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Topical Review

Plasma Lactate Concentration as a Prognostic Biomarker in Dogs With Gastric Dilation and Volvulus

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Initial and serial plasma lactate concentrations can be used to guide decision making in individual dogs with GDV but care is necessary in phrasing conversations with owners. Published data suggests that survival is more likely and the chance of complications less in dogs with an initial plasma lactate of <4 mmol/L. An initial lactate >6 mmol/L makes gastric necrosis and greater expense more likely. However, because of the overlap between groups and the good overall survival rates, exploratory laparotomy should always be recommended irrespective of the plasma lactate concentration. Falls in plasma lactate of greater than ~40% after fluid resuscitation are likely to indicate better survival. If the initial plasma lactate concentration is moderately to severely increased (5- > 10 mmol/L) and a sustained increase in plasma lactate occurs after fluid resuscitation, the cause should be aggressively pursued. Many dogs with persistent hyperlactatemia over 24-48 hours do not survive.

Introduction

Gastric dilation and volvulus (GDV) is an acute condition of dogs characterized by dilation of the stomach and rotation on its mesenteric axis. Affected dogs may suffer from circulatory shock, and a proportion of dogs develop gastric necrosis. Reported mortality rates for GDV vary between 10% and 33%.[1-6] Biomarkers, such as plasma lactate concentration, can help guide prognostication. Understanding lactate physiology and how GDV may cause hyperlactatemia is important, but knowing how to apply the results of studies of prognostic indicators to individual animals is vital so that reasonable and proportionate prognostic information can be provided to pet owners. A low lactate concentration is associated with a high survival rate, whereas more dogs with a higher lactate concentration die; however, there are exceptions in both cases. Hence, advice to owners about their individual pets based on initial lactate concentration should be offered carefully. Based on the published literature, the authors suggest that it is reasonable to inform owners of dogs with GDV and a lactate concentration of 6 mmol/L or above that there is a higher chance of gastric necrosis and other complications and that their hospital stay may be more costly but to be no more definitive than that. If the initial lactate concentration is within reference range or only mildly increased (2-4 mmol/L), then it is appropriate to say that complications are less likely but still possible. If plasma lactate concentration does not fall within the reference range in 24-48 hours, the clinician should aggressively pursue the underlying reason because survival rates are poor in many cases with prolonged hyperlactatemia.

Lactate Biochemistry and Physiology

Glycolysis, which occurs in both the presence and absence of oxygen, takes place in the cytoplasm, converts glucose into pyruvate, and produces 2 moles of adenosine triphosphate (ATP) per moles of glucose. Glycolysis also requires NAD^+ which is converted into NADH. When sufficient oxygen is available, pyruvate enters the mitochondria and is used in the tricarboxylic acid cycle and oxidative phosphorylation to produce 36 moles of ATP and regenerate NADH back to NAD^+ thereby allowing glycolysis to continue.[7] Alternatively, pyruvate can be converted into lactate in the cytosol which also consumes H^+ and regenerates NAD^+. The main physiological role of lactate production is to allow glycolysis and cellular energy (ATP) production to continue when cellular energy demands exceed the capacity of aerobic mitochondrial energy production. Although glycolysis produces less ATP on a molar basis than oxidative phosphorylation, it is much faster which allows it to temporarily meet cellular energy requirements.

When ATP is converted to adenosine diphosphate (hydrolyzed) to release energy, H^+ is also produced. If sufficient oxygen is available, this H^+ passes into mitochondria to maintain the proton

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gradient required for the electron transport chain and oxidative phosphorylation. But when cellular oxygen supply is inadequate, H^+ ions accumulate in the cytosol. Lactate production from pyruvate minimizes this by consuming H^+. Importantly, lactate is formed as the lactate ion without a concurrent H^+ ion. Lactate can then be cotransported out of the cell with an H^+ ion by the monocarboxylate transporter thereby further limiting intracellular acidosis. Hence, lactate production does not cause acidosis, it protects against it. Nevertheless, when ATP made from glycolysis is used to release energy, an H^+ ion is also generated so there is a 1:1 ratio of H^+ and lactate production but they are formed by different processes. That is, hyperlactatemia is directly proportional to H^+ but not the cause of the increase. Lactate is also protective because it can be the preferred metabolic fuel for vital tissues such as the brain[7] and heart[8] and the only fuel for red blood cells which lack mitochondria.

Hyperlactatemia

Hyperlactatemia occurs whenever the rate of lactate production exceeds that of lactate metabolism and clearance and has been categorized into types A and B.[9,10] Type A hyperlactatemia is the most common in emergency and critical care practice and occurs with clinical evidence of a relative or absolute tissue oxygen deficiency. A *relative* deficiency is usually due to increased muscle activity, for example, exercise, struggling, shivering, trembling, tremors, and seizures.[10-12] Exercise-related hyperlactatemia has been reported to range from 4.5 mmol/L in dogs following agility testing[13] to greater than 30 mmol/L in racing Greyhounds.[14,15] Physiological hyperlactatemia should resolve when muscle activity stops with an half-life of 30-60 minutes.[13,14,16] If appropriate resolution does not occur in a clinical patient, a concurrent disease process is likely. An *absolute* tissue oxygen deficiency is usually due to global hypoperfusion (shock) which may be hypovolemic, obstructive, maldistributive, or cardiogenic in origin or a combination thereof. The reference range for plasma lactate concentration measured in 60 conscious dogs was 0.3-2.5 mmol/L[17] but because these dogs underwent repeated sampling, it is likely that some had slightly increased concentrations owing to increased muscle activity. Using an upper limit of 2.0 mmol/L is probably more appropriate in dogs with little muscle activity. Type B hyperlactatemia occurs in the absence of clinical evidence of decreased oxygen delivery and has been subclassified into type B_1 associated with underlying disease (in particular, sepsis and systemic inflammatory response syndrome [SIRS], B_2 with drugs or toxins, and B_3 with congenital or hereditary metabolic defects).[10]

Hyperlactatemia With GDV

Most dogs with GDV have type A hyperlactatemia owing to variable degrees of global hypoperfusion. Most are hypovolemic owing to intragastric fluid sequestration and hemorrhage in dogs with torn gastric vessels. They also have a variable obstructive component owing to reduced venous return because of compression of major intra-abdominal veins such as the caudal vena cava and portal vein by the dilated stomach.[18]

Some may also have maldistributive shock and type B_1 hyperlactatemia owing to sepsis, septic shock, and SIRS. Many underlying mechanisms have been suggested for type B_1 hyperlactatemia associated with SIRS and sepsis including skeletal muscle Na^+-K^+-adenosine triphosphatase upregulation,[19] mitochondrial dysfunction, cytochrome inhibition,[20] increased hepatic lactate production, reduced hepatic lactate extraction,[21] impaired tissue oxygen extraction,[22] and capillary shunting.[22] Other possible mechanisms include reduced erythrocyte flexibility, increased leukocyte activation, altered neurohormonal control of endothelial smooth muscle, enhanced nitric oxide production, and pyruvate dehydrogenase inhibition.[23,24]

Other events during GDV may contribute to hyperlactatemia. Ischemic tissue within the gastric wall and spleen will produce lactate. Whether this lactate enters the systemic circulation depends on the remaining blood flow. With complete cessation of blood flow, there will be no lactate washout. But low flow or intermittent flow (perhaps from intermittent rotation and derotation of the stomach) will wash lactate from ischemic tissue into the circulating blood volume. Decompression of the stomach via trocarization or orogastric intubation may also allow blood flow and lactate release into the systemic circulation. Gastric necrosis and intestinal ischemia might allow bacterial translocation and bacteremia, leading to sepsis, septic shock, and SIRS. Additionally, dogs with GDV commonly experience cardiac arrhythmias and may have myocardial depression.[25,26]

Plasma Lactate Concentration as a Prognostic Indicator

With the increasing realization of its clinical utility and availability of point-of-care lactate analyzers, the measurement of lactate has become more mainstream in veterinary medicine over the past decade. Its prognostic value was recognized in human medicine almost 50 years ago,[1] and there are a multitude of clinical and experimental studies documenting its clinical and prognostic utility. Over the years, these have ranged the full gamut of investigations from simple, retrospective, observational studies to prospective, randomized trials of its use to guide therapy.

Studies in people have shown prognostic value in trauma,[27] sepsis,[28] septic shock,[28] SIRS,[28] cardiac arrest,[28] carbon monoxide toxicity,[29] head trauma,[28] malaria,[28] and liver failure.[9] Its use is now recommended in the consensus guidelines for sepsis.[30] The addition of treatment targeted toward lactate clearance to the Surviving Sepsis Campaign resuscitation bundle reduced mortality risk 2-fold in people with severe sepsis.

In addition to dogs with GDV, some degree of prognostic utility has been reported for ill and injured dogs in a veterinary intensive care unit,[31] systemically ill dogs receiving fluid therapy,[32] and dogs with SIRS,[33] immune mediated hemolytic anemia,[34] severe soft tissue infections,[35] heartworm-associated caval syndrome,[36] babesiosis,[37,38] and abdominal evisceration.[39] Lactate has also been demonstrated to have some limited prognostic value in cats with hypertrophic cardiomyopathy[40] and with septic peritonitis.[41,42] The Acute Patient Physiologic and Laboratory Evaluation for dogs and cats found lactate to be one of the most significant variables associated with mortality and included lactate in both the full and fast scoring systems for both species.[43,44] Despite a wealth of evidence supporting its overall value, the difficulty remains in how we, as clinicians, apply these data to our individual clinical cases.

Most veterinary studies show that the *population* of animals that die has a higher average lactate concentration than the *population* of animals that survive. Yet, *some* animals that survive may have very high lactate concentrations and *some* that die may have mildly increased or even reference range concentrations. This may seem contradictory, but the simple explanation is that, in general, the magnitude of the increase in lactate reflects the severity of lactate production (usually tissue hypoxia) not its reversibility. Whether the individual animal dies or survives depends on the underlying disease process that is associated with a concurrent hyperlactatemia.

Consider a dog with simple, uncomplicated, peracute hemorrhage that can be easily stopped and treated such as an acute, appendicular arterial laceration. In this instance, the maximum