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Correction of serum chloride concentration in dogs with congestive heart failure

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Abstract

Background: Hypochloremia associated with congestive heart failure (CHF) in dogs is likely multifactorial. Loop diuretics cause 1:2 sodium [Na^+]:chloride [Cl^-] loss, whereas water retention causes a 1:1 [Na^+]:[Cl^-] dilution. Mathematical [Cl^-] correction separates these effects on [Cl^-].

Hypothesis: We hypothesized that corrected [Cl^-] (c[Cl^-]) would not differ from measured [Cl^-] (m[Cl^-]) in dogs with controlled CHF because of loop diuretics, and dogs with refractory CHF would have higher c[Cl^-] than m[Cl^-], indicating relative water excess.

Animals: Seventy-one client-owned dogs with acquired heart disease, without CHF (NO-CHF), 76 with Stage C CHF and 24 with Stage D CHF.

Methods: Clinicopathological data from a previous study were retrospectively analyzed. Corrected [Cl^-], m[Cl^-], and differences were compared among NO-CHF, Stage C CHF, and Stage D CHF, using the formula: c[Cl^-] = (mid-reference range [Na^+]/measured [Na^+]) × m[Cl^-].

Results: Corrected [Cl^-] and m[Cl^-] were lower in Stage D vs Stage C and NO-CHF (all $P < .0001$). The c[Cl^-] was higher than m[Cl^-] in Stage D ($P < .0001$) but not Stage C or NO-CHF. Median difference between c[Cl^-] and m[Cl^-] was higher for Stage D vs Stage C ($P = .0003$). No hypochloremic Stage D dogs had normal c[Cl^-], but 11/24 had [Cl^-] that was increased by >2 mmol/L.

Conclusions and Clinical Importance: Serum [Cl^-] increased after mathematical correction in Stage D CHF dogs but not in Stage C and NO-CHF dogs. Although c[Cl^-] was higher than m[Cl^-] in Stage D dogs supportive of relative water excess, hypochloremia persisted, consistent with concurrent loop diuretic effects on electrolytes. Future study correlating c[Cl^-] to antidiuretic hormone concentrations is warranted.

Abbreviations: [Na^+], sodium concentration; ACVIM, American College of Veterinary Medicine; ADH, antidiuretic hormone; c[Cl^-], corrected chloride concentration; CHF, congestive heart failure; m[Cl^-], measured chloride concentration.

KEYWORDS
antidiuretic hormone, hypochloremia, sodium

1 | INTRODUCTION

Chloride is the most abundant extracellular anion in the body and balance is closely regulated by the kidneys.[1,2] By filtration and resorption, the kidneys conserve or excrete chloride as an adaptation to alkalosis or acidosis, respectively.[3] Because chloride is a major contributor to strong ion difference, chloride concentration [Cl^-] in the blood can be useful for interpretation of acid-base disorders in veterinary medicine.[2-5] Concentration results represent the amount of molecule dissolved in fluid, and so accurate interpretation of serum sodium [Na^+] and [Cl^-] requires assessment of vascular water (volume) and water regulation by antidiuretic hormone (ADH).[4,6] Clinical assessment of plasma water has been investigated using electrolyte-free water clearance calculation, plasma and urine osmolality ratios, hematocrit and hemoglobin ratios, indicator dilution methods, and indirectly by ADH measurement.[7-10]

Correction of serum [Cl^-] for serum [Na^+] is a simple clinical calculation that can determine the dilutional effect of water on [Cl^-].[4,11,12] Plasma water retention or excretion has diluting or concentrating effects on [Cl^-] and [Na^+] in a 1:1 relationship, respectively. Therefore, correction of chloride abnormalities into the reference interval indicates the relative effect of deficient or excessive water in the body.[4,11,12] Loop diuretics are a common reason for persistent hypochloremia, even after correction for [Na^+] ("corrected hypochloremia"), and their use usually is associated with metabolic alkalosis because of the strong ion difference resulting from chloride loss.[3,4] Other less common and readily apparent causes of corrected hypochloremia include severe vomiting causing loss of HCl, sodium bicarbonate administration, and fluid overload.[13]

Low serum [Cl^-] (<103.5 mmol/L) is a sensitive and specific differentiator of refractory (American College of Veterinary Medicine [ACVIM] Stage D) congestive heart failure (CHF) from controlled (ACVIM Stage C) CHF in dogs.[14] Additionally, hypochloremia is associated with presumed diuretic resistance in dogs and people with refractory CHF, and may contribute to cardiorenal syndrome.[14-17] Unbalanced loop diuretic-induced electrolyte depletion (as a result of urinary chloride loss twice that of sodium when the $Na^+/K^+/2Cl^-$ cotransporter in the ascending loop of Henle is inhibited) and nonosmotic ADH release causing electrolyte dilution are both potential contributors to CHF-associated hypochloremia and hyponatremia.[14,18] Serum [Cl^-] correction may provide information about relative water excess in dogs with CHF by indicating if hypochloremia is a result of loop diuretic-induced loss, dilution, or a combination of both mechanisms. This knowledge could lead to treatments addressing nonosmotic ADH effects in patients with corrected normochloremia (when low [Cl^-] increases into the reference range after mathematical correction) or in those experiencing increases in [Cl^-] after mathematical correction. Added knowledge about patient-specific pathophysiology in refractory CHF is needed because prognosis is poor and treatment is not clearly understood in this group of dogs.[19,20]

We sought to determine if mathematically corrected serum [Cl^-] (c[Cl^-]) differs from measured serum [Cl^-] (m[Cl^-]) in dogs with CHF. We hypothesized that mathematically corrected serum [Cl^-] would not deviate significantly from m[Cl^-] in most dogs with controlled CHF because of the effect of loop diuretics, but that dogs with refractory CHF would have higher c[Cl^-] than m[Cl^-], indicating relative water excess.

2 | METHODS

The clinicopathological data utilized for this retrospective study were obtained from a previously published study that compared renal function, electrolyte concentrations, indices of diuretic efficacy, and the renin-angiotensin-aldosterone system in 171 dogs of different heart disease stages.[14] The study was approved by the Institutional Animal Care and Use Committee at North Carolina State University Veterinary Hospital, and owner consent was obtained.

Recruitment and inclusion of dogs has been described previously.[14] Dogs with acquired heart disease, but without clinical or radiographic evidence of CHF (NO-CHF group), and without clinically relevant extra-cardiac diseases served as controls for comparison to ACVIM Stage C and Stage D CHF dogs because they were in a preclinical disease state and had not received diuretics. Dogs with NO-CHF were those that were staged as B1 or B2 by the ACVIM Heart Disease Staging Guidelines.[19] Dogs with CHF were those that were staged as C (controlled CHF) or D (refractory CHF) by the ACVIM Heart Disease Staging Guidelines in conjunction with a relevant publication as previously described.[14,19,20] Dogs with CHF were treated as stable outpatients, received only PO medications, and were free of clinically relevant extra-cardiac disease. Dogs that required hospitalization and parenteral diuretics to treat CHF were excluded. Serum [Na^+] and serum [Cl^-] were measured as previously described,[14] using an automated analyzer (Roche Cobas C501, Indianapolis, Indiana) at the clinical pathology laboratory of North Carolina State University Veterinary Hospital. The serum [Na^+] reference range for this analyzer is 140 to 156 mmol/L and the mid-point value is 148 mmol/L. The serum [Cl^-] reference range for this analyzer is 108 to 122 mmol/L. Measured serum [Cl^-] and [Na^+] were recorded for each dog. The c[Cl^-] was calculated using the formula: $c[Cl^-]^- = (\text{mid-reference range } [Na^+]/\text{measured } [Na^+]) \times m[Cl^-]$. The difference between m[Cl^-] and c[Cl^-] was calculated for each dog.

Statistical analysis was performed using commercially available software (GraphPad Prism 8, San Diego, California). The c[Cl^-], m[Cl^-], and the difference between these 2 values were compared among NO-CHF, Stage C, and Stage D dogs. Data were assessed for

normality using the Shapiro-Wilks test. Comparisons between paired data (m[Cl^-] and c[Cl^-]) were performed using 2-tailed, paired *t* test for normally distributed data and Wilcoxon signed-rank test for non-normally distributed data. Comparisons among groups were performed using 1-way analysis of variance if normally distributed and a Kruskall-Wallis test if not normally distributed. Fisher's exact test was used to compare the proportion of dogs with any increase in serum [Cl^-] after correction between Stage C and Stage D dogs and to compare the proportion of dogs with >2 mmol/L increase in serum [Cl^-] after correction between Stage C and Stage D dogs. The use of 2 mmol/L as a cutoff was chosen because 2.2 mmol/L was the 90th percentile value for NO-CHF dogs and 2 mEq/L (equivalent to 2 mmol/L) has been reported as the mean difference between m[Cl^-] and c[Cl^-] in healthy dogs.[11] The NO-CHF group was not included in these comparisons because dogs in this group did not receive loop diuretics and would not be clinically evaluated for diuretic resistance. Statistical significance was set at $P < .05$.

3 | RESULTS

Seventy-one ACVIM Stage B1 or B2 dogs without CHF (NO-CHF) dogs, 76 dogs with controlled CHF (ACVIM Stage C) and 24 dogs with refractory CHF (ACVIM Stage D) were included. The clinical details of these patients have been reported previously.[14]

Both m[Cl^-] and c[Cl^-] were significantly lower in Stage C and Stage D dogs compared with NO-CHF dogs, and in Stage D dogs compared with Stage C dogs ($P < .0001$ all comparisons; Table 1; Figure 1). Serum [Na^+] was significantly lower in Stage D dogs compared to Stage C dogs and compared to NO-CHF dogs ($P < .0001$ and .0004, respectively). The c[Cl^-] was higher than m[Cl^-] in Stage D dogs ($P < .0001$), but not in NO-CHF dogs ($P = .2$) or Stage C dogs ($P = .7$). Although mean [Cl^-] was within the reference range for NO-CHF dogs, 28/71 dogs (39%) in this group had mild hypochloremia. Mean [Cl^-] for Stage C and Stage D dogs was below the reference range with 43/76 Stage C dogs (56%) and 24/24 Stage D dogs (100%) having hypochloremia.

Median (95% confidence interval [95% CI]) difference between c[Cl^-] and m[Cl^-] was 1.4 mmol/L (95% CI, 1.2 to 3.8) with a range of −0.7 to 14.1 mmol/L for Stage D dogs which was significantly higher than that of Stage C dogs (median, 0.0; 95% CI, −0.3 to 0.6; range, −4.2 to 5.6 mmol/L; $P = .0003$; Figure 2).

After calculation of c[Cl^-], no hypochloremic Stage D dogs became normochloremic (serum [Cl^-] reference range, 108-122 mmol/L) despite some results that substantially increased after correction (Figure 3). Most Stage D dogs (22/24; 92%) had a positive change (increase) in [Cl^-] after mathematical correction and 11/24 (46%) Stage D dogs had c[Cl^-] that was >2 mmol/L higher than m[Cl^-] (Figure 3). Thirty-one Stage C dogs (41%) had a positive change (increase) in [Cl^-] after mathematical correction and 13/76 (17%) of Stage C dogs had c[Cl^-] that was >2 mmol/L higher than m[Cl^-] (Figure 3). The proportion of dogs with an increase in [Cl^-] after correction was significantly higher for Stage D dogs, compared to Stage C dogs ($P < .0001$). The proportion of dogs with >2 mmol/L increase in [Cl^-] after mathematical correction also was significantly higher for Stage D dogs, compared to Stage C dogs ($P = .007$).

4 | DISCUSSION

The most important finding of our study is that the degree of [Cl^-] correction (the difference between c[Cl^-] and m[Cl^-]) was higher for Stage D dogs compared to Stage C dogs. Although no Stage D dogs fully corrected into the reference range (ie, dogs that were measured to be hypochloremic did not become normochloremic according to the reference range after mathematical correction), Stage D dogs as a

TABLE 1 Measured serum sodium (m[Na^+]) serum chloride (m[Cl^-]), corrected serum chloride (c[Cl^-]) and the difference between c[Cl^-] and m[Cl^-] for NO-CHF dogs, Stage C dogs, and Stage D dogs

		m[Na] (mmol/L)	m[Cl^-] (mmol/L)	c[Cl^-] (mmol/L)	Difference between c[Cl^-] and m[Cl^-]	*P* value
NO-CHF (71 dogs)	Mean (SD)	147.7 (±2.2)	109.0 (± 2.6)	109.3 (± 2.5)	0.24 (±1.6)	.2
	Median (IQR)	147.0 (147.0-149.0)	109.0 (104.0-111.0)	109.0 (104.0-110.7)	0.71 (−0.7 to 0.8)	
Stage C (76 dogs)	Mean (SD)	147.8 (±2.8)	106.1 (±4.1)	106.2 (±3.5)	0.14 (±2.0)	.7
	Median (IQR)	148.0 (146.0-150.0)	106.0 (104.0-109.0)	106.2 (103.9-108.7)	0.0 (−1.4 to 1.5)	
Stage D (24 dogs)	Mean (SD)	144.4 (±4.6)	100.6 (±4.6)	103.1 (±2.4)	2.5 (±3.1)	<.0001
	Median (IQR)	146.0 (143.3-147.0)	102.0 (99.3-103.0)	102.7 (101.4-105.1)	1.4 (0.7-3.3)	
P value	NO-CHF vs Stage C	1.0	<.0001	<.0001	1.0	
	NO-CHF vs Stage D	.0004	<.0001	<.0001	.003	
	Stage C vs Stage D	<.0001	<.0001	<.0001	.0005	

Notes: Mean and standard deviation as well as median and interquartile ranges (IQR) are shown. *P* values are shown for comparisons between m[Cl^-] and c[Cl^-] for each group of dogs in the right column. Adjusted *P* values are shown for comparisons between groups for m[Na^+], m[Cl^-], c[Cl^-], and the difference between c[Cl^-] and m[Cl^-] in the bottom row. Serum [Cl^-] reference range is 108 to 122 mmol/L and serum [Na^+] reference range is 140 to 156 mmol/L.

Abbreviations: c[Cl^-], corrected chloride concentration; m[Cl^-], measured chloride concentration; m[Na^+], measured sodium concentration.

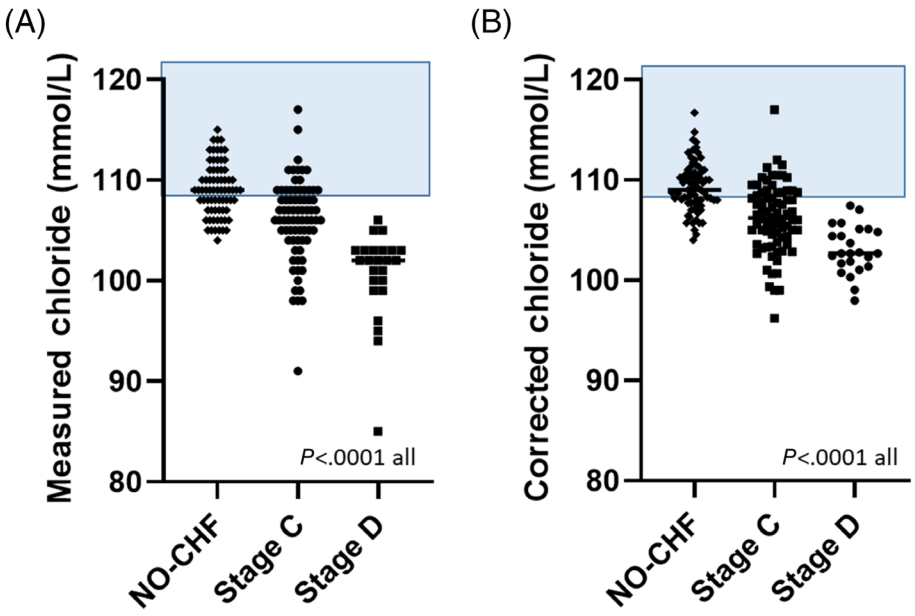

FIGURE 1 Scatterplot of individual data points with the central line representing the mean value. The shaded box is the reference range. A, Measured chloride (m[Cl^-]) in 71 NO-CHF dogs, 76 Stage C dogs, and 24 Stage D dogs. B, Corrected chloride (c[Cl^-]) in 71 NO-CHF dogs, 76 Stage C dogs, and 24 Stage D dogs

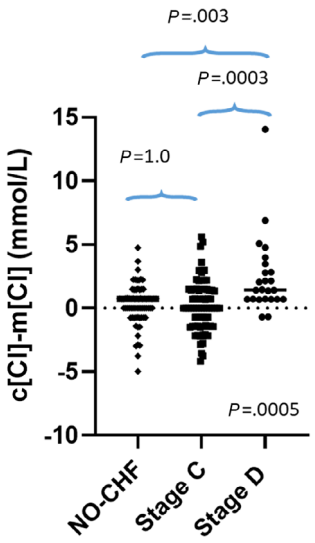

FIGURE 2 Scatterplot of individual data points depicting the difference between measured and corrected serum chloride (c[Cl^-]-m[Cl^-]) in 71 NO-CHF dogs, 76 Stage C dogs, and 24 Stage D dogs, with the central line representing the median value

whole (and some individuals more than others) showed notable increases in serum [Cl^-] after correction. In fact, the majority (92%) of Stage D dogs had some degree of increase in [Cl^-] after correction and nearly half had >2 mmol/L increase in [Cl^-]. The act of mathematical [Cl^-] correction removes the dilutional influence of intravascular volume expansion (relative water excess) on hypochloremia when c[Cl^-] is found to be higher than m[Cl^-], and likewise removes the influence of intravascular volume contraction (relative water deficit) when c[Cl^-] is found to be lower than m[Cl^-]). Therefore, a positive difference between c[Cl^-] and m[Cl^-] signals relative water excess, and the magnitude of this correction could represent the degree, although this conclusion requires further study. No hypochloremic Stage D CHF dogs became normochloremic after mathematical correction of [Cl^-] (ie, no dogs had corrected normochloremia), which can be explained by the coexistent action of loop diuretics being administered to all CHF dogs. Some Stage D dogs, therefore, appeared to have a mixed effect of loop diuresis and relative water excess, as evidenced by an increase in c[Cl^-] when compared to m[Cl^-] without reaching the reference range. Although less than observed in Stage D dogs, 41% of Stage C dogs also had increases in serum [Cl^-] after correction. This finding could indicate that some of these dogs with clinically controlled CHF also had relative water excess. This overlap may reflect the difficulty in separation of Stage C and Stage D dogs by current definitions and the influence of ADH even in dogs that appear to have clinically controlled CHF.

Interestingly, our study showed that 39% of dogs with heart disease but without CHF and not receiving diuretics were mildly hypochloremic. These dogs were without apparent clinically relevant extracardiac diseases that would predispose to hypochloremia. This finding is similar to previous reports of dogs with preclinical mitral valve disease.[21,22] Some dogs with advanced heart disease but without CHF may have had neurohormonal activation that resulted in different effects on serum electrolyte concentrations as a result of the complex interplay among angiotensin, aldosterone, and ADH.[23-25]

Correction of serum [Cl^-] for [Na^+] in our study did not alter the previously reported conclusion that hypochloremia is associated with Stage D (refractory) CHF in dogs, which is consistent with the strong effect of loop diuretics on serum electrolyte concentrations in this group of dogs.[14] The rationale for correcting serum [Cl^-] for normal [Na^+] is based on the premise that equal changes in sodium and chloride indicate extracellular intravascular dilution or contraction as a result of relative water changes, whereas unequal changes in these electrolytes indicate loss or gain through active mechanisms.[4] The most common active mechanism for unequal loss of sodium and

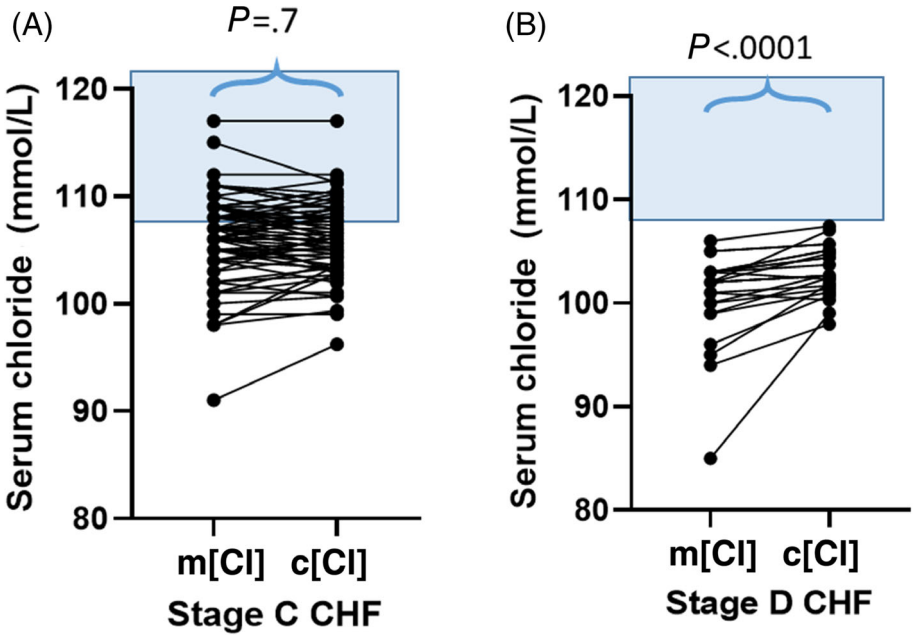

FIGURE 3 Measured chloride (m[Cl^-]) and corrected chloride (c[Cl^-]) in dogs with CHF. The shaded box is the reference range. A, Stage C dogs; B, Stage D dogs

chloride from the body is inhibition of the renal $Na^+/K^+/2Cl^-$ cotransporter by the action of loop diuretics such as furosemide or torsemide.[18] Our finding that corrected hypochloremia is more pronounced in Stage D dogs compared to Stage C dogs indicates that loop diuretic-induced 2:1 [Cl^-] to [Na^+] loss into the urine is a major cause of hypochloremia in late stage CHF. This finding is expected because of higher diuretic dosages employed in Stage D CHF dogs, as previously reported.[14] Our results aid interpretation of hypochloremia in this group of dogs with refractory CHF and suggest that loop diuretic effects and relative water excess may coexist and influence serum electrolyte concentrations to variable degrees in this clinical situation.

Nonosmotic ADH release is a possible mechanism of poor diuretic response in refractory CHF and current treatments to address the resulting relative water excess are limited. Although marked hyponatremia can be a good indicator of dilution from water retention,[2,6] detection of subtle dilution of serum sodium concentration may be challenging to appreciate when serum sodium concentrations remain within the reference range or are only mildly decreased, and this is potentially complicated by loop diuretic-induced electrolyte loss in CHF patients. Mathematical correction of chloride concentrations for sodium concentrations shows the influence of loop diuretics after removing the effect of relative water excess, thus identifying patients with water retention. The first step toward developing strategies to address relative water excess is identification, and our results provide preliminary data supportive of water excess in many Stage D dogs. Tolvaptan is an ADH antagonist that is used in people with hyponatremia and has been evaluated in a limited number of dogs.[26,27] The major limitation to the use of this medication is cost, but there is also debate regarding clinical benefit on outcomes in people.[28] Other medications can antagonize ADH, such as demeclocycline and acetazolamide, but reports are lacking in veterinary medicine.[2,29,30] Extracorporeal ultrafiltration is a nonpharmacological approach to removal of excess water that has been explored in people.[29] All of these methods could be pursued in dogs with CHF if supporting evidence of relative water excess can be identified. Our results may provide a clinically accessible way to determine the influence of water retention on serum electrolyte concentrations in dogs with refractory CHF.

The differential effect of loop diuretics on urinary sodium and chloride loss compared to the balanced effect of dilution from relative water excess allows chloride correction to provide insight into the mechanism of serum electrolyte concentration abnormalities in this population, regardless of whether hyponatremia or hypochloremia is the major concern. Therefore, the magnitude of hypochloremia relative to sodium concentration separates dilution and loop diuretics as causes. Recognition of the underlying mechanism for low serum electrolyte concentrations (eg, relative water excess, loop diuretics, or gastrointestinal loss, with the latter typically being clinically apparent) is critical for appropriate, directed treatment. For example, whereas low serum electrolyte concentrations secondary to relative water excess from nonosmotic ADH release would be best addressed using an ADH antagonist, low serum electrolyte concentrations secondary to loop diuretics would be best addressed by loop diuretic dose reduction coupled with optimizing nondiuretic approaches to treating CHF (eg, positive inotropy and renin-angiotensin-aldosterone system inhibition). Other supportive treatments sometimes are employed to address electrolyte deficiencies, such as sodium chloride fluid infusions and sometimes water restriction, but it is clear that such approaches may be either helpful or harmful, depending on whether the cause is dilution or loss.[2,31]

Our study had some limitations. Because of the retrospective nature of the study, blood gas analysis was not available to aid interpretation of serum [Cl^-]. The dogs in our study did not have clinical evidence of other metabolic or gastrointestinal abnormalities that would have influenced acid-base status, but interpretation of our

results should be limited to dogs with stable CHF receiving PO loop diuretics and without other clinical abnormalities. Additionally, our study assumed that the gap between c[Cl^-] and m[Cl^-] represented relative circulatory water excess. However, for this technique to be clinically applied with certainty, validation with definitive measures of intravascular volume would be required. Additionally, the degree of chloride correction that is clinically important remains to be determined. Comparison to a healthy group of dogs would have been helpful for the interpretation of hypochloremic results obtained in NO-CHF dogs, a group of dogs not receiving loop diuretics, but these data were not available.

Stage D dogs in our study showed greater increases in serum [Cl^-] after mathematical correction compared to Stage C dogs and NO-CHF dogs, supportive of a degree of relative water excess in refractory CHF. Despite increases in [Cl^-] in Stage D dogs after correction, serum [Cl^-] remained below the reference range for the group, consistent with concurrent loop diuretic effects on electrolytes. Notably, some individual Stage D dogs showed substantial increases in serum [Cl^-] after correction. Serum [Cl^-] correction might serve a role in heart disease staging, specifically for identification of Stage D (refractory) CHF dogs with water retention. Future studies correlating c[Cl^-] to clinical outcomes, serum ADH concentrations or intravascular volume measurements, and assessing the effect of ADH antagonists in CHF dogs with increases in serum [Cl^-] after correction are warranted.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Approved by the IACUC (#14-142-0) at North Carolina State University Veterinary Hospital, and owner consent was obtained.

HUMAN ETHICS APPROVAL DECLARATION

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

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