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

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The authors declare no conflict of interests

Running Title: Clinical use of plasma lactate concentration

ABSTRACT

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/vec.12708](https://doi.org/10.1111/vec.12708).

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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

NADH – Reduced nicotinamide adenine dinucleotide

TCA – Tricarboxylic acid

ATP – Adenosine triphosphate

ETC – Electron transport chain

FADH₂ – Reduced flavin adenine dinucleotide

CO₂ – Carbon dioxide

LDH – Lactate dehydrogenase

MCT – Monocarboxylate transporter

PDH – Pyruvate dehydrogenase

cAMP – Cyclic adenosine monophosphate

PRIS – Propofol infusion syndrome

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.^{1,2} In 1843, Johann Joseph Scherer identified lactic acid in human blood after death,¹ 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.¹ 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.^{1,3-10} 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).¹¹ 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, ($C_3CH(OH)COO^-$), is an anion and conjugate base to lactic acid, ($C_3CH(OH)COOH$).¹² (Figure 1) As the pKa of lactic acid is 3.8, at physiologic pH, lactic acid is essentially fully dissociated into lactate anions and protons (H^+).¹³ Lactic acid is not, however, produced *in vivo*.¹⁴⁻¹⁶ 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.¹⁴

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.^{13,17-19} D-lactate is formed either by the glyoxalase pathway or produced by commensal bacteria in the mammalian gastrointestinal tract and absorbed into circulation.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,^{16,22} and is a common cause of metabolic acidosis in the dog and cat.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 mitochondrion²⁴ where it undergoes decarboxylation to produce Acetyl-CoA.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 CO₂, NADH and FADH₂.²⁵ Protons from NADH and FADH₂ 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⁺.^{10,16,28-30} (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.^{42,43,48-51}

Lactate Transport

Lactate transport across cell membranes occurs predominantly via facilitated passive transport by proton-linked monocarboxylate transporters (MCT) and sodium-coupled MCTs.²² At least 14 MCTs have been identified although MCT1 and MCT4 are considered the most important in mammalian tissues.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 β -hydroxybutyrate down concentration gradients.^{22,53} MCT expression on erythrocyte membranes vary between species.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.⁵⁵⁻⁵⁷ Lactate shuttles have been shown to exist in the brain, striated muscle, liver, kidneys and myocardium.²⁷

Physiology – homeostasis in health

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.^{12,22,28,31,58-61} Other lactate producing tissues include the renal medulla, gastrointestinal tract, skin, red and white blood cells, and platelets.^{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.^{64,65}

Glycolysis and lactate production are increased during the oxidative burst of neutrophils⁶⁵ and experimentally induced sepsis has been shown to increase leukocyte production of lactate 6-fold.⁶⁴

The most important lactate consuming tissues are the liver (20-30%), the renal cortex (20%) and the myocardium (5-15%).^{16,22,28,31,62,66-68} The liver has a large reserve capacity for lactate metabolism.^{16,69,70} Hepatic lactate uptake is, however, a saturable process.^{16,71} As a valuable energy substrate, lactate is avidly reabsorbed by the renal proximal convoluted tubule.^{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.^{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.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]),³³⁹ while mild to moderate struggling associated with restraint for venipuncture did not have an appreciable effect.³⁴⁰ 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.^{80,84-89} 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,^{91,92} but occurs earlier in maldistributive shock due to impaired oxygen extraction from mitochondrial and microcirculatory dysfunction.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”.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 ScvO₂ (< 70%) suggesting ongoing tissue hypoperfusion despite normalization of routine hemodynamic parameters.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.^{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).¹⁰³

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.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,¹⁰⁷ whereas in another, only 33% (8/24) of dogs with plasma lactate $\geq$ 6 mmol/L (54.0 mg/dL) had gastric necrosis.¹⁰⁸ Furthermore, peripheral lactate concentrations can remain normal despite significant splanchnic ischemia.¹⁰⁹ 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.¹¹⁰

Anemia and Hypoxemia

The correlation between anemia and hyperlactatemia is highly dependent on chronicity of disease. Animals with chronic anemia can remain eulactatemic even when anemia is severe.¹¹¹ In contrast, animals with anemia resulting from acute hemorrhage or acute, severe hemolysis can develop clinically significant hyperlactatemia.¹¹¹ In experimental animal models of acute dilutional anemia, hyperlactatemia did not develop until packed cell volume was below 15%.¹¹²⁻¹¹⁴ Hyperlactatemia from hypoxemia alone is likely rare in veterinary medicine, as P_{aO_2} values need to be 25-40 mm Hg before lactate concentrations begin to rise.^{113,115}

Carbon Monoxide

Carbon monoxide binds to hemoglobin with a greater affinity than oxygen to produce carboxyhemoglobin which inhibits effective oxygen transport.¹¹⁶ Carbon monoxide also shifts the oxyhemoglobin curve to the left, further reducing oxygen delivery, and directly induces cellular damage and oxidative stress.¹¹⁶ Hyperlactatemia from carbon monoxide toxicity is suspected to result primarily from tissue hypoxia, although mitochondrial dysfunction and

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

Type B1 Hyperlactatemia – Hyperlactatemia Associated with Underlying Disease:

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 2,¹²⁰⁻¹²² increased production of glycolysis intermediates via upregulation of the pentose phosphate pathway,^{22,123} mitochondrial dysfunction, reduced hepatic clearance, and malnutrition causing thiamine deficiency.^{12,28} Malignant cells preferentially use glycolytic pathways despite readily available oxygen^{22,122} and lactate may alter the tumor micro-environment in a manner that inhibits destruction of neoplastic cells.^{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.^{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.^{22,29,129} In addition, pheochromocytoma is associated with catecholamine-induced hyperlactatemia.^{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.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.^{22,133-135} 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]).¹³⁶ 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 2.0 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}

Hepatic and Renal Disease

In people, severe liver disease is rarely associated with hyperlactatemia unless they are acutely challenged by a lactate load or are experiencing concurrent hypoperfusion.^{28,51,138,139} People with chronic liver disease demonstrate slowed lactate metabolism, but peak lactate values are often similar to healthy controls.^{51,140,141} In the presence of severe hepatic dysfunction or failure the liver can become a net lactate producer causing hyperlactatemia.^{51,142} Postulated mechanisms for hepatic lactate production include glycolytic upregulation, reduced PDH activity, and impaired hepatic gluconeogenesis.^{22,51} 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.¹⁴³ 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.¹⁴⁴ 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.¹³² 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.^{62,145-147}

Thiamine Deficiency

Thiamine deficiency (vitamin B₁) is an uncommon but well documented cause of hyperlactatemia.¹⁴⁸⁻¹⁵⁵ Thiamine plays an important role in several metabolic pathways after conversion to thiamine pyrophosphate.²² 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.^{148,149,154,156,157} Thiamine deficiency, also known as beriberi disease, leads to compromised cellular bioenergetics and the accumulation of pyruvate and lactate.^{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.^{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.^{22,152} In dogs and cats, thiamine deficiency has been reported in association with the ingestion of fish high in thiaminase,^{160,161} food with inactivated thiamine from processing,^{162,163} and sulfite-preserved meat.^{148,164-166} Thiamine deficiency in dogs and cats typically manifests as cervical ventroflexion, ataxia, mydriasis, depressed mentation and seizure activity.^{148,160-166}

Hyperthyroidism

Hyperthyroidism causes an increased basal metabolic rate leading to increased carbohydrate metabolism and hyperlactatemia through upregulation of glycolysis and the hexose monophosphate pathway.^{137,167-171} In addition, hyperthyroidism and thyroid storm are considered risk factors for thiamine deficiency due to depletion of thiamine stores.^{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).¹³⁷

Microcirculatory dysfunction

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.^{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.¹⁷³⁻¹⁷⁷ Erythrocyte aggregation, leukocyte adhesion, local edema and microvascular thrombosis also impair microcirculatory flow.^{92,174} Microcirculatory shunting likely contributes to the concurrent hyperlactatemia and increased SvO₂ seen in sepsis.¹⁷⁶ One of the most important features of microcirculatory dysfunction is that it can occur independently of macrocirculatory hemodynamic variables.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.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.¹⁸¹ Mitochondrial dysfunction has been implicated as a cause of aerobic hyperlactatemia particularly in the presence of severe inflammation, sepsis or oxidative stress.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.^{25,183-186}

In addition, mitochondrial respiration can be compromised by dysfunction of the pyruvate dehydrogenase complex (PDH).^{22,28,156,183,184,187} Alkalosis stimulates the rate limiting glycolytic enzyme phosphofructokinase, subsequently increasing pyruvate and therefore lactate concentrations.^{28,51,188,189} Similarly, the administration of glucose, increased NADH concentrations and ATP depletion promote lactate formation via concentration dependent effects.^{22,28,190}

Catecholamines

Adrenergic stimulation by catecholamines, particularly epinephrine, is likely to be an important cause of clinical hyperlactatemia.^{56,191} Epinephrine administration is associated with a progressive, dose-related increase in lactate due to increased cyclic adenosine monophosphate production (cAMP) via β_2 -adrenergic stimulation.¹⁹² This leads to enhanced glycogenolysis, glycolysis, lipolysis, and stimulation of $\text{Na}^+\text{-K}^+\text{-ATPase}$ pumps.¹⁹³⁻¹⁹⁹ $\text{Na}^+\text{-K}^+\text{-ATPase}$ pumps are associated with lactate-producing glycolytic pathways that are not coupled to mitochondrial respiration.^{196,200-207} (Figure 6) There is compelling evidence to support the upregulation of skeletal muscle $\text{Na}^+\text{-K}^+\text{-ATPase}$ associated glycolysis as a clinically significant source of lactate in septic and hemorrhagic shock, as well as exercise-related hyperlactatemia.^{191,195,196,201,203,204,208-219} Not only does plasma lactate correlate with catecholamine concentrations,^{83,88,212,220-222} but both selective $\text{Na}^+\text{-K}^+\text{-ATPase}$ and adrenergic blockade have been shown to prevent or decrease lactate concentrations in hemorrhagic shock,^{195,211,223-227} septic shock^{99,191,196} and during exercise.^{217,228,229} Hyperlactatemia has even been documented in healthy university students following a university exam.²³⁰ Catecholamine-induced hyperlactatemia likely explains the hyperlactatemia seen with pheochromocytoma²³¹⁻²³³ and acute asthmatic crisis (from endogenous catecholamine release as well as β_2 adrenergic agonist therapy).²³⁴⁻²³⁷

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.^{238,239}

Salicylates decrease the availability of CoA, inhibit succinate dehydrogenase and alpha-ketoglutarate dehydrogenase.^{28,29,240} 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.^{28,29,240} In people, hyperlactatemia associated with salicylate toxicity is usually mild.²⁴¹

Adrenergic Agonists and Sympathomimetics

Hyperlactatemia also occurs with drugs and toxins that cause adrenergic stimulation including: β_2 -receptor agonists (terbutaline, albuterol, salbutamol), methylxanthines (theophylline, theobromine), and cocaine.^{12,237,242-245} Terbutaline, albuterol and other β_2 -agonists cause hyperlactatemia as previously described.^{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.^{244,245,247,248} Cocaine has some sympathomimetic activity but also causes seizures at higher doses.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.²⁴⁹⁻²⁵¹ In a recent retrospective study on dogs presenting with

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]).²⁵¹

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.²⁵² Hyperkalemia, lactic acidosis, and renal failure are also common features of this syndrome.²⁵³ PRIS is most commonly seen in people receiving propofol for prolonged periods.²⁵⁴ Impaired fatty acid oxidation and mitochondrial dysfunction are believed to be the major underlying pathophysiologic mechanisms for PRIS.^{254,255} 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.^{22,29,256} Cyanide inhibits aerobic metabolism by non-competitively inhibiting ferric iron in cytochrome c oxidase (complex IV), the final step in the electron transport chain.²⁵⁷ This results in ATP depletion, acidosis, hyperlactatemia and venous hyperoxia due to impaired oxygen extraction.^{29,257,258}

As sodium nitroprusside is metabolized into one molecule of nitric oxide and 5 molecules of cyanide, iatrogenic cyanide toxicity occasionally occurs.^{257,259} Serial lactate measurements can be of value when monitoring for the development of cyanide toxicity

secondary to sodium nitroprusside therapy.^{257, 259,260} 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.^{197,261-267} 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.²⁶⁶ In dogs receiving 4 mg/kg/day of methyl-prednisolone injected intramuscularly for 7 days, plasma lactate concentrations increased 8 fold.²⁶¹ In dogs with lymphoma, there is a possible association between hyperlactatemia and prednisone administration as 85% of dogs with lymphoma on prednisone were hyperlactatemic.¹³²

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

Ethanol metabolism shifts the NAD^+/NADH ratio in favor of lactate production.^{22,268,269} 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.^{28,268-273} Methanol is found in paint remover, windshield washing fluid, antifreeze and some illicit alcohols.²² Alcohol dehydrogenase converts methanol into formaldehyde, which is subsequently converted into formate causing metabolic acidosis and inhibiting the electron transport chain promoting hyperlactatemia.^{22,274}

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.^{240,275,276} The reported LD₅₀ for oral consumption in dogs is 9.0 g/kg.²⁷⁵ 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.^{276,277} Propylene glycol is metabolized first to lactaldehyde, and then into L-lactate, acetate and pyruvate or is converted to methylglyoxyl and then D-lactate.^{22,240,275,276,278,279} Iatrogenic propylene glycol toxicity is well-documented in people treated with propylene glycol containing medications.^{276,278,280,281-283} 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.²⁷⁵ 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.^{279,284} 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.²⁸⁵

Ethylene glycol, the highly palatable organic solvent found in common antifreeze, is metabolized into the toxic metabolites glycolic acid, oxalate and glyoxylic acid.^{22,240,286} In this process, an increased NADH/NAD⁺ ratio develops and pyruvate metabolism is inhibited thereby

promoting lactate formation.²⁸⁷ Ethylene glycol toxicity typically results in a mild to moderate increase in lactate concentration.^{286,288}

Lactulose

Lactulose is a synthetic, non-digestible disaccharide that is broken down into lactate and acetate in the colon.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.²⁹⁰ In healthy people administered lactulose, only modest increases in plasma L and D-lactate are observed.²⁹¹ This has not yet been evaluated in dogs or cats.

Miscellaneous

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

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.²² Mitochondrial myopathies have been reported in a German Shepherd Dog,³¹¹ a Jack Russell Terrier,³¹² Old English Sheepdogs,^{313,314} Clumber spaniels,^{315,316} and Sussex spaniels.^{316,318}

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.³¹⁹⁻³²⁴ A small amount of D-lactate is normally produced through the glyoxalase pathway in mammalian species.^{17,18} Increased bacterial fermentation in the gastrointestinal tract or altered carbohydrate metabolism can increase D-lactate production causing D-lactic acidosis.^{17,18,325} Exogenous D-lactate may also be introduced via intravenous fluid solutions (such as racemic lactated Ringer's solution) or preservatives such as propylene glycol.^{21,22,284}

In people, D-hyperlactatemia induced encephalopathy is recognized with short bowel syndrome,³²⁶⁻³²⁹ and D-lactate is suspected to be an important contributor to the high anion gap seen in diabetic ketoacidosis.¹⁷ Both D and L-lactate are readily produced in ruminant species during the fermentation of carbohydrates by ruminal flora³²² and encephalopathy from D-lactic acidosis is well documented due to grain overload, ruminal acidosis, calf diarrhea, drunken lamb syndrome and floppy kid disease.^{322,330-336}

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]),³³¹ propylene glycol intoxication (up to 7.1 mmol/L [64.0 mg/dL]),²⁸⁴ exocrine pancreatic insufficiency (17.7 mmol/L [159.5 mg/dL]),³³⁷ and gastrointestinal disease (median 0.36 mmol/L [3.2 mg/dL], range 0.04-8.33

mmol/L [0.36-75 mg/dL]).³³⁸ D-lactate should be considered a potential contributing factor in high anion gap metabolic acidosis.³³⁷

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 $\approx$ 7.0 mmol/L [63.0 mg/dL]).³³⁹ In contrast, in another small study in cats, mild to moderate struggling associated with restraint for venipuncture in cats did not result in hyperlactatemia.³⁴⁰ Although prolonged occlusion of a vessel, such as with a tourniquet, can result in increased lactate concentrations,³⁴¹ transient occlusion for routine blood sampling does not have a significant effect.³⁴² 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.³⁴³⁻

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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^{57,346} and intraerythrocyte lactate concentrations are approximately 50% that of plasma at equilibrium.^{347,348} Intraerythrocytic lactate concentrations in dogs equilibrate at approximately 70% that of plasma within 5 minutes of incubation.⁵² In horses, erythrocyte lactate transport kinetics demonstrate marked interindividual variation, such that plasma lactate cannot reliably be used to estimate whole blood lactate concentrations.⁵² 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.¹³⁷ 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.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,^{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.^{351,352} Serum lactate concentrations will also significantly increase in the time required for blood to clot in a serum collection tube.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.^{137,351} The anticoagulant sodium citrate interferes with lactate measurement and therefore should be avoided.^{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.^{344,355-360} The gradient between sample sites can significantly increase in the face of hypoperfusion.³⁵⁹⁻³⁶⁵ In healthy dogs, small but statistically significant differences were found between samples from the cephalic vein, jugular vein and femoral artery,³⁶⁶ while no significant difference was noted between samples obtained from the jugular vein, lingual vein and dorsal pedal artery.³⁶⁷ In contrast, in a convenience sample of dogs referred to a university veterinary hospital, the association between jugular venous and capillary (pinna) lactate was poor.³⁶⁸ Samples from the medial saphenous and jugular veins have been shown to be comparable in healthy cats.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 hand-held, 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.³⁶⁹ 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.³⁸⁵ The majority of these methods require specialized laboratories and personnel, but automated methods of D-lactate measurement are becoming increasingly available.^{386, 387}

Interference

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.^a 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.³⁷⁰ 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.³⁷¹ These studies used racemic LRS with an equal mixture of L and D-lactate totaling 28 mmol/L (252.2 mg/dL).³⁷² Recent evidence has shown that D-lactate may have deleterious systemic effects^{372,373} 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).³⁷² 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.³⁷²

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.^{286,374-376} Analyzers that use lactate oxidase spectrophotometry do not appear to experience the same interference.²⁸⁶ In one case report describing a person with a profoundly elevated D-lactate

concentration (110 mmol/L [991.0 mg/dL]), positive interference by D-lactate was suspected to be the cause of erroneously reported L-hyperlactatemia.^{20,21} 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.^{135,137,339,340,366,377-382} Reference 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

a. Pouderoux L, Muguet-Chanoit A, Bonnet-Garin JJ, et al. Kinetics of lactate clearance and effect of intravenous lactated Ringer's solution infusion on lactate concentrations in healthy dogs. (Abstract). In Proceedings of the International Veterinary Emergency and Critical Care Symposium. 2006 Sept San Antonio, TX, USA

References:

1. Kompanje EJO, Jansen TC, van der Hoven B, Bakker J. The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814-1869) in January 1843. *Intensive Care Med.* 2007;33(11):1967-71.
2. Matejovic M, Radermacher P, Fontaine E. Lactate in shock: a high-octane fuel for the heart? *Intensive Care Med.* 2007;33(3):406-8.
3. Huckabee WE. Control of concentration gradients of pyruvate and lactate across cell membranes in blood. *J Appl Physiol.* 1956;9(2):163-70.
4. Huckabee WE. Abnormal resting blood lactate: II. Lactic acidosis. *Am J Med.* 1961;30(6):840-8.
5. Huckabee WE. Abnormal resting blood lactate: I. The significance of hyperlactatemia in hospitalized patients. *Am J Med.* 1961;30(6):833-9.
6. Huckabee WE. Relationships of pyruvate and lactate during anaerobic metabolism. III. Effect of breathing low-oxygen gases. *J Clin Invest.* 1958;37(2):264-71.
7. Huckabee WE. Relationships of pyruvate and lactate during anaerobic metabolism. II. Exercise and formation of O₂-debt. *J Clin Invest.* 1958;37(2):255-263.
8. Huckabee WE. Lactic acidosis. *Am J Cardiol.* 1963;12:663-666.
9. Huckabee WE. Relationship of pyruvate and lactate during anaerobic metabolism. V. Coronary adequacy. *Am J Physiol.* 1961;200:1169-76.
10. Huckabee WE. Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and of hyperventilation. *J Clin Invest.* 1958;37(2):244-54.
11. Broder G, Weil MH. Excess lactate: an index of reversibility of shock in human patients. *Science.* 1964;143(3613):1457-9.

12. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. *Mayo Clin Proc.* 2013;88(10):1127–40.
13. Ewaschuk JB, Naylor JM, Zello GA. D-lactate in human and ruminant metabolism. *J Nutr.* 2005;135(7):1619–25.
14. Robergs RA, Ghiasvand F, Parker D. Biochemistry of exercise-induced metabolic acidosis. *Am J Physiol Regul Integr Comp Physiol.* 2004;287(3):R502–16.
15. Brooks GA. What does glycolysis make and why is it important? *J Appl Physiol.* 2010;108(6):1450–1.
16. Madias NE. Lactic acidosis. *Kidney Int.* 1986;29(3):752–74.
17. Lu J, Zello GA, Randell E, Adeli K, Krahn J, Meng QH. Closing the anion gap: Contribution of d-lactate to diabetic ketoacidosis. *Clinica Chimica Acta.* 2011;412:286–91.
18. Nielsen C, Mortensen FV, Erlandsen EJ, Lindholt JS. L- and d-lactate as biomarkers of arterial-induced intestinal ischemia: An experimental study in pigs. *Int J Surg.* 2012;10(6):296–300.
19. McLellan AC, Phillips SA, Thornalley PJ. Fluorimetric assay of D-lactate. *Anal Biochem.* 1992;206(1):12–6.
20. Jorens PG. Accuracy of point-of-care measurements. *CMAJ.* 2007;177(9):1070.
21. Jorens PG, Demey HE, Schepens PJ, Coucke V, Verpooten GA, Couttenye MM, et al. Unusual D-lactic acid acidosis from propylene glycol metabolism in overdose. *J Toxicol.* 2004;42(2):163–9.
22. Adeva-Andany M, López-Ojén M, Funcasta-Calderón R, Ameneiros-Rodríguez E, Donapetry-García C, Vila-Altesor M, et al. Comprehensive review on lactate metabolism in human health. *Mitochondrion.* 2014;17:76–100.
23. Hopper K, Epstein SE. Incidence, nature, and etiology of metabolic acidosis in dogs and cats. *J Vet Intern Med.* 2012;26(5):1107–14.
24. Herzig S, Raemy E, Montessuit S, Veuthey J-L, Zamboni N, Westermann B, et al. Identification and functional expression of the mitochondrial pyruvate carrier. *Science.* 2012;337:93–6.
25. Ruggieri AJ, Levy RJ, Deutschman CS. Mitochondrial Dysfunction and Resuscitation in Sepsis. *Crit Care Clin.* 2010;26(3):567–75.
26. Bouzat P, Oddo M. Lactate and the injured brain: friend or foe? *Curr Opin Crit Care.*

2014;20(2):133–40.

27. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care*. 2013;3(1):12.
28. Kreisberg RA. Lactate homeostasis and lactic acidosis. *Ann Intern Med*. 1980;92(2 Pt 1):227–37.
29. Vernon C, LeTourneau JL. Lactic Acidosis: Recognition, Kinetics, and Associated Prognosis. *Crit Care Clin*. 2010;26(2):255–83.
30. Levy B, Sadoune LO, Gelot AM, Bollaert PE, Nabet P, Larcan A. Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. *Crit Care Med*. 2000;28(1):114–9.
31. van Hall G. Lactate kinetics in human tissues at rest and during exercise. *Acta Physiol (Oxf)*. 2010;199(4):499–508.
32. Gutierrez G, Wulf ME. Lactic acidosis in sepsis: Another commentary*. *Crit Care Med*. 2005;33(10):2420–2.
33. Robergs RA. Counterpoint: Muscle lactate and H⁺ production do not have a 1:1 association in skeletal muscle. *J Appl Physiol*. 2011;110(5):1489–91.
34. Dennis SC, Gevers W, Opie LH. Protons in ischemia: where do they come from; where do they go to? *J Mol Cell Cardiol*. 1991;23(9):1077–86.
35. Prakash ES. Good bye “lactic acid;” hello lactate and acid. *J Appl Physiol*. 2008;105(1):363–7.
36. Böning D, Strobel G, Beneke R, Maassen N. Lactic acid still remains the real cause of exercise-induced metabolic acidosis. *Am J Physiol Regul Integr Comp Physiol*. 2005;289(3):R902–3.
37. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol*. 1983;61:1444–61.
38. Sharkey LC, Wellman ML. Use of lactate in small animal clinical practice. *Vet Clin Small Anim Prac*. 2013;43(6):1287–97.
39. Robergs RA, Ghiasvand F, Parker D. Reply: the wandering argument favoring a lactic acidosis. *Am J Physiol Regul Integr Comp Physiol*. 2006;291:R238–9.
40. Constable PD. Clinical assessment of acid-base status: comparison of the Henderson-Hasselbalch and strong ion approaches. *Vet Clin Pathol*. 2000;29(4):115–28.

41. Lindinger MI. Applying physicochemical principles to skeletal muscle acid-base status. *Am J Physiol Regul Integr Comp Physiol*. 2005;289:R891–4.
42. Maciel AT, Park M. Unmeasured anions account for most of the metabolic acidosis in patients with hyperlactatemia. *Clinics (Sao Paulo)*. 2007;62(1):55–62.
43. Hopper K, Haskins SC. A case-based review of a simplified quantitative approach to acid-base analysis. *J Vet Emerg Crit Care*. 2008;18(5):467–76.
44. Vinnakota KC, Rusk J, Palmer L, Shankland E, Kushmerick MJ. Common phenotype of resting mouse extensor digitorum longus and soleus muscles: equal ATPase and glycolytic flux during transient anoxia. *J Physiol*. 2010;588(11):1961–83.
45. Marcinek DJ, Kushmerick MJ, Conley KE. Lactic acidosis in vivo: testing the link between lactate generation and H⁺ accumulation in ischemic mouse muscle. *J Appl Physiol*. 2010;108(6):1479–86.
46. Böning D, Klarholz C, Himmelsbach B, Hütler M, Maassen N. Causes of differences in exercise-induced changes of base excess and blood lactate. 2006;99(2):163–71.
47. Kowalchuk JM, Heigenhauser GJ, Lindinger MI, Sutton JR, Jones NL. Factors influencing hydrogen ion concentration in muscle after intense exercise. *J Appl Physiol*. 1988;65(5):2080–9.
48. Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment. *Crit Care Med*. 2009;37(10):2827–39.
49. Gutierrez G, Wulf ME. Lactic acidosis in sepsis: a commentary. *Intensive Care Med*. 1996;22:6–16.
50. Handy J. The origin and interpretation of hyperlactataemia during low oxygen delivery states. *Crit Care*. 2007;11:104.
51. Jeppesen JB, Mortensen C, Bendtsen F, Møller S. Lactate metabolism in chronic liver disease. *Scand J Clin Lab Invest*. 2013;73(4):293–9.
52. Koho NM, Raekallio M, Kuusela E, Vuolle J, Pösö AR. Lactate transport in canine red blood cells. *Am J Vet Res*. 2008;69(8):1091–6.
53. Halestrap AP, Wilson MC. The monocarboxylate transporter family--role and regulation. *IUBMB Life*. 2012;64(2):109–19.
54. Kitaoka Y, Endo Y, Mukai K, Aida H, Hiraga A, Takemasa T, et al. Effect of acute exercise on monocarboxylate transporters 1 and 4 in untrained and trained Thoroughbreds. *Am J Vet Res*. 2013;74(4):642–7.

55. Brooks GA. Lactate shuttles in nature. *Biochem Soc Trans.* 2002;30(2):258–64.
56. Gladden LB. Lactate metabolism: a new paradigm for the third millennium. *J Physiol.* 2004;558(1):5–30.
57. Draoui N, Feron O. Lactate shuttles at a glance: from physiological paradigms to anti-cancer treatments. *Dis Model Mech.* 2011;4(6):727–32.
58. Cohen RD, Simpson R. Lactate metabolism. *Anesthesiology.* 1975;43(6):661–73.
59. Juel C. Lactate-proton cotransport in skeletal muscle. *Physiol Rev.* 1997;77(2):321–58.
60. Issekutz B, Shaw WA, Issekutz AC. Lactate metabolism in resting and exercising dogs. *J Appl Physiol.* 1976;40(3):312–9.
61. Connett RJ, Gayeski TE, Honig CR. Lactate efflux is unrelated to intracellular PO₂ in a working red muscle in situ. *J Appl Physiol.* 1986;61(2):402–8.
62. Bellomo R. Bench-to-bedside review: lactate and the kidney. *Crit Care.* 2002;6(4):322–6.
63. Scaglione PR, Dell RB, Winters RW. Lactate concentration in the medulla of rat kidney. *Am J Physiol.* 1965;209(6):1193–8.
64. Haji-Michael PG, Ladrière L, Sener A, Vincent JL, Malaisse WJ. Leukocyte glycolysis and lactate output in animal sepsis and ex vivo human blood. *Metabolism.* 1999;48(6):779–85.
65. Kramer PA, Ravi S, Chacko B, Johnson MS, Darley-Usmar V. A review of the mitochondrial and glycolytic metabolism in human platelets and leukocytes: Implications for their use as bioenergetic biomarkers. *Redox Biol.* 2014;2:206–10.
66. Stanley WC. Myocardial lactate metabolism during exercise. *Med Sci Sports Exerc.* 1991;23(8):920–4.
67. Stanley WC. Changes in cardiac metabolism: a critical step from stable angina to ischaemic cardiomyopathy. *Eur Heart J Supplements.* 2001;3(Suppl O):O2–O7.
68. Yudkin J, Cohen RD. The contribution of the kidney to the removal of a lactic acid load under normal and acidotic conditions in the conscious rat. *Clin Sci Mol Med.* 1975;48(2):121–31.
69. Chioléro R, Tappy L, Gillet M, Revelly J-P, Roth H, Cayeux C, et al. Effect of Major hepatectomy on glucose and lactate metabolism. *Ann Surg.* 1999;229(4):505.
70. Tashkin DP, Goldstein PJ, Simmons DH. Hepatic lactate uptake during decreased liver

perfusion and hyposemia. *Am J Physiol.* 1972;223(4):968–74.

71. Naylor JM, Kronfeld DS, Freeman DE, Richardson D. Hepatic and extrahepatic lactate metabolism in sheep: effects of lactate loading and pH. *Am J Physiol.* 1984;247(10):E747–55.
72. Díes F, Ramos G, Avelar E, Lennhoff M. Renal excretion of lactic acid in the dog. *Am J Physiol.* 1969;216(1):106–11.
73. Boumezbeur F, Petersen KF, Cline GW, Mason GF, Behar KL, Shulman GI, et al. The contribution of blood lactate to brain energy metabolism in humans measured by dynamic ¹³C nuclear magnetic resonance spectroscopy. *J Neurosci.* 2010;30(42):13983–91.
74. van Hall G, Strømstad M, Rasmussen P, Jans O, Zaar M, Gam C, et al. Blood lactate is an important energy source for the human brain. *J Cereb Blood Flow Metab.* 2009;29(6):1121–9.
75. Cohen RD, Woods HF. Clinical and biochemical aspects of lactic acidosis. Oxford: Blackwell Scientific Publ; 1976.
76. Steiss J, Ahmad HA, Cooper P, Ledford C. Physiologic responses in healthy Labrador Retrievers during field trial training and competition. *J Vet Intern Med.* 2004;18(2):147–51.
77. Rovira S, Muñoz A, Benito M. Fluid and electrolyte shifts during and after agility competitions in dogs. *J Vet Med Sci.* 2007;69(1):31–5.
78. Baltzer WI, Firshman AM, Stang B, Warnock JJ, Gorman E, McKenzie EC. The effect of agility exercise on eicosanoid excretion, oxidant status, and plasma lactate in dogs. *BMC Vet Res.* 2012;8(1):249.
79. Toll PW, Gaehtgens P, Neuhaus D, Pieschl RL, Fedde MR. Fluid, electrolyte, and packed cell volume shifts in racing greyhounds. *Am J Vet Res.* 1995;56(2):227–32.
80. Pieschl RL, Toll PW, Leith DE, Peterson LJ, Fedde MR. Acid-base changes in the running greyhound: contributing variables. *J Appl Physiol.* 1992;73(6):2297–304.
81. Nold JL, Peterson LJ, Fedde MR. Physiological changes in the running greyhound (*Canis domesticus*): influence of race length. *Comp Biochem Physiol A Comp Physiol.* 1991;100(3):623–7.
82. Hill RC, Lewis DD, Scott KC, Omori M, Jackson M, Sundstrom DA, et al. Effect of increased dietary protein and decreased dietary carbohydrate on performance and body composition in racing Greyhounds. *Am J Vet Res.* 2001;62(3):440–7.

83. Ilkiw JE, Davis PE, Church DB. Hematologic, biochemical, blood-gas, and acid-base values in greyhounds before and after exercise. *Am J Vet Res.* 1989;50(4):583–6.
84. Holloway SA, Sundstrom D, Senior DF. Effect of acute induced metabolic alkalosis on the acid/base responses to sprint exercise of six racing greyhounds. *Res Vet Sci.* 1996;61(3):245–51.
85. Kappenstein J, Engel F, Fernandez-Fernandez J, Ferrauti A. Effects of Active and Passive Recovery on Blood Lactate and Blood pH After a Repeated Sprint Protocol in Children and Adults. *Pediatr Exerc Sci.* 2014;27(1):77–84.
86. Orringer CE, Eustace JC, Wunsch CD. Natural history of lactic acidosis after grand-mal seizures: a model for the study of an anion-gap acidosis not associated with hyperkalemia. *N Engl J Med.* 1977;297(15):796–9.
87. Rose RJ, Bloomberg MS. Responses to sprint exercise in the greyhound: effects on haematology, serum biochemistry and muscle metabolites. *Res Vet Sci.* 1989;47(2):212–8.
88. Matwichuk CL, Taylor S, Shmon CL, Kass PH, Shelton GD. Changes in rectal temperature and hematologic, biochemical, blood gas, and acid-base values in healthy Labrador Retrievers before and after strenuous exercise. *Am J Vet Res.* 1999;60(1):88–92.
89. Margaria R, Edwards HT. The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. *Am J Physiol.* 1933;106(3):689–715.
90. Vincent, Dufaye, et al. Serial lactate determinations during circulatory shock. *Crit Care Med.* 1983;11(6):449–51.
91. Vincent JL, De Backer D. Oxygen transport-the oxygen delivery controversy. *Intensive Care Med.* 2004;30(11):337–43.
92. Vincent JL, De Backer D. My paper 20 years later: effects of dobutamine on the VO_2/DO_2 relationship. *Intensive Care Med.* 2014;40(11):1643–8.
93. Nelson DP, Beyer C, Samsel RW, Wood LD, Schumacker PT. Pathological supply dependence of O_2 uptake during bacteremia in dogs. *J Appl Physiol.* 1987;63(4):1487–92.
94. Zhang H, Vincent JL. Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. *Circ Shock.* 1993;40(3):168–76.
95. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368–77.

96. Young BC, Prittie JE, Fox P, Barton LJ. Decreased central venous oxygen saturation despite normalization of heart rate and blood pressure post shock resuscitation in sick dogs. *J Vet Emerg Crit Care*. 2014;24(2):154–61.
97. Ronco JJ, Fenwick JC, Wiggs BR, Phang PT, Russell JA, Tweeddale MG. Oxygen consumption is independent of increases in oxygen delivery by dobutamine in septic patients who have normal or increased plasma lactate. *Am Rev Respir Dis*. 1993;147(1):25–31.
98. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA*. 1993;270(14):1724–30.
99. Levy B, Mansart A, Bollaert PE, Franck P, Mallie J-P. Effects of epinephrine and norepinephrine on hemodynamics, oxidative metabolism, and organ energetics in endotoxemic rats. *Intensive Care Med*. 2003;29(2):292–300.
100. Regueira T, Djafarzadeh S, Brandt S, Gorrasi J, Borotto E, Porta F, et al. Oxygen transport and mitochondrial function in porcine septic shock, cardiogenic shock, and hypoxaemia. *Acta Anaesthesiol Scand*. 2012;56(7):846–59.
101. Moomey CB, Melton SM, Croce MA, Fabian TC, Proctor KG. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD50 model of penetrating trauma. *Crit Care Med*. 1999;27(1):154–61.
102. Haskins SC, Pascoe PJ, Ilkiw JE. The effect of moderate hypovolemia on cardiopulmonary function in dogs. *J Vet Emerg Crit Care*. 2005;15(2):100–9.
103. Boag AK, Hughes D. Assessment and treatment of perfusion abnormalities in the emergency patient. *Vet Clin North Am Small Anim Pract*. 2005;35(2):319–42.
104. Lange H, Jäckel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. *Eur J Surg*. 1994;160(6-7):381–4.
105. Liao XP, She YX, Shi CR, Li M. Changes in body fluid markers in intestinal ischemia. *J Pediatr Surg*. 1995;30(10):1412–5.
106. Verma I, Kaur S, Goyal S, Goyal S, Multani JS, Narang APS. Diagnostic value of lactate levels in acute abdomen disorders. *Indian J Clin Biochem*. 2014;29(3):382–5.
107. de Papp E, Drobatz KJ, Hughes D. Plasma lactate concentration as a predictor of gastric necrosis and survival among dogs with gastric dilatation-volvulus: 102 cases (1995–1998). *J Am Anim Hosp Assoc*. 1999;215(1):49–52.
108. Green TI, Tonozzi CC, Kirby R, Rudloff E. Evaluation of initial plasma lactate values as a predictor of gastric necrosis and initial and subsequent plasma lactate values as a

- predictor of survival in dogs with gastric dilatation-volvulus: 84 dogs (2003-2007). *J Vet Emerg Crit Care*. 2011;21(1):36–44.
109. Moore RM, Muir WW, Bertone AL, Beard WL. Characterization of the hemodynamic and metabolic alterations in the large colon of horses during low-flow ischemia and reperfusion. *Am J Vet Res*. 1994;55(10):1444–53.
 110. Demir IE, Ceyhan GO, Friess H. Beyond lactate: is there a role for serum lactate measurement in diagnosing acute mesenteric ischemia?. *Dig Surg*. 2012;29(3):226–35.
 111. Holahan ML, Brown AJ, Drobatz KJ. Retrospective Study: The association of blood lactate concentration with outcome in dogs with idiopathic immune-mediated hemolytic anemia: 173 cases (2003-2006). 2010;20(4):413–20.
 112. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol Respir Environ Exerc Physiol*. 1977;42(2):228–34.
 113. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. *Am J Physiol*. 1965;209(3):604–10.
 114. Ari Jutkowitz L. Blood transfusion in the perioperative period. *Clin Tech Small Anim Prac*. 2004;19(2):75–82.
 115. Cillee RE, Scharenberg AM, Bongiorno PF, Guire KE, Bartlett RH. Low oxygen delivery produced by anemia, hypoxia, and low cardiac output. *J Surg Res*. 1991;51(5):425–33.
 116. Hampson NB, Piantadosi CA, Thom SR, Weaver LK. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. *Am J Resp Crit Care Med*. 2012;186(11):1095–101.
 117. Moon JM, Shin MH, Chun BJ. The value of initial lactate in patients with carbon monoxide intoxication: in the emergency department. *Hum Exp Toxicol*. 2011;30(8):836–43.
 118. Cervellin G, Comelli I, Rastelli G, Picanza A, Lippi G. Initial blood lactate correlates with carboxyhemoglobin and clinical severity in carbon monoxide poisoned patients. *Clin Biochem*. 2014;47(18):298–301.
 119. Doğan N, Savrun A, Levent S, Günaydın G, Celik G, Akkücüük H, et al. Can initial lactate levels predict the severity of unintentional carbon monoxide poisoning? *Hum Exp Toxicol*. 2015;34(3):324–9.
 120. Weinberg F, Chandel NS. Mitochondrial metabolism and cancer. *Ann N Y Acad Sci*. 2009;1177(1):66–73.
 121. Semenza GL. Hypoxia-inducible factors in physiology and medicine. *Cell*.

2012;148(3):399–408.

122. Parks SK, Chiche J, Pouyssegur J. Disrupting proton dynamics and energy metabolism for cancer therapy. *Nat Rev Cancer*. 2013;13(9):611–23.
123. Riganti C, Gazzano E, Polimeni M, Aldieri E, Ghigo D. The pentose phosphate pathway: An antioxidant defense and a crossroad in tumor cell fate. *Free Radic Biol Med*. 2012;53(3):421–36.
124. Choi SYC, Collins CC, Gout PW, Wang Y. Cancer-generated lactic acid: a regulatory, immunosuppressive metabolite? *J Pathol*. 2013;230(4):350–5.
125. Birsoy K, Wang T, Possemato R, Yilmaz OH, Koch CE, Chen WW, et al. MCT1-mediated transport of a toxic molecule is an effective strategy for targeting glycolytic tumors. *Nat Genet*. 2013;45(1):104–8.
126. Gerlinger M, Santos CR, Spencer Dene B, Martinez P, Endesfelder D, Burrell RA, et al. Genome-wide RNA interference analysis of renal carcinoma survival regulators identifies MCT4 as a Warburg effect metabolic target. *J Pathol*. 2012;227(2):146–56.
127. Le Floch R, Chiche J, Marchiq I, Naiken T, Ilk K, Ilk K, et al. CD147 subunit of lactate/H⁺ symporters MCT1 and hypoxia-inducible MCT4 is critical for energetics and growth of glycolytic tumors. *Proc Natl Acad Sci U S A*. 2011;108(40):16663–8.
128. Zu XL, Guppy M. Cancer metabolism: facts, fantasy, and fiction. *Biochem Biophys Res Commun*. 2004;313(3):459–65.
129. De Groot R, Sprenger RA, Imholz AL, Gerding MN. Type B lactic acidosis in solid malignancies. *Neth J Med*. 2011;69(3):120–3.
130. Keller U, Mall TH, Walter M, Bertel O, Mihatsch JM. Pheochromocytoma with lactic acidosis. *BMJ*. 1978;2(6137):606–7.
131. Bornemann M, Hill SC, Kidd GS. Lactic acidosis in pheochromocytoma. *Ann Intern Med*. 1986;105(6):880–2.
132. Touret M, Boysen SR, Nadeau M-E. Retrospective evaluation of potential causes associated with clinically relevant hyperlactatemia in dogs with lymphoma. *Can Vet J*. 2012;53(5):511–7.
133. Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YD. Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. *Diabetes*. 1988;37(8):1020–4.
134. Hasegawa H, Fukushima T, Lee J-A, Tsukamoto K, Moriya K, Ono Y, et al. Determination of serum D-lactic and L-lactic acids in normal subjects and diabetic patients by column-

switching HPLC with pre-column fluorescence derivatization. *Anal Bioanal Chem.* 2003;377(5):886–91.

135. Durocher LL, Hinchcliff KW, DiBartola SP, Johnson SE. Acid-base and hormonal abnormalities in dogs with naturally occurring diabetes mellitus. *J Am Vet Med Assoc.* 2008;232(9):1310–20.
136. Cox K, Cocchi MN, Saliccioli JD, Carney E, Howell M, Donnino MW. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. *J Crit Care.* 2012;27(2):132–7.
137. Christopher MM, O'Neill S. Effect of specimen collection and storage on blood glucose and lactate concentrations in healthy, hyperthyroid and diabetic cats. *Vet Clin Pathol.* 2000;29(1):22–8.
138. Kruse JA, Zaidi SA, Carlson RW. Significance of blood lactate levels in critically ill patients with liver disease. *Am J Med.* 1987;83(1):77–82.
139. Woll PJ, Record CO. Lactate elimination in man: effects of lactate concentration and hepatic dysfunction. *Eur J Clin Invest.* 1979;9(5):397–404.
140. Leatherdale BA, Chase RA, Rogers J, Alberti KG, Davies P, Record CO. Forearm glucose uptake in cirrhosis and its relationship to glucose tolerance. *Clin Sci.* 1980;59(3):191–8.
141. Almenoff PL, Leavy J, Weil MH, Goldberg NB, Vega D, Rackow EC. Prolongation of the half-life of lactate after maximal exercise in patients with hepatic dysfunction. *Crit Care Med.* 1989;17(9):870–3.
142. Murphy ND, Kodakat SK, Wendon JA, Jooste CA, Muiesan P, Rela M, et al. Liver and intestinal lactate metabolism in patients with acute hepatic failure undergoing liver transplantation. *Crit Care Med.* 2001;29(11):2111–8.
143. Sillos EM, Shenep JL, Burghen GA, Pui CH, Behm FG, Sandlund JT. Lactic acidosis: a metabolic complication of hematologic malignancies: case report and review of the literature. *Cancer.* 2001;92(9):2237–46.
144. Chrusch C, Bands C, Bose D, Li X, Jacobs H, Duke K, et al. Impaired hepatic extraction and increased splanchnic production contribute to lactic acidosis in canine sepsis. *Am J Resp Crit Care Med.* 2000;161:517–26.
145. Lalau JD, Race JM. Lactic acidosis in metformin therapy. *Drugs.* 1999;58(Suppl 1):55–60.
146. Scale T, Harvey JN. Diabetes, metformin and lactic acidosis. *Clin Endocrinol (Oxf).* 2011;74(2):191–6.
147. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol.*

2001;12(Suppl 17):S15-9.

148. Singh M, Thompson M, Sullivan N. Thiamine deficiency in dogs due to the feeding of sulphite preserved meat. *Aust Vet J.* 2005;83(7):412-7.
149. Garosi LS, Dennis R, Platt SR, Corletto F, Lahunta A, Jakobs C. Thiamine Deficiency in a Dog: Clinical, Clinicopathologic, and Magnetic Resonance Imaging Findings. *J Vet Intern Med.* 2003;17(5):719-23.
150. Shah S, Wald E. Type B lactic acidosis secondary to thiamine deficiency in a child with malignancy. *Pediatrics.* 2015;135(1):e221-4.
151. Klein M, Weksler N, Gurman GM. Fatal metabolic acidosis caused by thiamine deficiency. *J Emerg Med.* 2004;26(3):301-3.
152. Donnino M. Gastrointestinal beriberi: a previously unrecognized syndrome. *Ann Intern Med.* 2004;141(11):898-9.
153. Donnino MW, Vega J, Miller J, Walsh M. Myths and misconceptions of Wernicke's encephalopathy: what every emergency physician should know. *Ann Emerg Med.* 2007;50(6):715-21.
154. Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, et al. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care.* 2010;25(4):576-81.
155. Anderson DK, Prockop LD, Means ED, Hartley LE. Cerebrospinal fluid lactate and electrolyte levels following experimental spinal cord injury. *J Neurosurg.* 1976;44(6):715-22.
156. Naito E, Ito M, Yokota I, Saijo T, Matsuda J, Kuroda Y. Thiamine-responsive lactic acidaemia: role of pyruvate dehydrogenase complex. *Eur J Pediatr.* 1998;157(8):648-52.
157. Eudy JD, Spiegelstein O, Barber RC, Wlodarczyk BJ, Talbot J, Finnell RH. Identification and characterization of the human and mouse SLC19A3 gene: a novel member of the reduced folate family of micronutrient transporter genes. *Mol Genet Metab.* 2000;71(4):581-90.
158. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. *Curr Opin Clin Nutr Metab Care.* 2011;14(6):610-7.
159. Bonucchi J, Hassan I, Policeni B, Kaboli P. Thyrotoxicosis associated Wernicke's encephalopathy. *J Gen Intern Med.* 2008;23(1):106-9.
160. Jubb KV, Saunders LZ, Coates HV. Thiamine deficiency encephalopathy in cats. *J Comp Path.* 1956;66:217-27.

161. Houston DM, Hulland TJ. Thiamine deficiency in a team of sled dogs. *Can Vet J.* 1988;29(4):383–5.
162. Read DH, Jolly RD, Alley MR. Polioencephalomalacia of dogs with thiamine deficiency. *Vet Pathol.* 1977;14(2):103–12.
163. Loew FM, Martin CL, Dunlop RH, Mapletoft RJ, Smith SI. Naturally-occurring and experimental thiamin deficiency in cats receiving commercial cat food. *Can Vet J.* 1970;11(6):109–13.
164. Steel RJ. Thiamine deficiency in a cat associated with the preservation of “pet meat” with sulphur dioxide. *Aust Vet J.* 1997;75(10):719–21.
165. Malik R, Sibraa D. Thiamine deficiency due to sulphur dioxide preservative in “pet meat”-a case of déjà vu. *Aust Vet J.* 2005;83(7).
166. Studdert VP, Labuc RH. Thiamin deficiency in cats and dogs associated with feeding meat preserved with sulphur dioxide. *Aust Vet J.* 1991;68(2):54–7.
167. Jiang YZ, Hutchinson KA, Bartelloni P, Manthous CA. Thyroid storm presenting as multiple organ dysfunction syndrome. *Chest.* 2000;118(3):877–9.
168. Williams RH, Egana E, Robinson P, Asper SP, Dutoit C. Alterations in Biologic Oxidation in Thyrotoxicosis: I. Thiamine Metabolism. *Arch Intern Med.* 1943;72(3):353–71.
169. Sandler MP, Robinson RP, Rabin D, Lacy WW, Abumrad NN. The effect of thyroid hormones on gluconeogenesis and forearm metabolism in man. *J Clin Endocrinol Metab.* 1983;56(3):479–85.
170. Dimitriadis GD, Raptis SA. Thyroid hormone excess and glucose intolerance. *Exp Clin Endocrinol Diabetes.* 2001;109(Suppl 2):S225–39.
171. Monti M, Hedner P, Ikomi-Kumm J, Valdemarsson S. Erythrocyte metabolism in hyperthyroidism. *Acta endocrinologica (Copenh).* 1987;115(1):87–90.
172. Izumi K, Kondo S, Okada T. A case of atypical thyroid storm with hypoglycemia and lactic acidosis. *Endocr J.* 2009;56(6):747–52.
173. Elbers PWG, Ince C. Mechanisms of critical illness-classifying microcirculatory flow abnormalities in distributive shock. *Crit Care.* 2006;10(4):221.
174. Ince C. The microcirculation is the motor of sepsis. *Crit Care.* 2005;9(Suppl 4):S13–9.
175. Hangai-Hoger N, Nacharaju P, Manjula BN, Cabrales P, Tsai AG, Acharya SA, et al. Microvascular effects following treatment with polyethylene glycol-albumin in lipopolysaccharide-induced endotoxemia. *Crit Care Med.* 2006;34(1):108–17.

176. De Backer D, Ospina-Tascon G, Salgado D, Favory R, Creteur J, Vincent JL. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. *Intensive Care Med.* 2010;36(11):1813–25.
177. Ince C. The rationale for microcirculatory guided fluid therapy. *Curr Opin Crit Care.* 2014;20(3):301–8.
178. Uil den CA, Klijn E, Lagrand WK, Brugts JJ, Ince C, Spronk PE, et al. The microcirculation in health and critical disease. *Prog Cardiovasc Dis.* 2008;51(2):161–70.
179. Ospina-Tascon G, Neves AP, Occhipinti G, Donadello K, Büchele G, Simion D, et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med.* 2010;36(6):949–55.
180. Filbin MR, Hou PC, Massey M, Barche A, Kao E, Bracey A, et al. The microcirculation is preserved in emergency department low-acuity sepsis patients without hypotension. *Acad Emerg Med.* 2014;21(2):154–62.
181. Fink MP. Bench-to-bedside review: Cytopathic hypoxia. *Crit Care.* 2002;6(6):491–9.
182. Fink MP. Cytopathic hypoxia. Is oxygen use impaired in sepsis as a result of an acquired intrinsic derangement in cellular respiration? *Crit Care Clin.* 2002;18(1):165–75.
183. Lofacono LA, Shapiro DS. Detection of hypoxia at the cellular level. *Crit Care Clin.* 2010;26(2):409–21.
184. Vary TC. Sepsis-induced alterations in pyruvate dehydrogenase complex activity in rat skeletal muscle: effects on plasma lactate. *Shock.* 1996;6(2):89–94.
185. Levy RJ. Mitochondrial dysfunction, bioenergetic impairment, and metabolic down-regulation in sepsis. *Shock.* 2007;28(1):24–8.
186. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence.* 2014;5(1):66–72.
187. Shangraw RE, Rabkin JM, Lopaschuk GD. Hepatic pyruvate dehydrogenase activity in humans: effect of cirrhosis, transplantation, and dichloroacetate. *Am J Physiol.* 1998;274(37):G569–77.
188. Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med.* 2005 Sep;20(5):255–71.
189. Lagutchik MS, Ogilvie GK. Lactate kinetics in veterinary critical care: a review. 1999;6(2):81–95.
190. Bueding E, Goldfarb W. Blood changes following glucose, lactate, and pyruvate

- injections in man. *J Biol Chem.* 1943;147(1): 33-40.
191. Levy B, Desebbe O, Montemont C, Gibot S. Increased aerobic glycolysis through beta2 stimulation is a common mechanism involved in lactate formation during shock states. *Shock.* 2008;30(4):417-21.
 192. Griffith FR, Lockwood JE, Emery E. Adrenalin lactacidemia: proportionality with dose. *J Physiol.* 1939;127(3):415-21.
 193. Clausen SW. Anhydremic acidosis due to lactic acid. *Am J Dis Child.* 1925;29(6):761-6.
 194. Clausen T, Zauner A, Levasseur JE, Rice AC, Bullock R. Induced mitochondrial failure in the feline brain: implications for understanding acute post-traumatic metabolic events. *Brain Res.* 2001;908(1):35-48.
 195. McCarter FD, James JH, Luchette FA, Wang L, Friend LA, King JK, et al. Adrenergic blockade reduces skeletal muscle glycolysis and Na(+), K(+)-ATPase activity during hemorrhage. *J Surg Res.* 2001;99(2):235-44.
 196. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na⁺ K⁺ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet.* 2005;365:871-5.
 197. Issekutz B Jr., Allen M. Effect of catecholamines and methylprednisolone on carbohydrate metabolism of dogs. *Metabolism.* 1972;21(1):48-59.
 198. Bundgaard H, Kjeldsen K, Suarez Krabbe K, van Hall G, Simonsen L, Qvist J, et al. Endotoxemia stimulates skeletal muscle Na⁺-K⁺-ATPase and raises blood lactate under aerobic conditions in humans. *Am J Physiol Heart Circ Physiol.* 2003;284(3):H1028-34.
 199. Levy B, Perez P, Perny J, Thivillier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med.* 2011;39(3):450-5.
 200. Levy B. Bench-to-bedside review: Is there a place for epinephrine in septic shock? *Crit Care.* 2005;9(6):561.
 201. Gladden LB. A lactic perspective on metabolism. *Med Sci Sports Exerc.* 2008;40(3):477-85.
 202. Gladden LB. 200th anniversary of lactate research in muscle. *Exerc Sport Sci Rev.* 2008;36(3):109-15.
 203. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet.* 1999;354:505-8.

204. Marik PE, Bellomo R. Lactate clearance as a target of therapy in sepsis: a flawed paradigm. *OA Critical Care*. 2013;1(1):3–6.
205. James JH, Fang CH, Schrantz SJ, Hasselgren PO, Paul RJ, Fischer JE. Linkage of aerobic glycolysis to sodium-potassium transport in rat skeletal muscle. Implications for increased muscle lactate production in sepsis. *J Clin Invest*. 1996;98(10):2388–97.
206. Sepp M, Sokolova N, Jugai S, Mandel M, Peterson P, Vendelin M. Tight coupling of Na^+/K^+ -ATPase with glycolysis demonstrated in permeabilized rat cardiomyocytes. *PLoS ONE*. 2014;9(6):e99413.
207. Levy B. Lactate and shock state: the metabolic view. *Curr Opin Crit Care*. 2006;12(4):315–21.
208. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann Surg*. 1996;224(1):97–102.
209. Levy B, Perez P, Gibot S, Gerard A. Increased muscle-to-serum lactate gradient predicts progression towards septic shock in septic patients. *Intensive Care Med*. 2010;36(10):1703–9.
210. Luchette FA, Friend LA, Brown CC, Upputuri RK, James JH. Increased skeletal muscle Na^+ , K^+ -ATPase activity as a cause of increased lactate production after hemorrhagic shock. *J Trauma*. 1998;44(5):796–801.
211. Luchette FA, Jenkins WA, Friend LA, Su C, Fischer JE, James JH. Hypoxia is not the sole cause of lactate production during shock. *J Trauma Acute Care Surg*. 2002;52(3):415–9.
212. Mazzeo RS, Marshall P. Influence of plasma catecholamines on the lactate threshold during graded exercise. *J Appl Physiol*. 1989;67(4):1319–22.
213. Barth E, Albuszies G, Baumgart K, Matejovic M, Wachter U, Vogt J, et al. Glucose metabolism and catecholamines. *Crit Care Med*. 2007;35(Suppl 9):S508–18.
214. Liddell MJ, Daniel AM, MacLean LD, Shizgal HM. The role of stress hormones in the catabolic metabolism of shock. *Surg Gynecol Obstet*. 1979;149(6):822–30.
215. Halmagyi DF, Irving MH, Gillett DJ, Varga D. Effect of adrenergic blockade on consequences of sustained epinephrine infusion. *J Appl Physiol*. 1967;23:171–7.
216. Di Giantomasso D, Bellomo R, May CN. The haemodynamic and metabolic effects of epinephrine in experimental hyperdynamic septic shock. *Intensive Care Med*. 2005;31(3):454–62.
217. Issekutz B. Effect of beta-adrenergic blockade on lactate turnover in exercising dogs. *J*

Appl Physiol Respir Environ Exerc Physiol. 1984;57(6):1754–9.

218. Wutrich Y, Barraud D, Conrad M, Cravoisy-Popovic A, Nace L, Bollaert PE, et al. Early increase in arterial lactate concentration under epinephrine infusion is associated with a better prognosis during shock. *Shock*. 2010;34(1):4–9.
219. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34:2226–34.
220. Richardson RS, Noyszewski EA, Leigh JS, Wagner PD. Lactate efflux from exercising human skeletal muscle: role of intracellular PO₂. *J Appl Physiol*. 1998;85(2):627–34.
221. Richardson RS. What governs skeletal muscle VO₂max? New evidence. *Med Sci Sports Exerc*. 2000;32(1):100–7.
222. Musch TI, Friedman DB, Haidet GC, Stray-Gundersen J, Waldrop TG, Ordway GA. Arterial blood gases and acid-base status of dogs during graded dynamic exercise. *J Appl Physiol*. 1986;61(5):1914–9.
223. McCarter F, Evans J, Luchette F, Friend L, James J, Davis K, et al. Concurrent reduction of glycogenolysis, glycolysis, and NA(+)/K(+) pump activity after hemorrhagic shock. *Curr Surg*. 2000;57(6):639.
224. Luchette FA, Robinson BRH, Friend LA, McCarter F, Frame SB, James JH. Adrenergic Antagonists Reduce Lactic Acidosis in Response to Hemorrhagic Shock. *J Trauma Acute Care Surg*. 1999;46(5):873–80.
225. Irving MH, Varga D, Gillett DJ. The effect of adrenergic blockade upon shock-induced lactic acidosis in sheep. *Brit J Surg*. 1968;55(10):780–5.
226. Irving MH. The sympatho-adrenal factor in haemorrhagic shock. *Ann R Coll Surg Engl*. 1968;42(6):367–86.
227. Shibata K, Yamamoto Y, Murakami S. Effects of epidural anesthesia on cardiovascular response and survival in experimental hemorrhagic shock in dogs. *Anesthesiology*. 1989;71(6):953–9.
228. Podolin DA, Munger PA, Mazzeo RS. Plasma catecholamine and lactate response during graded exercise with varied glycogen conditions. *J Appl Physiol*. 1991;71(4):1427–33.
229. Watt MJ, Howlett KF, A FM, Spriet LL, M H. Adrenaline increases skeletal muscle glycogenolysis, pyruvate dehydrogenase activation and carbohydrate oxidation during moderate exercise in humans. *J Physiol*. 2001;534(1):269–78.
230. Hall JB, Brown DA. Plasma glucose and lactic acid alterations in response to a stressful

exam. Biol Psychol. 1979;8(3):179–88.

231. Suzuki K, Tanaka S, Uchida T, Nakazawa K, Makita K. Catecholamine release induces elevation in plasma lactate levels in patients undergoing adrenalectomy for pheochromocytoma. *J Clin Anesth.* 2014;26(8):616–22.
232. Brown AJ, Alwood AJ, Cole SG. Malignant pheochromocytoma presenting as a bradyarrhythmia in a dog. *J Vet Emerg Crit Care.* 2007;17(2):164–9.
233. Radhi S, Nugent K, Alalawi R. Pheochromocytoma Presenting as Systemic Inflammatory Response Syndrome and Lactic Acidosis. *ICU Dir.* 2010;1:257–60.
234. Rodrigo GJ. Serum lactate increase during acute asthma treatment: a new piece of the puzzle. *Chest.* 2014;145(1):6–7.
235. Raimondi GA, Gonzalez S, Zaltsman J, Menga G, Adrogué HJ. Acid-base patterns in acute severe asthma. *J Asthma.* 2013;50(10):1062–8.
236. Lewis L, Ferguson I, House SL, Aubuchon K, Schneider J, Johnson K, et al. Albuterol administration is commonly associated with increases in serum lactate in patients with asthma treated for acute exacerbation of asthma. *Chest.* 2014;145(1):53–9.
237. Meert KL, McCaulley L, Sarnaik AP. Mechanism of lactic acidosis in children with acute severe asthma. *Pediatr Crit Care Med.* 2012;13(1):28–31.
238. Shah AD, Wood DM, Dargan PI. Understanding lactic acidosis in paracetamol (acetaminophen) poisoning. *Br J Clin Pharmacol.* 2011;71(1):20–8.
239. Kanji HD, Mithani S, Boucher P, Dias VC. Coma, metabolic acidosis, and methemoglobinemia in a patient with acetaminophen toxicity. *J Popul Ther Clin Pharmacol.* 2013;20(3):e207–11.
240. Liamis G, Milionis DHJ, Elisaf M. Pharmacologically-Induced Metabolic Acidosis. *Drug Saf.* 2010;33(5):371–91.
241. Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med.* 2014;371(24):2309–19.
242. Bernard S. Severe lactic acidosis following theophylline overdose. *Ann Emerg Med.* 1991;20(10):1135–7.
243. Assadi FK. Therapy of acute bronchospasm complicated by lactic acidosis and hypokalemia. *Clin Pediatr (Phila).* 1989;28(6):258–60.
244. Schmidt A, Karlson-Stiber C. Caffeine poisoning and lactate rise: an overlooked toxic effect? *Acta Anaesthesiol Scand.* 2008;52(7):1012–4.

245. Rudolph T, Knudsen K. A case of fatal caffeine poisoning. *Acta Anaesthesiol Scand*. 2010;54(4):521–3.
246. Meert KL, Clark J, Sarnaik AP. Metabolic acidosis as an underlying mechanism of respiratory distress in children with severe acute asthma. *Pediatr Crit Care Med*. 2007;8(6):519–23.
247. Charytan D, Jansen K. Severe metabolic complications from theophylline intoxication. *Nephrology*. 2003;8(5):239–42.
248. Leventhal LJ, Kochar G, Feldman NH, Podolsky SM, Stanek MS. Lactic acidosis in theophylline overdose. *Am J Emerg Med*. 1989;7(4):417–8.
249. Catravas JD, Waters IW, Walz MA, Davis WM. Acute cocaine intoxication in the conscious dog: pathophysiologic profile of acute lethality. *Arch Int Pharmacodyn Ther*. 1978;235(2):328–40.
250. Reis MB, Garrido ADPG, Cruz RJ, Ribeiro EA, Silva MRE, de Figueiredo LFP. Early restoration of cocaine-induced splanchnic hypoperfusion in anesthetized dogs. *J Invest Surg*. 2007;20(5):291–9.
251. Catravas JD, Waters IW. Acute cocaine intoxication in the conscious dog: studies on the mechanism of lethality. *J Pharmacol Exp Ther*. 1981;217(2):350–6.
252. Loh NW, Nair P. Propofol infusion syndrome. *Continuing Education in Anaesthesia, Critical Care & Pain*. 2013;13(6):200–2.
253. Fodale V, La Monaca E. Propofol infusion syndrome: an overview of a perplexing disease. *Drug Saf*. 2008;31(4):293–303.
254. Vanlander AV, Okun JG, de Jaeger A, Smet J, De Lattre E, De Paepe B, et al. Possible pathogenic mechanism of propofol infusion syndrome involves coenzyme q. *Anesthesiology*. 2015;122(2):343–52.
255. Wolf A, Weir P, Segar P, Stone J, Shield J. Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet*. 2001;357(9256):606–7.
256. Reade MC, Davies SR, Morley PT, Dennett J, Jacobs IC, Australian Resuscitation Council. Review article: management of cyanide poisoning. *Emerg Med Australas*. 2012;24(3):225–38.
257. Lockwood A, Patka J, Rabinovich M, Wyatt K. Sodium nitroprusside-associated cyanide toxicity in adult patients—fact or fiction? A critical review of the evidence and clinical relevance. *Open Access J Clin Trials*. 2010;2:133–48.
258. Hamel J. A review of acute cyanide poisoning with a treatment update. *Crit Care Nurse*.

2011;31(1):72–81.

259. Hottinger DG, Beebe DS, Kozhimannil T, Prielipp RC, Belani KG. Sodium nitroprusside in 2014: A clinical concepts review. *J Anaesthesiol Clin Pharmacol*. 2014;30(4):462–71.
260. Baud FJ, Borron SW, Mégarbane B, Trout H, Lapostolle F, Vicaud E, et al. Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Crit Care Med*. 2002;30(9):2044–50.
261. Forbath N, Hall JD, Hetenyi G. The effect of methyl-prednisolone on the turnover of lactate and the conversion of lactate to glucose in dogs. *Horm Metab Res*. 1969;1(4):178–82.
262. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. *Diabetes Metab Rev*. 1988;4(1):17–30.
263. Connaughton S, Chowdhury F, Attia RR, Song S, Zhang Y, Elam MB, et al. Regulation of pyruvate dehydrogenase kinase isoform 4 (PDK4) gene expression by glucocorticoids and insulin. *Mol Cell Endocrinol*. 2010;315:159–67.
264. Jeong JY, Jeoung NH, Park K-G, Lee I-K. Transcriptional Regulation of Pyruvate Dehydrogenase Kinase. *Diabetes Metab J*. 2012;36(5):328–35.
265. Issekutz B Jr, Borkow I. Effect of catecholamines and dibutyryl-cyclic-AMP on glucose turnover, plasma free fatty acids, and insulin in dogs treated with methylprednisolone. *Can J Physiol Pharmacol*. 1972;50:999–1006.
266. Boysen SR, Bozzetti M, Rose L, Dunn M, Pang DSJ. Effects of prednisone on blood lactate concentrations in healthy dogs. *J Vet Intern Med*. 2009;23(5):1123–5.
267. Issekutz B, Allen M. Effect of methylprednisolone on carbohydrate metabolism of exercising dogs. *J Appl Physiol*. 1971;31(6):813–8.
268. Batstone GF, Alberti KG, Dewar AK. Reversible lactic acidosis associated with repeated intravenous infusions of sorbitol and ethanol. *Postgrad Med J*. 1977;53(623):567–9.
269. Zink BJ, Dronen SC, Syverud SA. Hemodynamic and metabolic effects of ethanol in canine hemorrhagic shock. *Circ Shock*. 1988;24(1):19–28.
270. Zentabchi S, Sinert R, Baron BJ, Paladino L, Yadav K. Does Ethanol Explain the Acidosis Commonly Seen in Ethanol-Intoxicated Patients? *Clin Toxicol (Phila)*. 2009;43:161–6.
271. MacDonald L, Kruse JA, Levy DB, Marulendra S, Sweeny PJ. Lactic acidosis and acute ethanol intoxication. *Am J Emerg Med*. 1994;12(1):32–5.
272. Ott A, Hayes J, Polin J. Severe lactic acidosis associated with intravenous alcohol for

- premature labor. *Obstet Gynecol.* 1976;48(3):362–4.
273. Kreisberg RA, Siegal AM, Owen WC. Glucose-lactate interrelationships: effect of ethanol. *J Clin Invest.* 1971;50(1):175–85.
274. Kruse JA. Methanol and Ethylene Glycol Intoxication. *Crit Care Clin.* 2012;28(4):661–711.
275. Claus MA, Jandrey KE, Poppenga RH. Propylene glycol intoxication in a dog. *J Vet Emerg Crit Care.* 2011;21(6):679–83.
276. Zar T, Graeber C, Perazella MA. Reviews: Recognition, Treatment, and Prevention of Propylene Glycol Toxicity. *Semin Dial.* 2007;20(3):217–9.
277. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. *Clin J Am Soc Nephrol.* 2008;3(1):208–25.
278. Zosel A, Egelhoff E, Heard K. Severe lactic acidosis after an iatrogenic propylene glycol overdose. *Pharmacotherapy.* 2010;30(2):219–23.
279. Fowles JR, Banton MI, Pottenger LH. A toxicological review of the propylene glycols. *Crit Rev Toxicol.* 2013;43(4):363–90.
280. Wilson KC, Reardon C, Theodore AC, Farber HW. Propylene Glycol Toxicity: A Severe Iatrogenic Illness in ICU Patients Receiving IV Benzodiazepines: A Case Series and Prospective, Observational Pilot Study. *Chest.* 2005;128(3):1674–81.
281. Miller MA, Forni A, Yogaratnam D. Propylene glycol-induced lactic acidosis in a patient receiving continuous infusion pentobarbital. *Ann Pharmacother.* 2008;42(10):1502–6.
282. Bedichek E, Kirschbaum B. A case of propylene glycol toxic reaction associated with etomidate infusion. *Arch Intern Med.* 1991;151:2297–8.
283. Cate JC, Hedrick R. Propylene glycol intoxication and lactic acidosis. *N Engl J Med.* 1980;303(21):1237–7.
284. Christopher MM, Eckfeldt JH, Eaton JW. Propylene glycol ingestion causes D-lactic acidosis. *Lab Invest.* 1990;62(1):114–8.
285. Burkitt JM, Haskins SC, Aldrich J, Jandrey KE, Rezende ML, Boyle JE. Effects of oral administration of a commercial activated charcoal suspension on serum osmolality and lactate concentration in the dog. *J Vet Intern Med.* 2005;19(5):683–6.
286. Meng QH, Adeli K, Zello GA, Porter WH, Krahn J. Elevated lactate in ethylene glycol poisoning: True or false? *Clinica Chimica Acta.* 2010;411(7-8):601–4.

287. Verelst S, Vermeersch P, Desmet K. Ethylene glycol poisoning presenting with a falsely elevated lactate level. *Clin Toxicol (Phila)*. 2009;47(3):236–8.
288. Sandberg Y, Rood PPM, Russcher H, Zwaans JJM, Weige JD, van Daele PLA. Falsely elevated lactate in severe ethylene glycol intoxication. *Neth J Med*. 2010;68(1):320–3.
289. Ito Y, Moriwaki H, Muto Y, Kato N, Watanabe K, Ueno K. Effect of lactulose on short-chain fatty acids and lactate production and on the growth of faecal flora, with special reference to *Clostridium difficile*. *J Med Microbiol*. 1997;46(1):80–4.
290. Mann NS, Russman HB, Mann SK, Tsai MF. Lactulose and severe lactic acidosis. *Ann Intern Med*. 1985;103(4):637–7.
291. Hove H, Mortensen PB. Colonic lactate metabolism and D-lactic acidosis. *Dig Dis Sci*. 1995;40(2):320–30.
292. Salpeter SR, Greyber E, Pasternak GA. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. 2010;4:CD002967.
293. Piel S, Ehinger JK, Elmér E, Hansson MJ. Metformin induces lactate production in peripheral blood mononuclear cells and platelets through specific mitochondrial complex I inhibition. *Acta Physiol (Oxf)*. 2015;213:171–80.
294. Renda F, Mura P, Finco G, Ferrazin F, Pani L, Landoni G. Metformin-associated lactic acidosis requiring hospitalization. A national 10 year survey and a systematic literature review. *Eur Rev Med Pharmacol Sci*. 2013;17(Suppl 1):45–9.
295. Heller JB. Toxicology Brief: Metformin overdose in dogs and cats. *Veterinary Medicine*. 2007;231–4.
296. De Vriese AS, Coster RV, Smet J, Seneca S, Lovering A, Van Haute LL, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis*. 2006;42:1111–7.
297. McKee EE, Ferguson M, Bentley AT, Marks TA. Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. *Antimicrob Agents Chemother*. 2006 Jun;50(6):2042–9.
298. Rachoin J-S, Weisberg LS, McFadden CB. Treatment of lactic acidosis: Appropriate confusion. *J Hosp Med*. 2010;5(4):E1–E7.
299. Plumbs DC. *Plumbs Veterinary drug handbook*, 8th Ed. Wiley Blackwell, Ames, IA. 2015.
300. Chin L, Sievers ML, Herrier RN, Picchioni AL. Convulsions as the etiology of lactic acidosis in acute isoniazid toxicity in dogs. *Toxicol Appl Pharmacol*. 1979;49(2):377–84.

301. Yeh KH, Cheng AL. High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. *Br J Cancer*. 1997;75(3):464–5.
302. Kondo K, Fujiwara M, Murase M, Kodera Y, Akiyama S, Ito K, et al. Severe acute metabolic acidosis and Wernicke's encephalopathy following chemotherapy with 5-fluorouracil and cisplatin: case report and review of the literature. *Jpn J Clin Oncol*. 1996;26(4):234–6.
303. Bergström J, Hultman E, Roch Norlund AE. Lactic acid accumulation in connection with fructose infusion. *Acta Med Scand*. 1968;184:359–64.
304. Wang YM, King SM, Patterson JH, Van Eys J. Mechanism of xylitol toxicity in the rabbit. *Metabolism*. 1973;22(7):885–94.
305. Xia Z, Cai L, He Y, Wan J, Yu J. Xylitol poisoning of dogs is associated with increased glycogenolysis, coagulopathy, and oxidative stress. *Toxicol Environ Chem*. 2013;95(2):337–43.
306. Boyd RE, Brennan PT, Deng JF, Rochester DF, Spyker DA. Strychnine poisoning. Recovery from profound lactic acidosis, hyperthermia, and rhabdomyolysis. *Am J Med*. 1983;74(3):507–12.
307. Yamarick W, Walson P, DiTraglia J. Strychnine Poisoning in an Adolescent. *Clin Toxicol (Phila)*. 1992;30(1):141–8.
308. Smith BA. Strychnine poisoning. *J Emerg Med*. 1990;8(3):321–5.
309. Meiser H, Hagedorn HW. Atypical time course of clinical signs in a dog poisoned by strychnine. *Vet Rec*. 2002;151(1):21–4.
310. Anastasio JD, Sharp CR. Acute aldicarb toxicity in dogs: 15 cases (2001-2009). *J Vet Emerg Crit Care*. 2011;21(3):253–60.
311. Paciello O, Maiolino P, Fatone G, Papparella S. Mitochondrial Myopathy in a German Shepherd Dog. *Vet Pathol*. 2003;40(5):507–11.
312. Olby NJ, Chan KK, Targett MP, Houlton JE. Suspected mitochondrial myopathy in a Jack Russell terrier. *J Small Anim Pract*. 1997;38(5):213–6.
313. Vijayasarathy C, Giger U, Prociuk U, Patterson DF, Breitschwerdt EB, Avadhani NG. Canine mitochondrial myopathy associated with reduced mitochondrial mRNA and altered cytochrome c oxidase activities in fibroblasts and skeletal muscle. *Comp Biochem Physiol A Physiol*. 1994;109(4):887–94.
314. Breitschwerdt EB, Kornegay JN, Wheeler SJ, Stevens JB, Baty CJ. Episodic weakness associated with exertional lactic acidosis and myopathy in Old English sheepdog

- littermates. *J Am Vet Med Assoc.* 1992;201(5):731–6.
315. Herrtage E, Houlton JE. Collapsing Clumber spaniels. *Vet Rec.* 1979;105(14):334.
316. Cameron JM, Maj MC, Levandovskiy V, MacKay N, Shelton GD, Robinson BH. Identification of a canine model of pyruvate dehydrogenase phosphatase 1 deficiency. *Mol Genet Metab.* 2007;90(1):15–23.
317. Abramson CJ, Platt SR, Shelton GD. Pyruvate dehydrogenase deficiency in a Sussex spaniel. *J Small Anim Pract.* 2004;45(3):162–5.
318. Houlton JE, Herrtage ME. Mitochondrial myopathy in the Sussex spaniel. *Vet Rec.* 1980 Mar 1;106(9):206–6.
319. Oh MS, Uribarri J, Alveranga D, Lazar I, Bazilinski N, Carroll HJ. Metabolic utilization and renal handling of D-lactate in men. *Metabolism.* 1985;34(7):621–5.
320. Flick MJ, Konieczny SF. Identification of putative mammalian D-lactate dehydrogenase enzymes. *Biochem Biophys Res Commun.* 2002;295(4):910–6.
321. de Vrese M, Koppenhoefer B, Barth CA. D-lactic acid metabolism after an oral load of DL-lactate. *Clin Nutr.* 1990;9(1):23–8.
322. Lorenz I, Gentile A. d-Lactic Acidosis in Neonatal Ruminants. *Vet Clin North Am Food Anim Pract.* 2014;30(2):317–31.
323. Ling B, Peng F, Alcorn J, Lohmann K, Bandy B, Zello GA. D-Lactate altered mitochondrial energy production in rat brain and heart but not liver. *Nutr Metab (Lond).* 2012;9(1):6.
324. Kowlgi NG, Chhabra L. D-lactic acidosis: an underrecognized complication of short bowel syndrome. *Gastroenterol Res Pract.* 2015;2015:476215.
325. Soghian B, Kröpfl A, Hölzenbein T, Khadem A, Redl H, Bahrami S. Increased circulating D-lactate levels predict risk of mortality after hemorrhage and surgical trauma in baboons. *Shock.* 2012;37(5):473–7.
326. Coronado BE, Opal SM, Yoburn DC. Antibiotic-Induced D-Lactic Acidosis. *Ann Intern Med.* 1995;122(11):839–42.
327. Stolberg L, Rolfe R, Gitlin N, Merritt J, Mann L Jr., Linder J, et al. d-Lactic acidosis due to abnormal gut flora: diagnosis and treatment of two cases. *N Engl J Med.* 1982;306(22):1344–8.
328. Gigante A, Sardo L, Gasperini ML, Molinaro A, Riggio O, Laviano A, et al. D-Lactic acidosis 25 years after bariatric surgery due to *Salmonella enteritidis*. *Nutrition.* 2012;28(1):108–11.

329. Zhang DL. D-lactic acidosis secondary to short bowel syndrome. *Postgrad Med J*. 2003;79(928):110–2.
330. Gentile A, Sconza S, Lorenz I, Otranto G, Rademacher G, Famigli-Bergamini P, et al. D-Lactic acidosis in calves as a consequence of experimentally induced ruminal acidosis. *J Vet Med A Physiol Pathol Clin Med*. 2004;51(2):64–70.
331. Christopher MM, Broussard JD, Fallin CW, Drost NJ, Peterson ME. Increased serum D-lactate associated with diabetic ketoacidosis. *Metabolism*. 1995;44(3):287–90.
332. Müller KR, Gentile A, Klee W, Constable PD. Importance of the Effective Strong Ion Difference of an Intravenous Solution in the Treatment of Diarrheic Calves with Naturally Acquired Acidemia and Strong Ion (Metabolic) Acidosis. *J Vet Intern Med*. 2012;26(3):674–83.
333. Lorenz I, Lorch A. D-lactic acidosis in lambs. *Vet Rec*. 2009;164(6):174–5.
334. Lorenz I. D-Lactic acidosis in calves. *Vet J*. 2009;179(2):197–203.
335. Angell JW, Jones GL, Voigt K, Grove-White DH. Successful correction of D-lactic acid neurotoxicity (drunken lamb syndrome) by bolus administration of oral sodium bicarbonate. *Vet Rec*. 2013;173(8):193–3.
336. Bleul U, Schwantag S, Stocker H, Corboz L, Grimm F, Engels M, et al. Floppy kid syndrome caused by D-lactic acidosis in goat kids. *J Vet Intern Med*. 2006;20(4):1003–8.
337. Packer RA, Cohn LA, Wohlstadter DR, Shelton GD, Naylor JM, Zello GA, et al. D-lactic acidosis secondary to exocrine pancreatic insufficiency in a cat. *J Vet Intern Med*. 2005;19(1):106–10.
338. Packer RA, Moore GE, Chang C-Y, Zello GA, Abeysekara S, Naylor JM, et al. Serum D-lactate concentrations in cats with gastrointestinal disease. *J Vet Intern Med*. 2012;26(4):905–10.
339. Rand JS, Kinnaird E, Baglioni A, Blackshaw J, Priest J. Acute stress hyperglycemia in cats is associated with struggling and increased concentrations of lactate and norepinephrine. *J Vet Intern Med*. 2002;16(2):123–32.
340. Redavid LA, Sharp CR, Mitchell MA, Beckel NF. Plasma lactate measurements in healthy cats. *J Vet Emerg Crit Care*. 2012;22(5):580–7.
341. Benzon HT, Toleikis JR, Meagher LL, Shapiro BA, Ts'ao CH, Avram MJ. Changes in venous blood lactate, venous blood gases, and somatosensory evoked potentials after tourniquet application. *Anesthesiology*. 1988;69(5):677–82.

342. Jones AE, Leonard MM, Hernandez-Nino J, Kline JA. Determination of the effect of in vitro time, temperature, and tourniquet use on whole blood venous point-of-care lactate concentrations. *Acad Emerg Med*. 2007;14(7):587-91.
343. Lactate in veterinary critical care: pathophysiology and management. *J Am Anim Hosp Assoc*. 2007;43(5):270-9.
344. Jackson EV, Wiese J, Sigal B, Miller J, Bernstein W, Kassel D, et al. Effects of crystalloid solutions on circulating lactate concentrations: Part 1. Implications for the proper handling of blood specimens obtained from critically ill patients. *Crit Care Med*. 1997;25(11):1840-6.
345. Allen SE, Holm JL. Lactate: physiology and clinical utility. *J Vet Emerg Crit Care*. 2008;18(2):123-32.
346. Skelton MS, Kremer DE, Smith EW, Gladden LB. Lactate influx into red blood cells of athletic and nonathletic species. *Am J Physiol*. 1995;268(37):R1121-8.
347. Mazzeo RS. Comments on point:counterpoint: "the lactate paradox does/does not occur during exercise at high altitude". *J Appl Physiol*. 2007;102:2403-5.
348. Foxdal P, Sjödin B, Rudstam H, Östman C, Östman B, Hedenstierna GC. Lactate concentration differences in plasma, whole blood, capillary finger blood and erythrocytes during submaximal graded exercise in humans. *Eur J Appl Physiol*. 1990;61:218-22.
349. Hopper K, Rezende ML, Haskins SC. Assessment of the effect of dilution of blood samples with sodium heparin on blood gas, electrolyte, and lactate measurements in dogs. *Am J Vet Res*. 2005;66(4):656-60.
350. Toffaletti J, Hammes ME, Gray R, Lineberry B, Abrams B. Lactate measured in diluted and undiluted whole blood and plasma: comparison of methods and effect of hematocrit. *Clin Chem*. 1992;38(12):2430-4.
351. Astles R, Williams CP, Sedor F. Stability of plasma lactate in vitro in the presence of antiglycolytic agents. *Clin Chem*. 1994;40(7):1327-30.
352. Karon BS, Scott R, Burritt MF, Santrach PJ. Comparison of Lactate Values Between Point-of-Care and Central Laboratory Analyzers. *Am J Clin Pathol*. 2007;128(1):168-71.
353. Wiener K. Blood sample tubes for lactate assay. *Clin Chem*. 1995;41(3):483.
354. Wiese J, Didwania A, Kerzner R, Chernow B. Use of different anticoagulants in test tubes for analysis of blood lactate concentrations: Part 2. Implications for the proper handling of blood specimens obtained from critically ill patients. *Crit Care Med*. 1997;25(11):1847-50.

355. Middleton P. Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emerg Med J*. 2006;23(8):622–4.
356. Lavery RF, Livingston DH, Tortella BJ, Sambol JT, Slomovitz BM, Siegel JH. The utility of venous lactate to triage injured patients in the trauma center. *J Am Coll Surg*. 2000;190(6):656–64.
357. Murdoch JA, Turner C, Dalton RN. Arterial or mixed venous lactate measurement in critically ill children. Is there a difference? *Acta Paediatr*. 1994;83(4):412–3.
358. Réminiac F, Saint-Etienne C, Runge I, Ayé DY, Benzekri-Lefevre D, Mathonnet A, et al. Are central venous lactate and arterial lactate interchangeable? A human retrospective study. *Anesth Analg*. 2012;115(3):605–10.
359. Gallagher EJ, Rodriguez K, Touger M. Agreement Between Peripheral Venous and Arterial Lactate Levels. *Ann Emerg Med*. 1997;29(4):479–83.
360. Younger JG, Falk JL, Rothrock SG. Relationship between arterial and peripheral venous lactate levels. *Acad Emerg Med*. 1996;3(7):730–4.
361. Adrogue HJ, Rashad MN, Gorin AB. Assessing acid-base status in circulatory failure. *N Engl J Med*. 1989;320(20):1312–6.
362. Theusinger OM, Thygesen C, Frascarolo P, Schramm S, Seifert B, Spahn DR. Mismatch of arterial and central venous blood gas analysis during haemorrhage. *Eur J Anesthesiol*. 2010;27(10):890–6.
363. Bloom B, Pott J, Freund Y, Grundlingh J, Harris T. The agreement between abnormal venous lactate and arterial lactate in the ED: a retrospective chart review. *Am J Emerg Med*. 2014;32(6):596–600.
364. Contenti J, Corraze H, Lemoël F, Levraut J. Effectiveness of arterial, venous, and capillary blood lactate as a sepsis triage tool in ED patients. *Am J Emerg Med*. 2015;33(2):167–72.
365. Adams JL, Hazard P. Comparison of Blood Lactate Concentrations in Arterial and Peripheral Venous Blood. *Crit Care Med*. 1988;16(9):913.
366. Hughes D, Rozanski ER, Shofer FS, Laster LL, Drobatz KJ. Effect of sampling site, repeated sampling, pH, and PCO₂ on plasma lactate concentration in healthy dogs. *Am J Vet Res*. 1999;60(4):521–4.
367. Pang DSJ, Allaire J, Rondenay Y, Kaartinen J, Cuvellez SG, Troncy E. The use of lingual venous blood to determine the acid-base and blood-gas status of dogs under anesthesia. *Vet Anaesth Analg*. 2009 Mar;36(2):124–32.

368. Ferasin L, Nguyenba TP. Comparison of canine capillary and jugular venous blood lactate concentrations determined by use of an enzymatic-amperometric bedside system. *Am J Vet Res.* 2008;69(2):208–11.
369. Acierno MJ, Mitchell MA. Evaluation of four point-of-care meters for rapid determination of blood lactate concentrations in dogs. *J Am Vet Med Assoc.* 2007;230(9):1315–8.
370. Us MH, Ozkan S, Oral L, Oğuş T, Acar HV, Cakir O, et al. Comparison of the effects of hypertonic saline and crystalloid infusions on haemodynamic parameters during haemorrhagic shock in dogs. *J Int Med Res.* 2001;29(6):508–15.
371. Vail DM, Ogilvie GK, Fettman MJ, Wheeler SL. Exacerbation of hyperlactatemia by infusion of lactated Ringer's solution in dogs with lymphoma. *J Vet Intern Med.* 1990;4(5):228–32.
372. Boysen SR, Dorval P. Effects of rapid intravenous 100% L-isomer lactated Ringer's administration on plasma lactate concentrations in healthy dogs. *J Vet Emerg Crit Care.* 2014;00(0):1–7.
373. Kuwabara K, Hagiwara A, Matsuda S, Fushimi K, Ishikawa KB, Horiguchi H, et al. A community-based comparison of trauma patient outcomes between D- and L-lactate fluids. *Am J Emerg Med.* 2013;31(1):206–14.
374. Morgan TJ, Clark C, Clague A. Artifactual elevation of measured plasma L-lactate concentration in the presence of glycolate. *Crit Care Med.* 1999;27(10):2177–9.
375. Brindley PG, Butler MS, Cembrowski G, Brindley DN. Falsely elevated point-of-care lactate measurement after ingestion of ethylene glycol. *CMAJ.* 2007;176(8):1097–9.
376. Hopper K, Epstein SE. Falsely increased plasma lactate concentration due to ethylene glycol poisoning in 2 dogs. *J Vet Emerg Crit Care.* 2013;23(1):63–7.
377. McMichael MA, Lees GE, Hennessey J. Serial plasma lactate concentrations in 68 puppies aged 4 to 80 days. *J Vet Emerg Crit Care.* 2005;15(1):17–21.
378. Tas O, De Rooster H, Baert E, Doom MH, Duchateau L. The accuracy of the Lactate Pro hand-held analyser to determine blood lactate in healthy dogs. *J Small Anim Pract.* 2008;49(10):504–8.
379. Stevenson CK, Kidney BA, Duke T, Snead ECR, Jackson ML. Evaluation of the Accutrend for lactate measurement in dogs. *Vet Clin Pathol.* 2007;36(3):261–6.
380. Lagutchik MS, Ogilvie GK, Hackett TB. Increased lactate concentrations in III and injured dogs. *J Vet Emerg Crit Care.* 1998;8(2):117–27.

381. Evans GO. Plasma lactate measurements in healthy beagle dogs. *Am J Vet Res.* 1987;48(1):131–2.
382. Tynan B, Kerl ME, Jackson ML, Mann FA. Plasma lactate concentrations and comparison of two point-of-care lactate analyzers to a laboratory analyzer in a population of healthy cats. *J Vet Emerg Crit Care.* 2015;25(4):521–7.
383. Moviat M, van den Boogaard M, Intven F, van der Voort P, van der Hoeven H, Pickkers P. Stewart analysis of apparently normal acid-base state in the critically ill. *J Crit Care.* 2013;28(6):1048–54.
384. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJC, Libório AB, et al. Metabolic acidosis in patients with severe sepsis and septic shock: A longitudinal quantitative study. *Crit Care Med.* 2009;37(10):2733–9.
385. Ewaschuk JB, Zello GA, Naylor JM, Brocks DR. Metabolic acidosis: separation methods and biological relevance of organic acids and lactic acid enantiomers. *J Chromatogr B.* 2002;781(1):39–56.
386. Angell JW, Jones GL, Voigt K, Grove-White DH. Successful correction of D-lactic acid neurotoxicity (drunken lamb syndrome) by bolus administration of oral sodium bicarbonate. *Vet Rec.* 2013;173(8):193–3.
387. Lorenz I, Hartmann I, Gentile A. Determination of D-lactate in calf serum samples – an automated enzymatic assay. *Comp Clin Path.* 2003;12(3):169–71.

Figure Legends:

Figure 1: Lactate ion and lactic acid

Lactate Ion

Lactic Acid

Figure 2: L-lactate and D-lactate

L - Lactate

D - Lactate

Figure 3: The 11 Steps of Glycolysis

Figure 4: Lactate to pyruvate catalyzed by lactate dehydrogenase

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

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

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

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.

Type A	Type B

Relative	Absolute	B1: Disease	B2: Drugs/Toxins		B3: Congenital
Exercise ^{§,+}	Hypoperfusion ^{§,+}	Malignancy ^{∞,§,*}	Glucocorticoids ^{∞,§,+}	Epinephrine ^{∞,§,+}	MELAS [*]
Muscle tremors [§]	Severe anemia [§]	Diabetes Mellitus ^{∞,§,*}	Acetylcholinesterase inhibitors [§]	Acetaminophen ^{∞,§,*}	Mitochondrial myopathy [*]
Shivering [§]	Severe hypoxemia [§]	Hepatic failure ^{∞,§}	Fructose [∞]	Salicylates ^{∞,§,†,*}	PDH deficiency [§]
Seizures [§]	Carbon monoxide [§]	Thiamine deficiency ^{§,†}	Xylitol [∞]	β-agonists ^{∞,§,+}	
Struggling ^{§,+}		Hyperthyroidism ^{∞,§}	Sorbitol [∞]	Cocaine ^{§,∞,+}	
		Microcirculatory dysfunction [§]	Glucose [∞]	Methylxanthines ^{∞,+}	
		Cytopathic hypoxia ^{∞,§,*}	Strychnine [§]	Cyanide [*]	
		Impaired gluconeogenesis [✧]	Biguanides [*]	Nitroprusside [*]	
		Alkalosis [∞]	Linezolid [*]	Ethylene glycol ^{§,†,#}	
		SIRS/Sepsis ^{§,§,+,*}	Isoniazid [§]	Methanol ^{§,*,#}	
		Pheochromocytoma ^{∞,+}	NRTI's [*]	Propylene glycol [✧]	
			Lactulose [✧]	Ethanol [#]	
			5-Fluorouracil [†]	Propofol [*]	
Miscellaneous: D-lactic acidosis [✧]					

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Title:

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

Date:

2018-03-01

Citation:

Rosenstein, P. G., Tennent-Brown, B. S. & Hughes, D. (2018). Clinical use of plasma lactate concentration. Part 1: Physiology, pathophysiology, and measurement. JOURNAL OF VETERINARY EMERGENCY AND CRITICAL CARE, 28 (2), pp.85-105. <https://doi.org/10.1111/vec.12708>.

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