Clinical use of plasma lactate concentration. Part 1: Physiology, pathophysiology and measurement

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ABSTRACT

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Objective – To review the current literature with respect to the physiology, pathophysiology and measurement of lactate.

Data Sources – Data was sourced from veterinary and human clinical trials, retrospective studies, experimental studies and review articles. Articles were retrieved without date restrictions and were sourced primarily via PubMed, Scopus and CAB Abstracts as well as by manual selection.

Human and Veterinary Data Synthesis – Lactate is an important energy storage molecule, the production of which preserves cellular energy production and mitigates the acidosis from ATP hydrolysis. Although the most common cause of hyperlactatemia is inadequate tissue oxygen delivery, hyperlactatemia can and does occur in the face of apparently adequate oxygen supply. At a cellular level, the pathogenesis of hyperlactatemia varies widely depending on the underlying cause. Microcirculatory dysfunction, mitochondrial dysfunction and epinephrine-mediated stimulation of Na⁺-K⁺-ATPase pumps are likely important contributors to hyperlactatemia in critically ill patients. Ultimately, hyperlactatemia is a marker of altered cellular bioenergetics.

Conclusion – The etiology of hyperlactatemia is complex and multifactorial. Understanding the relevant pathophysiology is helpful when characterizing hyperlactatemia in clinical patients.

Keywords: Hyperlactatemia, Lactic Acidosis, Shock, Sepsis, Dog, Cat

Abbreviations:

NAD⁺ - Nicotinamide adenine dinucleotide
**Introduction**

Once considered a simple by-product of anaerobic metabolism, lactate is now recognized as an important intermediate in cellular bioenergetics. Clinically, lactate is a valuable triage tool, prognostic indicator and potential therapeutic target. Research into this easily measured, once misunderstood metabolite has gained momentum over recent decades and lactate is now commonly accepted as a useful tool in the emergency and critical care practitioners’ diagnostic armamentarium. The first part of this review will address the biochemistry, physiology, pathophysiology and measurement of lactate. In the second part, we will review the evidence.
base in human and veterinary medicine and conclude with recommendations for the clinical application of lactate measurement in veterinary emergency and critical care practice.

History and Biochemistry

Lactic acid was first documented in sour milk by Karl Wilhelm Scheele in 1780. In 1843, Johann Joseph Seberer identified lactic acid in human blood after death, and in 1878 George Salomon documented lactate in the blood of people suffering from a range of illnesses including anemia, congestive heart failure, pericarditis and neoplasia. In the mid 1900s Huckabee performed a number of landmark studies characterizing the relationship between lactate and pyruvate under various conditions of reduced oxygen availability. In 1964, Broder and Weil showed that in undifferentiated shock, people with blood lactate concentrations greater than 4 mmol/L (36 mg/dL) had a poorer prognosis than those with blood lactate concentrations less than 4 mmol/L (36 mg/dL). These early investigations formed the essential foundation for our current understanding of lactate and hyperlactatemia.

Definitions

The terms lactate and lactic acid are often used erroneously as synonyms. Lactate, (\(C_3\)CH(OH)COO\(^-\)), is an anion and conjugate base to lactic acid, (\(C_3\)CH(OH)COOH). As the pKa of lactic acid is 3.8, at physiologic pH, lactic acid is essentially fully dissociated into lactate anions and protons (\(H^+\)). Lactic acid is not, however, produced in vivo. Instead, lactate is produced directly in its ionized form during carbohydrate metabolism, and the production of lactate from pyruvate involves the consumption of protons rather than their release.
Lactate exists in 2 stereoisomeric forms, L-lactate and D-lactate. (Figure 2) In health, L-lactate accounts for > 99% of total body lactate and is the isomer of major physiological significance. D-lactate is formed either by the glyoxalase pathway or produced by commensal bacteria in the mammalian gastrointestinal tract and absorbed into circulation.\(^\text{17}\) Unless otherwise specified, in this manuscript, “lactate” will be used in reference to L-lactate.

Hyperlactatemia indicates that serum, plasma or blood lactate concentration is above the relevant reference interval. Lactic acidosis refers to moderate to severe hyperlactatemia with concurrent metabolic acidosis,\(^\text{16,22}\) and is a common cause of metabolic acidosis in the dog and cat.\(^\text{23}\)

**Biochemistry**

Glycolysis is the cytosolic, biochemical cascade by which one 6-carbon glucose molecule is broken down into two 3-carbon molecules of pyruvate, 2 molecules of ATP and 2 molecules of reduced nicotinamide adenine dinucleotide (NADH). This process involves 11 distinct enzymatic reactions. (Figure 3)

Glycolysis requires a constant supply of glucose and oxidized nicotinamide adenine dinucleotide (NAD\(^+\)) to produce ATP, but does not require oxygen. Pyruvate is transported into the mitochondrion\(^\text{24}\) where it undergoes decarboxylation to produce Acetyl-CoA.\(^\text{16}\) This reaction is irreversible, requires NAD\(^+\), and is catalyzed by the pyruvate dehydrogenase complex. Acetyl-CoA then proceeds through the tricarboxylic acid (TCA) cycle to produce CO\(_2\), NADH and FADH\(_2\).\(^\text{25}\) Protons from NADH and FADH\(_2\) create the proton gradient required for the production of adenosine triphosphate (ATP) by the electron transport chain (ETC). When glycolysis, the
TCA cycle and the ETC are combined, the oxidation of one molecule of glucose produces approximately 36 molecules of ATP. 26,27

Under healthy, resting conditions, approximately 10% of pyruvate is converted into lactate by lactate dehydrogenase (LDH). This is a reversible, cytosolic reaction during which NADH is oxidized to NAD⁺ (Figure 4) When oxygen demand exceeds supply, NAD⁺ stores become depleted, pyruvate and NADH accumulate in the cytosol and LDH activity is upregulated. 27,31 Lactate formation reduces the cytosolic concentrations of pyruvate and H⁺ while replenishing NAD⁺ enabling glycolysis to continue supplying ATP. 31-33 Once oxygen supply is restored, LDH transforms lactate back into pyruvate, which can enter the TCA cycle or be used for gluconeogenesis. Fundamentally, lactate is a highly conserved, easily transported energy storage molecule, a form of energy currency that is transferred as required to suit metabolic demands. The metabolic acidosis that occurs with hyperlactatemia is the result of ATP hydrolysis without concurrent proton consumption by the ETC and subsequent proton accumulation. 14,34-36 (Figure 4)

As a strong anion, lactate also has acidifying effect in a manner similar to chloride as per Stewart’s physicochemical approach. 12,28,37-39 This is because an increase in lactate causes a decrease in the strong ion difference (SID). (Figure 5) In accordance with the law of electroneutrality, decreasing the SID results in a proportionate increase in [H⁺] and therefore, acidosis. 40-42

The quantitative approach to acid base indicates that for every 1 mmol/L (9 mg/dL) increase in lactate, SBE will decrease by 1 unit. 43 The precise relationship between lactate and acidosis is, however, complex and controversial. 15,33,35,41,44-47 The correlation between acidosis
and lactate concentration is particularly inconsistent in the presence of aerobic hyperlactatemia.\textsuperscript{42,43,48-51}

\textit{Lactate Transport}

Lactate transport across cell membranes occurs predominantly via facilitated passive transport by proton-linked monocarboxylate transporters (MCT) and sodium-coupled MCTs.\textsuperscript{22} At least 14 MCTs have been identified although MCT1 and MCT4 are considered the most important in mammalian tissues.\textsuperscript{52-54} These MCTs are variably expressed in different tissues and are relatively non-specific, moving a number of different substrates including lactate, pyruvate, acetate, propionate, butyrate, acetoacetate and $\beta$-hydroxybutyrate down concentration gradients.\textsuperscript{22,53} MCT expression on erythrocyte membranes vary between species.\textsuperscript{52} This explains the species-dependent variation seen between whole blood and plasma or serum lactate concentrations. Lactate transporters also play an essential role in “lactate shuttles,” a form of energy currency exchange between different cells and tissue types.\textsuperscript{55-57} Lactate shuttles have been shown to exist in the brain, striated muscle, liver, kidneys and myocardium.\textsuperscript{27}

\textit{Physiology – homeostasis in health}

\textit{Lactate production, metabolism and excretion}

While almost all tissues are capable of producing and consuming lactate, the majority of lactate produced at rest comes from skeletal muscle (40-50\%), the brain (13\%), and adipose tissue (variable) by virtue of their inherent production capacities and mass.\textsuperscript{12,22,28,31,58-61} Other lactate producing tissues include the renal medulla, gastrointestinal tract, skin, red and white blood cells, and platelets.\textsuperscript{22,28,58,62,63} Red blood cells, leukocytes (predominantly neutrophils) and
platelets are responsible for 80, 13 and 7% of lactate production in blood, respectively.\textsuperscript{64,65} Glycolysis and lactate production are increased during the oxidative burst of neutrophils\textsuperscript{65} and experimentally induced sepsis has been shown to increase leukocyte production of lactate 6-fold.\textsuperscript{64}

The most important lactate consuming tissues are the liver (20-30%), the renal cortex (20%) and the myocardium (5-15%).\textsuperscript{16,22,28,31,62,66-68} The liver has a large reserve capacity for lactate metabolism.\textsuperscript{16,69,70} Hepatic lactate uptake is, however, a saturable process.\textsuperscript{16,71} As a valuable energy substrate, lactate is avidly reabsorbed by the renal proximal convoluted tubule.\textsuperscript{16,62-72} During hyperlactatemia, certain tissues, including the brain and skeletal muscle, may switch from net lactate production to net lactate consumption sometimes even preferentially to readily available glucose.\textsuperscript{26,31,73,74}

**Pathophysiology – Dyshomeostasis in disease**

**Classification of Hyperlactatemia**

Lactic acidosis has been divided into 2 broad categories: Type A, due to an insufficient oxygen supply, and Type B, in the face of apparently adequate oxygen availability.\textsuperscript{75}(Table 1) Patients can experience Type A and Type B hyperlactatemia concurrently. Type A hyperlactatemia can be relative, resulting from increased oxygen demand, or absolute, resulting from inadequate oxygen delivery. Type B hyperlactatemia has conventionally been subdivided into three categories: B1, associated with underlying disease, B2, associated with drugs or toxins, and B3, resulting from congenital errors in metabolism.
Relative Type A Hyperlactatemia

Hyperlactatemia from increased oxygen demand can occur due to exercise, seizure activity, shivering, trembling and struggling. A 5 minute spray bath in cats dramatically increased plasma lactate concentrations (mean ≈ 7.0 mmol/L [63.0 mg/dL]). Exercise-induced hyperlactatemia can be marked but is highly variable. Maximal lactate concentrations after exercise range from 6.3 mmol/L (56.8 mg/dL) in Labrador Retrievers during field training,76 to 14.6 mmol/L (131.5 mg/dL) in dogs after agility testing,77,78 to over 30 mmol/L (270.3 mg/dL) in racing greyhounds.79-84 In healthy animals, lactate concentrations fall rapidly following cessation of muscle activity with an estimated half-life of 20-60 minutes.80-89 Seizure-induced hyperlactatemia results primarily from vigorous muscle activity and is associated with a similar half-life.86,90 A persistent increase in lactate concentration following cessation of seizure activity is cause for concern.28,86,90

Absolute Type A Hyperlactatemia

Hyperlactatemia from decreased oxygen delivery is observed with shock, local hypoperfusion, severe anemia, severe hypoxemia, and carbon monoxide poisoning.

Shock

Shock is likely to be the most common cause of pathologic hyperlactatemia in veterinary emergency and critical care practice. By definition, shock is associated with inadequate oxygen delivery to the tissues leading to impaired mitochondrial respiration and increased anaerobic metabolism. The onset of hyperlactatemia relative to oxygen delivery is similar in hypovolemic,
cardiogenic and obstructive shock,\textsuperscript{91,92} but occurs earlier in maldistributive shock due to impaired oxygen extraction from mitochondrial and microcirculatory dysfunction.\textsuperscript{91-94} Shock has traditionally been identified by physical exam parameters including tachycardia, hypotension, depressed mentation and inadequate urine output. Tissue hypoperfusion can, however, be present despite normal standard hemodynamic variables, a phenomenon termed “occult shock.”\textsuperscript{95} In a recent clinical trial, dogs presenting in hypovolemic or septic shock were resuscitated to satisfy traditional hemodynamic targets. In this study, 6/30 dogs had persistently increased plasma lactate concentrations and 11/30 dogs had persistently low ScvO\textsubscript{2} (< 70%) suggesting ongoing tissue hypoperfusion despite normalization of routine hemodynamic parameters.\textsuperscript{96} The hyperlactatemia of shock is unlikely to be solely due to impaired oxygen delivery leading to increased anaerobic metabolism. In several experimental animal models and human clinical trials, hyperlactatemia in shock was found to be independent of oxygen consumption and delivery.\textsuperscript{94,97-102} Several causes of Type B hyperlactatemia, to be elaborated on in later sections, are believed to be important contributors to shock-associated hyperlactatemia. Mild hypoperfusion seems to be associated with plasma lactate concentrations of 3-5 mmol/L (27-45 mg/dL), moderate with 5-7 mmol/L (45-63 mg/dL) and severe with >7 mmol/L (>63 mg/dL).\textsuperscript{103}

\textit{Regional Ischemia}

Hyperlactatemia is considered a non-specific indicator of mesenteric ischemia as peripheral blood lactate concentrations can also increase with other abdominal crises (i.e. bacterial peritonitis, acute pancreatitis) and may reflect global hypoperfusion more than regional ischemia.\textsuperscript{104-106} The ability of plasma lactate concentration to differentiate patients with gastrointestinal ischemia from those without varies between studies. For example, in one study
investigating dogs with gastric dilatation and volvulus, 74% (23/31) of dogs with plasma lactate > 6.0 mmol/L (54.0 mg/dL) had gastric necrosis, whereas in another, only 33% (8/24) of dogs with plasma lactate ≥ 6 mmol/L (54.0 mg/dL) had gastric necrosis. Furthermore, peripheral lactate concentrations can remain normal despite significant splanchnic ischemia. As peripheral plasma lactate concentrations are inconsistently and non-specifically increased in the presence of abdominal disease, caution must be exercised when using plasma lactate concentrations to rule in or rule out intra-abdominal catastrophes.

Anemia and Hypoxemia

The correlation between anemia and hyperlactatemia is highly dependent on chronicity of disease. Animals with chronic anemia can remain eu lactatemic even when anemia is severe. In contrast, animals with anemia resulting from acute hemorrhage or acute, severe hemolysis can develop clinically significant hyperlactatemia. In experimental animal models of acute dilutional anemia, hyperlactatemia did not develop until packed cell volume was below 15%. Hyperlactatemia from hypoxemia alone is likely rare in veterinary medicine, as P,O₂ values need to be 25-40 mm Hg before lactate concentrations begin to rise.

Carbon Monoxide

Carbon monoxide binds to hemoglobin with a greater affinity than oxygen to produce carboxyhemoglobin which inhibits effective oxygen transport. Carbon monoxide also shifts the oxyhemoglobin curve to the left, further reducing oxygen delivery, and directly induces cellular damage and oxidative stress. Hyperlactatemia from carbon monoxide toxicity is suspected to result primarily from tissue hypoxia, although mitochondrial dysfunction and

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catecholamine effects, which will be discussed further in later sections, may also contribute.\textsuperscript{22} In keeping with a multifactorial pathogenesis, lactate concentration is variably correlated with carboxyhemoglobin concentrations as well as the duration of carbon monoxide exposure.\textsuperscript{117-119}

\textit{Type B1 Hyperlactatemia – Hyperlactatemia Associated with Underlying Disease:}

\textbf{Malignancy}

A variety of potential mechanisms for malignancy-associated hyperlactatemia have been identified including: increased production of glycolytic enzymes by hypoxia-inducible factors 1 and 2,\textsuperscript{120-122} increased production of glycolysis intermediates via upregulation of the pentose phosphate pathway,\textsuperscript{22,123} mitochondrial dysfunction, reduced hepatic clearance, and malnutrition causing thiamine deficiency.\textsuperscript{12,28} Malignant cells preferentially use glycolytic pathways despite readily available oxygen\textsuperscript{22,122} and lactate may alter the tumor microenvironment in a manner that inhibits destruction of neoplastic cells.\textsuperscript{122,124-126} The inhibition of enzymes involved in lactate transport and metabolism has been found to inhibit tumor growth in various neoplastic cell lines. Regulation of lactate metabolism is, consequently, now a target of modern cancer therapy.\textsuperscript{22,53,121,122,124-128}

In people, hyperlactatemia has been associated with neoplasia of hematologic origin, lung cancer, prostate cancer, breast cancer, endometrial carcinoma, melanoma, prostate cancer, and cholangiocarcinoma.\textsuperscript{22,29,129} In addition, pheochromocytoma is associated with catecholamine-induced hyperlactatemia.\textsuperscript{29,130,131} In a retrospective study including 50 dogs with lymphoma, hyperlactatemia was documented in 20 cases, although 15 had concurrent confounding pathologies such as sepsis or hepatic dysfunction.\textsuperscript{132} An association between
hyperlactatemia and canine neoplasia may exist but is likely to be uncommon. In a clinical setting, neoplasia-associated hyperlactatemia should be considered a diagnosis of exclusion.

**Diabetes Mellitus**

Altered carbohydrate metabolism in patients with diabetes mellitus occurs due to upregulated glycolysis, impaired glycogenesis, reduced PDH activity, and reduced oxidative metabolism.\(^{22,133}\)

Lactate concentrations in people with Type 1 and Type 2 diabetes mellitus are approximately 0.3-1.0 mmol/L (2.7-9 mg/dL) higher than in non-diabetics.\(^{133,134}\) Hyperlactatemia is commonly observed in diabetic ketoacidosis due to a combination of hypovolemia and altered carbohydrate metabolism: median 3.5 mmol/L (31.5 mg/dL) (range: 1.2-8.3 mmol/L [10.8-74.8 mg/dL]).\(^{135}\) People with diabetic ketoacidosis also have significantly higher D-lactate concentrations (mean±SD: 2.14±2.18 mmol/L [19.3±19.6 mg/dL]) compared to diabetic, non-ketotic patients (mean±SD: 1.32±0.77 mmol/L [11.9±6.94 mg/dL]) and controls (mean±SD: 1.03±2.18 mmol/L [9.28±19.6 mg/dL]).\(^{17}\) This is speculated to be the result of increased methylglyoxal production and breakdown due to altered glucose and increased ketone metabolism.\(^{17}\) Dogs with diabetes mellitus also have statistically higher lactate than normal dogs: median 2.6 mmol/L (18.0 mg/dL) (range 0.9-5.8 mmol/L [8.1-52.2 mg/dL]) vs. median 1.0 mmol/L (9.0 mg/dL) (range 0.6-1.3 mmol/L [5.4-11.7 mg/dL]) respectively.\(^{135}\) The hyperlactatemia identified in these diabetic dogs was speculated to be the result of dehydration, decreased tissue perfusion, and impaired lactate metabolism.\(^{135}\) Although cats with diabetic ketoacidosis have been shown to have significantly higher D-lactate concentrations than controls,\(^{331}\) a significant increase in L-lactate has not been identified in cats with diabetes mellitus or diabetic ketoacidosis.\(^{137,331}\)
In people, severe liver disease is rarely associated with hyperlactatemia unless they are acutely challenged by a lactate load or are experiencing concurrent hypoperfusion. People with chronic liver disease demonstrate slowed lactate metabolism, but peak lactate values are often similar to healthy controls. In the presence of severe hepatic dysfunction or failure the liver can become a net lactate producer causing hyperlactatemia. Postulated mechanisms for hepatic lactate production include glycolytic upregulation, reduced PDH activity, and impaired hepatic gluconeogenesis. Although lactic acidosis is considered a rare complication of hematologic neoplasia, in one literature review, hepatic involvement was identified in 80% (42/52) of hyperlactatemic people with leukemia or lymphoma. In a canine model of experimentally induced septic shock, septic dogs demonstrated both increased hepatic lactate production and reduced hepatic lactate extraction compared to non-septic controls following lactic acid administration. In another study, 100% of dogs (10/10) with lymphoma and documented hepatic involvement were hyperlactatemic although 5/10 suffered from concurrent hemorrhage, sepsis or volume depletion. Although the kidneys play an important role in lactate metabolism, reports of hyperlactatemia from acute or chronic renal failure are scarce without contributing factors such as the use of biguanide anti-hyperglycemics or hypovolemia.

**Thiamine Deficiency**

Thiamine deficiency (vitamin B₁) is an uncommon but well documented cause of hyperlactatemia. Thiamine plays an important role in several metabolic pathways after conversion to thiamine pyrophosphate. Thiamine pyrophosphate is a cofactor in the PDH complex, alpha-ketoglutarate dehydrogenase in the TCA cycle, transketolase in the pentose
phosphate pathway, and ketoacid dehydrogenase.\textsuperscript{148,149,154,156,157} Thiamine deficiency, also known as beriberi disease, leads to compromised cellular bioenergetics and the accumulation of pyruvate and lactate.\textsuperscript{148,151} Thiamine deficiency can be caused by total parenteral nutrition without thiamine supplementation, malignancy, sepsis, critical illness, chronic malnutrition, chronic pyloric outflow obstruction, and hyperthyroidism.\textsuperscript{12,151,154,158,159} Thiamine deficiency manifests clinically in people as hyperlactatemia, vasodilation, peripheral edema, cardiac dysfunction, vomiting, peripheral neuropathy and Wernicke’s encephalopathy.\textsuperscript{22,152} In dogs and cats, thiamine deficiency has been reported in association with the ingestion of fish high in thiaminase,\textsuperscript{160,161} food with inactivated thiamine from processing,\textsuperscript{162,163} and sulfite-preserved meat.\textsuperscript{148,164-166} Thiamine deficiency in dogs and cats typically manifests as cervical ventroflexion, ataxia, mydriasis, depressed mentation and seizure activity.\textsuperscript{148,160-166}

\textit{Hyperthyroidism}

Hyperthyroidism causes an increased basal metabolic rate leading to increased carbohydrate metabolism and hyperlactatemia through upregulation of glycolysis and the hexose monophosphate pathway.\textsuperscript{137,167-171} In addition, hyperthyroidism and thyroid storm are considered risk factors for thiamine deficiency due to depletion of thiamine stores.\textsuperscript{159,168,172} One study reported higher plasma lactate concentrations in cats with hyperthyroidism than in healthy cats or cats with diabetes (mean±SD of 5.0±3.0 mmol/L [45.0±27.0 mg/dL] and 3.8±2.2 mmol/L [34.2±19.9 mg/dL] respectively).\textsuperscript{137}

\textit{Microcirculatory dysfunction

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Microcirculatory dysfunction is considered the most important cause of impaired oxygen extraction in maldistributive shock and is suspected to be an important contributing factor to hyperlactatemia in this patient group.\textsuperscript{92,173,174} Sepsis enhances nitric oxide production, alters the neurohormonal control of endothelial and smooth muscle cells, reduces erythrocyte flexibility, and activates leukocytes resulting in marked microcirculatory heterogeneity.\textsuperscript{173-177} Erythrocyte aggregation, leukocyte adhesion, local edema and microvascular thrombosis also impair microcirculatory flow.\textsuperscript{92,174} Microcirculatory shunting likely contributes to the concurrent hyperlactatemia and increased $\text{SvO}_2$ seen in sepsis.\textsuperscript{176} One of the most important features of microcirculatory dysfunction is that it can occur independently of macrocirculatory hemodynamic variables.\textsuperscript{177-179} This means that normalization of vital parameters does not necessarily imply normalization of perfusion at the tissue level. Microcirculatory dysfunction has been correlated with hyperlactatemia in people with sepsis despite normal hemodynamic parameters, supporting the concept that circulatory shunting at the capillary level may lead to local, heterogeneous tissue hypoxia and hyperlactatemia despite apparently adequate oxygen delivery.\textsuperscript{180}

**Altered Cellular Respiration**

Impaired cellular respiration, also known as cytopathic hypoxia, can lead to hyperlactatemia by a number of different pathways including mitochondrial dysfunction, upregulation of glycolysis, and impaired gluconeogenesis.\textsuperscript{181} Mitochondrial dysfunction has been implicated as a cause of aerobic hyperlactatemia particularly in the presence of severe inflammation, sepsis or oxidative stress.\textsuperscript{182} Mitochondrial respiration can fail as a result of direct cytochrome inhibition, impaired mitochondrial regeneration, or due to a loss of the normal electrochemical gradient between the mitochondrial matrix and intermembrane space resulting in impaired ATP production.\textsuperscript{25,183-186}
In addition, mitochondrial respiration can be compromised by dysfunction of the pyruvate dehydrogenase complex (PDH). Alkalosis stimulates the rate limiting glycolytic enzyme phosphofructokinase, subsequently increasing pyruvate and therefore lactate concentrations. Similarly, the administration of glucose, increased NADH concentrations and ATP depletion promote lactate formation via concentration dependent effects.

**Catecholamines**

Adrenergic stimulation by catecholamines, particularly epinephrine, is likely to be an important cause of clinical hyperlactatemia. Epinephrine administration is associated with a progressive, dose-related increase in lactate due to increased cyclic adenosine monophosphate production (cAMP) via β2-adrenergic stimulation. This leads to enhanced glycogenolysis, glycolysis, lipolysis, and stimulation of Na\(^+\)-K\(^-\)-ATPase pumps. Na\(^+\)-K\(^-\)-ATPase pumps are associated with lactate-producing glycolytic pathways that are not coupled to mitochondrial respiration. (Figure 6) There is compelling evidence to support the upregulation of skeletal muscle Na\(^+\)-K\(^-\)-ATPase associated glycolysis as a clinically significant source of lactate in septic and hemorrhagic shock, as well as exercise-related hyperlactatemia. Not only does plasma lactate correlate with catecholamine concentrations, but both selective Na\(^+\)-K\(^-\)-ATPase and adrenergic blockade have been shown to prevent or decrease lactate concentrations in hemorrhagic shock, septic shock and during exercise. Hyperlactatemia has even been documented in healthy university students following a university exam. Catecholamine-induced hyperlactatemia likely explains the hyperlactatemia seen with pheochromocytoma and acute asthmatic crisis (from endogenous catecholamine release as well as β2 adrenergic agonist therapy).
Type B2 Hyperlactatemia – Hyperlactatemia Associated with Drugs or Toxins

Acetaminophen and Salicylates

Acetaminophen toxicity causes hyperlactatemia by impairing mitochondrial respiration, by causing hepatic dysfunction leading to impaired lactate clearance, and by causing methemoglobinemia.\textsuperscript{238,239}

Salicylates decrease the availability of CoA, inhibit succinate dehydrogenase and alpha-ketoglutarate dehydrogenase.\textsuperscript{20,29,240} They also increase the permeability of the inner mitochondrial membrane leading to uncoupling of oxidative phosphorylation and stimulate phosphofructokinase all of which lead to increased lactate production.\textsuperscript{28,29,240} In people, hyperlactatemia associated with salicylate toxicity is usually mild.\textsuperscript{241}

Adrenergic Agonists and Sympathomimetics

Hyperlactatemia also occurs with drugs and toxins that cause adrenergic stimulation including: β\textsubscript{2}-receptor agonists (terbutaline, albuterol, salbutamol), methylxanthines (theophylline, theobromine), and cocaine.\textsuperscript{12,237,242-245} Terbutaline, albuterol and other β\textsubscript{2}-agonists cause hyperlactatemia as previously described.\textsuperscript{237,243,246} The methylxanthines promote hyperlactatemia by increasing plasma catecholamine concentrations, inhibiting cAMP breakdown enhancing β-receptor effects, and by directly stimulating the Na+-K+-ATPase pumps.\textsuperscript{244,245,247,248} Cocaine has some sympathomimetic activity but also causes seizures at higher doses.\textsuperscript{249} As cocaine-induced hyperlactatemia is not observed experimentally in dogs treated with muscle relaxants, the increased muscle activity is believed to be more important than the adrenergic effects.\textsuperscript{249-251} In a recent retrospective study on dogs presenting with

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presumptive cocaine toxicosis, 9/15 were hyperlactatemic defined as > 2.0 mmol/L (>18.0 mg/dL) with a median of 2.6 mmol/L (23.4 mg/dL) (range 0.8 – 8.6 mmol/L [7.2-77.5 mg/dL]).

Propofol

Propofol infusion syndrome (PRIS) refers to the development of acute metabolic acidosis, cardiac dysfunction, rhabdomyolysis, lipemia, and hepatomegaly or hepatic lipidosis in conjunction with propofol administration. Hyperkalemia, lactic acidosis, and renal failure are also common features of this syndrome. PRIS is most commonly seen in people receiving propofol for prolonged periods. Impaired fatty acid oxidation and mitochondrial dysfunction are believed to be the major underlying pathophysiologic mechanisms for PRIS. To the authors’ knowledge, PRIS has not yet been reported in dogs or cats.

Cyanide/Sodium Nitroprusside

Cyanide toxicity occurs secondary to smoke inhalation, ingestion of toxins including stone fruit pits, cassava roots, bitter almonds and bamboo shoots, or infusions of sodium nitroprusside. Cyanide inhibits aerobic metabolism by non-competitively inhibiting ferric iron in cytochrome c oxidase (complex IV), the final step in the electron transport chain. This results in ATP depletion, acidosis, hyperlactatemia and venous hyperoxia due to impaired oxygen extraction.

As sodium nitroprusside is metabolized into one molecule of nitric oxide and 5 molecules of cyanide, iatrogenic cyanide toxicity occasionally occurs. Serial lactate measurements can be of value when monitoring for the development of cyanide toxicity.
Sodium nitroprusside also has the potential to cause Type A hyperlactatemia by inducing hypotension.

**Glucocorticoids**

Glucocorticoids elicit hyperlactatemia by promoting amino acid conversion to pyruvate, inhibiting PDH, potentiating the hyperlactatemic effect of catecholamines and altering carbohydrate metabolism. Both anti-inflammatory (1 mg/kg/day) and immunosuppressive (4 mg/kg/day) doses of prednisone resulted in statistically significant and clinically relevant increases in lactate concentrations in healthy Beagles. In dogs receiving 4 mg/kg/day of methyl-prednisolone injected intramuscularly for 7 days, plasma lactate concentrations increased 8 fold. In dogs with lymphoma, there is a possible association between hyperlactatemia and prednisone administration as 85% of dogs with lymphoma on prednisone were hyperlactatemic.

**Alcohols (Ethanol, Methanol, Propylene Glycol, Ethylene Glycol)**

Ethanol metabolism shifts the NAD+/NADH ratio in favor of lactate production. The clinical relevance of ethanol induced hyperlactatemia remains controversial as it is mild and very uncommon in the absence of concurrent illness, such as decreased hepatic function, thiamine deficiency, seizure activity, or hypoperfusion. Methanol is found in paint remover, windshield washing fluid, antifreeze and some illicit alcohols. Alcohol dehydrogenase converts methanol into formaldehyde, which is subsequently converted into formate causing metabolic acidosis and inhibiting the electron transport chain promoting hyperlactatemia.
Propylene glycol is a commonly used preservative, carbohydrate source in processed foods, chemical agent in coolants and cosmetics, and solvent for numerous drugs including but not limited to: etomidate, pentobarbital, phenobarbital, nitroglycerin, silver sulfadiazine cream, lorazepam, esmolol, hydralazine, digoxin, trimethoprim-sulfamethoxazole, diazepam and some formulations of dexamethasone. The reported LD50 for oral consumption in dogs is 9.0 g/kg. Although the toxic dose for intravenous administration has not been established in dogs, current recommendations in people are to avoid intravenous administration of greater than 40 mg/kg/hr or 1 g/kg/day. Propylene glycol is metabolized first to lactaldehyde, and then into L-lactate, acetate and pyruvate or is converted to methylglyoxyl and then D-lactate.

Iatrogenic propylene glycol toxicity is well-documented in people treated with propylene glycol containing medications. Although propylene glycol toxicity from drug administration has not been reported in companion animals, it may be under-recognized and should be considered in patients developing unexplained high anion gap metabolic acidosis while receiving propylene glycol containing medications. Propylene glycol toxicity with hyperlactatemia, confirmed by toxicological analysis on serum, has been reported in a dog following ingestion of an unknown toxin on a construction site. Cats are also at risk for propylene glycol toxicity, developing erythrocyte Heinz bodies at comparatively lower doses than dogs due to their reduced glucuronidation capacity and clinically significant D-lactic acidosis at higher doses. Some formulations of activated charcoal contain propylene glycol along with the lactate precursor glycerol. The administration of 4 g/kg of activated charcoal containing propylene glycol has been experimentally associated with clinically significant but self-limiting hyperlactatemia (mean±SD 4.5±2.0 mmol/L [40.5±18.0 mg/dL]) in healthy dogs.

Ethylene glycol, the highly palatable organic solvent found in common antifreeze, is metabolized into the toxic metabolites glycolic acid, oxalate and glyoxylic acid. In this process, an increased NADH/NAD+ ratio develops and pyruvate metabolism is inhibited thereby...
promoting lactate formation.\textsuperscript{287} Ethylene glycol toxicity typically results in a mild to moderate increase in lactate concentration.\textsuperscript{286,288}

\textbf{Lactulose}

Lactulose is a synthetic, non-digestible disaccharide that is broken down into lactate and acetate in the colon.\textsuperscript{289} If excessive quantities of lactulose are administered, or if the lactulose is retained in the colon, lactate can potentially be absorbed by the colonic mucosa resulting in systemic L and D-hyperlactatemia.\textsuperscript{290} In healthy people administered lactulose, only modest increases in plasma L and D-lactate are observed.\textsuperscript{291} This has not yet been evaluated in dogs or cats.

\textbf{Miscellaneous}

Other known drugs and toxins that have the potential to cause hyperlactatemia include: nucleoside HIV reverse transcriptase inhibitors,\textsuperscript{240} the biguanide anti-hyperglycemic agents (phenformin, metformin)\textsuperscript{16,145,146,292-295}, linezolid,\textsuperscript{240,296-298} isoniazid,\textsuperscript{240,299,300} 5-fluorouracil,\textsuperscript{301,302} the sugar alcohols fructose, sorbitol and xylitol,\textsuperscript{29,268,303-305} as well as acetylcholinesterase inhibitor and carbamate pesticides.\textsuperscript{306-310}

\textbf{Type B3 Hyperlactatemia – Hyperlactatemia Resulting from Congenital Errors in Metabolism}

Hyperlactatemia is linked to various congenital defects including: mitochondrial encephalomyopathy with lactic acidosis and stroke syndrome, defects in the pyruvate dehydrogenase complex or the TCA cycle, and defects in gluconeogenesis affecting pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose 1,6 – bisphosphatase or glucose 6-
Phosphatase. Mitochondrial myopathies have been reported in a German Shepherd Dog, a Jack Russell Terrier, Old English Sheepdogs, Clumber spaniels, and Sussex spaniels.

**D-Lactate**

Early literature suggested that mammals had limited capacity for D-lactate metabolism, but a number of more recent studies have documented D-lactate dehydrogenase in mammalian tissue and have shown that D-lactate is efficiently metabolized and reabsorbed by the kidney. A small amount of D-lactate is normally produced through the glyoxalase pathway in mammalian species. Increased bacterial fermentation in the gastrointestinal tract or altered carbohydrate metabolism can increase D-lactate production causing D-lactic acidosis. Exogenous D-lactate may also be introduced via intravenous fluid solutions (such as racemic lactated Ringer’s solution) or preservatives such as propylene glycol.

In people, D-hyperlactatemia induced encephalopathy is recognized with short bowel syndrome and D-lactate is suspected to be an important contributor to the high anion gap seen in diabetic ketoacidosis. Both D and L-lactate are readily produced in ruminant species during the fermentation of carbohydrates by ruminal flora and encephalopathy from D-lactic acidosis is well documented due to grain overload, ruminal acidosis, calf diarrhea, drunken lamb syndrome and floppy kid disease.

Increased D-lactate concentrations have been documented in cats with diabetic ketoacidosis (mean ± SD: 0.37 ± 0.07 mmol/L [3.3 ± 0.6 mg/dL]), propylene glycol intoxication (up to 7.1 mmol/L [64.0 mg/dL]), exocrine pancreatic insufficiency (17.7 mmol/L [159.5 mg/dL]), and gastrointestinal disease (median 0.36 mmol/L [3.2 mg/dL], range 0.04-8.33...
mmol/L [0.36-75 mg/dL]). D-lactate should be considered a potential contributing factor in high anion gap metabolic acidosis.

**Clinical Measurement**

**Collection Technique**

Sampling technique is an important consideration when measuring plasma lactate concentrations. Struggling has a variable effect on plasma lactate concentrations likely dependent upon the degree of muscle activity. In one study in cats, a 5 minute spray bath test resulted in a rapid and dramatic increase in plasma lactate concentration (mean ≈ 7.0 mmol/L [63.0 mg/dL]). In contrast, in another small study in cats, mild to moderate struggling associated with restraint for venipuncture in cats did not result in hyperlactatemia. Although prolonged occlusion of a vessel, such as with a tourniquet, can result in increased lactate concentrations, transient occlusion for routine blood sampling does not have a significant effect. Nevertheless, patient struggling and extended venous stasis should be avoided when drawing blood samples for lactate analysis. When sampling from an intravenous catheter, inadvertent contamination with intravenous fluids can affect results and should be avoided.

**Sample Type**

Lactate concentrations can be measured in whole blood, plasma or serum. The term plasma lactate refers to the concentration of lactate in the plasma fraction alone, while whole blood lactate refers to the mean concentration of intraerythrocytic and plasma lactate fractions following red blood cell lysis. In people, the red blood cell fraction of the blood comprises...
approximately 30% of whole blood lactate and intraerythrocyte lactate concentrations are approximately 50% that of plasma at equilibrium. Intraerythrocytic lactate concentrations in dogs equilibrate at approximately 70% that of plasma within 5 minutes of incubation. In horses, erythrocyte lactate transport kinetics demonstrate marked interindividual variation, such that plasma lactate cannot reliably be used to estimate whole blood lactate concentrations. Lactate transport kinetics in feline erythrocytes have yet to be investigated, but as red blood cell lysis does not appear to affect lactate concentration, intracellular and extracellular lactate concentrations are believed to be similar. The majority of lactatometers used in clinical practice use whole blood as a test sample, but do not lyse the red blood cells in the sample and therefore actually report plasma lactate concentrations. This method facilitates rapid analysis without the delay associated with spinning and separating the sample and will not be affected by the lower lactate concentration in the intracellular fraction. Although sample type should be selected based on manufacturer specifications, the practitioner should be aware of what is reported by the analyzer to a) ensure an appropriate reference interval is used in practice and b) ensure results are comparable when consulting the scientific literature.

**Collection Tubes**

Sample handling guidelines for lactate measurement vary depending on whether the sample will be measured immediately or after a delay. Red blood cells, white blood cells and platelets consume glucose and produce lactate so a delay in the separation of serum and plasma from the cellular fraction can cause a progressive decrease in glucose and a progressive increase in lactate unless a glycolytic inhibitor is used. The preferred method of analysis is to collect the sample into a heparinized syringe, capillary tube or blood tube and process it as soon as possible but definitely within 15 minutes. The use of commercially available blood gas syringes...
or capillary tubes containing dry, lyophilized heparin are considered ideal, as manually heparinized syringes have been associated with dilutional errors in lactate measurement.\textsuperscript{349} At room temperature, lactate concentrations in heparinized whole blood will increase by 0.2-0.5 mmol/L (1.8-4.5 mg/dL) per 30 minutes,\textsuperscript{137,350,351} but should only rise by 0.2 mmol/L (1.8 mg/dL) after 120 minutes if stored in an ice bath.\textsuperscript{351,352} Serum lactate concentrations will also significantly increase in the time required for blood to clot in a serum collection tube.\textsuperscript{137}

Collection tubes with sodium fluoride, a glycolytic inhibitor, and potassium oxalate, an anticoagulant, are preferred for samples from dogs and cats being sent to an external lab.\textsuperscript{137,351} The anticoagulant sodium citrate interferes with lactate measurement and therefore should be avoided.\textsuperscript{353,354} These are, however, general recommendations and sample processing should be based on recommendations for the specific analyzer or reference laboratory.

**Sampling Site**

Blood samples for lactate measurement can be collected from peripheral venous, central venous, or arterial vessels as well as peripheral capillaries. In people, differences between arterial and central venous or peripheral venous lactate concentrations are small when lactate concentrations are normal to mildly increased.\textsuperscript{344,355-360} The gradient between sample sites can significantly increase in the face of hypoperfusion.\textsuperscript{359-365} In healthy dogs, small but statistically significant differences were found between samples from the cephalic vein, jugular vein and femoral artery,\textsuperscript{366} while no significant difference was noted between samples obtained from the jugular vein, lingual vein and dorsal pedal artery.\textsuperscript{367} In contrast, in a convenience sample of dogs referred to a university veterinary hospital, the association between jugular venous and capillary (pinnal) lactate was poor.\textsuperscript{368} Samples from the medial saphenous and jugular veins have been shown to be comparable in healthy cats.\textsuperscript{340} In practice, peripheral venous, central
venous or arterial samples can be used for lactate measurement, but the same site should be used for serial evaluations.

Analyzers

A range of handheld, bench-top and laboratory analyzers are now available to measure lactate. As expected, these analyzers vary with respect to methods, reported results, and reference intervals. Benchtop analyzers are generally more accurate and precise than handheld devices. The most common analytical methods for measurement of lactate are enzyme amperometry and spectrophotometry. Most newer benchtop analyzers use enzyme amperometry. These analyzers take a whole blood sample and allow plasma from the sample to pass through a membrane covering a platinum electrode. The membrane contains lactate oxidase that reacts with lactate in the sample to form hydrogen peroxide. The hydrogen peroxide is subsequently oxidized by the platinum electrode creating an electrochemical current proportional to lactate concentration. Other analyzers link the lactate oxidase to a peroxidase reaction with a dye-producing reagent such as 4-aminoantipyrine that is then quantified colorimetrically.

The enzymes used in both amperometric and spectrophotometric measurement of L-lactate are stereospecific. These analyzers cannot, therefore be used to measure D-lactate. D-lactate can be effectively measured by unique methods including: D-lactate-specific enzymatic techniques (such as with D-lactate dehydrogenase), gas chromatography, high-performance liquid chromatography or capillary electrophoresis. The majority of these methods require specialized laboratories and personnel, but automated methods of D-lactate measurement are becoming increasingly available.
Rapid infusion of lactated Ringer’s solution (LRS) has the potential to affect plasma lactate concentrations. Lactate concentrations remained within the reference interval in healthy adult dogs treated with LRS at 2 mL/kg/hr for 12 hours, and at 10 mL/kg/hr for 1 hour. In an experimental hemorrhage model in dogs comparing resuscitation with a 20 mL/kg bolus of LRS over 10-12 minutes to hypertonic saline, lactate concentrations did not significantly differ between groups. Administration of LRS at 4 mL/kg/hr for 6 hours in dogs with lymphoma with normal baseline lactate concentrations resulted in a mild to moderate increase in plasma lactate compared to controls in the first hour, but concentrations returned to baseline by the second hour of infusion. These studies used racemic LRS with an equal mixture of L and D-lactate totaling 28 mmol/L (252.2 mg/dL). Recent evidence has shown that D-lactate may have deleterious systemic effects and as such, non-racemic LRS containing only the L-lactate isomer has become available. Infusion of non-racemic L-LRS containing 28 mmol/L (252.2 mg/dL) of L-lactate at a rate of 180 mL/kg/hr in 6 healthy Beagles resulted in plasma lactate concentrations that were significantly higher at 60 minutes compared to dogs treated with 0.9% NaCl (mean±SD of approximately 3.2±0.6 mmol/L [28.8±5.4 mg/dL] and 1.4±0.6 mmol/L [12.6±5.4 mg/dL] respectively). The average increase in lactate concentration from T0 to T60 was 1.7±1.1 mmol/L [15.3±9.9 mg/dL]. Hyperlactatemia resolved within 60 minutes of discontinuing fluids in all patients.

Ethylene glycol is another well-recognized interferent. Several point-of-care analyzers using lactate oxidase amperometry erroneously measure the ethylene glycol metabolites glycolic acid and glyoxalic acid as lactate falsely reporting severe hyperlactatemia. Analyzers that use lactate oxidase spectrophotometry do not appear to experience the same interference.
concentration (110 mmol/L [991.0 mg/dL]), positive interference by D-lactate was suspected to be the cause of erroneously reported L-hyperlactatemia. Presently, there is no evidence to suggest D-lactate interference is of significant clinical concern except potentially in the rarest of scenarios associated with profound D-hyperlactatemia.

Reference Intervals:

Reference intervals for lactate have been established in dogs and cats on several benchtop and handheld analyzers. References intervals vary between analyzers, but the majority of studies demonstrate an upper limit varying between 2.5 and 3.0 mmol/L (22.5 and 27.0 mg/dL).

Conclusion

Lactate is an important energy storage molecule, the production of which preserves cellular energy production and mitigates the acidosis from ATP hydrolysis. Hyperlactatemia ultimately reflects a disruption in cellular bioenergetics of physiologic or pathophysiologic origin. Understanding the different etiologies of hyperlactatemia is helpful in determining 1) whether the presence of hyperlactatemia is of clinical concern and 2) how to best direct treatment. Lactate is an economic and accessible marker of tissue metabolism providing the clinician with valuable insight into tissue perfusion and cellular bioenergetics.

Footnote

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**Figure Legends:**

Figure 1: Lactate ion and lactic acid.
Figure 2: L-lactate and D-lactate
Figure 3: The 11 Steps of Glycolysis
Figure 4: Lactate to pyruvate catalyzed by lactate dehydrogenase

\[
\begin{align*}
\text{Pyruvate} & \quad \text{NADH} + H^+ \quad \text{NAD}^+ \\
\text{Lactate} & \quad \text{Lactate dehydrogenase}
\end{align*}
\]

Figure 5: Strong ion difference$^{383,384}$

\[
[SID^+] = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [lactate]
\]

Figure 6: Sites of action of the various causes of hyperlactatemia corresponding to Table 1. H$^+$ - proton, e$^-$ - electron

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Table 1: Type A vs. B classification system for hyperlactatemia with proposed mechanisms of hyperlactatemia corresponding to Figure 6. § - Inadequate oxygen supply, * - Dysfunction of the electron transport chain, ∞ - Upregulation of glycolysis, ₪ - Inhibition of the pyruvate dehydrogenase complex, + - Upregulation of the Na⁺-K⁺-ATPase and associated glycolytic chain, # - Increased NADH/NAD⁺ ratio, ¶ - Inhibition of the tricarboxylic acid cycle, ♦ - Direct production or lack of consumption of lactate. MELAS - Mitochondrial encephalomyopathy with lactic acidosis and stroke syndrome, SIRS – Systemic inflammatory response syndrome, NRTI - Nucleoside HIV reverse transcriptase inhibitors.
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<th>Relative</th>
<th>Absolute</th>
<th>B1: Disease</th>
<th>B2: Drugs/Toxins</th>
<th>B3: Congenital</th>
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<td>Malignancy*</td>
<td>Glucocorticoids*</td>
<td>Epinephrine*</td>
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<td>Diabetes Mellitus*</td>
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<td>5-Fluorouracil*</td>
<td>Propofol*</td>
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</table>

Miscellaneous: D-lactic acidosis*
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