Serial blood lactate concentrations in systemically ill dogs

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Background: Lactate concentration often is quantified in systemically ill dogs and interpreted based on human data. To our knowledge, there are no published clinical studies evaluating serial lactate concentrations as a prognostic indicator in ill dogs. **Objectives:** Our objective was to perform a prospective study, using multivariate analysis, to determine whether serial lactate concentrations were associated with outcome in ill dogs requiring intravenous fluids. **Methods:** Eighty sick dogs had lactate concentrations evaluated, using an analyzer that measures lactate in the plasma fraction of heparinized whole blood, at 0 hours and 6 hours after initiation of treatment. Severity of illness and outcome (survivor, nonsurvivor) were determined by reviewing the patient's record 2 weeks after admission. Lactate concentrations, age, body weight, gender, and severity of illness were evaluated using multivariate analysis to determine their effects on outcome. **Results:** Dogs with lactate concentrations greater than the reference interval at 6 hours were 16 times (95% confidence interval = 2.32–112.71 times, $P < .01$) more likely not to survive compared to dogs with lactate concentrations within the reference interval. Lactate concentrations above the reference interval at 0 hours were not significantly related to outcome. However, hyperlactatemia that did not improve by $\geq 50\%$ within 6 hours was significantly associated with mortality ($P = .024$). **Conclusion:** Dogs with a lactate concentration higher than the reference interval at 6 hours were more likely not to survive. These results indicate an association between lactate concentration and outcome and emphasize the importance of serial lactate concentrations in evaluating prognosis. (*Vet Clin Pathol.* 2007;36:234–239)
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L-Lactate (lactate) is the product of anaerobic glycolysis. Certain cells and tissues, including erythrocytes, skin, skeletal muscle, renal medulla, astrocytes, and glial cells produce more lactate than other cells under normal conditions.[1] Lactate is transported out of the cells via a membrane transporter and enters the bloodstream where it can be taken up and used by other cells. Cells with high oxidative capacity, such as skeletal and cardiac muscle, use lactate by converting it back to pyruvate and shunting it into the tricarboxylic acid cycle to produce ATP. However, the liver and, less so, the renal cortex, convert most of the lactate back to glucose via gluconeogenesis. The cellular metabolism of glucose to lactate, transport through the peripheral blood, hepatic uptake, gluconeogenesis, and release of glucose back into the peripheral blood is known as the Cori cycle. The Cori cycle provides vital peripheral tissues with energy that can be used under anaerobic conditions and prevents acidosis caused by an excess of lactate, at the expense of energy in the liver. The cycle uses more energy than it produces. Peripheral tissues make 2 moles of ATP for every mole of glucose when the end product is lactate, but the liver uses 6 moles of ATP to make 1 mole of glucose from lactate. This results in a total body deficit of 4 moles of ATP per mole of glucose.

Hyperlactatemia, in disease states, is the result of an imbalance between lactate production and lactate use caused by increased glycolysis under aerobic conditions, decreased tissue perfusion leading to anaerobic conditions, and/or diminished lactate use by the liver or kidneys.[2–5] Increased glycolysis with normal oxygenation has been reported to occur with sepsis, neoplasia, diabetes mellitus, severe liver disease, thiamine deficiency, epinephrine release or administration, alkalosis, hyperventilation, and with certain medications and toxins (acetaminophen, cyanide, and ethylene glycol). Classically, hyperlactatemia is associated with decreased tissue perfusion that can be the result of shock (hypovolemic, cardiogenic, and septic), local hypoperfusion (organ thrombosis and torsion), hypoxemia (severe anemia, carbon monoxide toxicity, and methemoglobinemia), or seizures. Decreased lactate use can result from decreased perfusion of the liver or sepsis affecting hepatic lactate metabolism.

Because lactate is produced during hypoperfusion and/or increased glucose use in a variety of disease conditions, it is a good indicator of severity of illness and a variable predictor of outcome in people.[6] Early studies in people showed that lactate concentrations before starting therapy (0 hour) were

different between survivors and nonsurvivors with cardiac disease, but others found little prognostic significance of initial lactate concentration in humans admitted to the surgical intensive care unit.[7,8] Research involving human subjects went on to establish that serial lactate measurements were more useful for prognostication of outcome for many different disease processes including injury, sepsis, and heart disease.[8–12]

We are aware of 3 published canine studies that have evaluated the role of initial blood lactate concentration in prognostication. Lagutchik was the first to evaluate whether lactate concentrations in dogs were different between survivors, dogs that died, and dogs that were euthanized.[13] He found, using univariate analysis, that initial lactate concentrations were significantly different between survivors and nonsurvivors; however, he recommended further evaluation of the usefulness of serial lactate measurements. In dogs with gastric dilatation-volvulus, a plasma lactate concentration <6.0 mmol/L was a good predictor of a positive outcome.[14] Jacobson found that in dogs with babesiosis, initial hyperlactatemia was predictive of a poor outcome.[15]

Reports of serial measurements of lactate concentrations in dogs are limited. One study in dogs with babesiosis used serial lactate concentrations as a prognostic indicator.[16] Dogs with hyperlactatemia at presentation, and with increasing lactate concentrations or lactate concentrations that did not decrease by more than 50% within 24 hours were more likely to die than those with lactate concentrations that decreased by more than 50%.[16] Zero-hour lactate concentrations ≥5 mmol/L and 8-hour lactate concentrations >2.5 mmol/L were valuable indicators of a negative outcome in the same study.[16] We hypothesized that lactate concentrations above the reference interval before starting intravenous fluid therapy (0 hour) and 6 hours after fluid therapy would be associated with a negative outcome and could be valuable prognostic indicators of negative outcomes when other factors that could also affect outcome (ie, age, gender, body weight, and severity of illness) were taken into consideration.

Materials and Methods

Eighty client–owned dogs admitted to the Veterinary Teaching Hospital at the Western College of Veterinary Medicine between May 30, 2005 and January 10, 2006 were assessed in this prospective study. The criteria for selection included sick dogs with a variety of illnesses that were deemed by the attending clinician to require intravenous fluids. Dogs were not included if they had received intravenous fluids within the previous 48 hours or if dextrose was included in the intravenous fluids.

Heparinized jugular venous or arterial blood samples were obtained at 0 hour (initiation of fluid therapy) using 2-mL blood gas syringes containing 80 IU of lyophilized heparin (PICO 50 Radiometer, Copenhagen, Denmark). Lyophilized heparin was used to decrease dilutional errors in lactate concentrations.[17] Samples were evaluated using a Rapidlab 865 blood gas analyzer (Bayer Diagnostics, East Walpole MA, USA) within 5 minutes of sample collection or within 15 minutes for samples maintained on ice to prevent in vitro

lactate production.[18,19] Testing was repeated 6 hours after the initiation of fluid therapy (80 samples).

The Rapidlab 865 uses a 3-layer electrochemical biosensor that uses an enzymatic reaction, lactate oxidase, and an amperometric endpoint measured at 675 mV through hydrogen peroxide, to measure lactate concentration. Using this method, lactate is measured in the plasma fraction of whole blood samples, so it often is referred to as blood lactate concentration, not plasma lactate concentration. The within-day CV is 2.8% and between-day CV is 4.6%. Results correlate (Pearson correlation coefficient 0.917) to lactate concentrations measured on a Nova-Stat Profile M (Nova Biomedical Corporation, Waltham, MA, USA), which is monitored using International Organization for Standardization (ISO) procedures in the Central Laboratories for Veterinarians (Langley, British Columbia, Canada). The Rapidlab 865 performs 1-point calibrations every 2 hours and 2-point calibrations every 4 hours with weekly maintenance. For this specific machine, the reference interval (mean ± 2 SD) for canine jugular venous blood lactate concentration is 0.46–2.31 mmol/L with a positive correlation to age (lactate concentrations in younger dogs are at the low end of the reference interval and lactate concentrations in older dogs are at the high end of the reference interval).[20] The reference interval was established previously from 100 clinically healthy dogs of which 52 were females (intact and neutered) and 48 were males (intact and neutered) with an age range from 2 months to 15 years (mean = 4.67 years).

The American Society of Anesthesiologists' physical status (ASAPS) scoring system was used to categorize the 80 ill dogs in this study.[21,22] Medical records from the 80 patients were reviewed and ASAPS scores assigned without knowledge of the lactate concentrations. Patients were then grouped into those with nonlife-threatening illness and likely to survive (ASAPS I-III) and those with life-threatening illness and less likely to survive even with intervention (ASAPS IV-V). Survivors were defined as dogs that were alive at 2 weeks after admission and nonsurvivors were defined as dogs that died naturally or were euthanized by 2 weeks after admission. The time of death was not assessed.

For analysis, dogs were grouped into 3 age categories: young (≤1 year), mature (>1 and <8 years), and geriatric (≥8 years). Dogs were grouped by body weight as <10 kg, 10–20 kg and >20 kg. Statistical software (Excel, Microsoft Corp, Seattle, WA, USA) was used to chart all of the data. Lactate concentrations at 0 hours and 6 hours were categorized as >2.3 mmol/L (the upper limit of the reference interval) or <2.3 mmol/L lactate. Lactate clearance was calculated for the 28 dogs that were hyperlactatemic at presentation using the following formula: lactate clearance = (lactate concentration$^{0 \text{ hour}}$ − lactate concentration$^{6 \text{ hour}}$)/lactate concentration$^{0 \text{ hour}}$ × 100%. Lactate clearance was categorized as ≥50% or <50%. Initially, the relationship between patient survival and the 3 lactate concentration variables as well as age, gender, body weight, and severity of illness categories were independently evaluated using a univariate chi-square analysis.[23] Further, a multivariate logistic regression model was used to determine whether lactate concentration remained significantly associated with patient survival when factors that might affect outcome (ie, age, gender, body weight, and severity of illness)

Table 1. Association between lactate concentration, lactate clearance in dogs with hyperlactatemia, age, gender, body weight, severity of illness, and outcome (survivors vs nonsurvivors) in 80 dogs.

Parameter	Group	% Survivors	% Nonsurvivors	P value*
0-h lactate	≤ 2.3 mmol/L	68.6	40.0	0.088
	> 2.3 mmol/L	31.4	60.0	—
6-h lactate	≤ 2.3 mmol/L	88.6	40.0	0.0042
	> 2.3 mmol/L	11.4	60.0	—
6-h lactate clearance	≥50%	68.2	16.7	0.024
	<50%	31.8	83.3	—
Age	≤1 year	31.4	20.0	0.023
	>1 to <8 years	48.6	20.0	—
	≥8 years	20.0	60.0	—
Gender†	Female	45.7	40.0	0.734
	Male	54.3	60.0	—
Body weight	< 10 kg	25.7	40.0	0.370
	10–20 kg	42.9	20.0	—
	>20 kg	31.4	40.0	—
Severity	ASAPS I–III	60.0	30.0	0.074
	ASAPS IV–V	40.0	70.0	—

*Univariate chi-square analysis comparing survivors vs. nonsurvivors for all groups within each parameter.

†Includes both intact and neutered dogs.

were considered as potential confounding variables.[24] The model's goodness-of-fit was checked using the Hosmer and Lemeshow statistic.[24] Both univariate and multivariate analyses were performed using Intercooled Stata 8.2 (StataCorp LP, College Station, TX, USA). The level of significance (α) was .05.

Results

The average age of the 80 dogs was 4.96 years (range, 2 months to 16 years). There were 36 females (intact and neutered) and 44 males (intact and neutered). Illnesses included nonparvovirus gastrointestinal disease (26 cases, 1 death), trauma (15 cases, 3 deaths), parvovirus infection (10 cases, 0 deaths), toxin exposure (8 cases, 0 deaths), neurologic disease (7 cases, 0 deaths), metabolic disease (4 cases, 2 deaths), neoplasia (4 cases, 3 deaths), respiratory distress (3 cases, 0 deaths), pyometra (2 cases, 0 deaths), and septicemia (1 case, 1 death). There were 70 survivors and 10 nonsurvivors (12.5% mortality rate).

Univariate analysis indicated that 6-hour lactate concentration, a failure to improve lactate concentration by >50% in hyperlactatemic dogs, and age were significantly different between survivors and nonsurvivors (Table 1). However, 0-hour lactate concentration, severity of illness, body weight, and gender were not different between survivors and nonsurvivors.

Multivariate analysis showed that lactate concentration at 6 hours remained significant ($P < .01$) (Table 2). The Hosmer

and Lemeshow goodness-of-fit χ^2 statistic indicated that the 6-hour lactate model fit the data well ($P = .59$).[24] Dogs with blood lactate concentrations >2.3 mmol/L at 6 hours were 16 times (95% CI = 2.3–112.7 times) more likely to not survive compared with dogs that had lactate concentrations within the reference interval (≤2.3 mmol/L) at 6 hours when age, gender, body weight, and severity of illness were considered.

Discussion

Many factors determine outcome for systemically ill dogs. These include type of illness, severity of the illness, treatment used, response to treatment, age, body weight, gender, body condition score, and financial considerations of the owner. Ideally all of these factors are considered when attempting to identify whether a single factor has prognostic significance. Using multivariate analysis, we determined that high lactate concentration at 6 hours was associated with a poor prognosis in systemically ill dogs. The variables assessed included age, gender, body weight, and ASAPS severity score of the dogs.

A definition of "serial" is "occurring in regular succession."[25] In this study we evaluated serial measurements of lactate concentration in 80 dogs. Lactate concentrations were evaluated independently at 0 and 6 hours. Lactate clearance between 0 and 6 hours was calculated for individual hyperlactatemic dogs.

To the authors' knowledge, only 2 studies report the use of multivariate analysis to determine whether lactate concentration assists prognostication, in dogs with gastric-dilation-volvulus[14] and babesiosis.[16] Neither study clearly defined the variables that were used in the multivariate analysis.

Table 2. Association between 6-hour lactate concentration and outcome by multivariate logistic regression analysis.*

Parameter†	Group	B	SE	P value	Odds Ratio	95% CI
6-h lactate	≤2.3 mmol/L	—	—	—	1	—
	>2.3 mmol/L	2.78	0.99	<0.01	16.17	2.32–112.70
Age	≤1 y	—	—	—	1	—
	>1 to <8 y	0.99	1.35	0.46	2.69	0.19–37.69
	≥ 8 y	2.32	1.21	0.057	10.17	0.93–110.69
Gender‡	Female	—	—	—	1	—
	Male	0.24	0.92	0.79	1.27	0.21–7.68
Body weight	<10 kg	—	—	—	1	—
	10–20 kg	−1.88	1.25	0.14	0.15	0.013–1.80
	>20 kg	−0.96	1.04	0.36	0.38	0.050–2.97
Severity	ASAPS I–III	—	—	—	1	—
	ASAPS IV–V	1.13	0.88	0.20	3.08	0.55–17.28
Constant		−3.92	1.27	<0.001	—	—

*B indicates regression coefficient; SE, standard error of B; CI, confidence interval of the odds ratio.

†Age, gender, body weight and severity of disease were kept in the model as potential confounding factors regardless of their significance.

‡Includes both intact and neutered dogs.

Multivariate analysis is important when determining whether a variable is a prognostic indicator because it takes into account the association that each variable has on each other as well as on the outcome.[26]

In *Babesia canis*-infected dogs, lactate concentrations were categorized into 3 groups (given in mg/dL but converted here to SI units): ≤2.5 mmol/L, >2.5 to <5 mmol/L, and ≥5 mmol/L.[16] At 0 and 8 hours, lactate concentrations ≥5 mmol/L were significantly different between survivors and nonsurvivors. Also at 8 hours, lactate concentrations of >2.5 to <5 mmol/L were significantly different between survivors and nonsurvivors. These results are similar to our results. However, *B canis* organisms may have contributed to the lactate concentration. In a recent study, an increase in lactate concentration was found in serum samples from a sheep infected with *Mycoplasma ovis*, also an erythrocyte parasite, caused by production of lactate by the organisms.[27]

The upper limit of the reference interval (2.3 mmol/L) was chosen as a cut-off point in our study because returning an elevated lactate concentration to within the reference interval is a goal of therapy in the clinical setting. Also, reference intervals depend on the instrument used, therefore, using the upper limit, regardless of the numerical value, may be a useful guideline. As with all laboratory values, individual variation and instrument precision and accuracy will affect single lactate concentrations. Additional studies will be required to determine whether the upper limit of the reference intervals for different instruments is an appropriate clinical decision limit or whether 2.3 mmol/L can be broadly applied.

The odds ratios, in this study, were estimates of the relative risk of nonsurvival at 2 weeks associated with 6-hour hyperlactatemia after adjusting for age, gender, body weight and severity score.[24] Odds ratios are clinically useful for allowing the strength or relative significance of a prognostic factor to be further investigated. In the babesiosis study, dogs with blood lactate concentrations >5 mmol/L at 0 hours were 8 times more likely to die than dogs with blood lactate concentrations ≤2.5 mmol/L. At 8 hours, dogs with blood lactate concentrations >2.5 to <5 mmol/L were 13 times more likely to die, and dogs with blood lactate concentrations >5mmol/L were 83 times more likely to die than dogs with blood lactate concentrations <2.5 mmol/L. In our study, we found that the odds of nonsurvival were significantly higher for dogs with 6-hour lactate concentrations >2.3 mmol/L when compared to dogs with lower 6-hour lactate concentrations. Interestingly, 0-hour lactate levels were not associated with survival. This suggests that lactate concentration at 6 hours after admission may be a good prognostic indicator in systemically ill dogs when age, gender, body weight, and severity of illness are considered.

In this study, dogs that initially had lactate concentrations >2.3 mmol/L and that failed to improve their lactate concentration by ≥50% were associated with a nonsurvivor outcome compared with dogs that improved their lactate concentration by ≥50%. In the canine babesiosis study, hyperlactatemia on presentation and an increase or a failure to decrease lactate by 50% was significantly associated with mortality compared to lactate concentrations that decreased by more than 50% ($P = .008$).[16] These results indicate an

association between response to therapy, in the form of improved lactate concentration, and outcome. As only 28 dogs had hyperlactatemia at presentation in our study, multivariate analysis could not be performed to assess the likelihood of dying. Not all dogs could be included in the clearance assessment because many dogs had lactate concentrations that were within the reference interval. Inclusion of this data would have caused a negative bias on clearance assessment.

Lactate concentration increases with excitement, agitation, exercise, and prolonged occlusion of the sampled vessel.[19] Serial lactate measurements may decrease error, as these physiologic increases in lactate concentration are less likely to persist. Serial lactate concentrations probably reflect response to therapy and severity of illness in systemically ill dogs. Future studies are indicated to evaluate lactate concentrations at additional time points (ie, 12, 24, and 48 hours) following initiation of therapy to verify this association.

Jugular venous and arterial blood samples were used because plasma lactate concentrations in healthy dogs are reported to vary by sample site; jugular lactate concentrations correlate best with arterial plasma lactate concentrations.[28] Chrusch et al[29] administered lactate to septic and nonseptic dogs, and found that jugular venous lactate concentrations were significantly lower than central venous lactate concentrations at the time of spiking, but that this difference was corrected within 15 minutes.

Intravenous fluids were prescribed and administered by the attending clinician in this study. In order for a dog to be included in the study, intravenous fluids could not contain dextrose, as prior studies have shown that use of such fluids increases the lactate concentration.[29] Lactated ringers solution was acceptable therapy as Didwania showed that intravenous administration did not affect lactate levels when blood was sampled from a different site than the fluid administration.[30]

The ASAPS scoring system was used to categorize the 80 ill dogs in the study: I is a healthy patient, II is a patient with mild systemic disease, III is a patient with severe systemic disease, IV is a patient with severe systemic disease that is a constant threat to life, and V is a moribund patient not expected to survive 24 hours with or without intervention.[21,22] This is a largely subjective severity scoring system based on clinical disease and clinical assessment of hydration status. Severity was very close to correlating with outcome in this study. The lack of statistical significance could be related to the subjective nature of the categorization, low numbers of dogs in the study, lack of equal representation of all categories, low number of dogs that did not survive, or nonmedical reasons for the outcome (financial considerations of the owners). To the authors' knowledge, there is no scoring system in veterinary medicine that has been tested to be associated with outcome. This study was not intended to evaluate the ASAPS scoring system and future investigation is required.

Mortality in this study was low, as only 10 of the 80 dogs (12.5%) did not survive. This mortality rate was almost half of that found in another study. Lagutchik et al[2] reported a prevalence of 24% for nonsurvivors. Despite the low mortality rate, 5 out of the 10 illness categories contained nonsurvivors indicating that mortality was not clustered with a single disease process. Future studies with more severely

affected dogs (increased likelihood of nonsurvival) are indicated to further assess the use of serial lactate concentrations as a prognostic indicator. In addition to age, gender, body weight, and severity of illness, other variables that could be evaluated relative to lactate concentrations in ill dogs are: type of illness, treatment used, response to treatment, mentation, blood pressure, PaO_2, PvO_2, pH, body temperature (including rectal to extremity difference), heart rate, pulse quality, mucous membrane color, capillary refill time, respiratory rate, hydration status, and body condition score.

A potential bias associated with this observational study was individual variability of patients and treatments. Many clinicians participated in the study and treatment protocols varied. More aggressive treatment and fluid therapy could have lowered lactate concentrations at 6 hours relative to less aggressive therapy. Euthanasia also was a factor relative to outcome and may have been more dependent on the owner's financial situation than on clinical disease. Specifically, this could have resulted in more nonsurvivors in one or both lactate concentration categories.

Lactate production also relates to disease type, as not all disease processes increase lactate concentration to the same extent. Hypoperfusion from blood loss or trauma can result in high initial lactate concentrations that often improve rapidly with restoration of tissue perfusion.[5,11] These patients would be expected to have marked improvement in lactate concentrations at 6 hours, which would have strengthened our data. The increase in lactate concentration with septic shock, on the other hand, is multifactorial because of hypoperfusion, downregulation of pyruvate dehydrogenase activity (decreased tricarboxylic acid cycle energy production), and increased glycolysis, with accelerated lactate production from various tissues include lung, intestines, and even liver.[5,10,27,31,32] These patients may have protracted illness and increased complications that may not relate to improvement in lactate concentrations at 6 hours. The low number of nonsurvivors and diversity of illnesses precluded drawing conclusions about specific diseases, lactate and outcome.

Some treatments increase blood lactate concentration and could have contributed to a bias. Activated charcoal, often used in patients exposed to toxins, often contains propylene glycol or glycerol, which can increase lactate concentration in dogs, with peak concentrations occurring at 4 hours.[33] Seven dogs received activated charcoal (Charcodote, Pharamscience Inc, Montreal, Canada) in the present study. This form of activated charcoal contains sorbitol and not propylene glycol or glycerol and, therefore, was unlikely to affect lactate concentrations in the current study.

In conclusion, dogs with high lactate concentrations at 6 hours, despite therapy, were 16 times more likely to not survive after age, gender, body weight, and ASAPS severity score were considered. Because lactate concentrations >2.3 mmol/L at presentation (0 hour) did not differ significantly between survivors and nonsurvivors, repeat or serial lactate measurement in systemically ill dogs may be particularly important. This argument was strengthened by the finding that hyperlactatemia that did not improve by ≥50% within 6 hours was significantly associated with mortality. The high odds ratio (16) could be helpful to clinicians to show strength of association between lactate concentration and likelihood of not surviving in systemically ill dogs requiring intravenous fluid therapy. Caution should be exercised in extrapolating population data to individual patients. No single piece of data should be used to prognosticate, and lactate concentrations in dogs should be interpreted relative to clinical signs and other clinical parameters. Further investigation is needed to evaluate prognostication capabilities of lactate concentration in conjunction with other clinical information.

References

1. Smith CM, Marks A, Lieberman M. *Marks' Basic Medical Biochemistry: A Clinical Approach.* Philadelphia, PA: Lippincott Williams & Wilkins; 2005:407–408, 412–414.

2. Lagutchik MS, Ogilvie GK, Wingfield WE, Hackett TB. Lactate kinetics in veterinary critical care: a review. *J Vet Emer Crit Care.* 1996;6:81–95.

3. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med.* 1995;98:75–84.

4. Kruse JA, Fink MP, Carlson RW. *Saunders Manual of Critical Care.* Philadelphia, PA: Saunders; 2003:158–160

5. Pittard AJ. Does blood lactate measurement have a role in the management of the critically ill patient? *Ann Clin Biochem.* 1999;36:401–407.

6. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation.* 1970;41:989–1001.

7. Henning RJ, Weil MH, Weiner F. Blood lactate as prognostic indicator of survival in patients with acute myocardial infarction. *Circ Shock.* 1982;9:307–315.

8. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. *Am J Surg.* 2003;185:485–491.

9. Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. *Crit Care Med.* 1983;11:449–451.

10. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med.* 2004;32:1637–1642.

11. Cerovic O, Golubovic V, Spec-Marn A, Kremzar B, Vidmar G. Relationship between injury severity and lactate levels in severely injured patients. *Intensive Care Med.* 2003;29:1300–1305.

12. Smith I, Kumar P, Molloy S, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. *Intensive Care Med.* 2001;27:74–83.

13. Lagutchik MS, Ogilvie GK, Wingfield WE, Hackett TB. Increased lactate concentrations in ill and injured dogs. *J Vet Emer Crit Care.* 1998;8:117–127.

14. de Papp E, Drobatz KJ, Hughes D. Plasma lactate concentration as a predictor of gastric necrosis and survival among dogs with gastric dilatation-volvulus: 102 cases. *J Am Vet Med Assoc.* 1999;215:49–52.

15. Jacobson LS, Lobetti RG. Glucose, lactate, and pyruvate concentrations in dogs with babesiosis. *Am J Vet Res.* 2005;66:244–250.

16. Nel M, Lobetti RG, Keller N, Thompson PN. Prognostic value of blood lactate, blood glucose and hematocrit in canine babesiosis. *J Vet Intern Med.* 2004;18:471–476.

17. Hopper K, Rezende ML, Haskins SC. Assessment of the effect of dilution of blood samples with sodium heparin on blood gas, electrolyte, and lactate measurements in dogs. *Am J Vet Res.* 2005;66: 656–660.

18. Burtis CA, Ashwood ER, Bruns DE. *Teitz Textbook of Clinical Chemstry and Molecular Diagnostics.* 4th ed. St. Louis, MO: Elsevier Saunders; 2006:877–878.

19. Christopher MM, O'Neill S. Effect of specimen collection and storage on blood glucose and lactate concentrations in healthy, hyperthyroid and diabetic cats. *Vet Clin Pathol.* 2000;29:22–28.

20. Stevenson CK, Kidney BA, Duke T, Snead ECR, Jackson ML. Evaluation of the Accutrend for lactate measurement in dogs. *Vet Clin Pathol.* 2007;36:**XX–XX**

21. Thurman JC, Tranquilli WJ, Benson GJ. *Lumb Jones Veterinary Anesthesia.* 3rd ed. Baltimore, MD: Williams and Wilkins; 1996:21–22.

22. Wolters U, Wolf T, Stutzer H, Schroder T. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth.* 1996;77:217–222.

23. Petrie A, Watson P. *Statistics for Veterinary and Animal Science. London, England: Blackwell Science;* 1999:56,134.

24. Hosmer DW, Lemeshow S. *Applied Logistic Regression.* New York: Wiley; 1989:307.

25. Babcock Gove P ed. *Webster's Third New International Dictionary of the English Language, Unabridged.* Springfield, MA: Merriam-Webster; 1993:2073.

26. Hermanek P. Prognostic factor research in oncology. *J Clin Epidemiol.* 1999;52:371–374.

27. Burkhard MJ, Garry F. Artifactual hypoglycemia associated with hemotrophic mycoplasma infection in a lamb. *Vet Clin Pathol.* 2004;33: 244–248.

28. Hughes D, Rozanski ER, Shofer FS, Laster LL, Drobatz KJ. Effect of sampling site, repeated sampling, pH and PCO_2 on plasma lactate concentration in healthy dogs. *A J Vet Res.* 1999;60:521–523

29. Chrusch C, Bautista E, Jacobs HK, et al. Blood pH level modulates organ metabolism of lactate in septic shock in dogs. *J Crit Care.* 2002;17: 188–202.

30. Didwania A, Miller J, Kassel D, Jackson EV Jr, Chernow B. Effect of intravenous lactated Ringer's solution infusion on the circulating lactate concentration: Part 3. Results of a prospective, randomized, double-blind, placebo-controlled trial. *Crit Care Med.* 1997;25:1851–1854.

31. Kellum JA. Metabolic acidosis in patients with sepsis: epiphenomenon or part of the pathophysiology? *Crit Care Resusc.* 2004;6:197–203.

32. Hart DW, Chinkes DL, Gore DC. Increased tissue oxygen extraction and acidosis with progressive severity of sepsis. *J Surg Res.* 2003;112: 49–58.

33. Burkitt JM, Haskins SC, Aldrich J, Jandrey KE, Rezende ML, Boyle JE. Effects of oral administration of a commercial activated charcoal suspension on serum osmolality and lactate concentration in the dog. *J Vet Intern Med.* 2005;19:683–686.