Appropriate Clinical Use of Lactate Measurements

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Blood lactate measurements have a longstanding history in clinical medicine to assess both disease severity in critical illness and the response to therapeutic interventions. Lactic acid was first discovered in sour milk in 1780 by Swedish pharmacist Carl Wilhelm Scheele and identified in blood during shock by the German physician Johann Joseph Scherer in 1843.[1] Early studies, summarized by Schuster,[2] demonstrated the value of assessing lactate in critically ill patients. A meta-analysis of more than 150 reports on lactate concluded that lactate concentrations are important in risk stratification in critically ill patients and a potential endpoint for resuscitation.[3] Because lactate is a product of anaerobic metabolism, it is broadly considered as an indicator of tissue hypoxia. However, hyperlactatemia can occur without hypoxia such as in adrenergic states and due to the administration of $ß_2$-agonists.[4,5]

Numerous studies have shown that blood lactate has a positive correlation with both short- and long-term patient morbidity and mortality.[6,7] The measurement of lactate has received increasing attention in recent years with its establishment as the first core element of the Hour-1 Surviving Sepsis 2016 Campaign bundle of care. The campaign recommends guiding patient fluid resuscitation to the normalization of lactate concentrations.[8] However, since elevated lactate can originate from a variety of pathophysiologic processes in addition to sepsis, and the application of the test and its interpretation are often misused, it is essential to understand the mechanism of lactate production and the various physiologic causes of elevated serum lactate.

Lactate Production and Metabolism

In normal states of oxygenation, mitochondria efficiently generate adenosine triphosphate (ATP) for aerobic metabolism. In this process, glucose is converted by glycolysis to pyruvate that enters the Krebs (citric acid) cycle with acetyl-coenzyme A serving as the intermediary to unleash the chemical energy of molecular oxygen to generate the majority of cellular ATP during oxidative phosphorylation. When there is insufficient oxygen to power the Krebs cycle and oxidative phosphorylation, the pyruvate produced by glycolysis is instead shunted toward the production of lactate by the enzyme lactate dehydrogenase.

Lactate is produced in all cells to varying degrees: muscles (25%), skin (25%), brain (20%), intestines (10%), and erythrocytes (20%).[9] Mature erythrocytes lacking mitochondria generate lactate through ATP synthesis from glycolytic enzymes associated with the cell membrane. When erythrocytes are exposed to low PaO_2, a conformational change of hemoglobin to deoxyhemoglobin dislodges the glycolytic complex, activates phosphofructokinase, and accelerates ATP production.[10] ATP *via* purinergic receptors stimulates vasomotor responses that increase blood flow to tissues.[10] Lactate is a signal molecule in the brain to link neuronal activity, metabolism, substrate availability, and blood flow[11] and may be involved with short-term memory[12] and panic disorders.[13]

Most body lactate production is from skeletal muscles. Lactate is released from the tissues into circulation and metabolized in the liver (60%) and kidneys (30%) back to glucose *via* gluconeogenesis for reuse in the various organs in glycolysis (fig. 1).[9] It is directly filtered and reabsorbed by the kidney with only a small percentage lost to urine.[14] This cycle, known as the Cori cycle, generates ATP in times of stress at the tissue level *via* glycolysis but at the overall net body metabolic expense of ATP during hepatic and renal gluconeogenesis.

Lactate *versus* Lactic Acid

Lactate and lactic acid are often used interchangeably without an understanding of some clinical biochemical basics. Lactate as anion $[lactate]^-$ is a weak base formed directly by the conversion from pyruvate. $[Lactate]^-$ is a buffer that accepts some of the protons generated during the hydrolysis of ATP to adenosine diphosphate. In times of demand, glycolysis can occur at several orders of magnitude quicker than the Krebs cycle and oxidative phosphorylation.[15] When excess hydrogen ions are unable to be utilized by aerobic metabolism or neutralized by bicarbonate, lactate, and other body buffer systems, acidosis results. Hyperlactatemia is therefore mostly a *consequence* of cellular acidosis and *not a direct cause* of acidosis. When arterial pH falls below normal range and is concurrent with hyperlactatemia, it is commonly termed lactic acidosis. It is more appropriate to use a term such as sepsis- or drug-associated lactic acidosis.

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Fig. 1. Elements of the Cori cycle. In skeletal muscle, lactate is the product of conversion from pyruvate generated from glycolysis and converted to glucose by the liver in ATP-dependent processes. The kidney is responsible for 25 to 30% of lactate metabolism. The remaining small amount is metabolized by other organs or lost in the urine.

Clinical Reasons for Increased Lactate

The average adult produces 15 to 25 milliequivalents per kilogram per day of lactate, with serum concentrations in the range of 0.5 to 1.5 mM. In critical illness, less than 2 mM is generally accepted as normal.[16] Blood samples from central venous and arterial catheters have similar values.[17] Peripheral venous lactate is acceptable when lactate is normal, but correlation to arterial and central venous lactate is poor during hyperlactatemia.[18] Lactate can accumulate due to increased production, decreased utilization, or both. Accordingly, blood lactate can be elevated in a variety of conditions not associated with tissue hypoxia. The administration of lactated Ringer's solution, which contains 28 mM lactate, does not increase serum lactate. In a double-blind study, there was no significant difference in serum lactate between the administration of 30 ml/kg lactated Ringer's solution and normal saline.[19]

Lactic acidosis is categorized as type A when it is due to tissue hypoxia or systemic hypoperfusion and type B caused by other factors.[20] Type B1 is secondary to underlying disease, type B2 is associated with toxins or drugs, and type B3 is associated with inborn errors of metabolism.[21] Significant overlap can exist between types A and B lactic acidosis.

Type A Lactic Acidosis

Anaerobic glycolysis is usually increased in critical illness. Any generalized circulatory shock state (hypovolemic, cardiogenic, distributive, obstructive) can cause decreased perfusion of tissues that will lead to tissue hypoxia and type A lactic acidosis. Regional hypoperfusion is also a common driver of lactic acidosis such as with limb or individual organ ischemia secondary to arterial or venous thrombosis, compartment syndrome, trauma, burns, necrotizing soft tissue infections, rhabdomyolysis, or iatrogenic surgical clamping. Even when there is normal perfusion, blood oxygen content can be diminished, leading to a type A lactic acidosis. Causes of low blood oxygen content can be secondary to hypoxemia from respiratory failure, severe anemia, or carbon monoxide poisoning. However, the critical level below which hypoxemia elevates lactate is considerably low (P_aO_2 less than 35 mmHg).[22] For all these pathophysiologic states, hyperlactatemia will occur when the rate of lactate production is greater than the rate of lactate clearance by

the liver[23] and exceeds the 5- to 6-mM threshold of renal excretion.[9]

Skeletal muscle has the greatest capacity to generate lactate among body tissues and is reflected clinically in several ways. During intense heavy exercise, lactate can rise to 15 to 20mM as a normal physiologic response to meet energy needs. This rise is transient and rapidly cleared by the body.[24] Generalized tonic–clonic epileptic activity can create profoundly elevated lactate from unhinged anaerobic skeletal muscle contractions that should clear within 1 to 2 h of seizure cessation.[25] Any disorder with acute muscle rigidity including serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia will produce elevations in lactate by the same mechanism. Increased respiratory muscle work can also contribute to elevated lactate independent of the ability to oxygenate. Hyperlactatemia from severe shivering during hypothermia and from agitated patients resisting physical restraints has also been described.[26] Seizures from conducted energy weapons, e.g. TASER, cause a transient increase in lactate that is not considered clinically relevant.[27]

Type B Lactic Acidosis

Type B lactic acidosis occurs in the absence of evidence for inadequate tissue oxygen delivery. Although much less common than type A lactic acidosis, type B has a very broad differential diagnosis (fig. 2). Elevated lactate due to failure of clearance can be seen in both hepatic and renal dysfunction but will be more pronounced with cirrhosis and end-stage liver disease as the liver is the primary site of gluconeogenesis. Many inborn disorders of carbohydrate metabolism, glycogen storage, or mitochondrial dysfunction can cause elevations in lactate by downstream defects leading to the buildup of pyruvate. These rare congenital diseases are generally only seen in pediatric populations.

Other pathologic states also contribute to lactic acidosis based on where they interfere with the cellular metabolic cascade. During ethanol intoxication, as well methanol and propylene glycol poisoning, alcohol dehydrogenase generates nicotinamide adenine dinucleotide, which increases the nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide ratio, favoring the conversion of pyruvate to lactate to achieve equilibrium.[28] Thiamine deficiency that is also present with nutritional deficits of alcohol use also precipitates anaerobic metabolism, because it is a necessary cofactor for multiple metabolic enzymes involved in utilizing pyruvate, including pyruvate dehydrogenase. Cyanide toxicity decouples the electron transport chain in oxidative phosphorylation, leading to elevations in serum lactate.[29]

Many drugs have been implicated with lactic acidosis. The classical example is the commonly used antihyperglycemic metformin. Metformin rarely causes lactic acidosis, but it is often associated with lactic acidosis in the presence of other comorbidities.[27] Metformin reduces the uptake of lactate by the liver via several proposed mechanisms to reduce hepatic gluconeogenesis. It augments lactate production through increased glycolysis by impairment of mitochondrial complex 1, which maintains a proton gradient required for ATP production. High doses of metformin will reduce lactate uptake in the liver and increase production in the intestine and other organs.[28] Interestingly, a study of 37,000 intensive care unit patients showed a lower mortality in metformin users (35%) compared to nonusers (43%) for those with lactates of 5 to 10 mM.[30] Diabetes independently has been linked to lactic acidosis unrelated to metformin use. The antibiotic linezolid and several nucleoside reverse transcriptase inhibitor therapies to treat human immunodeficiency virus are associated with mitochondrial toxicity. Any drug overdose resulting in hepatic or renal impairment or excess sympathetic activity can lead to lactic acidosis. Malignancy-associated lactic acidosis is possible from increased anaerobic metabolism within tumor cells.

Plasma lactate concentrations are altered by actions on ß2 receptors. Epinephrine, when used for septic shock, increases lactate via an enhanced lactate/pyruvate ratio and decreased splanchnic blood flow.[4] Infusions of epinephrine into healthy volunteers during aerobic conditions increased lactate thought to be due to the direct effect of epinephrine on carbohydrate metabolism, termed aerobic glycolysis.[4] An earlier study showed that infusions of norepinephrine result in small increases in lactate within the range of normal, while dobutamine did not affect the lactate concentration.[31] In sepsis, increases in epinephrine doses caused linear increases in lactate, while there were decreases with dobutamine.[32,33] Inhaled ß-agonists administered for the treatment of asthma can cause hyperlactatemia, with some values exceeding 4 mM.[5]

Knowledge of the potential effects of propofol on lactate metabolism is essential for the anesthesiologist. The identification of the propofol infusion syndrome after high doses and/or prolonged administrations with associated hyperlactatemia created a plethora of case reports.[34] However, in a well-controlled investigation, after 8 h of spine surgery under total intravenous anesthesia with propofol, there was no increase in serum lactate compared to a 7% rise with a sevoflurane anesthetic.[35]

D-lactate is the stereoisomer of L-lactate and is produced by certain intestinal bacteria through the methylglyoxal pathway in the presence of large undigested carbohydrate loads or from ingested food such as cheese.[36] D-lactate comprises a small fraction of tissue lactate, and type D lactic acidosis is a specific disorder that can occur in patients with short bowel syndrome. Results of studies that used D-lactate as a marker for gut ischemia have had inconsistent results.[36] The level of D-lactate in the urine is elevated in diabetes and, in conjunction with microalbuminuria, may be an initial indicator of nephropathy.[37] D-lactate is not identified on typical laboratory assays for lactate but should be on the differential in patients with

Fig. 2. Type A lactic acidosis is caused by decreased oxygenation of tissues as demonstrated by the ischemic bowel and ultrasound image of cardiomyopathy. Type B lactic acidosis is caused by increased lactate product in oxygenated tissue through organ dysfunction, metabolic factors, and drug effects. In both types of lactic acidosis, as well as cirrhosis, the accumulated lactate overwhelms the liver's capacity to metabolize it to glucose. HIV, human immunodeficiency virus.

short bowel syndrome and unexplained anion-gap metabolic acidosis.[37]

Sepsis

Sepsis is a unique clinical entity that is associated with both type A and type B lactic acidosis. As a dysregulated host response to infection, sepsis and septic shock result in macrocirculatory, microcirculatory, and cellular-level derangements. Even after adequate fluid resuscitation, multiple mechanisms can contribute to the continued generation of lactate. Capillary endothelial damage may impair the ability of erythrocytes to unload oxygen even when the hemodynamics are normal or have been corrected. Animal studies have shown that lactate interferes with erythrocyte ATP production and release in response to low PaO_2.[10] This unresponsiveness with hyperlactatemia, exemplified in Plasmodium falciparum infections, may be partly responsible for the hypotension of septic shock.[10]

Hypotension due to myocardial dysfunction is common in sepsis. Extrapolation of exercise studies may provide some insight about myocardial metabolism in sepsis. During exercise, myocardial oxidation of glucose and lactate is increased.[38] Glucose uptake by the myocardium is increased with mild/moderate exercise but, in contrast, decreased during high-intensity exercise.[39] These findings suggests that other substrates, such as lactate, might contribute to cardiac energy metabolism.[39]

Sepsis and critical illness can result in an overall state of adrenergy from both endogenous catecholamine release and exogenous administration that will stimulate glycolysis. Lactate production increased during experimental endotoxic shock from β2-stimulation was related to elevations in endogenous epinephrine, suggesting that hyperlactatemia may be an adaptive mechanism.[40] It has been postulated that enzymatic (including pyruvate dehydrogenase) and cellular mitochondrial dysfunction in sepsis also result in an inability to use oxygen even when available.[41] In addition to directly limited renal and hepatic perfusion, the capacity of these organs to undergo gluconeogenesis becomes severely reduced with profound academia. Stable septic patients infused with lactate who developed hyperlactatemia compared to those without this response had a lower lactate clearance, suggesting that the increases were secondary to a defect in utilization.[42]

Guiding Therapy

A patient presenting with initial elevated lactate should undergo a careful diagnostic approach and treatment tailored to an underlying cause. The measurement of lactate has three purposes: diagnosis of severe sepsis, stimulus for the initiation of goal-directed therapy, and establishment of a baseline when elevated to determine the efficacy of treatment.[43] Treatment of type A lactic acidosis should focus on restoration of local or global tissue perfusion with the core

principles of volume resuscitation, hemodynamic support with vasoactive medications, and source control. When the initial diagnosis remains unclear, tissue hypoperfusion can be assumed until proven otherwise. Disorders of type B lactic acidosis will generally require treatment by removal of an offending agent or correction of a primary metabolic deficit when possible. Often the origin of elevated serum lactate is difficult to determine.

Classic studies demonstrated that elevations in lactate portend poor outcomes and are associated with increased mortality.[43,44] By far the greatest emphasis on the utility of lactate has been in early identification and treatment of sepsis. The main tenets of the Hour-1 Surviving Sepsis 2016 Campaign in patients with suspected sepsis include measurement of initial lactate level, remeasurement within 2 to 4 h if it is greater than 2 mM, and rapid administration of 30 ml/kg crystalloid for hypotension or lactate greater than or equal to 4 mM.[45] Several randomized controlled trials demonstrate significant reduction in mortality with early lactate-guided resuscitation.[46]

After initial guideline-directed volume resuscitation, judicious continual reassessment of patient volume status is necessary to prevent fluid overload.[47] Mortality increases 2.3% for each additional liter of fluid administered above a 5-l resuscitation.[48] Failure to clear lactate should prompt the clinician to rebroaden the differential diagnosis for occult sources of elevation.

Using Lactate to Guide Therapy

Tissue perfusion is the balance between oxygen delivery and oxygen consumption. The traditional wisdom is that mixed venous oxygenation (sampled from the pulmonary artery) and lactate have a reciprocal relationship, but this is a fallacy. Initial proponents of goal-directed therapy focused on the use of mixed venous oxygen saturation from a central vein as the endpoint of resuscitation for sepsis.[49] In a study of more than 2,000 patients, lactate and mixed venous oxygen saturation from a central vein had poor correlation for patients with mixed venous oxygen saturation from a central vein less than or equal to 65%, normal kidney and liver function, and septic shock.[50] Similarly, for 79% of patients, there was no relationship between lactate clearance and mixed venous oxygen saturation from a central vein using mixed venous oxygen saturation from a central vein greater than or equal to 70% in the first 6 h of resuscitation.[51] When peripheral perfusion-targeted resuscitation was compared to changes in lactate, there was no difference in mortality seen.[52] In cardiogenic shock, the lactate/pyruvate ratio is high. When these patients are stabilized, the lactate/pyruvate ratio is only slightly elevated, suggesting that it is not superior to that of a lactate level.[9] In septic shock patients treated with catecholamines, hyperlactatemia with an elevated lactate/pyruvate ratio is more correlated with prognosis of multisystem organ failure and death.[53]

The assessment of lactate clearance is an important indicator of mortality as assessed in multicenter studies. After lactate-guided fluid resuscitation, the mortality for sepsis was 19% of the patients who cleared lactate in contrast to 60% who did not.[51] In a similar study, the goal was the reduction of lactate by greater than or equal to 20% for the initial 2 h of treatment compared to the control group that was blinded to postadmission lactate values. Although the lactate group received more fluids and vasodilators, there were no significant differences between the groups, but hospital mortality was lower in the lactate group.[54]

Additional Considerations

Lactate increases in the critically ill reflect more than just tissue hypoxia. Even in the presence of oxygen, cellular mitochondria are unable to process all the pyruvate presented to them, resulting in hyperlactatemia. Consequently, supranormal delivery of oxygen by increasing fraction of oxygen delivered is an ineffective therapy. The desire to return to a normal level of homeostasis has led many to suggest bicarbonate administration to neutralize lactic acidosis. Unfortunately, outside of a possible benefit in select populations such as those with renal failure[55] or right ventricular dysfunction,[56] studies to date have not consistently demonstrated effectiveness, and some even suggest harm.[57]

Vitamin C, corticosteroids, and thiamine have been proposed as therapeutic agents for sepsis.[58] Thiamine is an essential cofactor in aerobic metabolism for multiple enzymatic reactions, including pyruvate dehydrogenase within the Krebs cycle and the pentose-phosphate pathway for the regeneration of nicotinamide adenine diphosphate. It is tempting to speculate that the replenishment of thiamine deficiency due to increased mitochondrial stress in sepsis may lessen hyperlactatemia. Patients in septic shock who received thiamine within the first 24 h of admission had improved lactate clearance and a reduction in 28-day mortality.[59] Recent trials failed to show benefits. A blind, randomized control study was based on a 28-day mortality, but the initial lactate (1.6 to 3.2 mM) was not as elevated as clinicians commonly see in severe sepsis.[60] An open-label, multicenter study showed no mortality benefit or vasopressor reduction (calculated as the sum of norepinephrine doses and converted doses of epinephrine and vasopressin) at 7 days.[61] Baseline thiamine levels were not obtained in either report.

Conclusions

Increased blood lactate serves as a marker of metabolic derangement from a multitude of clinical etiologies. The approach to the patient with initial lactate elevation should focus on early identification of source to tailor treatment accordingly. Restoration of tissue perfusion is paramount. Lactate levels are strongly predictive of patient outcomes, but the relationship with fluid resuscitation is less

pronounced. Intravenous fluid boluses are not benign, and persistent hyperlactatemia warrants reevaluation for proper source control and consideration of alternative therapeutic interventions.

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Competing Interests

Dr. Pino reports financial relationships with CRICO (Boston, Massachusetts) and Morrison Mahoney (Boston, Massachusetts; expert legal testimony) and with Genentech/Roche (South San Francisco, California; stock options from spouse). The other author declares no competing interests.

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