

Lactate: physiology and clinical utility

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Abstract

Objective: To review the physiology of lactate production and metabolism, the causes of lactic acidosis, and the current applications of lactate monitoring in humans and animals.

Data sources: Human and veterinary studies.

Summary: Lactate production is the result of anaerobic metabolism. Tissue hypoxia due to hypoperfusion is the most common cause of lactic acidosis. Studies in critically ill humans have shown that serial lactate monitoring can be used to assess the severity of illness and response to therapy. Several veterinary studies have also shown lactate as a useful tool to assess severity of illness.

Conclusions: Lactate measurement in critically ill veterinary patients is practical and can provide information to assess severity of illness. Further veterinary studies are needed to establish the value of serial lactate measurements for prognostic and therapeutic purposes. Information regarding lactate measurement in cats is limited, and further studies are warranted.

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Introduction

Lactate is produced by cells under anaerobic conditions. Hyperlactatemia is an elevated lactate concentration, and lactic acidosis is an elevated lactate concentration accompanied by a decrease in systemic blood pH.^{1,2} Most commonly, lactic acidosis is produced as a result of tissue hypoperfusion and hypoxia that can occur with shock, severe anemia, respiratory distress, and hypermetabolic states.^{3,4} Lactic acidosis can also be a result of various drugs/toxins, mitochondrial defects, and disease states such as sepsis that compromise aerobic energy production and lactate consumption.^{3,4} Lactate has been extensively researched in critically ill humans and found to be useful to assess severity of illness and monitor response to therapy.^{5–13} Research in veterinary patients has shown lactate to be a practical and useful tool to assess severity of illness, but further studies are needed.^{14–19}

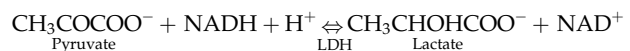
Review of Lactate Physiology

Glycolysis is the first step of glucose metabolism and is an anaerobic process that occurs in the cytoplasm of cells and results in the production of pyruvate. All cells

are capable of glycolysis with higher rates seen in the brain, heart, and skeletal muscles. The metabolism of glucose to pyruvate causes the reduction of the enzyme cofactor nicotinamide adenine dinucleotide (NAD⁺) to NADH and the production of 2 moles of adenosine triphosphate (ATP), the main energy source used to fuel cellular processes.



Under aerobic conditions, pyruvate diffuses into the mitochondria of the cell and, via the Krebs cycle and oxidative phosphorylation, an additional 36 moles of ATP are produced and the oxidation of NADH back to NAD⁺ occurs. In cells that do not contain mitochondria, such as red blood cells, pyruvate is catalyzed by the enzyme lactate dehydrogenase (LDH) to lactate. The conversion of pyruvate to lactate allows for the oxidation of NADH back to NAD⁺ and for glycolysis to continue.

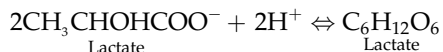


Lactate produced by red blood cells diffuses out of the cell and is transported to other tissues that are able to use it to produce energy. In the kidneys, heart, and liver, lactate is converted back to pyruvate and then transported into the mitochondria to produce ATP. In the liver and kidneys, lactate can be converted to glucose via gluconeogenesis. The glucose produced can then be stored as glycogen or released into the blood for

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utilization by other cells and tissues. The production of lactate by 1 tissue and conversion to glucose by another tissue is known as the Cori cycle.^{1,20}



During periods of hypoxia, tissues are forced to use glycolysis as their sole source of energy production. Glycolysis is a less efficient pathway and results in lower energy production but is able to occur at a much faster rate than aerobic metabolism. Hydrogen ions are produced from the continued utilization of ATP and the reduction of NAD^+ to NADH . These hydrogen ions are normally consumed by the aerobic process of oxidative phosphorylation and begin to accumulate in excess during anaerobic metabolism. As the concentrations of pyruvate, NADH , and hydrogen ions increase, the glycolytic process begins to slow due to the accumulation of these end-products. The increase in pyruvate and NADH concentrations causes them to react and be converted by LDH to form lactate, consume pyruvate and hydrogen ions, and regenerate NAD^+ . This reaction allows for glycolysis and cytosolic energy production to continue. As pyruvate is converted to lactate in hypoxic cells, the lactate to pyruvate ratio increases. Intracellular lactate levels become increased, and lactate crosses the cell membrane and moves into the blood via a bidirectional, monocarboxylate-proton cotransporter as well as an anion exchange system and free diffusion.²¹ If anaerobic conditions are widespread, other tissues are unable to convert the lactate to pyruvate or glucose to use for energy production. Lactic acid and lactate, an anionic base, exist in equilibrium in solution, but at physiologic pH the formation of lactate with free hydrogen ion is favored. The hydrogen ions are initially titrated by body buffers, but once the buffers are depleted, acidemia occurs in association with the lactate accumulation.^{1,3} Upon restoration of aerobic conditions, lactate and hydrogen ions are consumed when they are metabolized to glucose or oxidized to water and carbon dioxide (CO_2).^{1,3,4,20}

Normal Lactate Metabolism

Lactate is produced by humans under normal conditions at about 15–30 mmol/kg/day with blood levels maintained between 0.5 and 1.0 mmol/L by a balance between lactate production and consumption.¹ Skeletal muscle, brain, heart, skin, gastrointestinal, and red blood cells produce the most lactate under normal conditions (Table 1).^{3,4,6} The liver and kidneys are responsible for the majority of lactate clearance, metabolizing 50% and 20–30%, respectively, of the lactate produced.²² Basal clearance of lactate can be maintained

Table 1: Primary lactate producing/consuming tissues under normal conditions

Producers	Consumers
Skin	Liver
Erythrocytes	Renal cortex
Brain	Heart
Skeletal muscle	
Leukocytes	
Renal medulla	

despite chronic liver disease such as cirrhosis.²³ However, acute liver disease, including fulminant liver failure and acute hepatitis, may result in mild elevations in lactate.²⁴ Lactic acidosis in association with hepatic disease most commonly occurs in the presence of shock.⁵ Additionally, hepatic perfusion, oxygenation, and pH affect the liver's ability to process lactate. A reduction in hepatic blood flow by 70% allows for normal lactate clearance by the liver, but further decreases in blood flow may result in decreased lactate extraction.²⁵ A reduction in arterial blood oxygen content to a PaO_2 of <50 mmHg will decrease hepatic lactate clearance and, with more severe hypoxia, hepatic lactate production occurs.²⁵ A decrease in hepatic pH has been shown to decrease hepatic lactate clearance, possibly as a result of decreased gluconeogenesis at a pH of <7.10.^{26,27} Intrahepatic acidosis also favors hepatic lactate production.²⁸

Under normal physiologic conditions, the kidney is second only to the liver in extracting circulating lactate and removing it from the system by a combination of excretion and metabolism.^{6,22,29} Lactate is freely filtered by the glomerulus but is almost completely reabsorbed in the proximal tubule. An elevated blood lactate level increases urinary excretion of lactate, but excretion only accounts for 10–12% of the lactate cleared by the kidneys while the remainder is metabolized to glucose by gluconeogenesis.²⁹ Lactate metabolism in the cortex of the kidney continues until there is a 90% decrease in renal blood flow at which time renal lactate production occurs.³⁰ In contrast to the liver, acidosis increases renal lactate clearance. Renal lactate clearance increases from 16% at a pH of 7.45 to 44% at a pH of 6.75.²⁹ The increased renal lactate metabolism is accomplished by increased production of glucose from lactate via gluconeogenesis.³¹

D-Lactate

Lactate that is produced by cellular metabolism is the levorotatory isomer, also known as L-lactate. The D-lactate isomer is formed by bacterial glucose metabolism. Lactic acidosis due to increases in D-lactate production

is uncommon in monogastric mammals. D-lactic acidosis has been documented in humans with short bowel syndrome due to production by intestinal bacteria.³² D-lactic acidosis has been reported in a cat with exocrine pancreatic insufficiency and intestinal bacterial overgrowth.³³ Increased D-lactate production should be considered in veterinary patients with gastrointestinal disturbance and acidosis but a normal L-lactate. Total plasma lactate, including D-lactate and L-lactate, can be measured by gas chromatography and mass spectrometry while commercial lactate analyzers only measure L-lactate and do not detect increases in D-lactate.³³

Lactated Ringer's solution (LRS)^a is a balanced electrolyte solution that is commonly used in the treatment of veterinary patients. The lactate in this fluid is metabolized to glucose or oxidized to water and CO₂. Both of these processes result in the consumption of hydrogen ions and an overall alkalinizing effect.³⁴ LRS contains racemic lactate with an equal mixture of D- and L-stereoisomers. Although the D-lactate portion cannot be metabolized by mammals, infusion of LRS is not usually associated with an increase in blood lactate concentrations.³⁵ However, (see 'Discussion') lactate elevations after administration of LRS have been seen in dogs with lymphoma.³⁶ Small amounts of LRS that may contaminate catheters used for blood sampling can cause false increases in lactate concentrations.³⁷

Causes of Lactic Acidosis

Lactate accumulation demonstrates a breach in the balance between lactate production and consumption and may be due to excess production, insufficient utilization, or a combination of both.^{3,4,6} In humans, hyperlactatemia is defined as an increase in the plasma lactate concentration above normal (>1 mmol/L) when a normal body pH exists.^{1,6} Hyperlactatemia can occur as a result of conditions that increase the glycolytic flux of glucose to lactate where tissue perfusion is normal, and buffering systems are functioning appropriately.⁶ Lactic acidosis is defined as an elevation in plasma lactate concentration, usually to 5 mmol/L or greater, that results in a decrease in arterial pH to below 7.35.^{2,6}

Lactic acidosis has commonly been divided into 2 categories, Types A and B (Table 2).^{3,4,6} Type A lactic acidosis is most common and consists of increased lactate production due to tissue hypoxia with normal mitochondrial function.^{3,4,6} Tissue hypoxia may be the result of hypoperfusion from decreased cardiac output or hypovolemia, decreased arterial blood oxygen content from severe anemia, or decreased ability of the tissues to mobilize oxygen from the capillary blood as created by conditions such as edema.³⁸ Oxygen delivery (DO₂) to the tissues is the product of cardiac output

Table 2: Common causes of lactic acidosis in veterinary medicine

Type A – tissue hypoxia/hypoperfusion
Exercise
Seizures
Hypoxemia (pO ₂ < 30 mmHg)
Anemia (packed cell volume < 10%)
Shock: cardiogenic, hypovolemic, septic
Regional hypoperfusion
Global hypoperfusion
Carbon monoxide
Type B
B-1: Underlying disease
Liver disease
Diabetes mellitus
Sepsis
Renal failure
Neoplasia
Alkalosis
B-2: Drugs/toxins
Ethylene glycol
Propylene glycol
Epinephrine
Carbon monoxide
Salicylates
Acetaminophen
B-3: Mitochondrial diseases
Mitochondrial myopathies
Inborn
Acquired

and arterial oxygen content. Arterial oxygen content is the product of the hemoglobin concentration of blood (g/dL), the amount of oxygen carried by each hemoglobin molecule when fully saturated (1.36 mL oxygen/g Hb), and the oxygen saturation of hemoglobin.³⁹

$$\text{Oxygen Delivery} = \text{cardiac output} \times \text{arterial oxygen content} \\ = (\text{Heart Rate} \times \text{Stroke Volume}) \times (1.36 \times \text{Hemoglobin} \times \text{SaO}_2)$$

Oxygen delivery must meet tissue oxygen demands in order to maintain homeostasis and aerobic metabolism. Oxygen consumption (VO₂) is the oxygen used by tissues; the oxygen removed from capillary blood is believed to reflect VO₂ and tissue oxygen extraction. Oxygen delivery ideally exceeds VO₂ and, under normal conditions, oxygen extraction is independent of delivery with an extraction rate of 25–30%.³⁹ The main mechanism used by tissues to preserve aerobic metabolism during low-flow states is increased oxygen extraction. As oxygen delivery decreases, a point is reached (critical DO₂) at which oxygen extraction cannot be further increased in order to support adequate tissue oxygenation and aerobic metabolism.^{6,39,40} At this point, anaerobic metabolism ensues, and lactate is produced. Common causes of oxygen supply/demand imbalance and resultant tissue hypoxia include hypovolemic, cardiogenic, and septic shock as well as severe

anemia, hypoxemia, and hypermetabolism (case example 1).^{3,4,6} An increase in cardiac output can partially compensate for decreased blood oxygen content from anemia or hypoxemia. Compensation for hypoperfusion that is a result of hypovolemia or inadequate cardiac output is more difficult because no acute mechanism exists to effectively increase oxygen content.⁴⁰ A combination of hypoperfusion and decreased blood oxygen content can further complicate situations. As a result, tissue hypoperfusion is the most common cause of Type A lactic acidosis.^{3,4,6}

Type B lactic acidosis results under conditions of adequate oxygen delivery but altered mitochondrial function or carbohydrate metabolism. Type B lactic acidosis has 3 subdivisions, and the exact origin of lactic acidosis is not always completely understood or identified. Subdivision B₁ consists of disease processes believed to be creating lactic acidosis not due to hypoperfusion but possibly due to decreased lactate clearance. Subdivision B₂ consists of drugs/toxins that interfere with oxidative phosphorylation. Subdivision B₃ consists of mitochondrial defects. Conditions commonly associated with Type B lactic acidosis in veterinary medicine include diabetes mellitus, liver disease, neoplasia, and sepsis (case example 2).^{3,4,6} Alkalosis and catecholamines can increase the glycolytic flux of glucose to lactate resulting in hyperlactatemia, but will often not be associated with acidemia due to the presence of adequate buffering systems.^{3,4,6} Type-B lactate elevation in dogs has been documented as the result of activated charcoal administration.⁴¹ Activated charcoal containing propylene glycol and glycerol are commonly administered to veterinary patients for gastric decontamination after toxin ingestion. Dogs experimentally administered activated charcoal demonstrated significantly increased lactate 1 and 4 hours after administration. The increase in lactate was most likely due to the hepatic metabolism of propylene glycol to pyruvate and lactate. Mild elevations in lactate after activated charcoal administration should be anticipated by the practitioner and not misinterpreted as a side-effect of the treated intoxication. In dogs, an elevated resting lactate has been associated with lymphoma.³⁶ These dogs also demonstrated an increase in lactate when administered lactate-containing intravenous fluids. The increased lactate concentrations may be caused by increased lactate production and altered carbohydrate metabolism in neoplastic cells.⁴²

Lactic acidosis as a result of a combination of Types A and B causes can occur.^{3,4,6} Tissue hypoperfusion should always be considered in any case of lactic acidosis even when clinical evidence of poor tissue perfusion is absent (case example 3). Sepsis is a condition in which the cause of elevated lactate levels has not

been definitely identified but is believed to be the result of a combination of factors including decreased oxygen delivery, hypermetabolism due to inflammation, and alterations in mitochondrial function and glycolytic enzyme systems.⁴³⁻⁴⁶ Mitochondrial respiration dysfunction and overproduction of pyruvate with decreased pyruvate dehydrogenase activity is a possible mechanism that may lead to pyruvate accumulation and increased lactate production.⁴⁵ Another proposed mechanism is enhancement of phosphofructokinase, a rate-limiting enzyme of glycolysis, resulting in increased glycolysis and end-product production.⁴⁶ Clinical investigation in septic human patients has shown that elevated lactate levels and failure to clear lactate are markers of severe disease and cellular dysfunction.⁴³ Blood lactate concentration of >5 mmol/L in a septic patient at the time of admission to the intensive care unit is associated with a patient mortality rate of 59% at 3 days and 83% at 30 days.⁴⁷

Review of Human Literature and Research

Lactate physiology and lactic acidosis has been an area of research in human medicine for over 50 years. In this period of time, knowledge has progressed from identifying the causes of lactic acidosis in critically ill patients to using it as an aid to guide treatment and prognostication.⁶ In critically ill patients, lactic acidosis is most frequently the result of systemic hypoperfusion and tissue hypoxia.^{3,4,6} The degree of lactic acidosis correlates with the overall decrease in oxygen delivery, extent of tissue hypoperfusion, and severity of the disease process.^{6,7} Patients with lactic acidosis have been shown to have a higher mortality rate and are at a greater risk of developing multiple organ failure.⁸ Blood lactate as a prognostic indicator in humans has been studied extensively with results showing that as blood lactate concentrations increase, the probability of survival decreases.⁹⁻¹³ As conditions of varying severity can cause increases in serum lactate levels, emphasis has been placed on monitoring serial lactate concentrations. Clearance of lactate during the treatment period is correlated with greater survival while patients that did not clear their lactate load were more likely to die.^{10,13} Monitoring serial lactate concentrations has become routine in assessing response to therapy and guiding further intervention in critically ill humans.⁶

Review of Veterinary Literature and Research

Most of the early veterinary clinical research evaluating lactate involved horses. A study in 1976 evaluated the blood lactate of 36 horses that presented with colic.¹⁴ High blood lactate concentration was demonstrated to

be a poor prognostic indicator of survival. The study suggested that blood lactate might be used along with the results of the physical examination as a prognostic tool in equine colic.

In 1995, another study analyzed physical examination and laboratory values of horses with colic in order to determine differences between survivors and non-survivors.¹⁵ Blood lactate concentration was one of the 4 variables selected. Using the selected variables with assigned values, a Colic Severity Score, based on the approach of the human acute physiology and chronic health evaluation (APACHE) system, was developed to predict outcome and serve as a severity index for horses with colic.

Lactate studies in small animal medicine have been mainly limited to dogs.^{16–19,34,36,41,48–52} The majority of these studies have been performed on venous samples allowing venous lactate measurements to be used with increasing confidence to identify underlying hypoperfusion and assess response to treatment.^{16–19,34,36,41,48–52} A thorough review paper on lactate kinetics and relevance in veterinary critical care was published in 1996.⁵³ In 1998, Lagutchik et al.¹⁶ published a study that measured the lactate concentrations in 109 sick dogs and 20 clinically normal dogs. The sick dogs were divided into survivor and non-survivor groups and sub-grouped based on the presenting disease or injury. Of the affected dogs, 95% had lactate concentrations higher than the normal reference lactate value and higher than the median lactate value of the clinically normal dogs. Seventy-six percent of the sick dogs lived to be discharged from the hospital. The median lactate concentrations of non-survivors (including animals that were euthanized) were higher than those for both the normal and survivor groups. Dogs with neurological disease, toxin ingestion, and major trauma had blood lactate concentrations significantly higher than those of clinically normal dogs. A positive correlation was found between increased lactate concentrations and the non-survivors (including dogs that were euthanized). These results support the hypothesis that lactate measurement in critically ill or injured dogs may have value in predicting severity of disease and outcome.

In 1998, a retrospective study examined the relationship between plasma lactate concentrations and gastric necrosis and between plasma lactate concentrations and outcome for 102 dogs with gastric dilatation-volvulus.¹⁷ In this study, 23 of 31 (74%) of the dogs with a plasma lactate concentration >6.0 mmol/L had gastric necrosis while only 15 of 71 (21%) of the dogs with a lactate concentration <6.0 mmol/L had gastric necrosis. Sixteen of 20 dogs (80%) with plasma lactate concentrations >7.0 mmol/L, 11 of 12 (92%) dogs with plasma lactate concentrations >8.0 mmol/L, and 7 of 7

(100%) dogs with plasma lactate concentrations >10 mmol/L had gastric necrosis. Of the dogs with plasma lactate concentrations <6.0 mmol/L, 69 of 70 (99%) survived while only 18 of 31 (58%) of the dogs with plasma lactate concentrations >6.0 mmol/L survived. In this study, preoperative lactate concentrations were found to be a good predictor of gastric necrosis and prognosis of dogs with GDV. It is interesting to note that the lactate measurements in this study were obtained before treatment and serial lactate measurements may have provided different information about prognosis. It is not recommended that decisions on preoperative euthanasia of dogs with gastric dilatation-volvulus be based on the degree of lactate elevation.

A retrospective study published in 2004 monitored serial blood lactate concentrations of dogs being treated for babesiosis.¹⁸ A total of 4 blood samples were taken to measure lactate, glucose, and hematocrit. The first sample was obtained before treatment, and then subsequent samples were obtained at 8-hour intervals for a period of 24 hours. Dogs were grouped into survivor and non-survivor categories. Fifty percent of the dogs (45/90) had elevated lactate levels (>2.5 mmol/L). An admission blood lactate concentration >5.0 mmol/L along with an increase in the blood lactate or a $<50\%$ decrease in the blood lactate concentration at the 8- and 16-hour sampling interval was associated with increased mortality. Throughout the study, lactate concentrations between survivors and non-survivors differed with the difference increasing with each sample interval. These findings were supported by a separate study in 2005 where dogs with severe babesiosis and hyperlactatemia were found to be significantly different from diseased dogs with normal lactate with regard to the presence of clinical collapse, alanine transaminase activity, bilirubin, urea, creatinine, bicarbonate, $p\text{CO}_2$, and level of parasitemia.¹⁹ These authors found lactate concentration to be an indicator of disease severity and correlated with clinical illness and alterations in other blood levels.

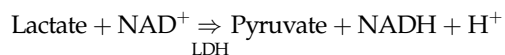
Lactate concentrations in body fluids other than blood may also provide important diagnostic information.^{48,49} One study examined the utility of comparing the lactate and glucose measurements on blood and peritoneal effusion in order to diagnose septic peritonitis.⁴⁸ A blood-to-fluid glucose difference of >20 mg/dL was found to be 100% sensitive and 100% specific for the diagnosis of septic effusion in dogs and 86% sensitive and 100% specific in cats. Septic peritoneal fluid was found to have a higher lactate concentration than blood, and a fluid-to-blood lactate difference of >2.0 mmol/L was found to be suggestive of septic peritonitis. The study could not draw a strong positive conclusion on the use of fluid-to-blood lactate differ-

ence due to a small sample size and recommended a study consisting of a larger sample size. Another study was performed comparing the lactate levels of pericardial fluid to peripheral blood in 41 dogs with pericardial effusion.⁴⁹ Sixty-one percent (25/41) of the dogs were hyperlactatemic. The pericardial fluid was found to have a significantly higher lactate level in all dogs examined. In dogs with confirmed neoplasia, the pericardial fluid lactate was significantly higher than in the pericardial fluid of dogs without evidence of neoplasia. Although the lactate in neoplastic effusions was significantly higher, there was too much overlap between the groups to recommend the use of lactate concentrations in differentiating neoplastic effusions from non-neoplastic effusions.

Lactate Measurement

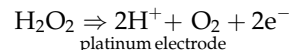
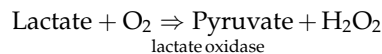
With the increased use of lactate as a monitoring tool in critically ill patients, developments have been made to improve the speed, accuracy, and ease of obtaining measurements. In the past, lactate measurements required a large blood sample to be obtained, and it was necessary to send the sample to a laboratory for analysis, creating a significant time delay. New point-of-care analyzers require smaller samples and decrease the amount of iatrogenic blood loss. Many lactate analyzers utilize whole blood samples and eliminate the time needed for sample coagulation and centrifugation. These analyzers can also be operated by non-laboratory staff. Overall, they provide rapid results as analysis can be performed at the patient's bedside eliminating the time lapse created by transport. Quality control is important in order to guarantee consistent and accurate test results. This quality assurance may require continued involvement of trained laboratory personnel to ensure that the equipment is functioning appropriately.^{54,55}

Two methods employed to measure lactate include enzymatic colorimetry and enzymatic amperometry. Enzymatic colorimetry uses spectrometric absorption to measure the NADH produced by oxidation of L-lactate by NAD^+ when catalyzed by LDH. The NADH is detected by absorption at 340 nm and is proportional to the amount of lactate in the sample. This procedure takes about an hour and is the most common method used by blood chemistry analyzers. Samples should be collected into tubes containing sodium fluoride and placed on ice to decrease erythrocyte lactate production. There is no increase in lactate in samples analyzed within one-half hour.⁵⁶



Enzymatic amperometry provides a lactate measurement based on the amount of hydrogen peroxide pro-

duced by the reaction of L-lactate with a lactate oxidase-containing membrane. The liberated hydrogen peroxide is oxidized by an applied electrical potential and generates an electron current on a platinum electrode that is measured and is proportional to the lactate level in the sample.⁵⁶



Enzymatic amperometry is now used in most blood gas analyzers as it is rapid and convenient, and whole blood may be used to achieve results within 2 minutes. Samples should not be placed into tubes containing sodium fluoride or sodium citrate due to interference of these anticoagulants with the lactate measurement.⁵⁷ Lactate results from samples obtained from catheters can be falsely elevated or decreased if crystalloid solutions are not appropriately cleared from the line.³⁷ Venous plasma lactate values of 0.42–3.58 mmol/L obtained from healthy beagles and analyzed by 2 different methods of enzymatic amperometry were found to be similar to previous reference ranges established by the colorimetric method.⁵⁰ The current canine reference range of 0.3–2.5 mmol/L is based on plasma lactate concentrations obtained by enzymatic amperometry on a Nova^b autoanalyzer.⁵¹

The veterinary practitioner now has several convenient and reasonably priced options for lactate measurement. Many veterinary clinics may already have the basic equipment in their facilities, and adding lactate to routine monitoring of critical patients will be simple and financially feasible. The ease in use of these analyzers allows trained support staff to be responsible for all steps of obtaining a lactate measurement including blood sampling and recording the results in the medical record.⁵⁴

Lactate analyzers available to veterinary practitioners include the Nova,^b i-Stat,^c and Accusport^d (Figure 1). The Nova is a bench-top blood gas/chemistry analyzer that can provide lactate measurements via enzymatic amperometry from a whole blood sample in minutes. The i-Stat is a tabletop, portable lactate analyzer that measures lactate via enzymatic amperometry on a whole blood sample. A minimum of 0.3 mL of arterial or venous blood is necessary for the i-Stat method, and the test should be performed within 3 minutes of collection as lactate can increase as much as 70% within 30 minutes at 25 °C as a result of glycolysis.⁵⁸ The i-Stat reference range is from 0.3–2.0 mmol/L.^e The Accusport is a handheld, portable lactate analyzer that uses enzymatic determination and reflectance photometry on a whole blood sample to read the lactate in the



Figure 1: Three common point-of-care lactate analyzers in veterinary medicine. (a) i-Stat, (b) Accusport, (c) Nova chemistry analyzer.

plasma portion of whole blood. An arterial or venous blood sample can be tested and a whole blood range of 0.8–22 mmol/L and plasma range of 0.7–27 mmol/L can be measured. A blood sample of 20–25 μ L is applied to the test strip that separates the red blood cells from the plasma and exposes the plasma to the test film where color change is measured by reflectance photometry.^{59,f}

Differences in blood lactate measurement based on sampling site (venous versus arterial) have been evaluated by several investigators.^{37,51,60,61} One study characterized the variation in plasma lactate concentrations obtained from various common sampling sites in 60 healthy, awake dogs and created a reference range based on these results.⁵¹ Sampling sites consisted of the jugular vein, cephalic vein, and femoral artery. Samples were taken from all 3 sites in all the dogs within 5 minutes. Groups were developed to create variation in sampling site sequence. The samples were analyzed by enzymatic amperometry. Results showed that lactate levels were highest from the cephalic vein, followed by the femoral artery, and then the jugular vein, but overall the differences were not clinically significant. It was hypothesized that lactate may be higher in the cephalic sample due to local production and lower in the jugular sample due to lactate utilization by the brain. Higher lactate measurements associated with the second and third sampling sites were believed to be due to restraint and increased muscular activity. A plasma lactate reference range of 0.3–2.5 mmol/L for healthy, adult dogs was established based on the data gathered in this study. This study demonstrated that there was no clinical difference between using venous and arterial sampling sites for obtaining lactate concentrations. These results, along with several human studies, provide no evidence of arterial blood as superior for obtaining accurate lactate measurements.^{37,60,61} Venous sites are more convenient to access, less painful for the patient, and safer to use.

Since a reference range for adult dogs had been previously established, a study was performed to establish a reference range for lactate in puppies.⁵² Serial plasma lactate concentrations were performed on 68 healthy, awake puppies at 6 intervals between 4 and 80 days of age. Samples were taken from the jugular vein to determine a reference range for venous lactate concentrations in neonatal dogs and to assess changes in lactate values with maturity. The results were compared with venous lactate values obtained from 30 healthy, adult dogs. The neonatal venous lactate concentrations were significantly higher than those of the adult dogs for the first 28 days of life with a reference range of 1.07–6.59 mmol/L at day 4 and 0.80–4.60 mmol/L from days 10 to 28. By day 70 of age, the lactate concentrations of the neonates were similar to those of the adult dogs. The increased lactate concentrations of the neonates were attributed to many mechanisms including ischemia/reperfusion injury during birth, higher baseline lactate levels to prevent hypoglycemia, or decreased hepatic clearance. This study documented elevated lactate levels in neonates <28 days of age and established a useful reference range for puppies in this age group.

No reference range exists for cats, making it difficult to use lactate in assessment of hypoperfusion in this species. Stress-induced hyperglycemia is a common finding on feline chemistry profiles and is more often noted in cats that struggle during restraint for venipuncture. Lactate production is increased with exercise, such as struggling and accumulated lactate is removed by oxidization to CO₂ and water as well as via gluconeogenesis once normal conditions are restored. Elevated lactate levels are often noted along with hyperglycemia in cats and lactate metabolism secondary to the stress of venipuncture may contribute to the hyperglycemia that is seen with cats.⁶² A lactate measured at the same time as the glucose may help to differentiate stress hyperglycemia from underlying dis-

ease. Feline red blood cells may produce increased lactate as a result of hyperglycemia and specific sampling handling may be necessary to ensure accurate results.⁶³

Conclusions

Lactate measurement can be a marker for detecting hypoperfusion, but limitations exist. Lactate can be increased due to altered clearance as well as excessive Type B production. In addition, regional hypoperfusion can create elevated lactate levels in the absence of global hypoperfusion and increased glycolysis from catecholamine release and alkalosis can also increase lactate levels.^{3,4,6} Continued research into the mechanism of increased lactate with septic patients is also needed in order to establish how to use lactate measurements in the treatment and monitoring of this group of patients.

In veterinary medicine, research is needed to further evaluate the use of serial lactate measurements and lactate clearance times in various disease states and the use of lactate as a prognostic indicator. Limited research has been performed in cats and future research is needed to establish the validity and usefulness of monitoring lactate in disease states in this species. Veterinary research to date combined with the information from research on critically ill humans is sufficient in allowing confident use of lactate in detecting tissue hypoxia and monitoring response to therapy in dogs. Lactate must always be interpreted in combination with other monitoring parameters and clinical evaluation of the patient. Lactate measurement is a minimally invasive and convenient monitoring value that can be used by veterinary practitioners. Veterinary research is limited in small animals but has demonstrated promise for its use in monitoring critically ill patients.

Case Examples

Refer to Table 3 for canine laboratory reference ranges.

Case example 1: type A lactic acidosis

A 13-year-old spayed female terrier was presented for a 1-week history of lethargy. Abnormal physical examination findings included pale mucous membranes, tachycardia (160 beats/min), and bounding femoral pulses. Initial point-of-care laboratory tests demonstrated severe anemia with a decreased packed cell volume of 10% and normal serum total solids of 7.0 g/dL. A venous blood gas diagnosed a lactic acidosis based on the following: decreased pH of 7.244, decreased CO₂ of 31.7 mmHg, decreased HCO₃ of 13.7 mmol/L, and increased lactate of 17.7 mmol/L. After a packed red blood cell transfusion, physical examination param-

Table 3: Canine reference ranges

	Reference range
Packed cell volume	28–45%
Total solids	6.0–7.5 g/dL
pH	7.344–7.441
Carbon dioxide (CO ₂)	32.6–48.3 mmHg
Bicarbonate (HCO ₃)	18–24 mmol/L
Glucose	75–120 mg/dL
Lactate	0.7–2.8 mmol/L

ters improved and a recheck packed cell volume was 18% with normal total solids of 6.5 g/dL. A recheck venous blood gas also showed improvement with a normal pH of 7.418 and mildly elevated lactate of 5.5 mmol/L. The clinical diagnosis was immune-mediated hemolytic anemia. This case is an example of hypoxia secondary to severe anemia resulting in a Type A lactic acidosis. The acidosis resolved and the lactate decreased in response to a packed red blood cell transfusion that improved oxygen delivery to the tissues.

Case example 2: type B lactic acidosis

An 11-year-old castrated male Bichon Frise with previously diagnosed diabetes mellitus was presented for vomiting, lethargy, and decreased appetite. Physical examination abnormalities included 5–7% dehydration and nausea on abdominal palpation; hemodynamic parameters were considered normal. Initial venous blood gas demonstrated a lactic acidosis based on the following: a decreased pH of 7.282, a decreased CO₂ of 27.4 mmHg, a decreased HCO₃ of 12.9 mmol/L, an increased glucose of 270 mg/dL, and an increased lactate of 18.7 mmol/L. A crystalloid fluid bolus of 45 mL/kg was administered and a recheck venous blood gas demonstrated a persistent lactic acidosis with a decreased pH of 7.30, normal CO₂ of 36.2 mmHg, normal HCO₃ of 17.9 mmol/L, and an increased lactate of 20 mmol/L. A crystalloid fluid bolus was repeated at 45 mL/kg and venous blood gas once again demonstrated lactic acidosis with a decreased pH of 7.33 and an elevated lactate of 19.6 mmol/L. This dog demonstrated normal hemodynamic parameters upon physical examination and a lactic acidosis that persisted despite fluid challenge to rule out hypovolemia and secondary tissue hypoperfusion. Diabetes mellitus is a known cause of Type B lactic acidosis due to abnormal glucose metabolism with insulin deficiency/resistance.

Case example 3: mixed-type lactic acidosis

A 9-year-old castrated male Pomeranian with previously diagnosed diabetes mellitus was presented for vomiting and voluminous hemorrhagic diarrhea of 12 hours duration. Abnormal physical examination find-

ings were consistent with hypovolemic shock and included dehydration estimated at 10%, pale mucous membranes, tachycardia (140 beats/min), and weak femoral pulses. Initial point-of-care laboratory tests demonstrated hemoconcentration with an increased packed cell volume of 51% and normal total solids of 6.7 g/dL. Venous blood gas abnormalities consisted of a decreased pH of 7.282, a decreased CO₂ of 28.9 mmHg, a decreased HCO₃ of 13.6 mmol/L, an increased glucose of 382 mg/dL and an increased lactate of 6.8 mmol/L. A complete blood count demonstrated the following changes consistent with sepsis: leukopenia, neutropenia, a left shift, and toxic neutrophil changes. The most likely source of sepsis in this patient was bacterial translocation from severe gastrointestinal disease. Aggressive fluid resuscitation therapy with crystalloids and colloids was initiated. Physical examination parameters improved after the fluid therapy and a recheck venous blood gas demonstrated resolution of the lactic acidosis based on a normal pH of 7.369 and a normal lactate of 2.5 mmol/L. The lactic acidosis in this case is an example of both Types A and B hyperlactatemia and is due to a combination of severe hypovolemic shock, sepsis, and alterations in glucose metabolism due to diabetes mellitus.

Footnotes

- ^a Lactated Ringer's Injection, Hospira Inc., Lake Forest, IL.
^b Nova chemistry analyzer, Nova Biomedical, Waltham, MA.
^c i-Stat, i-Stat Corporation, East Windsor, NJ.
^d Accusport, Sports Resource Group Inc., London, UK.
^e i-Stat Corporation: Lactate/LAC product information, 2004.
^f Sports Resource Group Inc.: Accusport/Acutrend Lactate Technical Information, 2003.

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