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Topical Review

Point of Care Measurement of Lactate

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Lactate is generated as a consequence of anaerobic glycolysis by all tissues of the body. Increased L-lactate, the isoform produced by most mammals, reflects increased anaerobic metabolism secondary to tissue hypoperfusion or tissue hypoxia in most clinical situations, and is called type A lactic acidosis. The utility of lactate measurement and serial lactate monitoring in veterinary patients has been demonstrated in multiple studies. Blood lactate concentration is significantly elevated in many disease processes including septic peritonitis, immune-mediated hemolytic anemia, Babesiosis, trauma, gastric dilation and volvulus, and intracranial disease. Lactate clearance can be used to assess response to fluid therapy, cardiovascular therapeutics, and blood product transfusion in patients affected by type A lactic acidosis. Lactate concentration in peritoneal, pericardial, and synovial fluid can also be used as a diagnostic tool. Point of care analyzers such as the Lactate Pro, Lactate Scout, Accutrend, iSTAT, and Lactate Plus have been shown to be accurate lactate measurement instruments in small animal patients.

Lactate Physiology

Lactate exists in 2 optical isoforms, L-lactate and D-lactate. D-lactate can only be produced by bacteria and is not common in monogastric animals.[1] D-lactic acidosis resulting from carbohydrate malabsorption and subsequent overgrowth of D-lactate producing bacteria has been rarely reported in cats with severe gastrointestinal disease.[2] L-lactate is the isomer produced by mammals and is the most important isomer affecting small animal patients.[1] Excess L-lactate almost always represents increased anaerobic metabolism due to tissue hypoperfusion. It is the only isoform measured by commercially available point of care (POC) analyzers.[1,3] This article reviews normal lactate metabolism, the clinical use of assessing L-lactate in dogs and cats, and several commercial POC monitors available to measure this important biomarker.

Lactate Production

Glycolysis is the first step in the metabolic pathway that breaks down glucose to produce energy in the form of adenosine triphosphate (ATP). Glycolysis takes place in the cytosol of cells and does not require the presence of oxygen. During glycolysis the breakdown of 1 mole of glucose generates 2 mole of ATP, 2 mole of reduced nicotinamide adenine dinucleotide (NADH), and 2 mole of pyruvate. In the presence of oxygen, pyruvate diffuses into the mitochondria where it is converted to acetyl-CoA and participates in the Kreb's cycle and ultimately oxidative phosphorylation. Under normal aerobic conditions, the breakdown of a single mole of glucose can generate a net total of 36 ATP, in addition to carbon dioxide and water.

In the absence of oxygen, both the Kreb's cycle and oxidative phosphorylation are inaccessible. Glycolysis continues to supply the cell with ATP, and because of pyruvate, protons, and NADH accumulate. The transformation of pyruvate to lactate by the enzyme lactate dehydrogenase provides the cell with a mechanism for the conversion of NADH to oxidized nicotinamide adenine dinucleotide (NAD+). This is essential as NAD+ is a necessary substrate for glycolysis and without it glycolysis would cease. Under normal aerobic conditions, small amounts of lactate are produced by erythrocytes, skeletal muscle, brain, and the renal medulla.[3,4] Under anaerobic conditions and in states in which the ratio of NADH to NAD+ is increased, the production of lactate exceeds normal clearance and accumulates.

Lactate Clearance

Lactate is freely filtered at the glomerulus, but is almost completely reabsorbed in the proximal tubule. Under normal conditions, less than 2% is excreted in the urine. Most lactate is cleared from blood by the liver; however, the kidneys and skeletal muscles also contribute to its removal.[3] Lactate may be cleared by oxidation via the Kreb's cycle or by gluconeogenesis via the Cori cycle.[3,5] When the lactate produced in 1 tissue, such as skeletal muscle or red blood cells, is converted back to glucose by another tissue such as the liver or kidneys, it is termed the Cori cycle. This is an energy consuming process and unlikely to occur in low energy states. The ability of the liver to clear lactate is concentration-dependent and progressively decreases as the concentration of blood lactate increases. Hepatic clearance is also impaired by acidosis, hypoperfusion, and hypoxia.[6] Hyperlactatemia, severe acidemia, and hepatic hypoxia all contribute to converting the liver from a net lactate consumer to a net lactate producer.[7]

Lactic Acidosis

Lactic acidosis is defined as an increase in the blood lactate concentration in association with academia.[6] The most frequent cause of lactic acidosis is poor tissue perfusion. When oxidative

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metabolism is impaired, ATP formation continues via anaerobic glycolysis resulting in increased production of lactate. There is no net production of hydrogen ions in this process, and therefore no production of acid. When cells hydrolyze ATP for energy, protons are released; as lactate is consumed, an equal number of protons is removed. When consumption equals production the internal acid-base balance is maintained.[7] Disruption of this balance signifies an increase in production, decrease in clearance, or a combination of both.

Classification of Lactic Acidosis by Etiology

There are many etiologies for lactic acidosis and its clinical and prognostic importance varies accordingly. Lactic acidosis is classified by its pathogenesis as either type A or type B. Type A occurs as a consequence of decreased oxygen delivery as might result from systemic hypoperfusion (shock, systemic inflammatory response syndrome [SIRS], and sepsis), local hypoperfusion (arterial thromboembolism, tourniquet placement, burns, and organ torsion and necrosis), impaired hemoglobin oxygen carrying capacity (carboxyhemoglobinemia and methemoglobinemia), severe, acute euvolemic anemia (hemoglobin level < 5 g/dL), severe hypoxemia (PaO2 $<$ 30 mm Hg), and increased oxygen demands (exercise, seizures, shivering, trembling, and tremors).[1,3,6-8]

Type B lactic acidosis occurs secondary to drugs, toxins, and pathological conditions that alter mitochondrial function or carbohydrate metabolism.[1] It can be divided into 3 subcategories. Type B1 lactic acidosis occurs secondary to a disease process associated with reduced lactate clearance during conditions of adequate oxygen delivery. Examples of type B1 lactic acidosis include severe liver disease, malignancy, sepsis, diabetes mellitus, thiamine deficiency, and kidney injury.[1,9] Type B2 lactic acidosis occurs secondary to exposure to drugs and toxins that act as inhibitors of oxidative phosphorylation. For example, propylene glycol, an additive found in activated charcoal and other drugs, can result in increased plasma lactate concentrations when administered at clinically relevant doses, and prednisone, used at anti-inflammatory and immunosuppressive doses, has been reported to lead to increased plasma lactate concentrations in normal dogs.[10,11] Type B3 lactic acidosis refers to inborn metabolic defects that primarily involve abnormal mitochondrial function.[1,3,6,8] Insufficient pyruvate dehydrogenase has been reported in the Sussex spaniel and mitochondrial myopathies in the Jack Russell terrier, German shepherd, and old English sheepdog.[12-15]

The most common cause of elevated plasma lactate concentrations in patients with hemodynamic disturbances is likely type A lactic acidosis; however, patients may be affected by a combination of both types.[3,9] For example, septic patients show evidence of hypoperfusion secondary to macrocirculatory and microcirculatory dysfunction (type A) as well as impaired lactate clearance and abnormal mitochondrial function (type B).[3,8,16] Carbon monoxide, in addition to decreasing oxygen transport (type A), interferes with oxidative phosphorylation (type B).[7] It seems likely that the exact pathogenesis of lactic acidosis in assorted disease states is multifactorial, disease specific, and patient specific. The possibility of a multifactorial etiology must be considered in any patient with an elevated plasma lactate concentration.

Lactate Reference Intervals and Sampling Techniques

Plasma lactate concentration intervals as measured by laboratory reference instruments have been reported in healthy cats and dogs.[17-19] The first study reported a mean lactate concentration in frozen plasma of 12 healthy adult cats as 1.6 $\pm$ 1 mmol/L with a reference interval of 0.5-2.2 mmol/L.[17] The second reported a mean lactate concentration in frozen plasma of 0.77 $\pm$ 0.01 mmol/L and a reference interval of 0.3-1.69 mmol/L in 20 cats of varying ages (estimate age of 9 months to 10 years).[18] A prospective study in healthy Beagle dogs aged 5-9 months established a reference interval of 0.42-3.58 mmol/L.[19]

Though blood sampling technique and sample handling can increase plasma lactate concentration, differences detected between various venous and arterial sampling sites are not clinically relevant.[20,21] However, measurement of lactate in capillary blood is not a reliable alternative when compared with jugular venous blood samples in dogs.[22] Vascular occlusion and patient restraint can be associated with mild elevations whereas patient trembling or excessive struggling can be more significant, resulting in moderate elevations.[3,18,23] Ideally when measuring lactate, blood should be processed immediately following sampling, especially when using POC instruments.[6] Whole blood samples for POC devices should be collected into lithium heparin or sodium fluoride, which is an inhibitor of in vitro glycolysis.[3,6,16] Typically, the package insert for the specific device would contain detailed information on the preferred sampling technique and handling method.

Clinical Utility of Lactate

Plasma lactate concentration has shown potential utility as a biomarker indicating severity of disease as well as response to treatment in many disease states in dogs and cats, including shock, infectious disease, immune-mediated hemolytic anemia, gastric dilatation and volvulus, and intracranial disease. In addition, measurement of lactate in cavitary effusions may provide useful adjunctive diagnostic information in a number of diseases. As with all biomarkers, lactate has little diagnostic and prognostic value when used in isolation, but as an adjunct to other disease-specific diagnostics and physical examination parameters, lactate can provide valuable additional information to the veterinary clinician managing patients with a wide variety of diseases. This section would review the veterinary literature on the clinical utility of lactate.

Shock and Resuscitation

Many companion animal studies have documented a significant association between high-blood lactate concentration at the time of admission and poor patient outcome in patients with shock.[24-38] In a retrospective study, evaluating lactate concentration in 67 critically ill dogs with systemic hypotension, dogs with plasma lactate concentrations < 2.0 mmol/L had significantly higher systolic blood pressure and were 3.23 (95% CI: 1.04-9.43) times as likely to survive, when compared with hypotensive dogs with a lactate > 2.0 mmol/L.[24] A prospective study of 80 systemically ill dogs requiring intravenous fluid therapy found that an initial lactate concentration above the reference interval (2.3 mmol/L) did not affect patient outcome.[34] However, dogs with lactate concentrations > 2.3 mmol/L 6 hours after initiation of fluid therapy were 16 times more likely to not survive when compared with dogs with lactate concentrations < 2.3 mmol/L (95% CI: 2.32-112.71 times, $P < 0.01$). Also, hyperlactatemia that did not improve by 50% within 6 hours was significantly associated with mortality ($P = 0.024$). Another study evaluated lactate concentration in 102 cats admitted to intensive care for intravenous fluid therapy.[37] Cats with an admission blood lactate > 4.0 mmol/L had increased duration of hospitalization ($P = 0.0450$) and a significantly decreased survival to discharge ($P = 0.0429$) compared to cats with normal lactate on admission. When a subset of 27 cats that had serial lactate measurements