AG. High AG acidosis results from a gain of acid with its associated anion while normal AG acidosis occurs from retention of protons or loss of HCO_3^- with associated increases in plasma chloride concentration. Although the HH approach recognizes respiratory and metabolic abnormalities, both components are not completely independent of each other and some aspects of the metabolic component remain uncharacterized. Thus, the HH approach may fail to describe underlying mechanisms of acid–base disturbances when patients have abnormal albumin, globulin, or hemoglobin concentrations that are frequent findings in critically ill dogs.[13,15,16]

The quantitative approach to acid–base uses 3 independent variables ($PvCO_2$, SID, and A_{tot}) to describe acid–base balance. The respiratory component is described by PCO_2 as for the HH approach and the metabolic component is characterized by SID and A_{tot}. The SID is the difference in charge between fully dissociated and therefore nonreactive or nonbuffering strong cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and strong anions (Cl^-, lactate, β-hydroxybutrate, acetoacetate, and SO_4^-) at physiologic pH.[17] In practice, changes of SID occur mainly as a result from changes in Na^+ and Cl^- concentrations. A decrease in SID causes the formation of strong ion acidosis, whereas an increase in SID causes strong ion alkalosis.[18,19] The A_{tot} is the total plasma concentration of nonvolatile buffers or weak acids such as albumin, globulins, and phosphate[20] and its variation results in nonvolatile buffer ion acidosis or alkalosis. Thus, the strong ion approach characterizes 6 primary acid–base disturbances (ie, respiratory acidosis and alkalosis, strong ion acidosis and alkalosis, nonvolatile buffer ion acidosis and alkalosis). Finally, the unmeasured strong anion concentration is quantified by calculating the SIG. This is an apparent difference between all unmeasured strong cations and anions. The SIG concept incorporates the impact of changes in albumin and phosphorus concentration but also the effect of other strong ion concentrations not included in the AG formula.[21,22] Thus, when albumin is low the AG may not allow identification of unmeasured anions that SIG calculation would identify.

The simplified strong ion model may offer a quantitative in-depth insight into the pathophysiology of acid–base disorders that could enable the development of treatment plans more specifically tailored to the patient's problem. However, the clinical utility of the simplified strong ion model remains controversial as some authors[3] point out that this approach is a more time consuming and less amenable in daily clinical practice than the standard HH approach.[24] The quantitative approach has been evaluated in human ICU patients[25–27] and reported anecdotally as an alternative method in veterinary medicine for horses,[28] pigs,[29] calves,[30] and dogs.[31–33] To date, there are no studies comparing the quantitative and traditional assessments of acid–base analyses in critically ill dogs. Based on the high incidence of acid–base disturbances and hypoalbuminemia in the critically ill patients, the implementation of a method that takes into account these disturbances could facilitate a more complete assessment of acid–base imbalances of such population. Therefore, the purpose of this study was to compare the interpretation of acid–base imbalances using the traditional and the quantitative approaches in hypoalbuminemic dogs admitted to an ICU.

Materials and Methods

Animals

This prospective observational study was performed at the intensive care unit of the veterinary teaching hospital at the Universitat Autònoma de Barcelona. Dogs admitted between February 2006 and January 2008 were enrolled in the study. To qualify for inclusion, dogs had to have hypoalbuminemia on admission (albumin <25 g/L [<2.5 g/dL) and absence of any previous therapy with natural or synthetic colloids. Dogs that fulfilled the inclusion criteria were included in the study for further evaluation. At the time of admission clinical signs, clinical and laboratory data were collected and recorded. In all included patients, the final diagnosis and the etiology of hypoalbuminemia was established based on clinical findings and supporting biochemical data. Further clinical patient classification in 2 groups was based on the severity of hypoalbuminemia. Group 1 included patients with albumin concentrations ≤ 2.0 g/dL [≤ 20 g/L] (severe hypoalbuminemia) and Group 2 included patients with albumin concentrations between 21–25 g/L (2.1–2.5 g/dL) (mild hypoalbuminemia).

In order to establish reference intervals for all the parameters described above, 135 clinically healthy dogs were selected as control animals. These dogs were considered to be clinically sound based on physical examination and serum biochemistry analyses. The group included 27 regular blood donors and 108 dogs undergoing minor or preventive major surgery (eg, neutering).

Sampling, processing, and analysis

Upon admission, samples were collected in a standard fashion before treatment was administered in hypoalbuminemic dogs and during routine physical exam just prior to the blood donation/surgical procedure in healthy dogs. Venous bloods were collected by venipuncture of the jugular vein into 2.5 mL lithium heparinized-anticoagulant tubes for biochemistry testing. Samples were centrifuged at 1,200 × *g* for 15 minutes to obtain plasma. Plasma was then frozen at −20°C for further analysis. Parameters determined in frozen plasma samples were as follows: total plasma protein (TP), plasma concentrations of albumin (Alb), inorganic phosphate (P_i), glucose (Glu), and blood-urea nitrogen. These parameters were measured using an automated biochemistry analyzer and standard colorimetric assays.[a]

Another venous blood sample was collected anaerobically from the other jugular vein into a 1-mL heparin-flushed polypropylene syringe.[b] The manual heparinization of the syringe was performed with 1,000 unit/mL of sodium heparin and after coating the barrel of the syringe, the excess heparin was forcefully expelled several times before the blood collection. Finally the syringe was filled with 0.9 mL of blood. Immediately after collection, blood gas analysis was performed using an automated portable blood gas analyzer[c] to determine pH, $PvCO_2$, sodium [Na^+], potassium [K^+], and chloride [Cl^-] concentrations.

Calculated parameters

Bicarbonate [HCO_3^-] and standardized base excess (SBE) were calculated by the analyzer using the Henderson–Hasselbach formula in conjunction with the Siggaard–Anderson equation and Van Slyke equations, respectively. The SBE equation used was recommended by the Clinical Laboratory Standards Institute (C46-A).[34] Traditional analysis was completed calculating the anion gap ($AG = Na^+ + K^+ - Cl^- - HCO_3^-$). The anion gap was adjusted for albumin (AG_{alb}) in all cases and also adjusted for phosphates ($AG_{alb\text{-}phos}$) in cases presenting with hyperphosphatemia. The described parameters were calculated using the following formulas:[35]

Anion gap adjusted for albumin

$$AG_{alb} = AG + 0.42 \times [3.77 - (Alb)]$$

Anion gap adjusted for albumin-phosphate

$$AG_{alb-phos} = AG_{alb} + [2.52 - 0.58 \times (P_i)]$$

where AG is measured in mEq/L, Alb is measured in g/dL, and P_i in mg/dL.

Quantitative analysis of acid–base balance was assessed using the method described by Stewart[36] and simplified by Constable.[13] The SID, A_{tot}, and SIG, were calculated using the following formulas:

Strong ion difference (SID):[37]

$$SID = (Na^+ + K^+) - Cl^-$$

Total concentration of nonvolatile weak buffers:[35]

$$A_{tot} = [TP] \times 0.27$$

where A_{tot} is calculated based on the TP concentration in gram per liter and whereas the effective dissociation constant (K_a) for plasma nonvolatile buffers is 0.17×10^{-7} ($pK_a = 7.77$)

Strong ion gap (SIG):[35]

$$SIG = [Alb] \times (0.348 + 0.469/\{1 + 10^{(7.77-pH)}\}) - AG$$

where SIG and AG are measured in mEq/L and Alb is measured in g/L.

Acid–base imbalances

Interpretation of acid–base status was performed on every patient using the traditional approach and the quantitative strong ion difference based analysis. Based on the HH approach, the parameters taken into account were pH, $PvCO_2$, HCO_3^-, SBE, and AG_{alb} or $AG_{alb\text{-}phos}$. Acid–base disorders were classified by this approach using the criteria described by de Morais and and Di Bartola.[38] The 4 acid–base disturbances described included respiratory alkalosis or acidosis, and metabolic alkalosis or acidosis. Briefly, respiratory acidosis was identified when $PvCO_2$ was above the reference interval and the pH was lower than reference interval, and respiratory alkalosis when $PvCO_2$ was lower and pH higher than the limits of the reference interval, respectively. Simple respiratory disorders were diagnosed when the compensatory changes in the HCO_3^- were within the range predicted by the compensatory calculations. Metabolic acidosis was identified when HCO_3^- or SBE values were below the reference interval and the pH was lower than the reference interval, and metabolic alkalosis when HCO_3^- or SBE values were above the reference interval and pH above the reference interval. Simple metabolic disorders were diagnosed when compensatory changes in $PvCO_2$ were within the expected range. Mixed disturbances were identified in cases when the compensatory calculations or values in the secondary system were not within the expected range. Patients showing alterations in the respiratory or metabolic component and a normal pH were also considered for evaluation of a possible compensated simple disorder or a mixed disturbances.

Patients with metabolic acidosis were further characterized considering the adjusted AG to characterize the presence of high-AG acidosis, that is, acidosis associated with an increased concentration of unmeasured anions. In addition, all patients showing no alterations in the metabolic parameters described above, but showing a normal or low pH in combination with a high AG_{alb} or $AG_{alb\text{-}phos}$ were included in the group of patients with metabolic acidosis.

Based on the quantitative approach the patients were classified by pH, $PvCO_2$, SID, A_{tot}, and SIG. The respiratory imbalances were classified according to the method previously described in the traditional approach.[39] Concerning metabolic imbalances, dogs were diagnosed with the following acid–base situations: metabolic acidosis when SID values were below the reference interval or A_{tot} concentration was above the reference interval; metabolic alkalosis when SID values were above the reference interval or A_{tot} concentration was below the reference interval. The SIG value was determined in every patient to estimate the effect of unmeasured strong anions in the acid–base imbalance according to the strong ion approach. In addition, all patients showing a normal or low pH in combination with only a high SIG were included in the group of patients with strong ion gap acidosis.

Statistical analysis

All data were analyzed using commercial statistical software.[d] Descriptive parameters and normality tests were done using the Univariate Procedure. All dependent variables (Na^+, K^+, Cl^-, Alb, TP, P_i, pH, $pvCO_2$, HCO_3^-, SBE, AG, SID, A_{tot}, SIG) were compared between control group and hypoalbuminemic groups using one way analysis of variance (ANOVA). Multiple pair-wise comparisons were obtained using Tukey´s correction. Reference intervals for comparisons were calculated as mean ± 1.96 standard deviations (SD) for healthy dogs. All reported values were presented as mean ± SD. Agreement between methods was studied using Kappa coefficient. Alpha level used for determination of significance was set at 0.05.

Results

One hundred and five hypoalbuminemic dogs were included in the study, 45 females (42.8%) and 60 males (57.2%), with a mean age of 6 years (range 6 months to 15 years). According to the severity of the hypoalbuminemia, 58 patients (55.2%) were included in the group with mild hypoalbuminemia (Alb = 21 − 25 g/L [2.1 − 2.5 g/dL]) and 47 dogs (44.8%) in the group of severe hypoalbuminemia (Alb ≤ 20 g/L [2.0 g/dL]). All patients included in the study were additionally classified according to its disease as being patients with systemic inflammatory response syndrome (SIRS) or sepsis 36/105 (34.3%), hepatic diseases 8/105 (7.6%), renal diseases 25/105 (23.8%), gastrointestinal diseases 15/105 (14.3%), or endocrine disorders 21/105 (20%). The control group was formed by healthy adult dogs, 82 males (61%), and 53 females (39%) with mean age of 5 years (range 2 to 8 years).

Mean values of the studied parameters for control, mild, and severe hypoalbuminemic dogs are listed in Table 1. Both mild and severe hypoalbuminemic dogs showed a significant decrease in Alb, TP, pH, HCO_3^-, SBE, SIG, and A_{tot}, and a significant increase in AG, AG_{alb}, and $AG_{alb\text{-}phos}$ compared to control dogs ($P < 0.001$ in all cases). Dogs affected by severe hypoalbuminemia also presented lower K^+ ($P = 0.048$), and P_i ($P < 0.01$) concentrations when compared to control. Finally, dogs affected by mild hypoalbuminemia, but not those affected by severe hypoalbuminemia, showed higher Na^+ ($P = 0.034$), and Cl^- ($P = 0.050$) concentrations than control animals. There were no significant differences between groups in $PvCO_2$ concentrations and SID values. According to the severity of the hypoalbuminemia,

Table 1: Comprehensive acid–base variables in dogs with and without hypoalbuminemia. The mean ± standard deviation is listed for each variable

Variable	mean ± SD Control ($n = 135$)	mean ± SD mild hypoalb ($n = 58$)	mean ± SD severe hypoalb ($n = 47$)	P-value
Na^+, mmol/L (mEq/L)	144 ± 2.9†	147 ± 7.6*	144 ± 8.9*†	0.027
K^+, mmol/L (mEq/L)	3.99 ± 0.412†	4.06 ± 1.411*†	4.35 ± 1.099*	0.061
Cl^-, mmol/L (mEq/L)	116 ± 4.1†	120 ± 10.6*	118 ± 8.8*†	0.007
Alb, g/L	35.7 ± 5.76*	22.5 ± 1.32†	17 ± 3.20‡	<0.001
g/dL	3.57 ± 0.576*	2.25 ± 0.132†	1.70 ± 0.320‡	<0.001
TP, g/L	68.5 ± 10.32*	61.3 ± 13.62†	53.3 ± 21.61‡	<0.001
g/dL	6.85 ± 1.032*	6.13 ± 1.362†	5.33 ± 1.596‡	<0.001
P_i, mmol/L	1.56 ± 0.476†	1.91 ± 1.263*†	2.20 ± 4.942*	<0.001
mg/dL	4.83 ± 1.475†	5.92 ± 3.912*†	6.83 ± 4.942*	<0.001
pH	7.42 ± 0.044*	7.32 ± 0.134†	7.30 ± 0.097†	<0.001
$PvCO_2$, mm Hg	33.3 ± 5.04	31.5 ± 7.95	32.4 ± 7.96	0.202
HCO_3^-, mmol/L(mEq/L)	21.2 ± 2.52*	17.0 ± 6.48†	16.4 ± 5.21†	<0.001
SBE, mmol/L(mEq/L)	−2.91 ± 2.874*	−9.04 ± 8.345†	−9.98 ± 6.439†	<0.001
AG, mmol/L(mEq/L)	11.1 ± 3.27†	14.2 ± 7.15†	14.5 ± 5.55*	<0.001
AG_{alb}, mmol/L(mEq/L)	11.1 ± 3.27†	20.6 ± 7.11†	23.2 ± 6.71*	<0.001
$AG_{alb\text{-}phos}$, mmol/L(mEq/L)	11.1 ± 3.27†	19.4 ± 7.39†	21.8 ± 6.71*	<0.001
SID, mmol/L(mEq/L)	32.3 ± 3.72	31.1 ± 8.32	30.9 ± 5.69	0.189
A_{tot}, mmol/L(mEq/L)	18.5 ± 2.79*	16.5 ± 3.68†	14.4 ± 5.83‡	<0.001
SIG, mmol/L(mEq/L)	6.46 ± 4.029*	−3.54 ± 7.379†	−6.57 ± 5.654‡	<0.001

*, †, ‡ Means presenting different super index within rows are significantly different ($P < 0.05$).

Na^+, sodium; K^+, potassium; Cl^-, chloride; Alb, albumin; TP, total protein; Pi, inorganic phosphorus, $PvCO_2$, partial pressure of CO_2; HCO_3^-, bicarbonate; SBE, standardized base excess; SD, standard deviation; AG, anion gap; SID, strong ion difference; A_{tot}, nonvolatile weak buffers; SIG, strong ion gap.

patients with severe hypoalbuminemia showed significant decrease in plasma total protein ($P = 0.011$), A_{tot} concentrations ($P = 0.050$), and SIG ($P = 0.011$), and a significant increase in adjusted AG ($P = 0.048$) compared to animals with mild hypoalbuminemia.

All 105 blood gas determinations performed in this study were evaluated using both methods of acid–base assessment. The interpretation of acid–base balance of each dog on admission is listed in Table 2. These results showed poor agreement (kappa < 0.20) between the traditional and quantitative approaches as in only 32 cases did the assessment match. Using a traditional approach, 95/105 (90%) determinations of acid–base status identified detectable disturbances; in most cases these were characterized as simple acid–base disorders (49 metabolic acidosis, 2 respiratory acidosis, 2 respiratory alkalosis, and 1 metabolic alkalosis). In the remaining 41 of these 95 disturbances, a mixed imbalance was identified: 24 had a combination of metabolic acidosis and respiratory acidosis, 12 respiratory alkalosis and metabolic acidosis, 4 metabolic acidosis and alkalosis, and 1 respiratory and metabolic alkalosis. Thus, using the traditional approach metabolic acidosis was detected in 89 patients (84.7%) as a simple acid–base disorder or as a component of a mixed disturbance. In 76/89 (85.4%) this metabolic imbalance was associated with an increased adjusted AG, but in 13 dogs simultaneous hyperchloremic metabolic acidosis was also detected.

Using a quantitative evaluation of acid–base balance, 94/105 (89%) blood gas analyses identified disturbances of which 33 were considered simple metabolic disorders: 25 SIG acidosis, 4 SID acidosis, 2 SID alkalosis, and 1 A_{tot} alkalosis. The remaining 61 of these 105 analyses showed complex acid–base disturbances: 20 A_{tot} alkalosis and SIG acidosis, 14 respiratory alkalosis associated with previous mentioned disorders and many other mixed disorders in low counts (Table 2).

Discussion

Hypoalbuminemia is a common finding in critically ill dogs.[40] Albumin is a weak acid that can affect pH value[41–43] and is considered a major buffer of the extravascular compartment. Consequently albumin plays a key role in the metabolic component of acid–base status, but is not accounted for in the traditional approach of acid–base interpretation.[44,45] Thus, the use of the traditional approach may lead to diagnostic errors in hypoalbuminemic dogs. The traditional approach to acid–base assessment is widely used because the process of interpretation is straightforward and does not require determination of a large number of parameters or complex calculations. The main goal of this study was to compare the traditional and the quantitative approaches for the assessment of acid–base status in hypoalbuminemic dogs.

Table 2: Interpretation of acid–base balance in hypoalbuminemic dogs ($N = 105$) using the quantitative and traditional approaches. The number of dogs affected are listed in each category and percentages are listed in parentheses. Dogs were stratified according to the severity of hypoalbuminemia: moderate hypoalbuminemia (MHA) – Albumin = 21–25 g/L [2.1 − 2.5 g/dL] and severe hypoalbuminemia (SHA) –Albumin <20g/L [<2.0 g/dL]

Quantitative approach	MHA	SHA	Total	Traditional approach	MHA	SHA	Total
Normal	**10**	**1**	**11(10.5%)**	**Normal**	**9**	**1**	**10(9.5%)**
Simple disorders			**33(31.4%)**	**Simple disorders**			**54(51.4%)**
Resp acidosis		1	1(0.9%)	Resp acidosis	1	1	2(1.9%)
SID acidosis	1	3	4(3.8%)	Resp alkalosis	2		2(1.9%)
SID alkalosis	2		2(1.9%)	Metabolic acidosis	23	26	49(46.7%)
A_{tot} alkalosis	1		1(0.9%)	Metabolic alkalosis	1		1(0.9%)
SIG acidosis	16	9	25(23.8%)	**Mixed disorders**			**41(39.0%)**
Complex disorders			**61(58.1%)**	Resp acidosis + metabolic acidosis	12	12	24(22.9%)
Resp acidosis + SIG acidosis	2	1	3(2.8%)	Resp alkalosis + metabolic acidosis	7	5	12(11.4%)
Resp alkalosis + SIG acidosis	7	2	9(8.6%)	Resp alkalosis + metabolic alkalosis	1		1(0.9%)
Resp alkalosis + SID acidosis	2		2(1.9%)	Metabolic acidosis (high AG acidosis) + metabolic alkalosis	2	2	4(3.8%)
SID acidosis + Atot alkalosis	1		1(0.9%)				
SID acidosis + SIG acidosis	1	1	2(1.9%)				
SID alkalosis + SIG acidosis	3	1	4(3.8%)				
A_{tot} acidosis + SIG acidosis	1	2	3(2.8%)				
A_{tot} alkalosis + SIG acidosis	5	15	20(19.0%)				
Resp acidosis + SID alkalosis + SIG acidosis		1	1(0.9%)				
Resp acidosis + A_{tot} alkalosis + SIG acidosis	2	2	4(3.8%)				
Resp alkalosis + SID acidosis + A_{tot} alkalosis	1		1(0.9%)				
Resp alkalosis + SID acidosis + SIG acidosis	1		1(0.9%)				
Resp alkalosis + A_{tot} alkalosis + SIG acidosis	1	4	5(4.7%)				
SID acidosis + A_{tot} acidosis + SIG acidosis	2		2(1.9%)				

A_{tot}, nonvolatile weak buffers; SID, strong ion difference; SIG, strong anion gap; Resp, respiratory.

When hypoalbuminemic patients were compared to control dogs, clear differences were detected in the metabolic component of acid–base status. In particular, hypoalbuminemic dogs showed lower pH combined with lower HCO_3 and higher AG compared to control dogs when the traditional approach was used, and lower A_{tot} and SIG when the quantitative method was used. The respiratory component represented by $PvCO_2$ values showed no differences between hypoalbuminemic and control dogs and only 15 dogs (14.3%) showed secondary respiratory alkalosis mainly as compensation to organic or hyperchloremic acidosis. The incidence of respiratory alkalosis in critically ill patients is controversial in human medicine.[46,47] In this sense, our findings agree with those by Rossing et al,[46] where hypocapnia or hyperventilation was observed in patients with hypoalbuminemia. The traditional acid–base method offers the possibility of calculating compensation, however, estimating compensatory processes in groups such as critical patients with different simultaneous acid–base disturbances can be difficult. To date there are no studies in veterinary medicine regarding the phenomena of compensation in cases of hypoproteinemic alkalosis.

Decreased pH was expected in many critically ill patients from the previously reported association of metabolic acidosis and illness in critically ill patients.[48] Using the traditional approach the most consistent disturbance found in the present study was a simple primary metabolic acidosis associated with a high AG (organic acidosis). This finding agrees with those by Hopper et al,[5] where primary metabolic acidosis was the most common disorder identified in ill dogs. The degree of change in pH varied depending on compensation and the presence of complex disorders, as shown by the results of this study. In fact, the pH value was within the reference interval in 48 dogs (45.7%) despite the presence of substantial acid–base disturbances. Thus, pH alone cannot be utilized to determine the severity and nature of an acid base disorder.

In the traditional approach, HCO_3^- or SBE quantify the metabolic component of acid–base balance; however, this approach has been criticized because HCO_3 is not independent of changes in the PCO_2.[49,50] For this reason, we opted to use the SBE to identify patients with metabolic acidosis in the present study regardless of concurrent pH, an approach that has been previously described.[51–53] Calculation of the AG can aid in determining the underlying cause of metabolic acidosis. In the traditional approach, AG is used as indirect evidence of increased unmeasured anions in patients with metabolic acidosis. Normal AG is largely a result of the charge on albumin, particularly in dogs.[35,54] Thus, AG may fail to detect increased concentrations of lactate or unmeasured anions, such as ketones, pyruvate, sulfate if

serum albumin concentration is low.[42,55] This finding has resulted in the proposal of adjusted equations in cases of hypoalbuminemia.[56–59] An interesting finding in the present study was that 21 patients were considered not to have any acid–base disturbance according to the values obtained for the pH, $PvCO_2$, SBE, and AG parameters. By calculating the adjusted AG (AG_{alb} or $AG_{alb\text{-}phos}$) enabled us to identify the presence of high AG acidosis in 78 hypoalbuminemic dogs. In contrast, when AG_{alb} or $AG_{alb\text{-}phos}$ was calculated, only 10 patients (9.5%) were considered free of any acid–base disturbance according to the traditional approach.

The quantitative approach has, in theory, advantages for the evaluation of critically ill dogs because it allows interpretation of acid–base equilibrium when electrolytes, albumin, or phosphorus concentrations are altered. The first variable in the quantitative approach, SID can change mainly due to variations in the free water content of plasma, changes in chloride concentration, and increases in the concentration of other strong anions. Therefore, the influence of SID on pH offers an understanding of clinical conditions such as dilutional acidosis, contraction alkalosis, hyperchloremic acidosis, hypochloremic alkalosis, and acidosis from unidentified anions (SIG).[55] However, in the clinical setting accurate measurements of SID are difficult to obtain in plasma samples because of the presence of unknown strong anions,[25] differences in equipment or methodology used to measure strong ion concentrations,[60] and different methods of calculation described in the literature.[42,61] Despite these limitations, assuming that in extracellular fluids Na^+ and Cl^- are the major strong ions present, SID may approximate the difference in concentrations between Na^+ and Cl^-. In body fluids, SID is on the order of +40 mmol/L (40 mEq/L)[62] and similar values for dogs have been reported in the veterinary literature.[35] In the present study, the mean values of SID for control animals were lower than previous published reference intervals, probably due to the chloride concentrations reported by the portable analyzer used in the study. However, no differences were found between control and hypoalbuminemic dogs.

The second variable in the quantitative approach, A_{tot}, is affected mainly by changes in plasma albumin and to a lesser degree by the phosphate or globulin concentrations.[35] The total concentration of plasma nonvolatile buffers and their effective dissociation constant (K_a) has been reported experimentally for canine plasma,[35] based on albumin or total protein concentration. In the present study, our control dogs had values close to the reference interval previously reported in the veterinary literature.[35] In the hypoalbuminemic patients, A_{tot} values were significantly different and proportionally lower according to the severity of hypoalbuminemia. Hypoproteinemic alkalosis is a common finding in human ICU patients.[58] However, in our study the number of patients with A_{tot} alkalosis was moderate (35; 33.3%) and many patients had A_{tot} values within the reference interval despite hypoalbuminemia. The presence of hyperglobulinemia associated with infectious, neoplastic, or immunomediated diseases in the patients included in study might have compensated for the expected alkalosis associated with the degree of hypoalbuminemia, especially in patients with kidney disease.[63] In people, there are some other formulas for A_{tot} calculation that include the phosphate effect, but in our study the impact of hyperphosphatemia in A_{tot}, could not be assessed. In the present study the A_{tot} determination allowed identification of metabolic alkalosis processes that otherwise had not been identified by the traditional approach (33.3% vs. 5.7%). Although the group with severe hypoalbuminemia showed the lowest A_{tot}, the mean pH value was the lowest in that group. This was probably due to the high percentage of patients with simultaneous SIG acidosis (27/33; 81.8%). Similar results have been described in people where hypoalbuminemia has been reported as common cause of alkalosis in critically ill patients with simultaneous SIG acidosis.[58,64]

The SIG determination provides an estimate for the difference between the unmeasured strong anion charge and unmeasured strong cation charge. Similar to SID, many different methods of calculation and consequently reference intervals have been reported in the literature.[35,65] In the present study SIG was calculated using an equation based on canine values for A_{tot} and K_a, and the values we found in control dogs were higher than the SIG range of −5.0 to 5.4 mEq/L reported by Constable et al.[35] A possible explanation for this finding could be related to the analyzer used in the study. According to the obtained values in the AG and SIG for control animals, the reference interval was much lower than other estimates by a similar amount.[14] Thus, each laboratory should establish its own reference interval for acid–base parameters based on the formula and the analyzers used. Nevertheless, nearly all of the hypoalbuminemic patients in our study showed SIG or adjusted AG values below or over the reference interval, respectively. As previously mentioned, albumin contributes most of the negative charge (A_{tot}) and the SIG calculation and adjusted AG calculations account for that contribution. The SIG and adjusted AG calculations more accurately estimate the unmeasured anion charge in animals with abnormal serum protein or phosphate concentrations than does the AG.[63] In our study, high correlations between SIG and AG_{alb} ($r = 0.93$, $P < 0.001$) or SIG and $AG_{alb\text{-}phos}$ ($r = 0.86$, $P < 0.001$) were documented but not between

SIG and AG ($r = 0.65$, $P < 0.001$). Similarly to the previously mentioned limitation about the A_{tot} formula, the SIG equation used in the study did not enable us to evaluate the impact of phosphate. This omission could explain the lower correlation encountered between the SIG and the $AG_{alb\text{-}phos}$. In accordance with other human studies,[55,66,67] if adjusted AG is used then the traditional method could perform at least as well as the quantitative approach in uncovering a hidden metabolic disorder.

The increased concentration of unidentified strong anions, such as lactate, ketoacids, pyruvate, citrate, acetate, urate, gluconate in plasma reflects the SIG acidosis.[68,69] This metabolic disorder has been reported in people associated with many life-threatening problems such as severe sepsis, diabetic ketoacidosis, and acute kidney failure, but its association with mortality remains controversial according to several recent publications.[70–72] Given the high incidence of this metabolic disturbance encountered in our study population further studies are warranted to document SIG's value as a predictor of morbidity and mortality in critically ill dogs.

Finally, there are some limitations in this study that should be mentioned. First, the patients included in the study were not stratified on admission to the ICU according to an injury severity scoring system. This could make it difficult to reproduce or compare our results with those of other studies. A second limitation relates to the point-of-care analyzer used in the study. Although the hand-held analyzer used in the study may not be as precise as bench top analyzers, it has been validated for use in dogs. Several studies have compared the accuracy of point of care analyzers with standard laboratory methods in people[73,74] and similar bias and precision were obtained in a population of healthy dogs.[75] Studies performed in hospital settings showed excellent correlation (≥90%) between methods for the studied acid–base parameters and electrolytes, except for the potassium.[76] The possible underestimation of the obtained values for the potassium did not affect the results of the SID and the metabolic disturbances associated with it. In people, falsely increased chloride results for blood samples with increased BUN have been reported with the hand-held analyzer used in our study,[77] but have not been documented in veterinary species. In the authors' opinion, a likely overestimation of chloride values could explain the reference interval produced and the values encountered in patients included in the study. A third limitation of the study relates to the L-lactate determination. This parameter was not included in the study because lactate could not be determined in all patients during their admission process in the ICU. In addition, the measurement of ketonemia using a portable ketometer could have been used to confirm the role of other nonroutinely measured strong anions, such as the ß-hydroxybutyrate in the acid–base status of DKA patients.[78,79]

In conclusion, the present study documented that the agreement between the traditional and quantitative methods of interpretation of acid–base balance was poor and that many imbalances detected using the quantitative approach would have been missed using the traditional approach to acid–base assessment. Moreover, these alterations varied according to the characteristics of the underlying disease. We conclude that by using the quantitative approach more rational treatments may be individually applied to patients with acid–base disturbances. Nevertheless, further studies are necessary to confirm the clinical utility of the quantitative approach in the decision-making process of the critically ill patients and the impact on outcome derived from this approach.

Footnotes

[a] Cobas Mira, Roche Diagnostics. Rotkreuz, Switzerland.
[b] Omnifix-F Duo, B. Braunn VetCare SA, Rubí, Barcelona, Spain.
[c] i-STAT Corporation, Abbott Laboratories, East Windsor, NJ.
[d] SAS 9.2, SAS Institute, Raleigh, NC.

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