Prognostic value of blood lactate, blood glucose and hematocrit in canine babesiosis

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Abstract
Canine babesiosis typically causes hemolytic anemia, but also can result in multiple organ dysfunction. Human patients with severe disease often have persistent hyperlactatemia, and blood lactate concentration is correlated with survival rate. In dogs, blood lactate concentration has been shown to be of prognostic value in patients with gastric dilatation-volvulus and in dogs admitted to intensive care units. Serial blood lactate and glucose concentrations and hematocrit on admission were determined in 90 dogs with naturally-occurring, severe or complicated canine babesiosis. Forty-five dogs (50%) had hyperlactatemia (blood lactate concentration > 22.5 mg/dL) and 20 (22.2%) had hypoglycemia (blood glucose concentration < 59.4 mg/dL) at presentation. Measurements significantly associated with mortality were hypoglycemia on admission, blood lactate concentration > 45 mg/dL on admission, blood lactate concentration > 22.5 mg/dL at 8, 16 and 24 h after admission, and increase or < 50% decrease in blood lactate concentration within 8 and 16 h after admission. Blood lactate concentration persistently > 40 mg/dL indicated a very poor prognosis. We conclude that serial blood lactate measurements are useful in predicting survival in dogs with severe and complicated canine babesiosis.

Key words
Dog, *Babesia canis rossi*

Canine babesiosis is a tick-borne disease caused by the hemoprotozoan parasites, *Babesia canis* or *B. gibsoni*. Three subtypes of *B. canis* exist of which *B. canis rossi* occurs in South Africa [1-3]. The disease typically causes hemolytic anemia, but also can result in multiple organ dysfunction[4]. The hemolytic crisis that develops can result in anemic hypoxia, anaerobic metabolism, and metabolic acidosis[5].

During carbohydrate metabolism, glucose is metabolized to pyruvate. Pyruvate then follows one of 5 different pathways: (1) lipogenesis, (2) oxidation via the Kreb's cycle, (3) formation of alanine, (4) gluconeogenesis, or (5) conversion to lactate[6] (Figure 1). During anaerobic conditions, pyruvate is converted to lactate as an energy substrate. Lactate is transported to the liver, which is primarily responsible for lactate metabolism[7]. When lactate production exceeds the capacity of the liver to metabolize it, hyperlactatemia occurs[8, 9]. During disease states, a pathological hyperlactatemia is seen either due to increased production or decreased utilization[10, 11]. Increased production is seen with tissue hypoxia and increased rate of metabolism[7], whereas decreased utilization of lactate usually involves tissue hypoxia, leading to a decreased functioning of the 3 aerobic pathways due to anaerobic conditions[10].

Hyperlactatemia in severe disease has been ascribed to a combination of tissue hypoxia and increased metabolism [9]. Human patients suffering from severe injury or infection can have persistent hyperlactatemia[12]. Studies investigating blood lactate concentrations in shock have shown a correlation between blood lactate concentration and survival rate[13-15], in which human patients who were in septic shock and in whom the lactate concentration remained high despite treatment, had a higher mortality rate compared to patients who experienced a decrease in lactate concentration[16]. One study in humans suffering from circulatory shock[17], showed that blood lactate concentrations started to decrease within the first h of starting appropriate therapy, whereas patients who did not respond to therapy showed no significant changes in blood lactate concentration. Lactate alone served as the best prognostic indicator of survival, and it was concluded that in patients who did not experience significant decreases in blood lactate concentration after 1 h of aggressive therapy, alternative therapy should be considered. Also, the ability to clear lactate within 24 h of starting appropriate therapy correlated well with survival in patients suffering from multiple trauma[18]. Several studies in human malaria patients suffering from acute, cerebral or severe malaria showed that increased blood lactate concentrations affected survival rate[19-23], and patients with persistent hyperlactatemia were far more likely to die when compared to patients who experienced a decrease in blood lactate concentration after initiation of therapy.

Blood lactate measurement has been shown to be of prognostic value in equine colic[24-30], and horses with the highest lactate concentrations had the highest mortality rates.

In dogs with gastric dilatation-volvulus, venous lactate concentration was a good predictor of gastric necrosis and outcome[31]. Another study in dogs admitted for emergency care for various diseases showed an association between the severity of the hyperlactatemia at admission and outcome, and dogs with the highest blood lactate concentrations were more likely to die[32].

To date, the serial measurement of lactate in severely ill dogs and its use as a prognostic indicator have not been reported. The aim of this study was to determine whether dogs with severe or complicated canine babesiosis suffer from hyperlactatemia, and whether blood lactate and blood glucose concentrations and hematocrit could be used as prognostic indicators.

Materials and Methods

The Animal Use and Care Committee and the Research Committee of the University of Pretoria approved this study. Ninety dogs with naturally-occurring, severe, uncomplicated and complicated canine babesiosis infection were used in this prospective study. Inclusion criteria were a positive identification of *B. canis rossi* parasites on a stained thin capillary blood smear using Cams Quick Stain[a], and admission to the Onderstepoort Veterinary Academic Hospital (OVAH) due to either severe anemia (hematocrit < 15%) or complications such as respiratory distress, acute renal failure (urine production < 1 ml/kg/h that did not respond to rehydration), hepatic involvement (abnormally high alanine amino transferase [ALT], alkaline phosphatase [ALP], icterus), pancreatitis, hemoconcentration, hypotensive shock, electrolyte imbalances (abnormal sodium or potassium concentrations), hypoglycemia, coagulopathy or immune-mediated hemolytic anemia.

Approximately 1 ml of blood was collected from the jugular vein into a heparinized syringe before treatment. Animals then were treated by standard OVAH protocol for canine babesiosis, which included an anti-babesial drug and blood transfusion as needed. All dogs with complications were treated for the specific complication as deemed necessary by the attending clinician. Attending clinicians were blinded to the results of blood lactate measurements performed for this study. Follow up blood samples were obtained at 8 hourly intervals for a period of 24 hours (4 samples per patient). Owners of dogs discharged from the hospital were contacted 2 weeks after the date of discharge to obtain information regarding survival and progress after discharge. At the end of the study period (2 weeks after discharge from the OVAH) dogs were classified as survivors or non- survivors. Blood lactate concentration was measured immediately after collection using the Accusport® blood lactate analyzer[b], according to the manufacturer's instructions. Blood glucose concentration was measured on a Technicon RA XT system[c] using the hexokinase method[d]. The microhematocrit was measured using a microhematocrit centrifuge[e] and microhematocrit tubes[f]. Tubes were sealed with vitrex plasticene and centrifuged at 11,800 rpm (14,000 g) for 5 min. The hematocrit was measured using a Hawksley hematocrit reader.

An in-saline-agglutination test was performed by mixing one drop of blood with 6 drops of saline. One drop of the mixture was placed on a glass slide, covered with a cover slip and examined under a microscope using 10X magnification. The test was deemed positive when red blood cells clumped together despite dilution with saline.

Data collected at presentation included signalment, mental status (alert, depressed or non-responsive), presence of neurological signs (seizures, coma, disorientation, confusion, vocalization, pacing, circling, head pressing, vision abnormalities, abnormal pupillary light responses, abnormal gait), presence of respiratory difficulty (dyspnea, tachypnea, Kussmaul's breathing [paroxysmal breathing], polypnoea, hypopnoea), microhematocrit, blood glucose concentration, and blood lactate concentration.

Data analysis

Data analysis was done using NCSS 2001[g] and Epicalc 2000[h] statistical software programs. Univariable analysis of the effects of hematocrit, blood glucose concentration and serial blood lactate concentrations on mortality was done using the Wilcoxon rank-sum test for differences between medians and the Fisher's exact test for categorical data. Variables with $P<0.3$ on univariable analysis were selected for testing using multivariable logistic regression. Two models were tested: one including lactate concentration on admission and the other including lactate concentration 8 h after admission. The models then were developed by backward elimination; variables remained in the model if they were significant (Wald $P<0.1$) or if their removal resulted in >10% change in the effect of other variables.

Results

Ninety dogs (47 males and 43 females) were included in the study. The median age of the dogs was 1 year (range, 1 month to 13 years). Breeds included 16 Boerboels, 11 mixed breeds, 8 German shepherd dogs, 7 Labrador Retrievers, 6 Rottweilers, 5 Maltese dogs, 5 Chow-chows, 5 Staffordshire terriers, 4 Dachshunds, 3 each of American Pitt Bull Terriers, Jack Russell Terriers and Fox Terriers, 2 each of Saint Bernard dogs, Rhodesian Ridgebacks and Boston Terriers, and 1 each of Bouvier des Flandres, Spaniel, Mastiff, Chihuahua, Boxer, Bull Terrier, Border Collie and Pekingese.

Median duration of disease before presentation was 2 days. Three dogs (3.3%) presented with neurological signs including seizures in 1 dog, and coma in the other 2. Forty-seven dogs (52.2%) showed respiratory signs such as tachypnea, polypnea and dyspnea. Fifteen dogs (16.6%) were alert, 38 dogs (42.2%) were depressed, and 37 dogs (41.1%) were non-responsive to stimuli. Twenty dogs (22.2%) were icteric at presentation. In-saline-agglutination was positive in 17 dogs (18.8%) and negative in 73 dogs (81.1%). Microhematocrit values ranged from 5 to 58% with a median of 10%. Eleven dogs (12%) died, and 79 dogs (88%) survived. Blood lactate concentrations of these 2 groups are shown in Figure 2.

Forty-five dogs (50%) presented with hyperlactatemia (blood lactate concentration > 22.5 mg/dL). Seven dogs died before the end of the 24 h sampling period. Five of these 7 dogs were hyperlactatemic at presentation. Twenty-four h after admission, 13 dogs were still hyperlactatemic, all of which had been hyperlactatemic on admission. Of these 13 dogs, 9 (69.2%) survived and 4 (30.8%) died. All 9 surviving dogs experienced a decrease in blood lactate concentration at the 8 h interval, with 7 of them showing a > 50% decrease. All 4 dogs with blood lactate concentration > 40 mg/dL at 24 h after admission died. All 4 had shown persistently high blood lactate concentrations (> 40mg/dL) at all sampling times and in 2 of them blood lactate concentration was higher at 24 h than on admission. On the other hand, all (n = 75) dogs with blood lactate concentration < 40 mg/dL at 24 h after admission survived.

Two dogs were euthanized during the study. They included 1 dog that was euthanized after 16 h, and 1 dog that was euthanized after 24 h. The first dog was euthanized after developing severe disseminated intravascular coagulation with widespread hemorrhages and bleeding from the nose, eyes, and gastrointestinal tract. The second dog developed neurological signs including coma and tremors. As the presence of neurological signs indicates a poorer prognosis[33], the owner decided not to spend any further money on treatment of the dog and it was euthanized. The second dog that was euthanized had an initial blood lactate concentration of 1.8 mg/dL, but by the 8 h sampling period, lactate concentration had risen to 30.6 mg/dL and by 16 h it was 63 mg/dL. The other non-surviving dog had a normal lactate concentration of 5.4 mg/dL but died within 30 min of admission. The dog was comatose, severely icteric, and hyperglycemic (176.4 mg/dL). Unfortunately, the owner did not give permission for a post-mortem examination.

Hematocrit, glucose and serial lactate measurements of survivors and non-survivors are compared in Table 1. Non-survivors had significantly higher blood lactate concentrations than survivors at each interval. Univariable associations between each variable and mortality are shown in Table 2, expressed in terms of the relative risk of mortality compared with a reference category.

In dogs admitted with hyperlactatemia, an increase or a < 50% decrease in blood lactate concentration at 8 h and at 16 h were significantly associated with mortality, compared to dogs in which lactate concentration decreased by > 50% (Table 3). There was no evidence of an association between hematocrit on admission and survival.

Blood lactate concentrations on admission and at 8 h after admission were the only predictor variables that remained significant in the 2 logistic regression models (Tables 4 and 5). Both measurements were significantly associated with mortality, but the 8 h measurement showed a

much stronger association (odds ratios of 13 and 83 for lactate concentrations >22.5 and >45 mg/dL, respectively).
Although hypoglycemia (blood glucose < 59.4 mg/dL) on admission was associated with an increased risk of mortality in the univariable analysis, it was eliminated from the logistic regression models because hypoglycemia and hyperlactatemia were highly associated (chi-squared test, $P < 0.0001$). Of the 20 dogs that were hypoglycemic on presentation, 19 (95%) were hyperlactatemic and 18 (90%) had blood lactate concentrations > 45 mg/dL.

Discussion

Babesiosis is a disease that results in hypoxia and sepsis[1, 2, 5]. In dogs with severe babesiosis, metabolic acidosis is principally due to generation of lactic acid[5] and lactate concentrations in non-survivors were higher than in controls and survivors. The mean blood lactate concentration in healthy dogs in that study was 13.8 mg/dL, for survivors of disease 39 mg/dL, and for fatally infected dogs it was 145 mg/dL.
In dogs, the normal blood lactate concentrations (amperometric autoanalyzer) are between 1.8 and 22.5 mg/dL[9, 31, 33]. According to the manufacturers of the Accusport® analyzer, normal dogs have blood lactate concentrations of up to 9 mg/dl. Values of 27-45 mg/dL, 45-90 mg/dL and > 90 mg/dL are seen in mild, moderate and severe hypoperfusion, respectively [9]. Blood lactate concentrations > 45 mg/dL usually are associated with acidemia[9].
Hyperlactatemia seen in humans suffering from severe disease or injury has been attributed to hypoxia[12]. During hypoperfused states, however, the lactate and pyruvate increase disproportionately whereas hyperlactatemia of injury or sepsis usually is accompanied by lactate and pyruvate increases that maintain the normal ratio between the 2 products. This observation suggests an equilibration phenomenon of hyperlactatemia during disease states[8, 12, 33]. Hyperlactatemia now is thought to be due to a combination of tissue hypoxia and hypermetabolism. Lactic acidosis can be classified as either type A (due to poor perfusion and hypoxia), or type B (in which poor tissue perfusion or poor arterial oxygenation is not apparent)[14, 15].
Serial lactate measurements are recommended in the human medicine, because pre-treatment lactate concentrations do not differ between survivors and non-survivors. Survivors in studies investigating blood lactate concentrations in ventilated babies and patients suffering from septic shock showed a decrease in blood lactate concentration within the first 24 h and lactate concentrations remained high for much shorter times compared to non-survivors[7, 16]. In this study, we found that lactate concentration differed between survivors and non-survivors at every time period, including pre-treatment. However, this difference tended to become greater at each subsequent measurement. The best prediction of survival was obtained at 24 h, when blood lactate concentrations > 40 mg/dL and < 40 mg/dL correctly predicted death and survival respectively in every case.
In studies of humans, blood lactate concentrations increased before clinical deterioration was observed, and thus lactate could serve as an early warning system of possible organ failure[7]. An observation made in our study is that clinical signs accompanied changes in blood lactate concentrations. Although attending clinicians were blinded to blood lactate concentrations, the investigators who were responsible for collecting the blood samples (MN and NK) observed that dogs showing decreasing blood lactate concentrations showed clinical improvement whereas dogs showing persistently high or rising blood lactate concentrations continued to deteriorate clinically. This observation was subjective, and grading of clinical signs should be evaluated in future studies to confirm this observation.
We conclude that blood lactate concentrations can serve as a predictor of outcome in dogs suffering from severe or complicated canine babesiosis. Although pre-treatment hyperlactatemia indicates a poorer prognosis, subsequent serial lactate concentrations show a much stronger association with mortality. Dogs with greater post-treatment decreases in blood lactate

concentrations have a higher survival rate whereas serial blood lactate concentrations persistently remaining > 40 mg/dL indicate a very poor prognosis. Although hypoglycemia on admission also was associated with an increased risk of mortality, hypoglycemia and hyperlactatemia tended to occur together and blood lactate concentration alone can serve as a prognostic indicator in dogs with severe or complicated canine babesiosis.

[a] CA Milsch P.O. Box 943, Krugersdorp, Johannesburg, 1740, South Africa
[b] Roche Products, Africa Region, P.O. Box 129, Isando, 1600, South Africa
[c] Technicon Instruments Corporation, Tarrytown, USA
[d] Bayer Health Care Division, P.O. Box 198, Isando, 1600, South Africa
[e] Jouan Hema-C microhaematocrit centrifuge, Hawksley and Sons, Ltd, Sussex, U.K.
[f] A&M Link Stiftung, Wertheim, Germany
[g] NCSS, Kaysville, Utah
[h] EpiCalc 2000 v1.02, Brixton Books, UK

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FIGURES, GRAPHS AND TABLES

Figure 1. Glucose metabolism.

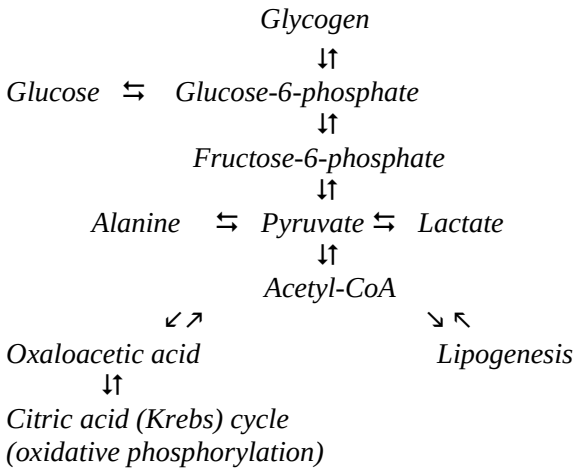

Figure 2. Mean blood lactate concentrations of survivors at each sampling interval compared to non-survivors. Lines within boxes indicate median values. The normal cut off value is 25 mg/dL. Dots represent outlying values. Whiskers represent the 10th and 90th percentiles.

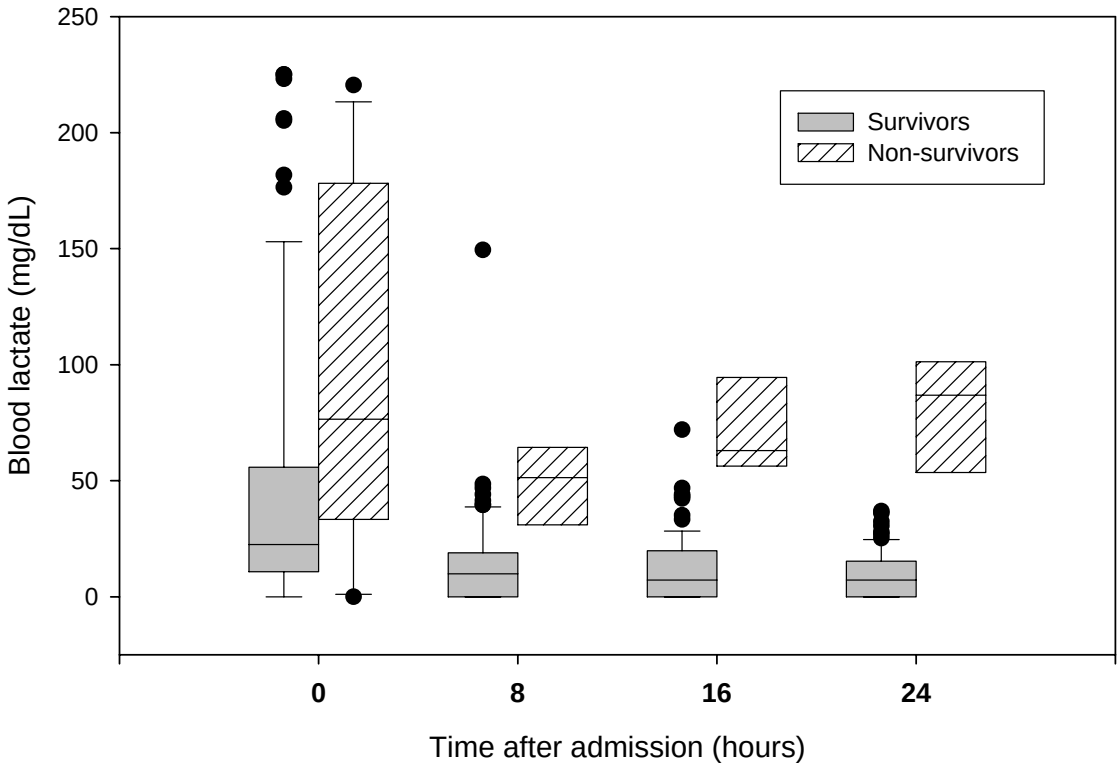

Table 1. Median hematocrit and blood glucose concentration on admission, and serial blood lactate concentrations in survivors and non-survivors of canine babesiosis.

	Ht (%)	Glucose (mg/dL)	Lactate (mg/dL)			
			0 hours	8 hours	16 hours	24 hours
Survivors	10 [a]	82.8 [a]	22.5 [a]	9.9 [a]	7.2 [a]	7.2 [a]
Non-survivors	11 [a]	61.2 [a]	76.5 [b]	51.3 [b]	63 [b]	86.9 [b]
TOTAL	10.5	80.1	23.4	10.8	8.1	8.1

[a,b] Values within columns with differing superscripts differ significantly (Wilcoxon rank-sum test, $P<0.05$)

Table 2. Association of hematocrit, blood glucose and blood lactate with mortality in canine babesiosis: univariable analysis

Variable	Category	Mortality		RR *	95% confidence interval	*P* §
		Yes	No			
Hematocrit (%)	<10	3	27	0.40	0.05 to 3.0	0.4
	10-14	5	38	0.47	0.07 to 3.1	0.4
	15-19	2	5	1.1	0.15 to 9.0	1.0
	20-39	1	3	1 †		
	≥40	0	6	0	0 to -	0.4
Glucose 0 hours (mg/dL)	<59.4	5	15	3.2	1.0 to 9.9	0.05
	59.4 to 118.8	5	59	1 †		
	>118.8	1	5	2.1	0.30 to 15	0.4
Lactate 0 hours (mg/dL)	≤22.5	2	43	1 †		
	22.6 to 45	1	14	1.5	0.15 to 15	1.0
	>45	8	22	6.0	1.4 to 26	0.01
Lactate 8 hours (mg/dL)	≤22.5	1	62	1 †		
	22.6 to 45	3	14	11	1.2 to 100	0.03
	>45	4	3	36	4.7 to 279	0.0002
Lactate 16 hours (mg/dL)	≤22.5	0	65	1 †		
	22.6 to 45	0	9	-	-	1.0
	>45	5	2	-	-	<0.0001
Lactate 24 hours (mg/dL)	≤22.5	0	66	1 †		
	22.6 to 45	1	9	-	-	0.1
	>45	3	0	-	-	<0.0001
TOTAL		11	79			

* Relative risk of mortality compared to reference category
† Reference category
§ *P*-value for Fisher's exact test

Table 3. Association between change in blood lactate concentration and mortality in canine babesiosis patients with hyperlactatemia on admission

Variable	Category	Mortality		RR *	95% confidence interval	*P* §
		Yes	No			
Decrease in lactate 0 to 8 hours	≤50%	5	6	7.3	1.6 to 32	0.008
	>50%	2	30	1 †		
Decrease in lactate 0 to 16 hours	≤50%	3	7	8.4	1.0 to 72	0.05
	>50%	1	27	1 †		
TOTAL		7	36			

* Relative risk of mortality compared to reference category
† Reference category
§ *P*-value for Fisher's exact test

Table 4. Multiple logistic regression model of risk factors for mortality in canine babesiosis: blood lactate on admission

Variable	Category	β	OR *	95% confidence interval	*P*
Lactate 0 hours (mg/dL)	≤22.5	0	1 †		
	22.6 to 45	0.429	1.5	0.13 to 18	0.7
	>45	2.06	7.8	1.5 to 40	0.01

* Odds ratio relative to reference category
† Reference category

Table 5. Multiple logistic regression model of risk factors for mortality in canine babesiosis: blood lactate 8 hours after admission

Variable	Category	β	OR *	95% confidence interval	*P*
Lactate 8 hours (mg/dL)	≤22.5	0	1 †		
	22.6 to 45	2.59	13	1.3 to 137	0.03
	>45	4.41	83	6.9 to 986	0.0005

* Odds ratio relative to reference category
† Reference category