REVIEW

Using lactate to detect occult hypoperfusion in sepsis

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Sepsis mortality remains high despite new innovations in care. For over 50 years research has focused on lactate as a potential marker of sepsis severity and predictor of outcome. Lactate has a complex metabolism influenced by many intracellular and extracellular factors. Elevated lactate has been shown to convincingly predict increased mortality risk. In addition to high initial lactate level, ineffective lactate clearance predicts worse outcome including organ failure and increased mortality.

Historically, only arterial lactate measurement was thought to be accurate. Recent studies have shown no significant difference in arterial versus venous lactate levels. There has also been debate over the validity of lactate measurement in whole blood versus plasma. Thus far, lower lactate levels (< 6 mmol/L) correlate adequately. The introduction of an enzymatic, substrate-specific electrode method of analysis enables the use of whole blood samples, resulting in a turnaround time of only a few minutes, as opposed to hours, and has transferred testing from the laboratory to the bedside. More recently, lactate measurement has been proposed and validated as a marker of quality of care as part of the Sepsis Resuscitation Bundle. Therefore, early lactate measurement should be considered in most patients with clinically suspected sepsis.

Sepsis commonly prompts admission of patients to the intensive care unit (ICU). Though it is difficult to precisely delineate the true costs of this disease, researchers have estimated that expenditures within the United States for sepsis treatment are at least $16 billion annually.[1] Additionally, sepsis mortality remains high despite new innovations in care, including early goal-directed therapy and drotrecogin alfa. Thus, recent research continues to focus on therapies that improve outcomes and also on disease markers that might guide such therapies. For over 50 years, sepsis research has focused on lactate as a potential marker of disease severity and predictor of outcome.[2] Initial lactate studies elucidated its basic science, what factors modified it and whether lactate was a true indicator of tissue hypoxia.[2] Decades of research have shown that many exogenous and endogenous factors affect lactate levels. Despite this complex metabolism, lactate has proven itself to be an effective and straightforward marker of sepsis severity. Even in patients with normal blood pressure, an elevated lactate predicts a markedly increased risk of mortality – the syndrome sometimes referred to as 'occult hypoperfusion' or 'cryptic shock'. Lactate's utility in predicting increased mortality has been established by measuring both initial lactate concentration and its clearance during treatment. Thus, further improvements in sepsis management may be gained by incorporating these findings into standard practice and future research.

WHERE DOES LACTATE COME FROM? UNDERSTANDING METABOLISM TO AVOID COMMON MISPERCEPTIONS

Many intracellular and extracellular factors influence lactate metabolism. A common perception is that lactate is simply the end product of anaerobic metabolism. With this understanding, lactate levels may be mistakenly interpreted as synonymous with oxygen debt. This assumption, however, oversimplifies lactate's complex metabolism. Rather, lactate levels are influenced by a multitude of variables including perfusion, mitochondrial function, and effective clearance from the body. Any disruption to any of these three factors may lead to increased lactate levels despite adequate oxygenation.

Perfusion is the initial step in lactate creation. This process is responsible for delivery of oxygen and glucose to the cells. Under aerobic conditions, glucose is converted to ATP (adenosine triphosphate) via the Krebs cycle. When metabolism is anaerobic, however, pyruvate enters the glycolytic (Emben-Meyerhof) pathway forming lactate and ATP as end products. Hypoxia of any aetiology shifts the body towards anaerobic metabolism. Besides low arterial oxygen content, a similar effect is seen with poor perfusion secondary to blood loss or vasodilation.[3] States in which oxygen cannot be successfully unloaded from red blood cells cause similar metabolic changes.

Intracellularly, the mitochondria serve as the location for metabolism. Under aerobic conditions, pyruvate dehydrogenase facilitates ATP creation. If, however, pyruvate dehydrogenase is dysfunctional or inactivated, lactate may be produced despite adequate oxygenation.[3] Additionally, there may be increased lactate without hypoxia if the mitochondria's metabolic demand exceeds its oxidative capacity. This modest increase was reported nearly 30 years ago in a septic patient during respiratory alkalosis.[4] In this, the anaerobic pathway serves as a reserve system for overwhelmed aerobic metabolism.

In addition to pyruvate dehydrogenase abnormalities, lactate levels are affected by many other disruptions in mitochondrial structure or function. Nitric oxide, TNF and endotoxin directly impair oxidative metabolism, thereby increasing lactate.[5] Medications are also commonly implicated in this disruption, and thus may result in hyperlactataemia that is usually asymptomatic.

Many medications alter lactate levels. Two ICU-specific medications are particularly notable. Nitroprusside is converted to cyanide and increases lactate levels by directly causing mitochondrial dysfunction. Epinephrine has a dual effect. First, epinephrine preferentially constricts the splanchnic vasculature, causing regional hypoperfusion and hypoxia leading to increased localised anaerobic metabolism.[6] Additionally, epinephrine accelerates aerobic glycolysis, increasing the concentration of pyruvate as an available substrate.[7] Once the aerobic pathway is saturated, the body may shunt substrate into the anaerobic pathway despite adequate available oxygen.[6] Among vasopressors, epinephrine is particularly associated with this effect: studies have revealed that epinephrine administration may result in significant increased lactate levels while norepinephrine and dobutamine may actually decrease lactate

levels.[6] This effect essentially resolves in 24 hours after withdrawal of vasopressor support.

Beyond the ICU setting, many familiar outpatient medications may increase lactate levels. Metformin and antiretroviral therapy for HIV are commonly implicated. Metformin may increase baseline lactate levels, thereby causing diagnostic confusion if a patient presents with suspected sepsis. A study of non-insulin-dependent diabetics found that those on metformin had both increased fasting plasma lactate levels and increased lactate turnover. These represented significant increases and were strongly correlated ($r = 0.68$, $p < 0.001$).[8] Increased hepatic gluconeogenesis is the proposed mechanism of this finding. When considering antiretroviral therapy, nucleoside reverse-transcriptase inhibitors (NRTIs) such as zidovudine (AZT), didanosine, zalcitabine, stavudine, lamivudine and abacavir are commonly implicated. These medications specifically alter mitochondrial function and structure. Among patients on these medications, asymptomatic lactic acidosis may be as prevalent as 15–35%.[9] Additionally, even prior therapy with stavudine or didanosine led to increased risk of hyperlactataemia.[9] Although lactate levels are commonly elevated, this effect very rarely causes symptomatic acidaemia.

Circulating levels of lactic acid also increase as a result of respiratory alkalosis, independent of hypoperfusion and hypoxia.[10,11] Since chronic respiratory alkalosis results in a compensatory reduction in serum bicarbonate, this situation (low HCO_3 with elevated lactate) may be incorrectly interpreted as a lactic acidosis (rather than a respiratory alkalosis) unless a blood gas measurement of pH is obtained. Additionally, resting lactate levels may be elevated after seizures, from muscle origin in severe respiratory distress, or with large or aggressive tumours.

Beyond increased production, inability to clear lactate effectively leads to increased baseline levels. Lactate catabolism primarily occurs in the liver,[3] so patients with hepatic dysfunction may have higher lactate levels. In one study of 24 stable septic patients, it was found that mild hyperlactataemia (2–3 mmol/L) was due to impaired clearance, rather than increased anaerobic metabolism.[12] Thus, elevated lactate levels may represent organ dysfunction or hypoperfusion during any systemic disease process.

Lactate production and metabolism encompasses a complex system. The aetiology of mild hyperlactataemia is likely multifactorial and may represent hypoperfusion, mitochondrial dysfunction or impaired clearance, rather than just tissue hypoxia.

HOW CAN WE MEASURE LACTATE? PREJUDICES AND PITFALLS

Historically, arterial blood analysis was purportedly the only accurate lactate measurement. Fifty years ago, correlation studies between arterial and venous lactate were performed in healthy individuals during exercise. In these preliminary reports, venous blood had a significantly lower value than mixed blood,[2] though this difference disappeared when subjects were at rest. Obviously there is a limited applicability of this study when generalised to an inpatient, infirmed population. Yet, the incorrect belief persists that only arterial lactate is valid despite substantial evidence to the contrary.

Recent studies have specifically addressed the validity in measuring either venous or arterial lactate. In simultaneous assessment of arterial and venous samples in critically ill patients, there was no significant difference between the obtained values ($p < 0.001$).[13] In another study of 221 patients, when samples were drawn within two minutes of each other, there was no significant difference between arterial versus venous lactate.[14] Tourniquet usage did not alter lactate levels significantly. Moreover there was no difference between peripheral and central venous samples.[14] Any misconceptions about the inferiority of peripheral venous testing should be dismissed. More importantly, as discussed below, research has clearly shown that venous lactate powerfully predicts outcome.

Furthermore, there has been debate over the validity of lactate measurement in whole blood versus plasma. Thus far, lower lactate levels correlate adequately. Concern remains that at lactate levels ≥ 6 mmol/L, correlation decreases and plasma analysis reports higher values. Ideally each institution would have only one type of analysis, either whole blood or plasma, to reduce discrepancies and improve standardisation.[15]

Regardless of specimen type, post-collection sample handling remains of primary importance. Delays in processing cause clinically meaningful – but erroneous – elevations in measured lactate.[16,17] Samples collected for lactate analysis must be processed promptly and kept on ice during transport. These interventions lessen the additional lactate the erythrocytes release prior to analysis.[16,18]

Once collected, lactate levels may be assessed by three different analysis methods. Historically, this was done by either the spectrophotometric or electrochemical method. With a processing time upwards of several hours, these methods are of limited utility in urgent situations.[19] Additionally, the spectrophotometric method requires separating red blood cells from plasma, thereby delaying analysis and increasing the risk of a falsely elevated level secondary to erythrocyte metabolism. More recently, there has been the introduction of an enzymatic, substrate-specific electrode. With this method, lactate is converted to hydrogen peroxide and pyruvate. The hydrogen peroxide is then converted back to oxygen, generating an electrical current that is directly proportional to lactate's concentration. This method enables the use of whole blood samples resulting in a turnaround time of only a few minutes. When compared to standard

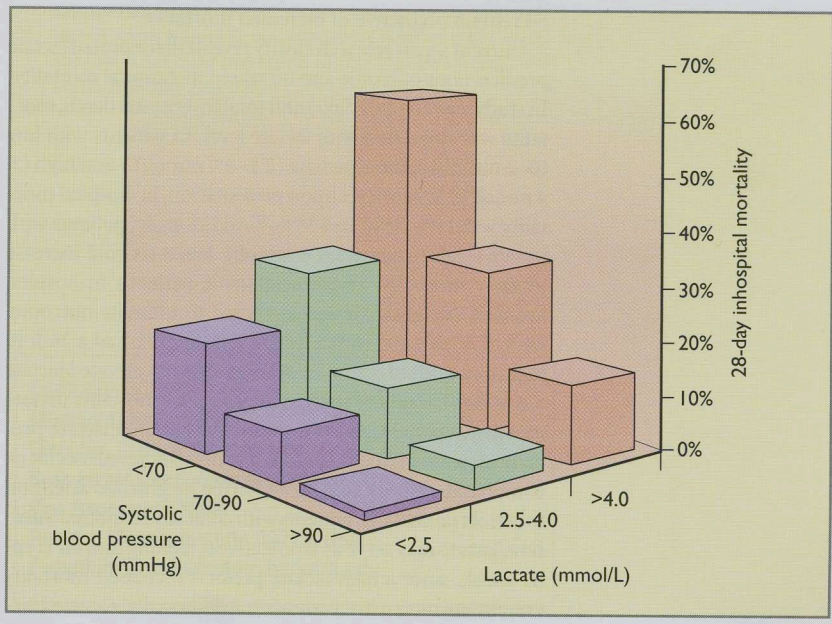

Figure 1. 28-day in-hospital mortality risk stratified by blood pressure and serum lactate level. Reproduced from Howell *et al.*[25] with kind permission from Springer Science & Business Media.

laboratory measures, the enzymatic substrate-specific electrode is equally accurate.[19]

With the rapid enzymatic substrate-specific electrode technique, lactate analysis has moved to the bedside. Point-of-care (POC) analysis may provide results in less than two minutes.[19] Lactate's utility in an acute setting continues to evolve. Of note, POC enzymatic electrode testing has been erroneously and greatly elevated in the setting of ethylene glycol ingestion.[20] Beyond this unique situation, however, its accuracy is well verified, and point-of-care testing may provide clinically useful information substantially more rapidly than sending samples to the central laboratory.

LACTATE AT THE BEDSIDE: PREDICTING OUTCOME AND DRIVING MANAGEMENT

Hypoxia and poor perfusion are thought to be the most significant contributors of elevated lactate within septic patients. In early septic shock studies, increased oxygen delivery was found to be associated with increased oxygen consumption, as well as decreased lactate levels.[21] Thus, decreasing lactate levels have long been believed to suggest reduced tissue-level hypoxia.

Within sepsis research, lactate's utility is being studied in three main categories. First, by facilitating better assessment of disease severity, lactate levels may help predict mortality. Second, during the inpatient stay, lactate clearance may serve as a marker of clinical improvement. Lastly, and somewhat theoretically, lactate has been proposed as a marker of quality of care.

Initial lactate level

For decades, studies have focused on initial lactate levels as predictive of mortality. Beyond sepsis, the prognostic value of an initial lactate level has been validated in a variety of populations including trauma and surgical patients. In these studies, lactate is significantly higher in nonsurvivors than in survivors.[22] Prior to early goal-directed therapy and other advances in critical care medicine, initial sepsis studies revealed hyperlactataemic patients have increased mortality. In one seminal study, if excess lactate levels were > 4 mmol/L, all patients had a fatal outcome.[23] This held true even if the lactate level was reduced prior to death. Though this represents an extreme example, initial blood lactate levels remain predictive of increased mortality.

Current sepsis research clearly reveals that elevated lactate predicts poor outcome and increased in-hospital mortality. In studying early (<3 days) and total in-hospital death, mortality was correlated with lactate level. In patients with low (0–2 mmol/L), intermediate (2.1–3.9 mmol/L) and high (> 4 mmol/L) lactate level upon presentation, in-hospital mortality was 15%, 25% and 38%.[24] Additionally, patients with lactate levels higher than 4 mmol/L had a six-fold increase in early mortality. Hyperlactataemic patient's in-hospital location was also assessed in regard to ultimate outcome. Non-ICU patients with a lactate > 4 mmol/L had a 28-fold increased odds of death. In other studies, an elevated lactate > 4 mmol/L was 96% specific in predicting mortality in normotensive patients.[19] Thus, markedly elevated lactate predicts increased patient mortality. This may reveal occult or compensated shock that should bring heightened attention to certain patients. In patients with clinically suspected infection, lactate may serve as an effective screening tool for cryptic shock, since a high lactate predicts increased mortality even in normotensive patients.[25] Additionally, elevated lactate may identify non-ICU or haemodynamically stable patients with an increased mortality risk thereby alerting clinicians that more aggressive care may be warranted. In most implementations of sepsis pathways, all patients with a lactate > 4 mmol/L are treated with early goal-directed therapy regardless of blood pressure.[26,27]

Poor lactate clearance

Ineffective lactate clearance predicts worse outcome including organ failure and increased mortality. In a study of surgical patients, duration of lactate elevation correlated with mortality risk.[22] Studies within septic populations reveal similar results.[28] Using the definition of hyperlactataemia > 2 mmol/L, duration of hyperlactataemia (termed 'lactime' by the authors) was the best predictor of survival.[29] Other time course studies reveal an inverse relationship between lactate clearance and mortality. In one study, for each 10% increase in lactate clearance, patients had an 11% decrease in likelihood of mortality.[30] These patients also required less vasopressor support and overall had better outcomes. Therefore, serial lactate measurement may be a useful tool during sepsis management to help the clinician predict mortality and assess response to treatment.

In addition to mortality, studies have verified the association between poor lactate clearance and organ dysfunction. Within severe sepsis, duration of hyperlactataemia may predict the development of multiple organ dysfunctions.[29] Other studies have found low lactate clearance was also associated with low platelets and elevated prothrombin time, both of which are associated with hepatic dysfunction.[30] In this, poor clearance may represent propagation of already present organ dysfunction into a multisystem process. Consequently, organ dysfunction and failed lactate metabolism as a result of, or independent to poor perfusion, likely contributes to overall mortality. This information may heighten the clinician's suspicions for occult organ dysfunction. This may prompt further diagnostic testing or facilitate discussions with specialty services at an earlier time in the patient's hospitalisation.

Additionally, poor lactate clearance has been proposed as one method for triaging septic patients given that it may be predictive of outcome. In a group of patients with initial lactate < 3 mmol/L, lactate was infused at 1 mmol/kg for 15 minutes. Lactate levels which increased at least 0.6 mmol/L at 45 minutes post-infusion were predictive of 28 day mortality with 53% sensitivity and 90% specificity.[31] Given that poor lactate clearance is not an indication for any one therapeutic intervention, such information as gained through a lactate challenge is questionably useful at this point. As interventions and therapies evolve, however, this may become a more effective tool.

Quality improvement in sepsis care

The Surviving Sepsis Campaign and the Institute for Healthcare Improvement have proposed lactate measurement within six hours of presentation as a quality measure for patients with severe sepsis, as part of the Sepsis Resuscitation Bundle.[32,33] Although there was some initial scepticism about this bundle approach to sepsis care, recent literature makes it clear that implementation of the sepsis bundle is associated with meaningfully reduced mortality in centres in England,[34] the United States,[35] and Spain.[36] Early lactate measurement should therefore probably be considered in all patients presenting with clinically suspected sepsis.

SUMMARY

Although lactate's metabolism is complex, high lactate levels convincingly predict increased mortality risk in patients with suspected infection. Arterial measurement of lactate is not required: venous values correlate strongly with arterial and are valid predictors of mortality. Therefore, measurement of either is reasonable to help risk-stratify patients with infection. Lactate is useful in a variety of hospital settings, including the emergency department, ICU and regular hospital wards. It may be particularly helpful in patients who have a normal blood pressure, since it may identify patients who need an increased level of care though currently haemodynamically stable. Institutions should strive to have rapid turnaround times (measured in minutes, not hours) for measurement of lactate, since elevated lactate levels should prompt consideration of early goal-directed therapy in patients with sepsis.[32] Additionally, ineffective lactate clearance over time predicts poor outcome with increased mortality and multiorgan failure. More recently, lactate measurement has been proposed[32,33] and validated[34–36] as a marker of quality of care as part of the sepsis resuscitation bundle. For all of these reasons, clinicians should consider early lactate measurement in most patients with clinically suspected sepsis.

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