

Ionized Hypocalcemia in Critically Ill Dogs

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Background: Ionized hypocalcemia (iHCa) is a common electrolyte disturbance in critically ill people, especially those with sepsis. The cause of the iHCa is not entirely understood and is likely multifactorial. Critically ill people with iHCa have longer hospital stays and higher mortality rates compared to people with normocalcemia. There are no published clinical studies evaluating the incidence and impact of iHCa in critically ill dogs.

Hypothesis: iHCa occurs in critically ill dogs, is more prevalent in dogs with systemic inflammatory response syndrome (SIRS) or sepsis, and is associated with longer hospital stays and higher mortality.

Animals: One hundred and forty-one client-owned dogs admitted to a companion animal intensive care unit (ICU) in a veterinary teaching hospital.

Methods: Prospective observational study of sequentially enrolled dogs. Blood was collected and analyzed within an hour of admission from all dogs presented to the ICU that met study inclusion criteria.

Results: The incidence of iHCa (iCa < 1.11 mmol/L) was 16%. The presence of iHCa was associated with longer ICU ($P = .038$) and hospital ($P = .012$) stays but not with decreased survival ($P = .60$). Dogs with sepsis as defined by ≥ 3 SIRS criteria and a positive culture were more likely to have iHCa ($P = .050$).

Conclusions and Clinical Relevance: In dogs not previously treated with fluids or blood products intravenously, the finding of iHCa upon admission to the ICU predicted a longer duration of ICU and hospital stay. Septic dogs with positive cultures were more likely to have iHCa.

Key words: Canine; Critical care; Intensive care medicine; Sepsis; Systemic inflammatory response syndrome; Trauma.

The incidence of ionized hypocalcemia (iHCa) in critically ill human patients is substantial, occurring in as many as 88% of ICU patients.¹ In the last 40 years, numerous investigators have sought to determine the relationship between iHCa and critical illness.^{1–11} Conditions most often associated with iHCa in critically ill people include surgery,² pancreatitis,³ severe trauma,^{4–6} and burn injuries.⁷ iHCa also occurs commonly in septic patients^{8,9,12,13} with an incidence of 20–82%.^{9,12,13}

The cause of iHCa in critically ill patients is not entirely understood and is likely multifactorial. Several mechanisms are proposed, including parathyroid gland dysfunction,^{10,12} cytokine-mediated suppression of parathyroid hormone release,^{8,14} vitamin D deficiency or lack of vitamin D activation,¹² hypomagnesemia,^{15–18} calcium chelation,^{14,19,20} or the accumulation of calcium in tissues, body fluids, and cells.^{21–23} In recent years, the focus of investigation has been on the calcitonin precursor procalcitonin and its role in ionized calcium alterations in critically ill and septic patients.^{24–27}

The development of iHCa appears to predict a more severe clinical course in hospitalized people. Critically ill people with iHCa spend a significantly longer time in ICU and have higher case fatality rates compared with

people with normocalcemia.¹¹ The same is true for septic people with iHCa when compared with normocalcemic septic patients.^{9,12} Additionally, human trauma patients with iHCa have more severe injuries and more frequently suffer prehospital cardiac arrest as the degree of iHCa worsens.⁴

The purpose of the current study was to prospectively determine the incidence of iHCa in dogs upon admission to a small animal ICU, to determine if iHCa at admission predicts longer hospital stays or increased risk of death, and to determine if iHCa is more common in dogs with particular diseases or that meet clinical criteria for SIRS or sepsis. The authors hypothesized that iHCa occurs in approximately 30% of critically ill dogs, and that iHCa upon presentation to the ICU predicts duration of hospital stay and outcome, and that dogs with iHCa are more likely to have SIRS and sepsis.

Materials and Methods

This study was performed at the Veterinary Teaching Hospital at North Carolina State University (NCSU) between March and June 2006. Dogs were included if a blood sample could be drawn within 1 hour of entry into the small animal ICU. Dogs were excluded if they were being treated for hyper- or hypocalcemia; if they had received fluids or blood products IV before admission to the ICU; if they were admitted to ICU merely for observation or as overflow from other wards in the hospital; or if a blood sample could not be obtained within 1 hour of admission to the ICU. The study was approved by the NCSU Institutional Animal Care and Use Committee.

A 1 mL blood sample was drawn from a jugular, cephalic, or saphenous vein with a heparinized 3-mL syringe and immediately analyzed with a blood gas analyzer.^a The syringe was heparinized by aspirating 0.5 mL of liquid sodium heparin^b (1,000 μ /mL) and then drawing the plunger back to the 3-mL mark to allow coating of the inner surface of the syringe with heparin. All of the air in the syringe was subsequently expelled, followed by 10 repetitions of 3 mL of air being drawn into the syringe and forcibly expelled to remove as

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much heparin from the syringe as possible. This protocol was used to prevent false lowering of ionized calcium by reducing the amount of heparin present that would exert chelating and dilutional effects.²⁸ The reference range for ionized calcium with this blood gas analyzer was determined using 20 healthy dogs.

For every dog, pH-corrected (to pH 7.40) ionized calcium concentrations were recorded along with date of hospital and ICU admission, date of hospital and ICU discharge or death, outcome (died, euthanized, discharged), primary disease, and documentation of criteria for the diagnosis of SIRS at the time of admission. Correction to a pH of 7.4 was performed according to the formula: $Ca_{corrected}^{2+} = Ca_{measured}^{2+} \times 10^{(-0.178 \times 7.4 - pH)}$.^c Criteria for SIRS included: (1) rectal temperature $< 100.4^{\circ}F$ ($< 38.0^{\circ}C$) or $> 102.2^{\circ}F$ ($39.0^{\circ}C$); (2) heart rate > 120 beats/min; (3) respiratory rate > 20 breaths/min; and (4) total WBC count $< 6,000/\mu L$ or $> 16,000/\mu L$ as defined previously.²⁹ CBCs were obtained at the discretion of the attending clinician and were not required for inclusion. The presence of leukocytosis or leukopenia was recorded based on the total WBC count used for the SIRS criteria. Cultures were collected at the discretion of the attending clinician and were considered positive if bacterial growth was documented or negative if there was no growth or no culture was obtained. Dogs were categorized by their primary disease into these groups: cardiac, gastrointestinal, hematologic, metabolic, neoplastic, neurologic, pulmonary, traumatic, urinary, or other.

Statistical Analysis

All analyses were performed with a commercial statistical software program.^d The effects of the categorical variables of "septic" (≥ 3 SIRS criteria and a positive culture), "WBC" (≥ 3 SIRS criteria in addition to leukopenia or leukocytosis), and "discharge status" (alive or died/euthanized) on corrected ionized calcium were evaluated with the Mann-Whitney rank-sum test. A Kruskal-Wallis 1-way analysis of variance was used to evaluate the effects of disease category on corrected ionized calcium, with Dunn's method for pair wise comparisons of categories if a significant category effect was found. For purposes of determining the effects of ionized calcium status on the duration of hospitalization and ICU stay, the pH-corrected ionized calcium was categorized as low (< 1.11 mEq/L) or not low (≥ 1.11 mEq/L), based on the laboratory normal reference range of 1.11–1.38 mEq/L, and the effect of calcium group was evaluated with the Mann-Whitney Rank-Sum test. For all analyses a *P*-value ≤ 0.050 was considered significant.

Results

Two hundred and sixty dogs were admitted to the ICU during the 3-month study period. One hundred and nineteen dogs were excluded from the study for the following reasons: recent IV administration of fluids or blood products (78), hospitalization in ICU because of overflow from other areas of the hospital (21), blood samples not obtained within an hour of admission to the ICU (15), blood samples not drawn because of respiratory distress (4), and diagnosis with primary hypoparathyroidism (1). The remaining 141 dogs were included in the study.

Twenty-two of 141 dogs (16%) were hypocalcemic (median, range of ionized calcium concentration; 1.03, 0.64–1.10 mEq/L) and 119 were not (1.26, 1.11–1.55 mEq/L). Ten dogs had ionized calcium values above the reference range of 1.11–1.38 mEq/L (1.41, 1.39–1.55 mEq/L) and for purposes of analysis were grouped with the normocalcemic dogs. iHCa was associated with a longer duration of hospitalization (*P* = .012) and a longer

duration of hospitalization in the ICU (*P* = .038). The median duration of hospitalization (interquartile range) for dogs with iHCa was 5 days (3–7 days) compared with 3 days (2–5 days) for dogs that did not have iHCa. Of 141 dogs included in the analysis, 107 survived to hospital discharge (76%), 24 were euthanized, and 10 died. Seventeen of 22 dogs (77%) with iHCa were discharged from the hospital, 3 were euthanized, and 2 died. The median ionized calcium (interquartile range) for dogs discharged from the hospital was 1.24 (1.15–1.33 mEq/L) and the median ionized calcium for dogs euthanized or died was 1.25 (1.15–1.29 mEq/L). Ionized calcium status had no effect on survival to discharge from the hospital (*P* = .60).

Dogs were categorized by their primary disease as follows: cardiac (31 dogs), neoplastic (25), pulmonary (16), traumatic (13), metabolic (13), gastrointestinal (13), hematologic (12), neurologic (11), urinary (6), and other (1). Disease category had a significant effect on ionized calcium, which was attributed to the comparatively high median ionized calcium concentration in dogs with hematologic disease (Table 1).

Samples were collected from 16 dogs for culture. Positive cultures were obtained in 14 dogs and included abdominal fluid (5), urine (4), blood (2), joint fluid (1), liver aspirate (1), and tracheal wash fluid (1). Eleven of 14 dogs (79%) with positive cultures had iHCa. One hundred and four dogs had a CBC performed within 24 hours of admission to the ICU and 55 dogs were diagnosed with either leukocytosis (*n* = 47) or leukopenia (*n* = 8). Thirty-four dogs had 1 SIRS criterion upon admission to the ICU, 49 had 2 criteria, 41 had 3, and 17 had 4. Dogs with ≥ 3 SIRS criteria tended to have iHCa, (*P* = .059) although the results did not reach statistical significance. iHCa was present in 9 of 10 dogs with sepsis defined by ≥ 3 SIRS criteria as well as a positive culture; these dogs were more likely to have iHCa than those without sepsis (*P* = .050). Dogs with ≥ 3 SIRS criteria and either leukocytosis or leukopenia (regardless of culture results) were not more likely to have iHCa (*P* = .13).

Discussion

The incidence of iHCa in this study population was 16%, suggesting that iHCa is less common in critically ill dogs that have not had previous IV administration of fluids or blood products compared with critically ill people. Additionally, the presence of iHCa was not associated with survival, but did predict an increased duration of hospital and ICU stay. Critically ill dogs with renal failure, diabetic ketoacidosis (DKA), and pancreatitis were more likely to have iHCa. Dogs diagnosed with sepsis based on ≥ 3 SIRS criteria and a positive culture were also significantly more likely to have iHCa. These results suggest that ionized calcium is an important variable to measure in certain subsets of critically ill dogs including those with metabolic or renal disease and sepsis. Although ionized calcium was not found to be a predictor of outcome in the overall ICU population, it was associated with prolonged hospitalization and could be more relevant in these particular animals.

Table 1. Median ionized calcium concentrations in each primary disease category.

Category	Primary disease	Number of dogs	Median ionized calcium (interquartile range)
Cardiac*	CHF (16), AVB (6), DCM (3), PE (3), SSS (1), SVT (1), VPC (1)	31	1.22 (1.14–1.30)
Gastrointestinal*	GDV (5), GI perforation (2), septic peritonitis (2), HGE (1), GI granuloma (1), GI ulceration (1), esophageal FB (1)	13	1.18 (1.12–1.28)
Hematologic	IMHA (7), TCP (4), IMT (1)	12	1.32 (1.28–1.37)
Metabolic*	Pancreatitis (3), DKA and pancreatitis (3), CD (3), DKA (2), hypoglycemia (2)	13	1.14 (0.98–1.17)
Neoplastic	HSA (6), carcinoma (5), LSA (5), HS (2), adrenal tumor (1), anal sac tumor (1), melanoma (1), osteosarcoma (1), thymoma (1), spinal tumor (1), PCS, post-chemotherapy sepsis (1)	25	1.24 (1.15–1.27)
Neurologic	Seizures (8), brain tumor (3)	11	1.29 (1.21–1.34)
Pulmonary	Respiratory distress (4), AP (4), BP (3), SP (2), CT (2), hypoxemia (1)	16	1.27 (1.25–1.34)
Traumatic	HBC (8), BDL (2), GSW (1), head trauma (1), burn injury (1)	13	1.25 (1.18–1.34)
Urinary*	ARF (4), CRF (2)	6	0.96 (0.90–1.27)
Other	Pyometra (1)	1	1.44

*Significant ($P < .05$) difference between this group and the hematology group.

CHF, congestive heart failure; AVB, 3rd degree atrioventricular block; DCM, dilated cardiomyopathy; PE, pericardial effusion; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; VPC, ventricular premature contractions; GDV, gastric dilation volvulus; GI, gastrointestinal; HGE, hemorrhagic gastroenteritis; FB, foreign body; IMHA, immune-mediated hemolytic anemia; TCP, thrombocytopenia; IMT, immune-mediated thrombocytopenia; DKA, diabetic ketoacidosis; CD, Cushing's disease; HSA, hemangiosarcoma; LSA, lymphosarcoma; HS, histiocytic sarcoma; PCS, postsepsis complication; AP, aspiration pneumonia; BP, bacterial pneumonia; SP, spontaneous pneumothorax; CT, collapsing trachea; HBC, hit by car; BDL, attacked by larger dog; GSW, gunshot wound; ARF, acute renal failure; CRF, chronic renal failure.

Trauma is one of the most important causes of iHcCa in critically ill humans. The mechanism for the iHcCa in these patients is not entirely understood, but massive tissue damage resulting in the accumulation of calcium intracellularly may contribute.⁴ A study evaluating 212 consecutive human trauma patients found that a more profound iHcCa was associated with more severe injuries and a higher incidence of prehospital cardiac arrest.⁴ Similarly, a recent study prospectively evaluated the impact of ionized calcium values in 396 trauma patients upon arrival to the emergency room.⁵ Mortality was increased, time to death shorter, and arterial hypotension necessitating vasopressor support increased significantly in those patients with iHcCa.⁵ In the present study, only 13 dogs suffering from trauma were included and the mean ionized calcium concentration for those dogs was within the reference range. Unfortunately, the majority of severely traumatized dogs admitted to the ICU had previously been resuscitated in the emergency department, and therefore were excluded because of prior IV administration of fluids or blood products, to prevent documenting a transiently low ionized calcium concentration because of hemodilution. Thus, a large population of severely affected dogs that were more likely to exhibit iHcCa may have been excluded from analysis.

The decision to exclude dogs administered fluids or blood products IV was done to remove the effect of dilution or chelation on the development of iHcCa. Previous studies evaluating iHcCa in human trauma patients have documented a “hypocalcemia of trauma” that occurs during posttrauma resuscitation. Interestingly, the final calcium concentration, before discharge or death, is a better predictor of outcome in these patients, whereas the minimum ionized calcium measured during fluid resus-

citation does not differentiate survivors from nonsurvivors.⁶ Thus, it is known that during resuscitation after a trauma, iHcCa is common, but that ionized calcium measured then does not correlate with outcome. Calcium concentration decreases linearly with increasing transfusion requirements after critical injury and this probably occurs because of the chelation of calcium with citrate in the blood products.⁶

Similarly, iHcCa is commonly documented in critically ill people after surgery.² A recent study, evaluating healthy dogs and cats also confirmed a decrease in ionized calcium postoperatively.³⁰ Although the fall in ionized calcium concentration was statistically significant, ionized calcium concentration remained within the normal range. For the present study, any dogs that entered the ICU after a surgical procedure were subsequently excluded, which may have excluded a population of dogs that potentially exhibited a higher incidence of iHcCa.

pH affects the plasma ionized calcium concentration, as alkalemia increases protein binding of calcium and reduces ionized calcium. For this analysis, all ionized calcium values were adjusted to a pH of 7.4, using a correction formula built into the analyzer that has not been validated for dogs. Although the uncorrected ionized calcium concentration is the biologically relevant value, we used the pH-corrected values to mitigate the confounding effect of the wide range of pH values identified in the dogs in this study. This approach is similar to that taken in several studies evaluating ionized calcium in critically ill people, wherein pH-adjusted ionized calcium concentrations were used in those analyses.^{4,9,11} One group that did not use pH-corrected ionized calcium values instead measured the pH and analyzed the relationship between the acid-base status and ionized

calcium measurement.⁵ After trauma, base deficit (suggesting acidosis) was more likely in patients with iHcA and these patients had a worse outcome.⁵ Although this relationship between iHcA and acidosis is opposite of the expected effect of acidemia, it suggests that factors such as the severity of injury in these patients could produce both acidosis and hypocalcemia.

There is a strong association between the severity of iHcA and the duration of hospital or ICU stay and mortality in people.^{4,9,12} The present study revealed an association between iHcA in critically ill dogs and the length of hospital and ICU stay, but failed to indicate any relationship between the presence of iHcA and survival. One possible explanation for this discrepancy is that the most severely ill dogs received IV fluids or blood products immediately upon arrival to the hospital and were subsequently excluded from enrollment.

There was an association between ionized calcium and disease category in the present study, with the lowest median ionized calcium concentrations found in dogs whose primary disorders were categorized as either urinary or metabolic. All of the dogs in the urinary category had renal failure and in 4 of 6 of these dogs the renal failure was acute. Hypocalcemia (low total serum calcium) occurs in dogs with acute renal failure. A retrospective analysis of 99 dogs with acute renal failure showed that dogs with serum total calcium concentrations <8.6 mg/dL had a poorer prognosis for survival and discharge from the hospital than did dogs with higher serum total calcium concentrations.³¹ Five dogs in the present study categorized as having metabolic disease had a diagnosis of DKA and 3 of those had iHcA. This is consistent with a recent study evaluating outcome in dogs with DKA, in which 52% of dogs with ionized calcium measurements had an ionized calcium concentration below the reference range.³² Additionally, dogs with iHcA in that study were more likely to die.³² Three dogs categorized as metabolic in the present study were diagnosed with pancreatitis and 2 of those 3 dogs exhibited iHcA. iHcA is a common finding in dogs with pancreatitis and a suggested cause includes the accumulation of calcium in soft tissues; however, the exact mechanism has not been determined and is likely multifactorial.³³

This study defined sepsis as the presence of ≥ 3 SIRS criteria present at admission to the ICU with documentation of a positive culture. Dogs that met this definition of sepsis were significantly more likely to have iHcA. The relationship between iHcA and patients with SIRS and positive cultures is similar to that which has been found in people.¹³ Although a significant relationship between sepsis and iHcA was found in dogs in this study, it should be noted that the criteria used to define sepsis were sensitive but nonspecific. Thus, there might have been dogs that were defined as “septic” based on a positive culture and alterations in the WBC count or vital signs but that were not severely ill. This is a downfall to using these particular criteria without other measurements of illness severity or biomarkers and subsequently, dogs that had only modest systemic complications of infection might have been included in this study. Unfortunately, there

are no commonly used severity of illness scoring systems for veterinary patients and other parameters of illness severity such as organ dysfunction or intensity of supportive care were not investigated. However, the authors made every effort to ensure that the dogs included were only those hospitalized in ICU, which in our tertiary referral institution includes the most severely ill patients in the hospital. The authors did evaluate the duration of hospital and ICU stay as an indirect measurement of illness severity, but recognized the limitations of that variable as it may be confounded by other factors in veterinary medicine such as euthanasia for financial reasons. At the time the study was designed, an assay for procalcitonin was not available, and unfortunately no blood was collected for measurement of other biomarkers.

Hospital stays are significantly longer and mortality rates significantly higher in people with sepsis and concurrent iHcA.¹² A difference in outcome in dogs was not seen in the present study. One explanation for this disparity is that the number of dogs enrolled that met criteria for sepsis was small (10 dogs). Another limitation of this study is that CBC results were not available for all patients. It was anticipated that all dogs deemed to be critically ill would have CBCs and cultures performed; however, this was not always the case. Cultures were not obtained from all dogs that had ≥ 3 SIRS criteria and negative cultures could have occurred in dogs previously on antibiotic therapy. Thus, some dogs that were truly septic may not have been classified as such.

In light of the results of studies in people, a comparatively low incidence of iHcA was detected among critically ill dogs in this study; however, this might have been due to the exclusion of previously fluid resuscitated dogs with more severe illness at presentation. Similarly, no difference in outcome was detected in this study, in contrast to the findings documented in studies evaluating iHcA in critically ill people. This could be due to the small numbers of dogs with metabolic and renal disease or sepsis included in this study, as these are the diseases, in which iHcA has been found to have an effect on survival. Future investigations should focus on these subsets of critically ill dogs, in addition to traumatized dogs, to determine whether ionized calcium can be used as a predictor of outcome. Similarly, several ionized calcium measurements during the course of hospitalization would be ideal, to determine whether changes in ionized calcium values have an impact on survival.

Footnotes

- ^a Gem Premier 3000, Instrumentation Laboratory, Lexington, MA
^b Heparin sodium injection, Baxter Healthcare Corporation, Deerfield, IL
^c Gem Premier 3000, Operator's Manual (Revised October 2003), Instrumentation Laboratory
^d SigmaStat v3.1, Systat Software, Chicago, IL
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