LACTATE: WHAT DOES IT REALLY TELL US?

Dez Hughes, BVSc, MRCVS, DACVECC
Greensborough, Australia and Massey University, Palmerston North, New Zealand

*For much of the 20th century, lactate was largely considered a dead end waste product of glycolysis due to hypoxia ... and a key factor in acidosis induced tissue damage. Since the 1970s a lactate revolution has occurred. At present we are in the midst of a lactate shuttle era; the lactate paradigm has shifted. There is essentially unanimous support for a cell to cell lactate shuttle. The bulk of the evidence suggests that lactate is an important intermediary in numerous metabolic processes, a particularly mobile fuel for **aerobic** metabolism, and perhaps a mediator of redox state among various compartments both within and between cells.* ***Lactate can no longer be considered the usual suspect for metabolic crimes, but is instead, a central player in cellular, regional and whole body metabolism.***

LB Gladden. Lactate metabolism: a new paradigm for the third millennium.
Journal of Physiology. 2004; 558 (1): 5-30

Lactate and lactic acid are not synonymous. Lactic acid, $CH_3CH(OH)COOH$, is a strong acid that, at physiological pH, is almost completely ionized to lactate, $CH_3CH(OH)COO^-$, and H^+. Increased blood lactate concentration is termed hyperlactatemia, however, this may or may not be associated with acidemia (a blood pH lower than 7.35) depending upon buffer reserves and concurrent acid/base disturbances. A plasma lactate concentration over 5 mmol/L is usually associated with acidemia. Lactic acidosis has been used to refer to a situation where lactate production exceeds lactate clearance and plasma lactate is thereby increased.
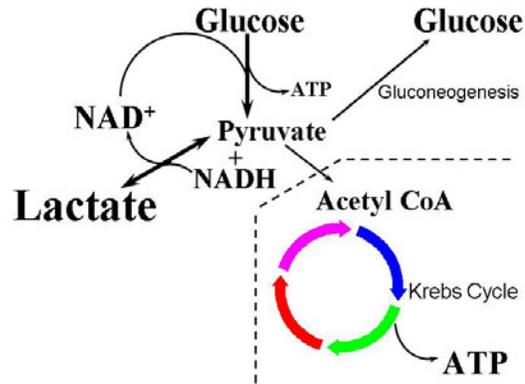
The main use of plasma lactate concentration is as an adjunct to a shrewd physical examination to detect and monitor hypoperfusion and as a prognostic indicator. Global hypoperfusion is by far the most common pathological cause of hyperlactatemia in dogs and cats and the magnitude of hypoperfusion-induced hyperlactatemia is far greater than most, if not all, other pathological causes. Furthermore, plasma lactate rises proportionally to the severity of hypoperfusion in dogs and the magnitude of hyperlactatemia seen is proportional to the severity of the insult (but not necessarily its reversibility). Failure of lactate to return to normal over 24-28 hours is a grave prognostic indicator in most situations. The clinical value of lactate was first reported nearly 50 years ago but its use in clinical patients has only become possible over the last 15-20 years. This is not for the lack of solid logic or evidence supporting its value, but merely because of the lack of simple and affordable equipment to measure it in a clinical setting.

The clinical use of lactate has been questioned on the basis that it is an insensitive indicator of mild hypovolemia. Lactate is insensitive in that it does not increase with mild hypovolemia, but that is exactly what one would expect given that the body can compensate in the early stages of hypoperfusion and thereby maintain tissue oxygen extraction relative to demand. Plasma lactate concentration does not rise until decompensation is occurring and there is an absolute or relative tissue oxygen deficiency. **Increased plasma lactate concentration is a not an indicator of mild hypoperfusion, it is an indicator of severe hypoperfusion.** Another criticism is that increased plasma lactate concentration is not specific for hypoperfusion. This is true for mild hyperlactatemia of which there are many causes. However, large increases in lactate (i.e. > 5 mmol/L) usually only occur due to hypoperfusion or muscle activity such as exercise or seizures. There is now a burgeoning clinical evidence base for the use of plasma lactate in human and veterinary medicine. As with any clinical parameter, the clinician must have a sound understanding of its physiological and pathophysiological role to use it appropriately in clinical decision making.

Biochemistry

Lactate production is a protective response by the body to allow cellular energy production to continue when tissue oxygen supply is inadequate for aerobic metabolism.

Cellular energy is generated in the form of high energy phosphate compounds via 3 processes: glycolysis, the citric acid cycle, and the electron transport chain/oxidative phosphorylation. Glycolysis occurs in the cytosol, whereas the citric acid (Krebs) cycle and electron transport chain/oxidative phosphorylation occur in mitochondria. The latter two processes require aerobic conditions, whereas glycolysis can occur with or without oxygen. Glycolysis therefore allows energy production to occur in conditions of relative or absolute cellular hypoxia.

Glycolysis generates much less energy than aerobic metabolism on a molar basis. Only 2 moles of adenosine triphosphate (ATP) are produced per mole of glucose converted to lactate (compared to 36 moles of ATP produced when glucose is fully oxidized to carbon dioxide and water via the citric acid cycle and electron transport chain/oxidative phosphorylation). Glycolysis, however, can proceed much faster than aerobic energy production which offsets the lower molar energy yield. Glycolysis produces pyruvate and consumes nicotinamide adenine dinucleotide (NAD^+). By converting pyruvate to lactate the cell disposes of excess pyruvate and regenerates NAD+ allowing anaerobic energy production to continue.

Lactate Production Does Not Produce Hydrogen Ions, Glycolysis Does

While the net effect of the 10 steps that comprise glycolysis is ATP production, some of the steps actually consume ATP. It is this ATP consumption that produces hydrogen ions. The overall reaction for the conversion of glucose to pyruvate is:

$$Glucose + 2ADP + 2P_i + 2NAD^+ \rightarrow 2Pyruvate + 2ATP^+ 2NADH + 2H_2O + 2H^+$$

When cellular oxygen is adequate, these H^+ ions pass into the mitochondria and are combined with oxygen during oxidative phosphorylation to produce water. Under hypoxic conditions, oxidative phosphorylation cannot function and H^+ ions accumulate in the cytosol resulting in intracellular and subsequently in extracellular acidosis.

Lactate Production Does Not Cause Acidosis. Lactate Protects Against Acidosis.

It does this in three ways:
1. When lactate is produced from pyruvate, hydrogen ions are consumed.

$$Pyruvate + NADH + H^+ \rightarrow Lactate + NAD^+$$

2. Lactate extrusion from the cell occurs via the monocarboxylate transporter which also extrudes H^+ from the cell with lactate. This is thought to be one of the main ways that cells are protected against intracellular acidosis.
3. Lactate can either be converted to glucose or oxidized to carbon dioxide and water both of which consume hydrogen ions.

It should be apparent from the above discussion that **lactate production occurs** in response to tissue oxygen deficiency **as a protective response** to allow cellular energy production to continue and to protect against acidosis. Plasma lactate concentration is therefore a marker of the severity of tissue hypoxia but it is not a cause of the metabolic acidosis, nor is it a mediator of the subsequent adverse consequences. Finally, it should now be apparent that the terms lactic acidosis and lactic acidemia are both misnomers!

Lactate Metabolism and Pharmacokinetics

Lactate is a charged molecule; nevertheless it equilibrates rapidly across cell membranes using a membrane transport system (the monocarboxylate transporter) that carries lactate across the membrane in conjunction with H^+.

Recent evidence suggests that this lactate excretion from the cell is vitally important in the regulation of intracellular pH. Increased cellular lactate production therefore results in an elevated interstitial and then blood lactate concentration. All tissues can produce lactate, but basal lactate production is highest in skin, red blood cells (which lack mitochondria), brain and muscle. Lactate consumption is highest in the liver and kidney. Because lactate is an important metabolic fuel, the kidney does not excrete lactate until a moderate degree of hyperlactatemia is present. Intraerythrocytic lactate concentration equilibrates with, but lags behind acute changes in plasma lactate concentration so plasma, rather than whole blood lactate concentration should be used in a clinical setting.

For severe hyperlactatemia to occur, increased lactate production must be associated with a reduction in lactate clearance. In patients with systemic hypoperfusion, organ blood flow is the major determinant of each tissue's relative contribution to lactate production and extraction. After mild hemorrhage in dogs, blood flow to the GI tract is reduced whereas blood flow to the liver is initially preserved. Although intestinal lactate production is increased, the liver is still able to extract and metabolize it. In severe hemorrhagic shock, the liver actually becomes a net producer of lactate. Numerous experimental studies have documented that increases in blood lactate concentration correlate well with oxygen debt and critical levels of oxygen delivery.

Clinical Use of Plasma Lactate Concentration

Lactate analyzers: There are now quite a few analyzers available that will measure lactate in minutes in a benchtop or "bedside" setting and the majority have been evaluated for clinical use in veterinary species. Advanced machines (such as those manufactured by Nova Biomedical and Radiometer) cost tens of thousands of dollars but provide a full blood gas/electrolyte/metabolite panel and have built in calibration and quality control. These more sophisticated analyzers can still be very cost effective for practices running a high number of samples but do require a fair degree of technical expertise. The I Stat is an advanced handheld machine which uses a range of cartridges that can measure blood gases, electrolytes, metabolites including lactate, and activated clotting time. More basic handheld units include the Accusport, Accutrend, Accu-Chek, Lactate Scout and the Lactate Pro. All analyzers vary in their accuracy and precision so careful research is necessary prior to purchase.

Sample site and sampling technique and reference ranges: Studies of lactate have traditionally used arterial blood samples, despite the fact that evidence supporting the use of arterial samples is largely absent. In normal dogs the differences between arterial, jugular and cephalic samples are minimal. In 60 healthy dogs, statistically significant but clinically irrelevant differences in plasma lactate concentrations were detected among blood samples from the cephalic vein (highest), femoral artery, and jugular vein (lowest). Mean plasma lactate concentration in the first sample obtained, irrespective of sampling site, was lower than in subsequent samples but the differences were also small. Clinical experience and data from human medicine suggest that differences between sample sites are also relatively minor in patients with hypoperfusion. Arterial blood is, in essence, a mixture of all venous blood so arterial lactate is the best reflection of total body lactate balance. A venous sample represents the net effect on arterial lactate concentration of the tissue through which the blood has just passed, hence a peripheral venous lactate may be a more sensitive detector of hypoperfusion.

Blood sampling technique and sample handling can increase plasma lactate concentration. Restraint and prolonged venous occlusion appear to cause only mild increases (2.5 - 3.5 mmol/L), whereas muscular activity during sampling is more important. In normal dogs, trembling during venipuncture can yield plasma lactate concentrations of 6 - 7 mmol/L and in cats, plasma lactate concentration is often increased due to muscular activity during restraint. The concern about an increase in lactate due to red blood cell glycolysis is unfounded in samples run within 30 minutes so glycolytic inhibition by fluoride is unnecessary. In whole blood samples kept at room temperature, lactate concentration only increases by approximately 0.2 mmol/L after 30 minutes.

The reference range for plasma lactate concentration in clinically normal, adult dogs by direct amperometry is < 2.5 mmol/L regardless of sample site. Puppies have been reported to have a higher lactate than adults. For 4 day old puppies the reference range was 1.1 – 6.6 mmol/L and for puppies aged 10 – 28 days it was 0.8 – 4.6 mmol/L. Lactate concentrations were similar to adults by 70 days of age. There is currently no published reference range for cats but experience suggests that it is similar to dogs in cats that do not struggle with venipuncture; which, of course is easier said than done!

Causes of hyperlactatemia: Hyperlactatemia occurs when lactate production exceeds lactate extraction. Causes of hyperlactatemia (See table below) have been divided into Type A (with clinical evidence of absolute or relative tissue hypoxia) and Type B (no clinical evidence of tissue hypoxia). Type A is by far the most common and usually occurs from tissue hypoxia due to hypoperfusion. Apart from muscle activity, other causes of Type A hyperlactatemia are rare. During muscle activity, Type A hyperlactatemia occurs due to relative, rather than absolute, tissue hypoxia when energy requirements exceed the capacity of aerobic metabolism, (e.g. exercise, trembling and seizures). Clinical experience

suggests that Type B hyperlactatemia is uncommon in veterinary medicine. In fact, in human medicine, many cases of Type B hyperlactatemia are actually thought to have occult hypoperfusion. Because the most common cause of increased plasma lactate concentration is systemic tissue hypoperfusion, hyperlactatemia should always prompt an aggressive search for an underlying reason.

TYPE A (clinical evidence of absolute or relative tissue hypoxia)	TYPE B (no clinical evidence of tissue hypoxia)
Shock (systemic hypoperfusion) Hypovolemic Cardiogenic Maldistributive	**B$_1$ (in association with underlying disease)** Diabetes mellitus Severe liver disease Neoplasia
Local hypoperfusion Gastric necrosis and other causes of splanchnic ischemia Aortic thromboembolism	Sepsis Pheochromocytoma Thiamine deficiency
Other causes of tissue hypoxia Severe hypoxemia ($P_aO_2 < 30\text{-}40$ mmHg) Severe euvolemic anemia (packed cell volume < 15%) Carbon monoxide toxicity	**B$_2$ (due to drugs or toxins)** Acetaminophen Cyanide Epinephrine
Increased glycolysis Excessive muscular activity Exercise	Ethanol Ethylene glycol Glucose
Trembling	Insulin
Seizures	Methanol Morphine Nitroprusside Propylene glycol (e.g. in activated charcoal) Salicylates Terbutaline
	B$_3$ (due to congenital metabolic defects) Mitochondrial myopathy **Miscellaneous** Alkalosis/hyperventilation Hypoglycemia

Lactate and hypoperfusion

In dogs, plasma lactate concentration seems to rise in a linear fashion with progressively worsening hypoperfusion. Mild systemic hypoperfusion is associated with a plasma lactate concentration of 3-4 mmol/L, moderate hypoperfusion with a lactate of 4-6 mmol/L and in severe hypoperfusion, lactate levels exceed 6 mmol/L. A retrospective pilot study by the author in 41 dogs with hemorrhagic shock secondary to anticoagulant rodenticide toxicity showed that lactate concentration was significantly higher in dogs with worse perfusion. Mean, (range) lactate concentration for each group, was 2.4 (1.4 - 3.4) mmol/L with mild hypoperfusion, 3.6 (2.3 - 5.5) mmol/L with moderate and 7.9 (6.1-10.5) mmol/L with severe hypoperfusion (unpublished data). In cats, lactate increases with hypoperfusion seem to be exponential rather than linear, that is, mild to moderate hypoperfusion results in a smaller lactate increase than in dogs. Following successful intravenous fluid therapy, as cardiovascular status improves, plasma lactate concentration will fall over a matter of hours. If cardiovascular status does not improve the clinician should look for ongoing causes of hypovolemic, maldistributive, or obstructive (but hopefully not cardiogenic!) shock. Occasionally, following fluid resuscitation, lactate remains above the reference range despite normalization of cardiovascular parameters. In some cases this may be due to concurrent disease such as neoplasia (especially lymphoma), hemolytic anemia, and diabetes mellitus.

Lactate and sepsis

Hyperlactatemia seen in patients with sepsis and septic shock appears to be a much more complicated situation. Certainly when these patients have more severe hypovolemia, lactate concentration is often increased. However, the hypermetabolic state seen with sepsis may result in increased glycolysis and pyruvate production at a rate faster than it

can enter the citric acid cycle. Some of the pyruvate is consequently converted to lactate. In these patients, although lactate is increased, the lactate: pyruvate ratio would be expected to be normal. There is increasing evidence from both experimental studies and clinical studies in people that the hyperlactatemia seen in volume replete septic patients is related to hypermetabolism. In the author's experience, patients with sepsis that are relatively volume replete have only mild hyperlactatemia and moderate to severe hyperlactatemia is usually associated with hypovolemia.

Other conditions

Hyperlactatemia due to increased muscular activity is different from other causes in that resolution is more rapid. Extreme exercise in greyhounds can generate lactate concentrations > 30 mmol/L, whereas seizures tend to cause elevations in the 6 - 10 mmol/L range. The degree of hypoxemia seen in most veterinary patients should not cause hyperlactatemia because arterial PaO_2 must be 30-40 mmHg or lower to increase plasma lactate. Severe anemia, however, may result in mild to moderate hyperlactatemia in the absence of hypoperfusion especially if the anemia is acute in onset. In experimental studies of euvolemic hemodilutional anemia, a PCV of less than 15% was necessary to increase plasma lactate. In chronic anemia, the PCV is usually in the single digits before hyperlactatemia is noted and even then some animals do not have a high lactate. Anemic animals may develop hyperlactatemia due to hypovolemia earlier than animals with normal red blood cell numbers. Hyperlactatemia in association with underlying disease processes in the absence of hypoperfusion and drug-induced causes remains largely undocumented in veterinary medicine. An activated charcoal (AC) suspension containing propylene glycol and glycerol has been reported to cause hyperlactatemia in dogs. Lymphoma in dogs is associated with elevated resting lactate concentration and a mild increase in lactate following glucose challenge. An increased susceptibility to hyperlactatemia following intravenous fluid therapy with lactate-containing crystalloids has also been reported in dogs with lymphoma. Clinical experience suggests that hyperlactatemia in a dog with relatively normal perfusion warrants a cancer search.

Lactate and prognosis

High lactate concentrations have prognostic implications. An early study in people demonstrated that as lactate concentrations increased from 2.1 to 8.0 mmol/L, survival decreased from 90% to 10%. However, due to the extremely heterogeneous nature of causes of hyperlactatemia, it has proved difficult to identify a critical level of oxygen delivery associated with lactic acidosis. A decrease in serum lactate concentration following therapy for hypoperfusion may be more useful prognostically and in people appears to discriminate between survivors and nonsurvivors better than peak or admission lactate concentration. This is entirely logical and predictable and experience indicates that this is true in dogs and cats and that it depends upon the severity and reversibility of the underlying disease. Severe hyperlactatemia following acute, severe hemorrhage that is rapidly controlled and treated will not be associated with a high mortality, whereas it usually is in dogs with sepsis, SIRS and MODS. Now that lactate quantitation is becoming more mainstream in veterinary medicine (at last!!!) there are an increasing number of papers being published that include lactate measurements even if it is not the main focus of the study.

In veterinary patients, the majority of clinical research has been performed in horses and dogs. Lactate concentration has been shown to be predictive of survival in horses with acute abdominal crises and in neonatal foals. Prognostic significance has also been demonstrated in dogs with heartworm caval syndrome, babesiosis, SIRS, severe soft tissue infections, dogs in a veterinary intensive care unit and dogs requiring intravenous fluid therapy. Lactate has also been shown to fall in cats with hypertrophic cardiomyopathy after treatment with diltiazem. There are two retrospective studies to date looking at plasma lactate concentration in dogs with gastric dilatation volvulus syndrome (GDV). The first, which looked only at lactate on admission, indicated that a high plasma lactate concentration was a moderately sensitive but specific indicator of the presence of gastric necrosis. In 102 dogs, 69 of 70 (99%) dogs with plasma lactate concentration < 6.0 mmol/L survived, compared with 18 of 31 (58%) dogs with plasma lactate concentration > 6.0 mmol/L. Median plasma lactate concentration in dogs with gastric necrosis (6.6 mmol/L) was significantly higher than concentration in dogs without gastric necrosis (3.3 mmol/L). The positive predictive value of a lactate > 6.0 mmol/L to predict the presence gastric necrosis was 75% i.e. 3 out of 4 dogs with a lactate greater than 6 mmol/L had gastric necrosis. The most recent retrospective study of serial lactate measurements in 64 dogs with GDV showed that 90% (36 of 40) of dogs with an initial lactate concentration ≤ 9.0 mmol/L survived, compared with only 54% (13 of 24) of dogs with a lactate concentration > 9.0 mmol/L. Within the group of dogs with an initial lactate concentration of > 9.0 mmol/L, survival rates for dogs with a final lactate concentration > 6.4 mmol/L (23%) was significantly lower than survival rates for dogs with a final lactate concentration ≤ 6.4 mmol/L (91%). Survival in dogs with an absolute change in lactate concentration ≤ 4 mmol/L was 10% compared to 86% when lactate fell by > 4 mmol/L. Finally, when the percentage change in lactate concentration was ≤ 42.5%, survival was 15%, compared to 100% when the percentage change was > 42.5%.

Recent studies in human medicine have continued to support the use of serial lactate measurements as prognostic indicators. In fact, there are now studies documenting the use of lactate guided therapy in ICU patients in the same vein as the seminal, goal directed therapy study by Rivers et al (that aimed to optimize oxygen delivery). In one multicenter, randomized, controlled trial, hospital mortality was lower in the group where lactate was used to guide therapy (hazard ratio 0.61, 95% CI 0.43-0.87, p=0.006) when adjusted for predefined risk factors. Additionally, in the lactate guided group, Sequential Organ Failure Assessment (SOFA) scores were lower between 9 and 72 hours, inotropes could be stopped earlier, and patients could be weaned from mechanical ventilation and discharged earlier from the ICU. The results of all these studies notwithstanding, it is important to note that for individual patients lactate concentration should always be in conjunction with all other clinical features to guide therapy and prognostication.

Other clinical uses of lactate measurement

Lactate quantitation in fluids other than blood has been suggested in people as a predictor of bacterial infection, as an indicator of a successful response to antibiotic therapy, and as a means of assessing the degree of tissue injury and therefore prognosis. Lactate concentration in abdominal fluid in patients with ascites may be useful as a diagnostic adjunct for detecting bacterial peritonitis. One of these studies suggested that an effusion to plasma lactate gradient of > 2 mmol/L was 100% sensitive and specific for bacterial peritonitis; however, this was based on only 7 dogs which is insufficient for the evaluation of a diagnostic test. In an (as yet) unpublished study by the author comparing abdominal fluid characteristics between 16 dogs and cats with bacterial peritonitis and 55 with non-bacterial effusions, the sensitivity and specificity of a lactate gradient of > 2 mmol/L was 56.2 and 81.5% respectively. Abdominal fluid from septic peritonitis had a low glucose, pO_2 and pH and a high pCO2 and lactate. An abdominal fluid glucose concentration of < 2.8 mmol/L (50 mg/dL) was 100% specific for bacterial peritonitis. Lactate in plasma and pericardial fluid has been evaluated in 41 dogs with pericardial effusion. Hyperlactatemia was seen in 93% of dogs and pericardial fluid lactate was significantly higher than in plasma. Although the neoplastic effusion group tended to have higher lactate in pericardial fluid and the difference between groups was significantly different, the overlap between groups meant that lactate concentration was not a clinically useful discriminator. In people, high lactate concentration in cerebrospinal fluid has been used to detect bacterial meningitis and correlates with the severity of central nervous system damage and prognosis. Similarly, a high synovial fluid lactate concentration may be helpful in the diagnosis of bacterial arthritis.

Treatment

Because hyperlactatemia is usually due to hypoperfusion from an underlying disease process, treatment comprises intravenous fluid resuscitation and the diagnosis and correction of the specific cause. Aggressive intravenous fluid therapy using crystalloids, colloids, or blood products is usually necessary in the absence of cardiopulmonary disease. Maintaining a packed cell volume of >20% seems wise with respect to the effects of anemia on arterial oxygen content and hyperlactatemia. The use of intravenous sodium bicarbonate should only be considered in patients with severe hemodynamic compromise and acidosis (pH<7.10) that are refractory to intravenous volume loading and with adequate pulmonary ventilation. Thiamine treatment could have a somewhat tenuous rationale in the treatment of lactic acidosis because it is an essential cofactor in the oxidation of pyruvate.

At long last, nearly half a century it was first convincingly demonstrated by the landmark studies of Weil et al, it seems that the clinical value of lactate quantitation has been realized in veterinary medicine.

In 1931, Howard A. Kelly MD, ruminated in the *Annals of Surgery*, (1931; 93: 323) *"Those who fill our professional ranks are habitually conservative. This salutary mental attitude expresses itself peculiarly in our communal relations; namely, when a new idea appears which is more or less subversive to old notions and practices, he who originates the idea must strike sledge hammer blows in order to secure even a momentary attention. This must then be followed by a long, patient, propaganda and advertising until in the grand finale, the public, indifferent at first, is aroused, proceeds to discuss, and finally accepts the iconoclastic proposal as a long accepted fact of its own invention and asks wonderingly, "Why such a bother? What after all is new about this? We knew it long ago!"*

References available upon request.