Survival analysis of critically ill dogs with hypotension with or without hyperlactatemia: 67 cases (2006–2011)

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Objective—To determine whether critically ill hypotensive dogs without hyperlactatemia have the same prognosis as critically ill hypotensive dogs with hyperlactatemia.

Design—Retrospective case series.

Animals—67 critically ill dogs with hypotension.

Procedures—Medical records were searched from January 2006 through December 2011 for dogs that were hospitalized in the intensive care unit and that had hypotension and measurement of blood lactate concentration. Blood lactate concentration, systolic blood pressure, and survival rate were compared between hypotensive dogs with and without hyperlactatemia.

Results—19 of 67 (28%) dogs survived and were discharged from the hospital. Hypotensive dogs without hyperlactatemia had a significantly higher systolic blood pressure and were 3.23 (95% confidence interval, 1.04 to 9.43) times as likely to survive, compared with hypotensive dogs with hyperlactatemia. Age, weight, severity of clinical illness, and duration of hospitalization did not differ significantly between hypotensive dogs with and without hyperlactatemia.

Conclusions and Clinical Relevance—Results suggested that hypotensive dogs without hyperlactatemia had a better prognosis and chance of surviving to hospital discharge than did hypotensive dogs with hyperlactatemia. Because blood lactate concentration was negatively associated with systolic blood pressure and survival probability, it may be a useful metric for determining the prognosis of hypotensive dogs. (*J Am Vet Med Assoc* 2015;246:100–104)

Blood lactate concentration is commonly measured in critically ill veterinary patients to monitor tissue perfusion and detect anaerobic energy production. Patients with hypotension commonly develop hyperlactatemia subsequent to tissue hypoperfusion and disruption of normal lactate production and metabolism. Generally, the liver and kidneys metabolize lactate to compensate for its overproduction; however, during periods of severe hypoperfusion, those organs convert from lactate metabolizers to lactate producers.[1] Although hypotensive patients frequently develop hyperlactatemia, some never develop hyperlactatemia despite clinically apparent circulatory insufficiency. The relevance of clinically normal blood lactate concentration in hypotensive patients is poorly understood, which has led to steadfast attempts to detect and understand the effects of hyperlactatemia in critically ill patients.

Lactic acidosis is classified into 2 categories: type A and type B. Type A lactic acidosis occurs most frequently and is characterized by hypotension and hypoperfusion.

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Abbreviations

SBP	Systolic blood pressure
SPI2	Survival prediction index 2
Spo_2	Oxygen saturation as measured by pulse oximetry

Type B lactic acidosis is characterized by clinically normal blood oxygen concentration and SBP.[1,2] Patients that are administered certain drugs or toxins or that have mitochondrial defects or conditions that result in inadequate oxygen use (eg, sepsis, neoplasia, diabetes mellitus, and renal failure) typically develop type B lactic acidosis.[3,4]

Results of multiple clinical studies[2,5–9] involving veterinary patients indicate that hyperlactatemia is a strong prognostic indicator for many diseases including septic and hypovolemic shock, traumatic injuries, gastric dilatation-volvulus, and babesiosis. In 1 study,[9] dogs with septic shock that survived had significantly lower serum lactate concentration at hospital admittance than did dogs with septic shock that subsequently died. Current guidelines for the treatment of human patients with severe sepsis or septic shock strongly recommend serial monitoring of blood lactate concentration during resuscitation.[10] In hypotensive patients, blood lactate concentrations within the reference range might be indicative of a distinct physiologic state that has a better prognosis than does the physiologic state associated with hyperlactatemia.

The purpose of the study reported here was to compare the survival probability of critically ill hypotensive

dogs with hyperlactatemia with that of similar dogs without hyperlactatemia. We hypothesized that the survival probability for critically ill dogs with hypotension and hyperlactatemia would be worse than that for critically ill dogs with hypotension without hyperlactatemia. Additionally, we wanted to assess the respective relationships between survival probability and blood lactate concentration, presence of sepsis, severity of disease, and SBP.

Materials and Methods

Case selection—The medical record database of the Matthew J. Ryan Hospital of the University of Pennsylvania was searched for dogs that were hospitalized in the intensive care unit and were charged for measurement of blood lactate concentration during the period of January 2006 through December 2011. To be included in the study, a dog had to be hospitalized in the intensive care unit and have an SBP ≤ 90 mm Hg within 30 minutes (ie, concurrently with) before or after determination of blood lactate concentration. A dog was excluded from the study if SBP was > 90 mm Hg; SBP was not determined within 30 minutes before or after measurement of blood lactate concentration; the medical record was incomplete; a cause of type B lactic acidosis such as neoplasia, thromboembolism, carbon monoxide toxicosis, asthma, seizure activity, diabetes mellitus, thiamine deficiency, or renal failure was definitively diagnosed; or certain intoxicants or medications such as ethylene glycol, xylitol, cyanide, strychnine, ethanol, salicylates, high dose of epinephrine (> 0.02 µg/kg/min [> 0.01 µg/lb/min]), high dose of norepinephrine (> 0.3 µg/kg/min [> 0.14 µg/lb/min]), nitroprusside, bicarbonate, halothane, acetaminophen, terbutaline, total parenteral nutrition, or activated charcoal were ingested or administered. For all dogs, infection was diagnosed on the basis of cytologic or culture results of appropriate samples, and sepsis was defined as the presence of a confirmed infection with evidence of systemic inflammatory response syndrome.

Medical records review—For each dog, signalment, body weight, primary diagnosis, measurements of SBP and blood lactate concentration, and other variables such as PCV, Pa_{O_2}, Sp_{O_2}, results of observations of respiratory effort obtained within 3 hours after measurement of blood lactate concentration, duration of hospitalization, and whether the dog survived and was discharged from the hospital were extracted from the medical record. Systolic blood pressure was measured with a Doppler flow detector[a] with a 9.5-MHz probe. Hypotension was defined as SBP ≤ 90 mm Hg, and severe hypotension was defined as SBP ≤ 70 mm Hg. Blood lactate was measured by use of a lactate analyzer.[b] Hyperlactatemia was defined as a blood lactate concentration ≥ 2.0 mmol/L (18 mg/dL).[3] For dogs with multiple concurrent measurements of SBP and blood lactate concentration, only the blood lactate concentration obtained with the lowest SBP measurement was analyzed. Anemia was defined as a PCV < 30%.[11] Hypoxemia was defined as Pa_{O_2} < 80 mmol/L or Sp_{O_2} < 93%.[12,13] The severity of illness was assessed on the basis of SPI2, which was retrospectively calculated as described[14] when the necessary information was available.

Statistical analysis—The primary outcome of interest was whether each dog survived to discharge from the hospital (yes or no; survival). The respective relationships between lactate concentration (< 2.0 or ≥ 2.0 mmol/L) and survival, SBP (≤ 70 or > 70 mm Hg), and sepsis (yes or no) were investigated by means of separate χ^2 analyses. The relationship between hypotension (SBP ≤ 90 mm Hg) and survival was also investigated by means of χ^2 analysis. To determine the strength of each relationship, φ coefficients and OR were calculated. The data distributions for age, weight, SBP, SPI2, and duration of hospitalization were assessed for normality by means of the Kolomogorov-Smirnov test and by looking at skewness and kurtosis. The respective relationships of lactate concentration with independent variables that were normally distributed (SPI2, age, and SBP) were assessed with *t* tests. The respective relationships of lactate concentration with independent variables that were not normally distributed (weight and duration of hospitalization) were assessed with the Mann Whitney *U* test. Kaplan-Meier survival analysis was performed to further elucidate the relationship between lactate concentration and survival probability during hospitalization. All analyses were conducted with standard statistical software,[c] and values of $P < 0.05$ were considered significant for all analyses.

Results

Dogs—Sixty-seven dogs were enrolled in the study, of which 24 were spayed females, 8 were sexually intact females, 27 were castrated males, and 8 were sexually intact males. The dogs were admitted to the intensive care unit because of problems associated with the respiratory tract (n = 16), sepsis (13), gastrointestinal tract (10), hepatobiliary disease (8), cardiac disease (5), kidney disease (3), or other undefined diseases (12). Three dogs were treated with corticosteroids prior to hospitalization, and 2 dogs had a history of thromboembolic disease but were hospitalized for reasons other than thrombosis. Four dogs were treated with low-dose epinephrine while hospitalized. Neither liver failure nor cirrhosis was diagnosed in any of the dogs, despite the fact that 22 dogs had liver enzyme activities that were increased from the reference ranges. Twenty-five dogs were anemic (PCV < 30%), and 17 dogs were hypoxemic (Sp_{O_2} < 93% or Pa_{O_2} < 80 mmol/L). Systolic blood pressure and lactate concentration measurements were obtained after or during IV fluid therapy for 57 (85%) and 10 (15%) dogs, respectively. Although all dogs were hypotensive (SBP ≤ 90 mm Hg), 26 (39%) dogs were severely hypotensive (SBP ≤ 70 mm Hg). Of the 67 study dogs, 38 (57%) had hyperlactatemia (lactate concentration ≥ 2.0 mmol/L), whereas 29 (43%) did not have hyperlactatemia. Survival to hospital discharge was not significantly ($P = 0.73$) associated with hypotension.

Comparisons between hypotensive dogs with and without hyperlactatemia—The distribution of data for lactate concentration was positively skewed. The median lactate concentration for dogs with hyperlactatemia was 3.6 mmol/L (interquartile range, 2.0 mmol/L), whereas that for dogs without hyperlactatemia was 1.2 mmol/L (interquartile range, 0.3 mmol/L). Results of

Table 1—Descriptive statistics for critically ill hypotensive (SBP ≤ 90 mm Hg) dogs with (n = 38) or without (29) hyperlactatemia (blood lactate concentration ≥ 2.0 mmol/L [18 mg/dL]) examined between 2006 and 2011.

Variable	Dogs with hyperlactatemia	Dogs without hyperlactatemia	*P* value
Age (y)	7.16 ± 4.31	6.43 ± 5.37	0.540
Weight (kg)	9.60 (4.3–29.2)	6.50 (4.2–14.6)	0.234
SBP (mm Hg)	68.53 ± 13.6	75.83 ± 14.5	0.038
SPI2*	0.57 ± 0.17	0.49 ± 0.17	0.120
Duration of hospitalization (d)	2 (1–4)	3 (2–8)	0.076

Values reported are mean ± SD (normally distributed data) or median (interquartile range [25th percentile to 75th percentile]; nonnormally distributed [positively skewed] data).
*The SPI2 could be calculated for only 44 dogs (22 with hyperlactatemia and 22 without hyperlactatemia).
Comparisons between dogs with and without hyperlactatemia were performed with *t* tests for normally distributed data (age, SBP, and SPI2) and with Mann-Whitney *U* tests for nonnormally distributed data (weight and duration of hospitalization).

Table 2—Results of comparisons for survival to hospital discharge, development of severe hypotension (SBP ≤ 70 mm Hg), and the prevalence of sepsis for the dogs in Table 1.

Variable	Dogs with hyperlactatemia	Dogs without hyperlactatemia	χ^2	*P* value	φ	OR (95% confidence interval)*
Survival to discharge						
Yes	7	12	4.23	0.039	0.25	3.23 (1.04–9.43)
No	31	17	—	—	—	—
SBP						
> 70 mm Hg	19	22	4.63	0.031	0.26	3.14 (1.09–9.09)
≤ 70 mm Hg	19	7	—	—	—	—
Sepsis						
Yes	10	4	1.56	0.220	–0.15	0.45 (0.22–0.65)
No	28	25	—	—	—	—

*The referent group was dogs with hyperlactatemia and that survived to hospital discharge, had an SBP > 70 mm Hg, or had sepsis, and the comparison group was dogs without hyperlactatemia and that survived to hospital discharge, had an SBP > 70 mm Hg, or had sepsis.
— = Not applicable.
See Table 1 for remainder of key.

comparisons between hypotensive dogs with and without hyperlactatemia were summarized (**Tables 1 and 2**). The mean age (*P* = 0.540) and SPI2 (*P* = 0.120), the median weight (*P* = 0.234) and duration of hospitalization (*P* = 0.076), and the prevalence of sepsis (*P* = 0.220) did not differ significantly between hypotensive dogs with and without hyperlactatemia. The mean SBP for dogs with hyperlactatemia was significantly (*P* = 0.038) lower than that for dogs without hyperlactatemia. The φ coefficient (0.26) suggested there was a medium-strength association between lactate concentration and severe hypotension (SBP ≤ 70 mm Hg). Dogs without hyperlactatemia were 3.14 times as likely to have an SBP > 70 mm Hg (ie, not have severe hypotension) than were dogs with hyperlactatemia.

Of the 67 study dogs, 19 (28%) survived to discharge from the hospital, whereas 45 (67%) were euthanized and 3 (4%) died. Of the 48 hypotensive dogs that were euthanized or died while hospitalized, 31 had hyperlactatemia and 17 did not have hyperlactatemia. Thus, only 7 of 38 (18%) dogs with hyperlactatemia and 12 of 29 (41%) dogs without hyperlactatemia survived to discharge from the hospital. The φ coefficient (0.25) suggested there was a medium-strength association between lactate concentration and survival, and hypotensive dogs without hyperlactatemia were 3.23 times as likely to survive to hospital discharge than were hypotensive dogs with hyperlactatemia (**Table 3**). Results of the Kaplan-Meier survival analysis did not quite reach significance (log rank test, *P* = 0.053; Breslow test, *P* = 0.052; and Tarone-Ware test, *P* = 0.048). The 10-day survival probability was 42.7% for dogs without hyperlactatemia and 18.4% for dogs with hyperlactatemia (**Figure 1**). Therefore, the data suggested that dogs with hyperlactatemia were more likely to die or be euthanized the longer they were hospitalized, compared with the probability of death for dogs without hyperlactatemia.

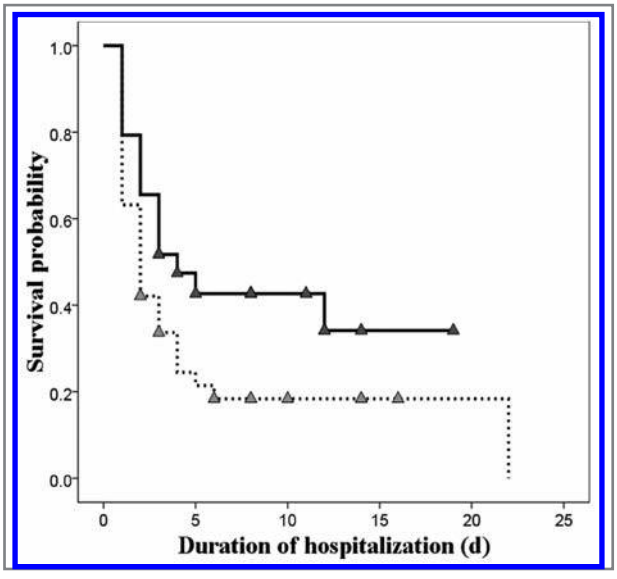

Figure 1—Kaplan-Meier survival curves for critically ill hypotensive (SBP ≤ 90 mm Hg) dogs with (n = 38; dotted line) and without (29; solid line) hyperlactatemia (lactate concentration ≥ 2.0 mmol/L [18 mg/dL]). The steps on each curve indicate the death of 1 or more dogs, and triangles indicate dogs that were censored (dogs that survived to hospital discharge).

Discussion

Results of the present study indicated that hypotensive dogs without hyperlactatemia had a better prognosis than did hypotensive dogs with hyperlactatemia. All 67 dogs evaluated in this study were critically ill as evidenced by the fact that the study population had a mean SPI2 (measure of disease severity) of 0.53 and 48 (72%) of the dogs were euthanized or died. Additionally, all of the dogs were treated in the intensive care unit and were hypotensive (SBP ≤ 90 mm Hg), with 57 (85%) remaining hypotensive and 38 (57%) having concurrent hyperlactatemia (lactate concentration ≥ 2.0 mmol/L) despite IV fluid therapy. On the basis of current guidelines for goal-directed therapy,[9,10] it is likely that patients such as these would have benefited from additional IV fluid therapy or other aggressive treatment (eg, administration of vasopressors).

Lactate is produced by cells during anaerobic metabolism caused by insufficient oxygen delivery to tissues subsequent to hypovolemia, blood loss, cardiogenic shock, septic shock, severe anemia, severe hypoxemia, carbon monoxide poisoning, or an increase in oxygen demand (eg, exercise, seizure activity, and shivering).[1,3,4] Lactate is derived from pyruvate and is converted to carbon dioxide, water, and ATP by oxidative decarboxylation in mitochondria during aerobic conditions.[1,2] However, in the absence of oxygen, the oxidative decarboxylation reaction cannot function and energy production relies on glycolysis.[1] The conversion of pyruvate to lactate by glycolysis yields only 2 moles of ATP per mole of glucose metabolized, whereas the conversion of pyruvate to lactate by oxidative decarboxylation yields 30 to 36 moles of ATP per mole of glucose metabolized.[1,2] Thus, although anaerobic metabolism is inherently less efficient than aerobic metabolism, it is vital for survival during periods of limited oxygen availability.

The role of hypoperfusion in the development of hyperlactatemia is critically important for understanding the overproduction and undermetabolism of lactate. Not all hypotensive animals develop hyperlactatemia. In the present study, 29 of 67 (43%) hypotensive dogs did not have hyperlactatemia, and the mean SBP for dogs with hyperlactatemia (68.53 mm Hg) was significantly lower than that for dogs without hyperlactatemia (75.83 mm Hg). This finding supports the concept that hypoperfusion-induced anaerobic metabolism causes hyperlactatemia.

The Kaplan-Meier survival analysis performed for the dogs of the present study resulted in 3 test statistics (Breslow [$P = 0.052$], Tarone-Ware [$P = 0.048$], and log rank [$P = 0.053$]) that were fairly consistent with each other and sufficiently close to the level of significance to warrant cautious interpretation. When assessing survival curves, the Breslow test investigates what happens early in the curve, the Tarone-Ware test investigates what happens in the middle of the curve, and log rank test investigates what happens late in the curve. Thus, the results suggested that dogs with hyperlactatemia were less likely to survive than were dogs without hyperlactatemia, especially after the first few days of hospitalization.

Results of 2 other studies[8,15] that involved critically ill dogs likewise indicated that blood lactate concentration was negatively associated with duration of survival. In 1 study,[8] dogs that had hyperlactatemia 6 hours after initiation of treatment were 16 times as likely to die, compared with dogs that did not have hyperlactatemia 6 hours after initiation of treatment. In the present study, hypotensive dogs without hyperlactatemia were 3.23 times as likely to survive to hospital discharge than were hypotensive dogs with hyperlactatemia, and the 10-day survival probability was only 18.4% for dogs with hyperlactatemia, compared with 42.7% for dogs without hyperlactatemia. Hyperlactatemia is indicative of impaired tissue perfusion and organ dysfunction, conditions that negatively affect survival probability; therefore, lactate concentration can be used as a prognostic indicator for clinically ill patients.

In human patients, the extent of lactic acidosis is associated with a decrease in oxygen delivery, extent of tissue hypoperfusion, and severity of disease.[16] Patients with lactic acidosis are at increased risk of developing multiple organ failure and dying, compared with patients without lactic acidosis.[17,18] The current Surviving Sepsis Campaign guidelines[10] recommend that blood lactate concentration be serially monitored during resuscitation of patients with severe sepsis, with the goal of returning lactate concentrations to within reference limits during the first 6 hours of resuscitation. The inclusion of hyperlactatemia in the definition for septic shock has been debated because it implies a poor prognosis. In a retrospective study[19] of 302 human patients with septic shock, 85 of 199 (42.9%) patients with hyperlactatemia died, whereas only 8 of 103 (7.7%) patients without hyperlactatemia died.

In the present study, hypotension (SBP ≤ 90 mm Hg) was not associated with dogs surviving to hospital discharge, which suggested that lactate concentration is a better indicator of tissue perfusion than is SBP. It is possible that survival might be associated with more severe hypotension (SBP ≤ 70 mm Hg). During analyses, we defined severe hypotension as an SBP ≤ 70 mm Hg on the basis of our own clinical experience that dogs with an SBP ≤ 70 mm Hg tend to have severe and often fatal disease. To our knowledge, studies to determine the appropriate SBP cutoffs for use as prognostic indicators of survival in critically ill dogs have not been performed.

The primary limitation of this study was its retrospective nature. Treatment protocols for each dog were not standardized, so continued hypovolemia as the cause of persistent hyperlactatemia cannot be ruled out. Evaluation of all critically ill dogs that met the inclusion criteria yielded a heterogeneous study population. The findings might have been different if the study population had been grouped on the basis of disease type, but this would have greatly reduced the sample size. Some of the dogs in the study might have had undiagnosed neoplasia. Necropsy results were not available for all of the dogs that were euthanized or died; therefore, we cannot rule out neoplasia as the cause of the hyperlactatemia in some of the dogs. Because critically ill dogs are very dynamic patients, measurement of variables such as PCV, Sa_{O_2}, Pa_{O_2}, and respiratory effort nearer to the time that lactate concentration was measured might have provided more precise clinical profiles for each

dog. Furthermore, evaluation of serial measurements of lactate concentration would have provided additional information, but this should be done prospectively for dogs treated with a standardized protocol to yield the most relevant results.

The mortality rates in the present study and most other veterinary studies should be interpreted with caution because dogs that were euthanized were not analyzed separately from those that died. A patient may be euthanized for reasons not directly related to its clinical condition; some patients with a poor prognosis might have been euthanized before severe secondary complications could develop, or some patients might have been euthanized because of financial constraints. We believe that most of the dogs in the present study were euthanized because of disease progression and a worsening prognosis rather than financial constraints, given that their owners had committed to having their pets treated in the intensive care unit. Prospective studies in which the reasons for euthanasia are recorded could provide information to better characterize similar patient populations.

Results of the present study suggested that critically ill hypotensive dogs without hyperlactatemia have a better prognosis than do critically ill hypotensive dogs with hyperlactatemia. Lactate concentration and SBP were negatively associated, and prospective studies are necessary to further elucidate this relationship. Prospective studies in which serial lactate concentrations are measured in patients with specific conditions (eg, traumatic injuries and septic shock) are warranted to determine whether lactate concentration can be used to accurately predict patient prognosis.

a. Accutrend, Parks Medical Electronics Inc, Aloha, Ore.
b. Roche Diagnostics GmbH, Mannheim, Germany.
c. IBM SPSS, version 21, IBM Corp, Armonk, NY.

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