

# Dependence of the apparent bicarbonate space on initial plasma bicarbonate concentration and carbon dioxide tension in neonatal calves with diarrhea, acidemia, and metabolic acidosis

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## Abstract

**Background:** Marked strong ion (metabolic) acidosis in neonatal diarrheic calves usually is corrected by IV administration of NaHCO<sub>3</sub>. The distribution space for IV-administered bicarbonate, called the apparent bicarbonate space (ABS), appears to depend on initial plasma bicarbonate concentration (cHCO<sub>3</sub>) and varies considerably in calves.

**Objective:** To determine whether ABS was associated with initial plasma cHCO<sub>3</sub> and other acid-base variables.

**Animals:** Twenty-five neonatal diarrheic calves with acidemia and metabolic acidosis.

**Methods:** Prospective observational study using a convenience sample. Calves received NaHCO<sub>3</sub> (10 mmol/kg) and glucose (1.4 mmol/kg) IV in a crystalloid solution at 25 mL/kg over 60 minutes. The ABS (L/kg) was calculated at 4 time points over 2 hours after the end of the infusion. The relationship between ABS and initial acid-base variables was characterized using nonlinear, linear, and stepwise regression.

**Results:** The median value for ABS calculated from the initial plasma cHCO<sub>3</sub> increased from 0.53 L/kg (range, 0.40-0.79) at the end of IV infusion to 0.96 L/kg (range, 0.54-1.23) 120 minutes later. Data obtained at the end of infusion provided the best fit to initial plasma cHCO<sub>3</sub> and jugular venous blood Pco<sub>2</sub>, such that: ABS = 0.41 + 1.06/cHCO<sub>3</sub> and ABS = 0.87-0.0082 × Pco<sub>2</sub>.

**Conclusions and Clinical Importance:** The observed median value for ABS of 0.53 L/kg in our study was similar to the empirically used value of 0.6. However, ABS values varied widely and were increased in calves with severe metabolic acidosis. We therefore recommend calculating ABS using the initial plasma cHCO<sub>3</sub> or venous blood Pco<sub>2</sub>, if respective measurements are available.

**Abbreviations:** (cHCO<sub>3</sub>)<sub>i</sub>, initial plasma bicarbonate concentration; (cHCO<sub>3</sub>)<sub>s</sub>, bicarbonate concentration of infusion solution; (cHCO<sub>3</sub>)<sub>t</sub>, plasma bicarbonate concentration at time t after infusion; ΔcHCO<sub>3</sub>, change in plasma bicarbonate concentration; A<sup>-</sup>-Alb, total net anion charge of nonvolatile weak acids calculated from plasma albumin concentrations; ABS, apparent bicarbonate space; ABS<sub>simplified</sub>, apparent bicarbonate space calculated using a simplified equation; AG, anion gap; A<sub>tot</sub>, concentration of nonvolatile weak acids; A<sub>tot</sub>-Alb, concentration of nonvolatile weak acids calculated from plasma albumin concentrations; A<sub>tot</sub>-TP, concentration of nonvolatile weak acids calculated from plasma total protein concentrations; A<sup>-</sup>-TP, total net anion charge of nonvolatile weak acids calculated from plasma total protein concentrations; cHCO<sub>3</sub>, plasma bicarbonate concentration; CI, confidence interval; DS, distribution space; Pco<sub>2</sub>, partial pressure of carbon dioxide; SG, strong ion gap; SID<sub>7</sub>, strong ion difference calculated from 7 strong cations and anions; TS, titration space; V<sub>i</sub>, apparent initial distribution volume for bicarbonate; V<sub>s</sub>, administered IV infusion volume; V<sub>t</sub>, distribution volume for bicarbonate at time t after the end of infusion.

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## KEYWORDS

acidemia, calves, d-lactate, sodium bicarbonate

## 1 | INTRODUCTION

Acidemia caused by strong ion (metabolic) acidosis frequently is observed in neonatal calves with diarrhea. Application of the simplified strong ion acid-base model indicates that metabolic acidosis is caused by a low SID as a result of hyponatraemia accompanied by normo- or hyper-chloroemia, or an increase in unmeasured strong anion concentration.<sup>1,2</sup> A nonvolatile buffer ion acidosis related to increases in serum protein concentration represents an additional but clinically less important mechanism for decreasing jugular venous pH in dehydrated neonatal calves with diarrhea.<sup>1</sup> Analyses of large datasets of diarrheic calves have shown that the unmeasured anion concentration (which can be quantified by calculating the anion gap [AG] or the strong ion gap [SG]) is the most important contributor to acidemia in neonatal diarrheic calves.<sup>1-3</sup> In this context, increased plasma concentration of D-lactate as a result of bacterial fermentation in the gastrointestinal tract also plays an important role<sup>2,4-6</sup> and is predominantly responsible for clinical signs that traditionally have been attributed to acidemia per se, such as changes of posture, behavior, and impairment of the palpebral reflex.<sup>7,8</sup>

Regardless of the cause of metabolic acidosis in calves with diarrhea and dehydration, IV or PO administration of sodium bicarbonate is the treatment of choice in affected animals.<sup>9-12</sup> A critical factor in determining the amount of sodium bicarbonate to administer is an accurate knowledge of the total bicarbonate deficit.<sup>10</sup> The mmol of sodium bicarbonate needed for IV correction of metabolic acidosis in neonatal calves traditionally has been calculated by multiplying the existing base deficit in mmol/L by body weight (BW) in kilogram and a factor of 0.5 to 0.6 that is thought to reflect the distribution space (DS) of sodium bicarbonate.<sup>11,13-18</sup> This factor is called the apparent bicarbonate space (ABS) and has units of L/kg of initial BW. The equation most commonly used in academic neonatal calves with metabolic acidosis to calculate the amount of bicarbonate to administer IV is therefore<sup>11</sup>:

$$\text{total bicarbonate deficit in mmol} = (\Delta \text{mmol/L}) \times (\text{BW in kg}) \times (0.5 \text{ or } 0.6) \quad (1)$$

A slightly higher value for ABS of 0.7 L/kg BW has been recommended for neonatal calves when IV fluids are administered over a 24 hour period<sup>19,20</sup> or when PO solutions containing sodium bicarbonate and metabolizable bases such as sodium propionate or acetate are administered to correct metabolic acidosis.<sup>21</sup> The value of 0.7 for PO fluids is consistent with an IV ABS value of 0.6 L/kg BW based on an assumed absorption efficiency of 85%-90% for PO-administered sodium salts in cattle.<sup>22</sup>

The value used for  $\Delta$ mmol/L in Equation (1) is the difference in bicarbonate concentration from the typical value for neonatal calves of 25 to 33 mmol/L<sup>2,23-25</sup> or the difference in base deficit from typical values of 1.8 to 11.6 mmol/L.<sup>24,25</sup> The base deficit corresponds to the

difference in plasma bicarbonate concentration ( $\text{cHCO}_3$ ) with some adjustment for buffering by plasma proteins and hemoglobin if in vitro base excess is calculated from the results of blood pH and gas analysis.<sup>26</sup> However, individual calves have sodium bicarbonate requirements above the calculated amount for correction of metabolic acidosis.<sup>9,19-21</sup> In general, the lower the initial plasma bicarbonate concentration ( $\text{cHCO}_3$ )<sub>i</sub> in diarrheic calves, the higher the true value for ABS appears, and this observation also has been reported in critically ill humans with metabolic acidosis<sup>27,28</sup> and dogs with experimentally induced metabolic acidosis.<sup>27,29</sup> Other studies in neonatal calves have identified large variability when retrospectively calculating ABS,<sup>19,20,30</sup> and a positive correlation between ABS and measured plasma D-lactate concentration has been reported.<sup>19</sup>

To the best of our knowledge, the value and determinants of the ABS have not been fully characterized in neonatal diarrheic calves. Consequently, our aims were to estimate the median value for ABS in neonatal diarrheic calves given sodium bicarbonate IV, and determine whether the value for ABS was associated with the initial plasma  $\text{cHCO}_3$  or related plasma constituents, such as blood  $\text{Pco}_2$  or pH, plasma SID, and the plasma concentration of nonvolatile buffers ( $A_{\text{tot}}$ ).

## 2 | MATERIALS AND METHODS

### 2.1 | Calves

Between November 2016 and March 2017, a prospective study was conducted involving 25 calves that were admitted to the Clinic for Ruminants with Ambulatory and Herd Health Services, Ludwig-Maximilians-Universität (LMU) Munich. Criteria for inclusion in this observational study were clinical diagnosis of neonatal diarrhea, age  $\leq 21$  days, and calculated in vitro base excess  $\leq -5$  mmol/L. Exclusion criteria were pretreatment with sodium bicarbonate-containing infusion solutions within 24 hours before hospitalization and severe concurrent health problems on admission including clinical signs of sepsis or central nervous system involvement, umbilical infections requiring surgical intervention, or clinical evidence of pneumonia. Written informed consent was obtained from the owners before inclusion in the study.

Because of regional preferences, 22 of the 25 calves belonged to the German Fleckvieh breed, the most common dairy breed in Bavaria. The mean age and BW of the calves were  $10.5 \pm 4.4$  days and  $43.9 \pm 6.9$  kg, respectively.

### 2.2 | Experimental protocol

Calves were weighed and an initial clinical examination was performed. The area over the right or left jugular vein was clipped,

antiseptically prepared, and 1 mL of a 2% procaine solution injected SC. A 16-gauge catheter (Cavafix Certo with Splittocan, B. Braun Melsungen AG, Melsungen, Germany) shortened to a length of 12 cm was placed in the jugular vein, secured in place with suture material and connected to a 13-cm elongation tube.

Calves received sodium bicarbonate IV at 10 mmol/kg BW. For this purpose, the respective volume of an 8.4% sodium bicarbonate solution (1000 mmol/L; B. Braun Melsungen AG) was diluted with the same volume of sterile water (Ampuwa, Fresenius Kabi GmbH, Germany) to produce a 500 mmol/L sodium bicarbonate solution; the volume of this solution administered to the calf was 20 mL/kg BW. A 5% glucose solution (B. Braun Melsungen AG) at a dosage of 5 mL/kg BW, corresponding to 0.25 g anhydrous glucose per kg BW, was added to the sodium bicarbonate solution to address presumed negative energy balance and potential hypoglycemia. This approach created a hypertonic infusion solution with a theoretical osmolarity of 856 mOsm/L (sodium bicarbonate, 400 mmol/L; anhydrous glucose, 56 mmol/L). The hypertonic sodium bicarbonate and glucose solution was administered IV at 25 mL/kg BW over 1 hour by means of an infusion pump (Volumat MC Agilia, Fresenius Kabi GmbH, Germany).

Lithium-heparinized blood samples were taken from the jugular vein catheter at baseline ( $T_{\text{initial}}$ ; immediately before start of infusion), and 0 minutes ( $T_0$ ), 30 minutes ( $T_{30}$ ), 60 minutes ( $T_{60}$ ), and 120 minutes ( $T_{120}$ ) after the end of the 1-hour infusion. The catheter was irrigated with heparinized saline (40 U heparin/mL) after administration of the hypertonic sodium bicarbonate and glucose solution and blood sampling.

After the end of the study period at time =  $T_{120}$ , calves were treated according to clinic protocols and received additional infusions based on their current acid-base and clinical dehydration status.

## 2.3 | Laboratory analysis

Lithium-heparinized blood samples were collected anaerobically using a 2-mL polypropylene syringe after removal of 3 mL of waste blood. Blood pH, partial pressure of carbon dioxide ( $P_{\text{CO}_2}$ ), sodium, chloride, potassium, and ionized calcium concentrations were measured using a blood gas and electrolyte analyzer (Rapidpoint 405, Siemens Healthcare Diagnostics Inc, Tarrytown, New York) with ion selective electrodes. Blood pH and  $P_{\text{CO}_2}$  were corrected for rectal temperature using standard algorithms.<sup>23</sup> After blood gas analysis, syringes were stored immediately at 4°C and centrifuged within 30 minutes after collection at 1500g for 10 minutes.

Harvested plasma samples were assayed for concentration of D-lactate (D-lactate dehydrogenase), L-lactate (lactate oxidase), total protein (biuret), albumin (bromocresol green), inorganic phosphorus (molybdenum), urea (urease), creatinine (picric acid), and total magnesium (xylydyl blue) by means of an automatic analyzer (Cobas c311, Roche Diagnostics, Mannheim, Germany).

## 2.4 | Calculations

Actual plasma  $\text{cHCO}_3^-$  was calculated automatically by the blood gas analyzer by the Henderson-Hasselbalch equation using measured blood pH and  $P_{\text{CO}_2}$  at 37°C:

$$\text{cHCO}_3^- = S \times P_{\text{CO}_2} \times 10^{(\text{pH} - \text{pK}_1')}. \quad (2)$$

Values used for the negative logarithm of the dissociation constant of carbonic acid ( $\text{pK}_1'$ ) and solubility of carbon dioxide (S) for plasma were 6.105 and 0.0307 mmol/L, respectively. After measuring the hemoglobin concentration (Hb in g/dL) photometrically, in vitro base excess was calculated automatically in mmol/L using the van Slyke equation<sup>31</sup> with measured blood pH at 37°C and the determined plasma  $\text{cHCO}_3^-$ :

$$\text{Base excess} = (1 - 0.014 \times \text{cHb}) \times [(\text{cHCO}_3^- - 24.8) + (1.43 \times \text{cHb} + 7.7) \times (\text{pH} - 7.4)]. \quad (3)$$

An estimate of the unmeasured anion concentration was obtained by calculating the AG, according to the equation:

$$\text{AG} = (\text{cNa}^+ + \text{cK}^+) - (\text{cCl}^- + \text{cHCO}_3^-). \quad (4)$$

Strong ion difference was obtained from 7 strong ions ( $\text{SID}_7$ ) using the measured value for  $\text{cCa}^{2+}$  determined by ion-selective potentiometry and assigning a charge +1.38 to magnesium assuming 69% dissociation<sup>32</sup> and assuming a charge of -1 for D-lactate and L-lactate based on 100% dissociation such that<sup>33</sup>:

$$\text{SID}_7 = \text{cNa}^+ + \text{cK}^+ + \text{cCa}^{2+} + \text{cMg}^{2+} - \text{cCl}^- - \text{cD} - \text{lactate}^- - \text{cL} - \text{lactate}^-. \quad (5)$$

The concentration of nonvolatile weak acids ( $A_{\text{tot}}$ ) in mmol/L was calculated from plasma concentrations of total protein (TP) and albumin (Alb)<sup>1</sup>:

$$A_{\text{tot}} - \text{TP} = 0.343 \times \text{c total protein}, \quad (6)$$

$$A_{\text{tot}} - \text{Alb} = 0.622 \times \text{c albumin}. \quad (7)$$

Based on these calculations, the net negative charge in mmol/L of nonvolatile weak acids ( $A^-$ ) was calculated as:

$$A^- - \text{TP} = A_{\text{tot}} - \text{TP} / \left(1 + 10^{(\text{pK}_a - \text{pH})}\right), \quad (8)$$

$$A^- - \text{Alb} = A_{\text{tot}} - \text{Alb} / \left(1 + 10^{(\text{pK}_a - \text{pH})}\right), \quad (9)$$

where  $\text{pK}_a$  (7.08) represents the experimentally determined value for the negative logarithm of dissociation constant of plasma nonvolatile weak acids in calf plasma.<sup>1</sup>

The SIG was calculated to obtain an estimate of the unmeasured strong anion concentration by means of the following equation<sup>1</sup>:

$$\text{SIG} = \text{A}^- - \text{TP} - \text{AG}. \quad (10)$$

The ABS (L/kg BW) was calculated by applying a mass balance equation that accounts for the effect of solution volume. The apparent initial distribution volume for bicarbonate ( $V_i$ ) has a measured ( $\text{cHCO}_3$ )<sub>i</sub> assuming plasma  $\text{cHCO}_3$  represents the bicarbonate concentration throughout the ABS. The infused hypertonic sodium bicarbonate and glucose solution has a known volume ( $V_s = 25 \text{ mL/kg BW}$ ) and solution bicarbonate concentration ( $\text{cHCO}_3$ )<sub>s</sub> = 400 mmol/L. The distribution volume for bicarbonate at time  $t$  after the end of infusion ( $V_t$ ) has a measured bicarbonate concentration ( $\text{cHCO}_3$ )<sub>t</sub>. On the assumption that bicarbonate and free water are not cleared from the ABS or added to the ABS during the investigated time interval, it can be assumed that:

$$V_t = V_i + V_s. \quad (11)$$

This assumption is reasonable when the infusion time is short and the time  $t$  of measurement after the end of infusion also is short.

Application of a mass balance equation based on the above assumptions indicates that the initial bicarbonate mass plus the infused bicarbonate mass equals the bicarbonate mass at time  $t$ , such that:

$$(\text{cHCO}_3)_i \times V_i + (\text{cHCO}_3)_s \times V_s = (\text{cHCO}_3)_t \times V_t. \quad (12)$$

Substitution for  $V_t$  from Equation (11) and algebraic rearrangement provides:

$$(\text{cHCO}_3)_i \times V_i - (\text{cHCO}_3)_t \times V_i = (\text{cHCO}_3)_t \times V_s - (\text{cHCO}_3)_s \times V_s. \quad (13)$$

Multiplication of both sides of Equation (13) by  $-1$  and further algebraic rearrangement provides:

$$[(\text{cHCO}_3)_t - (\text{cHCO}_3)_i] \times V_i = [(\text{cHCO}_3)_s - (\text{cHCO}_3)_t] \times V_s. \quad (14)$$

The components on the left-side of Equation (14) are equivalent to  $\Delta\text{cHCO}_3$  and ABS, respectively. Algebraic rearrangement of Equation (14) and indexing ABS to the initial BW of the calf produces the following equivalent equation, which should be regarded as the reference equation:

$$\text{ABS} = [(\text{cHCO}_3)_s - (\text{cHCO}_3)_t] \times V_s / [\Delta\text{cHCO}_3 \times \text{BW}]. \quad (15)$$

When  $(\text{cHCO}_3)_s \gg (\text{cHCO}_3)_t$ , Equation (15) is approximated by the following equation:

$$\text{ABS}_{\text{simplified}} \approx (\text{cHCO}_3)_s \times V_s / (\Delta\text{cHCO}_3 \times \text{BW}), \quad (16)$$

and because  $(\text{cHCO}_3)_s \times V_s$  in the numerator is the total amount of  $\text{HCO}_3$  administered, Equation (16) is equivalent to the following equation:

$$\text{ABS}_{\text{simplified}} \approx \text{Administered HCO}_3 / (\Delta\text{cHCO}_3 \times \text{BW}), \quad (17)$$

which is the equation commonly recommended to calculate ABS.<sup>28,34-36</sup> Values for ABS and  $\text{ABS}_{\text{simplified}}$  were calculated using Equations (15) and (17), respectively.

## 2.5 | Statistical analysis

Based on the results of a previous study on the ABS in children,<sup>28</sup> we expected to find a Spearman's correlation coefficient ( $r_s$ ) between  $(\text{cHCO}_3)_i$  and ABS of at least 0.6, which required 19 calves to be enrolled in the study to detect an  $r_s$  value that was significantly different from 0, based on an alpha of 0.05 and a study power of 0.8.

Statistical analyses were performed using SPSS for Windows (version 27.0, IBM); GraphPad Prism (version 7.01, Graphpad Software Inc, La Jolla, California); SAS 9.4 (SAS Inc, Cary, North Carolina), and MedCalc Statistical Software (version 19.1.3, MedCalc Software bvba, Ostend, Belgium, 2019). A  $P < .05$  was considered significant. Because most of the data was not normally distributed, as indicated by the Shapiro-Wilk test and visual examination of QQ-plots, data were reported as medians and corresponding minimum and maximum values. Associations among parameters were calculated using  $r_s$ . Passing-Bablok regression was used to evaluate the linear relationship between  $\text{ABS}_{\text{simplified}}$  and ABS (reference method). For Passing-Bablok regression, the intercept value reflects the constant error and the slope reflects the proportional error.

The relationship between ABS at time = 0, 30, 60, and 120 minutes after the end of infusion and the initial plasma  $\text{cHCO}_3$  was characterized using nonlinear regression to fit an inverse curvilinear equation, such that:

$$\text{ABS} = [\text{DS} + (\text{TS}/(\text{cHCO}_3)_i)] \times \text{BW}, \quad (18)$$

here DS approximates the extracellular fluid volume and TS indicates an abstract space where bicarbonate appears to be titrated by non-bicarbonate buffers.<sup>34</sup> Initial estimates for DS of 0.4 L/kg BW and TS of 2.5 L/kg BW were used based on studies fitting this inverse curvilinear equation to humans<sup>34</sup> and dogs.<sup>29</sup> The  $R^2$  value for the nonlinear regression equation was calculated as  $R^2 = 1 - \text{SS}_{(\text{Residual})} / \text{SS}_{(\text{Total corrected})}$ . The relationship between ABS at  $T_0$ ,  $T_{30}$ ,  $T_{60}$ , and  $T_{120}$  and the initial jugular venous blood  $\text{Pco}_2$  was characterized using linear regression, as were the relationships at  $T_0$  between ABS and the initial jugular venous blood pH and plasma SID and  $\text{A}_{\text{tot}}$  values. Forward stepwise regression using the variables that were significantly associated with ABS at  $T_0$  was used to identify independent predictors of ABS. Plasma  $\text{cHCO}_3$  was entered into separate stepwise regression procedures as  $\text{cHCO}_3$  or  $(1/\text{cHCO}_3)$ . A  $P < .05$  was used for variables to enter or exit the stepwise regression procedure.

## 3 | RESULTS

Median values and corresponding minimum and maximum values of selected laboratory parameters for calves on admission to the hospital are presented in Table 1. Median values (min – max) for  $\text{cHCO}_3$  at  $T_0$ ,

Variables	Median	Range	Reference values <sup>1, 12, 24, 37, 38</sup>
<b>Henderson-Hasselbalch model</b>			
Venous blood pH	7.00	6.58 to 7.26	[7.35 to 7.50]
Pco <sub>2</sub> (mm Hg)	38.6	26.9 to 56.7	[34 to 45]
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	9.9	3.8 to 22.6	[25 to 33]
Base excess (mmol/L)	-20.2	-36.3 to -5.1	[1.8 to 11.6]
AG (mmol/L)	29.1	18.4 to 36.9	[8.9 to 15.0]
<b>Simplified strong ion model</b>			
SID <sub>7</sub> (mmol/L)	31.3	13.9 to 45.4	n.a.
A <sub>tot</sub> -TP (mmol/L)	23.9	15.4 to 32.2	[20.2 to 24.0]
A <sub>tot</sub> -Alb (mmol/L)	15.9	13.3 to 26.7	[18.7 to 24.9]
A <sup>-</sup> -TP (mmol/L)	10.0	5.5 to 15.6	n.a.
A <sup>-</sup> -Alb (mmol/L)	7.0	3.9 to 12.1	n.a.
SIG (mmol/L)	-18.3	-29.2 to -6.3	[-3.0 to 3.0]
<b>Clinical biochemistry analysis</b>			
D-lactate (mmol/L)	11.3	0.1 to 16.7	[≤4.0]
L-lactate (mmol/L)	1.0	0.5 to 7.3	[≤2.2]
Phosphorus (mmol/L)	3.3	1.8 to 5.5	[2.0 to 3.5]
Total protein (g/L)	69.6	45.0 to 93.8	[59 to 70]
Albumin (g/L)	25.6	21.4 to 42.9	[30 to 40]
Urea (mmol/L)	14.0	5.5 to 36.9	[≤5.5]
Creatinine (μmol/L)	151.4	66 to 365	[110 to 180]
<b>Electrolytes</b>			
Na <sup>+</sup> (mmol/L)	140.1	124.2 to 159.4	[132 to 152]
K <sup>+</sup> (mmol/L)	5.18	3.29 to 7.27	[3.9 to 5.8]
Ionized Ca <sup>2+</sup> (mmol/L)	1.41	1.16 to 1.97	[1.0 to 1.3]
Total Mg <sup>2+</sup> (mmol/L)	0.99	0.79 to 1.72	[0.74 to 1.10]
Cl <sup>-</sup> (mmol/L)	106	91 to 128	[95 to 110]

Abbreviations: A<sup>-</sup>-Alb, total net anion charge of nonvolatile weak acids calculated from plasma albumin concentrations; AG, anion gap; A<sub>tot</sub>-Alb, concentration of nonvolatile weak acids calculated from plasma albumin concentrations; A<sub>tot</sub>-TP, concentration of nonvolatile weak acids calculated from plasma total protein concentrations; A<sup>-</sup>-TP, total net anion charge of nonvolatile weak acids calculated from plasma total protein concentrations; n.a., not available; Pco<sub>2</sub>, partial pressure of carbon dioxide; SID<sub>7</sub>, strong ion difference calculated from 7 strong cations and anions; SIG, strong ion gap.

T<sub>30</sub>, T<sub>60</sub>, and T<sub>120</sub> were 27.3 (16.0-44.6), 23.5 (13.5-40.4), 21.6 (13.3-42.0), and 19.9 (13.1-39.4) mmol/L, respectively. The resulting median values (min – max) for ABS calculated using Equation (15) at the same sampling times were 0.53 (0.40-0.79), 0.71 (0.48-1.00), 0.80 (0.46-1.09), and 0.96 (0.54-1.23) L/kg, respectively.

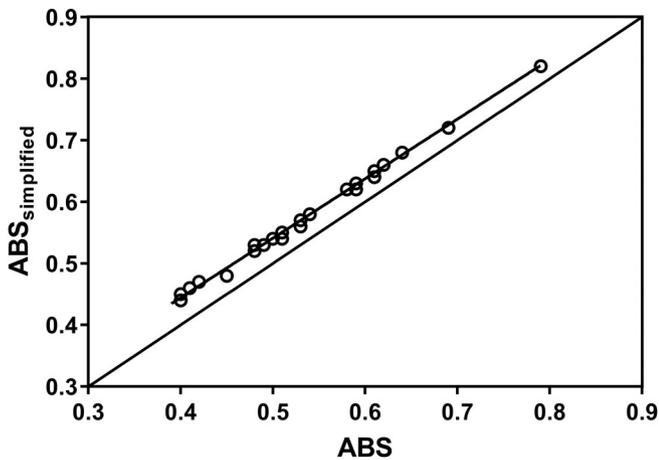
A scatterplot of the relationship between the ABS calculated using a simplified equation (ABS<sub>simplified</sub>; Equation 17) versus the ABS calculated using the recommended equation (Equation 15) in the 25 calves at the end of IV infusion (T<sub>0</sub>) is presented in Figure 1. Passing-Bablok regression indicated the presence of both proportional and systemic difference between the 2 values, such that ABS<sub>simplified</sub> = 0.058 + 0.967 × ABS. The 95% confidence interval (CI) for the intercept was 0.043 to 0.070. The 95% CI for the slope was 0.943 to 0.991. The calculated value for ABS<sub>simplified</sub> was 0.04 L/kg BW higher than the reference method of ABS (*P* < .001), based on a paired *t* test. This meant that the estimated value provided by

**TABLE 1** Acid-base variables and clinical biochemistry findings in 25 calves with diarrhea, acidemia and metabolic acidosis at initial examination

ABS<sub>simplified</sub> was approximately 8% higher than the true median value of 0.53 provided by ABS.

Scatterplots of initial bicarbonate concentration and observed values for ABS at 0, 30, 60, and 120 minutes after the end of infusion are presented in Figure 2. The resulting regression equations (ABS = DS + TS/(cHCO<sub>3</sub>)) for the inverse curvilinear relationship between ABS and (cHCO<sub>3</sub>) at 0, 30, 60, and 120 minutes after the end of infusion are presented in Table 2. The estimate for the intercept (approximating DS) was significantly (*P* < .001) different from 0 in all 4 equations and increased numerically from time = 0 to 120 minutes. The estimate for TS also was significantly (*P* < .001) >0 in all 4 equations, indicating that some of the bicarbonate appeared to be titrated by nonbicarbonate buffers.

The correlation (*r<sub>s</sub>*) between the calculated values for ABS at the 4 sampling times and initial acid-base and clinical biochemistry values on admission to the hospital are presented in Table 3. Of interest is

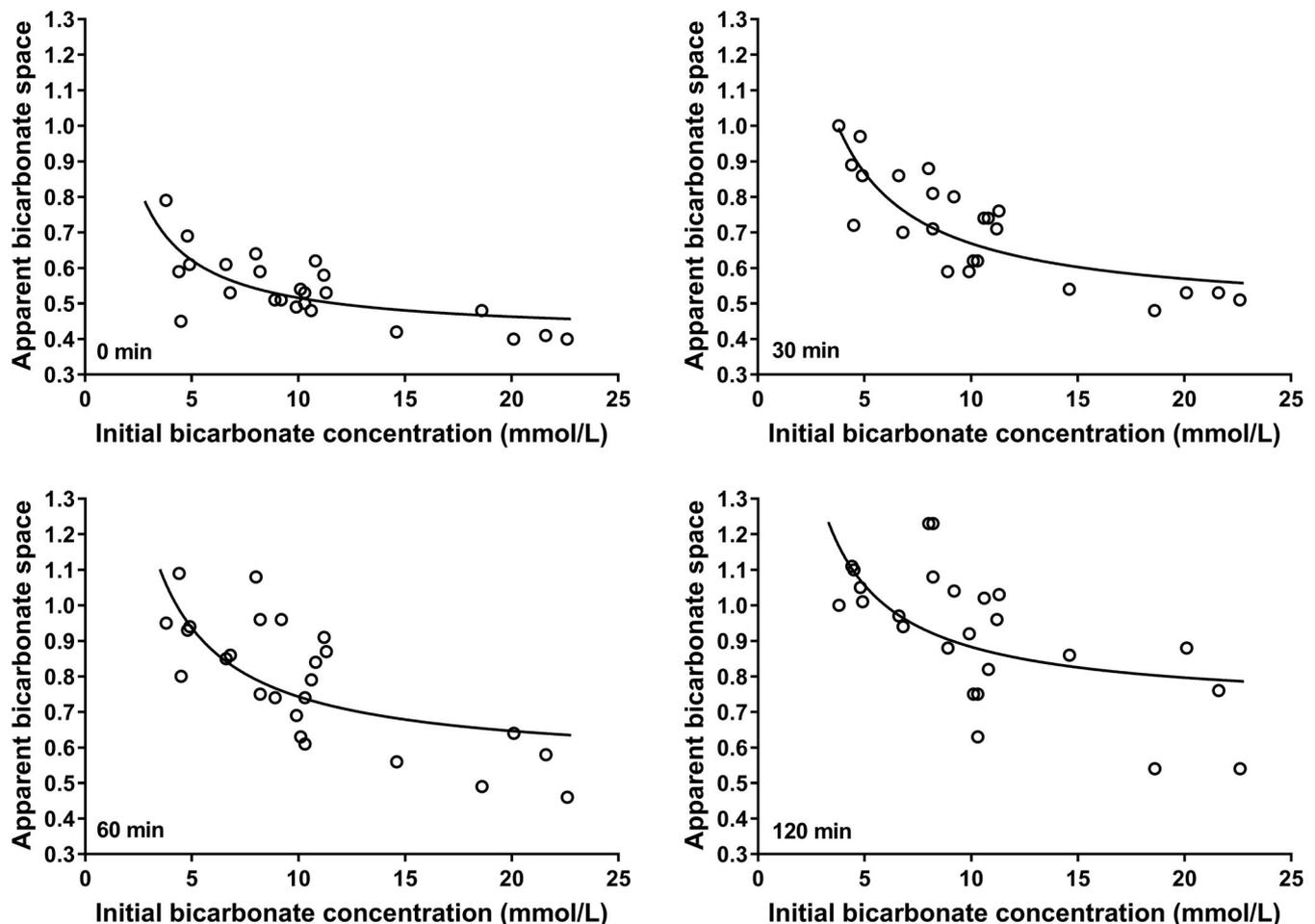


**FIGURE 1** Scatterplot of the relationship between the apparent bicarbonate space (ABS) calculated in L/kg BW using a simplified equation ( $ABS_{simplified}$ ) versus the ABS calculated using the recommended equation in 25 neonatal calves with diarrhea, acidemia, and metabolic acidosis and treated with an IV hypertonic sodium bicarbonate and glucose solution. Passing-Bablock regression indicated the presence of both proportional and systemic difference between the 2 spaces, such that  $ABS_{simplified} = 0.058 + 0.967 \times ABS$ . The calculated value for  $ABS_{simplified}$  was 0.04 L/kg BW higher than the reference method for calculating ABS ( $P < .001$ )

the finding that the ABS at  $T_0$  was most strongly correlated with jugular venous blood  $Pco_2$ , which was a proxy for the rate of alveolar ventilation. Median values (min – max) for  $Pco_2$  at  $T_0$ ,  $T_{30}$ ,  $T_{60}$ , and  $T_{120}$  were 46.6 (35.8–61.8), 46.2 (32.5–60.4), 46.1 (34.1–61.5), and 43.4 (32.3–59.9) mm Hg, respectively; these values all were higher than the initial median  $Pco_2$  of 38.6 mm Hg. Forward stepwise regression using the 11 variables that were significantly associated with ABS at  $T_0$  (Table 3) identified  $Pco_2$  as the only predictor of ABS, producing the same linear regression equation and  $R^2$  value as presented in Table 2. The relationship between ABS values at  $T_0$  and the initial jugular venous blood pH,  $Pco_2$ ,  $SID_7$ , and  $A_{tot}$  is illustrated by Figure 3.

## 4 | DISCUSSION

Our major findings were that the ABS value in neonatal calves with diarrhea and strong ion (metabolic) acidosis was impacted by the method of calculation, moderately associated ( $r_s = -0.67$ ) with the initial plasma  $chCO_3$ , and more strongly associated ( $r_s = -0.80$ ) with the initial  $Pco_2$ . Our findings provide a plausible explanation for the large variability of retrospectively determined estimates for ABS in previous studies of calves.<sup>16,19,20,30,39</sup>



**FIGURE 2** Relationship between the calculated apparent bicarbonate space (ABS, L/kg BW) and the initial plasma bicarbonate concentration in 25 neonatal calves with diarrhea, acidemia, and metabolic acidosis at 4 different times after the end of IV treatment. Calves received a hypertonic sodium bicarbonate and glucose solution that was administered over a period of 1 hour. Values for ABS were determined at 0, 30, 60, and 120 minutes after the end of the 1-hour infusion. Lines represent the results of nonlinear regression analysis

One form of Equation (17) was first used by Palmer and Van Slyke in 1917 in their study on the renal response to PO-administered sodium bicarbonate in humans, although they assumed that the apparent DS for bicarbonate was fixed.<sup>40</sup> Another study applied Equation (17) in 1972 to data from dogs given a hypertonic sodium bicarbonate solution (1000 mmol/L) at 7 to 10 mL/kg BW.<sup>35</sup> This study<sup>35</sup> appears to be the first to identify that the ABS was increased in animals with low plasma  $\text{cHCO}_3$ . Since 1972, Equation (17) has been the standard equation used to calculate ABS in several species, including dogs,<sup>27,29,41</sup> humans,<sup>28,34</sup> and calves.<sup>19,20,30</sup> The simplified method of calculation in Equation (17) results in minimal error when  $V_s$  is small relative to ABS, or when the concentration of the infused sodium bicarbonate solution is much higher than typical  $\text{cHCO}_3$ . In other words, Equation (17) is best used when small-volume hypertonic sodium bicarbonate solutions are administered, such as the 1000 mmol/L  $\text{NaHCO}_3$  solution used previously.<sup>35</sup> However, ABS also has been calculated using Equation (17) when large volume isotonic or slightly hypertonic sodium bicarbonate solutions are administered,<sup>19,20,27,30</sup> and these studies typically provide high estimates for ABS. It would therefore be of value to use Equation (15) that accounts for the effect of infusion volume, to recalculate estimates for ABS reported in previous studies<sup>19,20,27,30</sup> that calculated ABS using Equation (17).

We observed an inverse curvilinear association between ABS and the initial plasma  $\text{cHCO}_3$ , similar to all previous studies.<sup>27-29</sup> Based on theoretical considerations and data from human patients, the

following equation was developed to calculate the ABS in human patients based on the initial plasma  $\text{cHCO}_3$ <sup>34</sup>:

$$\text{ABS} = 0.4 + 2.6 / (\text{cHCO}_3)_i \quad (19)$$

This equation was similar to that obtained using nonlinear regression of data obtained at the end of infusion ( $T_0$ ) in our study:

$$\text{ABS} = 0.41 + 1.06 / (\text{cHCO}_3)_i \quad (20)$$

(Table 2) and to that in a previous study in dogs<sup>29</sup> that reported an intercept value of 0.36 and an inverse curvilinear coefficient of 2.44.

Several aspects need to be considered to explain the inverse curvilinear association between ABS and initial plasma  $\text{cHCO}_3$ . Physiologically, the ABS does not represent a true anatomical space because it has 2 components, an actual body fluid volume through which a fraction of administered bicarbonate is diluted (dilutional space), and an abstract volume (titration space [TS]) in which infused bicarbonate is titrated by nonbicarbonate buffers consisting of intracellular and extracellular proteins, phosphate ions, and hemoglobin.<sup>34</sup> In acidemic conditions, nonbicarbonate buffers exist in a highly protonated form, and it was formerly considered that a higher portion of administered sodium bicarbonate would be titrated by those buffers in animals with existing acidemia and metabolic acidosis, thereby explaining the larger value for ABS.<sup>27</sup> However, this hypothesis was questioned by a

**TABLE 2** Relationships between the apparent bicarbonate space (ABS) in L/kg BW at time = 0 ( $\text{ABS}_0$ ), 30 ( $\text{ABS}_{30}$ ), 60 ( $\text{ABS}_{60}$ ), and 120 ( $\text{ABS}_{120}$ ) minutes after the end of IV sodium bicarbonate infusion and initial jugular venous plasma bicarbonate concentration ( $\text{cHCO}_3$ )<sub>i</sub>, initial jugular venous blood carbon dioxide tension ( $\text{Pco}_2$ )<sub>i</sub>, and selected acid-base indices before IV administration of sodium bicarbonate in 25 neonatal calves

Variable	Intercept (95% CI or SE)	Slope (95% CI or SE)	R <sup>2</sup>	P value intercept	P value slope
Curvilinear inverse relationship between ABS and ( $\text{cHCO}_3$ ) <sub>i</sub>					
$\text{ABS}_0$	0.41 (0.35-0.48)	1.06 (0.58-1.54)	0.48	<.001	<.001
$\text{ABS}_{30}$	0.47 (0.39-0.55)	1.99 (1.37-2.61)	0.66	<.001	<.001
$\text{ABS}_{60}$	0.55 (0.43-0.68)	1.93 (1.02-2.85)	0.46	<.001	<.001
$\text{ABS}_{120}$	0.71 (0.53-0.82)	1.73 (0.65-2.82)	0.33	<.001	<.001
Linear relationship between ABS and ( $\text{Pco}_2$ ) <sub>i</sub>					
$\text{ABS}_0$	0.87 (0.06)	-0.0082 (0.0014)	0.61	<.001	<.001
$\text{ABS}_{30}$	1.21 (0.09)	-0.0125 (0.0023)	0.56	<.001	<.001
$\text{ABS}_{60}$	1.31 (0.12)	-0.0129 (0.0030)	0.44	<.001	<.001
$\text{ABS}_{120}$	1.30 (0.16)	-0.0094 (0.0039)	0.20	<.001	.02
Linear relationship between ABS and selected acid-base parameters at initial examination					
$\text{ABS}_0$ and (blood pH) <sub>i</sub>	2.63 (0.75)	-0.298 (0.108)	0.25	.002	.01
$\text{ABS}_0$ and plasma ( $\text{SID}_{7}$ ) <sub>i</sub>	0.81 (0.07)	-0.0087 (0.0021)	0.43	<.001	<.001
$\text{ABS}_0$ and base excess <sub>i</sub>	0.39 (0.04)	-0.007 (0.002)	0.39	<.001	.001
No relationship between ABS and selected acid-base parameters at initial examination					
$\text{ABS}_0$ and plasma ( $\text{A}_{\text{tot}}\text{-TP}$ ) <sub>i</sub>	0.59 (0.11)	-0.0021 (0.0048)	0.01	<.001	.66
$\text{ABS}_0$ and plasma ( $\text{A}_{\text{tot}}\text{-Alb}$ ) <sub>i</sub>	0.61 (0.11)	-0.0042 (0.0063)	0.02	<.001	.51

Abbreviations: ( $\text{A}_{\text{tot}}\text{-Alb}$ )<sub>i</sub> (mmol/L), initial plasma nonvolatile weak acid concentration calculated from the albumin concentration; ( $\text{A}_{\text{tot}}\text{-TP}$ )<sub>i</sub> (mmol/L), initial plasma nonvolatile weak acid concentration calculated from the total protein concentration; ( $\text{SID}_{7}$ )<sub>i</sub> (mmol/L), plasma strong ion difference calculated from 7 strong cations and anions.

**TABLE 3** Spearman correlation coefficients between the apparent bicarbonate space (ABS) calculated using Equation (15) at time = 0 (ABS<sub>0</sub>), 30 (ABS<sub>30</sub>), 60 (ABS<sub>60</sub>), and 120 (ABS<sub>120</sub>) minutes after the end of IV sodium bicarbonate infusion and the initial findings of acid-base status and clinical biochemistry analysis of jugular venous blood in 25 neonatal calves with diarrhea, acidemia, and metabolic acidosis

Variable	ABS <sub>0</sub>	ABS <sub>30</sub>	ABS <sub>60</sub>	ABS <sub>120</sub>
H-H acid-base model				
Venous blood pH	-0.51*	-0.72***	-0.64**	-0.65***
pCO <sub>2</sub>	-0.80***	-0.75***	-0.69***	-0.46*
HCO <sub>3</sub> <sup>-</sup>	-0.67***	-0.77***	-0.71***	-0.67***
Base excess	-0.58**	-0.73***	-0.68***	-0.70***
Anion gap	0.20 <sup>NS</sup>	0.22 <sup>NS</sup>	0.11 <sup>NS</sup>	0.30 <sup>NS</sup>
SID acid-base model				
SID <sub>7</sub>	-0.64**	-0.63**	-0.61**	-0.36 <sup>NS</sup>
A <sub>tot</sub> -TP	-0.04 <sup>NS</sup>	-0.01 <sup>NS</sup>	-0.15 <sup>NS</sup>	0.05 <sup>NS</sup>
A <sub>tot</sub> -Alb	-0.26 <sup>NS</sup>	-0.30 <sup>NS</sup>	-0.32 <sup>NS</sup>	-0.19 <sup>NS</sup>
A <sup>-</sup> -TP	-0.44*	-0.59**	-0.59**	-0.51*
A <sup>-</sup> -Alb	-0.40*	-0.59**	-0.52**	-0.52**
SIG	-0.40*	-0.44*	-0.36 <sup>NS</sup>	-0.48*
Clinical biochemistry analysis				
D-lactate	0.56**	0.52**	0.48*	0.42*
L-Lactate	-0.40*	-0.28 <sup>NS</sup>	-0.36 <sup>NS</sup>	-0.10 <sup>NS</sup>
Phosphorus	0.05 <sup>NS</sup>	0.04 <sup>NS</sup>	-0.05 <sup>NS</sup>	0.23 <sup>NS</sup>
Urea	-0.28 <sup>NS</sup>	-0.19 <sup>NS</sup>	-0.16 <sup>NS</sup>	-0.05 <sup>NS</sup>
Creatinine	-0.23 <sup>NS</sup>	-0.12 <sup>NS</sup>	-0.15 <sup>NS</sup>	0.01 <sup>NS</sup>
Electrolytes				
Na <sup>+</sup>	0.44*	0.57**	0.56**	0.46*
K <sup>+</sup>	-0.18 <sup>NS</sup>	-0.16 <sup>NS</sup>	-0.27 <sup>NS</sup>	-0.01 <sup>NS</sup>
Cl <sup>-</sup>	0.58**	0.71***	0.73***	0.58**

Abbreviation: NS, not significant.

\* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ .

subsequent study<sup>29</sup> that showed that the expansion of ABS was not a result of acidemia, but strictly dependent on a low plasma  $\text{HCO}_3^-$  per se. After experimentally inducing metabolic and respiratory acid-base imbalances in dogs, these investigators observed that the ABS decreased with acidemia caused by respiratory acidosis (low pH, high plasma  $\text{HCO}_3^-$ ), but increased under conditions of alkalemia caused by an existing respiratory alkalosis (high pH, low plasma  $\text{HCO}_3^-$ ). Also in agreement to other studies, metabolic acidosis resulted in an increase of the ABS, whereas metabolic alkalosis resulted in a decrease of the ABS.<sup>29</sup> These findings were explained by the bicarbonate buffering system being an open system that is impacted by the rate of alveolar ventilation.

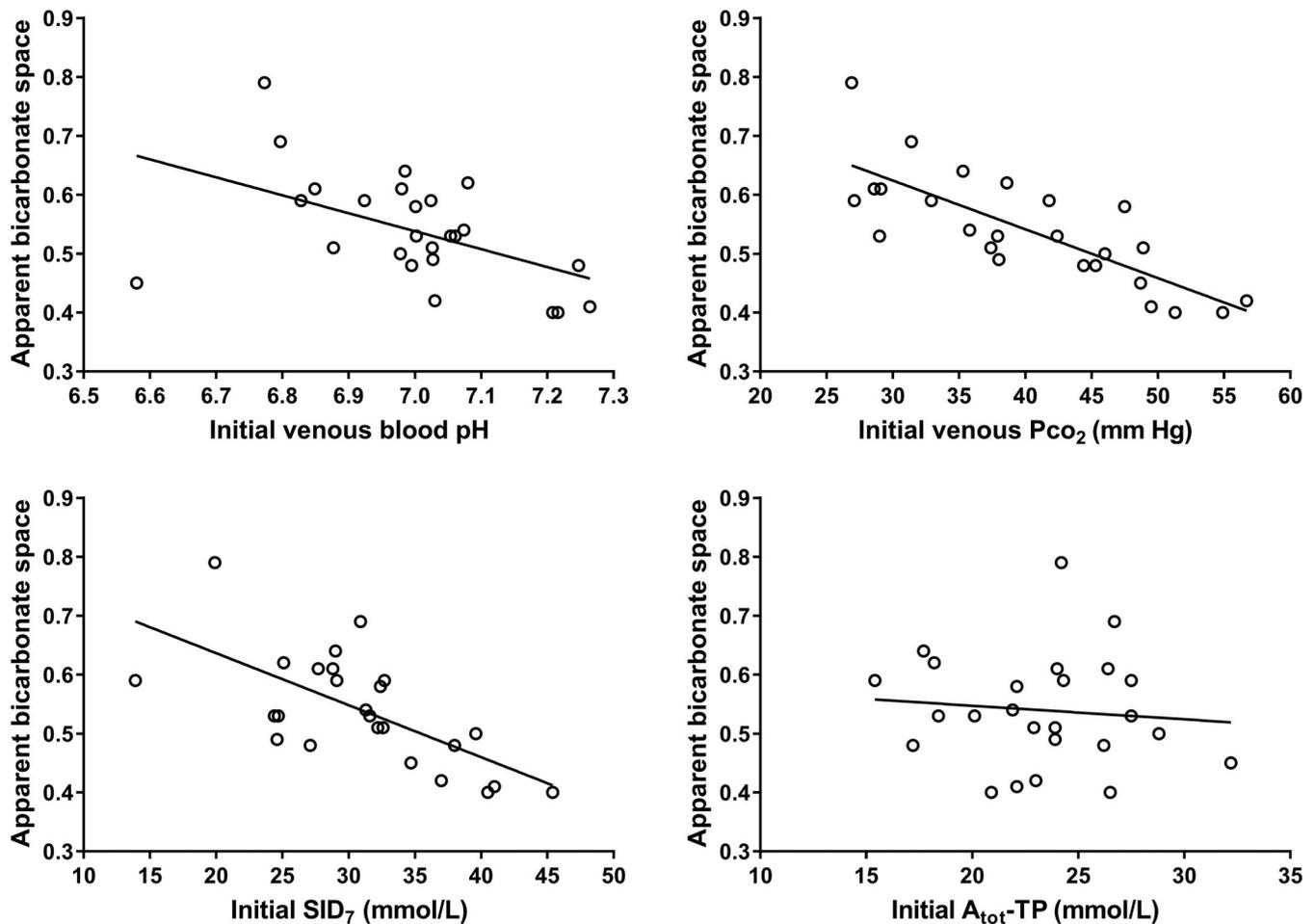
We observed a negative linear association between ABS and the initial jugular venous blood  $\text{Pco}_2$ . This negative linear relationship does not appear to have been previously reported. The following equation was obtained at the end of infusion ( $T_0$ ) in our study (Table 2):

$$\text{ABS} = 0.87 - 0.0082 \times (\text{Pco}_2)_i \quad (21)$$

Equation (21) had a higher  $R^2$  value (0.61) than did Equation (20) (0.48) at  $T_0$ , and stepwise regression identified that  $\text{Pco}_2$  was the only predictor of ABS at  $T_0$ , indicating that venous blood  $\text{Pco}_2$  was a stronger predictor of ABS calculated at the end of IV infusion than was plasma  $\text{HCO}_3^-$ . The latter finding suggests that the TS represents bicarbonate loss via respiratory exhalation of carbon dioxide as well as nonbicarbonate buffering.

Acid-base disturbances in acidemic neonatal calves with diarrhea and dehydration are typically a strong ion (metabolic) acidosis, nonvolatile buffer ion acidosis, and respiratory alkalosis or acidosis, depending on the magnitude of the acidemia and presence of concurrent respiratory disease,<sup>1-3</sup> similar to the calves in our study. Based on median values for  $\text{Pco}_2$  and  $\text{HCO}_3^-$  in healthy neonatal calves of 51 mm Hg and 33 mmol/L,<sup>24</sup> respectively, the value of  $\Delta\text{Pco}_2/\Delta\text{HCO}_3^-$  for calves on admission compared to healthy calves was 0.54 (12.4/23.1). A ratio  $<1$  for  $\Delta\text{Pco}_2/\Delta\text{HCO}_3^-$  suggests the presence of respiratory dysfunction,<sup>36</sup> despite respiratory abnormalities not being clinically detected in the calves on admission. Evidence of respiratory dysfunction remained during the 2-hour monitoring period after IV infusion of sodium bicarbonate, based on values for  $\Delta\text{Pco}_2/\Delta\text{HCO}_3^-$  at  $T_0$ ,  $T_{30}$ ,  $T_{60}$ , and  $T_{120}$  of 0.77, 0.51, 0.43, and 0.58, respectively. Because increased alveolar ventilation would be expected to increase the loss of infused bicarbonate because of proton buffering by bicarbonate producing  $\text{CO}_2$  that then is removed from the body during respiration, it is possible that the ABS could be slightly higher in calves without respiratory dysfunction than that observed in our study. However, measurement of  $\text{Pco}_2$  in venous blood is of limited value in assessing pulmonary function because of the extensive and variable effects of blood flow through capillary beds on venous blood gas tensions.<sup>12</sup> In addition, increased venous carbon dioxide tension in diarrheic calves was associated with indices of dehydration and hemoconcentration in previous studies.<sup>42,43</sup> It is therefore conceivable that ongoing dehydration because of the relatively small volume of administered infusion solutions in the calves of our study might have had an impact on the observed  $\text{Pco}_2$  values after administration of sodium bicarbonate. For those reasons, arterial blood gas analyses might be added in future studies to assess the potential impact of respiratory alterations on the ABS.

Similar to previous investigations,<sup>19,29</sup> we also observed an increase in the calculated value for ABS over time, as well as larger variability and poorer fit of the curve to the data when compared to previous sampling times (Figure 2). These findings might be related to infusion of the administered sodium bicarbonate dose over 1 hour instead of a shorter time period and the occurrence of resulting potential confounders at these sampling times such as ongoing bicarbonate loss via respiration, variable glomerular filtration rate, free water losses in feces or urine, and ongoing absorption of D-lactate from the gastrointestinal tract. Therefore, the infusion time should be kept as short as possible, and blood sampling should occur as close to the end of infusion as possible when estimating ABS. Doing so is important because of the assumptions that free water and



**FIGURE 3** Relationship between the calculated apparent bicarbonate space (ABS, L/kg BW) and the initial jugular venous blood pH,  $P_{CO_2}$ , plasma strong ion difference ( $SID_7$ ), and plasma total concentration of nonvolatile buffers ( $A_{tot}$ ) calculated from the total protein concentration in 25 neonatal calves with diarrhea, acidemia, and metabolic acidosis. Calves received a hypertonic sodium bicarbonate and glucose solution that was administered over a period of 1 hour. Values for ABS were determined immediately after the end of the 1-hour infusion. Lines represent the results of linear regression analysis

bicarbonate are neither added to nor removed from ABS during the study period, except for free water and bicarbonate contained in the IV fluid administered. The significant increase in ABS with time after the end of infusion most likely represents the removal of bicarbonate from the ABS by respiration as  $CO_2$  or that buffered by protons and is further confounded by the potential for increased free water losses or ongoing production of protons.

The  $ABS_{simplified}$  was estimated to be 0.40 L/kg BW when isotonic sodium bicarbonate solution was infused IV in 1-month old calves in low infusion volumes of 288 to 863 mL (5, 10, and 15 mL/kg BW) over 30 minutes.<sup>39</sup> Much higher estimates for  $ABS_{simplified}$  of 0.73 and 0.78 L/kg BW in euvolemic healthy calves given isotonic solutions of sodium bicarbonate over 3.5 hours<sup>30</sup> likely are overestimates because of the low solution osmolarity (150 mmol/L) relative to a typical  $cHCO_3$  of 33 mmol/L, the large infusion volume of 2659 mL, and the long infusion time, resulting in clearance of infused bicarbonate via respiration or urinary excretion.<sup>30</sup> Similarly, a mean estimate for  $ABS_{simplified}$  of 0.63 L/kg BW in dehydrated diarrheic calves given

isotonic or slightly hypertonic solutions of sodium bicarbonate over 3.5 hours<sup>19</sup> also is likely an overestimate because of the large infusion volume of 2500 mL, and the long infusion time, resulting in clearance of infused bicarbonate via respiration. In addition, this study<sup>19</sup> used blood samples obtained 30 minutes after the end of infusion, which has been associated with an increased estimate for  $ABS_{simplified}$ , as demonstrated in our study, as well as another study.<sup>29</sup> Consequently, recommended values of 0.7 to 0.8 in Equation (1) for calculating sodium bicarbonate requirements for IV correction of acidosis in neonatal calves over a 24-hour period should be regarded as dosage factors<sup>19</sup> that only partly reflect the ABS when large infusion volumes are administered.

A limitation of our study was that it only included 25 calves and consequently our findings should be confirmed in a larger study population. A more rapid infusion of sodium bicarbonate probably would have resulted in more accurate results because bicarbonate distribution into the extracellular space is rapid, being complete within 15 minutes.<sup>44</sup>

## 5 | CONCLUSIONS

Our results indicated that the ABS in neonatal diarrheic calves with marked acidemia (mean jugular venous pH, 7.00), low mean  $\text{cHCO}_3$  (9.9 mmol/L), and large base deficit (20.2 mmol/L) had a median value of 0.53 L/kg BW, but ABS was dependent on the initial plasma  $\text{cHCO}_3$  and jugular venous blood  $\text{Pco}_2$ . If values for  $\text{cHCO}_3$  and  $\text{Pco}_2$  are available, sodium bicarbonate requirements in neonatal calves with diarrhea should be calculated using Equation (20) or Equation (21). Based on these equations, values for the ABS of 0.68, 0.59, 0.52, and 0.46 L/kg should be used in diarrheic calves with a plasma  $\text{cHCO}_3$  of 4, 6, 10, and 20 mmol/L, respectively. Alternatively, ABS values of 0.62, 0.54, 0.46, and 0.38 L/kg should be used in diarrheic calves with a jugular venous blood  $\text{Pco}_2$  of 30, 40, 50, and 60 mm Hg, respectively.

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### CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

### INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Ethics committee of the Centre of Veterinary Clinical Medicine, LMU Munich (permit no. 79-12-08-2016).

### HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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