Retrospective Study

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Incidence of ionized hypocalcemia in septic dogs and its association with morbidity and mortality: 58 cases (2006–2007)

Maureen A. Luschini, VMD; Daniel J. Fletcher, PhD, DVM, DACVECC and Gretchen L. Schoeffler, DVM, DACVECC

Abstract

Objective – To determine the incidence rate and prognostic significance of ionized hypocalcemia (iHCa) among septic dogs.
Design – Retrospective study
Setting – Veterinary teaching hospital
Animals – Fifty-eight septic dogs that were presented to Cornell University Hospital for Animals between January 2006 and December 2007.
Procedure – Cases were diagnosed with sepsis if they exhibited 2 or more criteria of the systemic inflammatory response syndrome with a concurrent documented infectious focus. Cases were excluded if diagnosed with a concurrent illness reportedly associated with calcium derangements. Lowest, mean, and highest blood ionized calcium concentrations were recorded and statistically analyzed for an association with morbidity, as measured by duration of hospitalization and number of blood product transfusions, and outcome. In addition, the incidence rate of iHCa was recorded.
Results – Of the 58 cases included in this study, iHCa was documented in 4 of 6 (67%) patients that died, 5 of 19 (26%) euthanized patients and 5 of 33 (15%) patients that survived to discharge, with an overall incidence of 24%. Dogs that died during hospitalization had more severe iHCa than patients that were discharged or euthanized as well as significantly lower mean ionized calcium concentrations than patients who were discharged. Severity of iHCa was also associated with a longer duration of hospitalization. The highest ionized calcium concentration was not associated with outcome.
Conclusion and Clinical Relevance – This study is the first to document the incidence of iHCa among septic dogs. Because both low mean ionized calcium and the lowest documented ionized calcium concentration are associated with poor outcome, it is likely that both the severity and duration of hypocalcemia are important in these patients. Further prospective studies investigating the prognostic significance, etiology and treatment of iHCa among septic veterinary patients are needed to better understand its role in sepsis.

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Introduction

In human medicine, ionized hypocalcemia (iHCa) has been well-documented among the critically ill suffering from such diseases as burns, severe trauma, and sepsis. The incidence rate of iHCa among these patients ranges from 11% to 88% and among septic patients the incidence rate ranges from 20% to 50%.[1–7] The presence and degree of iHCa has also been associated with greater disease severity, morbidity, and mortality in critically ill people.[1,2] Despite documentation of iHCa in the human literature for over 30 years, only 1 published case report documenting iHCa in a septic dog exists in the veterinary literature.[3] A recent article documented a 16% incidence of iHCa among a heterogeneous population of critically ill dogs on admission to an ICU; although the presence of iHCa was associated

From the Department of Emergency and Critical Care, Cornell University Hospital for the Animals, Ithaca, NY 14850.

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Address correspondence and reprint requests to
Dr. Maureen Luschini, VMD, 217 Brooktondale Rd, Apt D, Brooktondale, NY 14817, USA.
Email: ml398@cornell.edu
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with longer hospitalization in this population, no association with outcome was observed. Patients with sepsis, however, were more likely to have iHCa on admission to the ICU.[4] To the authors' knowledge, this is the first study documenting the incidence of iHCa among septic dogs and its association with morbidity and mortality.

Calcium is involved in many life-sustaining physiologic processes, such as cardiac muscle contraction, cardiac nodal conduction, vascular tone, neuronal conduction and membrane stabilization, skeletal and smooth muscle contraction, hormone release and response, enzymatic pathways, coagulation, and cell signaling pathways including mitosis and apoptosis.[5] Because ionized calcium is the physiologically active form of calcium within the body, regulation of blood ionized calcium within a narrow range is essential to ensure normal function of these physiologic processes.[5] The following 3 hormones are responsible for calcium homeostasis: parathyroid hormone (PTH), calcitriol, and calcitonin.[5] In response to hypocalcemia, the parathyroid gland releases PTH which stimulates calcium mobilization from bone and decreases calcium excretion through the kidneys.[5] In addition, PTH promotes the formation of calcitriol (1,25-dihydroxyvitamin D_3), which increases gastrointestinal calcium absorption.[5] Therefore, PTH and calcitriol function to raise blood ionized calcium concentrations to normal limits. In response to hypercalcemia, the thyroid gland releases calcitonin, which decreases calcium mobilization from the bones and absorption from the gastrointestinal tract, and promotes calcium excretion through the kidneys.[5] Thus, the antagonistic effects of PTH with calcitriol and calcitonin function to maintain calcium homeostasis through their effects on bone, the kidneys, and the gastrointestinal tract.

Although iHCa in critically ill people has been well studied for over 3 decades, the exact mechanism(s) remain to be determined. Potential causes include the following: impaired PTH secretion or action, impaired vitamin D synthesis or action, hypomagnesemia, chelation of calcium, alkalemia, accumulation of calcium in tissues or cells, or elevation of calcitonin precursors.[6–10] In addition, some authors suggest iHCa may actually be protective, as elevated blood ionized calcium concentrations promote the intracellular influx of calcium.[11–13] An increase in intracellular calcium leads to activation of proteases and other digestive enzymes as well as uncoupling of oxidative phosphorylation that can lead to further intracellular influx of calcium through damaged cellular membranes. This intracellular calcium influx leads to irreversible cell injury with concomitant cytokine release, which initiates or perpetuates multiorgan dysfunction, a syndrome commonly observed with sepsis that often leads to multiorgan failure and death.[14,15] Furthermore, Hotchkiss and Karl[15] found the use of calcium channel blockers, such as dantrolene, ameliorates many of these detrimental physiologic effects of sepsis, such as increased protein catabolism, increased glucose cellular uptake and utilization, and increased lactate production. Although calcium supplementation in critically ill patients with iHCa has yielded conflicting results in regards to its association with morbidity and outcome, enteral or parenteral calcium supplementation to normalize blood ionized calcium concentrations remains the current recommendation in human medicine.[6,16,17] Nevertheless, identification of the pathophysiologic mechanism for iHCa during sepsis may allow for more specific and appropriate treatment.

The present study was designed to retrospectively identify the incidence rate of iHCa among septic canine patients as well as to determine its association with morbidity and outcome. As inferred from the human literature, we hypothesized that iHCa would be present in $>10\%$ of septic dogs.

Materials and Methods

Patient population

Records of dogs that were presented or admitted to Cornell University Hospital for Animals between January 2006 and December 2007 and diagnosed as having one or more of the following conditions were evaluated: pneumonia, septic peritonitis, pyothorax, central empyema, pyelonephritis, pyometritis, infectious meningitis, sepsis, septicemia, bacteremia, abscess, septic arthritis. Patients younger than 1 year of age were excluded to rule out any effects of increased bone turnover on blood ionized calcium concentrations in young growing dogs. Any patients diagnosed with a septic condition but with previous or concurrent diagnoses (either antemortem or postmortem) of any condition known to alter blood ionized calcium concentrations were excluded. These conditions included: diabetes mellitus, pancreatitis, renal failure, humoral hypercalcemia of malignancy, hypo-/hyperparathyroidism, hypoadrenocorticism, protein-losing enteropathy, and idiopathic hypercalcemia. Medical records were screened for the diagnosis of sepsis, which was defined as the presence of an infectious focus and the concurrent documentation of 2 or more of the following parameters: Temperature <38.1°C (100.6°F) or >39.2°C (102.6°F); heart rate >120/min; respiratory rate >20/min, WBC count $>16 \times 10^9$/L (16,000/μL) or $<6 \times 10^9$/L (6000/μL) or percentage of bands $>3\%$ of the total WBC count.[18] Infectious foci were identified via cytologic evaluation or culture/susceptibility of body

fluids, or both. The diagnosis of pneumonia was often a clinical diagnosis based on radiographic findings, clinical findings, and patient histories and is thus an exception to the diagnosis of an infectious focus.

Blood ionized calcium concentrations

Ionized calcium concentrations, as measured by blood gas analysis[a] that was obtained from the time of diagnosis of sepsis until final outcome were recorded. The standard protocol employed in our hospital for blood gas analysis involves collection of approximately 0.2–1.0 mL of blood by direct venipuncture or use of the 3-syringe technique from a sampling catheter directly into lyophilized lithium heparin syringes[b] which are then capped and run within 1–2 minutes of acquisition. Samples are handled anaerobically from the time of collection until analysis. From this data, the lowest, mean, and highest ionized calcium values during hospitalization were identified, calculated, and recorded. The lowest concentration of ionized calcium provided an estimate of the severity of hypocalcemia during hospitalization. The mean ionized calcium concentration provided a measure reflecting the persistence of abnormalities in blood ionized calcium concentrations during hospitalization. The highest ionized calcium concentration revealed whether patients ever achieved normocalcemia during hospitalization. iHCa was diagnosed if a patient's blood ionized calcium concentration was <1.17 mmol/L (4.68 mg/dL), which is the lower limit of the reference interval for dogs established for the blood gas analyzer used in this study.

Morbidity

The following 2 measurements of morbidity were recorded: duration of hospitalization and the number of transfusions. Longer durations of hospitalization and greater numbers of transfusions administered inferred greater morbidity, whereas a short hospitalization and no transfusions were considered to imply less morbidity.

Outcome

Patient outcome was divided into the following 3 categories: survival to discharge, cardiac or respiratory arrest during hospitalization with unsuccessful resuscitation, or euthanasia. Because it was not always possible from the medical records to determine whether patients were euthanized due to financial constraints of the owners, due to progressive decline in the patient's status, or due to both, all euthanized patients were included in the same group.

Statistical analyses

To determine the incidence rate of iHCa, patients were considered hypocalcemic if the lowest ionized calcium concentration recorded during hospitalization was <1.17 mmol/L (4.68 mg/dL), the low end of the reference interval for the analyzer used in this study. Data were tested for normality with the Shapiro-Wilk test, and were found not to be normally distributed; therefore, Kruskal-Wallis rank sum tests were used to evaluate the differences between the lowest, mean, and highest ionized calcium values between groups. When a statistically significant difference was found, Wilcoxon rank-sum tests were done to make pairwise comparisons between each outcome category. The associations between iHCa and morbidity were examined using Spearman's rank correlation coefficient (ρ). Statistical significance was set at $P<0.05$.

Results

Database search results yielded 274 cases, of which 216 were excluded for the following reasons: lack of blood gas analysis; previous, concurrent, or postmortem diagnosis of a condition associated with iHCa or hypercalcemia; lack of identification of a septic focus; missing or incomplete paper records; and erroneous diagnoses entered in the database. Thus, 58 cases were included in this study (Table 1), of which 6 (10.3%) died during hospitalization, 19 (32.8%) were euthanized, and 33 (56.9%) survived to discharge. iHCa was documented in 4 of 6 (67%) of the patients that died, 5 of 19 (26%) of the euthanized patients, and 5 of 33 (15%) patients that survived to discharged, with an overall incidence of 24%.

Lowest ionized calcium concentrations and mean ionized calcium concentrations were significantly different between the outcome groups ($P = 0.01$ and 0.003, respectively). Septic dogs that died during hospitalization from cardiac/respiratory arrest had more severe iHCa (median lowest ionized calcium, 1.09 mmol/L [4.36 mg/dL]; range, 0.79–1.21 mmol/L [3.16–4.84 mg/dL]) than those that were discharged (median lowest ionized calcium, 1.24 mmol/L [4.96 mg/dL]; range, 1.09–1.37 mmol/L [4.36–5.48 mg/dL]) ($P = 0.004$) or euthanized (median lowest ionized calcium, 1.21 mmol/L [4.84 mg/dL]; range, 0.86–1.32 mmol/L [3.44–5.28 mg/

Table 1: Distribution of septic dogs and incidence of ionized hypocalcemia (iHCa) according to outcome

	Total distribution	Incidence of iHCa
Died	6 (10.3%)	4/6 (67%)
Euthanized	19 (32.8%)	5/19 (26%)
Survived	33 (56.9%)	5/33 (15%)
Total	58 cases	14/58 (24%)

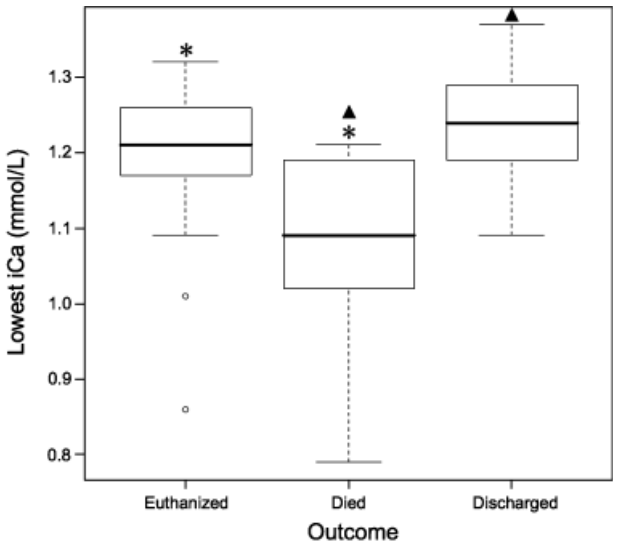

Figure 1: Box and whisker plots of the lowest ionized calcium during hospitalization in septic dogs in each of the outcome groups (euthanized: median lowest ionized calcium = 1.21 mmol/L [4.84 mg/dL], range = 0.86–1.32 mmol/L [3.44–5.28 mg/dL]; died: median lowest ionized calcium = 1.09 mmol/L [4.36 mg/dL], range = 0.79–1.21 mmol/L [3.16–4.84 mg/dL]; discharged: median lowest ionized calcium = 1.24 mmol/L [4.96 mg/dL], range = 1.09–1.37 mmol/L [4.36 mg/dL]). Septic dogs that died had significantly more severe iHCa than dogs that were discharged ($P = 0.004$) or euthanized ($P = 0.04$). The asterisks and triangles denote statistically significant differences between compared groups (Wilcoxon rank-sum, $P < 0.05$).

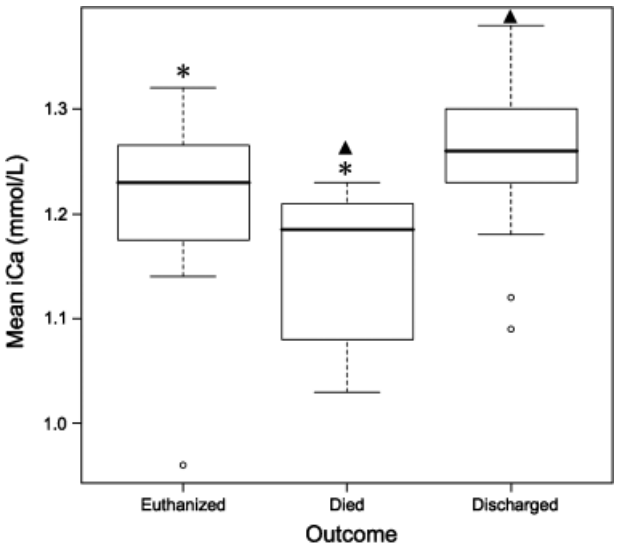

Figure 2: Box and whisker plots of mean ionized calcium concentrations during hospitalization in septic dogs (euthanized: median mean ionized calcium = 1.23 mmol/L [4.92 mg/dL], range = 0.96–1.32 mmol/L [3.84–5.28 mg/dL]; died: median mean ionized calcium = 1.19 mmol/L [4.76 mg/dL], range = 1.03–1.23 mmol/L [4.12 mg/dL–4.92 mg/dL]; discharged: median mean ionized calcium = 1.26 mmol/L [5.04 mg/dL], range = 1.09–1.38 mmol/L [4.36–5.52 mg/dL]). Patients that died had statistically significantly lower mean ionized calcium concentrations than those that were discharged ($P = 0.002$). No statistically significant difference in mean ionized calcium concentrations was found between those patients that died and were euthanized ($P = 0.11$) and between those that were euthanized and were discharged (median = 1.23 mmol/L [4.92 mg/dL], range = 0.96–1.32 mmol/L [3.84–5.28 mg/dL]; $P > 0.11$). The asterisks and triangles denote significant differences between compared groups (Wilcoxon-rank sum, $P < 0.05$).

dL]) ($P = 0.04$) (Figure 1). Septic canine patients that died had a significantly lower mean ionized calcium concentrations (median, 1.19 mmol/L [4.76 mg/dL]; range, 1.03–1.23 mmol/L [4.12–4.92 mg/dL]) than patients who were discharged (median, 1.26 mmol/L [5.04 mg/dL]; range, 1.09–1.38 mmol/L [4.36–5.52 mg/dL]) ($P = 0.002$). No statistically significant difference in mean ionized calcium concentrations was found between those patients that died and were euthanized ($P = 0.11$) and between those that were euthanized and were discharged (median, 1.23 mmol/L [4.92]; range, 0.96–1.32 mmol/L [3.84–5.28 mg/dL]) ($P = 0.11$) (Figure 2). No difference was found when comparing the highest ionized calcium concentrations and outcome ($P = 0.06$).

The association between lowest ionized calcium during hospitalization and morbidity was evaluated in patients surviving to discharge. A statistically significant association between the lowest ionized calcium and duration of hospitalization was found ($P = 0.045$; ρ, –0.35), demonstrating that a lower ionized calcium concentration during hospitalization was associated with a longer duration of hospitalization (Figure 3). No association between mean ionized calcium or highest ionized calcium and duration of hospitalization was found.

Three patients received packed RBC transfusions (2 patients that died received 22 and 16.9 mL/kg and 1 that was euthanized received 11.5 mL/kg). Patients that died received significantly more packed RBCs than patients that survived to discharge or that were euthanized ($P = 0.003$). Among patients receiving packed RBCs, there was no association between the total dose of packed RBCs received (on a mL/kg basis) and the lowest, mean, or highest ionized calcium concentrations. Fourteen patients received plasma transfusions (2 that died, 6 that were euthanized, and 6 that were discharged). There was no association between dose of plasma received and outcome, nor was there an association between dose of plasma administered and lowest, mean, or highest ionized calcium concentrations among patients receiving plasma transfusions.

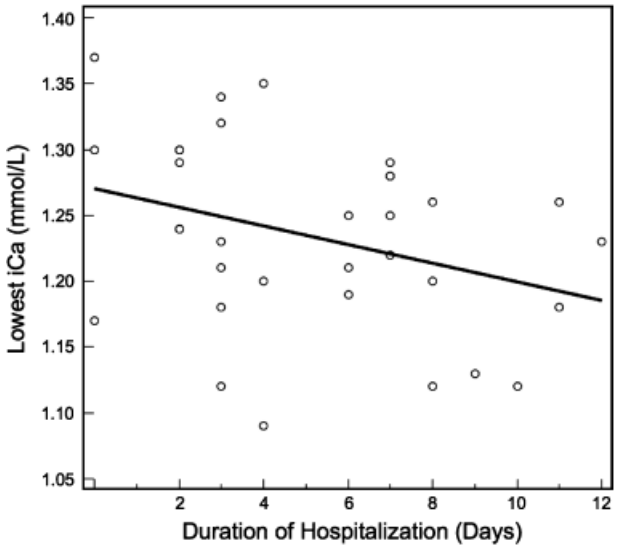

Figure 3: Scatter plot showing a linear relationship between lowest ionized calcium concentration during hospitalization and duration of hospitalization among dogs that survived to discharge. As depicted, a lower ionized calcium concentration was associated with a longer duration of hospitalization (Spearman's rank correlation, $\rho = -0.35$, $P = 0.045$).

Discussion

The incidence rate of iHCa among septic dogs in this study was 24%, similar to that reported in the human literature. Additionally, dogs with a worse outcome, namely cardiac or respiratory arrest during hospitalization, had a lower iCa compared with dogs that were euthanized or discharged. Furthermore, a statistically significant association was found between the degree of iHCa and morbidity as measured by duration of hospitalization. As described previously, in this study, the lowest concentration of ionized calcium was used to assess the severity of hypocalcemia during hospitalization, whereas the mean ionized calcium concentration was used to assess the trend in calcium concentrations throughout hospitalization. Because both lower mean and lowest ionized calcium concentrations were associated with poor outcome, the results of this study suggest that both severity and possibly duration of hypocalcemia may be important prognostic indicators in septic dogs.

As with all retrospective studies, there are several limitations of this study that must be acknowledged when interpreting these results. A large amount of variability existed in the frequency and number of blood gas analyses recorded; however, no statistically significant difference in the median number of ionized calcium measurements during hospitalization was noted between groups (euthanized = 1, range, 1–10; died = 2, range, 1–28; survived = 2, range 1–25). Although standard protocol for blood gas sample acquisition exists in this teaching hospital, the retrospective nature of this study precludes the ability to ensure protocol adherence. The use of mean ionized calcium concentration during the course of hospitalization as a summary measure reflecting the persistence of iHCa is a limitation that is unavoidable in this retrospective study, as there was no standardization in sampling frequency, making it likely that more data were collected early in hospitalization when the patient was more critically ill, which would potentially result in a bias toward lower mean ionized calcium concentrations, especially in animals that did not survive, and these data should be interpreted cautiously. The cause for euthanasia could not be discerned in most cases, and many patients with disease progressing toward arrest may have been included in this group. Because many cases were euthanized or died shortly after presentation to the hospital, the presence of other diseases that affected ionized calcium concentrations could not be definitively ruled out. Therefore, it is possible that such comorbidities affected the data. The contribution of blood component therapy to iHCa has been reported in both veterinary and human medicine; however, it is considered a transient result (minutes to hours) of calcium chelation by citrate used as an anticoagulant for blood storage.[19,20] Because hypocalcemia was documented in those patients that received packed RBCs at least 6 hours after transfusion, it is unlikely that citrate chelation was the cause of the iHCa in these cases. This finding is supported by the relatively low volume of packed cells administered, as no patient received volumes close to those defined as massive transfusion volumes, which may have led to more prolonged iHCa. The use of blood transfusions and duration of hospitalization as measures of morbidity must also be interpreted with caution given the retrospective study design. Because financial constraints can significantly affect the treatments administered in veterinary medicine, but the reasons behind treatment decisions can rarely be extracted from the medical record, it is not possible to fully discern the degree to which financial limitations may have played a role in these morbidity measures. Unfortunately, of the possible alternative morbidity measures, such as hypotension or pressor requirements, only duration of hospitalization and blood product usage could be independently verified from the medical record. Finally, the diagnosis of sepsis was determined based on the presence of an infectious focus; however, the exact etiologic agent(s) involved in these infections was not identified in many of these cases.

Because of the limitations of this study, a prospective study to evaluate the incidence rate or risk of iHCa among septic dogs is warranted. A prospective study would enable consistency in frequency and number of blood gas analyses, better evaluation of persistence of hypocalcemia, and more consistent confirmation and categorization of the underlying septic foci. With a more standardized approach, stronger inferences can be drawn from the association of iHCa with morbidity and outcome. Studies investigating the etiology of iHCa among critically ill veterinary patients are also warranted, as identification of the pathophysiologic mechanism(s) may allow more targeted therapy.

In critically ill human patients, the presence and degree of iHCa has also been associated with greater disease severity, morbidity, and mortality.[1,2] Studies investigating the etiology of iHCa in these patients suggest the pathophysiologic mechanism is multifactorial. Concentrations of PTH have been associated with disease severity and mortality in human patients suffering from iHCa of critical illness, suggesting derangements in the parathyroid axis as a possible cause for iHCa.[21] Of recent interest is the role of calcitonin precursors, namely procalcitonin (ProCT), in the development of iHCa. ProCT is a protein precursor to calcitonin produced during calcitonin synthesis. Extrathyroid expression of ProCT as well as increased serum concentrations of ProCT have been documented in critically ill patients, and have been shown to be a sensitive marker of sepsis as well as a prognostic indicator.[7,8,22,23] With the recent identification of the canine ProCT gene (the CALC-1 gene) expression using real-time polymerase chain reaction, a prospective investigation of ProCT's role in sepsis is now possible.[24]

Sepsis is the leading cause of death in human medical ICUs, and mortality rates from sepsis remain high, partially due to the delay in diagnosis and treatment.[25–27] The identification of early markers and prognostic indicators of sepsis may allow earlier diagnosis and treatment, which would likely reduce patient mortality. iHCa has been well documented as a prognostic indicator among critically ill human patients. iHCa among critically ill veterinary patients, however, has been a minimally researched topic. Knowledge of the incidence and prognostic significance of iHCa in septic veterinary patients may provide clinical indication for earlier aggressive therapy to improve outcome.

In addition to prospectively documenting the incidence and prognostic significance of iHCa in septic dogs, further investigations regarding the treatment of iHCa should be considered. Because of the life-threatening effects of iHCa, the current recommendation in human medicine is to treat iHCa with enteral or parenteral calcium supplementation.[1,6,17,28] Studies investigating calcium supplementation in critical illness, however, show conflicting results. Vincent et al [11]treated hypocalcemic critically ill patients with IV calcium chloride and documented an increase in arterial pressure. Alegre and Vincent[29] also documented dopamine dependence in hypocalcemic critically ill patients, and showed that calcium supplementation improved blood pressures and allowed rapid discontinuation of pressor therapy. Many other studies document similar positive effects of calcium supplementation in critically ill patients with iHCa.[30–37] Studies of calcium supplementation in animal models with experimentally induced sepsis or endotoxemia and iHCa, however, reveal variable outcomes. While some reports show similar positive hemodynamic effects of calcium supplementation as reported in the human literature,[38] others show no effect[14,39] or a detrimental effect with increased mortality among supplemented animals.[10,40,41] To the author's knowledge, no studies investigating the effects of parenteral calcium supplementation in critically ill veterinary patients with iHCa and naturally occurring disease exist.

In conclusion, iHCa may be an under-appreciated phenomenon in septic dogs, and further studies investigating its clinical ramifications are needed. This study documents the existence of iHCa in septic dogs, and shows an association between iHCa with morbidity (longer duration of hospitalization) and mortality (cardiopulmonary arrest). These data suggest that prospective studies investigating the incidence, etiology, and clinical sequelae of iHCa among septic dogs are warranted, and will offer the ability to more fully explore morbidity measures such as hypotension and pressor dependence.

Footnotes

[a] Bayer RapidPoint 400, Holliston, MA.
[b] MARQUEST™, Gaslyte, Englewood, CO.

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